ZOONOSES AND COMMUNICABLE DISEASES COMMON TO MAN AND ANIMALS

Third Edition

Volume I

Bacterioses and Mycoses

Scientific and Technical Publication No. 580

PAN AMERICAN HEALTH ORGANIZATION
Pan American Sanitary Bureau, Regional Office of the
WORLD HEALTH ORGANIZATION
525 Twenty-third Street, N.W.
Washington, D.C. 20037 U.S.A.

2001

Also published in Spanish (2001) with the title:
Zoonosis y enfermedades transmisibles comunes al hombre a los animales
ISBN 92 75 31580 9

PAHO Cataloguing-in-Publication
Pan American Health Organization
Zoonoses and communicable diseases common to man and animals
3rd ed. Washington, D.C.: PAHO, © 2001.
3 vol.—(Scientific and Technical Publication No. 580)

ISBN 92 75 11580 X
I. Title II. Series
1. ZOONOSES
2. BACTERIAL INFECTIONS AND MYCOSES
3. COMMUNICABLE DISEASE CONTROL
4. FOOD CONTAMINATION
5. PUBLIC HEALTH VETERINARY
6. DISEASE RESERVOIRS

NLM WC950.P187 2001 En

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PROLOGUE

Zoonoses and communicable diseases common to man and animals continue to have high incidence rates and to cause significant morbidity and mortality. Infections and parasitoses of cattle can reduce meat or milk production and can lead to the death or destruction of the animals, all of which diminishes the supply of available food for man. These diseases are also an obstacle for international trade, as well as a serious financial drain for cattle farmers and, more broadly, for a community's or a country's economy, which can have wide repercussions for a society's health.

With the aim of helping to solve these problems, the Pan American Health Organization (PAHO)—an international public health organization that has devoted itself to improving the health and living conditions of the people of the Americas for nearly one hundred years—established the Veterinary Public Health Program. The Program's overall objective is to collaborate with PAHO's Member Countries in the development, implementation, and evaluation of policies and programs that lead to food safety and protection and to the prevention, control, or eradication of zoonoses, among them foot-and-mouth disease.

To this end, PAHO's Veterinary Public Health Program has two specialized regional centers: the Pan American Foot-and-Mouth Disease Center (PANAFTOSA), created in 1951 in Rio de Janeiro, Brazil, and the Pan American Institute for Food Protection and Zoonoses (INPPAZ), established on November 15, 1991 in Buenos Aires, Argentina. INPPAZ's precursor was the Pan American Zoonoses Center (CEPANZO), which was created through an agreement with the Government of Argentina to help the countries of the Americas combat zoonoses, and which operated from 1956 until 1990.

Since its creation in 1902, PAHO has participated in various technical cooperation activities with the countries, among them those related to the surveillance, prevention, and control of zoonoses and communicable diseases common to man and animals, which cause high morbidity, disability, and mortality in vulnerable human populations. PAHO has also collaborated in the strengthening of preventive medicine and public health through the promotion of veterinary health education in learning, research, and health care centers. An example of this work is the preparation of several publications, among which the two previous Spanish and English editions of *Zoonoses and Communicable Diseases Common to Man and Animals* stand out.

Scientific knowledge has progressed since the last edition. Also, the countries of the Americas have modified their livestock production strategies in recent years, which has affected the transmission of zoonotic infections and their distribution. The publication of this third edition is an attempt to address these changes. The third edition is presented in three volumes: the first contains bacterioses and mycoses; the second, chlamydioses, rickettsioses, and viroses; and the third, parasitoses.

We believe that this new edition will continue to be useful for professors and students of public health, medicine, and veterinary medicine; workers in public health and animal health institutions; and veterinarians, researchers, and others interested in the subject. We also hope that this publication is a useful tool in the elaboration of national zoonosis control or eradication policies and programs, as well as in risk

evaluation and in the design of epidemiological surveillance systems for the prevention and timely control of emerging and reemerging zoonoses. In summary, we are confident that this book will contribute to the application of the knowledge and resources of the veterinary sciences for the protection and improvement of public health.

GEORGE A.O. ALLEYNE
DIRECTOR

PREFACE TO THE FIRST EDITION

This book considers two groups of communicable diseases: those transmitted from vertebrate animals to man, which are—strictly speaking—zoonoses; and those common to man and animals. In the first group, animals play an essential role in maintaining the infection in nature, and man is only an accidental host. In the second group, both animals and man generally contract the infection from the same sources, such as soil, water, invertebrate animals, and plants; as a rule, however, animals do not play an essential role in the life cycle of the etiologic agent, but may contribute in varying degrees to the distribution and actual transmission of infections.

No attempt has been made to include all infections and diseases comprised in these two groups. A selection has been made of some 150 that are of principal interest, for various reasons, in the field of public health. The number of listed zoonoses is increasing as new biomedical knowledge is acquired. Moreover, as human activity extends into unexplored territories containing natural foci of infection, new zoonotic diseases are continually being recognized. In addition, improved health services and better differential diagnostic methods have distinguished zoonoses previously confused with other, more common diseases. A number of diseases described in this book have only recently been recognized, examples of which include the Argentine and Bolivian hemorrhagic fevers, angiostrongyliasis, rotaviral enteritis, Lassa fever, Marburg disease, and babesiosis.

The principal objective in writing this book was to provide the medical professions a source of information on the zoonoses and communicable diseases common to man and animals. Toward that end, both medical and veterinary aspects, which have traditionally been dealt with separately in different texts, have been combined in a single, comprehensive volume. As a result, physicians, veterinarians, epidemiologists, and biologists can all gain an overview of these diseases from one source.

This book, like most scientific works, is the product of many books, texts, monographs, and journal articles. Many sources of literature in medicine, veterinary medicine, virology, bacteriology, mycology, and parasitology were consulted, as were a large number of reports from different biomedical disciplines, in order to provide up-to-date and concise information on each disease. It is expected that any errors or omissions that may have been committed can, with the collaboration of the readers, be corrected in a future edition.

Where possible, explanations were attempted with special emphasis on the Americas, particularly Latin America. An effort was made, one which was not always successful, to collect available information on diseases in this Region. Data on the incidence of many zoonoses are fragmentary and frequently not reliable. It is hoped that the establishment of control programs in various countries will lead to improved epidemiologic surveillance and disease reporting.

More space has been devoted to those zoonoses having greatest impact on public health and on the economy of the countries of the Americas, but information is also included on those regionally less important or exotic diseases.

The movement of persons and animals over great distances adds to the risk of introducing exotic diseases that may become established on the American continent

given the appropriate ecologic factors for existence of the etiologic agents. Today, public health and animal health administrators, physicians, and veterinarians must be familiar with the geographic distribution and pathologic manifestations of the various infectious agents so that they can recognize and prevent the introduction of exotic diseases.

We, the authors, would like to give special recognition to Dr. Joe R. Held, Assistant Surgeon-General of the United States Public Health Service and Director of the Division of Research Services of the U.S. National Institutes of Health, who gave impetus to the English translation and reviewed the bacterioses sections.

We would also like to express our utmost appreciation to the experts who reviewed various portions of this book and offered their suggestions for improving the text. These include: Dr. Jeffrey F. Williams, Professor in the Department of Microbiology and Public Health, Michigan State University, who reviewed the chapters dealing with parasitic zoonoses; Dr. James Bond, PAHO/WHO Regional Adviser in Viral Diseases, who read the viroses; Dr. Antonio Pío, formerly PAHO/WHO Regional Adviser in Tuberculosis and presently with WHO in Geneva, and Dr. James H. Rust, PAHO/WHO Regional Adviser in Enteric Diseases, both of whom reviewed the bacterioses; and Dr. F. J. López Antuñano, PAHO/WHO Regional Adviser in Parasitic Diseases, who read the metazooses.

We would like to thank Dr. James Cocozza, PAHO/WHO Veterinary Adviser, for his review of the translation and Dr. Judith Navarro, Editor in the Office of Publications of PAHO, for her valuable collaboration in the editorial revision and composition of the book.

PEDRO N. ACHA
BORIS SZYFRES

PREFACE TO THE SECOND EDITION

The fine reception accorded the Spanish, English, and French versions of this book has motivated us to revise it in order that it still may serve the purpose for which it was written: to provide an up-to-date source of information to the medical profession and allied fields. This book has undoubtedly filled a void, judging by its wide use in schools of public health, medicine, and veterinary medicine, as well as by bureaus of public and animal health.

The present edition has been considerably enlarged. In the seven years since the first edition was published, our knowledge of zoonoses has increased broadly and rapidly, and new zoonotic diseases have emerged. Consequently, most of the discussions have been largely rewritten, and 28 new diseases have been added to the original 148. Some of these new diseases are emerging zoonoses; others are pathologic entities that have been known for a long time, but for which the epidemiologic connection between man and animal has been unclear until recently.

The use this book has had outside the Western Hemisphere has caused us to abandon the previous emphasis on the Americas in favor of a wider scope and geomedical view. Moreover, wars and other conflicts have given rise to the migration of populations from one country or continent to another. A patient with a disease heretofore known only in Asia may now turn up in Amsterdam, London, or New York. The physician must be aware of these diseases in order to diagnose and treat them. "Exotic" animal diseases have been introduced from Africa to Europe, the Caribbean, and South America, causing great damage. The veterinary physician must learn to recognize them to be able to prevent and eradicate them before they become entrenched. It must be remembered that parasites, viruses, bacteria, and other agents of zoonotic infection can take up residence in any territory where they find suitable ecologic conditions. Ignorance, economic or personal interests, and human customs and needs also favor the spread of these diseases.

Research in recent years has demonstrated that some diseases previously considered to be exclusively human have their counterparts in wild animals, which in certain circumstances serve as sources of human infection. On the other hand, these animals may also play a positive role by providing models for research, such as in the case of natural leprosy in nine-banded armadillos or in nonhuman primates in Africa. Of no less interest is the discovery of *Rickettsia prowazekii* in eastern flying squirrels and in their ectoparasites in the United States, and the transmission of the infection to man in a country where epidemic typhus has not been seen since 1922. A possible wild cycle of dengue fever is also discussed in the book. Is Creutzfeldt-Jakob disease a zoonosis? No one can say with certainty, but some researchers believe it may have originated as such. In any case, interest is aroused by the surprising similarity of this disease and of kuru to animal subacute spongiform encephalopathies, especially scrapie, the first known and best studied of this group. Discussion of human and animal slow viruses and encephalopathies is included in the spirit of openness to possibilities and the desire to bring the experience of one field of medicine to another. In view of worldwide concern over acquired immunodeficiency syndrome (AIDS), a brief section on retroviruses has also been added, in which the relationship between the human disease and feline and simian AIDS is

noted. Another topic deeply interesting to researchers is the mystery of the radical antigenic changes of type A influenza virus, a cause of explosive pandemics that affect millions of persons around the world. Evidence is mounting that these changes result from recombination with a virus of animal origin (see Influenza). That this should occur is not surprising, given the constant interaction between man and animals. As a rule, zoonoses are transmitted from animal to man, but the reverse may also occur, as is pointed out in the chapters on hepatitis, herpes simplex, and measles. The victims in these cases are nonhuman primates, which may in turn retransmit the infection to man under certain circumstances.

Among emerging zoonoses we cite Lyme disease, which was defined as a clinical entity in 1977; the etiologic agent was found to be a spirochete (isolated in 1982), for which the name *Borrelia burgdorferi* was recently proposed. Emerging viral zoonoses of note in Latin America are Rocio encephalitis and Oropouche fever; the latter has caused multiple epidemics with thousands of victims in northeast Brazil. Outstanding among new viral disease problems in Africa are the emergence of Ebola disease and the spread of Rift Valley fever virus, which has caused tens of thousands of human cases along with great havoc in the cattle industry of Egypt and has evoked alarm around the world. Similarly, the protozoan *Cryptosporidium* is emerging as one of the numerous agents of diarrheal diseases among man and animals, and probably has a worldwide distribution.

As the English edition was being prepared, reports came to light of two animal diseases not previously confirmed in humans. Three cases of human pseudorabies virus infection were recognized between 1983 and 1986 in two men and one woman who had all had close contact with cats and other domestic animals. In 1986, serologic testing confirmed infection by *Ehrlichia canis* in a 51-year-old man who had been suspected of having Rocky Mountain spotted fever. This is the first known occurrence of *E. canis* infection in a human. These two diseases bear watching as possible emerging zoonoses.

The space given to each zoonosis is in proportion to its importance. Some diseases that deserve their own monographs were given more detailed treatment, but no attempt was made to cover the topic exhaustively.

We, the authors, would like to give special recognition to Dr. Donald C. Blenden, Professor in the Department of Medicine and Infectious Diseases, School of Medicine, and Head of the Department of Veterinary Microbiology, College of Veterinary Medicine, University of Missouri; and to Dr. Manuel J. Torres, Professor of Epidemiology and Public Health, Department of Veterinary Microbiology, College of Veterinary Medicine, University of Missouri, for their thorough review of and valuable contributions to the English translation of this book.

We would also like to recognize the support received from the Pan American Health Organization (PAHO/WHO), the Pan American Health and Education Foundation (PAHEF), and the Pan American Zoonoses Center in Buenos Aires, Argentina, which enabled us to update this book.

We are most grateful to Dr. F. L. Bryan for his generous permission to adapt his monograph “Diseases Transmitted by Foods” as an Appendix to this book.

Mr. Carlos Larranaga, Chief of the Audiovisual Unit at the Pan American Zoonosis Center, deserves our special thanks for the book's artwork, as do Ms. Iris Elliot and Mr. William A. Stapp for providing the translation into English. We would like to express our most sincere gratitude and recognition to Ms. Donna J. Reynolds, editor in the PAHO Editorial Service, for her valuable collaboration in the scientific editorial revision of the book.

PEDRO N. ACHA
BORIS SZYFRES

INTRODUCTION

This new edition of *Zoonoses and Communicable Diseases Common to Man and Animals* is published in three volumes: I. Bacterioses and mycoses; II. Chlamydioses and rickettsioses, and viroses; and III. Parasitoses. Each of the five parts corresponds to the location of the etiologic agents in the biological classification; for practical purposes, chlamydias and rickettsias are grouped together.

In each part, the diseases are listed in alphabetical order to facilitate reader searches. There is also an alphabetical index, which includes synonyms of the diseases and the etiologic agents' names.

In this edition, the numbers and names of the diseases according to the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), are listed below the disease title. However, some zoonoses are not included in ICD-10 and are difficult to classify within the current scheme.

In addition, for each disease or infection, elements such as synonyms; etiology; geographical distribution; occurrence in man and animals; the disease in man and animals; source of infection and mode of transmission; role of animals in the epidemiology; diagnosis; and control are addressed. Patient treatment (for man or other species) is beyond the scope of this work; however, recommended medicines are indicated for many diseases, especially where they are applicable to prophylaxis. Special attention is paid to the epidemiological and ecological aspects so that the reader can begin to understand the determining factors of the infection or disease. Some topics include simple illustrations of the etiologic agent's mode of transmission, showing the animals that maintain the cycle of infection in nature. Similarly, other graphics and tables are included to provide additional information on the geographical distribution or prevalence of certain zoonoses.

The data on the occurrence of the infection in man and animals, along with data on the geographical distribution, may help the reader judge the relative impact that each disease has on public health and the livestock economy in the different regions of the world, given that the importance of different zoonoses varies greatly. For example, foot-and-mouth disease is extremely important from an economic standpoint, but of little importance in terms of public health, if animal protein losses are not considered. In contrast, Argentine and Bolivian hemorrhagic fevers are important human diseases, but their economic impact is minimal, if treatment costs and loss of man-hours are not taken into account. Many other diseases, such as brucellosis, leptospirosis, salmonellosis, and equine encephalitis, are important from both a public health and an economic standpoint.

Finally, each disease entry includes an alphabetical bibliography, which includes both the works cited and other relevant works that the reader may consult for more information about the disease.

ACTINOMYCOSIS

ICD-10 A42.9

Synonyms: Actinostreptotrichosis, mandibular cancer, ray fungus disease.

Etiology: *Actinomyces israelii* is the principal etiologic agent in man, and *A. bovis* the main one in animals. *A. naeslundi*, *A. viscosus*, *A. odontolytical*, *A. meyeri* and *Arachnia propionica* (*A. propionicus*) are isolated less often, although *A. viscosus* plays an important role in canine actinomycosis. Some reports indicate isolation of *A. israelii* from animals (Georg, 1974) and *A. bovis* from man (Brunner *et al.*, 1973). Actinomyces are higher bacteria with many characteristics of fungi. They are gram-positive, do not produce spores, are non–acid-fast, range from anaerobic to microaerophilic, and are part of the normal flora of the mouth and of women's genital tract (Burden, 1989).

Geographic Distribution: Worldwide.

Occurrence in Man: Infrequent; however, data are very limited. Fewer than 100 cases of the disease are recorded each year by the Public Health Laboratory Service's Communicable Disease Surveillance Centre in Great Britain (Burden, 1989). According to older data, 368 cases were recorded in Wales and England over 12 years (1957–1968), with an incidence of 0.665 per million inhabitants, with a higher incidence among industrial workers (Wilson, 1984). In Scotland, the annual incidence was three per million and the rate of attack was 10 times higher in agricultural workers than among others.

The historical ratio of two cases in men to one in women is probably no longer valid because of the number of cases of genital actinomycosis in women using intrauterine contraceptive devices (IUDs).

Occurrence in Animals: The frequency of the disease varies widely among regions and is also influenced by different livestock management practices. The disease usually appears as sporadic cases. Small outbreaks have occurred in some marshy areas of the United States and the former Soviet Union.

The Disease in Man: *A. israelii*, the main causal agent in man, is a normal component of the flora of the mouth. As a result of wounds or surgery, it can enter the soft tissues and bones, where it causes a suppurative granulomatous process that opens to the surface through fistulas. Several clinical forms have been identified according to their location: cervicofacial, thoracic, abdominal, and generalized. Cervicofacial, which is the most common (from 50% to more than 70% of cases), is usually caused by a tooth extraction or a jaw injury; it begins with a hard swelling under the mucous membrane of the mouth, beneath the periosteum of the mandible, or in the skin of the neck. At a later stage, softened areas, depressions, and openings to the exterior with a purulent discharge are evident. These secretions usually contain the characteristic "sulphur granules," which are actinomyces colonies. The thoracic form is generally caused by breathing the etiologic agent into the bronchial tubes where it establishes a chronic bronchopneumonia that affects the lower portions of the right lung (Burden, 1989), with symptoms similar to pulmonary tuberculosis. As the disease progresses, invasion of the thoracic wall and its perforation

by fistulous tracks may occur. The abdominal form usually occurs after surgery and appears as an encapsulated lesion that often becomes localized in the cecum and the appendix, where it produces hard tumors that adhere to the abdominal wall.

The generalized form is infrequent and results from the erosive invasion of blood vessels and lymphatic system, resulting in liver and brain disease.

In recent years, reports of actinomycosis in the genital tract of women using intrauterine contraceptive devices have multiplied, with the rate of infection increasing in proportion to the duration of IUD use. In one study (Valicenti *et al.*, 1982), the infection was found in 1.6% of women in the general population of IUD users and in 5.3% of those attending the clinics. Another study of 478 IUD users found a rate of infection of 12.6% based on Papanicolaou (Pap) smears (Koebler *et al.*, 1983). Attempts to isolate the bacteria in Pap smears rarely yield positive results. However, *A. israelii* is also isolated from the genital tract of women who do not use IUDs, indicating that actinomyces are part of the normal flora (Burden, 1989). In the vast majority of cases, colonization by actinomyces produces only a superficial or asymptomatic infection.

Treatment consists of prolonged high doses of penicillin (weeks or months). Erythromycin, clindamycin, and tetracycline may also be used. Surgical drainage of abscesses is important. In women with an endometrium colonized by actinomyces, removing the IUD is sometimes enough for the endometrium to return to normal.

The Disease in Animals: *A. bovis* is the principal agent of actinomycosis in bovines and, occasionally, in other animal species. In bovines, it centers chiefly in the maxillae where it forms a granulomatous mass with necrotic areas that develop into abscesses. These open via fistulous passages and discharge a viscous, odorless, yellow pus. The pus contains small, yellow, sulphur granules, which are rosette-shaped when viewed under a microscope. In some cases chewing becomes very difficult, and the animal stops eating and loses weight.

The cost-benefit ratio must be measured when treating bovine and equine actinomycosis. Long-standing chronic lesions do not respond readily to treatment. If the lesions are small and circumscribed, they may be removed surgically. In other cases, curettage can be performed on the abscesses and fistulas, which are then packed with gauze saturated with iodine tincture. Medical treatment is the same as for human actinomycosis, preferably using penicillin.

In swine the etiologic agent localizes principally in the sow's udder, where it gives rise to abscesses and fistulas. Its pathway of penetration is the lesion caused by the teeth of suckling pigs. This infection is attributed to *Actinomyces suis*, whose taxonomy is still uncertain.

In dogs, the disease produces cervicofacial abscesses, empyemas accompanied by pleurisy and osteomyelitis, and, more rarely, abdominal abscesses and cutaneous granulomas. The most common agent encountered prior to 1982 was *A. viscosus* (Hardie and Barsanti, 1982).

Source of Infection and Mode of Transmission: The infection is endogenous. Actinomyces develop as saprophytes within and around carious teeth, in the mucin on dental enamel and in the tonsillar crypts. In studies carried out in several countries, actinomyces have been found in 40% of excised tonsils and have been isolated in 30% to 48% of saliva samples or material from decayed teeth, as well as from the vaginal secretions of 10% of women using IUDs (Benenson, 1992).

Infections and pathological developments are the product of tissue trauma, lesions, or prolonged irritation. It has not been possible to isolate the agent of actinomycosis from the environment. It is believed that the causal agent penetrates the tissues of the mouth through lesions caused by foods or foreign objects, or by way of dental defects. From the oral cavity, the bacteria can be swallowed or breathed into the bronchial tubes.

Role of Animals in the Epidemiology of the Disease: The species of *Actinomyces* that attack man are different from those that affect animals. Rarely is *A. israelii* found in animals or *A. bovis* found in man. The designation of species prior to 1960 is doubtful (Lerner, 1991) and thus, distinguishing one species from another presents great problems. The infection in animals is not transmitted to man, nor is it transmitted from person to person or animal to animal.

Diagnosis: The clinical picture may be confused with other infections, such as actinobacillosis, nocardiosis, and staphylococcosis, as well as neoplasia and tuberculosis. The first step in confirming the diagnosis is to obtain pus, sputum, or tissue samples for microscopic examination and culture, and to inspect them for granules. Filament masses are visible by direct observation. In smears of crushed granules or pus stained by the Gram and Kinyoun methods, gram-positive and non–acid-fast filaments or pleomorphic forms, occasionally with bacillary-sized branching, may be seen (Cottral, 1978). It is possible to identify the species of actinomyces causing the disease only by culturing and typing the isolated microorganism. In testing women who use IUDs, direct immunofluorescence has yielded good results (Valicenti *et al.*, 1982).

Control: Prevention in man consists of proper oral hygiene and care after dental extractions or other surgery in the oral cavity. No practical means have been established yet to prevent actinomycosis in animals.

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AEROMONIASIS

ICD-10 AO5.8 other specified bacterial foodborne intoxications

Etiology: The genus *Aeromonas* is classified within the family *Vibrionaceae* and shares some characteristics with members of other genera of this family. However, genetic hybridization studies indicate that the genus *Aeromonas* is sufficiently different to place it in a new family, with the suggested name of *Aeromonadaceae*. Two groups can be distinguished in the genus *Aeromonas*. The first group is psychrophilic and nonmotile and is represented by *Aeromonas salmonicida*, an important pathogen for fish (the agent of furunculosis). It does not affect man because it cannot reproduce at a temperature of 37°C. The second group is mesophilic and motile, and it is this group that causes aeromoniasis, a disease common to man and animals. These aeromonas are gram-negative, straight bacilli ranging from 1 to 3 microns in length. They have a polar flagellum and are oxidase positive and facultatively anaerobic. They essentially include the species *A. hydrophila*, *A. sobria*, and *A. caviae* (Janda and Duffey, 1988), to which *A. veronii* and *A. schuberti* were added later, as well as the genospecies *A. jandae* and *A. trota*. However, only *A. hydrophila* and *A. sobria* are of clinical interest.

More recent hybridization studies show that the *A. hydrophila* complex is genetically very variable. Thirteen different genospecies have been established, but from a practical standpoint the three principal phenospecies are retained. It is possible to identify 95% of isolates on the basis of their biochemical properties (Janda, 1991).

A system of 40 serogroups was established based on the somatic antigens (O) of *A. hydrophila* and *A. caviae*. All the O antisera contain antibodies to the rugose form (R) of the bacillus, and thus the antisera must be absorbed by culturing the R form before being used (Sakazaki and Shimada, 1984). Typing is done by gel protein electrophoresis, isoenzyme analysis, and genetic analysis. Isoenzyme analysis made it possible to identify genospecies through four enzymes. All these methods have

shown that the clinical strains are very diverse and that no single clone is responsible for most of the infections (Von Graevenitz and Altwegg, 1991).

Over the last decade, researchers have tried to define the virulence factors of this genus, both in terms of structural characteristics and the extracellular products they secrete. Considered important among the structural characteristics is a type of pilus, the "flexible" or curvilinear pilus. It is expressed when stimulated by certain environmental conditions that give the bacteria the ability to colonize. Another structural characteristic that was first discovered in autoagglutinating strains of *A. salmonicida* is the S layer, which is outside the cell wall. The loss of this layer—which can be seen with an electron microscope—decreases pathogenicity for fish 1,000 to 10,000 times. A similar layer was later discovered in certain strains of *A. hydrophila* and *A. sobria* in infected fish and mammals, but their functional role seems to differ substantially from the same S layer in *A. salmonicida* (it does not make the surface of the bacteria hydrophobic).

The substances externally secreted by aeromonas include beta-hemolysin that is produced by certain strains of *A. hydrophila* and *A. sobria*. It has been determined that this hemolysin has enterotoxigenic effects on lactating mice and ligated ileal loops of rabbits. Purified beta-hemolysin inoculated intravenously into mice is lethal at a dose of 0.06 µg. The cytotonic enterotoxin that causes an accumulation of fluid in the ligated ileal loop of the rabbit, as well as other effects, has also been described. Between 5% and 20% of the strains produce a toxin that cross reacts with the cholera toxin in the ELISA test (Janda, 1991).

Based on tests conducted in mice and fish (the latter are much more susceptible), it can be concluded that *A. hydrophila* and *A. sobria* are more virulent than *A. caviae*. In addition, there is a great difference in the virulence of the strains within each species (Janda, 1991). These variations cannot be attributed to a single virulence factor. In addition, it was not possible to detect a common mechanism in the pathogenic capacity of *Aeromonas* spp. in humans or in animals.

An enzyme (acetylcholinesterase) isolated from fish infected by *A. hydrophila* proved to be highly active against the central nervous system. The toxin was lethal for fish at a dose of 0.05 µg/g of bodyweight; no lesions were observed in the tissues. The same toxin was obtained from six different strains (Nieto *et al.*, 1991).

A comparison was made of 11 environmental strains and 9 human strains. All the environmental strains and four of the human strains proved to be pathogenic for trout, at a dose of 3×10^7 colony forming units (CFU). Only the human strains caused death or lesions through intramuscular inoculation of mice. The virulent strains produced more hemolysis and cytotoxins in cultures at 37°C than at 28°C (Mateos *et al.*, 1993).

Geographic Distribution: The motile aeromonas appear worldwide. Their principal reservoir is in river and estuary waters, as well as in salt water where it meets fresh water. Population density is lower in highly saline waters and waters with limited dissolved oxygen. It has sometimes been possible to isolate *Aeromonas* from chlorinated water, including muncipal water supplies. These bacteria are more prolific in summer than in winter (Stelma, 1989).

Occurrence in Man: Aeromoniasis generally occurs sporadically. There is no evidence that water or foods contaminated by *Aeromonas* spp. have been the source of outbreaks (as happens with other agents, such as enterobacteria). The only cases

that suggest the possibility of outbreaks are those described in 1982 and 1983. In late 1982, some 472 cases of gastroenteritis associated with the consumption of raw oysters occurred in Louisiana (USA). One year later, another outbreak affected seven people in Florida. This was also attributed to raw oysters that came from Louisiana. Pathogenicity tests were performed on 23 of the 28 strains identified as *A. hydrophila*; 70% tested positive in at least one of the virulence tests (Abeyta *et al.*, 1986). There may have been other outbreaks that were not recognized because food and patient stools were not examined for detection and identification of *A. hydrophila* (Stelma, 1989).

Occurrence in Animals: *A. hydrophila* is a recognized pathogen in fish, amphibians, and reptiles. The disease may occur individually or epidemically, particularly in fish-farming pools. The agent affects many fish species, particularly fresh water species. Its economic impact varies, but can be severe (Stoskopf, 1993). Aeromoniasis due to *A. hydrophila* also causes significant illness in colonies of amphibians and reptiles bred for experimental purposes.

The Disease in Man: For some time the aeromonas were considered opportunistic bacteria. Clinical and epidemiological information amassed in recent years seems to confirm that *A. hydrophila* and *A. sobria* are the primary human pathogens, particularly as agents of enteritis in children.

The disease appears in two forms: enteric and extraenteric. Studies on the pathogenic role of *Aeromonas* spp. in gastroenteritis have been conducted in Australia, the United States, England, Thailand, and, more recently, in Rosario, Argentina (Notario *et al.*, 1993). Patients with and without diarrhea have been compared, with the latter group consisting of patients suffering from other diseases or healthy individuals. In Argentina, 8 strains (2%) were isolated from 400 fecal samples and from a colon biopsy in children with diarrhea, and no strains were isolated from 230 children without diarrhea. In the United States, the agent was found in 1.1% of the cases and in none of the controls (Agger *et al.*, 1985). The tests in the other countries also isolated *A. hydrophila* and *A. sobria* with greater frequency and in greater numbers from diarrheal feces than from nondiarrheal feces.

Enteritis due to *Aeromonas* spp. occurs more frequently in summer and predominantly in children from 6 months to 5 years of age. The clinical symptoms include profuse diarrhea, slight fever, and abdominal pains; vomiting is occasionally seen in patients under 2 years of age. Cases of gastroenteritis with blood and mucus in the feces have also been described. The disease is generally benign in children and lasts only a few days. Gastroenteritis is much less frequent in adults, but can occur with diarrhea of longer duration (from 10 days to several weeks or months), weight loss, and dehydration. The predominant species are *A. hydrophila* and *A. sobria*, but *A. caviae* has also been implicated in some cases (Janda and Duffey, 1988).

The extra-intestinal clinical form can affect different organs and tissues. One very common form of contamination is through wounds and various traumas. The wound generally becomes infected through contact with river water, ponds, or other water reservoirs. The most common clinical expression is cellulitis. The patient recovers completely in such cases.

Some 20 cases have been described of infection caused by medicinal leeches (*Hirudo medicinalis*) used to treat postoperative venous congestion after grafts or replantations. The leeches inject a very powerful anticoagulant, causing the

congested area to bleed for one to two hours (or longer) and preventing loss of the graft. Leeches may harbor *A. hydrophila* in their digestive tract and suckers and transmit the bacteria to the patient. These infections are usually limited to contamination of the wound, but can cause extensive tissue loss and septicemia (Lineaweaver *et al.*, 1992).

Untreated cellulitis can become complicated by myonecrosis and require amputation of a limb. If there is bacteremia, the infection may ultimately be fatal. Septicemia occurs primarily in immunodeficient patients and rarely in immunocompetent patients. The clinical manifestations are similar to septicemia caused by other gram-negative bacteria and consist of fever and hypotension. Mortality is high in these cases (Janda and Duffey, 1988). Other clinical forms are rare.

Gastroenteritis in children is a self-limiting disease and does not require treatment, except in prolonged cases. All other forms should be treated with antibiotics, such as gentamicin, amikacin, chloramphenicol, and cyprofloxacin. All strains of *A. hydrophila* and *A. sobria* are resistant to ampicillin (Gutierrez *et al.*, 1993), *A. trota* is not.

The Disease in Animals: Aeromoniasis is primarily a disease that affects fish, amphibians, and reptiles. The disease is rare in wild or domestic mammals and birds.

FISH: *A. hydrophila* is the agent of bacterial hemorrhagic septicemia in fish. All species of fresh water fish are considered susceptible to this disease. The clinical picture is very varied and sometimes other pathogens are isolated that can confuse the diagnosis and signs of the disease. In the very acute form of the disease, death may occur without warning signs. In other cases, scales are lost and localizaed hemorrhages appear in the gills, mouth, and base of the fins. Ulcers in the skin, exophthalmia, and abdomen-distending ascites may also be found. Renal and hepatic lesions are seen in very prolonged cases (Stoskopf, 1993). The disease occurs sporadically or in outbreaks. Mortality is variable but can be high.

Intensive fish farming can create conditions that favor infection, such as overpopulation and adverse environmental factors (increase in organic material and decrease in dissolved oxygen). These factors reduce the resistance of the fish and favor the pathogenic action of *A. hydrophila* and other bacteria. *Pseudomonas* spp. often accompanies *A. hydrophila* in ulcerous lesions in the skin of fish (erythrodermatitis, fin disease). In northern Greece, where great losses of carp (*Cyprinus carpio*) occurred in ponds due to a disease characterized primarily by cutaneous ulcers, both *A. hydrophila* and various species of *Pseudomonas* were isolated. It was possible to reproduce the disease experimentally through subcutaneous inoculation of *A. hydrophila* without the simultaneous presence of other bacteria (Sioutas *et al.*, 1991). Previously, there was an outbreak in Argentina of fin disease in young black catfish (*Rhamdia sapo*). Both *A. hydrophila* and *Pseudomonas aeruginosa* were isolated from fin lesions. When the disease was reproduced experimentally, there was not much difference between the fish inoculated with *A. hydrophila* alone and those inoculated with both bacteria (Angelini and Seigneur, 1988).

Infection of striped (grey) mullet (*Mugil cephalus*) by *A. hydrophila* results in an acute septicemic disease. The agent can be isolated from the blood of mullet with the experimentally reproduced disease one or two days after inoculation. The disease is characterized by inflammatory and proliferative changes and later by

necrotic lesions. Enteritis and hepatic necrosis are constant lesions (Soliman *et al.*, 1989).

Aeromoniasis in fish can be treated with antibiotics.

AMPHIBIANS: Frogs used for experimental purposes—whether in laboratory colonies or under natural conditions—die from a disease called "red leg" that causes cutaneous ulceration and septicemia. The Louisiana frog (*Rana catesbeiana*) suffered various epizootics in 1971 and 1972. Of 4,000 tadpoles separated from their natural habitat and kept under laboratory conditions, 70% died during metamorphosis and 20% died after completing it.

Of the wild frogs brought to the laboratory, 10% became ill and died during the first year. The tadpoles born in the laboratory that became ill during metamorphosis demonstrated lassitude, edema, and hemorrhage in the tail; accumulation of bloody lymph around the leg muscles; and small ulcers on the operculum and the skin of the abdomen. Death occurred 24 hours after onset of the disease. The disease progressed slowly in adults; it sometimes lasted up to six months and ended in death. Sick frogs had petechial or diffuse hemorrhages on the skin of their entire bodies. The lymphatic sacks were full of a bloody serous fluid and intramuscular hemorrhages were found on the hind legs and on the periosteum (Glorioso *et al.*, 1974).

"Red leg" disease in *Xenopus leavis* (a frog of African origin of the family *Pipidae*) was described in Cuba, the United States, Great Britain, and South Africa. In Cuba, the outbreak of the disease occurred three weeks after the frogs were transferred from the laboratory (where they were kept at 22°C) to ambient temperature in order to acclimate them. The disease lasted for about 48 days and the principal symptoms were lethargy, anorexia, petechiae, and edema. Autopsy revealed subcutaneous edemas, hemorrhages, and ascites. *Aeromonas hydrophila* was isolated from 14 of the 50 frogs (Bravo Fariñas *et al.*, 1989). According to the authors, the disease was unleashed by environmental changes, infrequent changes of water, and traumas, as well as other factors.

In Johor, Malaysia, where there is a small frog-breeding industry, an outbreak occurred that affected 80% of the animals in a population of 10,000. The disease was characterized by ulcers and petechial hemorrhages on the skin and opaque corneas, but no visceral lesions. In a second outbreak, the disease followed a more chronic course, with symptoms such as ascites, visceral tumefaction, and nervous disorders (Rafidah *et al.*, 1990).

The indicated treatment is antibiotics to which *A. hydrophila* is susceptible.

REPTILES: In a variety of lizards and snakes, infection due to *Aeromonas* is associated with ulcerous stomatitis. The lesions may result in septicemia, with hemorrhages and areas with ecchymoses on the integument. The animals are anorexic and suffer deterioration in their general health. One complication is pneumonia. At autopsy, exudates are found in the lungs and secondary air passages. The viscera and gastrointestinal tract show pronounced congestion with hemorrhagic areas. Treatment consists of removing the necrotic tissue from the mouth, followed by irrigation with 10% hydrogen peroxide. The use of such antibiotics as chloramphenicol and gentamicin is indicated (Jacobson, 1984).

OTHER ANIMALS: A case was described in Nigeria of aeromoniasis in a caracal lynx (*Felis caracal*) at a zoo. The animal was found with profuse diarrhea, anorexia,

and depression. Despite antidiarrheal treatment, it died in a month. The lesions suggested that the cause of death was acute septicemia. *A. hydrophila* was isolated from the animal's internal organs (Ocholi and Spencer, 1989). Similar cases had appeared in young ferrets at a research institute in Japan. The agent isolated was identified as *A. sobria* (Hiruma *et al.*, 1986). A case of polyarthritis in a 3-day-old calf was described in Australia. *A. hydrophila* was isolated from the synovial fluid (Love and Love, 1984). In Germany, a septicemic condition attributed to *A. hydrophila* has been described in turkeys at 3 to 16 weeks of life, with morbidity of 10% and mortality of 1%. Cases have also been recorded in canaries and in a toucan suffering from enteritis; *A. hydrophila* was isolated from the viscera. *A. hydrophila* was isolated in a routine postmortem examination of 15 wild, farm, and pet birds. The isolates were taken primarily in the cold months (Shane *et al.*, 1984). A pure culture of *A. hydrophila* was isolated from a parrot (*Amazona versicolor*) with bilateral conjunctivitis (García *et al.*, 1992). In all cases, the stressful conditions that contributed to the development of the disease were emphasized.

Source of Infection and Mode of Transmission: The primary reservoir of *A. hydrophila* and *A. sobria* is fresh water in rivers, ponds, and lakes. It is also found in estuaries and in low-salinity salt water. Even treated municipal water supplies can contain *Aeromonas*. In a French hospital, intestinal and extraintestinal aeromoniasis in 12 patients was attributed to the drinking water (Picard and Goullet, 1987).

Due to the increased numbers of motile *Aeromonas* in the water supply in The Netherlands, health authorities established maximum indicative values for the density of these bacteria in drinking water. These values are 20 CFU/100 ml for the drinking water in water treatment plants and 200 CFU/100 ml for water being distributed (Van der Kooij, 1988).

Motile *Aeromonas* have not caused outbreaks with multiple cases (Altwegg *et al.*, 1991). It is difficult to understand why, since the bacteria are widely distributed in nature, water, animal feces, and foods of animal origin, and since they also multiply at refrigeration temperatures.

The distribution of the agents in water reaches its highest level during the warm months, as does the disease. The situation seems to be different in tropical countries. In India, the most frequent isolates from river water occur in late winter, declining in summer and the monsoon season (Pathak *et al.*, 1988). These authors believe that fish are an independent or additional reservoir, since *Aeromonas* can be isolated from them independent of the bacteria's density in river water.

Water contaminated by virulent strains of *A. hydrophila* or *A. sobria* is the source of infection for man and other animals. Domestic animals, especially cattle and pigs, eliminate in their feces a large amount of *Aeromonas* that are probably of aquatic origin. There are indications that, in addition to water, other contaminated foods, such as oysters and shrimp, may be a source of infection for man. A case of enteritis caused by eating a shrimp cocktail occurred in Switzerland in a healthy 38-year-old. Only *A. hydrophila* and no other pathogen was isolated from the patient's stool. The strain isolated from the shrimp was biochemically identical and had the same ribosomal DNA sequence (Altwegg *et al.*, 1991).

Enteric disease occurs in normal children and the route of infection is through the mouth. In contrast, both enteric and extraintestinal aeromoniasis in individuals older than 5 years of age occurs in combination with other conditions, such as an under-

lying disease, trauma, or other stress factors. Wounds become infected upon contact with water. Medicinal leeches can infect the wound they produce with the aeromonas they harbor in their digestive tract and suckers. The most serious form of the disease, septicemia and its various organic complications, occurs in immunodeficient individuals and the route of infection is usually extraintestinal.

Fish, amphibians, and reptiles—especially in intensive breeding programs—are infected through the mouth. The factors that contribute to infection are stress from overpopulation, temperature changes, lack of hygiene, and inadequate feeding.

Role of Animals in the Epidemiology of the Disease: Aeromoniasis is primarily a disease common to man and animals. Fish may act as a reservoir in addition to water. Other animals contribute to contamination of the environment with their feces.

Diagnosis: Diagnosis can be obtained by isolating and identifying the species of the etiologic agent. As a selective medium, Rimler-Shotts agar can be used; it contains citrate, novobiocin, and sodium deoxycholate as selective agents, and lysine, ornithine, and maltose as differential agents. Another commonly used medium is agar with ampicillin and sodium deoxycholate as selective agents and trehalose as a differential agent (García-López *et al.*, 1993).

Control: Until more is known about the disease's epidemiology and the factors that determine its virulence, the consumption of raw foods of animal origin should be avoided.

Aeromonas are sensitive to heat, and pasteurization is an effective means for destroying them in milk.

The measure introduced by health authorities in The Netherlands of setting a maximum indicative value for the density of aeromonas in the water in water treatment plants and in the water distribution network should be considered by other countries when warranted by the number of human cases.

Wounds should be cleaned and disinfected to prevent contamination.

In cases of replantation surgery that require the application of medical leeches, it is recommended that the patient be given antibiotics to which *A. hydrophila* and *A. sobria* are sensitive a few days prior to surgery, so as to eliminate them from the digestive tract of the leeches.

Preventing aeromoniasis in aquatic and semi-aquatic animals in intensive breeding programs requires avoiding overpopulation, changing the water, and maintaining proper temperature and feeding regimes. Work is being done to develop vaccines for fish. Tests indicate that they can provide good protection (Plumb, 1984; Lamers *et al.*, 1985; Ruangpan *et al.*, 1986).

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ANIMAL ERYSIPELAS AND HUMAN ERYSIPELOID

ICD-10 A26.0 cutaneous erysipeloid

Synonyms: Rosenbach's erysipeloid, erythema migrans, erysipelotrichosis, rose disease (in swine).

Etiology: The etiologic agent is *Erysipelothrix rhusiopathiae* (*E. insidiosa*), a gram-positive (with uneven coloration), facultatively aerobic or anaerobic, non-motile bacillus 0.6 to 2.5 microns long that does not produce spores. When found in the rugose phase it tends to form filaments. It is resistant to environmental factors, and survives 5 days in water and 15 days in mud (Jones, 1986). The number of serotypes is increasing: in 1987, 23 (from 1 to 23) had been recognized, with subserotypes 1a, 1b and 2a, 2b (Norrung *et al.*, 1987), and by 1991, there were already 26 serotypes (Norrung and Molin, 1991). Serotyping is important in epidemiology and immunization.

A second species, *E. tonsillarum*, was isolated from the tonsils of apparently healthy swine (Takahashi *et al.*, 1987).

The classification and nomenclature of the genus *Erysipelothrix* is still under investigation. DNA:DNA hybridization studies have shown that one group of *E. rhusiopathiae* serotypes is genetically more related to this species, while another is genetically more related to *E. tonsillarum*. Two serotypes, 13 and 18, possibly belong to a new species, given their low level of hybridization with both species (Takahashi *et al.*, 1992).

Geographic Distribution: The etiologic agent is distributed on all continents among many species of domestic and wild mammals and birds. It has also been isolated from aquatic animals, such as dolphins, American alligators and crocodiles, and sea lions.

Occurrence in Man: Human erysipeloid is for the most part an occupational disease affecting workers in slaughterhouses and commercial fowl-processing plants, fishermen and fish-industry workers, and those who handle meat (particularly pork) and seafood products. It is not a notifiable disease and little is known of its incidence. In the former Soviet Union, nearly 3,000 cases were reported between 1956 and 1958 in 13 slaughterhouses in the Ukraine, and 154 cases were reported in the Tula region in 1959. From 1961 to 1970, the U.S. Centers for Disease Control and Prevention confirmed the diagnosis of 15 cases in the US. A few isolated cases have occurred in Latin America. Some epidemic outbreaks have occurred in the former Soviet Union, in the United States, and on the southern Baltic coast (see section on source of infection and mode of transmission).

Occurrence in Animals: The disease in swine (rose disease, swine erysipelas) is important in Asia, Canada, Europe, Mexico, and the United States. It has also been seen in Brazil, Chile, Guatemala, Guyana, Jamaica, Peru, and Suriname, but the incidence is low in these countries. However, the disease seems to be increasing in importance in Chile (Skoknic *et al.*, 1981). Polyarthritis in sheep due to *E. rhusiopathiae* has been described in many sheep-breeding areas of the world.

The Disease in Man: The cutaneous form is known by the name erysipeloid to distinguish it from erysipelas caused by a hemolytic streptococcus. The incubation period ranges from one to seven days. Erysipeloid localizes primarily in the hands and fingers and consists of an erythematous, edematous skin lesion with violet coloration around a wound (the inoculation point) that may be a simple abrasion. Arthritis in the finger joints occurs with some frequency. The patient experiences a burning sensation, a pulsating pain, and at times an intense pruritus.

The course of the disease is usually benign and the patient recovers in two to four weeks. If the infection becomes generalized, septicemia and endocarditis may cause death. In the US, most cases reported in recent years have been the septicemic form generally associated with endocarditis (McClain, 1991). An analysis of 49 cases of systemic infection occurring over a 15-year period (Gorby and Peacock, 1988) found that *E. rhusiopathiae* has a peculiar tropism toward the aortic valve. In 40% of the cases, there was a concomitant cutaneous erysipeloid lesion and fatality was 38%. In slightly more than 40%, there was a history of prior valvular disease. Only 17% had a history that could be characterized as involving a compromised immune system. The principal symptoms were fever (92%), splenomegaly (36%), and hematuria (24%).

Nelson (1955) did not record any cases of endocarditis among 500 cases of erysipeloid in the US, which would indicate that the systemic disease is rather rare. The first case of endocarditis in Brazil was described by Rocha *et al.* (1989). The disease began with an erysipeloid and progressed to septicemia and endocarditis. The patient was an alcoholic with a prior history of aortic insufficiency, who had pricked himself with a fishbone.

The preferred treatment is penicillin, to which *E. rhusiopathiae* is very sensitive. Treatment with cephalosporins can be substituted for patients who are allergic to penicillin (McClain, 1991).

The Disease in Animals: Many species of domestic and wild mammals and birds are hosts to the etiologic agent. In several animal species, *E. rhusiopathiae* produces pathologic processes. Swine are the most affected species.

SWINE: Swine erysipelas is an economically important disease in many countries. In several central European countries, swine can only be raised profitably where systematic vaccination is practiced. Morbidity and mortality vary a great deal from one region to another, perhaps due to differences in the virulence of the etiologic agent. At present, acute forms are infrequent in western Europe and in North America.

The incubation period lasts from one to seven days. There are three main clinical forms: acute (septicemia), subacute (urticaria), and chronic (arthritis, lymphadenitis, and endocarditis). These forms may coexist in a herd or appear separately. The acute form begins suddenly with a high fever. Some animals suffer from prostration, anorexia, and vomiting, while others continue to feed despite the high fever. In some animals, reddish purple spots appear on the skin, particularly in the ears. There is splenomegaly and swelling of the lymph nodes. In the final phase of septicemic erysipelas, dyspnea and diarrhea are the most obvious symptoms. The disease has a rapid course and mortality is usually very high (Timoney *et al.*, 1988). The subacute form is characterized by urticaria, which initially appears as reddish or purple rhomboid-shaped spots on the skin. These spots are found particularly on the abdomen, the inside of the thighs, the neck, and the ears. The plaques later become necrotic, dry up, and fall off.

The chronic form is characterized by arthritis. At first, the joints swell and movement is painful; later, the lesion may develop into ankylosis. Losses from arthritis are considerable because the animals' development and weight gain are affected and because they may be confiscated from the abattoirs. The chronic form may also appear as endocarditis, with progressive emaciation or sudden death. Lymphadenitis is another manifestation of the chronic form (Timoney *et al.*, 1988; Blood and Radostits, 1989).

Among the isolates of *E. rhusiopathiae* obtained from swine with clinical erysipelas, serotypes 1 (subtypes 1a and 1b) and 2 predominate. Subtype 1a is usually isolated from the septicemic form, serotype 2 from the urticarial and arthritic form, and serotypes 1 and 2 from endocarditis. A study conducted in Japan typed 300 isolates from swine with erysipelas. Most belonged to serotypes 1a, 1b, or 2. Serotype 1a was also isolated in 9.7% of arthritis and lymphadenitis cases. Only 6.7% belonged to other serotypes: 3, 5, 6, 8, 11, 21, and N (could not be typed), isolated from the chronic form of erysipelas. These latter strains were analyzed experimentally for their pathogenicity in swine and were found to produce the urticarial form.

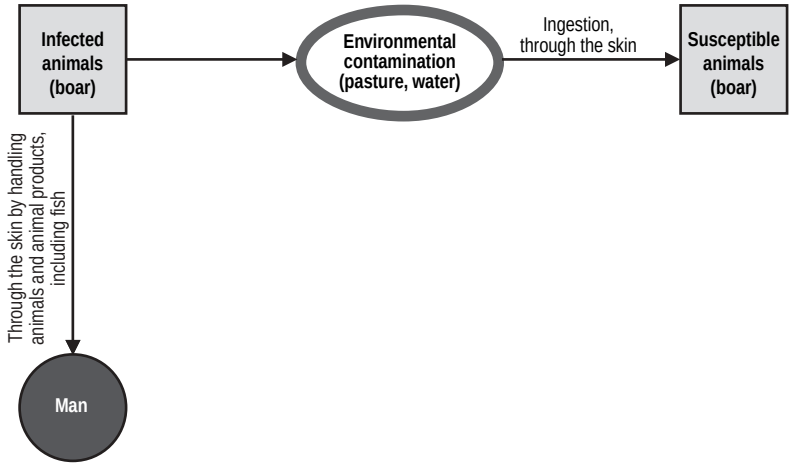
The strains of serotype 1a isolated from swine with arthritis or lymphadenitis produced various symptoms: generalized urticaria with depression and anorexia in some animals, localized urticaria lesions in other animals, and no symptoms in the remaining animals (Takahashi, 1987).

Acute cases can be treated with simultaneous administration of penicillin and antiserum.

SHEEP AND CATTLE: *E. rhusiopathiae* causes arthritis in lambs, usually after tail docking or sometimes as a result of an umbilical infection. The infection becomes established about two weeks after tail docking or birth, and the main symptoms are difficulty in movement and stunted growth. Recovery is slow.

In Argentina, Brazil, Chile, Great Britain, and New Zealand, a cutaneous infection caused by *E. rhusiopathiae* has been observed on the hooves of sheep a few

Figure 1. Animal erysipelas and human erysipeloid (*Erysipelothrix rhusiopathiae*). Mode of transmission.



days after they have undergone a benzene hexachloride dip. The lesions consist of laminitis and the animals experience difficulty moving. The disease lasts about two weeks. As with human erysipeloid, the infection gains entry through small skin abrasions. It can be prevented by adding a disinfectant such as a 0.03% solution of cupric sulfate to the dip. Serotype 1b was the most common of the isolates found in Australia, not only in swine but in domestic and wild sheep and fowl as well. Serotypes 1a and 2 were less frequent in sheep (Eamens *et al.*, 1988).

Other forms of erysipelas in sheep are valvular endocarditis, septicemia, and pneumonia (Griffiths *et al.*, 1991).

Arthritis has been observed in calves, and the agent has been isolated from the tonsils of healthy adult cows.

FOWL: A septicemic disease caused by *E. rhusiopathiae* occurs in many species of domestic and wild fowl; turkeys are the most frequently affected. Symptoms include general weakness, diarrhea, cyanosis, and a reddish-purple swollen comb. The disease tends to attack males in particular. Mortality can vary between 2.5% and 25%. The lesions consist of large hemorrhages and petechiae of the pectoral and leg muscles, serous membranes, intestine, and gizzard. The spleen and liver are enlarged. Symptoms and lesions are similar in chickens, ducks, and pheasants.

Source of Infection and Mode of Transmission (Figure 1): Many animal species harbor *E. rhusiopathiae*. The principal reservoir seems to be swine; the etiologic agent has been isolated from the tonsils of up to 30% of apparently healthy swine. In a study carried out in Chile, the agent was isolated from tonsil samples of 53.5% of 400 swine in a slaughterhouse (Skoknic *et al.*, 1981). *E. rhusiopathiae* was isolated from 25.6% of soil samples where pigs live and from their feces (Wood and

Harrington, 1978). Alkaline soil is particularly favorable to the agent's survival. A great variety of serotypes may be isolated from apparently healthy swine. In experimental tests, some serotypes prove to be highly virulent, others moderately pathogenic (producing only localized urticaria), and others avirulent (Takahashi, 1987).

Fish, mollusks, and crustaceans are an important source of infection. The etiologic agent has been isolated from fish skin. In the former Soviet Union, an epidemic of erysipeloid was caused by handling fish brought in by several different boats; on the Baltic coast there was another outbreak of 40 cases. In Argentina, where swine erysipelas has not been confirmed but where cases of human erysipeloid have been described, the agent was isolated from 2 out of 9 water samples from the Atlantic coast, and from 1 out of 40 samples of external integument of fish (de Diego and Lavalle, 1977). Subsequently, these strains were identified as belonging to serotypes 21 and 22.

In meat and poultry processing plants, rodents can be important reservoirs and disseminators of the infection. Fourteen different serotypes of *E. rhusiopathiae* were isolated from 38 samples (33.9%) obtained from pork in 112 shops in Tokyo. Some samples contained more than one serotype (Shiono *et al.*, 1990).

E. rhusiopathiae can survive a long time outside the animal organism, both in the environment and in animal products, which contributes to its perpetuation.

Man is infected through wounds and skin abrasions, but is very resistant to other entry routes. The infection is contracted by handling animals and animal products, including fish. Veterinarians have contracted the infection when they pricked themselves while administering the simultaneous vaccination (virulent culture and serum). This procedure is no longer in use. In Chile, a case of human endocarditis was attributed to the ingestion of smoked fish sold on the street (Gilabert, 1968).

The agent can multiply in an apparently healthy carrier under stress, and can cause disease and contaminate the environment. A pig with the acute form of erysipelas sheds an enormous amount of the bacteria in its feces, urine, saliva, and vomit, thus becoming a source of infection for the other pigs on the farm (Timoney *et al.*, 1988).

The routes of infection are believed to be digestive and cutaneous, through abrasions and wounds. The long survival of the agent in the environment ensures endemism in affected areas. Other animals and fowl may also contribute to maintaining the infection or to causing outbreaks.

Role of Animals in the Epidemiology of the Disease: Man is an accidental host who contracts the infection from sick animals, carriers, animal products, or objects contaminated by animals.

Diagnosis: Clinical diagnosis, based on the patient's occupation and on the characteristics of the cutaneous lesion, can be confirmed by isolation and identification of the etiologic agent. *E. rhusiopathiae* can be isolated from biopsies of the lesion. The sample is cultured in trypticase soy broth and incubated at 35°C for seven days; if there is growth, the culture is repeated in blood agar. The blood of septicemic patients can be cultured directly in blood agar (Bille and Doyle, 1991).

In septicemic cases in animals, the etiologic agent can be isolated from the blood and internal organs. In cases of arthritis or skin infections, cultures are made from localized lesions. Isolations from contaminated materials are accomplished through inoculation of mice, which are very susceptible.

Diagnosis of animal erysipelas makes use of several serologic tests, such as agglutination, growth inhibition, passive hemagglutination, and complement fixation. Given the frequency of subclinical infections and vaccination in animals, serologic tests are often difficult to interpret. A comparative study of the growth inhibition test and the complement fixation test concluded that the latter is more useful for diagnosis, since it eliminates low titers caused by subclinical infection or vaccination (Bercovich *et al.*, 1981). Another serologic method is the indirect enzyme-linked immunosorbent assay (ELISA), which is as sensitive as the growth inhibition test and is easier and less expensive to conduct (Kirchhoff *et al.*, 1985).

Control: In persons exposed as a result of their occupations, prevention of erysipeloid primarily involves hygiene, namely frequent hand washing with disinfectant and proper treatment of wounds. Establishments where foods of animal origin are processed should control rodent populations.

The control of swine erysipelas depends mostly on vaccination. There are two vaccines in use that have given good results: a bacterin adsorbed on aluminum hydroxide and a live avirulent vaccine (EVA=*erysipelas vaccine avirulent*). Vaccination confers immunity for five to eight months. The bacterin is first administered before weaning, followed by another dose two to four weeks later. The avirulent vaccine is administered orally via drinking water. The vaccines are not entirely satisfactory in preventing chronic erysipelas and it is even suspected that vaccination may contribute to arthritic symptoms (Timoney *et al.*, 1988). On the other hand, the great reduction or near elimination of the acute form in western Europe, Japan, and the US is probably due to systematic vaccination. In the case of an outbreak of septicemic erysipelas, it is important to destroy the carcasses immediately, disinfect the premises, and to treat sick animals with penicillin and the rest of the herd with anti-erysipelas serum. Rotation of animals to different pastures and environmental hygiene measures are also of great help in control.

Bacterins are used on turkey-raising establishments, where the infection is endemic. A live vaccine administered orally via drinking water has yielded good results in tests (Bricker and Saif, 1983).

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ANTHRAX

ICD-10 A22.0 cutaneous anthrax; A22.1 pulmonary anthrax; A22.2 gastrointestinal anthrax

Synonyms: Malignant pustule, malignant carbuncle, charbon, hematic anthrax, bacterial anthrax, splenic fever, woolsorters' disease.

Etiology: *Bacillus anthracis*, an aerobic, nonmotile, gram-positive bacillus 3–5 microns long that forms centrally located spores. It should be differentiated from *B. cereus*, which is quite similar. One of the media used to differentiate them is the gamma phage specific for *B. anthracis*. The etiologic agent is found in a vegetative state in man and animals. When exposed to oxygen in the air, it forms spores that are highly resistant to physical and chemical agents.

In nature, *B. anthracis* occurs in a virulent form—the pathogenic agent of anthrax—and in an avirulent form. Virulence is determined by a capsule that inhibits phagocytosis and an exotoxin, both of which are plasmid mediated. In turn, the toxin consists of three protein factors: the protective antigen, the lethal factor, and the edema factor. None of these factors is toxic by itself. When injected intravenously at the same time, the protective antigen and the lethal factor are lethal in some animal species. The combination of the protective agent and the edema factor produces edema when injected subcutaneously (Little and Knudson, 1986).

Geographic Distribution: Worldwide, with areas of enzootic and sporadic occurrence.

Occurrence in Man: The infection in humans is correlated with the incidence of the disease in domestic animals. In economically advanced countries, where animal anthrax has been controlled, it occurs only occasionally among humans. Some cases stem from the importation of contaminated animal products. Human anthrax is most common in enzootic areas in developing countries, among people who work with livestock, eat undercooked meat from infected animals, or work in establishments where wool, goatskins, and pelts are stored and processed. The incidence of human illness in developing countries is not well known because those sick with the disease do not always see a doctor, nor do doctors always report the cases; in addition, the diagnosis often is based only on the clinical syndrome.

According to data from recent years, epidemic outbreaks continue to occur despite the availability of excellent preventive measures for animal anthrax and, therefore, for the occurrence of the disease in humans. There are some hyperendemic areas, as was shown in Haiti when an American woman contracted the infec-

tion after acquiring some goatskin drums. Compilation of data in that country revealed a high incidence of human anthrax in the southern peninsula, Les Cayes, which has a population of approximately 500,000. From 1973 to 1977, 1,587 cases were recorded in the 31 clinics in that region (La Force, 1978).

In Zambia, at least 30 people died from anthrax in 1992. Eastern Nigeria has a very high incidence of human anthrax (Okolo, 1985). On the borders between Thailand, Myanmar (Burma), and Laos that are crossed by animals transported from as far away as India, outbreaks occur frequently. In one Thai village, several of the approximately 200 inhabitants participated in cutting up a buffalo that had supposedly drowned; eight of them became ill and one died with symptoms suspected of being anthrax (Ngampachjana *et al.*, 1989). In a settlement in eastern Algeria, 6 cases of anthrax occurred in an extended family of 59 members. Those who fell ill had participated in slaughtering and butchering a sheep with symptoms that included hemorrhage, black blood, and splenomegaly. Fourteen animals of various ruminant species had died before the appearance of the index case, a child who later died (Abdenour *et al.*, 1987). In the former Soviet Union, at least 15,000 cases of human anthrax occurred prior to 1917 and 178 cases were reported as late as 1985 (Marshall, 1988).

In enzootic areas, the human disease is usually endemosporadic with epidemic outbreaks. The latter are caused primarily by ingestion of meat, often by many people, from animals who were dead or dying from anthrax when slaughtered (Rey *et al.*, 1982; Fragoso and Villicaña, 1984; Sirisanthana *et al.*, 1984). In 1978, in a region in the Republic of Mali, there were 84 cases with 19 deaths. High mortality, possibly due to intestinal anthrax, was also seen in Senegal in 1957, with 237 deaths out of 254 cases (Simaga *et al.*, 1980).

In 1979, an epidemic outbreak in Sverdlovsk, in the former Soviet Union, led to a controversy between that country and the United States. According to the former Soviet Union, fewer than 40 people died from gastric anthrax in this epidemic, while US intelligence sources claimed that several hundred to a thousand people perished from pulmonary anthrax within a few weeks. Later Soviet sources indicated a total of 96 victims, 79 suffering from intestinal infection (64 of whom died), and no pulmonary cases (Marshall, 1988). The controversy centered on whether the epidemic was natural or man-induced, since the US intelligence source suspected that an accident had occurred at a plant presumably engaged in biological warfare projects. If so, this would have indicated a violation of the 1975 treaty against biological weapons (Wade, 1980). Sverdlovsk is located in an enzootic area and, according to Marshall (1988), the source of infection was probably a bone meal food supplement on State-run and private farms. Using preserved tissue, Russian and American researchers were ultimately able to determine that at least 42 people had died from inhaling rather than ingesting the etiological agent. They thus confirmed the suspicion that the source of infection was airborne and probably came from an illegal plant that the Soviet authorities did not allow to be inspected.

Occurrence in Animals: Anthrax is common in enzootic areas where no control programs have been established.

In a hyperenzootic area of eastern Nigeria, animals submitted for emergency slaughter were studied. There is no *ante mortem* inspection of animals in that region, thus increasing the risk of human exposure. Of 150 animals, 34 (22.7%) were posi-

tive through culture and inoculation of laboratory animals. Of 35 cows, 42.9% were positive, and of 70 bulls, 14.3% were positive. The milk from 43 cows and 8 sheep was also examined; 15 and 2 of the samples, respectively, were positive (Okolo, 1988).

Some outbreaks and occasional cases of human infection have also been reported in industrialized countries, such as the US (Hunter *et al.*, 1989).

In Africa, wildlife reserves periodically suffer great losses, especially among herbivores. A thesis presented at the University of Nairobi, Kenya, estimated that anthrax accounts for about 11% of the mortality in the animal population each year, excluding calves. At Etosha National Park in Namibia, anthrax caused the death of 1,635 wild animals of 10 species, or 54% of total mortality between January 1966 and June 1974. The source of infection was artificial ponds (Ebedes, 1976). An outbreak occurred on a reserve in Zambia between June and November of 1987, with a total loss of over 4,000 animals. The victims were primarily hippopotamuses (*Hippopotamus amphibius*). Other species, such as the Cape buffalo (*Syncerus caffer*) and the elephant (*Loxodonta africana*), also seem to have been affected (Turnbull *et al.*, 1991).

The Disease in Man: The incubation period is from two to five days. Three clinical forms are recognized: cutaneous, pulmonary or respiratory, and gastrointestinal.

The cutaneous form is the most common and is contracted by contact with infected animals (usually carcasses) or contaminated wool, hides, and fur. The exposed part of the skin begins to itch and a papule appears at the inoculation site. This papule becomes a vesicle and then evolves into a depressed, black eschar. Generally, the cutaneous lesion is not painful or is only slightly so; consequently, some patients do not consult a doctor in time. If left untreated, the infection can lead to septicemia and death. The case fatality rate for untreated anthrax is estimated at between 5% to 20%.

The pulmonary form is contracted by inhalation of *B. anthracis* spores. At the onset of illness, the symptomatology is mild and resembles that of a common upper respiratory tract infection. Thus, many patients do not see a doctor in the early stage of the disease when it would be easily cured. Some three to five days later the symptoms become acute, with fever, shock, and resultant death. The case fatality rate is high.

Gastrointestinal anthrax is contracted by ingesting meat from infected animals and is manifested by violent gastroenteritis with vomiting and bloody stools. Mortality ranges from 25% to 75% (Brachman, 1984).

The recommended treatment for cutaneous anthrax is intramuscular administration of 1 million units of procaine penicillin every 12 to 24 hours for five to seven days. In the case of serious illness, as in pulmonary anthrax, the recommendation is 2 million units of penicillin G per day administered intravenously or 500,000 units administered intravenously through a slow drip every four to six hours until temperature returns to normal. Streptomycin, in 1 g to 2 g doses per day, has a synergistic effect if administered at the same time as penicillin. Some penicillin-resistant strains of *B. anthracis* have been found (Braderic and Punda-Polic, 1992). Penicillin sterilizes the organism in a short time, even in a single day in patients suffering from cutaneous anthrax, but it should be borne in mind that the toxin remains and the patient is still not cured.

The Disease in Animals: It takes three forms: apoplectic or peracute, acute and subacute, and chronic. The apoplectic form is seen mostly in cattle, sheep, and goats, and occurs most frequently at the beginning of an outbreak. The onset is sudden and death ensues rapidly. The animals show signs of cerebral apoplexy and die.

The acute and subacute forms are frequent in cattle, horses, and sheep. The symptomatology consists of fever, a halt to rumination, excitement followed by depression, respiratory difficulty, uncoordinated movements, convulsions, and death. Bloody discharges from natural orifices as well as edemas in different parts of the body are sometimes observed.

Chronic anthrax occurs mainly in less susceptible species, such as pigs, but is also seen in cattle, horses, and dogs. During outbreaks in swine herds, some animals fall victim to the acute form, but most suffer from chronic anthrax. The main symptom of this form is pharyngeal and lingual edema. Frequently, a foamy, sanguinolent discharge from the mouth is observed. The animals die from asphyxiation. Another localized chronic form in pigs is intestinal anthrax.

Anthrax also affects free-roaming wild animals and those in zoos and national parks (see section on occurrence in animals).

Autopsies of acute cases reveal bloody exudate in the natural orifices. Decomposition is rapid and the carcass becomes bloated with gases. Rigor mortis is incomplete. Hemorrhages are found in the internal organs; splenomegaly is almost always present (but may not be in some cases), with the pulp being dark red or blackish and having a soft or semifluid consistency; the liver, kidneys, and lymph nodes are congested and enlarged; and the blood is blackish with little clotting tendency.

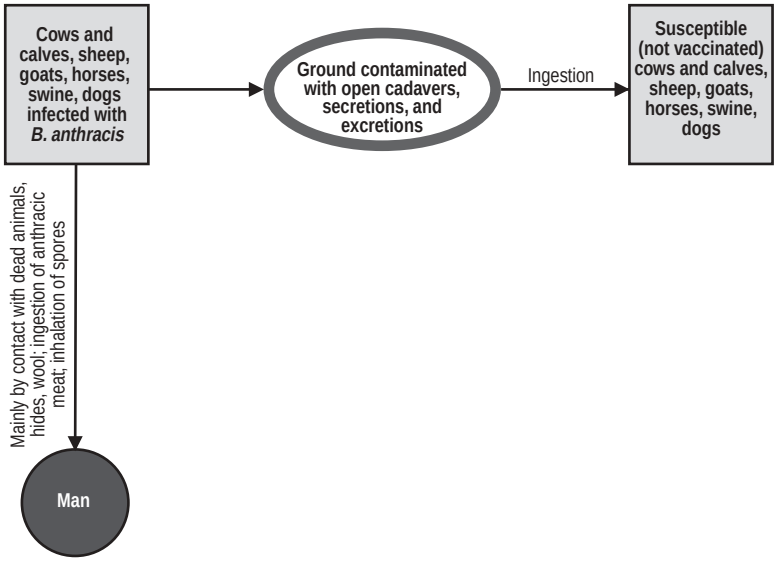
Animals treated early with penicillin recover. Treatment consists of intravenous administration of 12,000 to 17,000 units/kg of bodyweight of sodium benzylpenicillin followed by intramuscular administration of amoxicillin.

Source of Infection and Mode of Transmission (Figure 2): Soil is the reservoir for the infectious agent. The process followed by spores in the earth is a subject of controversy. It has been suggested that there is a cycle of germination and subsequent resporulation, but there is no evidence to this effect. The lifecycle of spores under laboratory conditions (in culture media) or in sterile soil is extremely long. However, under natural conditions, it seems that their survival is limited to a few years, due to the activity of saprophytic microbes in the soil. This is probably the case in wild animal reserves in Africa, where attempts to isolate *B. anthracis* from the soil or water one or two years after an epizootic yielded negative results, except near the remains of some animals that died from sporadic cases of anthrax. Turnbull *et al.* (1991) believe that in order for an enzootic area to be maintained, it would be necessary for the etiologic agent to multiply in animals. However, a fact to be noted is the long survival of *B. anthracis* on the Scottish island of Gruinard, which was abundantly seeded with *B. anthracis* during the Second World War for purposes of experimentation with biological weapons. Some 40 years later, viable spores of *B. anthracis* were still detected. It is speculated that this long survival is due to the island's acidic soil and cold, moist climate, which are unfavorable to the activity of microbial flora.

For man, the source of infection is always infected animals, contaminated animal products, or environmental contamination by spores from these sources.

Cutaneous anthrax is contracted by inoculation during the process of skinning or butchering an animal or by contact with infected leather, pelts, wool, or fur. Broken

Figure 2. Anthrax. Transmission cycle.



skin favors transmission. Products made from contaminated hair (e.g., shaving brushes), skins (e.g., drums), and bone meal (e.g., fertilizer) may continue to be sources of infection for many years. Transmission from animals to man is possible by means of insects acting as mechanical vectors, but reliably documented cases are few. A recent case occurred in a Croatian villager who was probably stung by a horsefly and developed a case of cutaneous anthrax on the back of her neck. The presumed source of infection was a cow close to her home that had died of anthrax (Braderic and Punda-Polic, 1992).

Pulmonary anthrax comes from inhaling spores released from contaminated wool or animal hair.

The source of infection for the gastrointestinal form is domestic and wild animals that died from anthrax. The pathway of transmission is through the digestive tract. Cases have been observed in Asia, Africa, and Latin America.

Animals contract the infection mainly by ingestion of pasture or water contaminated with *B. anthracis* spores, especially in places near anthrax-infected carcasses. An animal dying of anthrax produces an enormous quantity of *B. anthracis* in its tissues, and if the carcass is opened, the bacilli sporulate, contaminating the soil, grass, and water. Animals that graze in the contaminated area become infected themselves and produce new foci of infection. Animals and birds that feed on carrion can transport the infection some distance. The most serious outbreaks occur during dry summers after heavy rains. The rain washes spores loose and concentrates them in low spots, forming so-called “cursed fields,” that are usually damp areas with glacial calcareous soils containing abundant organic material and having a pH above 6 (Van Ness, 1971). Nevertheless, outbreaks of anthrax may occur in acidic soil, as hap-

pened in the 1974 epizootic in Texas (USA), during which 218 cattle, 6 horses, and 1 mule died. Eighty-three percent of the fields where the outbreak took place had acid pH soil and 94% had subsoil with an alkaline pH (Whitford, 1979).

Contaminated animal by-products, especially bone meal and blood meal used as food supplements, can also give rise to distant foci of infection.

Another mode of transmission is cutaneous entry through insect bites, but this is considered of minor epidemiologic importance.

Role of Animals in the Epidemiology of the Disease: Animals are essential. Anthrax is transmitted to humans by animals or animal products. Transmission between humans is exceptional.

Diagnosis: The presence of the etiologic agent must be confirmed by microscopic examination of stained smears of vesicular fluid (in man), edemas (in swine), and blood (in other animals); by culturing the microorganism from the liquid aspirated from malignant pustules or from blood samples of a dead or dying animal; and by inoculation of laboratory animals (guinea pigs and mice). If the material is contaminated, cutaneous inoculation (by scarification) should be used. The use of antibiotics quickly reduces the possibility of isolating the etiologic agent.

The fluorescent antibody technique applied to fresh stains or blood smears can prove useful for presumptive diagnosis. Smears of blood or other bodily fluids can also be stained using the Giemsa or Wright method to make the pink capsule that surrounds the bacillus stand out. The Ascoli precipitation test has limited value due to its limited specificity, but is still used in some laboratories for animal products, from which the agent cannot be isolated.

The ELISA and Western Blot tests can be used to detect antibodies to the protective antigen in individuals who have had anthrax and from whom the agent cannot be isolated, i.e., in retrospective studies (Thurnbull *et al.*, 1986; Sirisanthana *et al.*, 1988; Harrison *et al.*, 1989). Antibodies have also been found in people living near animal reserves in Africa who have been exposed to anthrax in wild animals without becoming ill themselves (Thurnbull *et al.*, 1991).

Control: In man, the prevention of anthrax is based mainly on: (a) control of the infection in animals; (b) prevention of contact with infected animals and contaminated animal products; (c) environmental and personal hygiene in places where products of animal origin are handled (adequate ventilation and work clothing); (d) medical care for cutaneous lesions; and (e) disinfection of fur and wool with hot formaldehyde. Occupational groups at risk may benefit from vaccination with the protective antigen.

The human vaccine used in the US and Great Britain is acellular and consists of a filtrate of *B. anthracis* culture from a nonencapsulated strain that is adsorbed with aluminum hydroxide. This vaccine is not very potent and may not protect against all field strains. In the countries of Eastern Europe and in China, a live attenuated spore vaccine is administered by scarification.

In animals, anthrax control is based on systematic vaccination in enzootic areas. Sterne's avirulent spore vaccine is indicated because of its effectiveness and safety. The vaccine consists of spores from the nonencapsulated 34F2 strain with an adjuvant—usually a saponin—and is currently used worldwide, with a few exceptions. It is suitable for all domestic animal species. However, goats sometimes have severe

reactions and the recommendation is thus to administer the vaccine in two doses in this species, with a month between doses (administer one-fourth of the dose in the first month and the full dose the following month). Pregnant females of any species should not be vaccinated unless they are at high risk of contracting anthrax. Antibiotics should not be administered a few days before or a few days after vaccination. In general, annual vaccination is sufficient; only in hyperenzootic areas is vaccination at shorter intervals recommended. Immunity is established in approximately one week in cattle, but takes longer in horses. In regions where anthrax occurs sporadically, mass vaccination is not justified and should be limited to affected herds. Rapid diagnosis, isolation, and treatment of sick animals with antibiotics (penicillin) are important.

Autopsies should not be performed on animals that have died from anthrax. An unopened carcass decomposes rapidly and the vegetative form of *B. anthracis* is destroyed in a short time. To make the diagnosis, it is recommended that blood be taken from a peripheral vessel with a syringe and sent to the laboratory in a sterile container. Dead animals should be destroyed where they lie as quickly as possible, preferably by incineration. The alternative is to bury them two meters deep and cover them with a layer of lime.

In areas where these procedures are not possible, the dead animal should be left intact so that it will start to decompose and, as much as possible, natural orifices and the surrounding soil should be treated with 10% formol (25% formalin).

Affected herds should be placed in quarantine, which should last until two weeks after the last case is confirmed, with no animal or animal product allowed out.

If anthrax is suspected at a slaughterhouse, all operations should be halted until the diagnosis is confirmed. If positive, all exposed carcasses should be destroyed and the premises carefully disinfected (with a 5% caustic lye solution for eight hours) before operations are resumed.

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BOTULISM

ICD-10 A05.1

Synonyms: Allantiasis; “lamziekte” (bovine botulism in South Africa); “limberneck” (botulism in fowl).

Etiology: Toxins produced by *Clostridium botulinum*, which are the most potent known. *C. botulinum* is an obligate, spore-forming anaerobe. It has been sub-classified (Smith, 1977) into four groups (I to IV), according to culture and serological characteristics. Seven different types of botulinum antigens have been identified (A–G), according to their serological specificity. Classical botulism results from

preformed toxins ingested with food. In wound botulism, the toxin forms by contamination of the injured tissue. In 1976, a new clinical type, infant botulism, was identified. It is caused by colonization of the infant's intestinal tract by *C. botulinum* and the resultant production and absorption of toxins.

The species *C. botulinum* is very heterogeneous. The different groups (I to IV) are differentiated according to their ability to digest proteins and break down sugars. Group I is highly proteolytic and saccharolytic and includes all the type A strains as well as various type B and F strains. Group II includes all the type E strains and the nonproteolytic type B and F strains that are highly saccharolytic. Group III consists of the type C and D strains, which are not proteolytic (except that they digest gelatin). Group IV contains only type G, which is proteolytic but not saccharolytic (Sakaguchi *et al.*, 1981; Concon, 1988).

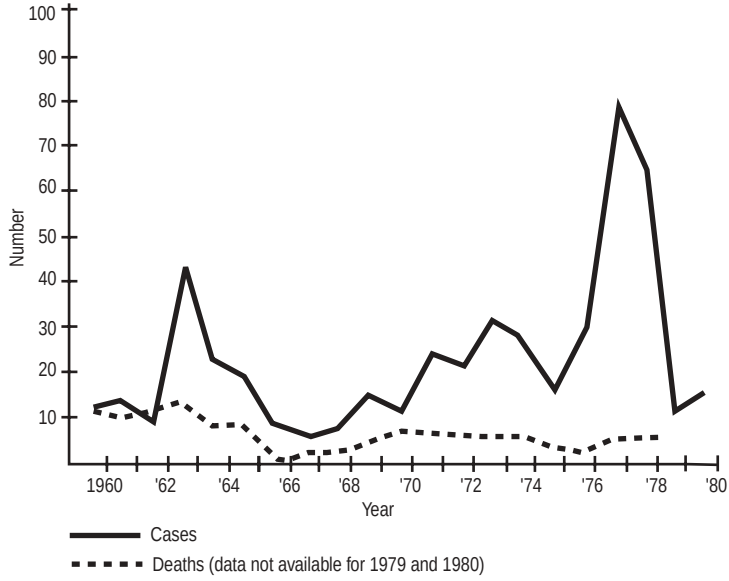
Despite the metabolic and DNA differences among them, these groups of clostridia have until now been classified in a single species because they all produce a botulinum neurotoxin that acts similarly in animal hosts (Cato *et al.*, 1986). However, not all researchers agree with this scheme and one argument of those favoring a reclassification is the recent discovery of neurotoxigenic strains in *Clostridium baratii* and *C. butyricum*.

In effect, two cases of type E infant botulism in Rome, Italy, caused by *C. butyricum* (Aureli *et al.*, 1986) have been described and another case was described in New Mexico (USA) in a child suffering from a neurotoxigenic type F botulism produced by a clostridium that was later identified as *C. baratii* (Hall *et al.*, 1985). These clostridia were identified on the basis of their phenotype characteristics and were later confirmed through DNA hybridization (Suen *et al.*, 1988a). The neurotoxin isolated from *C. baratii* was similar in structure and amino acid sequence to *C. botulinum* types A, B, and E (Giménez *et al.*, 1992). The proponents of reclassification, such as Suen *et al.* (1988b), have suggested renaming group IV, which contains the single toxigenic type G, as *Clostridium argentinense*. Arnon (1986) agrees that reclassification would be justified based on logical criteria and taxonomic purity, but questions whether this would improve clinical, microbiological, and epidemiological knowledge.

Geographic Distribution: Occurs on all continents, with a marked regional distribution that probably reflects the presence in the soil of the microorganism and its different types of toxins.

Occurrence in Man: The disease occurs more frequently in the northern hemisphere than in the southern hemisphere, and can appear sporadically and among groups of people who ingest the same food with the preformed toxin. From 1950 to 1973, an average of 15.1 outbreaks occurred annually in the US, with 2.4 cases per outbreak. In that period, there were only three outbreaks affecting more than 10 people, but in 1977, an outbreak of 59 cases involving type B botulinum toxin was described, caused by food eaten in a restaurant (Terranova *et al.*, 1978). Figure 3 illustrates the reported cases and deaths by year in the US during the period 1960–1980 (PAHO, 1982). More than half of the cases reported since 1899 from 45 states occurred in five western states. Table 1 shows the foods and type of botulinum toxin that caused the illness. In the United States, only 4% of the outbreaks originated in restaurants, but they represent 42% of the 308 cases occurring between 1976 and 1984. The most widespread outbreak recorded in the United States

Figure 3. Botulism (transmitted by foods). Reported cases and deaths per year, United States of America, 1960–1980.



Source: PAHO Epidemiol Bull 3(4):2, 1982.

occurred in Michigan in 1977, when 59 people became sick after eating restaurant food that had been home-canned and contained botulinum toxin B (MacDonald *et al.*, 1986). In Canada, between 1979 and 1980, 15 incidents were investigated (PAHO, 1982). In Argentina, during the period 1967–1981, 139 cases were reported (Figure 4). In 1958, several suspected cases of botulism occurred in Brazil when six members of the same family died and others became ill after eating home-canned boiled fish. In 1981, two other suspected cases occurred in Rio de Janeiro, caused by ingestion of an industrially processed food.

In Europe and Asia, the occurrence of the illness varies from one country to another. In Poland, which seems to be the country hardest hit by botulism, the majority of cases have occurred in rural areas, as they have in other countries. From 1979 to 1983, there were a total of 2,390 cases and 45 deaths, with an average of 478 cases per year (Hauschild, 1989). The largest outbreak known to date took place in Dniepropetrovsk (former USSR), in 1933, with 230 cases and 94 deaths. More recently, about 14 outbreaks per year have occurred. In France, botulism is infrequent, with about four outbreaks annually. However, during World War II, 500 outbreaks were recorded with more than 1,000 cases in that country. Germany is second to Poland in the incidence of the illness. In the rest of Europe botulism is rare. During the period 1958–1983, there were 986 outbreaks, 4,377 cases, and 548 deaths in China; most of the cases (81%) occurred in the northwest province of Xinjiang (Ying *et al.*, 1986). During the period 1951–1984, there were 96 outbreaks,

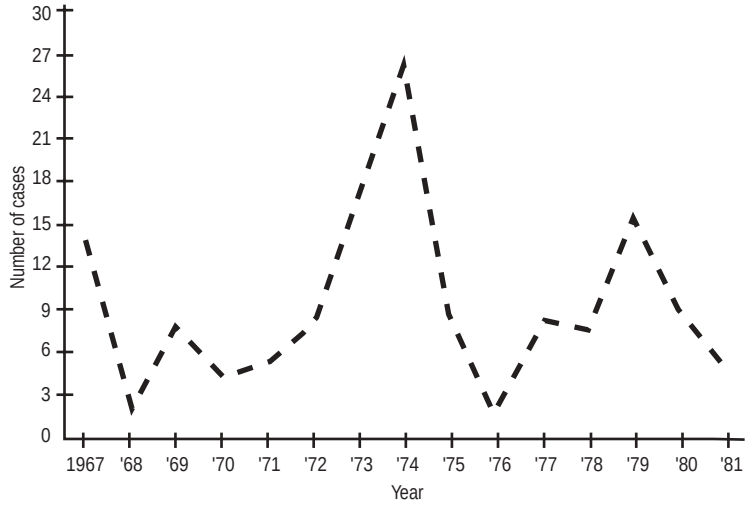
Table 1. Foods giving rise to botulism, and number of outbreaks, United States of America, 1899–1977.[a, b]

Type of botulinum toxin	Vegetables	Fish and fish products	Fruits	Condi-ments[c]	Beef[d]	Milk and milk products	Pork	Fowl	Others[e]	Unknown[e]	Total
A	115	11	22	17	6	3	2	2	8	9	195
B	31	4	7	5	1	2	1	2	3	3	59
E	1	25	—	—	—	—	—	—	3	1	30
F	—	—	—	—	1	—	—	—	—	—	1
A and B	2	—	—	—	—	—	—	—	—	—	2
Unknown[e]	2	1	—	1	—	—	—	—	—	6	10
Total	151	41	29	23	8	5	3	4	14	19	297

[a]For the period 1899–1973, only outbreaks in which the type of toxin was confirmed are included; for 1974–1977, all outbreaks are included.
[b]Prepared by the Centers for Disease Control and Prevention, Atlanta, Georgia, USA.
[c]Includes outbreaks caused by tomato condiments, hot sauces, and salad dressings.
[d]Includes one type F outbreak caused by venison, and one type A outbreak caused by mutton.
[e]Categories added for the period 1974–1977.

Source: PAHO Epidemiol Bull 3(4):2, 1982.

Figure 4. Reported cases of botulism per year, Argentina, 1967–1981.



Source: PAHO Epidemiol Bull 3(4):2, 1982.

478 cases, and 109 deaths in Japan (Hauschild, 1989). In the rest of Asia and in Africa, few cases have been identified (Smith, 1977).

Infant botulism was recognized for the first time in the United States, and then in Canada, several European countries, and Australia. From 1976 to 1980, 184 cases were recorded in the United States, 88 of which occurred in California and 96 in 25 other states. Currently, infant botulism is the predominant form in the United States, with approximately 100 cases reported each year (Suen *et al.*, 1988). The disease has also been described in Argentina, Australia, Canada, the former Czechoslovakia, Great Britain, and Italy. Almost all cases occurred in children under 6 months of age (Morris, 1983) though some occurred in children up to 1 year.

The first case of wound botulism was recognized in the United States in 1943. By 1982, 27 cases were recorded, 20 of them in states west of the Mississippi River (CDC, 1982). In 1986, MacDonald *et al.* reported on the incidence of botulism in the United States between 1976 and 1984, including 16 cases of wound botulism (two of these in drug addicts using intravenous drugs).

Occurrence in Animals: Botulism in animals, including birds, is caused by types C (C alpha and C beta) and D, but there are also outbreaks due to A, E, and B. Botulism in bovines is becoming economically important in some areas, where it can affect a large number of animals. Such areas, generally poor in phosphorus, are found in the southwestern United States, in Corrientes province in Argentina, and in Piaui and Matto Grosso in Brazil. However, bovine botulism occurs even more frequently in South Africa (“lamziekte”) and Australia. It is also important in Senegal, where it is believed to cause more cattle loss than any other disease. In other countries, sporadic outbreaks and cases occur, primarily caused by ingestion of fodder

and silage containing the preformed toxins (Smith, 1977). Recently, various important outbreaks have been recorded due to consumption of bedding silage and bird droppings. In Great Britain, 80 out of 150 stabled cattle became sick and 68 died. Type C toxin was detected in 18 of the 22 sera examined and the same toxin was confirmed in the remains of dead chickens found in the silage (McLoughlin *et al.*, 1988). Similar outbreaks also occurred in Brazil and Canada because the bird bedding used to feed the cattle contained the type C toxin (Bienvenue *et al.*, 1990; Schocken-Iturrino *et al.*, 1990). Animal remains are usually found when botulism outbreaks occur in cattle, especially due to silage; however, no animal remains could be found in the fodder in various cases in the United States and Europe.

Bovine poisoning by type B is rare; outbreaks have occurred in Europe (Blood *et al.*, 1983), the United States (Divers *et al.*, 1986), and Brazil (Lobato *et al.*, 1988).

Botulism in sheep is due to type C and has been identified only in western Australia and South Africa.

In horses, botulism cases are sporadic and for the most part are caused by *C. botulinum* type C. It has been diagnosed in various European countries, the US, Israel, Australia, and South Africa. A special form occurs in colts at 6 to 8 weeks old ("shaker foal syndrome"); it is due to the type B neurotoxin and its pathogenesis is similar to botulism in children, since apparently *C. botulinum* has to colonize first in the intestine and other sites in order to produce the neurotoxin later. Outbreaks of this form have been described in the United States and Australia (Thomas *et al.*, 1988).

Botulism in swine is rare because of the natural high resistance of this species to botulinum toxin. Outbreaks diagnosed in Senegal and Australia were caused by type C beta and one in the United States was caused by type B.

Botulism in mink can be an important problem owing to their eating habits, if they are not vaccinated as recommended. Mink are highly susceptible to type C, which causes almost all the outbreaks.

Botulism in fowl occurs practically worldwide and is caused principally by type C alpha. Outbreaks of types A and E have been recorded in waterfowl. In the western United States, type C is responsible for massive outbreaks in wild ducks during the summer and early fall. Many other species of wild fowl are susceptible to botulism and outbreaks also occur in domestic chickens and farm-bred pheasants (Smith, 1977). Botulism in domestic fowl has been related to cannibalism and the ingestion of maggots in decomposing carcasses. The explanation is that the body temperature of fowl (41°C) favors the type C toxin, which would be produced and absorbed in the caecum, whose pH of 7.4 also favors the toxin (Castro *et al.*, 1988).

Botulism in dogs is rare and is caused primarily by ingesting bird carcasses, with type C being responsible for the disease (Hatheway and McCroskey, 1981).

The Disease in Man: (a) Botulism poisoning by foods is produced primarily by types A, B, and E and rarely by F or G. Outbreaks in man described as type C have not been confirmed, as the toxin has not been found in the patients' blood or feces nor in foods they ate. An outbreak of type D was identified in Chad, Africa, among people who had eaten raw ham (Smith, 1977). A new toxicogenic type, *C. botulinum* type G, was isolated from the soil in Argentina in 1969 (Giménez and Ciccarelli, 1970). The first human cases were recognized in Switzerland (Sonnabend *et al.*, 1981). The microorganism was isolated in autopsy specimens from four adults and

an 18-week-old child. In addition, the presence of the toxin could be confirmed in the blood serum of three of these persons who died suddenly at home. The symptoms were similar to those of classic botulism. Nine additional cases of sudden and unexpected death were described (Sonnabend *et al.*, 1985).

The incubation period is usually from 18 to 36 hours, but the illness can show up within a few hours or as long as eight days after ingestion of the contaminated food. The clinical signs of the different types vary little, although the mortality rate seems to be higher for type A. The disease is afebrile, and gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain, precede neurological symptoms. Neurological manifestations are always symmetrical, with weakness or descending paralysis. Diplopia, dysarthria, and dysphagia are common. Consciousness and sensibility remain intact until death. The immediate cause of death is usually respiratory failure. The mortality rate in botulinum poisonings is high. The highest rate is recorded in patients with short incubation periods, i.e., those who have ingested a high dose of the toxin. In the United States, the fatality rate has been reduced from 60% in 1899–1949 to 15.7% in 1970–1977, by means of early and proper treatment. In patients who survive, complete recovery, especially of ocular movement, may take as long as six to eight months.

Treatment should be initiated as soon as possible through administration of the trivalent botulinum antitoxin (A, B, and E). The patient must be hospitalized in intensive care in order to anticipate and treat respiratory distress, which is the immediate cause of death (Benenson, 1990).

(b) Infant botulism is an intestinal infection caused by the ingestion of *C. botulinum* spores, which change in the intestine into the vegetative form, multiply, and produce toxins. Of 96 cases studied (Morris *et al.*, 1983) in the United States, excluding California, 41 were caused by *C. botulinum* type A, 53 by type B, one by type F, and another by type B together with F. Type A appeared almost exclusively in the western states, while type B predominated in the East. This distribution is similar to that of the spores in the environment (see the section on source of poisoning or infection and mode of transmission). In addition, two cases in Italy due to type E produced by *Clostridium butyricum* and one case in New Mexico (USA) due to type F produced by *Clostridium baratii* have been described; i.e., by two species other than *C. botulinum* (see section on etiology). The case of a girl under age 6 months with paroxystic dyspnea due to *C. botulinum* type C toxin was also described. The child survived the illness, but may have been left with a cerebral lesion probably caused by hypoxia (Oguma *et al.*, 1990). Sonnabend *et al.* (1985) had previously identified the bacteria and C toxin in the colon of a child who died suddenly in Switzerland.

The fact that *C. botulinum* primarily colonizes the caecum and colon, and that 96% of patients with infant botulism are under 6 months of age led to research on the characteristics of the intestinal microflora that allow the clostridium to multiply. Using a normal mouse as a model, it was established that the microflora in adults prevent the establishment of *C. botulinum*; however, if adult "germ-free" mice are used, the clostridium multiplies in their intestines. The same thing happens to conventional mice from 7 to 13 days old, which are very susceptible. In addition, breast-fed infants have feces with a lower pH (5.1–5.4) than those fed with formula (pH 5.9–8.0). This difference may be significant, because the multiplication of *C. botulinum* declines as pH falls and ceases below 4.6. In addition, breast-feeding has the

advantage of transferring immunogenic factors to the infant (Arnon, 1986). Another important factor seems to be the frequency of defecation: of 58 patients who were at least 1 month old, 37 (64%) had a usual pattern of one defecation per day, as compared to 17 (15%) of the 115 in the control group (Spika *et al.*, 1989).

In adults, botulism may occur without the presence of preformed toxin in food: it may occur through colonization of the large intestine by *C. botulinum*, the production of toxins, and their absorption. Such cases are rare and primarily affect those who have alterations in intestinal structure and microflora.

The disease in infants begins with constipation, followed by lethargy and loss of appetite, ptosis, difficulty swallowing, muscular weakness, and loss of head control. Neuromuscular paralysis may progress from the cranial nerves to the peripheral and respiratory muscles, resulting in death. The severity of the illness varies from moderate to life-threatening, causing sudden death of the child. It has been estimated that infant botulism is responsible for at least 5% of the cases of sudden infant death syndrome (Benenson, 1990).

(c) Wound botulism is clinically similar to classic botulism in its neurological syndrome. It is a toxin infection produced as the result of a contaminated wound that creates anaerobic conditions where *C. botulinum* can become established, reproduce, and develop a neurotoxin that is absorbed by the vessels. Of the 27 known cases, 15 were associated with type A, 5 with type B, 1 with both A and B, and one was undetermined.

The Disease in Animals: Botulism in domestic mammals is caused primarily by types C and D, and in fowl, by type C. Outbreaks in bovines are usually associated with a phosphorus deficiency and the resultant osteophagea and compulsive consumption ("pica") of carrion containing botulinum toxins. In locations where types C beta and D are found, such as South Africa, *C. botulinum* spores multiply rapidly in carrion and produce toxins to which bovines are very susceptible. The main symptom is the partial or complete paralysis of the locomotor, masticatory, and swallowing muscles. The animals have difficulty moving, stay motionless or recumbent for long periods of time, and, as the illness progresses, cannot hold their heads up and so bend their necks over their flanks. The mortality rate is high.

In sheep, botulism is associated with protein and carbohydrate deficiencies, which lead the animals to eat the carcasses of small animals they find as they graze.

In horses, as in other mammals, the incubation period varies widely according to the amount of toxin ingested. In very acute cases, death may ensue in one or two days. When the course is slower, the disease generally begins with paralysis of the hind quarters and progresses to other regions of the body until it produces death due to respiratory failure. A toxin infection similar to infant botulism and wound botulism has been described in young colts. The neuromuscular paralytic syndrome affects colts from 2 to 8 weeks old; they show signs of progressive motor paralysis that includes muscular tremors (shaker foal syndrome), dysphagia with flaccid paralysis of the tongue, difficulty remaining on their feet, a tendency to collapse, dyspnea, mydriasis, and constipation (Thomas *et al.*, 1988). Sometimes they die without signs of disease ("sudden death"). The disease is produced by the type B toxin that requires prior colonization of *C. botulinum* in gastric, intestinal, umbilical, hepatic (necrosis), muscular, or subcutaneous lesions. Necrotic lesions seem to be necessary for toxicity, as in wound botulism in man (Swerczek, 1980).

Outbreaks with high death rates have been observed on mink farms. Food poisoning in these animals is due primarily to type C beta.

In ducks and other waterfowl, the first symptom of poisoning is paralysis of the wings, which then extends to other muscles, and finally to those of the neck. The birds drown when they can no longer hold their heads above water. An outbreak due to type E occurred in waterfowl on Lake Michigan (USA).

The illness in chickens is produced mainly by type C alpha. It has been given the name "limberneck" because flaccid paralysis is frequently observed in afflicted birds.

Treatment with botulinum antitoxin produced variable results in bovines. Better results were obtained from antitoxin C in mink and ducks, but the cost can be excessive. Control and prevention must be the principal tools for combating losses due to animal botulism.

Source of Poisoning or Infection and Mode of Transmission: The reservoir of *C. botulinum* is the soil, river and sea sediments, vegetables, and the intestinal tracts of mammals and birds. The spores formed by the bacteria are very resistant to heat and desiccation. The etiologic agent is distributed on all continents, though irregularly. The distribution of the toxicogenic types also varies according to region. In a study (Smith, 1978) carried out across the United States, subdividing it into four transverse sections, *C. botulinum* was found in 23.5% of 260 soil samples. Type A was most prevalent in the western states with neutral or alkaline soil. Type B had a more uniform distribution, but predominated in the East, a pattern which seems to be associated with highly organic soils. Type C was found in acid soils on the Gulf Coast, type D in some alkaline soils in the West, and type E in the humid soils of several states. In the former Soviet Union, *C. botulinum* was isolated from 10.5% of 4,242 soil samples, with type E accounting for 61% of all positive cultures. The greatest concentration of spores was found in the European section of the country south of 52° N latitude (Kravchenko and Shishulina, 1967).

The wide distribution of *C. botulinum* in nature explains its presence in food. Vegetables are contaminated directly from the soil. Foods of animal origin are probably contaminated via the animals' intestinal tract and by spores in the environment. The main source of botulinum poisoning for man and animals is food in which the microorganism has multiplied and produced the powerful toxin. After ingestion, the toxin is absorbed through the intestine, primarily the upper portion, and carried by the bloodstream to the nerves. It acts upon the presynaptic union of cholinergic nerve endings by inhibiting the release of acetylcholine.

Any food, whether of vegetable or animal origin, can give rise to botulism if conditions favor the multiplication of *C. botulinum* and, consequently, the production of toxins. The main requirements for the multiplication of *C. botulinum* are anaerobiosis and a pH above 4.5, but once the toxin is formed an acid medium can be favorable. Home-canned foods are generally responsible for the disease, although incorrectly sterilized or preserved commercial products are sometimes the cause. Poisoning ensues after eating a raw or insufficiently cooked product that was preserved some time earlier. The types of food responsible for poisoning vary according to regional eating habits.

The most common sources of types A and B botulism in the United States and Canada are home-canned fruits and vegetables. In Europe, on the other hand, meat

and meat products seem to play the most important role. In Japan, the former Soviet Union, the northern United States, Alaska, and northern Canada, type E, which is associated with foods of marine origin, predominates.

Ethnic customs and food habits often favor food poisoning. In 1992, a family of Egyptian origin living in New Jersey (USA) became sick from type E botulism after consuming "moloha," an uneviscerated salt-cured fish (CDC, 1992). There had been an earlier outbreak in which two Russian immigrants in New York and five people in Israel became ill with type E botulism; all of them had eaten uneviscerated salt-cured, air-dried fish ("ribyetz") from the same source (CDC, 1989). A preserved regional dish that is popular in the Orient, a soft cheese prepared with soy milk, led to 705 (71.5%) of the 986 outbreaks of botulism recorded in China (Ying and Shuan, 1986).

In contrast to classic botulism (acquired through foods), infant botulism begins as an intestinal infection caused by *C. botulinum*, where the spores germinate, multiply, and produce the toxin that is absorbed through the intestinal wall. Honey has been implicated as a source of infection, since it is frequently a supplementary food for the nursing child. However, results of research on the presence of botulinum spores in this food, as well as epidemiological investigations, are inconclusive. In any case, there is no doubt that the infection is caused by ingestion.

The source of wound botulism is environmental. Botulism in bovines results from grazing ("lamziekte") or the consumption of bailed fodder or silage. Poisoning contracted while grazing usually occurs in areas lacking or deficient in phosphorus. Many species of animals in the area contain *C. botulinum* in their intestinal flora; when an animal dies, these bacteria invade the whole organism and produce great quantities of toxin. Bovines suffering from pica ingest animal remains containing the preformed toxin and contract botulism. After dying, these same bovines are a source of poisoning for the rest of the herd. Mortality in cattle has also been ascribed to drinking water that contained the decomposed bodies of small animals. Botulism contracted through the consumption of fodder or silage is produced by the accidental presence of a small animal's body (usually a cat) or the remains of birds and the diffusion of the botulinum toxin around them into the food (Smith, 1977). The sources of poisoning for other mammalian species are similar.

For wild ducks, the source of poisoning is insect larvae that invade the bodies of ducks that died from various causes. If a duck had *C. botulinum* in its intestinal flora, the bacteria invades the whole organism after its death. The larvae then absorb the toxin produced, constituting a source of toxin for birds. It is estimated that a duck need only ingest a few such larvae for death by botulism to ensue.

Research on outbreaks among pheasants has found that they ate maggots from the bodies of small animals.

Role of Animals in the Epidemiology of the Disease: No epidemiological relationship between human and animal botulism has been established. *C. botulinum* type A spores have been isolated from animal feces, and types A and B botulism microorganisms have been found in the intestine and liver of bovines that died from other causes. The microorganism has also been isolated from the intestine and bone marrow of healthy dogs. Thus the possibility exists that these animals are carriers of the microorganism and serve to transport and disseminate *C. botulinum* from one place to another.

Diagnosis: Clinical diagnosis should be confirmed with laboratory tests. The most conclusive evidence is the presence of botulinum toxin in the serum of the patient. Stomach contents and fecal material of persons exposed to the suspected food should also be examined for the toxin. The food in question should be cultured to isolate and identify the microorganism. In infant botulism, the attempt is made to isolate the agent and the toxin from the infant's feces, since the toxin is rarely detected in serum. An enzyme-linked immunosorbent assay (ELISA) test has been developed for the detection of A and B toxin in children's fecal samples; this may be useful as a screening test in clinical specimens (Dezfulian *et al.*, 1984). When a wound is the suspected origin of the poisoning, fluid is aspirated from the wound and biopsies are performed for bacteriological examination.

Control: With regard to man, control measures include: (a) regulation and inspection of industrial bottling, canning, and food-preserving processes, and (b) health education to point out the dangers of home canning and to make the public aware of important factors in the preservation of home products, such as duration, pressure, and temperature of sterilization. Home-canned foods should be boiled before being served to destroy the toxins that are thermolabile. Foods from swollen cans or food altered in taste, smell, or appearance should not be eaten even after cooking. Any food that is bottled, canned, or prepared in some other way (salted, dried, etc.) and has led to a case or outbreak should be seized.

Immediate epidemiological investigation and prompt diagnosis of an outbreak are essential to both the prevention of new cases and the recovery of the patient.

In areas where botulism in animals is a problem, the diet of livestock should be supplemented with feed rich in phosphorus to avoid osteophagia or pica; vaccination of animals with the appropriate toxoid can yield good results. When bird bedding is used as silage for cattle or for pasture fertilizer, any remains of birds or other animals should be carefully eliminated. When an outbreak occurs in a fowl facility, carcasses must be removed as soon as possible to prevent its progression.

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BRUCELLOSIS

ICD-10 A23.0 brucellosis due to *Brucella melitensis*; A23.1 brucellosis due to *Brucella abortus*; A23.2 brucellosis due to *Brucella suis*; A23.3 brucellosis due to *Brucella canis*

Synonyms: Melitococcosis, undulant fever, Malta fever, Mediterranean fever (in man); contagious abortion, infectious abortion, epizootic abortion (in animals); Bang's disease (in cattle).

Etiology: Six species are presently known in the genus *Brucella*: *B. melitensis*, *B. abortus*, *B. suis*, *B. neotomae*, *B. ovis*, and *B. canis*.

The first three species (called "classic brucella") have been subdivided into biovars that are distinguished by their different biochemical characteristics and/or reac-

tions to the monospecific *A.* (*abortus*) and *M.* (*melitensis*) sera. Thus, *B. melitensis* is subdivided into three biovars (1–3); *B. abortus*, into seven (1–7)—biovars 7 and 8 were discarded and the current biovar 7 corresponds to 9 in the old classification; and *B. suis*, into five (1–5). From an epidemiological viewpoint, the taxonomic system of the genus *Brucella* has eliminated confusion arising from the naming of new species or subspecies that did not agree with epidemiological reality. Moreover, typing by biovars constitutes a useful research tool in that field. The characteristics of *B. abortus* determined by conventional methods vary greatly, such as sensitivity or tolerance to aniline dyes, production of H_2S, and CO_2 requirements for growth. Less plasticity is shown by *B. melitensis* or *B. suis* (Meyer, 1984). In various parts of the world, strains of *B. abortus* and, to a lesser extent, of *B. suis* or *B. melitensis* have been discovered that are difficult to place within the current scheme, in that they differ in some characteristics (Ewalt and Forbes, 1987; Corbel *et al.*, 1984; Banai *et al.*, 1990).

However, the genome of the genus *Brucella* is very homogeneous as shown by Verger *et al.* (1985) in a DNA:DNA hybridization study. These researchers propose maintaining a single species, *B. melitensis*, subdivided into six biogroups, which would correspond to the six previous species. For all practical purposes, and especially for epidemiological purposes, the previous scheme that divides the genus into species and biovars is still in effect.

Geographic Distribution: Worldwide. The distribution of the different species of *Brucella* and their biovars varies with geographic areas. *B. abortus* is the most widespread; *B. melitensis* and *B. suis* are irregularly distributed; *B. neotomae* was isolated from desert rats (*Neotoma lepida*) in Utah (USA), and its distribution is limited to natural foci, as the infection has never been confirmed in man or domestic animals. Infection by *B. canis* has been confirmed in many countries on several continents, and its worldwide distribution can be asserted. *B. ovis* seems to be found in all countries where sheep raising is an important activity.

Occurrence in Man: Each year about a half million cases of brucellosis occur in humans around the world (WHO, 1975). The prevalence of the infection in animal reservoirs provides a key to its occurrence in humans. *B. abortus* and *B. suis* infections usually affect occupational groups, while *B. melitensis* infections occur more frequently than the other types in the general population. The greatest prevalence in man is found in those countries with a high incidence of *B. melitensis* infection among goats, sheep, or both species. The Latin American countries with the largest number of recorded cases are Argentina, Mexico, and Peru. The same pattern holds true for Mediterranean countries, Iran, the former Soviet Union, and Mongolia.

In Saudi Arabia, 7,893 human cases of brucellosis were recorded in 1987 (74 per 100,000 inhabitants). Brucellosis probably became very important in public health because during the period 1979 to 1987, Saudi Arabia imported more than 8 million sheep, more than 2 million goats, more than 250,000 cattle, and other animals (buffalo, camels). In Iran, 71,051 cases (13 per 100,000) were recorded in 1988 and it is estimated that 80,000 cases have occurred each year since 1989. In Turkey, 5,003 cases (9 per 100,000) were recorded in 1990, an incidence three times higher than during the period 1986–1989 (3 per 100,000).

Programs for the control and eradication of bovine brucellosis markedly reduce the incidence of disease in humans. For example, in the United States, 6,321 cases

were recorded in 1947, while in the period 1972–1981, the annual average was 224 cases (CDC, 1982). In Denmark, where some 500 cases per year were reported between 1931 and 1939, human brucellosis had disappeared by 1962 as a result of the eradication of the infection in animals. In Uruguay, where there is no animal reservoir of *B. melitensis* and where the few foci of *B. suis* had been eliminated (although they have recently been reintroduced through importation), the disease in humans has almost disappeared since compulsory vaccination of calves was begun in 1964. China and Israel have been able to significantly reduce the incidence of human brucellosis thanks to vaccination campaigns for sheep and goats. In the western Mediterranean area, there has also been a marked reduction of human brucellosis cases caused by *B. melitensis* due to vaccination of the small ruminants with the Rev. 1 vaccine. In Spain, for example, the incidence fell from 4,683 cases in 1988 to 3,041 in 1990.

Occurrence in Animals: Bovine brucellosis is found worldwide, but it has been eradicated in Finland, Norway, Sweden, Denmark, the Netherlands, Belgium, Switzerland, Germany, Austria, Hungary, the former Czechoslovakia, Rumania, and Bulgaria, as well as other countries (Timm, 1982; Kasyanov and Aslanyan, 1982). Most European countries are free of bovine brucellosis (García-Carrillo and Lucero, 1993). The large meat-producing countries, such as France, Great Britain, Australia, New Zealand, Canada, and the United States, among others, are free of bovine brucellosis or close to being so. Three important cattle-raising countries, Argentina, Brazil, and Mexico, still have limited control programs. A country-by-country analysis can be found in a monograph on bovine brucellosis (García-Carrillo and Lucero, 1993). In the rest of the world, rates of infection vary greatly from one country to another and between regions within a country. The highest prevalence is seen in dairy cattle. In many countries, including most of those Latin American countries that have no control programs, the data are unreliable. Nevertheless, available information indicates that it is one of the most serious diseases in cattle in Latin America as well as in other developing areas. Official estimates put annual losses from bovine brucellosis in Latin America at approximately US$ 600 million, which explains the priority given by animal health services to control of this disease.

Swine brucellosis is infrequent and occurs sporadically in most of Europe, Asia, and Oceania. In China, *B. suis* biovar 3 was introduced with breeding stock from Hong Kong in 1954 and spread rapidly through the southern part of the country (Lu and Zhang, 1989). In many European countries, swine brucellosis shows an epidemiological relationship to brucellosis caused by *B. suis* biovar 2 in hares (*Lepus europaeus*). With the new swine-breeding technology, swine have little access to hares and outbreaks have thus shown a marked decline. The disease has never been present in Finland, Norway, Great Britain, and Canada. Many predominantly Muslim countries and Israel are probably free of *B. suis* infection as a result of religious beliefs that have limited swine raising (Timm, 1982).

In most of Latin America, swine brucellosis is enzootic and, while the available data have little statistical value, this region is thought to have the highest prevalence in the world. However, recent surveys of breeding operations for purebreds and hybrids in Argentina and Rio Grande do Sul (Brazil) have shown the percentage of infected herds to be low. The problem is possibly rooted in commercial operations where animals of different origins are brought together. Thus far, only *B. suis* bio-

var 1, which predominates worldwide, has been confirmed from Latin America. Biovar 2 is limited to pigs and hares in central and western Europe, while biovar 3 is limited to the corn belt of the United States and to some areas of Asia and Africa. The US and Cuba have successful national eradication programs.

Goat and sheep brucellosis constitute a significant problem in the Mediterranean basin of Europe and Africa, in the southeastern part of the former Soviet Union, in Mongolia, in the Middle East, and Saudi Arabia. In Latin America, the prevalence of *B. melitensis* infection in goats is high in Argentina, Mexico, and Peru. To date, sheep infection with *B. melitensis* in Argentina has been identified only in flocks living with infected goats in the north of the country (Ossola and Szyfres, 1963). In Venezuela's goat-raising region, a serological and bacteriological examination was conducted in 1987. *B. abortus* biovar 1 was isolated from milk and lymph nodes. *B. melitensis* was not isolated (De Lord *et al.*, 1987). Goat brucellosis does not appear to exist in Brazil, which has a sizable number of goats. In Chile, where the rate of infection in Cajón de Maipo was significant, the Government reported that the disease had been eradicated (Chile, Ministerio de Agricultura, 1987). Other American countries, including the US, are free of goat brucellosis at the present time.

Ram epididymitis caused by *B. ovis* is widespread. It has been confirmed in New Zealand, Australia, Africa, and Europe. It is present in Argentina, Brazil (Rio Grande do Sul), Chile, Peru, Uruguay, and the US, i.e., in all American countries where sheep are raised on a large scale. Prevalence is high.

Infection of dogs with *B. canis* has been found in almost every country in the world where it has been studied. Prevalence varies according to region and diagnostic method used. It constitutes a problem for some dog breeders, since it causes abortions and infertility, but the infection is also found in family dogs and strays. In the latter, the incidence of infection is usually higher. In a study carried out in Mexico City, for example, 12% of 59 stray dogs were positive in the isolation of the etiologic agent (Flores-Castro *et al.*, 1977).

The Disease in Man: Man is susceptible to infection caused by *B. melitensis*, *B. suis*, *B. abortus*, and *B. canis*. No human cases caused by *B. ovis*, *B. neotomae*, or *B. suis* biovar 2 have been confirmed. The most pathogenic and invasive species for man is *B. melitensis*, followed in descending order by *B. suis*, *B. abortus*, and *B. canis*.

In general, the incubation period is one to three weeks, but may sometimes be several months. The disease is septicemic, with sudden or insidious onset, and is accompanied by continued, intermittent, or irregular fever. The symptomatology of acute brucellosis, like that of many other febrile diseases, includes chills and profuse sweating. Weakness is an almost constant symptom, and any exercise produces pronounced fatigue. Temperature can vary from normal in the morning to 40°C in the afternoon. Sweating characterized by a peculiar odor occurs at night. Common symptoms are insomnia, sexual impotence, constipation, anorexia, headache, arthralgia, and general malaise. The disease has a marked effect on the nervous system, evidenced by irritation, nervousness, and depression. Many patients have enlarged peripheral lymph nodes or splenomegaly and often hepatomegaly, but rarely jaundice. Hepatomegaly or hepatosplenomegaly is particularly frequent in patients infected by *B. melitensis* (Pfischner *et al.*, 1957). *Brucella* organisms localize intracellularly in tissues of the reticuloendothelial system, such as lymph nodes, bone marrow, spleen, and liver. Tissue reaction is granulomatous. The duration of

the disease can vary from a few weeks or months to several years. Modern therapy has considerably reduced the disease's duration as well as the incidence of relapses. At times, it produces serious complications, such as encephalitis, meningitis, peripheral neuritis, spondylitis, suppurative arthritis, vegetative endocarditis, orchitis, seminal vesiculitis, and prostatitis. A chronic form of the disease occurs in some patients and may last many years, with or without the presence of localized foci of infection. The symptoms are associated with hypersensitivity. Diagnosis of chronic brucellosis is difficult.

Separate mention should be made of human infection caused by the *B. abortus* strain 19 vaccine, which is the vaccine used most often to protect cattle. Cases have been described of accidents among those administering the vaccine (veterinarians and assistants) who have pricked a finger or hand with the syringe needle or have gotten aerosol in their eyes. If someone has no prior exposure to brucellae and has no antibodies to the agent, the disease sets in abruptly after a period of 8 to 30 days. The course of the disease is usually shorter and more benign than that caused by the field strains of *B. abortus*, but there are severe cases that require hospitalization. In individuals who have been exposed to brucellae, as is usually the case with veterinarians and vaccinators, a different, allergic-type syndrome appears that is characterized by painful swelling at the inoculation site. After some hours, the patient may experience systemic symptoms similar to those described in individuals infected by strain 19 without prior exposure. The symptoms usually abate in a few days with or without treatment. Local and general symptoms may recur if the person has another accident (Young, 1989). Considering the millions of doses of strain 19 vaccine used each year throughout the world, the rate of incidence of the disease due to this strain is insignificant.

Another strain that is used to vaccinate small ruminants, *B. melitensis* Rev. 1, can also infect the vaccinator. Under the aegis of the World Health Organization (WHO) and its collaborative centers, Rev. 1 vaccine was administered to 6 million animals in Mongolia between 1974 and 1977. Six trained vaccinators inoculated themselves accidentally; four of them showed clinical symptoms but recovered after immediate hospital treatment.

There are many infections that occur asymptomatically in areas with enzootic brucellosis, particularly the bovine form.

The recommended treatment for acute brucellosis is a daily dose of 600 mg to 900 mg of rifampicin, combined with 200 mg per day of doxycycline for at least six weeks. Relapses are very rare with this treatment. If there is a Jarisch-Herxheimer reaction upon starting antibiotic treatment, intravenous administration of cortisol is recommended. Sometimes various series of treatment are needed. If antibiotic therapy is not successful, a chronic focus of infection should be sought, particularly in infections caused by *B. melitensis* and *B. suis* (WHO, 1986). In the event of a relapse, the treatment indicated above should be restarted. Steroids may be administered to counteract toxicity in patients who are very ill (Benenson, 1992).

The Disease in Animals: The principal symptom in all animal species is abortion or premature expulsion of the fetus.

CATTLE: The main pathogen is *B. abortus*. Biovar 1 is universal and predominant among the seven that occur in the world. The distribution of the different biovars varies geographically. In Latin America, biovars 1, 2, 3, 4, and 6 have been con-

firmed, with biovar 1 accounting for more than 80% of the isolations. In the United States, biovars 1, 2, and 4 have been isolated. In eastern Africa and China, biovar 3 predominates and affects both native cattle and buffalo (Timm, 1982). Biovar 5, which occurred in cattle in Great Britain and Germany, has biochemical and serological characteristics similar to *B. melitensis*. This similarity was a source of confusion for years until new methods of species identification (oxidative metabolism and phagocytolysis) established the biovar as *B. abortus*. The other biovars also have a more or less marked geographic distribution. Cattle can also become infected by *B. suis* and *B. melitensis* when they share pasture or facilities with infected pigs, goats, or sheep. The infection in cattle caused by heterologous species of *Brucella* are usually more transient than that caused by *B. abortus*. However, such cross-infections are a serious public health threat, since these brucellae, which are highly pathogenic for man, can pass into cow's milk. Infection caused by *B. suis* is not very common. By contrast, infections caused by *B. melitensis* have been seen in several countries, with a course similar to those caused by *B. abortus*.

In natural infections, it is difficult to measure the incubation period (from time of infection to abortion or premature birth), since it is not possible to determine the moment of infection. Experiments have shown that the incubation period varies considerably and is inversely proportional to fetal development: the more advanced the pregnancy, the shorter the incubation period. If the female is infected orally during the breeding period, the incubation period can last some 200 days, while if she is exposed six months after being bred, incubation time is approximately two months. The period of "serologic incubation" (from the time of infection to the appearance of antibodies) lasts several weeks to several months. The incubation period varies according to such factors as the virulence and dose of bacteria, the route of infection, and the susceptibility of the animal.

The predominant symptom in pregnant females is abortion or premature or full-term birth of dead or weak calves. In general, abortion occurs during the second half of the pregnancy, often with retention of the placenta and resultant metritis, which may cause permanent infertility. It is estimated that the infection causes a 20% to 25% loss in milk production as a result of interrupted lactation due to abortion and delayed conception. Cows artificially inseminated with infected semen may come into estrus repeatedly, as happens in cases of vibriosis or trichomoniasis. Nonpregnant females show no clinical symptoms and, if infected prior to breeding, often do not abort.

In bulls, brucellae may become localized in the testicles and adjacent genital glands. When the clinical disease is evident, one or both testicles may become enlarged, with decreased libido and infertility. Sometimes a testicle may atrophy due to adhesions and fibrosis. Seminal vesiculitis and ampullitis are common. Occasionally, hygromas and arthritis are observed in cattle.

Brucellae entering the animal's body multiply first in the regional lymph nodes and are later carried by the lymph and blood to different organs. Some two weeks after experimental infection, bacteremia can be detected and it is possible to isolate the agent from the bloodstream. Brucella organisms are most commonly found in the lymph nodes, uterus, udder, spleen, liver, and, in bulls, the genital organs. Large quantities of erythritol, a carbohydrate that stimulates the multiplication of brucellae, have been found in cow placentas. This could explain the high susceptibility of bovine fetal tissues.

Once an infected cow aborts or gives birth normally, the pathogen does not remain long in the uterus. The infection becomes chronic and the brucellae are harbored in the cow's lymph nodes and mammary glands. Brucellae may remain in the udder for years (García-Carrillo and Lucero, 1993).

Individual animals within a herd manifest different degrees of susceptibility to infection depending on their age and sex. Male and female calves up to 6 months of age are not very susceptible and generally experience only transitory infections. A bull calf fed milk containing brucella organisms can harbor the agent in its lymph nodes, but after six to eight weeks without ingesting the contaminated food, the animal usually rids itself of the infection.

Heifers kept separate from cows, as is routine in herd management, often have lower infection rates than adult cows. Heifers exposed to infection before breeding can become infected, but generally do not abort. In view of this, at the beginning of the century heifers were inoculated before breeding with virulent strains or with strains of unknown virulence to prevent abortion. This practice had to be abandoned, however, when it was found that a large number of animals remained infected.

Cows, especially when pregnant, are the most susceptible; infection is common and abortion frequently results.

Bulls are also susceptible, although some researchers maintain that they are more resistant to infection than females. This conclusion may reflect herd management practices more than natural resistance in males, however, since bulls are usually kept separate from cows. On the other hand, neutered males and females do not play a role in the epizootiology of brucellosis, since they cannot transmit brucellae to the exterior environment.

In addition to age and sex, it is important to take individual susceptibility into account. Even in the most susceptible categories—cows and heifers—some animals never become infected, or if they do, their infection is transient. Some less susceptible cows have generalized infections and suffer losses in reproductive function and milk production for one or more years, but then gradually recover. In such animals, the agglutination titer becomes negative, the shedding of brucellae may cease, and both reproductive function and milk production return to normal. However, most cows become infected, and their agglutination titers remain positive for many years or for life; although after one or two abortions they may give birth normally and resume normal production of milk, many continue to carry and shed brucellae. Other cows remain totally useless for breeding and milk production.

In a previously uninfected herd, brucellosis spreads rapidly from animal to animal, and for one or two years there are extensive losses from abortions, infertility, decreased milk production, and secondary genital infections. This acute or active phase of the disease is characterized by a large number of abortions and a high rate of reactors in serological tests. Because of individual differences in susceptibility to the infection, not all animals become infected and not all those that are serologically positive abort. After a year or two, the situation stabilizes and the number of abortions decreases. It is estimated that only between 10% and 25% of the cows will abort a second time. In this stabilization phase, it is primarily the heifers—not previously exposed to the infection—that become infected and may abort. A final, decline phase can be observed in small and self-contained herds. In this phase, the infection rate gradually decreases, and most of the cows return to normal reproductive function and milk production. Nevertheless, when a sufficient number of sus-

ceptible animals accumulates—either heifers from the same herd or newly introduced animals—a second outbreak can occur. In large herds, there are always enough susceptible animals to maintain the infection, and abortions continue. Trading and movement of animals also help maintain active infection.

SWINE: The main etiologic agent of brucellosis in swine is *B. suis*. In Latin America, only biovar 1 infection has been confirmed, while in the United States both 1 and 3 have been involved. Biovar 2 is found only in Europe. Infection by biovars 1 and 3 is spread directly or indirectly from pig to pig. In contrast, biovar 2 (or Danish biovar) is transmitted to pigs when they ingest European hares (*Lepus europaeus*). Pigs can also be infected by *B. abortus*, although it is less pathogenic for pigs and apparently not transmitted from one animal to another; the infection is generally asymptomatic, with the affected organisms limited to the lymph nodes of the head and neck.

When brucellosis is introduced into a previously healthy herd, the symptoms are those of acute disease: abortions, infertility, birth of weak piglets, orchitis, epididymitis, and arthritis. In small herds, the infection tends to die out or decrease in severity because of a lack of susceptible animals owing to the normal sale of some pigs and to the spontaneous recovery of others. In large herds, the infection is persistent and transmitted from one generation to the next.

Early abortions, which occur when the female is infected during coitus, generally go unnoticed under free-range conditions. The aborted fetuses are eaten by the pigs, and the only abnormality that may be noted by the owner is the sows' repeated estrus. Abortions occur in the second half of gestation when the females are infected after one or two months of pregnancy. Affected sows rarely have a second abortion, and females infected before sexual maturity rarely abort.

Infection is usually temporary in suckling pigs. However, a few may retain the infection and become carriers. It rarely results in recognizable clinical symptoms. Occasionally, arthritis is observed, but transient bacteremia and low agglutination titers may be found.

In infected pigs, abscesses of different sizes frequently occur in organs and tissues. Spondylitis is often found.

Infection of the genital organs lasts for a shorter period of time in the female than in the male. In the latter it may last for the life of the animal.

GOATS: The main etiologic agent of brucellosis in goats is *B. melitensis* with its three biovars. All types of goats are susceptible to infection by *B. melitensis*. Infection by *B. suis* and *B. abortus* has occasionally been found.

The symptomatology is similar to that observed in other species of animals and the main symptom is abortion, which occurs most frequently in the third or fourth month of pregnancy. In natural infections occurring in the field, other symptoms, such as arthritis, mastitis, spondylitis, and orchitis, are rarely found. These symptoms can be seen when the animals are inoculated experimentally with large doses of the agent. Sexually mature female goats that are not pregnant are susceptible and suffer from a chronic infection that may have no clinical symptoms, but that represents a risk for the other animals in the flock. Infection of the mammary gland is common (Alton, 1985). In chronically infected flocks, the signs of the disease are generally not very apparent. Gross pathological lesions are also not usually evident, though the pathogen can frequently be isolated from a large number of tissues and organs.

Several researchers have observed that young goats can be born with the infection or become infected shortly after birth. Most of them recover spontaneously before reaching reproductive age, but in some the infection may persist longer.

The primitive conditions under which goats are raised constitute one of the most important factors in the maintenance and spread of the infection in Latin America (Argentina, Mexico, and Peru) and in the rest of the developing world. In goat-raising areas, it is common to find community-shared pastures, a lack of hygiene in makeshift corrals, nomadic flocks, and owners with little understanding of herd management.

SHEEP: Two disease entities are distinguishable in sheep: classic brucellosis and ram epididymitis. Classic brucellosis is caused by *B. melitensis* and constitutes a public health problem equally or even more important than goat brucellosis in areas where the agent is found outside the American continent. In Latin America, the infection in sheep has been confirmed only in some mixed goat and sheep flocks raised far away from intensive sheep-raising areas.

While sheep brucellosis is similar in its symptomatology to the disease in goats, sheep appear to be more resistant to infection and, in mixed flocks, fewer sheep than goats are found to be infected. Susceptibility varies from breed to breed. Maltese sheep are very resistant, while Middle Eastern Awassi (fat tail) sheep are very susceptible (Alton, 1985). Abortions are also less common. The infection tends to disappear spontaneously, and the high prevalence of the disease in some areas can best be attributed to poor herd management.

Occasionally, sheep have been found to be infected by *B. suis* (biovar 2 in Germany) and *B. abortus* (in various parts of the world). These agents are not very pathogenic for sheep; they are acquired through contact with infected animals of other species, and are usually not transmitted from sheep to sheep. However, transmission can occur, as in the case described in an outbreak occurring on a ranch in the US (Luchsinger and Anderson, 1979).

Ram epididymitis is caused by *B. ovis*. The clinical signs consist of genital lesions in rams, associated with varying degrees of sterility. Sometimes the infection in pregnant ewes can cause abortion or neonatal mortality. Epididymitis is generally unilateral but can be bilateral and the tail of the organ is most commonly affected. Adhesions may occur in the tunica vaginalis testis, and the testicle may be atrophied with varying degrees of fibrosis. Lesions cannot be seen or palpated in many infected rams, even though *B. ovis* may be isolated from their semen. Some of these animals develop lesions in more advanced stages of the disease. Early in the infection, the semen contains many brucellae, but with time the number decreases, and eventually the semen may be free of the infectious agent. When localized in the kidneys, *B. ovis* is also shed through the urine.

HORSES: *B. abortus* and *B. suis* have been isolated from this species. The disease usually manifests itself in the form of fistulous bursitis, “poll evil” and “fistulous withers.” Abortions are rare but they do occur (Robertson *et al.*, 1973). *B. abortus* has been isolated from horse feces, but this is uncommon. Horses acquire the infection from cattle or swine, but transmission from horses to cattle has also been proven. Man can contract the infection from horses that have open lesions. In general, horses are more resistant to the infection. Cases of horse-to-horse transmission are unknown. In areas where there is a high rate of infection, it is common to find horses with high agglutination titers.

DOGS AND CATS: Sporadic cases of brucellosis caused by *B. abortus*, *B. suis*, and *B. melitensis* occur in dogs. They acquire the infection primarily by eating contaminated material, especially fetuses, afterbirth, and milk. The course of the infection is usually subclinical, but sometimes the symptomatology can be severe, with fever, emaciation, orchitis, anestrus, arthritis, and sometimes abortion. Cases of dog-to-dog transmission are rare. In some cases, the infection may last for more than 150 days. Although it is rare, dogs can eliminate brucellae in their urine, vaginal secretions, feces, and aborted fetuses. A study conducted in Canada collected 14 dogs from 10 cattle properties with bovine brucellosis. Positive cultures were obtained from vaginal mucus and from the bladder of a single dog. The final positive vaginal secretion sample was obtained 464 days after the probable date when the dog was infected. In other dogs, *Brucella* was isolated from organs that do not discharge to the environment (Forbes, 1990). Several human cases have been described in which the source of infection was dogs (especially fetuses).

A canine disease that occurs worldwide and can reach epizootic proportions is that caused by *B. canis*. This form of brucellosis is characterized by a prolonged afebrile bacteremia, embryonic death, abortions, prostatitis, epididymitis, scrotal dermatitis, lymphadenitis, and splenitis. Abortion occurs about 50 days into gestation. The pups may be stillborn at full term or die a few days after birth. Survivors usually have enlarged lymph nodes and often have bacteremia.

In an experimental treatment, minocycline (27.5 mg/kg twice a day) was administered to 18 infected dogs. Fifteen of them had positive cultures in autopsies conducted between 6 and 28 weeks after treatment ended (WHO, 1986).

Man is susceptible to *B. canis*, though less so than to classic brucellae. Several cases have been confirmed in the United States, Mexico, Brazil, and Argentina in laboratory and kennel personnel as well as in members of families with infected dogs.

Cats are resistant to *Brucella* and no cases of natural disease occurrence are known.

OTHER DOMESTIC MAMMALS: Brucellosis caused by *B. abortus* occurs in domestic buffalo (*Bubalus bubalis*) and in yaks (*Bos grunniens*) with symptomatology similar to that in cattle. The disease has also been observed in Old World camels (*Camelus bactrianus*), in dromedaries (*Camelus dromedarius*), and in American Camelidae. Infection in Camelidae is caused primarily by *B. melitensis*, although *B. abortus* has been isolated (Al-Khalaf and El-Khaladi, 1989). An outbreak of brucellosis caused by *B. mellitus* biovar 1, accompanied by abortions and neonatal mortality, occurred on an alpaca (*Lama pacos*) ranch in the high plateau (altiplano) region of Peru; a serious outbreak also occurred in the human population of that ranch (Acosta *et al.*, 1972).

WILD ANIMALS: Natural infections caused by *Brucella* occur in a wide range of wild species. There are natural foci of infection, for example, among the desert rats of the United States (*Neotoma lepida*), which are the reservoir of *B. neotomae*. In Kenya, *B. suis* biovar 3 has been isolated from two species of rodents (*Arvicanthis niloticus* and *Mastomys natalensis*). In Australia, there are as yet unclassified biovars of *Brucella* in various species of rodents. In the Caucasus, rodents infected by *Brucella* were found; it was initially classified as *B. muris* and later as *B. suis* biovar 5. In Europe, the infection of hares (*Lepus europaeus*), which are the reservoir of *B. suis* biovar 2, is transmitted to domestic swine. Caribou (*Rangifer caribou*),

which is the reservoir of *B. suis* biovar 4 in Alaska, can transmit the infection to man and to sled dogs. The infection can also be transmitted in the opposite direction, from domestic animals to wild animals. This is the case in Argentina, where infection in foxes (*Dusicyon gymnocercus, D. griseus*) (Szyfres and González Tomé, 1966) and grisons (*Galictis furax-huronax*) is caused by *B. abortus* biovar 1, infection in European hares (*Lepus europaeus*) is caused by *B. suis* biovar 1 (Szyfres *et al.*, 1968), and that in opossums (*Didelphis azarae*), by *B. abortus* biovar 1 and *B. suis* biovar 1 (De la Vega *et al.*, 1979). Carnivores acquire the infection by eating fetuses and afterbirth. There is no evidence that the infection is transmitted from one individual to another among carnivores, and it probably dies out when brucellosis is controlled in domestic animals. The situation is different when domestic animals transmit the infection to wild ruminants, such as the steppe antelope (*Saiga tatarica*) or the American bison (*Bison bison*), in which brucellosis persists.

Fur-bearing animals, such as minks and silver foxes, may contract brucellosis when fed viscera of infected animals, and they may in turn transmit this infection to man.

The etiologic agent has been isolated from many species of arthropods. Ticks can harbor the organism for lengthy periods and transmit the infection through biting. They also eliminate the bacteria in their coxal gland secretions. Nevertheless, the number of ticks harboring brucellae is insignificant (in one study done in the former Soviet Union, eight strains of *Brucella spp.* were isolated from 20,000 ticks) and there are few brucellae per tick. The species that have been isolated from arthropods are *B. melitensis* and *B. abortus*. In Brazil, *B. canis* was isolated from specimens of *Rhipicephalus sanguineus* attached to a bitch suffering from brucellosis (Peres *et al.*, 1981). There is consensus that arthropods play only a small role, if any, in the epidemiology of brucellosis.

FOWL: In a few cases, *Brucella* has been isolated from naturally infected domestic fowl. The symptomatology described is quite varied, and there is no certainty that it always involves brucellosis. The infection may not be evident, with symptoms such as weight loss, reduction in egg production, and diarrhea. Fowl do not play a role in maintaining the infection in nature. *Brucella* has been isolated from some wild bird species such as ravens (*Corvus corvix*) and crows (*Tripanscorax fragilecus*).

Source of Infection and Mode of Transmission: The natural reservoirs of *B. abortus*, *B. suis*, and *B. melitensis* are, respectively, cattle, swine, and goats and sheep. The natural host of *B. canis* is the dog and that of *B. ovis* is the sheep.

INFECTION IN HUMANS: Man is infected by animals through direct contact or indirectly by ingestion of animal products and by inhalation of airborne agents. The relative importance of the etiologic agent's mode of transmission and pathway of penetration varies with the epidemiological area, the animal reservoirs, and the occupational groups at risk. Fresh cheese and raw milk from goats and sheep infected with *B. melitensis* are the most common vehicles of infection and can cause multiple cases of human brucellosis. Sometimes more widespread outbreaks occur when infected goat's milk is mixed with cow's milk. Cow's milk infected by *B. melitensis* or *B. suis* has also been known to produce outbreaks of epidemic proportions. Cow's milk and milk products containing *B. abortus* may give rise to sporadic cases. The organisms rarely survive in sour milk, sour cream and butter, or fermented cheese (aged over three months).

In arctic and subarctic regions, there have been confirmed cases that resulted from eating bone marrow or raw meat from reindeer or caribou infected with *B. suis* biovar 4. Brucellae are resistant to pickling and smoke curing, therefore some meat products thus prepared could possibly cause human infection; however, this mode of transmission has never been verified.

It is also possible for raw vegetables and water contaminated with the excreta of infected animals to serve as sources of infection.

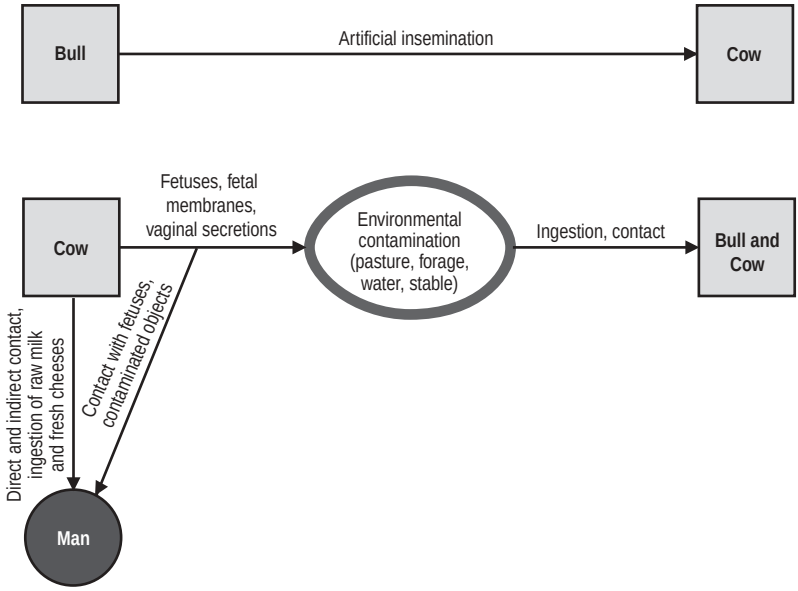
Transmission by contact predominates in areas where bovine and porcine brucellosis are enzootic. Human brucellosis is, for the most part, an occupational disease of stockyard and slaughterhouse workers, butchers, and veterinarians. The infection is usually contracted by handling fetuses and afterbirth, or by contact with vaginal secretions, excreta, and carcasses of infected animals. The microorganism enters through skin abrasions as well as through the conjunctiva by way of the hands. In slaughterhouses, prevalence of the disease is higher among recently employed staff. The practice in some companies of employing workers with negative serology is misguided, since an individual who is asymptomatic but has a positive serology is less likely to become sick.

In areas where goat and sheep brucellosis is enzootic, transmission by contact also occurs when shepherds handle newborn animals or fetuses. In some countries with hard winters, goats share the beds of goatherds and their families for protection against the cold, which results in infection of the whole family (Elberg, 1981).

Airborne transmission has been proved by experimentation and research. In laboratories, centrifugation of brucellosis suspensions poses a special risk when done in centrifuges that are not hermetically sealed. An epidemic outbreak of 45 cases occurred among students at Michigan State University (USA) in 1938–1939. The 45 students were attending classes on the second and third floors of a building that housed a brucellosis research laboratory in the basement. In the ensuing investigation, it was shown that the only possible means of transmission was by aerosol particles. Subsequent epidemiological studies have supplied proof that airborne transmission in meat lockers and slaughterhouses plays an important role, and perhaps is more frequent than transmission by direct contact with infected tissue. When air in the killing area is allowed to disperse, it leads to high rates of infection among workers in adjoining areas. The minimum infective dose for man by way of the respiratory passages seems to be small. When the killing area is completely separate, or maintained at a negative air pressure, the risk to surrounding areas is reduced (Kaufmann *et al.*, 1980; Buchanan *et al.*, 1974).

Some cases of possible human-to-human transmission of brucellosis have been described. One of them occurred in Kuwait due to transmission of *B. melitensis* to a 30-day-old girl through her mother's milk. The mother had experienced fever, discomfort, and arthralgia for at least two weeks prior to the child's becoming sick. *B. melitensis* biovar 1 was repeatedly isolated from the blood of both mother and child (Lubani *et al.*, 1988). In a hospital laboratory in the US, eight microbiologists were exposed to accidental dispersion of a clinical specimen in aerosol and *B. melitensis* biovar 3 was isolated from five of them. The spouse of one of the patients became ill six months after her husband had been admitted to the hospital and *B. melitensis* of the same biovar was isolated from her blood; it is suspected that the infection was sexually transmitted (Ruben *et al.*, 1991). A probable case of transmission during childbirth occurred in Israel. The mother had a fever on the first day postpartum and

Figure 5. Bovine brucellosis (*Brucella abortus*). Mode of transmission.



B. melitensis biovar 3 was identified in a cervical culture. Cervical and blood cultures continued to be positive. Although the child was asymptomatic, a positive blood culture of the same biovar and an agglutinating titer of 1:100 were obtained. Splenomegaly was the only abnormality found in the child at 13 days. Prior to these cases, there were descriptions of human-to-human transmission due to transfusion or bone marrow transplants.

INFECTION IN CATTLE (Figure 5): The main sources of infection for cattle are fetuses, afterbirth, and vaginal discharges containing large numbers of brucellae. To a lesser extent, farm areas can be contaminated by fecal matter of calves fed on contaminated milk, since not all the organisms are destroyed in the digestive tract.

The most common route of transmission is the gastrointestinal tract following ingestion of contaminated pasture, feed, fodder, or water. Moreover, cows customarily lick afterbirth, fetuses, and newborn calves, all of which may contain a large number of the organisms and constitute a very important source of infection. Cows' habit of licking the genital organs of other cows also contributes to transmission of the infection.

It has been shown experimentally that the organism may penetrate broken and even intact skin. The extent to which this mode of transmission is involved in natural infection is unknown.

Bang and others experimentally reproduced infection and disease via the vaginal route. The results of those experiments indicate that a large number of brucellae are necessary to infect a cow by this means. However, there is no doubt that the

intrauterine route used in artificial insemination is very important in transmitting the infection. The use of infected bulls for artificial insemination constitutes an important risk, since the infection can thus be spread to many herds.

In closed environments, it is likely that infection is spread by aerosols; airborne infection has been demonstrated experimentally.

Congenital infection and the so-called latency phenomenon have also been described. An experiment was carried out in France (Plommet *et al.*, 1973) in which calves born to cows artificially infected with a high dose of *B. abortus* were separated from their mothers and raised in isolation units. At 16 months of age, the heifers were artificially inseminated. In six experiments (Fensterbank, 1980) using 55 heifers born to infected cows, 5 were infected and brucellae were isolated during calving and/or after butchering six weeks later. At 9 and 12 months of age, two of these animals had serologic titers that were unstable until pregnancy. The other three heifers did not have serological reactions until the middle or end of pregnancy (latency). The authors of the experiment admit that under natural range conditions the frequency of the latency phenomenon could be much lower. In herds in which vaccination of calves is systematically carried out, the phenomenon may go unnoticed. In a similar vein, other research projects (Lapraik *et al.*, 1975; Wilesmith, 1978) have been undertaken on the vertical transmission of brucellosis accompanied by a prolonged and serologically unapparent phase of the infection. In a retrospective study of highly infected herds (Wilesmith, 1978), it was found that 8 of 317 heifers (2.5%) born to reactive cows tested serologically positive. One study conducted on 150 calves born to naturally infected mothers (with positive culture for *B. abortus*), taken from 82 herds in three southern states in the US, suggests that the latency phenomenon does not occur very frequently. The calves were raised in isolation until sexual maturity and breeding. *Brucella* was not isolated from the progeny of 105 infected cows, nor from the 95 fetuses and newborns of these heifers (second generation). Two heifers from the first generation had positive and persistent serological reactions from an undetermined source (Ray *et al.*, 1988). The extent of the latency phenomenon is still not known, but it has not prevented the eradication of bovine brucellosis in vast areas and many countries. On the other hand, it has undeniably slowed its eradication in some herds.

INFECTION IN SWINE (Figure 6): In swine, the sources of infection are the same as in cattle. The principal routes of transmission are digestive and venereal. Contrary to the situation in cattle, natural sexual contact is a common and important mode of transmission. The infection has often been introduced into a herd following the acquisition of an infected boar. Pigs, because of their eating habits and the conditions in which they are raised, are very likely to become infected through the oral route. It is also probable that they become infected by aerosols entering via the conjunctiva or upper respiratory tract.

INFECTION IN GOATS AND SHEEP (Figure 7): Goats and sheep are infected with *B. melitensis* in a manner similar to cattle. The role of the buck and ram in transmission of the infection is not well established. Infection of goats *in utero* is not unusual, and kids can also become infected during the suckling period; such infection may persist in some animals.

In ram epididymitis caused by *B. ovis*, semen is the main and possibly the only source of infection. The infection is commonly transmitted from one ram to another

by rectal or preputial contact. Transmission may also occur through the ewe when an infected ram deposits his semen and another ram breeds her shortly thereafter. The infection is not very common in ewes, and when it occurs it is contracted by sexual contact. *B. ovis* does not persist very long in ewes and is generally eliminated before the next lambing period.

**Figure 6. Swine brucellosis (*Brucella suis*).
Mode of transmission.**

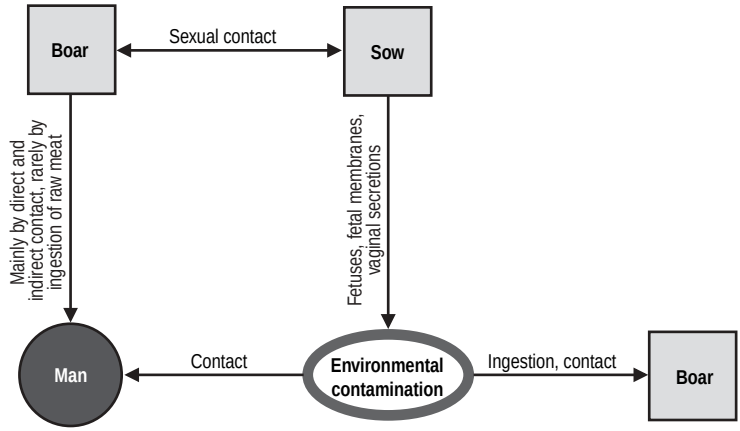
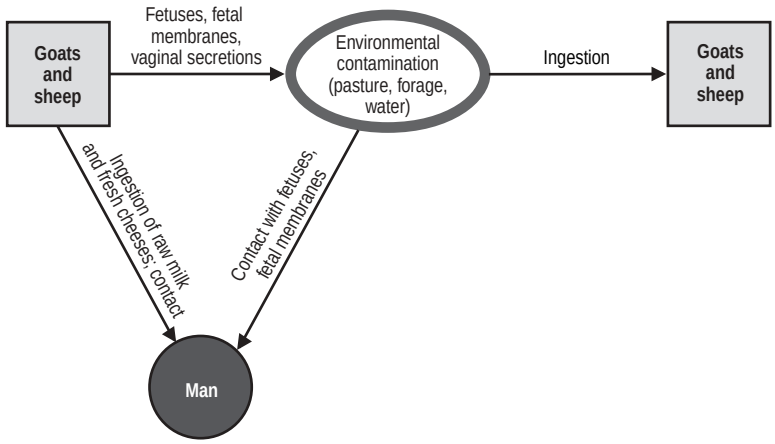


**Figure 7. Caprine and ovine brucellosis (*Brucella melitensis*).
Mode of transmission.**



INFECTION IN DOGS: The transmission of *B. canis* occurs as a result of contact with vaginal secretions, fetuses, and fetal membranes. Infected males may transmit the infection to bitches during coitus. The milk of infected bitches is another possible source of infection. Human cases recorded in the literature amount to several dozen, many resulting from contact with bitches that had recently aborted.

Role of Animals in the Epidemiology of the Disease: The role of animals is essential. Cases of human-to-human transmission are exceptional. Brucellosis is a zoonosis par excellence.

Diagnosis: In man, a clinical diagnosis of brucellosis based on symptoms and history should always be confirmed in the laboratory. Isolation and typing of the causal agent is definitive and may also indicate the source of the infection. Blood or marrow from the sternum or ileal crest taken while the patient is febrile is cultured in appropriate media. Culture material may also be taken from lymph nodes, cerebrospinal fluid, and abscesses. It is recommended that the cultures be repeated several times, especially in enzootic areas of *B. abortus*. Due to the widespread use of antibiotics before diagnosis in febrile patients, bacteriologic examinations, particularly of blood, often yield negative results, and serologic tests become increasingly necessary. The serum agglutination test, preferably in tubes, is the simplest and most widely used procedure. A high titer (more than 100 international units, IU) and increasing titers in repeated serum samples provide a good basis for diagnosis. Cross-reactions in serum agglutination have been observed in cases of cholera or tularemia (or as a result of vaccination against these diseases) and in infections caused by *Yersinia enterocolitica* 0:9, as well as *Escherichia coli* 0:157 and 0:116, *Salmonella* serotypes of Kauffmann-White group N, and *Pseudomonas maltophila* (Corbel *et al.*, 1984). The serum agglutination test reveals both M and G immunoglobulins. It is generally accepted that in an active stage of brucellosis IgG is always present. Thus, when low serum agglutination titers are found, tests to detect the presence of IgG must be performed, such as the 2-mercaptoethanol (ME) and complement fixation (CF) test (in man, IgGs fix complement but often lack agglutinating power). These tests are of special interest in chronic brucellosis, where active infection may continue even though agglutination titers return to low levels. The intradermal test with noncellular allergens is useful for epidemiological studies, but not for clinical diagnosis.

The 2-mercaptoethanol test is also useful in following the treatment and cure of the patient. In one study (Buchanan and Faber, 1980), the titers of 92 brucellosis patients were followed for 18 months with tube agglutination and ME tests. Despite antibiotic treatment, the tube agglutination test continued positive for 18 months in 44 (48%) of the patients, but the ME titers were positive in only 8 (9%) of the patients at the end of one year and in 4 (4%) at 18 months. None of the 84 patients testing negative by ME at the end of a year of treatment had signs or symptoms of brucellosis and none acquired chronic brucellosis. By contrast, four of the eight patients testing positive by ME after a year continued to have symptoms of brucellosis and had to continue treatment. Thus, a negative result by ME provides good evidence that a patient does not have chronic brucellosis and that the antibiotic treatment was successful. If effective treatment is begun early, it is possible that IgG antibodies (resistant to ME) never develop. This was probably the case in three patients who acquired brucellosis in the laboratory and in whom infection was confirmed by blood culture. Diagnosis and treatment were done early enough that at no time dur-

ing the two-year follow-up did these patients show ME-resistant antibodies (García-Carrillo and Coltorti, 1979). However, other researchers dispute the usefulness of this test in the diagnosis of brucellosis (Díaz and Moriyon, 1989).

Other useful methods for the diagnosis of human brucellosis are the rose bengal test and counterimmunoelectrophoresis. The rose bengal test is easily performed and is recommended over the plate agglutination test or the Huddleson method. In a study of 222 cases (Díaz *et al.*, 1982), rose bengal was the most sensitive test, with 98.3% positive results. Counterimmunoelectrophoresis was positive in 84.9% of the acute cases and in 91.6% of the chronic cases.

The indirect enzyme-linked immunosorbent assay (ELISA) test has been used for some years with good results in terms of specificity and sensitivity in research (Díaz and Moriyón, 1989). It is a very versatile test and, once it is introduced in a laboratory, it can be adapted for use with many other diseases.

The Joint FAO/WHO Expert Committee on Brucellosis (WHO, 1986) calls attention to the limited value of serological tests in individuals who are repeatedly exposed to brucellae because they can be serologically positive in the absence of symptoms. This category would include veterinarians, vaccinators, and laboratory personnel involved in the production of antigens, vaccines, and cultures of clinical specimens.

In serologic diagnosis of humans or animals, it is necessary to bear in mind that at the outset of the infection only IgM antibodies are produced; consequently, the agglutination test will provide the best standard for diagnosis, since ME will yield negative results. As the infection progresses, IgG antibodies resistant to the ME test will appear and will increase unless appropriate treatment is begun.

Diagnosis of infection caused by *B. melitensis*, *B. suis*, and *B. abortus* is carried out with a properly standardized antigen of *B. abortus* (Alton *et al.*, 1976). However, this antigen does not permit diagnosis of infection caused by *B. canis*, since this species of *Brucella* (as well as *B. ovis*) is found in a rugose (R) phase, lacking the lipopolysaccharidic surface that characterizes "classic brucellae" (for diagnosis of *B. canis* and *B. ovis*, see below).

In cattle, the diagnosis is based primarily on serology. A great many serologic tests are presently available, all of which are useful when applied with judgment. Both a serologic test reaction and the test's usefulness in each circumstance are a result of the sensitivity it shows to antibodies of different immunoglobulin types and of the seric concentration of each type of antibody (Chappel *et al.*, 1978). The most thoroughly studied immunoglobulins in bovine brucellosis are IgM and IgG. Although available tests are not qualitative enough to identify an individual immunoglobulin, they do indicate which one predominates. In the diagnosis of bovine brucellosis, the evolution of immunoglobulins during infection and vaccination is of special interest. In both cases, the IgMs appear first, followed by the IgGs. The difference is that in infected animals, the IgGs tend to increase and persist, while in calves vaccinated at between three and eight months, the IgGs tend to disappear about six months after vaccination. Based on this fact, complementary tests are used to distinguish infection from the agglutination titer, which may persist after vaccination with strain 19, and also from heterospecific reactions caused by bacteria that share surface antigens with the brucellae and that give rise to antibodies that, in general, are the IgM type.

According to their use in different countries, serologic tests may be classified as follows: (1) routine or operative, (2) complementary, (3) epidemiological surveil-

lance, and (4) screening tests. A single test might serve as operative, as diagnostically definitive, as a screen, or as complementary, depending on the program employing it.

Serum agglutination tests (tube and plate) have been and continue to be widely used. They contributed greatly to the reduction of infection rates in Europe, Australia, and the Americas. Nevertheless, when the proportion of infected herds and worldwide prevalence is reduced, their limitations become apparent in so-called "problem" herds and it becomes necessary to use other tests to help eradicate the infection. The tests are internationally standardized, easy to carry out, and allow the examination of a great many samples. In agglutination tests, the IgM reaction predominates. In animals classified as suspect or marginally positive, complementary tests are used to clarify their status. However, it is necessary to keep in mind that low agglutination titers could be due to recent infection and it is thus advisable to repeat the test.

The rose bengal test (with buffered antigen) is fast, easy, and allows processing of many samples per day. It is qualitative and classifies animals as positive or negative. In regions where incidence of infection is low or where systematic vaccination of calves is practiced, the rose bengal test gives many "false positives," and so is unspecific if used as the only and definitive test. In many countries, such as Great Britain and Australia, it is used as a preliminary or screening test. Animals showing a negative test result are so classified and those testing positive are subjected to other tests for confirmation. In regions of high incidence, results are very satisfactory. Rose bengal may also be used as a complementary test for those animals classified as suspect by agglutination. Many suspect sera test negative to rose bengal, and since this test is very sensitive (there are few "false negatives") and detects the infection early, there is little risk of missing infected animals.

The principal complementary tests are complement fixation, 2-mercaptoethanol, and rivanol. Other tests have been developed, such as indirect hemolysis, ELISA for different types of immunoglobulins, and radial immunodiffusion with a polysaccharide antigen. All these tests are used to distinguish antibodies caused by the infection from those left by vaccination or stimulated by heterospecific bacteria.

Both the direct and the competitive ELISA tests are appropriate for diagnosis of brucellosis in all species according to the consensus of groups of experts that have met several times in Geneva. WHO, with the collaboration of FAO, the International Organization of Epizootics, the International Atomic Energy Agency, and these organizations' reference laboratories, is coordinating a project to evaluate and standardize these assays as well as the antigens and other technical variables.

In Australia, the ELISA technique and the complement fixation test have been very useful in recent phases in the eradication of bovine brucellosis, when many "problem herds" occur with "latent carrier animals." In comparison with the CF test, ELISA revealed a significantly higher number of reactive animals in infected herds, both vaccinated (with strain 19) and unvaccinated, but gave negative results in herds free of brucellosis, whether vaccinated or not. The specificity of ELISA in the group of infected herds was less than that of CF, but sensitivity—which is what was needed—was greater (Cargill *et al.*, 1985). It costs less to eliminate some false positive animals in the final phase of eradication than to allow the infection to reassert itself and spread in the herd because one or more infected animals remained (Sutherland *et al.*, 1986). The competitive enzymatic immunoassay also lends itself to differentiating the reactions of animals vaccinated with strain 19 and animals naturally infected, using the O polysaccharide antigen (Nielsen *et al.*, 1989).

The complement fixation test is considered the most specific, but it is laborious, complicated, and involves many steps and variables. Moreover, it is not standardized internationally. Other, simpler tests can take its place, such as 2-mercaptoethanol and rivanol, which measure the IgG antibodies.

Animal health laboratories in the US and various laboratories in Latin America have successfully used the BAPA (buffered antigen plate agglutination) or BPA (buffered plate antigen) screening test, which is performed on a plate with a buffered antigen at pH 3.65 (Angus and Barton, 1984). BAPA greatly simplifies the work when numerous blood samples must be examined, because it eliminates the negative samples and many of the sera with nonspecific reactions. The test results classify the samples as negative (which are definitively discarded) and presumably positive; the latter are submitted to one or more definitive and/or complementary tests, such as tube agglutination, complement fixation, or 2-mercaptoethanol. This test was also evaluated in Canada (Stemshorn *et al.*, 1985) and Argentina (González Tomé *et al.*, 1989) with very favorable results.

Epidemiological surveillance of brucellosis is carried out separately on dairy and meat-producing herds, at strategic checkpoints and using different diagnostic tests. The principal objective is to identify infected herds and monitor healthy ones. For beef cattle, screening tests or other tests of presumed high sensitivity are used, such as BAPA, and the checkpoints for collecting samples are cattle markets and slaughterhouses. The sera that test positive are then subjected to standard tests and the animals are traced back to their points of origin. For dairy cattle, the milk-ring test is used. It is very simple and allows the examination of many herds in a short time. The composite samples are gathered from milk cans or tanks at collection points and dairy plants or on the dairy farm itself. If a positive sample is found, individual serologic examinations of the animals belonging to the source herd must then be carried out.

Bacteriologic examinations are of more limited use. The samples most often tested in this way are taken from fetuses, fetal membranes, vaginal secretions, milk, and semen. Infected cows may or may not abort, but a high percentage will eliminate brucellae from the genital tract beginning a few days before parturition and continuing some 30 days afterwards. It is estimated that 85% of recently infected cows and more than 15% of chronically infected cows eliminate brucellae during calving. Since elimination through milk may be constant or intermittent, milk can be an excellent material for the isolation of *Brucella* if examinations are repeated. Serologic testing of bulls should be done using blood serum and seminal fluid. Bacteriologic examination of semen should be repeated if results are negative, since brucellae may be shed intermittently.

In swine, serologic tests are not indicated for individual diagnosis but rather to reveal the presence of herd infection. Agglutination (tube or plate), complement fixation, buffered-acid antigen (rose bengal), or BAPA tests may be used. The latter is preferable because it is negative in herds having only low and nonspecific agglutination (tube or plate) titers. For a herd to be classified as positive with the agglutination test (tube or plate), there must be one or more animals with titers of 100 IU or more.

In goats, serologic tests are also applied on a flock basis and not on individual animals. In infected flocks, one or more individuals are found with titers of 100 IU or more; in such cases, titers of 50 IU should be adopted as indicative of infection. The

complement fixation test is considered superior to the agglutination test, especially in herds vaccinated with *B. melitensis* Rev. 1, where agglutinating antibodies persist for long periods. The 2-mercaptoethanol test has also given very good results in vaccinated flocks. The results from the buffered-acid antigen (rose bengal) test are promising, but experience with it is limited and definitive conclusions cannot be drawn at this time. The ELISA test is the most promising.

In diagnosing infections caused by *B. melitensis* in sheep, the Coombs' test (antiglobulin test) modified by Hajdu can reveal 70% of infected animals. The other tests (agglutination, complement fixation) give less satisfactory results. In using the agglutination and complement fixation tests, adoption of significant titer levels lower than those for other animal species is recommended. Counterimmunoelectrophoresis would detect antibodies against intracellular antigens that appear late in the serum but which remain a long time. Consequently, its use would be appropriate for sheep with chronic brucellosis that test negative by agglutination, rose bengal, and complement fixation (Trap and Gaumont, 1982). Experts agree that the diagnostic methods for brucellosis caused by *B. melitensis* in goats and sheep leave much to be desired and that more attention should be given to this problem given its public health importance.

In diagnosing ram epididymitis caused by *B. ovis*, antigen prepared with this agent must be used. The preferred tests are gel diffusion, complement fixation, and ELISA. A study conducted in Australia in flocks infected by *B. ovis* and flocks free of infection showed that this enzyme immunoassay detected more reactive animals and that the complement fixation test failed to detect some rams that excreted *B. ovis*. In infection-free flocks, both ELISA and CF produced false positives at a rate of 0.5% (Lee *et al.*, 1985). Bacteriologic examination of semen is an appropriate diagnostic method, but it should be kept in mind that the shedding of brucellae can be intermittent.

For dogs infected by *B. canis*, the surest diagnostic method is isolation of the etiologic agent from blood, vaginal discharges, milk, or semen, or from fetal tissue and placenta. Bacteremia can last from one to two years, but after the initial phase it may become intermittent; thus, a negative blood culture does not exclude the possibility of brucellosis.

The most common serologic tests are plate and tube agglutination using *B. canis* antigen, immunodiffusion in agar gel with antigens extracted from the cell wall, 2-mercaptoethanol plate agglutination, and the modified 2 ME tube agglutination test. Possibly the most specific test to date, but also the least sensitive, is the immunodiffusion test in agar gel that utilizes antigens extracted from the cytoplasm of *B. canis*. To a greater or lesser degree, all these tests give nonspecific reactions. Zoha and Carmichael (1982) showed that the immunodiffusion test using sonicated antigens (internal cellular antigens) is satisfactory shortly after the onset of bacteremia and can detect infected animals for up to six months after it disappears, i.e., when other tests give equivocal results. A new test has been developed that uses a nonmucoid (M–) variant of *B. canis* as the antigen in tube agglutination, after treating the sera with 2 ME. The test is more specific without reducing sensitivity (Carmichael and Joubert, 1987).

Control: The most rational approach for preventing human brucellosis is the control and elimination of the infection in animal reservoirs, as has been demonstrated

in various countries in Europe and the Americas. Some human populations may be protected by mandatory milk pasteurization. In many goat- and sheep-herding regions, pasteurization of milk is an unattainable goal for the time being. Prevention of the infection in occupational groups (cattlemen, abattoir workers, veterinarians, and others who come into contact with animals or their carcasses) is more difficult and should be based on health education, the use of protective clothing whenever possible, and medical supervision.

Protecting refrigerator plant and slaughterhouse workers against brucellosis is particularly important because they constitute the occupational group at highest risk. Protection is achieved by separating the slaughter area from other sections and controlling air circulation. In countries with eradication programs, slaughter of reactive animals is limited to one or more designated slaughterhouses (cold storage plants) with official veterinary inspection in each region. These animals are butchered at the end of the workday with special precautions and proper supervision to protect the workers. Employees should be instructed in personal hygiene and provided with disinfectants and protective clothing. A 5% solution of chloramine or an 8% to 10% solution of caustic soda should be used to disinfect installations after slaughter (Elberg, 1981). Instruments should be sterilized in an autoclave or boiled for 30 minutes in a 2% solution of caustic soda. Clothes may be disinfected with a 2% solution of chloramine or a 3% solution of carbolic acid soap followed by washing. Hands should be soaked for five minutes in a solution of 1% chloramine or 0.5% caustic soda, and then washed with soap and water.

The immunization of high-risk occupational groups is practiced in the former Soviet Union and China. In the former Soviet Union, good results have apparently been obtained with the use of a vaccine prepared from strain 19-BA of *B. abortus* (derived from strain 19 used for bovine brucellosis), applied by skin scarification. Annual revaccination is carried out for those individuals not reacting to serologic or allergenic tests. To avoid the discomfort caused by the vaccine in man, a vaccine was recently developed that consists of chemically defined fractions of the lipid-polysaccharide (LPS) component of the strain 19-BA (Drannovskaia, 1991). In China, an attenuated live vaccine made from *B. abortus* strain 104M is applied percutaneously. These vaccines are not used in other countries because of possible side effects. Promising trials have also been conducted in France with antigenic fractions of *Brucella*.

Vaccination is recommended for control of bovine brucellosis in enzootic areas with high prevalence rates. The vaccine of choice is *B. abortus* strain 19, confirmed by its worldwide use, the protection it gives for the useful lifetime of the animal, and its low cost. To avoid interference with diagnosis, it is recommended that vaccination be limited (by legislation) to young animals (calves of 3 to 8 months), as these animals rapidly lose the antibodies produced in response to the vaccine. It is estimated that 65% to 80% of vaccinated animals remain protected against the infection. The antiabortive effect of the vaccine is pronounced, thus reducing one of the principal sources of infection, the fetuses. In a systematic vaccination program, the best results are obtained with 70% to 90% annual coverage in calves of the proper age for vaccination. Male calves and females over 8 months of age should not be vaccinated. Where possible, the upper limit should be 6 months. Revaccination is not recommended. The main objective of systematic and mandatory vaccination of calves in a given area or country is to reduce the infection rate and obtain herds

resistant to brucellosis, so that eradication of the disease may then begin. It is estimated that 7 to 10 years of systematic vaccination are necessary to achieve this objective.

In regions or countries with a low prevalence of the disease, an eradication program can be carried out by repeated serologic diagnostic tests applied to the entire herd, and elimination of reactors until all foci of infection have disappeared. This procedure can be used alone (in countries with a low prevalence) or in combination with the vaccination of calves. Epidemiological surveillance and control of animal transport are very important in such programs. Countries that are close to eradication may suspend vaccination with strain 19 or any other vaccine.

Until a few years ago, the vaccination of adult cows with strain 19 was inadvisable because of the prolonged resistance of antibodies that could interfere with diagnosis. In the 1950s, several researchers proved that vaccination of adult animals with a smaller dose could impart an immunity comparable to that of a full dose, while at the same time agglutination titers stayed lower and disappeared faster. In 1975, Nicoletti (1976) began a series of studies in the US using a reduced dose in highly infected herds; he concluded that vaccination decreases the spread of the infection within the herd, that antibodies disappear approximately six months after vaccination, and that less than 1% of the females remained infected by the vaccine strain from three to six months after vaccination. Complementary tests were very useful in distinguishing between reactions due to infection and those due to vaccination. Other studies, done under both controlled and natural conditions, confirmed these findings (Nicoletti *et al.*, 1978; Alton *et al.*, 1980; Viana *et al.*, 1982; Alton *et al.*, 1983). Vaccination of adult females may be considered in herds suffering acute brucellosis characterized by abortions and rapidly spreading infections, as well as in large herds where chronic brucellosis has proven hard to eradicate. The recommended dose is one to three billion cells of strain 19 *Brucella* administered subcutaneously. Only animals testing negative should be vaccinated and they should be indelibly marked under government supervision. At the beginning of the operation, reactors should be eliminated immediately. Vaccinated animals should be examined serologically 6 months later, using tests such as rivanol, mercaptoethanol, and complement fixation, and those that have become infected should be slaughtered. Using periodic serologic examination, it is estimated that a problem herd can be free of infection in 18 to 24 months (Barton and Lomme, 1980).

The control of swine brucellosis consists of identifying and certifying brucellosis-free herds. If infection is diagnosed in an establishment where pigs are raised for market, it is advisable to send the entire herd to the abattoir and reestablish it with animals from a brucellosis-free herd. If the infected pigs are valuable for breeding or research, suckling pigs should be weaned at 4 weeks and raised in facilities separate from the main herd. Periodic serologic tests (such as rose bengal) are recommended to eliminate any reactor. Finally, when no brucellosis is found in the new herd and it is well established, the original herd should be sent to slaughter. There are no effective vaccines for swine.

Control of the infection caused by *B. melitensis* in goats and sheep is based mainly on vaccination. The preferred vaccine is *B. melitensis* Rev. 1, which is administered to 3- to 6-month-old females. Adult females can receive a smaller dose (20,000 times fewer bacterial cells than in the dose for young females) of the same vaccine (Alton *et al.*, 1972).

As goats are generally raised in marginal areas where socioeconomic conditions are very poor, it is difficult to carry out eradication programs. In these areas, reinfection occurs constantly, flocks are often nomadic, and animal-raising practices make sanitary control difficult. Another important factor is that diagnostic methods for small ruminants are deficient. Experience with Rev. 1 vaccine in Italy, Turkey, Iran, Mongolia, Peru, and the Caucasian Republics of the former Soviet Union has proven it to be an excellent means of control. In Mongolia, 6 million animals were vaccinated between 1974 and 1977; as a result, the prevalence of from 3 to 4 per 10,000 animals was reduced by half or more, as was the incidence of human cases. In Malta, after seven years of vaccination of small ruminants with Rev. 1, the number of human cases per year fell from 260 to 29. The same thing happened in Italy, although there are no reference data (Alton, 1987). However, the control procedure of diagnosing and sacrificing reactor animals has produced satisfactory results in areas of low prevalence.

Rev. 1 vaccine has some limitations, such as residual virulence, the possibility of abortions when pregnant females are vaccinated, and the limited stability of the vaccine, which necessitates constant monitoring. These disadvantages should not eliminate use of the vaccine as the basis for control of brucellosis in small ruminants, at least until there is a better vaccine. A Chinese strain of *B. suis* biovar 1, known as *B. suis* strain 2, is considered reliable. This strain was isolated from a swine fetus and its virulence was attenuated by continuous and repeated replications in culture media over years, reaching an attenuation that remains stable. Vaccine *B. suis* strain 2 has been used in China with very good results for more than 20 years, not only in small ruminants but in cattle and swine as well. Its use began in the semiarid regions of northern China, where vaccination operations were very difficult due to the lack of fetters and traps, and thus the vaccine was administered in the drinking water (Xin, 1986). Various research institutes have conducted tests on conjunctive, oral (with syringes of the type used to administer antiparasitic agents), and subcutaneous vaccines in small ruminants; it has generally been possible to confirm the results obtained in China. Elimination of the vaccine strain in milk or through the vagina has not been confirmed and studies continue on this vaccine.

Ram epididymitis can be successfully controlled by a combination of the following measures: elimination of rams with clinically recognizable lesions, elimination of clinically normal rams positive to the gel diffusion or the complement fixation test, and separation of young rams (those not yet used for breeding) from adult males. In some countries, such as New Zealand and the US, a bacterin prepared from *B. ovis* and adjuvants is used. Animals are vaccinated when weaned, revaccinated one or two months later and annually thereafter. This vaccine produces antibodies against *B. ovis* but not *B. abortus*. The *B. melitensis* Rev. 1 vaccine is effective against epididymitis, but also produces *B. abortus* antibodies, which could be confused with infection by *B. melitensis*. The *B. suis* strain 2 vaccine does not provide protection against ram epididymitis.

Brucellosis caused by *B. canis* in dog kennels can be controlled by repeated serologic tests and blood cultures, followed by elimination of reactor animals. No vaccines are available yet. Veterinary clinics should advise owners of the risk of keeping a dog with brucellosis and should recommend that the dog be put to sleep.

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CAMPYLOBACTERIOSIS

ICD-10 A04.5 campylobacter enteritis

The genus Campylobacter *(heretofore* Vibrio*) contains several species of importance for both public and animal health. The principal pathogenic species are* C. jejuni *and* C. fetus *subsp.* fetus *(previously subsp.* intestinalis*) and* C. fetus *subsp.* venerealis. *Occasionally* C. coli, C. laridis, *and* C. upsaliensis *cause enteritis in man and animals. These bacteria are gram-negative, microaerophilic, thermophilic, catalase positive (with the exception of* C. upsaliensis*), and have a curved or spiral shape.*

The importance of campylobacteriosis as a diarrheal disease became evident when better knowledge was gained about its requirements for culture and isolation, particularly oxygen pressure (strictly microaerophilic) and an optimum temperature of 42°C (thermophilic).

Increased medical interest since 1977 in enteritis caused by C. jejuni *and the enormous bibliography on this new zoonosis make it advisable to discuss this disease separately from those caused by* C. fetus *and its two subspecies. Furthermore, the disease caused by* C. jejuni *and those caused by* C. fetus *are clinically different.*

1. Enteritis caused by *Campylobacter jejuni*

Synonym: Vibrionic enteritis.

Etiology: *Campylobacter jejuni* and occasionally *C. coli*. Two principal schemes have been proposed for serotyping *C. jejuni*. The scheme proposed by Penner uses somatic antigens and includes 60 serotypes, which are identified using the passive hemagglutination method (Penner and Hennessy, 1980; McMyne *et al.*, 1982). The scheme proposed by Lior uses a flaggelar antigen and identifies 90 serotypes with the slide plate agglutination method (Lior, 1982). Patton *et al.* (1985) compare both schemes in 1,405 isolates of human, animal, and environmental origin, and find that

96.1% could be typed using the Penner system and 92.1% could be typed using the Lior system. They also conclude that these schemes complement each other and are useful for epidemiological research.

Geographic Distribution: Worldwide.

Occurrence in Man: At present, *C. jejuni* is considered to be one of the principal bacterial agents causing enteritis and diarrhea in man, particularly in developed countries. In these countries, the incidence is similar to that of enteritis caused by *Salmonella*. As culture media and isolation methods have been perfected, the number of recorded cases caused by *C. jejuni* has increased. In Great Britain, the 200 public health and hospital laboratories had been reporting isolations of salmonellas exceeding those of *Campylobacter*, but beginning in 1981, the proportions were reversed: 12,496 isolations of *Campylobacter* as opposed to 10,745 of *Salmonella* (Skirrow, 1982). According to Benenson (1990), campylobacteriosis causes 5% to 14% of diarrhea cases worldwide. Based on records from private medical practice, it has been estimated that 20% of office consultations for enteritis in Great Britain were associated with campylobacteriosis and that there are a projected 600,000 cases annually at the national level (Skirrow, 1982). It is harder to establish the incidence in developing countries; because of deficiencies in hygiene, *C. jejuni* is isolated from 5% to 17% of persons without diarrhea (Prescott and Munroe, 1982) and from 8% to 31% of persons with diarrhea. Thus, it is likely that *Campylobacter* is an important cause of infantile diarrhea in the Third World (Skirrow, 1982).

The illness affects all age groups. In developing countries, it particularly affects children under the age of 2 years; in developed countries, children and young adults become ill more frequently. Campylobacteriosis is also an important cause of "travellers' diarrhea" (Benenson, 1990). The disease is primarily sporadic, although there are also epidemic outbreaks. The largest known epidemics originated from common sources, such as unpasteurized milk or contaminated water from the municipal supply of two European cities. In countries with a temperate climate, the disease is most prevalent in the warm months.

In Great Britain, the US, Canada, and Switzerland, consumption of unpasteurized milk or products prepared with raw milk has caused campylobacteriosis outbreaks. The largest outbreak in Great Britain affected approximately 3,500 people (Jones *et al.*, 1981). Outbreaks may be due to milk contaminated by fecal matter or, less frequently, to milk from udders with mastitis caused by *C. jejuni*. Another outbreak affected more than 30 people in a small town in Great Britain. The ensuing investigation showed that the source of infection was two cows with mastitis caused by *C. jejuni* that contaminated the bulk milk of 40 cows (Hutchinson *et al.*, 1985). The same serotypes of *C. jejuni* were isolated from the cows, patients' feces, milk filters, and bulk milk.

It is estimated that *C. jejuni* causes more than 90% of human cases of the disease (Karmali and Skirrow, 1984) and only 10% in other species.

Occurrence in Animals: Domestic and wild mammals and birds constitute the large reservoir of *C. jejuni*, but it is difficult to implicate this agent as a cause of diarrheal disease because a high rate of infection is found in clinically healthy animals.

The Disease in Man: Enteritis caused by *C. jejuni* is an acute illness. In general, the incubation period is from two to five days. The principal symptoms are diarrhea,

fever, abdominal pain, vomiting (in one-third of the patients), and visible or occult blood (50% to 90% of patients). Fever is often accompanied by general malaise, headache, and muscle and joint pain. The feces are liquid and frequently contain mucus and blood. The course of the illness is usually benign, and the patient recovers spontaneously in a week to 10 days; acute symptoms often fade in two to three days. Symptoms may be more severe in some patients, similar to those of ulcerative colitis and salmonellosis, and may lead to suspicion of appendicitis and an exploratory laparatomy. In some cases, septicemia has been confirmed, either simultaneous to the diarrheic illness or afterward. Complications are rare and consist of meningitis and abortions.

Enteric campylobacteriosis is a self-limiting disease and does not usually require medication, except for electrolyte replacement. In cases that require medication, erythromycin is the antibiotic of choice.

The Disease in Animals: *C. jejuni* has been identified as an etiologic agent in several illnesses of domestic animals (Prescott and Munroe, 1982).

CATTLE: Enteritis caused by *C. jejuni* in calves is clinically similar to that in man. Calves suffer a moderate fever and diarrhea that may last as long as 14 days. It is also possible that this agent causes mastitis in cows, as demonstrated by the fact that experimental inoculation of the udder with a small number of bacteria causes acute mastitis (see outbreaks due to raw milk in the section on occurrence in man).

SHEEP: *C. jejuni* is a major cause of abortions in sheep. In the number of outbreaks, it is assigned a role similar to that of *C. fetus* subsp. *fetus* (*intestinalis*). Sheep abort toward the end of their pregnancy or give birth at term to either dead or weak lambs that may die within a few days.

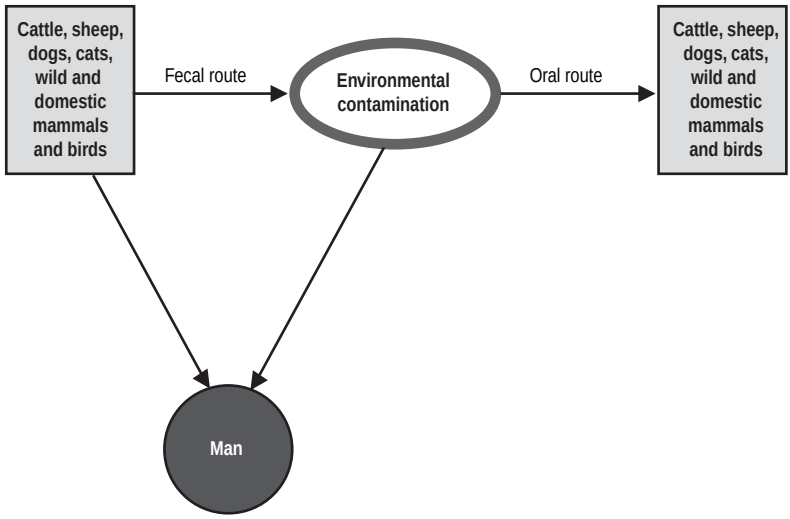
DOGS AND CATS: Puppies with diarrhea constitute a source of infection for their owners. Diarrhea is the predominant symptom and vomiting seems to be frequent. The disease is more frequent in puppies, but may occur in adult animals as well. Fox *et al.* (1984) described an outbreak caused by *C. jejuni* in nine of 10 young beagles that had diarrheal feces with traces of bile and occasionally blood. In England, a study of dogs treated at various veterinary clinics isolated *C. jejuni* from 59 (11.6%) of the 505 dogs with diarrhea and from only 2 (1.6%) of the 122 dogs without diarrhea. In another study (Fleming, 1983), 39 dogs had either persistent or intermittent chronic diarrhea.

Burnens and Nicolet (1992) cultured 241 samples of fecal matter from dogs and 156 from cats with diarrhea. The cultures were positive for *Campylobacter* spp. in 20% of the dog samples and in 13% of the cat samples. The frequency of *C. upsaliensis* among the positive cultures was approximately equal in dogs and cats. However, the authors present no conclusions regarding the pathogenic role of *C. upsaliensis* in dogs and cats because they did not examine animals without diarrhea.

OTHER MAMMALS: Enteritis caused by *C. jejuni* probably occurs in many other animal species. It has been described in monkeys and in one outbreak in young horses.

FOWL: Fowl are an important reservoir of *C. jejuni*. Although it was possible to cause diarrhea in 3-day-old chicks with orally administered *C. jejuni*, it is not known if the illness occurs naturally, since a high proportion of healthy birds harbor the bacteria in their intestines.

Figure 8. Campylobacteriosis (*Campylobacter jejuni*). Mode of transmission.



Source of Infection and Mode of Transmission (Figure 8): Mammals and birds, both domestic and wild, are the principal reservoir of *C. jejuni*. In studies by various authors (Skirrow, 1982; Prescott and Munroe, 1982), *C. jejuni* was found in the ceca of 100% of 600 turkeys and in the droppings of 38 out of 46 chickens and 83 out of 94 ducks that had large numbers of the bacteria in their intestines prior to slaughter. The organism has been found in several species of wild birds, for example, in 35% of migratory birds, 50% of urban pigeons, and 20% to 70% of seagulls. The agent has been isolated from the feces of 2.5% to 100% of healthy cows, from the gallbladder of 20 out of 186 sheep, from the feces of 0% to 30% of healthy dogs, and also from a wide variety of wild mammal species.

C. jejuni is commonly found in natural water sources, where it can survive for several weeks at low temperatures. However, it is interesting to note that it has always been found in the presence of fecal coliforms, and therefore the contamination presumably stems from animals (mammals and fowl) and, in some circumstances, from man. The source of infection is almost always food, although it is sometimes difficult to identify the immediate source. Given the common occurrence of *C. jejuni* and *C. coli* in the intestines of mammals and fowl *(C. jejuni* can survive for several weeks at 4°C on the moist surface of chickens), it can easily be assumed that contamination of bird and animal meat is a frequent occurrence. One study conducted by various laboratories in the US demonstrated that approximately 30% of the 300 chickens included in the sample had *C. jejuni* and that 5.1% of the 1,800 samples of red meat were contaminated. *C. coli* was isolated from pork and *C. jejuni* was isolated from other meats (Stern *et al*., 1985).

The infection in man may be caused by cross contamination in the kitchen of meats with *C. jejuni* and other foods that do not require cooking, or that are undercooked (Griffith and Park, 1990). Other sources of infection are unpasteurized milk and milk products, river water, and inadequately treated municipal water. In some cases, the infection is acquired directly from animals, especially from puppies and cats with diarrhea. The victims are almost always children who play with these animals and come in contact with the animal's feces.

In peripheral urban areas of Lima (Peru), Grados *et al.* (1988) studied 104 children under the age of 3 years who had diarrhea and compared them to the same number of children without gastrointestinal disorders (control group) in order to identify the various risk factors. The authors concluded that the presence of chickens and hens in the home environment constitutes an important risk factor. Children become infected by contact with the droppings of birds in the household environment. Another interesting fact is that slaughterhouse workers—particularly those who come into direct contact with animals and their by-products—have a much higher rate of positive reactions to *Campylobacter* spp. than the blood donors who served as controls (Mancinelli *et al.*, 1987).

Person-to-person transmission may occur, but is unusual. Among the few cases described was a nosocomial infection of children in Mexico (Flores-Salorio *et al.*, 1983). Untreated patients may eliminate *C. jejuni* for six weeks, and a few for a year or more. As in the case of other enteric infections, entry is through the digestive tract.

Diagnosis: Consists mainly of isolating the agent from the patient's feces. Diagnosis is made using selective media that are incubated in an atmosphere of 5% oxygen, 10% carbon dioxide, and 85% nitrogen, preferably at a temperature of 43°C. Serologic diagnosis may be done using direct immunofluorescence or other tests on paired sera.

In animals, because of the high rate of healthy carriers, isolation of the agent is inadequate proof that it is responsible for the illness, and it is advisable to confirm an increase in titers with serologic testing.

Control: According to present knowledge of the epidemiology of the illness, preventive measures can be only partial in scope. In a study of risk factors in Colorado (USA), where sporadic cases of infection were caused by *C. jejuni*, it was estimated that approximately one-third of the cases could have been prevented by such measures as avoiding the consumption of untreated water, unpasteurized milk, or undercooked chicken (Hopkins *et al.*, 1984). People in contact with dogs and cats with diarrhea should follow personal hygiene rules, such as thorough handwashing. Sick animals should not be in contact with children. The same recommendations on personal hygiene apply to homemakers. In the kitchen, care should be taken to separate raw animal products from other foods, particularly in the case of fowl. Control of the infection in animals is clearly desirable, but is not presently feasible, given the wide diffusion of the agent and its presence in wild animal reservoirs.

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2. Diseases caused by *Campylobacter fetus*

Synonyms: Vibriosis, vibrionic abortion, epizootic infertility, bovine genital vibriosis, epizootic ovine abortion.

Etiology: *Campylobacter* (*Vibrio*) *fetus* subsp. *fetus* (*intestinalis*) and *C. fetus* subsp. *venerealis*. *C. fetus* develops in such media as blood agar and *Brucella* agar; it is microaerophilic, but is unlike *C. jejuni* in that it grows at 25°C but not at 42°C.

Geographic Distribution: Worldwide.

Occurrence in Man: Uncommon. Up to 1981, the literature recorded at least 134 confirmed cases (Bokkenheuser and Sutter, 1981), most of them occurring in the US and the rest in various parts of the world. The incidence is believed to be much higher than that recorded.

Occurrence in Animals: The disease is common in cattle and sheep and occurs worldwide.

The Disease in Man: The strains isolated from man have characteristics similar to those of *C. fetus* subsp. *fetus* (*intestinalis*), which causes outbreaks of abortion among sheep and sporadic cases in cattle. Two cases caused by *C. fetus* subsp. *venerealis* have also been described (Veron and Chatelain, 1973). Campylobacteriosis is generally recognized when accompanied by predisposing debilitating factors, such as pregnancy, premature birth, chronic alcoholism, neoplasia, and cardiovascular disease. The majority of isolations are from pregnant women, premature babies, and men and women over 45 years of age. The proportion of cases is higher in men than in women.

Infection by *C. fetus* causes septicemia in man. In more than half of the cases, bacteremia is secondary and follows different localized infections. Between 17% and 43% of septicemic patients die (Morrison *et al.*, 1990). Most cultures have been obtained from the bloodstream during fever, but the etiologic agent has also been isolated from synovial and spinal fluid, and sometimes from the feces of patients with acute enteritis.

In pregnant women, the illness has been observed from the fifth month of pregnancy, accompanied by a sustained fever and often by diarrhea. Pregnancy may terminate in miscarriage, premature birth, or full-term birth. Premature infants and some full-term infants die from the infection, which presents symptoms of meningitis or meningoencephalitis. The syndrome may begin the day of birth with a slight fever, cough, and diarrhea; after two to seven days, the signs of meningitis appear. The case fatality rate is approximately 50%. Malnourished children, and at times apparently healthy ones, can develop bacteremia along with vomiting, anorexia, diarrhea, and fever. The patient usually recovers spontaneously or after antibiotic treatment. In adults, often those already weakened by other illness, the disease appears as a generalized infection with extremely variable symptomatology (Bokkenheuser and Sutter, 1981). *C. fetus* subsp. *fetus* is above all an opportunistic pathogen that gives rise to a systemic infection but rarely causes enteritis, in contrast to *C. jejuni*. Some cases of gastroenteritis caused by *C. fetus* subsp. *fetus* have been noted in men without a compromised immune system (Devlin and McIntyre, 1983; Harvey and Greenwood, 1983).

Gentamicin is the recommended antibiotic in the case of bacteremia and other clinical forms of nonenteric infection. Chloramphenicol is recommended when the central nervous system is involved. Prolonged antibiotic treatment is necessary to prevent relapses (Morrison *et al.*, 1990).

The Disease in Animals: In cattle and sheep, vibriosis is an important disease that causes considerable losses due to infertility and abortions.

CATTLE: In this species, the principal etiologic agent is *C. fetus* subsp. *venerealis* and, to a lesser degree, subsp. *fetus*. Genital vibriosis is a major cause of infertility, causing early embryonic death. The principal symptom is the repetition of estrus after service. During an outbreak, a high proportion of cows come into heat repeat-

edly for three to five months, but only 25% to 40% of them become pregnant after being bred twice. Of the cows or heifers that finally become pregnant, 5% to 10% abort five months into gestation. An undetermined proportion of females harbor *C. fetus* subsp. *venerealis* during the entire gestation period and become a source of infection for the bulls in the next breeding season. After the initial infection, cows acquire resistance to the disease and recover their normal fertility, i.e., the embryo develops normally. However, immunity to the infection is only partial and the animals may become reinfected even though the embryos continue to develop normally. Resistance decreases substantially after three to four years.

The infection is transmitted by natural breeding or artificial insemination. Bulls are the normal, though in most cases temporary, carriers of the infection. They play an important role in its transmission to females. The etiologic agent is carried in the preputial cavity. Bulls may become infected while servicing infected cows, as well as by contaminated instruments and equipment used in artificial insemination. The etiologic agent is sensitive to antibiotics that are added to the semen used in artificial insemination.

C. fetus subsp. *fetus* is responsible for sporadic abortions in cattle. Some females are carriers of the infection, house the infectious agent in the gallbladder, and eliminate it in fecal matter.

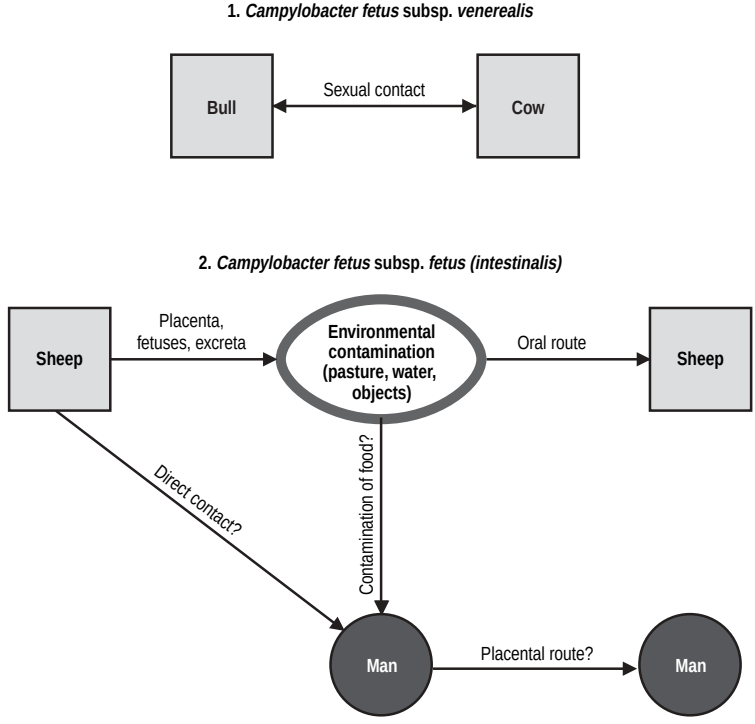
SHEEP: The principal agents of epizootic abortion in sheep are *C. fetus* subsp. *fetus* and *C. jejuni* and, to a lesser extent, *C. fetus* subsp. *venerealis*. The disease is characterized by fetal death and abortions in the final months of gestation, or by full-term birth of dead lambs or lambs that die shortly thereafter. The infection also gives rise to metritus and placentitis, both of which may result in septicemia and death of the ewe. Losses of 10% to 20% of the lambs and 5% of the ewes that abort are common. The rate of abortions varies and depends on the proportion of susceptible ewes. Infected animals acquire immunity. Ewes do not abort again for about three years. If the infection is recent in the flock, the abortion rate can be quite high, at times up to 70% of the pregnant ewes. The infection is transmitted orally; venereal transmission apparently plays no role.

Source of Infection and Mode of Transmission (Figure 9): The reservoir of *C. fetus* is animals, but it is not clear how man contracts the infection. It is presumed that he can become infected by direct contact with infected animals, by ingestion of contaminated food (unpasteurized milk, raw liver) or water, by transplacental transmission, exposure during birth, or sexual contact. It should be noted, however, that some patients have denied any contact with animals or even with products of animal origin. It is also suspected that the infection may be endogenous. The etiologic agent would be an oral commensal parasite that could penetrate the bloodstream during a dental extraction. Another hypothesis is that *C. fetus* could be harbored in the human intestine without becoming evident until the host loses resistance due to some illness. It would then invade through the mucosa, causing a generalized infection. In summary, the source and pathogenesis of *C. fetus* in man continue to be unknown (Morrison *et al.*, 1990).

The sources of infection in cattle are carrier bulls and also cows that remain infected from one parturition to the next. The mode of transmission is sexual contact.

For sheep, the source of infection is environmental contamination. The placentas of infected sheep that abort or even of those that give birth normally, as well as

Figure 9. Campylobacteriosis (*Campylobacter fetus*). Probable mode of transmission.



NOTE: It is not known how the disease is transmitted to humans; transmission is assumed to occur through direct contact, contamination of foods, or transplacental passage.

aborted fetuses and vaginal discharges, contain a large number of *Campylobacter*. A few infected ewes become carriers by harboring the infection in the gallbladder and shedding the agent in fecal matter. Contaminated grass, tools, and clothing are the vehicles of infection. Transmission is oral. Sexual transmission has not been demonstrated, but knowledge on this subject is inadequate.

Role of Animals in the Epidemiology of the Disease: Animals are the natural reservoir of *C. fetus*. The agent has been observed to lodge in the human gallbladder, but it is not known how often man may become a carrier and give rise to human foci of infection. It is probably an exceptional occurrence. The mechanism of transmission from animals to humans is unclear.

Diagnosis: So far, diagnosis of campylobacteriosis in man has been largely fortuitous, when *C. fetus* is discovered in hemocultures of patients in whom the etiology was not suspected. During the febrile period, repeated blood samples should be taken for culture. In cases of meningitis, cultures of cerebrospinal fluid should also

be made. For isolation from vaginal fluid, repeated cultures on antibiotic media are recommended.

In cattle, diagnosis of epizootic infertility is based on the history of the herd, on the culture of the preputial secretion and semen from bulls and of vaginal mucus from nonpregnant cows and heifers, and also on culture of fluid from the abomasum and from the liver of aborted fetuses. All samples should be cultured within six hours of collection. The highest rate of isolation of *C. fetus* from the cervicovaginal mucus is obtained in the two days immediately before or after estrus.

When the infection is suspected in a herd of beef cattle, bacteriologic examination of the cervicovaginal mucus of about 20 heifers that were bred but remained barren is recommended. Samples should be taken six months after the start of the breeding season.

A good diagnostic technique for herd infection, though not for individual infection, is the agglutination test using cervicovaginal mucus. Another test in use is indirect hemagglutination, also employing vaginal mucus. Immunofluorescence is nonspecific in cows, since *C. fetus* subsp. *venerealis* gives cross-reactions with *C. fetus* subsp. *fetus*.

Individual diagnosis is difficult in bulls. An isolation obtained from the preputial secretion is conclusive if the culture is positive but not if it is negative. It is accepted that before a bull is introduced into an artificial insemination center, he must pass four consecutive bacteriological tests at one-week intervals or four immunofluorescence tests. An excellent test is to have him service virgin heifers and subsequently culture their cervicovaginal mucus.

In sheep, diagnosis is carried out primarily by culture of fetal tissue, afterbirths, and vaginal fluid. Fluid from the abomasum and liver of the fetus is preferable for isolation.

Control: The few facts available at present on the epidemiology of the human infection are insufficient to determine control measures.

The best method for preventing epizootic infertility in cattle is to use semen from infection-free bulls in artificial insemination. In herds where this procedure is not practical, cows and heifers can be vaccinated annually some two or three months before breeding using commercial bacterins with an adjuvant. Several trials offer evidence that vaccination with bacterins can also eliminate the carrier state in bulls and cows. The curative properties of the vaccines provide a new perspective in control. Nevertheless, it must be borne in mind that while this method can reduce the infection in bulls under range conditions, vaccination of infected animals will not eliminate the infection from the herd. In one experiment (Vázquez *et al.*, 1983), *C. fetus* subsp. *venerealis* was isolated from 2 out of 10 artificially infected bulls five weeks after administration of the recommended two doses one month apart.

In sheep, good control can be obtained based on the vaccination of females with both monovalent (with the subsp. *fetus*) and bivalent (*fetus* and *venerealis*) bacterins with adjuvants, although the combined product is preferable. In flocks where adult females have acquired natural immunity, good results have been obtained by vaccinating only the yearly replacement ewes. Proper sanitary management is important, especially such measures as immediate removal of fetuses and afterbirths, isolation of sheep that have aborted, and protection of water from contamination.

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CAT-SCRATCH DISEASE

ICD-10 A28.1

Synonyms: Cat-scratch fever, benign inoculation lymphoreticulosis, cat-scratch syndrome.

Etiology: For many years, microbiologists were unable to identify the etiologic agent. Various microbes considered the etiologic agent at one time or another were isolated; these included viruses, chlamydiae, and various types of bacteria. In 1983, Wear *et al.* conducted a histopathologic examination of the lymph nodes of 39 patients and demonstrated in 34 of them the presence of small, gram-negative, pleomorphic bacilli located in capillary walls or near areas of follicular hyperplasia and inside microabscesses. The observed bacilli were intracellular in the affected areas; they increased in number as lesions developed and diminished as they disappeared. The sera of three convalescent patients and human anti-immunoglobulin conjugated with peroxidase resulted in a precipitate with bacilli from the histological sections of different patients, demonstrating that they were serologically related (Wear *et al*., 1983). This finding was later confirmed by other researchers during the period 1984–1986 in skin lesions, lymph nodes, and conjunctiva.

Researchers managed to culture and isolate the bacillus in a biphasic medium of brain-heart infusion broth, as well as in tissue cultures (English *et al.*, 1988; Birkness *et al.*, 1992). It is a bacillus that is difficult to isolate and its dimensions are at the light microscope's limit of resolution. A polar flagellum could be seen in electron microscope images. Depending on the temperature at which cultures are incubated, vegetative forms (at 32°C) or forms with defective walls (at 37°C) are seen. There are more vegetative bacilli in lesions of the skin and conjunctiva (at 32°C), and fewer in lymph node lesions (37°C). This would also explain why cat-scratch disease (CSD) could only be reproduced in armadillos and not in guinea pigs and other common laboratory animals.

This bacillus, for which the name *Afipia felis* was suggested (Birkness *et al.*, 1992), satisfies Koch's postulates for being the etiologic agent of CSD, according to English *et al.* (1988). Birkness *et al.* were very cautious about considering *A. felis* the etiologic agent of CSD. This caution appears to be well-founded, as a microor-

ganism belonging to the rickettsiae, *Bartonella* (formerly *Rochalimaea*) *henselae*, was recently detected, which could be the agent responsible for most cases of cat-scratch disease and which also causes other diseases in man (see Infections caused by *Rochalimaea henselae*, in Volume 2: Chlamydioses, Rickettsioses, and Viroses).

Geographic Distribution: Worldwide (Benenson, 1990). It occurs sporadically. According to Heroman and McCurley (1982), more than 2,000 cases occur each year. Approximately 75% of the cases occurred in children. Small epidemic outbreaks and familial clustering have been reported in several countries. When an outbreak occurs in a family, there are usually several familial contacts in whom intracutaneous tests will be positive to the Hanger-Rose antigen. It is possible, but questionable, that several endemic areas exist around Toronto (Canada), New York City (USA), and Alfortville (France). Positive intracutaneous tests have been obtained in 10% of the population living in the vicinity of Alfortville, a result that is difficult to interpret.

The Disease in Man: Seven to twenty days or more can elapse between the cat scratch or bite (or other lesion caused by some inanimate object) and the appearance of symptoms. The disease is characterized by a regional lymphadenopathy without lymphangitis. In about 50% of the cases, primary lesions are seen at the point of inoculation. These consist of partially healed ulcers surrounded by an erythematous area, or of erythematous papules, pustules, or vesicles. Lymphadenitis is generally unilateral and commonly appears in the epitrochlear, axillary, or cervical lymph nodes, or in the femoral and inguinal lymph glands. Swelling in the lymph glands, which is generally painful and suppurates in about 25% of patients, persists for periods ranging from a few weeks to a few months. A high proportion of patients show signs of systemic infection, which consist of a low, short-lived fever and, less frequently, chills, anorexia, malaise, generalized pain, vomiting, and stomach cramps. Morbilliform cutaneous eruptions sometimes occur.

In general, the disease is benign and heals spontaneously without sequelae. Complications have been observed in a small proportion of the patients. The most common is Parinaud's oculoglandular syndrome; encephalitis, osteolytic lesions, and thrombocytopenic purpura are less frequent. The lymph gland lesions are not pathognomonic, but they follow a certain pattern, which helps in diagnosis. Histopathologic studies have shown that alterations begin with hyperplasia of the reticular cells, followed by an inflammatory granulomatous lesion. The center of the granuloma degenerates and becomes a homogenous eosinophilic mass, in which abscesses and microabscesses later appear.

In a study of 76 cases with neurological complications (51 with encephalopathy and 15 with disorders of the cranial or peripheral nerves), 50% of the patients had a fever, but only 26% had temperatures above 30°C. Forty-six percent of the patients had convulsions and 40% displayed aggressive behavior. Lethargy, with or without coma, was accompanied by various neurological symptoms. Of the other 15 patients without encephalopathy, 10 had neuroretinitis, two children had facial paresis, and three women had peripheral neuritis. Seventy-eight percent of the patients recovered without sequelae within a period of 1 to 12 weeks and the rest recovered within a year. Treatment consisted of controlling the convulsions and support measures. Commonly used antibiotics were apparently ineffective (Carithers and Margileth, 1991). Infection of the viscera is rare, but has been reported as well (Delahoussaye and Osborne, 1990).

Most cases have occurred in children, who have more contact with cats.

In temperate climates, the disease tends to be seasonal, with most cases occurring in fall and winter. In hot climates, there are no seasonal differences.

Source of Infection and Mode of Transmission: The most salient fact in the epidemiology of this disease is its causal relation with a cat scratch. It is estimated that about 65% of patients were scratched or bitten by cats and that 90% of the cases had some contact with these animals. Nevertheless, cases have been observed in which the skin lesion was inflicted by such inanimate objects as splinters, thorns, or pins.

Cats undoubtedly play an important role in the epidemiology, but there is doubt about whether it is as host for the etiologic agent or simply as a mechanical vector. Another possibility is that the etiologic agent is part of the normal flora of the cat's mouth and is transferred to the nails when the cat grooms itself (Hainer, 1987). Several observations—among them the fact that some cases were caused by inanimate agents—suggest that cats could be mechanical transmitters. Cats implicated in human cases were healthy animals, almost always young, that did not react to the Hanger-Rose intradermal test. It is also interesting to note that cats inoculated with material from the lymph nodes of human patients did not become ill. In summary, it has not yet been possible to show that cats are infected with the disease or are carriers of its causal agent, despite the many attempts made. According to Margileth (1987), cats are only able to transmit the infection for a short time (two to three weeks). CSD is usually transmitted from cats to man through a scratch and, less frequently, through a bite or licking. In Parinaud's oculoglandular syndrome, the point of entry for the agent is the conjunctiva or eyelids when a person rubs his or her eyes after picking up a cat (August, 1988).

Diagnosis: CSD can be clinically confused with other diseases that cause regional lymphadenopathies, such as tularemia, brucellosis, tuberculosis, pasteurellosis, infectious mononucleosis, Hodgkin's disease, venereal lymphogranuloma, lymphosarcoma, and lymphoma. All these diseases must be excluded before considering a diagnosis of CSD. The symptoms described above, a history of a skin lesion caused by a cat scratch or bite, the histopathology of biopsy material taken from the affected lymph node, and the Hanger-Rose intradermal test constitute the basis for diagnosis. The Hanger-Rose antigen is prepared by suspending pus taken from an abscessed lymph node in a 1:5 saline solution and heating it for 10 hours at 60°C. The antigen is very crude and difficult to standardize. The test is carried out by intradermal inoculation with 0.1 ml of the antigen. The reaction may be read in 48 hours. Edema measuring 0.5 cm and erythema of 1 cm are considered a positive reaction. The test is very useful, since 90% of 485 clinically diagnosed cases gave positive results, while only 4.1% out of 591 controls tested positive.

There is a danger of transmitting viral hepatitis with this antigen; therefore, the preparation should be heat-treated for a lengthy period, as indicated above. It may be very useful to demonstrate the presence of the putative etiologic agent, *A. felis*, using Warthin-Starry stain on histological sections from the skin or lymph nodes.

Control: Prevention is limited to avoiding cat scratches and bites. Cutting the cat's nails, washing and disinfecting any scratch or bite, and washing one's hands after petting or handling a cat are also recommended (August, 1988).

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CLOSTRIDIAL FOOD POISONING

ICD-10 A05.2 foodborne *Clostridium perfringens* [*Clostridium welchii*] intoxication

Synonyms: Clostridial gastroenteritis, clostridial toxicosis.

Etiology: *Clostridium perfringens* (*C. welchii*) is an anaerobic, gram-positive, sporogenic, nonmotile, encapsulated bacillus that produces extracellular toxins. The optimum temperature for its growth is between 41°C and 45°C. At these temperatures, *C. perfringens* reproduces at what is considered record speed for most bacteria. This growth potential is very important in food protection. A temperature of 60°C is lethal for the vegetative form of *C. perfringens* in culture media. It is more resistant to heat when found in foods (Labbe, 1989). Five different toxigenic types are known, designated by the letters A through E; these produce four principal toxins. The vegetative forms produce large quantities of enterotoxins during sporulation in the intestine. The optimum temperature for sporulation is between 35°C and 40°C.

Geographic Distribution: *C. perfringens* type A is ubiquitous in the soil and in the intestinal tract of humans and animals worldwide. The other types are found only in the intestinal tract of animals. Types B and E have a marked regional distribution.

Occurrence in Man: Outbreaks of food poisoning due to *C. perfringens* type A probably occur the world over, but most of the information comes from developed countries.

In Great Britain, where food poisoning is a notifiable disease, clostridial poisoning is estimated to cause 30% of all cases, as well as many general and familial outbreaks; an average of 37 people are affected per outbreak.

In the United States, during the period 1976–1980, 62 outbreaks affecting 6,093 persons were reported, representing 7.4% of all outbreaks of food toxicoses with known etiology and 14.8% of the total number of known cases in the country over the same period. The median number of cases per outbreak was 23.5, but six outbreaks affected more than 200 persons (Shandera *et al.*, 1983).

Even in developed countries, cases are greatly underreported, because the disease is mild and usually lasts no more than 24 hours. Moreover, laboratory diagnosis cannot always be performed, as it depends on obtaining food and patient stool samples that are not always available.

Outbreaks affecting large numbers of people are usually reported. These are caused by meals prepared in restaurants or institutions. An outbreak occurred in Argentina at the farewell ceremony for 60 participants in an international course. The food served included meat pies, canapés, and sweet cakes provided by a restaurant. Of the 41 people who were still in the country during the epidemiological investigation, 56% reported having developed symptoms typical of gastroenteritis. The meat pies were considered the source of the poisoning (Michanie *et al.*, 1993).

In New Guinea, necrotic enteritis in man caused by *C. perfringens* type C has been confirmed.

Occurrence in Animals: In domesticated ruminants, several types of exterotoxemias due to *C. perfringens* types B, C, D, and E are known. Enterotoxemia results

from the absorption into the bloodstream of toxins produced in the intestine by the various types of *C. perfringens* that form part of the normal intestinal flora.

The Disease in Man: The disease is contracted upon ingestion of foods (especially red meat and fowl) in which *C. perfringens* type A has multiplied. It is now known that illness is caused by thermoresistant strains, which can survive at 100°C for more than an hour, as well as by thermolabile and hemolytic strains, which are inactivated after approximately 10 minutes at 100°C.

The incubation period is from 6 to 24 hours after ingestion, but has been as short as two hours in a few people, which indicates that the food ingested contained preformed toxin. The disease begins suddenly, causing abdominal cramps and diarrhea, but usually not vomiting or fever. It lasts a day or less and its course is benign, except in debilitated persons, in whom it may prove fatal. Food poisoning caused by *C. perfringens* type A does not usually require medical treatment.

In recent years, an intestinal infection with diarrhea not associated with food consumption has been described. The disease is due to an infection caused by colonization of *C. perfringens* in the intestine and the production of enterotoxin. Its clinical picture is very different from that of clostridial food poisoning and more closely resembles an infection caused by *Salmonella* or *Campylobacter*. In England, a series of cases was described involving 50 elderly patients (ages 76 to 96) who were hospitalized with diarrhea not associated with food consumption. The diarrhea lasted for an average of 11 days, but lasted for a shorter period in two-thirds of the patients. Sixteen of 46 patients had bloody stools (Larson and Borriello, 1988).

Necrotic enteritis produced by the ingestion of food contaminated with *C. perfringens* type C is characterized by a regional gangrene in the small intestine, especially the jejunum.

A rare type of necrotizing enteritis caused by *C. perfringens* type A was described in the Netherlands in a 17-year-old girl. The patient recovered after resection of three meters of her intestine and intravenous treatment with gentamicin, cefotaxime, and metronidazole for seven days. Counterimmunoelectrophoresis of blood samples indicated the presence of antibodies for the alpha toxin that is predominant in type A. A similar illness appeared in Germany and Norway after the Second World War. Currently, necrotic enteritis is rare in the Western world, though some cases among adolescents and the elderly have been described (Van Kessel *et al.*, 1985).

On rare occasions, gastroenteritis due to *C. perfringens* type D has been confirmed in man. This type causes enterotoxemia in sheep and goats.

The Disease in Animals: *C. perfringens* type A is part of the normal flora of the intestine, where it does not usually produce its characteristic alpha toxin. Few cases of illness caused by type A have been confirmed in cattle. In California and Oregon (USA), a disease produced by type A in nursing lambs ("yellow lamb disease") has been described. The disease occurs in spring, when there is a large population of nursing animals. The lambs suffer depression, anemia, jaundice, and hemoglobinuria. They die 6 to 12 hours after the onset of clinical symptoms (Gillespie and Timoney, 1981).

Type B is the etiologic agent of "lamb dysentery," which occurs in Great Britain, the Middle East, and South Africa. It usually attacks lambs less than 2 weeks old. It is characterized by hemorrhagic enteritis, and is frequently accompanied by ulceration of the mucosa. It also affects calves and colts.

Type C causes hemorrhagic enterotoxemia ("struck") in adult sheep in Great Britain, as well as necrotic enteritis in calves, lambs, suckling pigs, and fowl in many parts of the world (Timoney *et al.*, 1988).

Type D is the causal agent of enterotoxemia in sheep. It is distributed worldwide and attacks animals of all ages. The disease is associated with abundant consumption of food, whether milk, pasture, or grains. Outbreaks have also been described in goats and, more rarely, in cattle.

Type E causes dysentery or enterotoxemia in calves and lambs, and has been confirmed in the US, England, and Australia (Timoney *et al.*, 1988).

Source of Infection and Mode of Transmission: The natural reservoir of *C. perfringens* type A is the soil and the intestine of man and animals. Some studies (Torres-Anjel *et al.*, 1977) have shown that man harbors higher numbers of *C. perfringens* than fowl or cattle and that some people excrete great quantities of these bacteria, making man the most important reservoir of clostridial food poisoning. The amount of *C. perfringens* type A in the intestine varies with the animal species and location. *C. perfringens* is found in large numbers in the small intestine of pigs, in small amounts in sheep, goats, and cattle, and is practically nonexistent in horses (Smith, 1965).

Type A enterotoxemia is caused primarily by the alpha toxin, which forms in the intestine and is released during sporulation, for which the small intestine is a favorable environment. The source of poisoning for man is food contaminated by spores that survive cooking. Heat (heat shock) activates the spores, which then germinate. The vegetative forms multiply rapidly if the prepared food is left at room temperature, and can reach very high concentrations if the temperature is high for a sufficient amount of time (see the section on etiology). The vegetative forms carried to the intestine by the food sporulate, releasing the enterotoxin in the process. The food vehicle is almost always red meat or fowl, since they provide *C. perfringens* with the amino acids and vitamins it needs. Less frequently, other foods, such as pigeon peas, beans, mashed potatoes, cheeses, seafood, potato salad, noodles, and olives have given rise to the disease (Craven, 1980). Immersing meat in broth or cooking it in large pieces creates anaerobic conditions that favor the multiplication of the bacteria during cooling or storage. The foods that cause poisoning are usually prepared in large quantities by restaurants or dining halls and are served later that day or the next. The spores of some strains of *C. perfringens* can be destroyed by adequate cooking, but other spores are heat-resistant. Reheating food before serving it can stimulate the multiplication of bacteria if the heating temperature is not high enough. It is now known that high concentrations of the vegetative form of *C. perfringens* in food cannot be destroyed by stomach acid, and thus pass into the intestine. The enterotoxin synthesized in the intestine when the bacteria sporulate is resistant to intestinal enzymes, has a cytotoxic effect on the intestinal epithelium, affects the electrolyte transport system, and thus causes diarrhea (Narayan, 1982).

It should be borne in mind that not all strains of *C. perfringens* are toxigenic. One study of strains implicated in food poisonings found that 86% were toxigenic, while another study found that 2 strains out of 174 isolated from other sources produced the enterotoxin (Narayan, 1982).

In lamb dysentery caused by *C. perfringens* type B, the animals are infected during the first days of life, apparently from the mother or the environment. Young

lambs that receive a lot of milk are particularly likely to fall ill. The bacteria multiply and produce beta toxin when they sporulate (Timoney *et al.*, 1988).

In hemorrhagic enteritis or "struck" caused by *C. perfringens* type C in adult sheep in England, the agent is found in the soil of areas of Romney Marsh and it is possible that most of the sheep in the region are infected. Beta toxin predominates. The soil and the intestinal tract of healthy sheep are the reservoir for type D, which is the agent of enterotoxemia in sheep. Epsilon toxin is the most important (Timoney *et al.*, 1988).

The intestines of 75 animals with diarrhea of unknown origin were examined postmortem to detect the presence of *C. perfringens* enterotoxins. Positive results were found in 8 of 37 swine, 4 of 10 sheep, 1 of 3 goats, 1 of 16 cattle, and none of 9 horses (Van Baelen and Devriese, 1987).

In animals, *C. perfringens* seems to multiply primarily in the intestine, where it sporulates and produces toxins. The types of *C. perfringens* (B, C, D, E) that produce enterotoxemia in animals multiply rapidly in the intestine and produce toxins when animals are suddenly released to rich pastures, are given too much fodder, or consume large quantities of milk.

Role of Animals in the Epidemiology of the Disease: Human food poisoning is caused by foods contaminated by *C. perfringens* type A, usually foods consisting mainly of red meat or fowl. The animals themselves do not play a direct role in the epidemiology, since the etiologic agent is ubiquitous and can be found in the soil or in dust. Foods of animal origin are important as substrates for the multiplication of the bacteria and as vehicles for the disease. The soil and the intestines of humans and animals are the reservoir of the etiologic agent. *C. perfringens* type A is found in the muscles and organs of animals a few hours after slaughter, unless they are rapidly refrigerated.

Heat-resistant strains of *C. perfringens* may be found in the mesenteric lymph nodes of some animals after slaughter. Strains are isolated at a lower rate in animals allowed to rest 24 to 48 hours before butchering.

Diagnosis: The incubation period and clinical picture make it possible to distinguish clostridial food poisoning, which is afebrile, from salmonellosis, shigellosis, or colibacillosis, which produce fever. Staphylococcal intoxication usually results in vomiting, while this symptom is rare with clostridial poisoning. Laboratory confirmation is based on the *C. perfringens* count in the implicated food and in the patient's stool (within 48 hours of onset of illness). The existence of 10^5 cells per gram of food and 10^6 per gram of fecal material is considered significant. Serotyping of strains from food and feces with a battery of 70 sera has provided good results in epidemiological research in Great Britain, but not in the United States, where only 40% of the strains received by the Centers for Disease Control and Prevention could be typed. There is no proof that only certain serotypes are related to the disease (Shandera, 1983).

Laboratory diagnosis of animal enterotoxemias is performed by mouse inoculation to demonstrate the presence of specific toxins. Some mice are inoculated only with intestinal contents and others are inoculated with both intestinal contents and antitoxin. Tests to directly detect the toxin can also be performed and are currently preferred. These include reverse passive latex agglutination, enzyme immunoassay, or culturing of Vero cells with neutralizing antibodies to inhibit the cytopathic effects (Bartlett, 1990).

Control: In man, the control measures are as follows. Meat dishes should be served hot and as soon as possible after cooking. If food must be kept for a while before eating, it should be rapidly refrigerated. If possible, meat should be cut into small pieces for cooking. Broth should be separated from the meat. The use of pressure cookers is a good preventive measure. If necessary, food should be reheated at a temperature high enough to destroy the agent's vegetative cells.

Educating those who prepare meals in restaurants or at home is very important, since it is impossible to avoid the presence of *C. perfringens* in red meats and raw chicken (Michanie *et al.*, 1993).

In animals, enterotoxemia control consists of good herd management, avoidance of a sudden change from poor to rich pasture, and active immunization with specific toxoids. Two doses of toxoid a month apart, followed by a booster at six months (type D) or a year (type C), are recommended.

To protect lambs, ewes should be vaccinated with two doses, with the second dose administered two weeks before lambing. To prevent lamb dysentery (type B), ewes can be vaccinated with the specific toxoid or lambs can be passively immunized with antiserum at birth. In *C. perfringens* types B and C, the beta toxin predominates, and therefore a toxoid or antiserum from one type will give cross-immunity.

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CLOSTRIDIAL WOUND INFECTIONS

ICD-10 A48.0 gas gangrene

Synonyms: Gas gangrene, clostridial myonecrosis, histotoxic infection, anaerobic cellulitis; malignant edema (in animals).

Etiology: Wound infection is characterized by mixed bacterial flora. The most important species are *Clostridium perfringens* (*welchii*), *C. novyi*, *C. septicum*, *C. sordelli*, *C. histolyticum*, and *C. fallax*. Like all clostridia, these bacteria are gram-positive, anaerobic, sporogenic bacilli. These species produce potent exotoxins that destroy tissue. In human gas gangrene, the most important etiologic agent is *C. perfringens*, toxigenic type A. Infection by *C. septicum* predominates in animals.

Geographic Distribution: Worldwide.

Occurrence in Man: Gas gangrene used to be more prevalent in wartime than in peacetime. It has been estimated that during World War I, 100,000 German soldiers died from this infection. However, its incidence has decreased enormously during more recent wars. During the eight years of the Vietnam War, there were only 22 cases of gas gangrene out of 139,000 wounds, while in Miami (USA), there were 27 cases in civilian trauma patients over a 10-year period (Finegold, 1977). The disease is relatively rare and occurs mainly in traffic- and occupational accident victims. However, in natural disasters or other emergencies, it constitutes a serious problem. Gas gangrene also occurs after surgery, especially in older patients who have had a leg amputated. It may also develop in patients receiving intramuscular injections, especially of medications suspended in an oil base. Gas gangrene can occur in soft tissue lesions in patients with vascular insufficiency, such as diabetics (Bartlett, 1990).

Occurrence in Animals: The frequency of occurrence in animals is not known.

The Disease in Man: Pathogenic species of *Clostridium* may be found as simple contaminants in any type of traumatic lesion. When infection occurs, the microorganisms multiply and produce gas in the tissues. Gas gangrene is an acute and serious condition that produces myositis as its principal lesion. The incubation period lasts from six hours to three days after injury. The first symptoms are increasing pain around the injured area, tachycardia, and decreased blood pressure, followed by fever, edematization, and a reddish serous exudate from the wound. The skin becomes taut, discolored, and covered with vesicles. Crepitation is felt upon palpation. Stupor, delirium, and coma develop in the final stages of the disease. The infection may also begin in the uterus following an abortion or difficult labor. These cases show septicemia, massive hemolysis, and acute nephrosis, with shock and anuria.

C. perfringens type A, alone or in combination with other pathogens, caused 60% to 80% of gas gangrene cases in soldiers during the two world wars.

Treatment consists primarily of debridement with extensive removal of the affected muscle. Amputation of the limb affected by gas gangrene should be considered. Penicillin G is generally the preferred antibacterial. However, better results have been obtained with clindamycin, metronidazole, rifampicin, and tetracycline (Bartlett, 1990). Mortality is still very high.

The Disease in Animals: *C. septicum* is the principal agent of clostridial wound infection, known as "malignant edema." *C. septicum* produces four toxins that cause tissue damage. The incubation period lasts from a few hours to several days. This disease is characterized by an extensive hemorrhagic edema of the subcutaneous tissue and intermuscular connective tissue. The muscle tissue turns dark red; little or no gas is present. The infected animal exhibits fever, intoxication, and lameness. Swellings are soft and palpation leaves depressions. The course of the disease is rapid and the animal can die a few days after symptoms appear. Cattle are the most affected species, but sheep, horses, and swine are also susceptible. The infection is rare in fowl.

C. perfringens type A is sometimes responsible for infection of traumatic wounds in calves, lambs, and goats. As in man, the infection gives rise to gas gangrene. Edema with a large amount of gas develops around the injury site, spreads rapidly, and causes death in a short time.

In animals, as in man, other clostridia (e.g., *C. novyi*, *C. sordelli*, and *C. histolyticum*) can cause wound infection and the wound's bacterial flora may be mixed.

Treatment with high doses of penicillin or broad-spectrum antibiotics may yield results if administered at the onset of disease.

Source of Infection and Mode of Transmission: Clostridia are widely distributed in nature, in the soil, and in the intestinal tract of man and most animals. The sources of infection for man and animals are the soil and fecal matter. Transmission is effected through traumatic wounds or surgical incisions. Gas gangrene can also occur without any wound or trauma (endogenous or spontaneous gas gangrene) in patients weakened by malignant disease and those with ulcerative lesions in the gastrointestinal or urogenital tract or in the bile ducts (Finegold, 1977). In animals, the infection may originate in minor wounds, such as those produced by castration, tail docking, and shearing.

Role of Animals in the Epidemiology of the Disease: Wound clostridiosis is a disease common to man and animals, not a zoonosis.

Diagnosis: Diagnosis is based primarily on clinical manifestations, such as the color around the lesion or wound, swelling, toxemia, and muscle tissue destruction. The presence of gas is not always indicative of clostridial infection. A smear of exudate from the wound or a gram-stained muscle tissue sample may be helpful in diagnosis if numerous large gram-positive bacilli are found. The culture of anaerobic bacilli from human cases is generally of little value because of the time required and the urgency of diagnosis. Moreover, isolation of a potentially pathogenic anaerobe from a wound may only indicate contamination and not necessarily active infection (penetration and multiplication in the human or animal organism). In animals, culture can be important in distinguishing infection caused by *C. chauvoei* (symptomatic anthrax, blackleg, or emphysematous gangrene) from infections caused by *C. septicum*. The latter bacterium rapidly invades the animal's body after death; thus, the material used for examination should be taken before or very shortly after death.

The fluorescent antibody technique permits identification of the pathogenic clostridia in a few hours and can be very useful in diagnosis.

Control: Prevention of the infection consists of prompt treatment of wounds and removal of foreign bodies and necrotic tissue. Special care must be taken to ensure that tourniquets, bandages, and casts do not interfere with circulation and thus create conditions favorable to the multiplication of anaerobic bacteria by reducing local oxidation-reduction potential.

Combined vaccines of *C. chauvoei* and *C. septicum* are used for active immunization of calves and lambs. Vaccination with bacterins or alpha toxoid must be carried out prior to castration, tail docking, shearing, or removal of horns. Calves can be vaccinated at 2 months of age.

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COLIBACILLOSIS

ICD-10 A04.0 enteropathogenic *Escherichia coli* infection;
A04.1 enterotoxigenic *Escherichia coli* infection;
A04.2 enteroinvasive *Escherichia coli* infection;
A04.3 enterohemorrhagic *Escherichia coli* infection

Synonyms: Colibacteriosis, colitoxemia, enteropathogenic diarrhea.

Etiology and Physiopathogenesis: *Escherichia coli* belongs to the family *Enterobacteriaceae*. *E. coli* is a normal component of the flora in the large intestine of warm-blooded animals, including man. It is a gram-negative, motile or non-motile, facultatively anaerobic bacillus.

It is classified into different serotypes according to the scheme originally developed by Kauffmann, which is based primarily on the somatic O antigens (polysaccharide and thermostable) that differentiate *E. coli* into more than 170 serogroups. The flagellar H antigen, which is thermolabile and proteinic, distinguishes the serotypes (56 to date) of each serogroup. The K (capsular) and F (fimbrial) antigens are also important (Doyle and Padhye, 1989). The pathogenic strains, which cause enteric disease, are grouped into six categories: (a) enterohemorrhagic (EHEC), (b) enterotoxigenic (ETEC), (c) enteroinvasive (EIEC), (d) enteropathogenic (EPEC), (e) enteroaggregative (EAggEC), and (f) diffuse-adherent (DAEC). The last two categories are not yet well defined, and the last category is not dealt with here. These categories differ in their pathogenesis and virulence properties, and each comprises a distinct group of O:H serotypes. Their clinical symptoms and epidemiological patterns may also differ (Chin, 2000).

In terms of the zoonoses, the most important category is the enterohemorrhagic, which is also the most severe.

a) Enterohemorrhagic *E. coli* (EHEC). The principal etiologic agent of this colibacillosis is *E. coli* O157:H7. Since it was first recognized in 1983 (Riley *et al.*, 1983), this category has been a public health problem in Europe and the US, which became more serious with an outbreak that occurred in the latter between November 15, 1992 and February 28, 1993. In Washington State and other western US states, 470 people fell ill and four died—three in Washington and one in San Diego, California (Spencer, 1993; Dorn, 1993). Griffin and Tauxe (1991) conclude that O157:H7 is an emerging and new pathogen, because they feel that such a distinctive illness—which often has serious consequences (hemolytic uremic syndrome)—would have attracted attention in any period. Later, O26:H11, O45:H2, and three nonmotile *E. coli*—O4, O111, and O145—were added to this serotype. This group is characterized by a 60-megadalton virulence plasmid and by its secretion of Shiga-like toxins or verotoxins. The Shiga-like toxin was thus named because it is similar in structure and activity to the toxin produced by *Shigella dis-enteriae* type 1, and is neutralized by the Shiga toxin antiserum. There are actually two toxins, Shiga-like toxin I and Shiga-like toxin II (or verotoxins I and II). Both are cytotoxic (lethal to Vero and HeLa cells), cause fluid accumulation in rabbit ligated ileal loops, and paralysis and death in mice and rabbits (O'Brien and Holmes, 1987). Verotoxin II produces hemorrhagic colitis in adult rabbits. The two toxins are antigenically different.

Geographic Distribution and Occurrence in Man: Worldwide. Serotype O157:H7 has been isolated in outbreaks in Canada, Great Britain, and the United States. It has also been isolated in Argentina, Australia, Belgium, the former Czechoslovakia, China, Germany, Holland, Ireland, Italy, Japan, and South Africa (Griffin and Tauxe, 1991). These isolates were obtained from fecal samples taken from sporadic cases of hemorrhagic diarrhea submitted to public health or hospital laboratories for examination.

From 1982 to 1992, 17 outbreaks occurred in the US; the smallest affected 10 people and the largest 243. In November 1992, an outbreak occurred among people who had eaten undercooked hamburgers at a fast food restaurant chain. The same *E. coli* serotype was isolated from the ground beef found in these restaurants (CDC, 1993). Seventeen more outbreaks occurred in 1993. Case-reporting is now compulsory in 18 US states. It is estimated that there are 8 cases each year per 100,000 inhabitants in Washington State (approximately the same incidence as for salmonellosis).

During the same period (1982–1992), there were three outbreaks in Canada and two in Great Britain (Griffin and Tauxe, 1991).

Occurrence in Animals: Based on outbreaks in the US, studies were conducted to evaluate the infection rate in cattle. The agent was isolated from only 25 suckling calves of the approximately 7,000 examined in 28 states. This study indicated that the agent is widely distributed in the US, but that the rate of animals harboring this serotype is low. The prevalence of infected herds is estimated at approximately 5%. In Washington State, between 5% and 10% of herds harbor *E. coli* O157:H7 (Spencer, 1993). This serotype was also isolated from cattle in Argentina, Canada, Egypt, Germany, Great Britain, and Spain. In Argentina and Spain, there was an association between serotype O157:H7 and a diarrheal disease in cattle, whereas in the other countries the isolates were produced from apparently normal cattle (Dorn, 1993).

The Disease in Man: The incubation period is from two to nine days. The appearance of the disease ranges from a slight case of diarrhea to severe hemorrhagic colitis, with strong abdominal pains and little or no fever. At the outset, diarrhea is watery but later becomes hemorrhagic, either with traces of blood or highly hemorrhagic stools. Diarrhea lasts an average of four days and about 50% of patients experience vomiting. Hemorrhagic diarrhea was present in more than 95% of a large number of sporadic cases recorded. In some outbreaks in nursing homes, where stricter surveillance was possible, it was shown that between 56% and 75% of affected patients had hemorrhagic stools and the rest had diarrhea without blood; asymptomatic infections were also confirmed (Griffin and Tauxe, 1991). *E. coli* O157:H7 infection is feared primarily because of its complications. One of these is hemolytic uremic syndrome, which is the principal cause of acute renal deficiency in children and frequently requires dialysis and transfusions. Another complication is thrombotic thrombocytopenic purpura, which is characterized by thrombocytopenia, hemolytic anemia, azotemia, fever, thrombosis in the terminal arterioles and capillaries, and neurological symptoms that dominate the clinical picture. Depending on the population, cases involving hemolytic uremic syndrome probably represent between 2% and 7% of the total number of cases due to *E. coli* O157:H7 (Griffin and Tauxe, 1991).

Although *E. coli* O157:H7 is susceptible to many commonly used antibiotics, they should not be used as a preventive measure. During an outbreak in a nursing home, antibiotics were considered a risk factor for contracting infection (Carter *et al.*, 1987). It is believed that antibiotics may increase the risk of infection and complications, probably by stimulating the production of toxin and altering the normal intestinal flora, thus allowing greater growth of serotype O157:H7. There is also a risk of producing resistant strains (Dorn, 1993).

Source of Infection and Mode of Transmission: Of nine outbreaks in the US, six were caused by undercooked ground beef and three by roast beef. An outbreak in Canada was caused by raw milk. These facts point to cattle as the reservoir of the EHEC agent. Other foods, such as cold sandwiches and uncooked potatoes, were also investigated; calf feces was the suspected contaminant in the potatoes. A later study indicated that undercooked meat (especially from calves and heifers) was the source of infection in more than 75% of the outbreaks. Another outbreak that occurred in 1989 in Cabool, Missouri (USA) and affected 243 people (one of every 12 people in the town) was caused by city-supplied water. The water may have been contaminated by deer feces. Human-to-human transmission also occurs, as secondary cases, through the fecal-oral route. A baby-sitter contracted the infection while caring for a sick child. Secondary cases have also occurred in day-care centers (Dorn, 1993).

Diagnosis: Sorbitol-MacConkey (SMAC) agar is recommended for isolation of *E. coli* O157:H7 from fecal samples. Various enzyme immunoassay techniques can be used to detect Shiga-like toxins in fecal matter or cultures. Isolation becomes difficult beyond one week after the onset of symptoms.

Control and Prevention: Ground beef should be cooked until it is no longer pink. Meat from cattle, like that of other mammalian and avian species, can be contaminated by feces during slaughter and processing. Thus, all precautions should be taken to minimize this risk, and foods of animal origin should be well cooked before they are eaten. Personal hygiene, particularly handwashing after relieving oneself, is also important (Doyle and Padhye, 1989).

b) Enterotoxigenic *E. coli* (ETEC). Enterotoxigenic *E. coli* has been the category most intensely studied in recent years. Research has not only added knowledge about the physiopathogenic action mechanisms of these bacteria, but has also provided means to prevent diarrheal disease in several animal species. Enterotoxigenic strains synthesize various types of toxins—a heat-labile (LT) toxin that is immunologically related to the cholera toxin, a heat-stable (ST) toxin that is not antigenic, or both (LT/ST). The toxins are plasmid-dependent and may be transferable from one ETEC strain to other strains that lack them.

Enterotoxigenic strains are distributed heterogeneously among the different O:H serotypes. ETEC strains make use of fimbriae or pili (nonflagellar, proteinic, filamentous appendices) to adhere to the mucosa of the small intestine, multiply, and produce one or more toxins. These pili interact with epithelial cells, are very important virulence elements, and are called colonization factors. Since the toxins are plasmid-dependent, the antigenic characteristics of the pili differ in different animal species. In man, there are seven colonization factors: CFA-1 and CS1 through CS6 (WHO, 1991). In calves and lambs, the implicated pili are primarily F5 (formerly

K99). Although F4 (K88) and 987P have also been isolated, they are not believed to play a role in ETEC virulence in these animals. The pili associated with enterotoxigenic colibacillosis in suckling pigs are F4 (K88), F5 (K99), F41, and 987P.

In the developing countries, the enterotoxigenic *E. coli* group primarily affects children under 2 or 3 years of age. In unhygienic homes, children may frequently suffer from ETEC. The incidence of the disease declines after the age of 4 and remains low. In addition, ETEC is the most common cause of "traveller's diarrhea" in adults who visit endemic countries. This epidemiological characteristic suggests that the population in endemic countries acquires immunity, while in industrialized countries the population is little exposed to these agents and does not acquire immunity.

The disease in man produces symptoms that closely resemble those caused by *Vibrio cholerae*. After an incubation period of 12 to 72 hours, there is profuse, watery diarrhea; abdominal colic; vomiting; acidosis; and dehydration. The feces do not contain mucus or blood and there may be fever. The duration of the illness is short and the symptoms generally disappear in two to five days.

ETEC can be diagnosed in man by demonstrating the presence of enterotoxin TL, TS, or both through an enzyme immunoassay. DNA probes can also be used to identify the genes in the bacteria that encode the toxins.

Man is the main reservoir and source of infection is the feces of patients and carriers. The route of transmission is fecal-oral. The vehicle of infection may be food and water contaminated by human feces.

ETEC is the cause of some outbreaks that affected many people in the developed countries. Some occurred in children's hospitals in Great Britain and the US, although the source of infection was not definitively determined. There have been outbreaks among adults that affected hundreds of people and were attributed to specific foods and contaminated water. One of the largest outbreaks, affecting more than 2,000 people, occurred in 1975 in a national park in Oregon (USA). Other outbreaks were due to imported Brie cheese that caused enterocolitis in several US states as well as in Denmark, the Netherlands, and Sweden. A large outbreak affecting 400 people occurred among diners at a restaurant in Wisconsin (USA). In this case, the source of infection was believed to be an employee who had diarrhea two weeks prior to the outbreak. A passenger on a cruise ship suffered two episodes of gastroenteritis caused by ETEC, one of them due to the ship's contaminated water (Doyle and Padhye, 1989).

c) Enteroinvasive *E. coli* (EIEC). This category represents a small group of *E. coli*. Many components are nonmotile (lacking the H antigen) and they are slow to ferment lactose or are nonlactose fermenting. The disease they cause is very similar to bacillary dysentery caused by *Shigella*. Their somatic antigens may cross-react with those of *Shigella*. Enteroinvasive *E. coli* can invade and multiply in the cells of the intestinal mucosa, especially in the colon.

EIEC colitis begins with strong abdominal pains, fever, malaise, myalgia, headache, and watery feces containing mucus and blood. The incubation period is from 10 to 18 hours. If diarrhea is severe, the patient can be treated with ampicillin.

The reservoir seems to be man and the source of infection contaminated water or food. However, the source of infection is not always definitively identified.

EIEC is endemic in the developing countries and accounts for 1% to 5% of all patients with diarrhea who see a doctor (Benenson, 1990). Studies conducted with

volunteers indicate that a very high bacterial load is needed to reproduce the disease. Some outbreaks due to contaminated water and food have occurred in the developed countries.

EIEC can be suspected when a large number of leukocytes is found in a preparation made from fecal mucus. The guinea pig-keratoconjunctivitis test (Sereny test) has diagnostic value. This test uses enteroinvasive *E. coli* cultures to demonstrate the capacity to invade epithelial cells. An enzyme immunoassay has been developed to detect a polypeptide in the surface membrane of the bacteria that determines virulence (invasive capacity).

d) Enteropathogenic *E. coli* (EPEC). The etiologic agents of the enteropathogenic disease belong to 15 O serogroups of *E. coli*. The disease occurs primarily in nursing babies under 1 year, in whom it can cause a high mortality rate.

The disease is characterized by watery diarrhea containing mucus but no visible blood; fever; and dehydration. The incubation period is short.

The disease occurs primarily in developing countries and has practically disappeared in Europe and the US. It occurs mostly in the warm seasons (summer diarrhea) and the sources of infection are formula milk and weaning foods that become contaminated due to poor cleaning of bottles and nipples, or deficient hygiene on the mother's part. Children in poor socioeconomic groups are frequently exposed to EPEC and generally acquire immunity after the first year of life. In epidemic diarrhea in newborns in nurseries, airborne transmission is possible through contaminated dust. Some outbreaks have also been described in adults.

E. coli isolated from feces must be serotyped. Once the EPEC serotype has been determined, a DNA probe should be used to try to identify the EPEC adherence factor (EAF), which is plasmid-dependent. EPEC strains also show localized adherence to HEp-2 cells.

In epidemics, hospitals and nurseries should have a separate room for sick babies. Treatment consists primarily of electrolyte replacement with oral saline solutions, or with intravenous solutions, if necessary. In most cases, no other treatment is needed. In serious cases, the child can be given oral cotrimoxazole, which reduces the intensity and duration of the diarrhea. Feeding, including breast-feeding, should continue (Benenson, 1990).

e) Enteroaggregative *E. coli* (EAggEC). This name is given to a group of *E. coli* that has an aggregative adherence pattern in an HEp-2 assay rather than a localized (as in EPEC) or diffuse one. This category is provisional until it is better defined. A study was done on 42 cultures—40 from children with diarrhea in Santiago (Chile), 1 from Peru, and 1 from a North American student who had visited Mexico. All these strains tested negative for enterohemorrhagic, enterotoxigenic, enteropathogenic, and enteroinvasive *E. coli* with DNA probes. They also failed to fit in one of these categories on the basis of serotyping. This group causes characteristic lesions in rabbit ligated ileal loops and mice (Vial *et al.*, 1988; Levine *et al.*, 1988).

EAggEC causes persistent diarrhea in nursing babies. The incubation period is estimated at one to two days (Benenson, 1990).

The Disease in Animals: In addition to sporadic cases of mastitis, urogenital infections, abortions, and other pathological processes, *E. coli* is responsible for several important diseases.

CATTLE: Calf diarrhea (white scours) is an acute disease that causes high mortality in calves less than 10 days old. It manifests as serious diarrhea, with whitish feces and rapid dehydration. It may last from a few hours to a few days. Colostrum-deprived calves are almost always victims of this disease. Colostrum, with its high IgM content, is essential in preventing diarrhea in calves. In the first 24 to 36 hours of life, the intestinal membrane is permeable to immunoglobulins, which pass quickly into the bloodstream and protect the animal against environmental microorganisms.

Enterotoxigenic strains that cause diarrhea in newborn calves are different from human strains. They generally produce a heat-stable toxin and the pili antigen is almost always type F5 (K99).

The septicemic form of colibacillosis in colostrum-deprived calves includes diarrhea as well as signs of generalized infection. Animals that survive longer usually suffer from arthritis and meningitis (Gillespie and Timoney, 1981).

Mastitis due to *E. coli* appears particularly in older cows with dilated milk ducts. In milk without leukocytes, coliforms multiply rapidly, causing an inflammatory reaction that destroys the bacteria and releases a large quantity of endotoxins. This produces acute mastitis, with fever, anorexia, cessation of milk production, and weight loss. In the next lactation period, the mammary glands return to normal function.

SHEEP: A disease with white diarrhea, similar to that in calves, has been reported in lambs in several countries. In South Africa, colipathogens were indicated as the cause of a septicemic illness in lambs, with neurological symptoms, ascites, and hydropericarditis, but without major gastrointestinal disorders.

HORSES: A long-term study of horse fetuses and newborn colts found that close to 1% of abortions and 5% of newborn deaths were due to *E. coli*.

SWINE: Neonatal enteritis in suckling pigs, caused by *E. coli*, begins 12 hours after birth with profuse, watery diarrhea and may end with fatal dehydration. Mortality is particularly high in suckling pigs from sows giving birth for the first time. About 50% of isolated strains are toxicogenic and some produce both thermostable (ST) and thermolabile (LT) toxins (Gillespie and Timoney, 1981). In newborn piglets, the colonization factors are F4 (K88), F5 (K99), F41, and 987P and there is probably one other factor. Diarrhea in weaned piglets is caused by hemolytic strains of ETEC that have the F4 (K88) colonization factor, but there are also some strains that express no known factor (Casey *et al.*, 1992). Diarrhea begins shortly after weaning and is a very common complication. The animals also suffer from anorexia and depression. Mortality is lower than in newborn suckling pigs and the pathogenesis may be similar.

Edema in suckling pigs is an acute disease that generally attacks between 6 and 14 weeks of age. It is becoming increasingly important in swine-producing areas. It is characterized by sudden onset, uncoordinated movement, and edema of the eyelids, the cardiac region of the stomach, and occasionally other parts of the body. Body temperature is usually normal. Neurological symptoms may be preceded by diarrhea (Nielsen, 1986). The disease usually occurs in winter. Morbidity ranges from 10% to 35% and mortality from 20% to 100%. The disease seems to be triggered by stress due to weaning, changes in diet, and vaccination against hog cholera. The disease mechanism could be an intestinal toxemia caused by specific strains of *E. coli*. A variant toxin similar to Shiga-like toxin II (see enterohemorrhagic *E. coli*) was identified

as the principal factor in the edema. This variant is toxic for Vero cells, but not HeLa cells (Dobrescu, 1983; Marques *et al.*, 1987; Kausche *et al.*, 1992).

FOWL: Pathogenic serotypes of *E. coli* have been isolated in septicemic diseases of fowl, as well as in cases of salpingitis and pericarditis. Contamination of eggs by feces or through ovarian infection is the source of colibacillosis in newborn chicks. Colibacillosis in adult chickens and turkeys primarily affects the lungs, though it may also invade the circulatory system and cause septicemia and death (Timoney *et al.*, 1988). Another avian disease, "swollen head" syndrome, has also been described. It is characterized by swelling of the orbital sinuses, torticollis, opisthotonos, and a lack of coordination. The illness lasts two to three weeks, and mortality is between 3% and 4% (O'Brien, 1985). Its etiology is uncertain. Viruses, *E. coli*, and some other bacteria have been isolated. The viral infection (paramyxovirus, coronavirus, pneumovirus) is thought to cause acute rhinitis and prepare the way for *E. coli* to invade subcutaneous facial tissue. It was possible to reproduce the disease with some strains of *E. coli*; in contrast, the disease could not be reproduced with the viruses (White *et al.*, 1990; Pages Mante and Costa Quintana, 1987). A colibacillary etiology has also been attributed to Hjarre's disease (coligranuloma), which causes granulomatous lesions in the liver, cecum, spleen, bone marrow, and lungs of adult fowl. The lesions resemble those of tuberculosis and mucoid strains of *E. coli* have been isolated from them. The disease can be reproduced in laboratory animals and chickens by parenteral inoculation but not by oral administration.

Source of Infection and Mode of Transmission: Man is the reservoir for all categories except enterohemorrhagic *E. coli* (EHEC), for which there are strong indications that the reservoir is cattle.

Cattle and swine may occasionally harbor strains of enterotoxigenic *E. coli* (ETEC) in their intestines, as Doyle and Padhye (1989) point out. In Bangladesh, three ETEC cultures were isolated from healthy calves and cows; these were of the same serotype and toxin variety as those taken from patients with diarrhea who had been in contact with the animals (Black *et al.*, 1981). In the Philippines, an ETEC serotype (O78:H12, LT^+ST^+) was isolated from a rectal swab from a pig; this serotype was considered to be the agent of human diarrhea in many countries (Echeverría *et al.*, 1978, cited in Doyle and Padhye, 1989). However, volunteers were fed an ETEC strain isolated from a pig, but none of them had diarrhea (Du Pont *et al.*, 1971, cited in Doyle and Padhye, 1989). The source of infection is the feces of infected persons (primarily sick persons, secondarily carriers) and objects contaminated by them. The most common mode of transmission is the oral-fecal route. Contaminated foods, including those from animals (meat, milk, cheeses), are a common vehicle in various categories of human colibacillosis. In EHEC, beef is considered the principal source of human infection. In the case of epidemic diarrhea in newborn infants in nurseries, airborne transmission by contaminated dust is possible.

In animals, the source of infection and mode of transmission follow the same patterns as in human infection. Animals with diarrhea constitute the main source of infection.

Diagnosis: Diagnosis in man is based on isolation of the etiologic agent and on tests that can identify it as enterohemorrhagic, enterotoxigenic, enteroinvasive, or enteroaggregative (see each separate category for the most suitable diagnostic method).

In the case of diarrhea in newborn cattle, sheep, and swine, fresh feces or the intestinal contents of a recently dead or slaughtered animal can be cultured.

The immunofluorescence test is very useful for detecting colonization factors; sections of the ileal loop of a recently dead animal are stained with conjugate for this purpose (Timoney *et al.*, 1988).

Control: For man, control measures include: (a) personal cleanliness and hygienic practices, sanitary waste removal, and environmental sanitation; (b) provision of maternal and child hygiene services; (c) protection of food products, pasteurization of milk, and compulsory veterinary inspection of meat; and (d) special preventive measures in hospital nursery wards. These measures should include keeping healthy newborns separate from sick nursing infants or older children. Nurses who tend the nurseries should not have contact with other wards, and those in charge of feeding bottles should not change diapers. Special precautions should be taken in the laundry.

To prevent colibacillosis in animals, the commonly accepted rules of herd management should be followed. For calves, colostrum is important for the prevention of white scours, and for pigs, all unnecessary stress should be avoided during weaning in order to prevent edema.

In recent years, investigations of the factors that permit enterotoxigenic *E. coli* strains to colonize the small intestine have opened up new horizons in colibacillosis prevention in animals. Vaccines for cattle and swine have been developed based on fimbria (pili) antigens. These antigens inhibit *E. coli* from adhering to the mucosa of the small intestine. To this end, gestating cows and sows are vaccinated with vaccines based on F5 (K99) and F4 (K88) antigens, respectively. Newborns acquire passive immunity via colostrum and milk, which contain antibodies against these factors. In the same way, good results have been obtained in protecting newborn lambs by vaccinating ewes with F5 (K99). In addition, studies (Rutter *et al.*, 1976; Myers, 1978; Nagy, 1980) are being carried out with oral vaccines for humans using toxicogenic *E. coli* toxoids of both thermolabile and thermostable toxins as well as antiadherence factors (purified fimbriae). Genetic engineering is another approach being used to obtain vaccines with attenuated *E. coli* virulence (Levine and Lanata, 1983).

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CORYNEBACTERIOSIS

ICD-10 A48 other bacterial diseases, not elsewhere classified

Etiology: The genus *Corynebacterium* consists of slightly inflexed, gram-positive, non–acid-fast, nonmotile, nonsporogenic, nonencapsulated, facultatively aerobic or anaerobic, catalase-positive bacilli. The genus is related to *Nocardia*, *Rhodococcus*, and *Mycobacterium*.

The genus *Corynebacterium* includes species such as *C. diphtheriae* (type species), the agent of human diphtheria, and such animal pathogens as *C. pseudotuberculosis* (*C. bovis*) and *C. renale*. There are also species that are pathogenic for

plants and others that are saprophytes. Corynebacteria, with the exception of the species *C. diphtheriae*, are often called diphtheroids.

The species that are animal commensals or pathogens and are transmitted to man are *C. pseudotuberculosis*, *C. ulcerans*, *C. bovis* (the latter two are still not recognized as species), *C. kutscheri*, and a group of three species: *C. renale*, *C. pilosum*, and *C. cystitidis*.

Geographic Distribution: Worldwide.

Occurrence in Man: Few cases have been recognized.

Occurrence in Animals: *C. pseudotuberculosis* (*C. ovis*) occurs in many parts of the world among sheep and goats. It is less frequent in horses and camels. *C. bovis* is a commensal bacteria in the udder and genital tract of bovines. It may occasionally cause mastitis (Gillespie and Timoney, 1981). *C. ulcerans* is found in the nose and throat of man and horses (Wiggins *et al.*, 1981). The species of the group *C. renale* are frequent etiological agents of cystitis, ureteritis, and pyelonephritis in bovines. *C. kutscheri* is a commensal and pathogen in rodents.

The Disease in Man: Twelve human cases caused by *C. pseudotuberculosis* (*C. ovis*) have been described. The common lesion in these patients was a suppurative granulomatous lymphadenitis. There was only one different clinical picture: a veterinary student who contracted eosinophilic pneumonia after exposure in a microbiology laboratory. The victims were treated with erythromycin or tetracycline for several weeks (Brown, 1990). Almost all strains of *C. pseudotuberculosis* produce a dermonecrotic toxin.

C. ulcerans has caused a variety of pathological symptoms in man, particularly pharyngitis, but also ulcers in the limbs, presumed cases of pneumonia, and a disease similar to diphtheria, with pseudomembranes and cardiac and neurological manifestations (Brown, 1990; Krech and Hollis, 1991).

C. bovis is a common commensal in cow's milk, whose fat it hydrolyzes. The literature describes seven human cases of disease caused by this agent. Three of these had CNS impairment and the others had prosthetic valve endocarditis, chronic otitis, and a persistent ulcer on one leg (Vale and Scott, 1977; Brown, 1990).

C. renale has caused rectal and chest abscesses.

C. kutscheri is an opportunistic pathogen in wild and laboratory rodents (rats and mice). There are only two known human cases of disease caused by this agent: one with septic arthritis and the other a premature infant with chorioamnionitis (Krech and Hollis, 1991). The species is not clearly defined in the human cases described in the literature.

The recommended treatment is simultaneous administration of rifampicin and erythromycin (Brown, 1990).

The Disease in Animals: The corynebacterioses are much more important in veterinary medicine. Some of the diseases are described briefly below (Timoney *et al.*, 1988).

C. pseudotuberculosis is the usual etiologic agent of caseous lymphadenitis in sheep and goats, which occurs in many parts of the world where these animal species are raised. The agent gains entry through wounds and localizes in the regional lymph nodes, where it forms a caseous greenish pus. Abscesses may also be found in the lungs, as well as in the mediastinal and mesenteric lymph nodes.

Two different pathological conditions have been found in horses. One is ulcerative lymphangitis, with metacarpal and metatarsophalangeal abscesses that contain a thick, greenish pus and at times leave an ulceration that is slow to heal. The other consists of large and painful abscesses on the chest and in the inguinal and abdominal regions. It may also affect camels, deer, mules, and bovines.

C. pseudotuberculosis has two serotypes. Serotype 1 predominates in sheep and goats, and serotype 2 in buffalo and cows. It produces an exotoxin, phospholipase D, which gives the bacteria much of its virulence by increasing vascular permeability. The other virulence factors are a thermostable pyogenous factor that attracts leukocytes and a surface lipid that is toxic to leukocytes.

C. renale is the most frequent agent in the group that causes pyelonephritis. It is also responsible for many cases of cystitis and ureteritis, particularly in cows. This bacteria produces diphtherial inflammation of the bladder, ureters, kidneys, and pelvis. It can be found in healthy cows in herds with sick animals. *C. renale* also affects horses and sheep sporadically. *C. pilosum* is not very virulent and is only occasionally the agent of pyelonephritis. *C. cystitidis* causes severe hemorrhagic cystitis, followed by pyelonephritis. *C. bovis* is usually a commensal in the udder and is only sometimes the primary agent of mastitis.

C. ulcerans is a commensal in bovines and horses. It has been isolated from milk and is presumed to occasionally cause mastitis in cows (Lipsky *et al.*, 1982). An outbreak of gangrenous dermatitis caused by *C. ulcerans* occurred in Richardson ground squirrels (*Spermophilus richardsonii*) captured within the city limits of Calgary (Canada). Between two and five months after capture, 63 (18%) of the animals fell ill with symptoms of dermatitis and cellulitis. Some of the 350 squirrels captured died, probably due to toxemia and/or septicemia, and had lesions from acute necrotic dermatitis over a large part of their bodies. Pharyngitis was found in 4 of the 10 that were examined (Olson *et al.*, 1988). The infection is assumed to have spread through bites, in a manner similar to that described in monkeys (May, 1972).

Most infections due to *C. kutscheri* in rodents are subclinical. Clinical cases show nasal and ocular secretion, as well as dyspnea, arthritis, and cutaneous abscesses that form gray nodules some 15 mm in diameter. Upon autopsy, abscesses are found in the liver, kidneys, lungs, and lymph nodes. Diagnosis can be performed through culture and isolation of the etiologic agent or serology (ELISA, complement fixation, agglutination). Treatment with penicillin can prevent the appearance of clinical symptoms in animals in an affected colony, but does not eliminate carrier status (Fraser *et al.*, 1991).

C. diphtheriae is an exclusively human pathogen. However, in an outbreak that occurred in a colony of 300 guinea pigs in Nigeria, 60 died with pneumonia lesions, endometritis, and slight intestinal congestion. *C. diphtheriae* was considered the cause of death, since it was isolated from the lungs and heart blood. The source of infection could not be determined (Okewole *et al.*, 1990).

Treatment with high doses of penicillin is effective if begun early in the course of the disease.

Source of Infection and Mode of Transmission: The corynebacteria described here are considered zoonotic, with the exception of *C. diphtheriae*, for which the reservoir is man and transmission is from human to human.

The reservoir of *C. pseudotuberculosis* is sheep and goats. Man acquires the infection through contact with sick animals, their organs, or products (skins, milk). Among sheep and goats, the infection is transmitted from an animal with an open abscess to another animal with abrasions, such as those produced during shearing. Sometimes *C. pseudotuberculosis* can penetrate through abrasions in the oral mucosa, or it can be inhaled and cause abscesses in the lungs (Timoney *et al.*, 1988).

C. ulcerans is a common commensal in bovines and horses. The bacteria is probably transmitted to man through raw milk. The infection may also be transmitted via the airborne route (Brown, 1990).

C. bovis is a commensal in the reproductive system of bovines and can frequently be found in milk; only occasionally does it cause mastitis. In a survey conducted in 74 dairy farms in Ontario (Canada), *C. bovis* was found in the milk of 36% of the cows (Brooks *et al.*, 1983).

The reservoir of *C. renale*, *C. pilosum*, and *C. cystitidis* is bovines. The mode of transmission from bovines to man is unclear. *C. renale* and *C. pilosum* are transmitted among bovines when the urine from a sick cow reaches the vulva of a healthy cow. *C. cystitidis* is a commensal of the prepuce of bulls and can be transmitted sexually. It can also be transmitted when drops of urine are sprinkled from one cow to another.

Diagnosis: A diagnosis of human corynebacteriosis can only be confirmed through isolation and identification of the species.

The same applies to animal corynebacteriosis, although in the case of caseous lymphadenitis in the surface lymph nodes of sheep and goats, the lesions, along with a gram-stained smear, are sufficiently characteristic for diagnosis. Several serological tests have been used to detect healthy carriers of *C. pseudotuberculosis*.

Control: The few human cases identified to date do not justify the establishment of special preventive measures. However, correct diagnosis is important for effective treatment.

To prevent caseous lymphadenitis due to *C. pseudotuberculosis*, it is essential to avoid lesions during shearing. When they do occur, they should be treated promptly and correctly.

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DERMATOPHILOSIS

ICD-10 A48.8 other specified bacterial diseases

Synonyms: Streptothrichosis, mycotic dermatitis (in sheep).

Etiology: *Dermatophilus congolensis* (*D. dermatonomus*, *D. pedis*) is a bacterium belonging to the order *Actinomycetales*. It is facultatively anaerobic, gram-positive, and non–acid-fast. *D. congolensis* is characterized by branched filaments with transverse and longitudinal septation. When the filaments mature, they fragment and release motile, flagellate spores, called zoospores, which constitute the infective agent. In turn, the zoospores germinate and form filaments that produce new zoospores, thus repeating the cycle.

Geographic Distribution: Worldwide. Dermatophilosis has been confirmed in many areas of Africa, Australia, Europe, and New Zealand, as well as in North and South America.

Occurrence in Man: The first known cases were identified in 1961 in New York (USA), where four people became ill after handling a deer with dermatophilosis

lesions. Subsequently, several other cases were described: one in a student at the University of Kansas (USA), three cases in Australia, and two in Brazil (Kaplan, 1980; Portugal and Baldassi, 1980). A case was recorded in Costa Rica of a veterinarian who came into contact with infected cattle.

Occurrence in Animals: The disease has been observed in several species of domestic and wild animals. Those most frequently affected are cattle, sheep, goats, and horses. The disease is most prevalent in tropical and subtropical climates. The importance of dermatophilosis lies in the economic losses it causes, due to the damage to leather, wool, and pelts. In some African countries, from 16% (Kenya) to 90% (Tanzania) of cow hides have been damaged. In Great Britain, it has been estimated that affected fine wool loses 20% of its commercial value. Moreover, shearing is difficult in chronically sick woolbearing animals.

The Disease in Man: In the few known cases, the disease has been characterized by pimples and multiple pustules (2–25) on the hands and forearms, containing a serous or yellowish white exudate. Upon rupturing, they left a reddish crateriform cavity. The lesions healed in 3 to 14 days, leaving a purplish red scar.

The Disease in Animals: In dermatophilosis or streptotrichosis in bovines, sheep, horses, or goats, a serous exudate at the base of hair tufts dries and forms a scab. When the scab comes off, it leaves a moist alopecic area. The lesions vary in size; some may be very small and go unnoticed, but at times they are confluent and cover a large area. In general, they are found on the back, head, neck, and places where ticks attach. In sheep, the disease known as mycotic dermatitis (lumpy wool) begins with hyperemia and swelling of the affected area of skin, and an exudation that becomes hard and scablike. In chronic cases, conical hard crusts with a horny consistency form around tufts of wool. In mild cases, the disease is seen only during shearing, since it makes the operation difficult. Animals do not experience a burning sensation and are not seen to scratch themselves against posts or other objects. Secondary infections may cause death in lambs. Dermatophilosis is also a factor favoring semispecific myiases (see section on myiases in Volume III: Parasitic Diseases), caused in Australia by *Lucillia cuprina* (the principal agent of "body strike"). The fly not only prefers the moist areas affected by dermatophilosis above other moist areas in the fur for egg laying, but larval development is aided by the skin lesion caused by *D. congolensis* (Gherardi *et al.*, 1981).

In Great Britain, a localized form of the disease in the distal regions of the extremities of sheep has been confirmed and named proliferative hoof dermatitis. This form is characterized by extensive inflammation of the skin and formation of thick scabs. The scabs come loose, revealing small hemorrhagic dots that cause the lesion to resemble a strawberry, from which the disease's common name, "strawberry foot rot," is derived. In cases without complications and in the dry season, the lesions heal spontaneously in about three weeks.

In dermatophilosis cases described in domestic cats, the lesions differ from those of other domestic species in that they affect deeper tissues. In cats, granulomatous lesions due to *D. congolensis* have been found on the tongue, bladder, and popliteal lymph nodes (Kaplan, 1980).

Source of Infection and Mode of Transmission: The etiologic agent, *D. congolensis*, is an obligate parasite that has been isolated only from lesions in animals.

However, according to Bida and Dennis (1977), the agent can be found in the soil during the dry season.

Environmental humidity and moist skin are predisposing factors in the disease. The zoospore needs moisture to mobilize and be released. The rainy seasons in tropical climates are the most favorable to spread of the infection. Another important factor in sheep is malnutrition, which usually occurs during the dry season due to the lack of pasture. Malnourished animals have more persistent and chronic lesions than well-nourished animals. The difference is probably due to the reduced growth of wool and reduced production of lanoline in malnourished animals (Sanders *et al.*, 1990). Most researchers assign great importance to the level of tick infestation in cattle (Koney and Morrow, 1990) and other animal species, as well as to infestation by other insects.

Human cases have arisen from direct contact with animal lesions. Man is probably quite resistant to the infection, as the number of human cases is small despite the frequency of the disease in animals.

The most common means of transmission between animals seems to be mechanical transport by arthropod vectors, including ticks, flies, and mosquitoes. The infective element is the zoospore. Most infections occur at the end of spring and in summer, when insects are most abundant. An important factor in transmission is moisture, which allows the zoospore to detach from the mycelium.

The most serious outbreaks occur during prolonged humid seasons and during the rainy season in tropical areas. Sheep with long wool that retains moisture are most susceptible to the infection. During dry seasons, the agent can survive in moist spots on the body, such as the axilla or in skinfolds.

The infection may also be transmitted by means of objects, such as plant thorns or shears that cause lesions on the extremities or on the lips.

Role of Animals in the Epidemiology of the Disease: The infection is transmitted from one animal to another and only occasionally from animal to man. The only known reservoirs of the agent are domestic and wild animals.

Diagnosis: Clinical diagnosis is confirmed by microscopic examination of stained smears (Giemsa, methylene blue, or Wright's stain) made from exudates or scabs. This is the simplest and most practical method. Immunofluorescence may also be used on smears or tissue samples.

The isolation of the agent should be done in rich media such as blood agar. This culture method is often difficult due to contamination. To overcome this difficulty, passage through rabbits has been used.

Several serological methods have been used to detect antibodies to *D. congolensis*. In a study comparing passive hemagglutination, immunodiffusion in agar gel, and counterimmunoelectrophoresis, the last test gave the best results in terms of both sensitivity and specificity (Makinde and Majiyagbe, 1982).

Control: Given the few cases of dermatophilosis in man, special control measures to protect against infection are not justified. Nevertheless, it would be prudent not to handle animals with lesions with bare hands (especially if one has abrasions or skin wounds).

In Africa, tick control has been shown to be effective in preventing bovine dermatophilosis.

Sheep with mycotic dermatitis should be shorn last or, preferably, in a separate place. Affected wool should be burned. Satisfactory results have been obtained using

1% alum dips. In chronic cases, an intramuscular injection of 70 mg of streptomycin and 70,000 units of penicillin may be administered two months before shearing. This drug therapy seems to be very effective and prevents difficulties in shearing.

The use of antibiotics (streptomycin, penicillin, and others) was effective in producing clinical cure or improvement in affected animals, but did not always eliminate the causal agent.

The infection is controlled by isolating or eliminating chronically sick animals and combating ectoparasites. Externally applied insecticides are used to combat biting insects.

The study of a vaccine against animal dermatophilosis is in an experimental stage (Sutherland and Robertson, 1988; How *et al*., 1990).

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DISEASES CAUSED BY NONTUBERCULOUS MYCOBACTERIA

ICD-10 A31.0 pulmonary mycobacterial infection; A31.1 cutaneous mycobacterial infection; A31.8 other mycobacterial infections

Synonyms: Mycobacteriosis, nontuberculous mycobacteriosis, nontuberculous mycobacterial infection.

Etiology: The etiologic agents of nontuberculous mycobacteriosis (NTM) form a group separate from those that cause tuberculosis in mammals, *Mycobacterium tuberculosis*, *M. bovis*, *M. africanum*, and *M. microti* (the agent of tuberculosis in rodents). Previously called anonymous, atypical, or unclassified mycobacteria, they have since been characterized and given specific names.

Mycobacteria potentially pathogenic for man and animals currently include some 15 species. The most important group among these species is *Mycobacterium avium* complex (MAC), replacing what was formerly called MAI (*M. avium-intracellulare*) or MAIS (*M. avium-intracellulare-scrofulaceum*). These mycobacteria are important pathogens for birds (avian tuberculosis) and some mammals (swine tuberculosis). MAC has become important as a human pathogen due to the AIDS epidemic.

There are both genetic and antigenic indications that *M. paratuberculosis*, the agent of chronic hypertrophic enteritis in cattle and sheep, should be included in the same complex as *M. avium* (Grange *et al.*, 1990). There are also data suggesting that the mycobacterial strains isolated from patients with Crohn's disease are genetically related to *M. paratuberculosis* (Sanderson *et al.*, 1992).

M. paratuberculosis is characterized by its requirement of mycobactin (a lipid that binds iron) for growth in culture media. There are also strains similar to MAC that are mycobactin-dependent to a greater or lesser degree, among them the strains isolated from the wild pigeon (*Palumba palumbus*), which through experimental inoculation in cattle produces a disease similar to paratuberculosis.

DNA:DNA hybridization studies demonstrated that *M. avium*, *M. paratuberculosis*, and the mycobacteria of the European wild pigeon (*Palumba palumbus*) belong to a single genomic species. Based on numerical taxonomy studies of mycobactin-dependent mycobacteria, DNA sequences, and genotype and other studies, Thorel *et al.* (1990) suggest dividing the species into *M. avium* subsp. *avium*, *M. avium* subsp. *paratuberculosis*, and *M. avium* subsp. *silvaticum*. The latter would correspond to the mycobacteria isolated from the wild pigeon.

MAC is composed of 28 serotypes (1–28); the first three belong to *M. avium*, and the rest to *M. intracellulare*. Serotyping has been valuable in research but is not applicable in routine laboratories and has been discontinued. Runyon's classification, developed in 1959, is still in use. It subdivides the mycobacteria into four large groups: photochromogens (Group 1), scotochromogens (Group 2), nonchromogens (Group 3), and rapid growers (Group 4). The different species of mycobacteria are distinguished by their phenotypic characteristics, such as optimum growth temperature, rapid or slow growth, utilization of niacin, nitrate reduction, and other biochemical properties (Wayne and Kubica, 1986).

The mycobacteria that are potentially pathogenic for man and animals include the slow-growing MAC, *M. kansasii*, *M. marinum*, *M. xenopi*, *M. szulgai*, and *M. simiae*; and the fast-growing *M. fortuitum* and *M. chelonae* (or *M. fortuitum* complex).

Geographic Distribution: Their presence, distribution, and relative importance as a cause of disease have been studied primarily in the more developed countries, where the prevalence of tuberculosis is also lower. Some species are distributed worldwide, while others predominate in certain areas. For example, the pulmonary disease in man caused by *M. kansasii* is prevalent in England and Wales (United Kingdom), and in Kansas City, Chicago, and the state of Texas (USA). On the other hand, the disease caused by MAC is more frequent in the southeastern United States, western Australia, and Japan (Wolinsky, 1979). The situation has changed radically with the advance of the AIDS epidemic.

Distribution is similar in animals, since the infection comes from an environmental source. These agents are believed to be more important in hot and humid areas than in temperate and cold climates.

Occurrence in Man: A distinction must be made between colonization and temporary sensitivity, infection, and cases of disease. Since diagnosis depends on the isolation and typing of the etiologic agent, most confirmations come from countries with a good system of laboratories. In Australia, the annual rate of pulmonary infection has been estimated at 1.7 to 4 cases per 100,000 inhabitants in Queensland and from 0.5 to 1.2 per 100,000 in the entire country. In the Canadian province of British Columbia, the annual rate for all nontuberculous mycobacterial diseases increased from 0.17 to 0.53 per 100,000 inhabitants between 1960 and 1972 (Wolinsky, 1979). The incidence of MAC in AIDS patients continues to increase. In the US, it was 5.7% in the period 1985–1988, while it reached 23.3% in 1989–1990 (Havlik *et al.*, 1992). Isolates of nontuberculous mycobacteria from 727 AIDS patients in the US (sample from the entire country) were sent to the Centers for Disease Control and Prevention for serotyping. It was possible to type 87% and almost all the isolates belonged to MAC serotypes 1 to 6 and 8 to 11. Most *M. avium* isolates and the isolates that could not be typed were taken from blood samples. *M. intracellulare* made up of only 3% of the isolates. More than 50% of all the cultures came from New York and California (Yakrus and Good, 1990).

A prospective study of AIDS patients was able to diagnose MAC only in those who had a CD4+ count of less than 100 cells/mm^3. These patients had fever, diarrhea, and weight loss (Havlik *et al.*, 1992).

In Zurich (Switzerland), a retrospective study covering the period 1983–1988 examined patients negative for human immunodeficiency virus (HIV). Nontuberculous mycobacteria were isolated from 513 cases, 34 of whom had an obvious disease. In 23 of the 34 cases, the disease was pulmonary; the soft tissues were affected in 10 cases and there was 1 case of disseminated infection (Debrunner *et al.*, 1992).

In Argentina, 8,006 cultures from 4,894 patients were studied. Of these cultures, 113 (1.4%) were identified as nontuberculous mycobacteria, belonging to 18 cases (0.37% of the total number of patients). The agents isolated were *M. kansasii* in eight cases, MAIS in another eight cases, *M. marinum* in one case, and an infection caused by both *M. tuberculosis* and *M. kansasii* in another case. Localization was

pulmonary in 16 cases and cutaneous in 2 (Di Lonardo *et al.*, 1983). A study conducted by 15 laboratories in 6 regions of Argentina obtained 13,544 mycobacteria cultures from 7,662 patients. The etiologic agent was *Mycobacterium tuberculosis* in 99.17% of the patients, *M. bovis* in 0.47%, and MAIS in 0.35% (Barrera and De Kantor, 1987). Between June 1985 and December 1991, at the Muñiz Hospital (for infectious diseases) in Buenos Aires, the prevalence of nontuberculous mycobacterial diseases was 6.2% in HIV-positive or AIDS patients, and 0.5% in HIV-negative patients (Di Lonardo *et al.*, 1993).

In Mexico, 547 cultures were made from samples taken from patients diagnosed with tuberculosis using bacterioscopy. Of these cultures, 89.6% were identified as *M. tuberculosis* and 8.9% as potentially pathogenic nontuberculous mycobacteria, such as *M. fortuitum*, *M. chelonae*, *M. scrofulaceum*, and *M. kansasii*.

Occurrence in Animals: The same considerations that apply to man are also valid for animals. The disease has been confirmed in many mammalian and avian animal species, as well as poikilotherms. Among domestic animals, the disease is economically important in swine due to the losses it causes. MAC serotypes 1 and 2 are the most commonly isolated from swine. These two serotypes are also responsible for avian tuberculosis. Serotype 8 is an important pathogen for both man and animals (Thoen *et al.*, 1981). Serotypes 4 and 5 are also isolated from swine in the US.

Surveillance and identification of mycobacteriosis in animals is mainly carried out in countries where bovine tuberculosis has been controlled, as in the United States. Nontuberculous mycobacteria may interfere in the diagnosis of tuberculosis, causing unnecessary losses due to the slaughter of nontuberculous animals. There is little information on animal mycobacteriosis in other areas.

The Diseases in Man: The most common diseases in people with intact cellular immunity are: (a) pulmonary disease, (b) lymphadenitis, and (c) soft tissue lesions. Other organs and tissues may be affected and, in some cases, hematogenous dissemination occurs (Wolinsky, 1979).

a) Chronic pulmonary disease resembling tuberculosis is the most important clinical problem caused by nontuberculous mycobacteria. The most common etiologic agents of this disease are MAC and *M. kansasii*. *M. xenopi*, *M. scrofulaceum*, *M. szulgai*, *M. simiae*, and *M. fortuitum-chelonae* are found less frequently. As with tuberculosis, there is great variation in the clinical presentation of the disease, from minor lesions to an advanced disease with cavitation. Most cases occur in middle-aged persons who have preexisting pulmonary lesions (pneumoconiosis, chronic bronchitis, and others). Persons taking immunosuppressant drugs or with acquired immune deficiency are also susceptible. However, an appreciable percentage of patients have acquired the disease without having previous damage to the respiratory or immune systems (Wolinsky, 1979).

b) Mycobacterial lymphadenitis occurs in children from 18 months to 5 years of age. The affected lymph nodes are primarily those of the neck close to the jaw bone, and generally on one side only. They soften rapidly and develop openings to the outside. The child's general health is not affected. Calcification and fibrosis occur during the healing process.

In countries at low risk for tuberculous infection, lymphadenitis due to MAC is prevalent, unlike countries with a medium to high prevalence of tuberculosis. In

British Columbia (Canada), the case rate was 0.37 per 100,000 inhabitants, while for tuberculous lymphadenitis due to *M. tuberculosis*, it was only 0.04 per 100,000 inhabitants annually. In Great Britain, as in many other parts of the world, *M. tuberculosis* is prevalent in cases of lymphadenitis caused by *Mycobacterium* (Grange and Yates, 1990). The most common etiologic agents are different MAC serotypes, *M. scrofulaceum*, and *M. kansasii*. The proportion of each of these mycobacteria varies by region. Other mycobacteria are isolated from lesions less frequently (Wolinsky, 1979).

c) Diseases of the skin and subcutaneous tissue are caused by *M. marinum*, *M. ulcerans*, *M. fortuitum*, and *M. chelonae*.

Localized abscesses ensue, particularly after injections, surgical interventions, war wounds, thorn penetration, and various traumas.

Granulomas (swimming pool granuloma, fish tank granuloma) develop on the extremities as a group of papules that ulcerate and scab over. Lesions may persist for months. Healing is usually spontaneous. The etiologic agent is *M. marinum*, which inhabits and multiplies in fresh and salt water. *M. marinum* is a photochromogen also found in marine animals; it grows well at 32°C and little or not at all at 37°C (Sanders and Horowitz, 1990). In Glenwood Spring, Colorado (USA), 290 cases of granulomatous lesions were found among children who swam in a pool of tepid mineral water.

Infections caused by *M. ulcerans* occur in many tropical areas of the world, particularly in central Africa. They start as erythematous nodules on the extremities and gradually become large, indolent ulcers with a necrotic base. This lesion is known as “Buruli ulcer” in Africa and “Bairnsdale ulcer” in Australia.

Infections caused by nontuberculous mycobacteria have also been described in the joints, spinal column, and the urogenital tract, and as osteomyelitis of the sternum after heart operations. A generalized, highly lethal infection may occur mainly in leukemia patients or those undergoing treatment with immunosuppressants. Generalized infection with bacteremia detectable through hemoculture has been confirmed only in AIDS patients.

Many other species of mycobacteria generally considered saprophytes can cause pathological processes in man.

There has been much interest and much controversy over the possibility that *M. paratuberculosis*, or a similar MAC mycobacteria, is the agent of Crohn’s disease. This chronic disease in man is of unknown etiology and causes a granulomatous process in the terminal ileum, although lesions are also found in other parts of the intestine as well as the skin, the liver, and the joints. A mycobacterium that is the agent of chronic enteritis in cattle, sheep, and occasionally nonhuman primates (with characteristics very similar to *M. paratuberculosis*) was isolated from a few patients. It is a mycobactin-dependent mycobacterium that has biochemical, genomic, and culturing characteristics similar to *M. paratuberculosis* (except in the arylsulfatase and niacin reactions). It is experimentally pathogenic and capable of producing a granulomatous disease in the intestine of goats. Further research is needed to determine whether this mycobacterium is actually the agent of Crohn’s disease (McFadden *et al.*, 1987; Thorel, 1989; Sanderson *et al.*, 1992). A primary objective should be to improve culture media so that the mycobacterium can be isolated.

Treatment of the pulmonary forms caused by MAC is difficult due to the resistance of these mycobacteria to the antimicrobials commonly used in treating tuber-

culosis. It is generally advisable to treat with various medications, selecting them after conducting a sensitivity test on the isolated mycobacteria (Benenson, 1990). Such drugs would include isoniazid, rifampicin, and ethambutol, adding streptomycin at the start, and treatment must be sufficiently prolonged. Clarithromycin has proven to be highly active *in vitro* and *in vivo*. The intracellular activity of clarithromycin increases with ethambutol and rifampicin. An evaluation of the various drugs can be found in the article by Inderlied *et al.* (1993). In cases of serious or disseminated pulmonary disease, the patient may benefit from the addition of other medications (Sanders and Horowitz, 1990). If the disease is limited—such as a localized pneumopathy, a nodule, cervical lymphadenitis, or a subcutaneous abscess—surgical resection should be considered (Benenson, 1990).

The Diseases in Animals: Many species of mammals and birds are susceptible to nontuberculous mycobacteria. The various MAC serotypes are the most important etiological agents. The most frequent clinical form in mammals is lymphadenitis, but other tissues and organs may be affected (Thoen *et al.*, 1981).

CATTLE: In cattle, the most common nontuberculous mycobacterial infection affects the lymph glands. In the United States during the period 1973–1977, nontuberculous mycobacteria were isolated from more than 14% of specimens submitted to laboratories on suspicion of tuberculosis (Thoen *et al.*, 1979). More than 50% of the isolates corresponded to serotypes 1 and 2 of the *M. avium* complex; the rest primarily consisted of other serotypes from the same complex, and only 2.7% were other species, such as *M. fortuitum*, *M. paratuberculosis*, *M. kansasii*, *M. scrofulaceum*, and *M. xenopi*.

In São Paulo (Brazil), attempts at isolations from lesions in 28 cows and 62 caseous lesions in slaughterhouse carcasses yielded 18 isolations of *M. bovis* and one each of *M. tuberculosis*, *M. fortuitum*, and *M. kansasii* (Correa and Correa, 1973).

Although nontuberculous mycobacteria usually cause lesions only in lymph nodes, granulomas are sometimes found in other tissues.

The principal problem presented by nontuberculous mycobacteria in cattle lies in the paraspecific sensitization for mammalian tuberculin, which causes confusion in diagnosis as well as the unnecessary slaughter of animals. The comparative tuberculin test (mammalian and avian) carried out in several countries shows that sensitization to MAC is common in some countries and rare in others (Grange *et al.*, 1990).

SWINE: In swine, MAC infection causes serious economic losses in many parts of the world due to confiscations of animals from slaughterhouses and lockers. In countries that have carried out successful programs to eradicate bovine tuberculosis, swine confiscated for "tuberculosis" are primarily infected by MAC. Serotypes 1, 2, 4, 5, and 8 of this complex are the principal causes of mycobacterial infection in swine in the United States (Songer *et al.*, 1980). Serotype 8, in particular, has caused outbreaks with great losses for swine producers in several countries, including the United States, Japan, and South Africa. Lesions in these animals are usually restricted to cervical and mediastinal lymph glands, that is particularly near the digestive tract. Generalized lesions are usually due to *M. bovis*, but nontuberculous mycobacteria may sometimes be responsible. In addition to the various MAC serotypes, other nontuberculous mycobacteria have also been isolated from swine, including *M. kansasii*

and *M. fortuitum*. Strains similar to *M. fortuitum*, but differing in several biochemical characteristics, were isolated from swine with lymphadenitis; the name *M. porcinum* has been proposed for these strains (Tsukamura *et al.*, 1983).

MAC bacteria can sometimes be isolated from the apparently healthy lymph nodes of a large percentage of animals inspected in slaughterhouses (Brown and Neuman, 1979).

In the US, any mycobacterial lesion is considered tuberculous for purposes of inspecting pork. Economic losses due to tuberculosis were US$ 2.3 million in 1976, but fell 73% in 1988 (Dey and Parham, 1993).

CATS AND DOGS: In cats, nodular lesions, with or without fistulation, are seen in the cutaneous and subcutaneous tissues, primarily on the venter. *M. fortuitum* is among the mycobacteria identified; on one occasion, *M. xenopi* was also found. This disease should be distinguished from "cat leprosy," whose etiologic agent is *M. lepraemurium* and which is probably transmitted by rat bite. The cutaneous or subcutaneous nodules of "leprosy" can localize in any part of the body (White *et al.*, 1983). Skin infections caused by nontuberculous mycobacteria also occur in dogs. Although dogs are resistant to MAC, 10 cases were confirmed in basset hounds; their susceptibility may be due to a genetic immunodeficiency (Carpenter *et al.*, 1988).

OTHER SPECIES: In addition to infections caused by the prevalent tuberculosis mycobacteria (*M. tuberculosis* and *M. bovis*), infections caused by nontuberculous mycobacteria, such as various MAC serotypes, also occur in nonhuman primates kept in captivity. The infection is predominantly intestinal and manifests as diarrhea and emaciation. Lesions in these animals differ from those caused by *M. tuberculosis* and *M. bovis* in that tubercles do not form and necrosis and giant cells are absent. The lamina propria of the intestine is infiltrated by epithelioid cells (Thoen *et al.*, 1981). In a cage of macaques (*Macaca arctoides*), MAC infection was prevalent among various diseases and caused the death of 44 of 54 animals over a period of two-and-a-half years. The lesions found upon autopsy indicated an enteric origin for the disease process. Histopathological examination and clinical laboratory examinations suggested that the common basis of the diseases was an immunologic abnormality (Holmberg *et al.*, 1985).

Infection due to nontuberculous mycobacteria also occurs in other animal species kept in captivity. In poikilotherms, the disease may be caused by various species of mycobacteria, such as *M. chelonae*, *M. marinum*, *M. fortuitum*, and *M. avium*.

An infection due to *M. ulcerans* was described in koalas (*Phascolarctos cinereus*) on Raymond Island (Australia). The animals had ulcers on the flexor muscles of their extremities. This is the first confirmation of infection due to *M. ulcerans* in animals other than man (Mitchell and Johnson, 1981).

Disease among aquarium or aquiculture fish may be caused by several mycobacteria, particularly *M. marinum* and *M. fortuitum*. The clinical symptoms are variable and may resemble other diseases, with emaciation, ascites, skin ulcerations, hemorrhages, exophthalmos, and skeletal deformities. Upon necropsy, grayish white necrotic foci are found in the viscera. Exposure to *M. marinum* in fish kept in aquariums may cause skin infections in man (Leibovitz, 1980; Martin, 1981).

Unculturable mycobacteria that can be confused with *M. leprae* have been found in several animal species, such as frogs in Bolivia (*Pleurodema cinera* and *P. marmoratus*) and water buffalo in Indonesia (*Bubalus bubalis*).

In the province of Buenos Aires (Argentina), the lymph nodes of 67 apparently normal armadillos were cultured. Potentially pathogenic mycobacterial strains were isolated from 22 (53.7%) of 41 hairy armadillos (*Chaetophractus villosus*) examined. These strains included *M. intracellulare*, *M. fortuitum*, and *M. chelonae*. Mycobacterial cultures were not obtained from 26 *Dasypus hybridus* armadillos ("mulitas") (De Kantor, 1978).

To avoid errors, leprologists doing experimental work with armadillos must take into account both identified mycobacteria from these animals as well as those insufficiently characterized to be identified (Resoagli *et al.*,1982).

FOWL: Avian tuberculosis is due to *M. avium* serotypes 1, 2, and 3. Serotype 2 is the most common in chickens, and serotype 1, in wild or captive birds in the US (Thoen *et al.*, 1981). *M. intracellulare* is usually not pathogenic for fowl (Grange *et al.*, 1990). The lesions are found mainly in the liver, spleen, intestine, and bone marrow, and, infrequently, in the lungs and kidneys. Avian tuberculosis is common; it has a high incidence on farms where chickens have been kept for many years and the enclosures and grounds are contaminated. *M. avium* can survive in the soil for several years. In industrial establishments, the infection is rare because of the rapid replacement of fowl, maintenance conditions, and hygienic measures.

Turkeys can contract tuberculosis by living in association with infected chickens. Ducks and geese are not very susceptible to *M. avium*.

The disease has been observed in several species of wild birds. It may affect any species kept in zoos. Among birds kept as family pets, tuberculosis infections have occasionally been found in parrots, with *M. tuberculosis* as the etiologic agent causing infections localized on the skin and in the natural orifices. This situation is exceptional among birds.

Source of Infection and Mode of Transmission: Man and animals contract the infection from environmental sources, such as water, soil, and dust. Human-to-human transmission has never been reliably demonstrated. *M. fortuitum* abounds in nature and the ability of this mycobacteria, as well as *M. chelonae*, to multiply in soil has been confirmed experimentally. The natural hosts of serotypes 1, 2, and 3 of *M. avium* are fowl, whose droppings help to contaminate the soil, which would be the real reservoir. Other MAC serotypes have been isolated repeatedly from water. In one study (Gruft *et al.*, 1981), MAIS complex mycobacteria were isolated from 25% of 250 water samples collected along the eastern coast of the United States, primarily from the warmer waters of the southeast coast. Similarly, isolations were more abundant from estuarine samples than from river or sea water. During this study, *M. intracellulare* was isolated from aerosols, which would explain the mechanism of transmission to man. Various MAC serotypes were also isolated from soil and house dust in research carried out in Australia and Japan. *M. kansasii* and *M. xenopi* were isolated from drinking water systems. The habitat of *M. marinum* is water, and it has been isolated from snails, sand, and infected aquarium fish.

Many nontuberculous mycobacteria are able to colonize the mucosa of the nasopharynx, bronchia, and intestines of immunocompetent people, who may experience mycobacterial disease when their defenses are low. However, colonization is generally temporary in normal people, as demonstrated by PPD-A (avian) and PPD-B (Battey bacillus or *M. intracellulare*) tuberculin tests that become negative over time. However, the more virulent MAC strains and serotypes that are able to estab-

lish themselves in normal subjects and immunodeficient individuals, such as AIDS patients, now constitute an important pathogen.

Nontuberculous mycobacteria are particularly abundant in soil contaminated by infected animals, such as in pigsties, from where they may be carried to surface waters (Kazda, 1983).

MAC and other mycobacteria can colonize drinking water. In a hospital in Boston (USA), MAC was cultured from 11 of 16 hot water faucets and shower heads, as well as from 3 of 18 cold water faucets. Serotype 4 was predominant (du Moulin *et al.*, 1988 cited in Grange *et al.*, 1990).

It is likely that the pulmonary disease in man is acquired through the respiratory system via aerosols. On the other hand, judging from the affected lymph nodes, lymphadenitis in man, cattle, and swine is possibly acquired through the intestine. Obviously, the mycobacteria that cause abscesses, cutaneous granulomas, and ulcers penetrate through skin lesions.

Tuberculosis in birds is transmitted by way of the intestine, through contaminated food, soil, and water.

Role of Animals in the Epidemiology of the Disease: Mycobacteriosis is not a zoonosis but rather a disease common to man and animals. Both acquire the infection from environmental sources. Animals help to contaminate the environment, as in the case of birds and swine with MAC.

Diagnosis: A reliable diagnosis can only be obtained through culture and identification of the causal agent. The possibility of environmental contamination of the culture media should be kept in mind, as well as the fact that sputum, gastric wash, and saliva may contain nontuberculous mycobacteria without these causing disease. Repeated cultures with abundant growth of a potentially pathogenic *Mycobacterium* species isolated from a patient with symptoms consistent with the disease should be considered significant. The diagnosis is certain when nontuberculous mycobacteria are isolated from surgical resection specimens. Differential diagnosis between tubercular pulmonary infections (*M. tuberculosis*, *M. bovis*, and *M. africanum*) and nontuberculous mycobacterial infections is important, since *M. avium-intracellulare* is naturally resistant to anti-tuberculosis medications, while *M. kansasii* is sensitive to rifampicin and slightly resistant to the other medications (Wolinsky, 1979). The other common forms of infection due to nontuberculous mycobacteria present fewer problems in diagnosis.

Infection in cattle and swine is generally diagnosed using lymph nodes obtained in the slaughterhouse or lockers and sent to the laboratory for culture.

Clinical diagnosis of avian tuberculosis can be confirmed through autopsy and laboratory techniques. The avian tuberculin test on the wattle is useful for diagnosing the disease on farms. The agglutination test with whole blood is considered more useful in birds than the tuberculin test (Thoen and Karlson, 1991).

The enzyme-linked immunosorbent assay (ELISA) has proven to be highly sensitive for detecting antibodies to mycobacteria in swine, fowl, cattle, and other animals (Thoen *et al.*, 1981).

Control: Prevention of the pulmonary disease in man would consist of removing the environmental sources of infection, which are difficult to recognize. Consequently, the recommended alternative is prevention and treatment of predisposing causes.

Specific measures for preventing lymphadenitis in children are not available either. On the other hand, proper skin care, proper treatment of wounds, and avoidance of contaminated swimming pools can prevent dermal and subcutaneous infections.

The source of infection in swine affected by lymphadenitis has been determined on several occasions, such as in cases described in Australia, the US, and Germany (Songer *et al.*, 1980). When other materials were substituted for sawdust and shavings used as bedding, the problem disappeared.

The control of avian tuberculosis should focus primarily on farms. Given the long-term survival of *M. avium* in the environment contaminated with the droppings of tubercular fowl, the only remedy is to eliminate all existing birds on a farm and repopulate with healthy stock in an area not previously inhabited by fowl.

Similar measures are needed to control mycobacteriosis in fish. Infected fish should be destroyed and the aquarium disinfected. In addition, the introduction of contaminated fish or products should be avoided.

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DISEASES IN MAN AND ANIMALS CAUSED BY NON-O1 *VIBRIO CHOLERAE*

ICD-10 A00.0 cholera due to *Vibrio cholerae* O1, biovar cholerae

Etiology: *Vibrio cholerae*, a slightly curved, comma-shaped, gram-negative, motile bacillus, 1.5 microns long by 0.4 microns in diameter. This species includes O1 *V. cholerae*, the etiologic agent of pandemic cholera, and non-O1 *V. cholerae*, which sometimes causes disease in man and animals.

V. cholerae is serologically divided on the basis of its somatic O antigen. The etiological agents of typical, Asiatic, or epidemic cholera belong to serogroup O1. All the rest that do not agglutinate with the O1 antigen are non-O1 *V. cholerae*, formerly called nonagglutinable vibrios (NAGs).

In March 1993, an epidemic strain of non-O1 *V. cholerae* was identified in South Asia and was designated as serogroup O139 (WHO, 1993). The first outbreak occurred in November 1992 in Madras (India) and quickly assumed epidemic proportions in India and Bangladesh, with thousands of cases and high mortality (Das *et al.*, 1993). Isolated strains of serogroup O139 produce a cholera toxin (CT) and hybridize with the CT's DNA probe (Nair and Takeda, 1993). *V. cholerae* O139 contains a large number of gene copies of the toxin and is capable of producing it in large quantities so as to produce a severe pathogenic reaction (Das *et al.*, 1993).

Non-O1 *Vibrio cholerae* has biochemical and culturing properties that are very similar to those of the El Tor biotype of *V. cholerae* that is currently causing the seventh cholera pandemic, which began in Indonesia in 1958 and spread to a large part of the Third World. Non-O1 *V. cholerae* does not agglutinate with a polyvalent serum against El Tor or against the Ogawa and Inaba subtypes. In addition, there is a great similarity between the O1 and non-O1 strains in numeric taxonomy, isoenzyme analysis, and DNA:DNA hybridization analysis (Benenson, 1991).

There are various schemes that classify non-O1 *V. cholerae* in serovars (or serotypes). One of them (currently used in the US) is the Smith scheme (Smith, 1977), which distinguishes more than 70 serovars. Serotyping is limited to reference laboratories for epidemiologic studies.

Geographic Distribution: Worldwide. The presence of non-O1 *V. cholerae* has been confirmed on all inhabited continents, either in the environment (particularly in bodies of water), or in man and animals. In Asia, serogroup O139 has spread from Bangladesh and India to China, Malaysia, Nepal, Pakistan, and Thailand, and may spread further. The first case introduced into the US was a California resident who had traveled to India. There was also a case in the UK.

Occurrence in Man: In man, it appears as sporadic cases or small outbreaks. In areas where cholera is endemic, patients have frequently suffered a disease similar to cholera, but caused by non-O1 *V. cholerae*. In India and Pakistan, nonagglutinable vibrios were isolated (i.e., non-O1 *V. cholerae*) from a small percentage of patients with choleriform symptoms. In 1968, an outbreak attributed to this agent occurred in Sudan and caused gastroenteritis in 544 people, 31 of whom died (Kamal, 1971). In the former Czechoslovakia, an outbreak of gastroenteritis affected 56 young people at a training center. NAGs were isolated from 42 of the 56, but not from 100 controls. The disease was attributed to this etiologic agent and the vehicle of infection was thought to be potatoes (possibly contaminated after cooking) that the patients ate. The disease was mild and short lived (Aldová *et al.*, 1968). There was also an outbreak on a flight from London to Australia that was attributed to an asparagus and egg salad (Dakin *et al.*, 1974). Sporadic cases are more common and have occurred in several countries.

The appearance of serogroup O139 completely changed the scenario. This serogroup is not distinguished from serogroup O1 as an epidemic agent of cholera. The epidemic it is causing has affected tens of thousands of people, with approximately a 5% mortality rate (WHO, 1993). The fear is that this new agent has the potential to cause a pandemic. The epidemic wave has already moved from India to Thailand, Bangladesh, and other countries.

Occurrence in Animals: Non-O1 *V. cholerae* has been isolated from many domestic and wild mammalian species, as well as from birds. In India, 14% of more than 500 dogs harbored "noncholeric vibrios" in their intestines. In the same geographic area, the same vibrios were found in ravens (Sack, 1973). In another area of India, far from the endemic cholera area, 195 domestic animals were examined (goats, cows, dogs, and birds) in a search for an animal reservoir for *V. cholerae*. Fifty-four strains were isolated, 8 of which were O1 *V. cholerae* and 46 of which were non-O1. Serotype O1 was found only during the months when cholera was highly prevalent in the population, whereas the other serotype was found throughout the year (Sanyal *et al.*, 1974).

The Disease in Man: It appears in two forms: intestinal, which is prevalent, and extraintestinal.

Gastroenteritis caused by non-O1 *V. cholerae* is usually of short duration and the symptoms are mild to moderate. The disease is only occasionally severe, as occurs in epidemic cholera (Morris, 1990). The clinical picture is usually variable. In a group of 14 patients in the US, 100% had diarrhea (25% of the patients had bloody

diarrhea), 93% had abdominal pain, 71% had fever, and 21% had nausea and vomiting. Eight of the 14 patients required hospitalization (Morris, 1990). A severe disease was diagnosed in two young tourists who returned to Canada from the Dominican Republic (Girouard *et al.*, 1992).

Of three strains given to volunteers, only one reproduced the diarrheal disease with stool volumes of 140 ml to 5,397 ml (Morris *et al.*, 1990).

In contrast with epidemic *V. cholerae*, which is exclusively intestinal, non-O1 was isolated from different localizations, such as blood (20,8%), wounds (approximately 7%), the respiratory tract (5%), the ears (11.9%), and others (cystitis, cellulitis, peritonitis).

Septicemia caused by non-O1 *V. cholerae* occurs primarily in immunodeficient individuals (chronic hepatopathy, malignant hematological diseases, transplants), with a fatal outcome in more than 60% of cases. In other localizations, non-O1 is often found with other pathogens, and thus it is difficult to discern its true role (Morris, 1990). A case of spontaneous peritonitis and sepsis caused by non-O1 vibrio was described in Argentina. The underlying disease was hepatitis B and non-O1 *Vibrio cholerae* was isolated through blood culture as well as from ascitic fluid in a pure state (Soloaga *et al.*, 1991). In addition, serotype O139 was isolated from the blood of a hepatic patient in India, something that does not occur with patients suffering from cholera caused by O1 *V. cholerae*.

The disease caused by serogroup O139 is not distinguished from that caused by O1. Infection due to O1 *Vibrio cholerae* apparently does not confer cross immunity against O139, as the latter occurs in areas where people of all ages should have some level of immunity to cholera.

In severe cases, dehydration must be treated through fluid and electrolyte replacement. In addition, patients should be treated with tetracycline.

Treatment for patients infected by O139 is the same as for patients infected by O1 *V. cholerae*: rehydration and, in severe cases, administration of tetracycline.

The Disease in Animals: There are few records of the disease in animals; most species seem to be asymptomatic carriers.

In western Colorado (USA), there was an outbreak of the disease in which 7 of approximately 100 American bison (*Bison bison*) died in about three days. The sick bison were depressed and separated themselves from the rest of the herd. The principal symptoms were diarrhea, vomiting, serous nasal discharge, weepy eyes, and conjunctival congestion. Upon necropsy, lesions were found only in the digestive tract. Non-O1 *V. cholerae* was isolated from the abomasum, duodenum, and colon of one animal and from an intestinal swab from another animal. The agent had been isolated previously in the same region from a colt and a sheep (Rhodes *et al.*, 1985). Rhodes *et al.* (1986) studied several bodies of water, from freshwater to salt water (17 mmol of sodium/L). In western Colorado, 16 different serovars of non-O1 *V. cholerae* were found.

In Argentina, an outbreak occurred in young bulls, affecting 20% of 800 animals, with 50% mortality. The main symptom was diarrhea with dark green feces and weight loss. Upon necropsy, hypertrophy of the mesenteric lymph node chain was found. A bacterium with the characteristics of non-O1 *V. cholerae* was isolated from the lymph nodes (Fain Binda *et al.*, 1986).

In addition to these outbreaks, sporadic cases have been recorded in several countries.

Source of Infection and Mode of Transmission: Non-O1 *V. cholerae* is a natural inhabitant of the surface waters of estuaries, rivers, streams, lakes, irrigation channels, and the sea. It has also been isolated from wastewater from an Argentine city (Corrales *et al.*, 1989). Thus, water constitutes the principal reservoir of this etiologic agent.

Non-O1 *V. cholerae* has been isolated from many animal species in different parts of the world. However, their role as reservoirs is still in dispute (Morris, 1990).

Man can be a carrier of the agent and the source of infection for others. In a study conducted on Iranian pilgrims returning from Mecca, several of their contacts acquired the infection and had diarrhea (Zafarí *et al.*, 1973). The source of infection is different in each country. In the US, the main source of infection is raw oysters. Of 790 samples of fresh oysters, 14% contained non-O1 *V. cholerae*. The number of isolations was higher in the summer months, when there are more vibrios in the water (Twedt *et al.*, 1981). As expected, the highest number of human cases has also occurred in summer and autumn. A variety of contaminated foods have been implicated in other countries (see the section on occurrence in man). Surface water adjacent to a cistern was possibly the vehicle of infection for an outbreak in Sudan in 1968 (Kamal, 1971). In a refugee camp in Thailand, 16% of drinking water samples were contaminated by non-O1 *V. cholerae* (Taylor *et al.*, 1988).

A case of cystitis occurred in a woman after she swam in Chesapeake Bay (USA). Ear and wound infections have almost always been caused by exposure to seawater. It is more difficult to establish the source of infection in septicemias. Some are associated with diarrhea, which would indicate infection via the oral route. Shellfish have been suspected in several cases.

Only a minority of strains of non-O1 *V. cholerae* are pathogenic. At present, it can be stated that strains isolated from patients are more virulent than environmental strains. Strains are differentiated based on hemolysins, their ability to colonize the intestine (adherence factor), and the production of a toxin similar to cholera toxin, Shiga-like toxin, and a thermostable enterotoxin similar to that produced by enterotoxigenic *Escherichia coli*. In India and Bangladesh, non-O1 strains that produce cholera toxin were isolated, but this happens less frequently in other countries. In Thailand, only 2% of 237 environmental non-O1 strains and none of 44 strains isolated from clinical cases carried gene sequences homologous with the cholera toxin gene. In summary, strains of *V. cholerae* vary greatly in terms of the factors that could determine virulence and no single characteristic has been identified that could be used to differentiate pathogenic strains from avirulent strains (Morris, 1990).

Role of Animals in the Epidemiology of the Disease: Although the agent has been isolated from many animal species and many researchers consider such animals reservoirs or possible sources of infection for man (Sack, 1973; Sanyal *et al.*, 1974), their actual role is questionable.

Diagnosis: Culture, isolation, and characterization of the microorganism is the only irrefutable method for diagnosing the disease. Alkaline peptone water (APW) and Monsur broth with tellurite and bile salts are useful enrichment media. The recommended selective medium is thiosulfate citrate bile salts sucrose agar (TCBS) (Corrales et al., 1989).

The corresponding antiserum should be used for specific diagnosis of the O139 strain (WHO, 1993).

Control and Prevention: The few recommendations that can be made are not to eat raw or inadequately cooked shellfish and other seafood, and to drink only potable water.

To prevent infection by serogroup O139, the same recommendations as for classic cholera (serogroup O1) apply.

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ENTEROCOLITIC YERSINIOSIS

ICD-10 A04.6 enteritis due to *Yersinia enterocolitica*

Etiology: *Yersinia enterocolitica* is a gram-negative coccobacillus that is motile at 25°C and belongs to the family *Enterobacteriaceae*. This species includes a very heterogeneous group of bacteria that differ greatly in their biochemical properties. Currently, the biochemically atypical strains have been classified as seven different additional species: *Y. aldovae*, *Y. bercovieri*, *Y. frederiksenii*, *Y. intermedia*, *Y. mollaretii*, *Y. kristensenii,* and *Y. rohdei*. These are generally environmental species, can be confused with *Y. enterocolitica*, and at times cause some extraintestinal infections (Farmer and Kelly, 1991). The suggestion has been made to subdivide the species *Y. enterocolitica* into biotypes and serotypes. Biotyping is based on biochemical characteristics, while serotyping is based on the O antigen. The species has been subdivided into more than 50 serotypes, but only some have proven to be pathogenic for man or animals. More recently, the use of ribotyping was suggested for serotype O:3, permitting the differentiation of four clones. Most O:3 isolates belong to clones I and II. These same ribotypes were isolated in Japan. Ribotype I was isolated in Canada and ribotypes II and IV were isolated in Belgium (Blumberg *et al.*, 1991).

A 40- to 50-megadalton plasmid is apparently responsible for the virulence of *Y. enterocolitica*. Strains with this plasmid are characterized by autoagglutination, calcium dependence (antigens V and W cause dependence on calcium for growth at 37°C), and absorption of Congo red. There are also strains that do not contain the plasmid; these are pathogenic and generally negative to pyrazinamide, salicin, and aesculin (Riley and Toma, 1989). Several researchers have found inconsistencies between virulence markers and disease. A study conducted in Santiago (Chile) on a cohort of children up to 4 years of age isolated *Y. enterocolitica* from the feces of 1.1% of children with diarrhea and from 0.2% of the controls. In a subgroup of this cohort, 6% of the children with weekly fecal cultures were bacteriologically posi-

tive without presenting clinical symptoms. The isolates of *Y. enterocolitica* from the asymptomatic children were serotype O:3, but did not have the virulence properties attributed to virulent strains (Morris *et al.*, 1991).

Geographic Distribution: Worldwide. The agent has been isolated from animals, man, food, and water. The human disease has been confirmed on five continents and in more than 30 countries (Swaminathan *et al.*, 1982). There are geographic differences in the distribution of serotypes. Serotypes 3, 5, 9, and 27 are found in Europe and many countries on other continents with temperate or cold climates. Serotypes 8, 13, 18, 20, and 21 appear primarily in the US. Serotype 8 has caused several epidemic outbreaks (Carniel and Mollaret, 1990). Outside the Americas, serotype 8 has been isolated from the fecal matter of a healthy dog and a piglet in Nigeria. None of these strains had virulence markers (Trimnell and Adesiyun, 1988).

The serotype pattern is changing in the US. In New York City and New York State, serotype 3 appears most frequently; this is also true in California. From 1972 to 1979, only two isolates of O:3 were confirmed in California, but the frequency of this serotype began to increase such that from 1986 to 1988 it was part of 41% of all isolates of *Y. enterocolitica* (Bissett *et al.*, 1990). This trend seems to be spreading as serotype O:3 in children has emerged in Atlanta, Georgia and in other US cities (Lee *et al.*, 1991).

Occurrence in Man: There are marked differences in disease incidence between different regions and even between neighboring countries. The highest incidence rates are observed in Scandinavia, Belgium, several eastern European countries, Japan, South Africa, and Canada. The disease is less common in the United States, Great Britain, and France. In Belgium, the agent was isolated from 3,167 patients between 1963 and 1978, with isolations increasing since then. Of the strains isolated, 84% belonged to serotype 3, but isolations of serotype 9 have risen since then (de Groote *et al.*, 1982). In Canada from 1966 to 1977, 1,000 isolations (serotype 3) were made from human patients, while in the US from 1973 to 1976, 68 cases occurred, with serotype 8 predominating. Approximately 1% to 3% of acute enteritis cases in Sweden, the former West Germany, Belgium, and Canada are caused by *Y. enterocolitica* (WHO Scientific Working Group, 1980). The lack of laboratory facilities hinders knowledge of disease incidence in developing countries. In tropical areas, *Y. enterocolitica* seems to be a minor cause of diarrhea (Mata and Simhon, 1982).

Most cases are sporadic or appear as small, familial outbreaks, but several epidemics have also been described. Three of these outbreaks occurred in Japan in 1972 and affected children and adolescents, with 189 cases in one epidemic, 198 in another, and 544 in the third. The source of infection could not be determined. In 1976, an outbreak in the state of New York affected 218 school children. The source of the infection was thought to be chocolate milk (possibly made with contaminated chocolate syrup). An outbreak in 1982 in the US affected three states (Tennessee, Arkansas, and Mississippi), and caused 172 patients to be hospitalized. Serotypes 13 and 18 of *Y. enterocolitica*, which are rare in the US, were isolated from these patients. Statistical association indicated milk from a single processing plant as the source of infection (Tacket *et al.*, 1984). An outbreak was reported in 1973 in Finland that affected 94 conscripts (Lindholm and Visakorpi, 1991). A study conducted in a hospital in the Basque country of Spain on 51 cases of yersiniosis

recorded during the period 1984–1989 found that most of the patients were urban, 62% were male, their average age was 16–19 years, and the hospital stay was 6 to 12 days for adults and less for children (Franco-Vicario *et al.*, 1991). However, this scenario varies from country to country. In many industrialized countries, *Y. enterocolitica* is one of the principal causes of gastroenteritis in children and sometimes is second to *Salmonella* in isolates taken from the pediatric population (Cover and Aber, 1989). In late 1989 and early 1990, an outbreak occurred in Atlanta, Georgia (USA) among black children. *Y. enterocolitica* serotype 3 was isolated from 38 (0.78%) of 4,841 fecal samples from seven hospitals in different American cities. Twenty of the 38 children had eaten pig intestines ("chitterlings"), which were probably undercooked. Other intestinal pathogens isolated were *Shigella* (1.01%), *Campylobacter* (1.24%), and *Salmonella* (2.02%) (Lee *et al.*, 1991). An outbreak affecting 80 children was recorded in Rumania (Constantiniu *et al.*, 1992).

Most cases occur in fall and winter in Europe and from December to May in South Africa.

Occurrence in Animals: *Y. enterocolitica* has been isolated from many domestic and wild mammals, as well as from some birds and cold-blooded animals. The serotypes isolated from most animal species differ from those in man. Important exceptions are swine, dogs, and cats, from which serotypes 3 and 9, the most prevalent causes of human infection in many countries, have been isolated. In addition, serotype 5 was found in swine and is common in people in Japan (Hurvell, 1981).

In some countries, the rate of isolations from animals is very high. In Belgium, serotypes that affect man were isolated from 62.5% of pork tongues collected from butchers (de Groote *et al.*, 1982). Studies done in Belgium and Denmark revealed that 3% to 5% of swine carry the agent in their intestines.

The Disease in Man: *Y. enterocolitica* is mainly a human pathogen that usually affects children. The predominant symptom in small children is an acute enteritis with watery diarrhea lasting 3 to 14 days; blood is present in the stool in 5% of cases. In older children and adolescents, pseudoappendicitis syndrome predominates, with pain in the right iliac fossa, fever, moderate leukocytosis, and a high rate of erythrosedimentation. The syndrome's great similarity to acute appendicitis has frequently led to surgery. In adults, especially in those over 40 years of age, an erythema nodosum may develop one to two weeks after enteritis. The prognosis is favorable for almost all those affected, 80% of whom are women. Reactive arthritis of one or more joints is a more serious complication. About 100 cases of septicemia have been described, mainly in Europe. Other complications may be present, but are much rarer.

Of 1,700 patients with *Y. enterocolitica* infection in Belgium, 86% had gastroenteritis, nearly 10% had the pseudoappendicitis syndrome, and less than 1% had septicemia and hepatic abscesses (Swaminathan *et al.*, 1982).

An epidemic with 172 cases occurred in the United States in 1982 and was attributed to pasteurized milk: 86% had enteritis and 14% had extraintestinal infections localized in the throat, blood, urinary tract, peritoneum, central nervous system, and wounds. Extraintestinal infections were more common in adults. In patients with enteritis (mostly children), the disease caused fever (92.7%), abdominal pain (86.3%), diarrhea (82.7%), vomiting (41.4%), sore throat (22.2%), cutaneous eruptions (22.2%), bloody stool (19.7%), and joint pain (15.1%). The last symptom was seen only in patients 3 years of age or older (Tacket *et al.*, 1984).

Although extraintestinal complications are rare, they can be fatal (mortality is estimated at 34% to 50%) (Marasco *et al.*, 1993). Complications, such as hepatic or splenic abscesses, occur in adults and generally in immunodeficient patients. Mortality is very high in septicemia caused by transfusion of red blood cells contaminated by *Y. enterocolitica*. Of 35 cases counted, 23 were fatal. Fever and hypotension are the principal symptoms and appear in less than one hour (see the section on source of infection and mode of transmission).

In Norway during the period 1974–1983, 458 cases of yersiniosis were diagnosed and patients were followed up for 10 years. Upon admission to the hospital, 184 patients had abdominal pain, 200 had diarrhea, 45 experienced vomiting, and 36 experienced weight loss. Mesenteric lymphadenitis or ileitis was found in 43 of 56 who underwent laparotomy. Four to 14 years after discharge, 38 were readmitted with abdominal pain, and 28 with diarrhea. High mortality was confirmed in 16 of 22 patients who suffered from chronic hepatitis as a result of the infection (Saebo and Lassen, 1992a and 1992b).

Treatment may be useful in the case of gastrointestinal symptoms and is highly recommended for septicemia and complications from the disease (Benenson, 1992). *Y. enterocolitica* is susceptible to commonly used antimicrobials, except for ampicillin and cephalothin. There are indications that there is no good correlation between *in vitro* assays and clinical efficacy (Lee *et al.*, 1991). Aminoglycosides are the antibiotics recommended most often in cases of septicemia. Other indicated antimicrobials are cotrimoxazole and ciprofloxacin.

The Disease in Animals: In the 1960s, several epizootics in chinchillas occurred in Europe, the United States, and Mexico, with many cases of septicemia and high mortality. These outbreaks were originally attributed to *Y. pseudotuberculosis*, but the agent was later determined to be *Y. enterocolitica* serotype 1 (biotype 3), which had never been isolated from man. The principal clinical symptoms consisted of sialorrhea, diarrhea, and weight loss. In the same period, cases of septicemia were described in hares, from which serotype 2 (biotype 5) was isolated; this serotype also does not affect man. *Y. enterocolitica* has been isolated from several species of wild animals, in some of which intestinal lesions or hepatic abscesses were found. In the former Czechoslovakia and the Scandinavian countries, *Y. enterocolitica* was isolated from 3% to 26% of wild rodents, but necropsy of these animals revealed no lesions. Similar results were obtained in southern Chile, where the agent was isolated from 4% of 305 rodents of different species and from different habitats (Zamora *et al.*, 1979). Serotypes isolated from rodents are generally not those pathogenic for man. Among wild animals in New York State, serotype O:8 has been isolated from a gray fox (*Urocyon cinereoargenteus*) and from a porcupine (*Erethizon dorsatum*); serotype O:3 has been isolated from another gray fox. Both serotypes are pathogenic for man (Shayegani *et al.*, 1986).

Studies carried out on swine, dogs, and cats are of particular interest, since these animals harbor serotypes that infect man. The agent has been isolated from clinically healthy swine and from animals destined for human consumption. In one study, a much higher rate of isolations was obtained from swine with diarrhea than from apparently healthy animals. In another study, however, the agent was isolated from 17% of healthy swine and from 5.4% of swine tested because of various symptoms (Hurvell, 1981). *Y. enterocolitica* has been isolated from swine during out-

breaks of diarrhea, with no other pathogen detected. Blood or mucus do not generally appear in the feces, but may be found in the stool of some animals. Diarrhea is accompanied by a mild fever (Taylor, 1992). Swine that are carriers of *Y. enterocolitica* serotypes that infect man have been noted primarily in countries where the incidence of human disease is higher, such as in the Scandinavian countries, Belgium, Canada, and Japan. The rate of isolation from swine varies from one herd to another and depends on the level of contamination in each establishment. On one farm the agent may be isolated only sporadically and at a low rate, while on another, isolations may be continuous and reach 100% of the groups examined (Fukushima *et al.*, 1983).

Y. enterocolitica has been isolated from young sheep with enterocolitis in New Zealand and also in southern Australia. The sheep from 14 herds in New South Wales from which the agent (serotypes 2, 3) was isolated had diarrhea and some showed delayed growth and died (Philbey *et al.*, 1991). In Great Britain, *Y. enterocolitica* was thought to have caused abortions in sheep. The etiologic agent was isolated from sheep fetuses and most of the serotypes were 6,30 and 7, which did not have the plasmid that determines the markers to which virulence is attributed (Corbel *et al.*, 1990). An O:6,30 strain isolated from the liver of an aborted sheep fetus was inoculated intravenously in a group of sheep that had been pregnant for approximately 90 days; the infection produced a necrotizing placentitis and abortions (Corbel *et al.*, 1992).

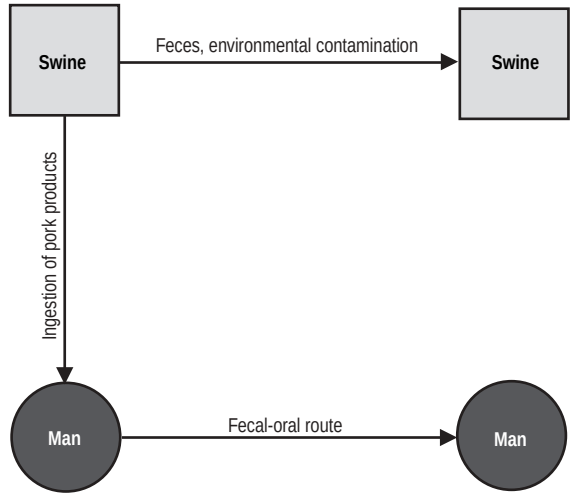
Abortions have been described in association with *Y. enterocolitica* in cattle in the former Soviet Union and Great Britain and in buffalo in India. In the latter country, serotype O:9 was isolated from nine buffaloes that aborted; this serotype shares common antigens with *Brucella* and gives serologic cross reactions with that bacterial species (Das *et al.*, 1986).

Serotypes of *Y. enterocolitica* were isolated from 5.5% of 451 dogs in Japan (Kaneko *et al.*, 1977) and from 1.7% of 115 dogs in Denmark (Pedersen and Winblad, 1979). In contrast, the incidence of canine carriers in the US and Canada is low. The disease seems to occur rarely in dogs, but it should be borne in mind that many clinical cases are not diagnosed because isolation is not attempted. In two cases of enteritis described in Canada, the dogs manifested neither fever nor abdominal pains, but they had frequent defecations covered with mucous and blood (Papageorges and Gosselin, 1983). *Y. enterocolitica* has also been isolated from apparently healthy cats. Serotypes O:8 and O:9 are among the types isolated from dogs and cats.

Infection caused by *Y. enterocolitica* has been confirmed in several monkey species. In one colony of patas monkeys (*Erythrocebus patas*) in Missouri (USA), two monkeys died less than one month apart from a generalized infection caused by *Y. enterocolitica*. The remaining 20 monkeys were examined and the agent was isolated from rectal swabs taken from five of the clinically normal monkeys (Skavlen *et al.*, 1985).

Source of Infection and Mode of Transmission (Figure 10): The epidemiology of enterocolitic yersiniosis is not entirely clear. The agent is widespread in water, food, many animal species, and man. Of interest is the fact that the serotypes isolated from water and food often do not correspond to the types that produce disease in man. This is also true of the serotypes found in the majority of animal species,

Figure 10. Enterocolitic yersiniosis (*Yersinia enterocolitica*). Supposed mode of transmission.



with the exception of pigs and, to some extent, dogs and cats. In countries with the highest incidence of human disease, pigs are frequently carriers of serotypes pathogenic for man. In contrast, in those countries where the incidence of human disease is low, such as the US or Great Britain, serotypes pathogenic for man are rarely isolated from pigs (Wooley *et al.*, 1980; Brewer and Corbel, 1983).

Research conducted in Scandinavia, Canada, and South Africa strongly suggests that the probable reservoir of the agent is swine. In other countries, however, the reservoir is still unknown. Serotype 8, which predominated in the United States, was isolated from 2 of 95 asymptomatic individuals after an outbreak in New York State due to chocolate milk and caused by the same serotype. Serotype 8 was isolated from water and foods in the former Czechoslovakia, but no human cases were seen (Aldova *et al.*, 1981). Some nosocomial outbreaks indicate that human-to-human transmission is possible. A study was conducted in a university hospital in the United States between 1987 and 1990 to evaluate nosocomial transmission of the infection. Of 18 patients from whom *Y. enterocolitica* was isolated, 8 acquired the infection outside the hospital, 5 were infected in the hospital 18 to 66 days after being admitted for causes other than gastroenteritis, and in 5 cases, the origin could not be identified (Cannon and Linnemann, 1992). Some familial outbreaks have been attributed to exposure to dogs. Nevertheless, dogs and cats are not considered important reservoirs.

At present, serotype O:3 predominates throughout the world as a human pathogen. Swine are the primary reservoir and source of infection. In Denmark, where there are approximately 2,000 human cases each year, it was demonstrated that more than 80% of swine herds are infected. Healthy pigs show a high prevalence of *Y. enterocolitica* serotype O:3. A study conducted at a slaughterhouse in

Denmark examined 1,458 pigs; serotype O:3 was isolated from the feces of 360 (24.7%) animals. Fecal contamination of the carcass varied with the evisceration technique. In the manual procedure, which is the traditional technique, frequency was 26.3%, while in the mechanical procedure—suggested along with plugging the anus and rectum with a plastic bag—it fell by 1% to 2.2%, depending on the region of the carcass (Andersen, 1988). The clinically important serotypes, O:3, O:5,27, and O:8, have been isolated from chopped pork, pig tongue, and from chicken.

Swine slaughterhouse workers are an occupational group at risk of being infected. Enzyme-linked immunosorbent assay (ELISA) was used to examine serum samples from 146 workers in Finland; antibodies were found for serotype O:3 in 19% of them and in 10% of blood donors used as controls. The tonsils of 31 of 120 pigs from the same slaughterhouse yielded positive cultures for serotype O:3 (Merilahti-Palo *et al.*, 1991). In a similar study conducted in Norway, 25 (11.1%) of 316 slaughterhouse workers and 9.9% of 171 veterinarians were positive for IgG antibodies to serotype O:3. Counter to expectations, of 813 army recruits, prevalence was higher among those from urban areas (15.2%) than from rural areas (Nesbakken *et al.*, 1991).

Milk and water are vehicles of infection, among others. An outbreak in 1976 was attributed to pasteurized chocolate milk. Another outbreak occurred in New York in 1981, when 239 people became ill. The largest outbreak of all occurred in several U.S. states and affected 1,000 people who drank recontaminated pasteurized milk. Unlike other outbreaks, the infection was caused by very rare serotypes (O:13a, O:13b). Pasteurization is effective in destroying the agent, and thus it is assumed that contamination occurred afterward. Water contaminated by animal fecal matter has been assumed to be the common source of infection in various Nordic countries in Europe and in the US. A small familial outbreak occurred in Canada; it was caused by serotype O:3, which is responsible for about 75% of all human cases in that country. The agent was isolated from two family members and from water from a shallow well that may have been contaminated by dog feces swept in by heavy rains. The strains from the patients and the water had the same characteristics (Thompson and Gravel, 1986).

It is often difficult to identify the source of infection. Foods may contain a small number of pathogenic *Y. enterocolitica* within a large population of other bacteria, primarily environmental species of *Yersinia* spp. and nonpathogenic serotypes of *Y. enterocolitica*. Isolation and enrichment procedures are not always able to detect the etiologic agent (Schiemann, 1989).

Blood transfusion is another route for human-to-human transmission. Although rare, the consequences of such cases are usually serious. From April 1987 to February 1991, there were 10 cases in the US of bacteremia caused by transfusion of red blood cells. The final six of these patients showed fever and hypotension within 50 minutes of transfusion. One patient suffered explosive diarrhea within 10 minutes of transfusion. Four of the six died within a period of 12 hours to 37 days. The serotypes isolated were O:5,27 (4 cases), O:3 (one case), and O:20 (one case) (CDC, 1991). Blood donors were interviewed and some acknowledged having had diarrhea in the 30 days prior to donating blood; one had diarrhea the same day and two indicated they had had no gastrointestinal complaints. In Great Britain, four of a total of six cases were fatal in 1988. Two cases occurred in Scotland in four months alone and both people died (Prentice, 1992; Jones *et al.*, 1993). Prentice (1992) esti-

mates that outside Great Britain there have been 27 cases of septicemia caused by blood transfusion, 17 of them fatal. One case of autologous transfusion has also been described (Richards *et al.*, 1992).

The mode of transmission is not well known either, but it is widely accepted that the infection is contracted by ingestion of contaminated foods, as in the case of other enterobacterial diseases, as well as by contact with carrier animals and by human-to-human transmission. It is known that *Y. enterocolitica* can multiply at refrigeration temperature. It is believed that this led to the 1982 epidemic in the US (see the section on occurrence in man) produced by recontaminated pasteurized milk. This epidemic also reveals that serotypes other than 3, 5, 8, and 9 can give rise to the disease, although less commonly.

Role of Animals in the Epidemiology of the Disease: Although not providing definitive proof, the accumulated data in countries with a high incidence of the human disease indicate that swine are probably an important reservoir of *Y. enterocolitica*, particularly serotype O:3, which is currently the prevalent type, and type O:9, which is also frequent in swine. The disease caused by a dish prepared with pig intestines ("chitterlings") in various American cities is good evidence that the infection is transmitted through food.

Diagnosis: In cases of enteritis, appendicitis, erythema nodosum, and reactive arthritis, the possibility of *Y. enterocolitica* infection should be considered. The agent can be isolated from the patients' feces. MacConkey agar and a selective agar called cefsulodina irgasan novobiocin (CIN), created specifically for *Yersinia*, can be used for this purpose. Both biotype and serotype should be identified. The cold enrichment technique is useful, particularly in the case of carriers that may excrete few *Y. enterocolitica* cells. Samples are suspended in peptone culture broth or a buffered phosphate solution for 3 to 7 days at 4°C to encourage the growth of *Y. enterocolitica* and suppress that of other bacteria. However, routine diagnosis is an impractical procedure, takes a long time (about 1 month), and does not exclude nonpathogenic *Yersinia*.

Tube serum agglutination and the ELISA test can be used with good results as additional diagnostic techniques. Active infections produce high titers that decline over time. Serum agglutination titers of 1/40 to 1/80 are rare in healthy individuals, but common in yersiniosis patients and can rise to very high titers. Positive cultures without clear evidence of gastroenteritis are not always accompanied by a high serum agglutination titer.

Very high titers are common in patients with acute appendicitis (Schiemann, 1989). In countries where serotype 9 is a frequent pathogen for man and is also harbored by swine, cross-reaction between *Brucella* and that serotype may cause difficulties.

Antibodies in swine against serotype 9 of *Y. enterocolitica* can be differentiated from those against *Brucella* by flagellar antigens, which *Y. enterocolitica* has and brucellae do not. *Y. enterocolitica* also possesses the common enterobacterial antigen, which *Brucella* does not have and which therefore may also be used to distinguish them (Mittal *et al.*, 1984). Other animals that have been exposed to serotype 9 can also show cross-reactions with *Brucella*.

A comparison of three tests for serum diagnosis of type O:3 (immunoelectrophoresis, ELISA, and agglutination) produced similar results in terms of sensitivity and specificity (Paerregaard *et al.*, 1991).

A method has been developed for direct identification of *Yersinia enterocolitica* in blood using polymerase chain reaction (PCR). This procedure can detect the agent in 500 bacteria per 100 microliters of blood (Feng *et al.*, 1992).

Control: Currently recommended measures are to observe food hygiene rules; to ensure that animal products, particularly pork, are well cooked; and to not drink raw milk or water of doubtful purity.

An important step in prevention is to avoid contaminating swine carcasses with fecal matter (see the section on source of infection and mode of transmission). Given the possibility of interhuman infection in hospitals, generally recommended measures for nosocomial infections should be implemented.

A practical method for preventing transmission through transfusions is to screen with hematology stains (Wright, Wright-Giemsa) any blood bank unit that has been refrigerated for 25 days or more. Testing has shown that when the contamination is from a single colony forming unit (CFU) of *Y. enterocolitica*, the bacterial count at 26 days rises to 10^7–10^8 CFU and ≥ 1 ng/mL of endotoxin is detected (CDC, 1991).

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ENTEROCOLITIS DUE TO *CLOSTRIDIUM DIFFICILE*

ICD-10 A04.7

Synonyms: Pseudomembranous enterocolitis, antibiotic-associated diarrhea, hemorrhagic necrotizing enterocolitis.

Etiology: *Clostridium difficile* is an anaerobic, gram-positive bacillus 3–16 microns long and 0.5–1.9 microns in diameter that forms oval, subterminal spores.

Some strains produce chains of two to six cells. *C. difficile* is generally motile in broth cultures.

C. difficile produces two types of toxins: enterotoxin A and cytotoxin B. Toxin A is lethal to hamsters when administered orally. Toxin B is cytotoxic for cultured cells of all types. A picogram of toxin B is enough to produce the cytotoxic effect (Cato *et al.*, 1986). Not all strains produce toxins. Another virulence factor is a substance that affects intestinal motility.

Various subclassification schemes have been devised for a better understanding of the pathogenicity of *C. difficile* as well as for epidemiological purposes. One of them is based on electrophoretic patterns of proteins on the cellular surface due to the different protein profiles produced by SDS-PAGE (polyacrylamide gel electrophoresis with sodium dodecyl sulphate), staining and autoradiography of radiomarked proteins. This method has made it possible to distinguish 15 types of *C. difficile* (Tabaqchali, 1990). In addition, 15 serogroups were distinguished using the plate serotyping system. Six of these serogroups proved to be cytotoxigenic. The cultures were isolated from patients who had pseudomembranous colitis or antibiotic-associated diarrhea (Toma *et al.*, 1988).

Geographic Distribution: Probably worldwide. The agent has been isolated from several sources, such as soil; marine sediment; and fecal matter from dogs, cats, cattle, camels, horses and other animals; as well as from people without diarrhea (Cato *et al.*, 1986). The number of animals and environmental samples (non-nosocomial) studied to determine *C. difficile* carriage was very limited (Levett, 1986).

Occurrence in Man: The disease appears sporadically and in nosocomial outbreaks. Most cases of pseudomembranous colitis are nosocomial infections (Lyerly *et al.*, 1988). It is estimated that more than 90% of pseudomembranous colitis cases are due to *C. difficile* and that about 20% of diarrhea cases are associated with antibiotics.

Occurrence in Animals: Outbreaks of enterocolitis have occurred in horses, rabbits, hamsters, guinea pigs, and dogs.

In Australia, a study was done of dogs and cats treated in two veterinary clinics. *C. difficile* was successfully cultured in 32 of 81 fecal samples (39.5%). Of the 29 animals that received antibiotics, 15 (52%) tested positive in cultures for *C. difficile.* There was no difference in carriage rate between dogs and cats. The environment of both clinics was also surveyed for contamination. In one clinic, 15 of 20 sites were contaminated; in the other, 6 of 14 sites were contaminated. There were both cytotoxigenic and noncytotoxigenic isolates. Fifty percent of the animal isolates and 71.4% of the environmental isolates were not cytotoxigenic. Both dogs and cats may be potential reservoirs (Riley *et al.*, 1991).

The Disease in Man: *C. difficile* produces pseudomembranous colitis or antibiotic-associated diarrhea in man. The clinical symptoms range from watery diarrhea, with varying degrees of abdominal pain, to pseudomembranous hemorrhagic necrotizing colitis. Infections outside the intestine caused by *C. difficile* are less important and occur less frequently. Abscesses, wound infections, pleurisy, and other organic effects have been described. Arthritis may also occur as a complication of acute colitis caused by *C. difficile* (Limonta *et al.*, 1989).

Forty to fifty percent of infants have a high load of *C. difficile* in their intestines, with a high rate of A and B toxins; despite this, they do not become ill. There is no satisfactory explanation for this phenomenon yet (Lyerly *et al.*, 1988). Children who suffer from other diseases or have undergone surgery are at risk of developing pseudomembranous colitis (Adler *et al.*, 1981). In contrast, *C. difficile* is part of the normal flora in a very small percentage (approximately 3%) of adults (Limonta *et al.*, 1989).

Pseudomembranous colitis was described in the late 1800s, but its importance was established in the 1970s with the use of antibiotics against anaerobes. Pseudomembranous colitis emerged as reports began to appear on the death of patients treated with clindamycin, a derivative of lincomycin that had proven effective against serious anaerobe infections. Diarrhea had already been observed in patients treated with lincomycin, but with the new antibiotic a severe inflammation of the mucosa of the colon with pseudomembranes occurred as well. The mortality rate among patients treated sometimes reached 10%, but was generally less (Lyerle *et al.*, 1988). It was soon seen that other antibiotics, such as ampicillin and cephalosporins, could cause enterocolitis as well (George, 1984). In essence, antibiotics altered the normal flora of the intestine, disturbing the balance among the different bacterial species and allowing *C. difficile* to multiply.

The first step in treatment should be to stop treatment with the antibiotic that may have caused the disease. The most common treatment is with vancomycin, which is not absorbed in the intestine and can reach high concentrations. The patient recovers rapidly. Metronidazole, which is less expensive and widely used in Europe, is also effective. It should be kept in mind that vancomycin and metronidazole may, in turn, cause the disease if their concentration in the colon is below an inhibitory level (Lyerly *et al.*, 1988). Relapses occur in approximately 20% of the patients treated. One study compared the efficacy of vancomycin and teicoplanin. Clinical cure was achieved in 100% of 20 patients treated with vancomycin; 96.2% of 25 patients treated with teicoplanin were cured. After treatment, five (25%) of those treated with vancomycin and two (7.7%) of those treated with teicoplanin were carriers of *C. difficile* (de Lalla *et al.*, 1992).

The Disease in Animals: The difference between the disease in humans and animals lies in the different sites affected. While the disease appears primarily as enterocolitis in man, in animals the disease may be cecitis or ileocecitis. Typhlocolitis also occurs.

In the state of Missouri (USA), an outbreak of colitis associated with the possibly accidental contamination of feed by lincomycin was described. Seven horses developed diarrhea. Autopsy of a stallion revealed that the cecum was black and contained some 20–30 L of a serosanguineous fluid; the abdominal cavity contained some 5 L of a clear liquid. Two other outbreaks affecting 15 horses occurred in the same state (Raisbeck *et al.*, 1981).

An outbreak of diarrhea in colts 2 to 5 days old occurred in Colorado (USA). *C. difficile* was isolated from the feces of 27 of 43 neonates with diarrhea (63%) and the cytotoxin was detected in the feces of 65% of the animals. *C. difficile* could not be isolated from healthy foals and adults. This outbreak was not associated with antimicrobial treatment. One foal that died had hemorrhagic necrotizing enteritis; an abundant culture was obtained from the contents of the small intestine (Jones *et al.*,

1987). Hemorrhagic necrotizing enteritis in neonate foals is usually caused by other clostridia, such as *C. perfringens* types B and C, and *C. sordelli*. Some cases may be due to *C. difficile*. *C. difficile* was isolated from four foals that died at three ranches, and the presence of the cytotoxin was also confirmed (Jones *et al.*, 1988). A case of typhlocolitis was also described in an adult horse (Perrin *et al.*, 1993). Traub-Dargatz and Jones (1993) recently reviewed the literature on the disease in horses.

Chronic diarrhea due to *C. difficile* was described in dogs; it was successfully treated with metronidazole (Berry and Levett, 1986).

A rabbit breeder observed green, watery diarrhea in approximately 25% of his 130 animals. Upon autopsy, lesions (of varying intensity) were found only in the cecum. The total loss was 40 rabbits. A study confirmed that the feed was contaminated by a food meant for swine, to which lincomycin had been added (permitted only in feed for pigs and fowl). The situation returned to normal when the feed was changed (Thilsted *et al.*, 1981).

Hamsters (*Mesocricetus auratus*) are very susceptible to *C. difficile* and are used as model animals. Proliferative ileitis is seen in young animals; in adult hamsters, the disease is characterized by chronic typhlocolitis with hyperplasia of the mucosa (Rehg and Lu, 1982; Chang and Rohwer, 1991; Ryden *et al.*, 1991).

Outbreaks of typhlitis not induced by antibiotics also occur in guinea pigs. An outbreak occurred in a colony of 400 female specific-pathogen free guinea pigs, maintained gnotobiologically with mice; 123 animals became ill, died, or were sacrificed. The disease was attributed to deficient intestinal flora (Boot *et al.*, 1989).

Source of Infection and Mode of Transmission: Diarrhea due to *C. difficile* occurs in both man and animals absent any association with antibiotics. However, the use of antibiotics and the resulting imbalance in the normal intestinal flora is a predominant factor inducing pseudomembranous enteritis or diarrhea varying from slight to profuse and hemorrhagic. The implicated antibiotics are, in particular, clindamycin and lincomycin, but other antimicrobials may also be responsible (ampicillin and cephalosporins). An intraperitoneal injection of ampicillin given to mice increased the rate of *C. difficile* fecal isolates from 19.4% to 63.6% (Itoh *et al.*, 1986).

The main reservoir of *C. difficile* seems to be infants in the first months of life. The carriage and excretion of cytotoxigenic strains in diarrheal dogs may also be an additional zoonotic source of infection (Berry and Levett, 1986; Weber *et al.*, 1989; Riley *et al.*, 1991).

Another aspect to consider is that *C. difficile* forms spores that are resistant to environmental factors. Environmental contamination by *C. difficile* plays an important role in the epidemiology of the disease, in both hamsters and man. *C. difficile* was isolated from 31.4% of the environmental samples from a hospital ward (Kaatz *et al.*, 1988). Studies conducted with epidemiological markers demonstrate cross infection between nosocomial patients and hospital acquisition of the infection, as well as a direct relationship between symptoms and the type of *C. difficile* (Tabaqchali, 1990). A recent study on nosocomial transmission is illustrative in this regard. Rectal swabs taken from 49 chronic-care patients in a geriatric hospital confirmed the presence of *C. difficile* in 10 of them (20.4%). A prospective study took samples from 100 consecutive patients admitted to an acute care ward in the same hospital, upon admission and every two weeks thereafter. Two patients (2%) were

positive upon admission and 12 of the initial 98 negatives became colonized by *C. difficile,* representing a 12.2% nosocomial acquisition rate. The length of hospitalization was the most important determinant in colonization (Rudensky *et al.*, 1993).

Role of Animals in the Epidemiology of the Disease: Animals play a limited role in the transmission of the infection.

Diagnosis: Clinical diagnosis of pseudomembranous enterocolitis can be obtained through endoscopy to detect the presence of pseudomembranes or microabscesses in the colon of diarrheal patients with *C. difficile* toxins in their feces (Lyerly *et al.*, 1988).

Laboratory diagnosis consists of culturing the patient's feces in CCFA medium (cycloserine cefoxitin fructose egg yolk agar), which is a selective and differential medium. Patients generally have an elevated number (10^7 or more) of *C. difficile* in their feces (Bartlett *et al.*, 1980). The medium can be improved by substituting sodium taurocholate for egg yolk.

Since not all strains are toxigenic, detection of the toxin in the feces confirms the diagnosis. One of the assays used most often is tissue culture, which is extremely sensitive: it can detect a picogram of toxin B (cytotoxin). The mouse lethality test can also be used. Currently, a commercially available system containing a monolayer of preputial fibroblasts in a 96-well microdilution plate is used (Allen and Baron, 1991).

Prevention: Avoid abuse of antibiotics. This factor is particularly acute in the developing countries, where antibiotics can often be obtained without a prescription.

Hypochlorite solutions have been recommended for disinfection of surfaces in hospital settings (Kaatz *et al.*, 1988); glutaraldehyde-based disinfectants have been recommended for instruments, particularly endoscopes (Rutala *et al.*, 1993).

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FOOD POISONING CAUSED BY *VIBRIO PARAHAEMOLYTICUS*

ICD-10 A05.3 foodborne *Vibrio parahaemolyticus* intoxication

Etiology: *Vibrio parahaemolyticus*, belonging to the family *Vibrionaceae*, is a gram-negative, motile, curved or straight bacillus that does not produce spores. It is a halophile that develops best in media with 2% to 3% sodium chloride but can multiply in an 8% concentration of this salt. In most cases, isolated strains are urease negative, but urease-positive strains are also found; this difference may serve as an epidemiological marker.

Based on O (somatic) and K (capsular) antigens, 20 O groups and 65 K serotypes are serologically distinguished. Most clinical strains can be typed, but environmental strains cannot.

Many clinical strains of *V. parahaemolyticus* cultured in Wagatsuma agar (which contains human red blood cells) are beta-hemolytic, while environmental isolates from water are not. This has been called the Kanagawa phenomenon or test. Given the difference in hemolytic capacity between clinical and environmental strains, it was assumed that hemolysin is a virulence factor. This toxin is called thermostable direct hemolysin (TDH). However, it has been demonstrated that TDH-negative strains can cause disease and produce an immunologically related toxin, thermostable related hemolysin (TRH), with very similar properties. The two hemolysins are coded by two different genes. In some strains, it was possible to find both hemolysins. Of 112 *V. parahaemolyticus* strains studied, 52.3% had the TDH gene alone, 24.3% had the TRH gene, and 11.2% had both genes (TDH and TRH). It can thus be stated that TDH and TRH are important factors in virulence (Shirai *et al.*, 1990). In addition, strains from diarrhea patients producing TRH were compared with environmental strains of *V. parahaemolyticus* (isolated from seawater or seafood) producing TRH. The results show that they were indistinguishable (Yoh *et al.*, 1992).

Pili are another important factor in intestinal colonization and thus in virulence. Various researchers have shown that pili attach to rabbit intestinal epithelium and that adhesive capacity is blocked by treating the vibrios with anti-pilus antibodies (Fab fraction). This does not produce an antihemolysin serum (Nakasone and Iwanaga, 1990 and 1992; Chakrabarti *et al.*, 1991).

Geographic Distribution: *V. parahaemolyticus* has been isolated from sea and estuary waters on all continents. The agent's distribution shows marked seasonal variations in natural reservoirs. During cold months, it is found in marine sediment; during warm months, it is found in coastal waters, fish, and shellfish (Benenson, 1990). There have been a few reports of the isolation of *V. parahaemolyticus* from continental waters and fish in rivers or lakes. It is assumed that these waters had a high concentration of sodium chloride, which would allow the agent to survive (Twedt, 1989). The factors that determine the abundance of the bacteria include water temperature, salinity, and plankton, among other factors.

The countries most affected by the disease are Japan, Taiwan, and other Asian coastal regions, though cases of disease have been described in many countries and on many continents.

Occurrence in Man: Food poisoning caused by this agent occurs sporadically or in outbreaks. Much of the knowledge about this disease is due to researchers in Japan, where the disease was first described in 1953. Subsequent studies showed that during the summer months, 50% to 70% of food poisoning cases and outbreaks were caused by *V. parahaemolyticus* (Snydman and Gorbach, 1991).

It is difficult to estimate the number of sporadic cases that occur. Many of those who fall ill do not see a doctor, and if they do, diagnosis is limited to a clinical examination without laboratory confirmation. Outbreaks can affect few or many people. During an outbreak that occurred in 1978, two-thirds of the 1,700 people who attended a dinner in Port Allen, Louisiana (USA) fell ill. The source of the outbreak was probably undercooked shrimp (CDC, 1978). The attack rate of people exposed during outbreaks in the US varied from 24% to 86% and the number of those affected ranged from 6 to 600. In the four years between 1983 and 1986, there was an outbreak that affected two people (Snydman and Gorbach, 1991).

Another outbreak that affected several hundred people occurred in the Bahamas in 1991. At the most critical point in the outbreak, 348 cases were treated in a hospital on the island. The outbreak was attributed to a gastropod (*Strombus gigas*), commonly called "conch," that the population usually eats raw or partially cooked. Kanagawa-positive *V. parahaemolyticus* was isolated from 5 of 14 patients' stool samples; two positive cultures were also isolated from eight conch samples. Although the number of cultures was limited, it is thought that *V. parahaemolyticus* was the causative agent of the diarrheal disease, which during the entire course of the outbreak affected more than 800 people, most of them adults.

In British Columbia (Canada), *V. parahaemolyticus* cultures were isolated from 13 patients as well as from 221 environmental samples; 23% and 1.4%, respectively, were Kanagawa positive. The cases of infection contracted locally were urease positive and Kanagawa negative; the patients who were infected during a trip abroad were urease negative and Kanagawa positive. Eight percent of the environmental samples were also urease positive and Kanagawa negative. These results suggest that the hemolysin identified by the Kanagawa test is not the only hemolysin involved in the pathogenesis of the infection (Kelly and Stroh, 1989. Also see the section on etiology).

In Recife, in northeastern Brazil, in 8 (38%) of 21 fecal samples from adult patients with gastroenteritis, cultures were also isolated that were urease positive and Kanagawa negative (Magalhães *et al.*, 1991b). Also in Recife, *V. parahaemolyticus* was isolated from 14 (1.3%) of 1,100 diarrheal fecal samples. If only adult samples are taken into account, the isolation rate would be 7.1%. It was also possible to show that the cultures belonged to seven different K antigen serovars (Magalhães *et al.*, 1991a).

Occurrence in Animals: *V. parahaemolyticus* is frequently isolated from fish, mollusks, and crustaceans in coastal waters, throughout the year in tropical climates and during the summer months in cold or temperate climates.

The Disease in Man: The incubation period is from 12 to 24 hours, but may vary from 6 to more than 90 hours. The most prominent symptom is watery diarrhea, which becomes bloody in some cases, as has been seen in Bangladesh, the US, and India. The other common symptoms are abdominal pains, nausea, vomiting, cephalalgia, and sometimes fever and chills (Twedt, 1989).

The disease is usually mild and lasts from one to seven days, but there have been fatal cases (Klontz, 1990). Some extraintestinal cases have occurred, such as infection of wounds, ears, and eyes, and there have also been isolates from blood. In some of these latter cases, there is doubt as to whether they were caused by *V. parahaemolyticus* or other halogenous *Vibrios*. Sautter *et al.* (1988) described the case of a foot wound infected by Kanagawa-negative *V. parahaemolyticus*. A hospital employee suffered a superficial abrasion and a small bruise on the ankle and traveled the following day to the eastern coast of the US. The abrasion began to ulcerate, edema and erythema formed around the ulcer, and the area became painful. By the sixth day, the erythema had grown to 18 cm and a 4 cm ulcer appeared. The patient was treated with dicloxacillin for 14 days. After two days of treatment, the ulcer began to leak a serosanguineous fluid, from which *V. parahaemolyticus* was isolated. Treatment was completed, the patient recovered, and the cultures were negative.

Generally no treatment other than rehydration is required for food poisoning caused by *V. parahaemolyticus*. The use of antibiotics should be reserved for prolonged or severe cases.

The Disease in Animals: *V. parahaemolyticus* causes only an inapparent contamination or infection in fish, mollusks, and crustaceans.

Source and Mode of Transmission: The major reservoir is seawater. Fish, mollusks, and crustaceans acquire the infection from seawater. When humans eat them raw or insufficiently cooked, they act as a source of infection. Humans need a load of 10^5–10^7 of *V. parahaemolyticus* to become infected (Twedt, 1989).

Recently caught fish have a *V. parahaemolyticus* load of only 1,000 per gram or less and recently harvested mollusks have a load of some 1,100 per gram; i.e., a load lower than that needed to infect humans (Twedt, 1989). It is thus assumed that the higher load is caused by handling of these seafoods, permitting multiplication of *V. parahaemolyticus* in the food. *V. parahaemolyticus* reproduces in a very short time (approximately 12 minutes) and exposure of the food to room temperature for a few hours is enough to allow the bacterial load to produce poisoning in man.

A very important factor in the epidemiology of the disease in many countries is the custom of eating raw seafood. Japan is one of the countries with the most outbreaks of food poisoning caused by *V. parahaemolyticus* because raw fish, shellfish, and crustaceans are consumed there. In the US, the most common source of poisoning is the consumption of raw oysters and even some uncooked or undercooked crustaceans.

Carrier status lasts for a few days and there are no known cases of secondary infection.

Role of Animals: The role is indirect and transmission is through food. The only vertebrates involved in the chain of transmission to man are fish, along with mollusks and crustaceans.

Diagnosis: A diarrheal disease occurring during the warm months and in association with the ingestion of seafood should lead one to suspect the possibility of food poisoning caused by *V. parahaemolyticus*. Certain diagnosis is obtained through isolation and characterization of the etiologic agent.

The medium most often used for culturing feces is thiosulfate citrate bile salts sucrose (TCBS) agar. The colonies in this medium take on a green or bluish color,

with a darker green center. As a pre-enrichment medium, water with 1% peptone and 3% salt can be used. Wagatsuma medium is used to determine whether the culture is Kanagawa-positive or negative.

Prevention: The main recommendation is to cook shellfish, crustaceans, and fish at a sufficiently high temperature (15 minutes at 70°C) to destroy *V. parahaemolyticus*, with particular attention to the volume of the seafood in order to achieve the appropriate temperature.

However, the well-established custom in some countries of eating raw seafood makes it very difficult to enforce the recommendation to inactivate *V. parahaemolyticus* in fish, crustaceans, and mollusks by sufficiently cooking these foods.

An experiment conducted to study the increase of hemolysin in comparison with the bacterial count reached the conclusion that the toxin appears when *V. parahaemolyticus* reaches the level of 10^6 per gram and continues to increase with multiplication of the microbe. At 35°C it reached 32 units of hemolysin per gram after 24 hours; at 25°C it reached this level after 48 hours. Once formed, hemolysin is quite stable. Hemolysin showed its maximum heat resistance at a pH of between 5.5 and 6.5. The Kanagawa hemolysin in shrimp homogenate proved to be stable for 17 days when kept at 4°C; at temperatures between 115°C and 180°C, it took between 48.1 and 10.4 minutes for thermal inactivation as demonstrated in rats (Bradshaw *et al.*, 1984).

The results of this and other experiments indicate that from the outset it is necessary to prevent the load of *V. parahaemolyticus* in seafood as much as possible. A contra-indicated practice is washing fish or other seafood in contaminated estuarine water. Cold storage is recommended as soon as possible after cooking. Table surfaces where these products are processed should be waterproof and must be completely cleaned with fresh water (without salt) as there may be cross contamination, particularly from salted foods.

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GLANDERS

ICD-10 A24.0

Synonyms: Farcy, cutaneous glanders, equine nasal phthisis, maliasmus.

Etiology: *Pseudomonas* (*Malleomyces*, *Actinobacillus*) *mallei*, a nonmotile, gram-negative bacillus that is not very resistant to environmental conditions; this is the only nonmotile species in the genus *Pseudomonas*.

Geographic Distribution: At one time, the disease was distributed worldwide. It was eradicated in Europe and the Americas, but foci reappeared in 1965 in Greece, Romania, and Brazil (FAO/WHO/OIE, 1972). The present distribution is not well known, but there are indications that it persists in some African and Asian countries; Mongolia is or was the area of greatest incidence. According to official country reports to the Food and Agriculture Organization of the United Nations (FAO), the International Office of Epizootics (OIE), and the World Health Organization (WHO), no government currently reports cases of glanders. Isolated suspected cases were noted in Mongolia and diagnostic tests were being conducted. No cases have been reported since 1991 in India and since 1987 in Iraq (FAO/WHO/OIE, 1992).

Occurrence in Man: At present, the disease in man is exceptional, if it occurs at all. Attenuated strains of *P. mallei* are found in Asia, where the infection is assumed to persist.

Occurrence in Animals: According to various sources, incidence in solipeds is now low or nonexistent in Myanmar (Burma), China, India, Indonesia, Vietnam, and Thailand, and the disease is seen only occasionally. Cases used to occur sporadically in Pakistan and rarely in Iran. In June 1982, 826 foci with 1,808 cases were reported in solipeds in Turkey and in 1984, 274 foci were reported (OIE, 1982, 1984). The incidence in Mongolia is believed to have been high. The present situation in Ethiopia and the Central African Republic is not known, but cases have occurred in these countries in recent years. The most recent information available is from the "Geographic Distribution" section of the *Animal Health Yearbook* (FAO/WHO/OIE, 1993). Based on the reports obtained, it would seem that the disease is becoming extinct.

In endemic areas, the incidence of infection was higher during the rainy season.

The Disease in Man: The incubation period is usually from 1 to 14 days. Cases of latent infection that became clinically evident after many years have been described. The disease course may be either acute or chronic. In addition, subclinical infections have been discovered during autopsy.

In man as well as in animals, *P. mallei* tends to localize in the lungs, nasal mucosa, larynx, and trachea. The infection is manifested clinically as pneumonia, bronchopneumonia, or lobar pneumonia, with or without bacteremia. Pulmonary abscesses, pleural effusion, and empyema may occur. In the acute forms, there is mucopurulent discharge from the nose, and in the chronic forms, granulomatous nodular lesions are found in the lungs.

Ulcers appear in the mucosa of the nostrils and may also be found in the pharynx. Cellulitis with vesiculation, ulceration, lymphangitis, and lymphadenopathy is seen on the skin at the etiologic agent's point of entry. Mortality in clinical cases is high.

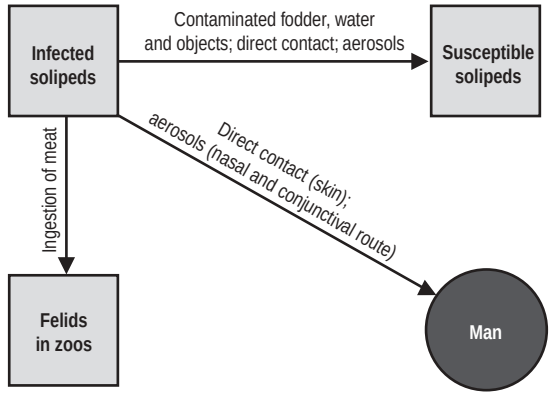
The Disease in Animals: Glanders is primarily a disease of solipeds. The disease course is predominantly chronic in horses and is almost always acute in asses and mules. The acute form results in high fever, depression, dyspnea, diarrhea, and rapid weight loss. The animal dies in a few weeks. The chronic form may last years; some animals recover, others die.

Chronic glanders is characterized by three clinical forms, occurring alone or simultaneously: pulmonary glanders, upper respiratory tract disease, and cutaneous glanders.

Pulmonary glanders can remain inapparent for lengthy periods. When clinical symptoms do occur, they consist of intermittent fever, cough, depression, and weight loss. In more advanced stages, there is dyspnea with rales. Pulmonary lesions usually consist of nodules or pneumonic foci. The nodules are grayish white with red borders; in time, the center becomes caseous or soft, or undergoes calcification and becomes surrounded by grayish granulated or whitish fibrous tissue.

The upper respiratory disease is characterized by ulcerations of the mucosa (necrosis of the nodules is the initial lesion) of one or both nostrils and, frequently, of the larynx and trachea. The ulcers have a grayish center with thick, jagged borders. There is a mucous or mucopurulent discharge from one or both nostrils that forms dark scabs around them.

Figure 11. Glanders. Mode of transmission.



The cutaneous form (farcy) begins with superficial or deep nodules; these later become ulcers that have a gray center and excrete a thick, oily liquid that encrusts the hair. The lymph vessels form visible cords, and the lymph nodes are swollen.

Most authors consider upper respiratory glanders and cutaneous glanders to be secondary forms of pulmonary glanders.

In zoos and circuses, carnivores have contracted glanders as a consequence of eating meat from infected solipeds. The dog is another accidental host.

Source of Infection and Mode of Transmission (Figure 11): Man contracts the infection through contact with sick solipeds, especially those kept in crowded conditions, such as army stables. The portals of entry are the skin and the nasal and ocular mucosa. Nasal discharges, skin ulcer secretions, and contaminated objects constitute the source of infection.

Solipeds acquire the infection from conspecifics, mainly via the digestive route, but probably also through inhalation and wound infection.

Role of Animals in the Epidemiology of the Disease: The reservoir of *P. mallei* is solipeds. The great epizootics of glanders have occurred in metropolitan stables, especially during wartime. Horses with chronic or latent infection are responsible for maintaining the disease in an establishment or region, and their movement from one place to another contributes to its spread. Man and carnivores are accidental hosts.

Diagnosis: Diagnosis of glanders is based on: (a) bacteriologic examinations by means of culture or inoculation into hamsters of nasal or skin secretions or tissue from internal organs, especially the lungs; (b) allergenic tests with mallein (the intrapalpebral test is preferred); and (c) serologic tests, especially complement fixation. Although this last test is considered specific, false positives have occurred.

Control: Prevention in humans consists primarily of eradication of the infection in solipeds. Greatly improved diagnostic methods have made successful eradication campaigns possible, as have the disapperance of stables from cities and the almost complete substitution of automobiles for horses. Eradication procedures consist of identification of infected animals with allergenic or serologic tests, and sacrifice of reactors. Installations and equipment must then be disinfected.

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INFECTION CAUSED BY *CAPNOCYTOPHAGA CANIMORSUS* AND *C. CYNODEGMI*

ICD-10 A28.8 other specified z oonotic bacterial diseases, not elsewhere classified; T14.1 open wound of unspecified body region

Synonyms: Infection caused by DF-2 and DF-2–like bacteria.

Etiology: Among the bacterial strains sent for identification to the US Centers for Disease Control and Prevention (CDC), there was a group that was named DF-2 (dysgonic fermenter-2). It consisted of small, gram-negative bacilli that grow slowly and with difficulty in common laboratory media. The first strain was received in 1961 and the first report on the human disease—a person bitten by two dogs—was published in 1976. Another group was named DF-2–like. These organisms were ultimately described according to the rules of nomenclature and bacterial classification.

There are two different species: *Capnocytophaga canimorsus* and *C. cynodegmi* (Brenner *et al.*, 1989). Both species consist of gram-negative bacilli 1 to 3 microns long that form filaments and are longer in blood agar. They do not have flagella, but do have gliding motility. They are microaerophilic and grow better in an atmosphere to which 5% to 10% carbon dioxide has been added. The best medium for their growth is heart infusion agar with 5% sheep or rabbit blood. They are oxidase- and catalase-positive, unlike CDC group DF-1 (*C. ochracea*, *C. gingivalis*, and *C. sputigena*), which is involved in dental processes and is not of zoonotic interest. *C. cynodegmi* differs from *C. canimorsus* in that it ferments raffinose, sucrose, and melibiose (Brenner *et al.*, 1989), and exhibits marked pathogenic differences.

Geographic Distribution: Worldwide, as are their reservoirs and sources of infection, cats and dogs. CDC received strains of *C. canimorsus* not only from the US, but also from Australia, Canada, Denmark, France, Great Britain, the Netherlands, New Zealand, South Africa, and Sweden.

Occurrence in Man: From 1961 to February of 1993, CDC received 200 cultures of *C. canimorsus* isolated from man (CDC, 1993). *C. canimorsus* occurs primarily in people who have had a splenectomy, alcoholics, and those with chronic pulmonary disease or a malignant blood disease. The disease may occur at any age, but people over age 50 predominated in a series of cases. In 77% of the cases, the disease was preceded by a dog bite or, less frequently, a cat bite, or some other exposure to these animals (a scratch, for example).

C. cynodegmi occurs in healthy individuals, without any preceding or concurrent disease.

Occurrence in Animals: *C. canimorsus* and *C. cynodegmi* have been isolated from the saliva of healthy dogs and cats, and thus are assumed to make up part of the normal flora in the mouths of these animals.

The Disease in Man: In infections caused by *C. canimorsus*, the spectrum of clinical manifestations varies from cellulitis that heals spontaneously to fatal septicemia. Serious cases are usually associated with people who have had a splenectomy or whose liver has been affected by alcoholism. This would indicate that *C. canimorsus* is opportunistic and not very virulent. However, a fatal case was

described in Australia of a 66-year-old woman with septicemia who was hospitalized 48 hours after having been bitten by her dog. The patient presented with symptoms of septicemic shock, hemorrhagic eruption, and altered consciousness. She had no prior illness that could have predisposed her to this syndrome. She died 16 hours after being admitted, despite having received intravenous antibiotic treatment (Clarke *et al.*, 1992).

A similar case occurred in Belgium in a 47-year-old woman without any history of prior illness. She was admitted to the emergency room with septic shock five days after receiving a small lesion on the hand from her dog. *C. canimorsus* was isolated from her blood. Despite intensive treatment, she developed multiple organic deficiencies and died 27 days after being admitted (Hantson *et al.*, 1991).

The clinical picture includes meningitis, endocarditis, septic arthritis, gangrene, disseminated intravascular coagulation, and keratitis. The literature records a total of five cases of ophthalmic infections due to cat scratches or close exposure to this animal. There was also one case attributed to a dog (Paton *et al.*, 1988).

Capnocytophaga cynodegmi causes infection in wounds inflicted by dogs. It does not produce systemic infection.

C. canimorsus and *C. cynodegmi* are sensitive to various antibiotics, including penicillin, erythromycin, minocycline, and doxycycline. Penicillin G is usually preferred by doctors for wounds caused by dogs (Hicklin *et al.*, 1987). It should be kept in mind that 3% to 23% of the gram-negative bacteria isolated from the oropharynx of dogs may be resistant to penicillin (Hsu and Finberg, 1989).

The Disease in Animals: *C. canimorsus* and *C. cynodegmi* are normal components of the bacterial flora in the oropharynx of dogs, cats, sheep, and cattle. They are not pathogenic for these animal species.

Source of Infection and Mode of Transmission: The reservoir of the infection is dogs and cats. The source is the saliva of these animals and transmission is effected by a bite.

C. canimorsus was isolated from the nose and mouth of 4 out of 50 clinically normal dogs (8%). The agent was also isolated from dogs and cats whose bites caused infection in man (Bailie *et al.*, 1978; Chen and Fonseca, 1986; Martone *et al.*, 1980; Carpenter *et al.*, 1987). A broader study indicated that in a sample of 180 dogs, 24% were carriers of *C. canimorsus* and 11% were carriers of *C. cynodegmi*; in a sample of 249 cats, 17% carried *C. canimorsus* and 8% carried *C. cynodegmi* in their mouths. The agent was also isolated in a significant percentage of sheep and cattle (25% and 33%, respectively). In contrast, these agents could not be isolated from the normal flora of man (Westwell *et al.*, 1989).

C. canimorsus is primarily an opportunistic pathogen that infects individuals weakened by concurrent diseases. Those who have had a splenectomy comprise a high-risk group. Asplenic individuals suffer deficient IgM and IgG production and delayed macrophage mobilization. They also produce less tuftsin, a protein derived from IgG that stimulates phagocytosis (August, 1988). Liver disease caused by alcoholism is another predisposing factor for the infection. Predisposition is associated with susceptibility to bacteremia (Kanagasundaram and Levy, 1979).

Role of Animals in the Epidemiology of the Disease: This is a zoonosis in which dogs and, to a lesser extent, cats, play an essential role.

Diagnosis: *C. canimorsus* can be isolated from blood (see the culture medium and atmosphere indicated in the section on etiology). In asplenic patients, it is useful to make a gram-stained preparation of the leukocyte layer of the extracted blood sample.

C. cynodegmi is isolated from wounds.

Prevention and Control: The treatment for any bite should first be thorough irrigation with water, then cleaning with soap and water. In the case of asplenic patients and alcoholics, it is advisable to administer antibiotics prophylactically. It is recommended that such people not own dogs or cats. However, not all authors agree with this recommendation.

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LEPROSY

ICD-10 A30.9 leprosy, unspecified

Synonyms: Hansen's disease, hanseniasis.

Etiology: *Mycobacterium leprae*, a polymorphic acid-alcohol-fast bacillus that up to now has been impossible to culture in artificial laboratory media or in tissue cultures. *M. leprae* is difficult to distinguish from other unculturable mycobacteria naturally affecting animals.

The failure of attempts to culture *M. leprae in vitro* constitutes a great barrier to better determining its biochemical characteristics for identification purposes as well as for therapeutic and immunologic studies. In part, this difficulty has been overcome, first by *in vivo* culture on mouse footpads and later in nine-banded armadillos (*Dasypus novemcinctus*). At present, the latter serve as a model for lepromatous leprosy and provide a large number of bacilli for research.

In identification of *M. leprae*, the dopa (3,4-dihydroxyphenylalanine) oxidation test and extraction with pyridine are of value. Homogenate of human leproma (granulomatous nodule rich in *M. leprae* and characteristic of lepromatous leprosy) oxidizes dopa to indole. Extraction with pyridine eliminates the acid-fast quality of *M. leprae*, but not that of other mycobacteria.

In recent years, more precise identification of *M. leprae* has been achieved by structural analysis of its mycolic acids, analysis by immunodiffusion of its antigens, and interaction of leprosy bacilli with bacteriophages specific for mycobacteria (Rastogi *et al.*, 1982).

Occurrence in Man: Leprosy is endemic in 93 countries. Eighty percent of all recorded cases are concentrated in five countries: India, Brazil, Nigeria, Myanmar (Burma), and Indonesia (WHO, 1988). The highest prevalence is found in the tropical and subtropical regions of Asia, Africa, Latin America, and Oceania. Leprosy is very prevalent in India, Southeast Asia, the Philippines, Korea, southern China, Papua New Guinea, and some Pacific islands. Ninety percent of the cases reported in Latin America come from five countries: Argentina, Brazil, Colombia, Mexico, and Venezuela (Brubaker, 1983). Chile is the only South American country free of the infection. In the United States, most cases occur among immigrants. Autochthonous cases arise in Hawaii, Puerto Rico, Texas, and Louisiana. The infection's prevalence is related to the population's socioeconomic level. The fact that the disease has practically disappeared in Europe is attributed to the improved standard of living there.

There are differences in the regional or racial prevalence of tuberculoid and lepromatous leprosy. Ninety percent of the cases in endemic areas of Africa and 80% of the cases in India are of the tuberculoid type. The lepromatous form represents 30% to 50% of cases among the white population or in some Asian countries such as Japan, China, and Korea (Bechelli *et al.*, 1972).

In countries with efficient control programs, it was expected that prevalence would fall by 60% to 80% by the year 2000. Of the cases reported worldwide, 49.1% were under multidrug treatment in 1990 (Noorden, 1990). The cumulative rate of coverage with polychemotherapy has reached 82%. Each year 1.4 million patients are freed from the disease (WHO, 1993).

Occurrence in Animals: Natural infection has been found in nine-banded armadillos (*Dasypus novemcinctus*) in Louisiana and Texas (USA) and in Mexico. By 1983, the infection had been observed in some 100 armadillos captured in Louisiana (Meyers *et al.*, 1983). Depending on their place of origin, between 4% and 29.6% of 1,033 armadillos examined were infected. On the Gulf Coast of Texas, leprosy lesions were found in 4.66% of 451 armadillos captured (Smith *et al.*, 1983). The disease form found in these animals was a lepromatous leprosy identical to the type produced by experimental inoculation with material from humans. On the other hand, the search for naturally infected armadillos carried out by other researchers in Louisiana, Texas, and Florida, as well as in Colombia and Paraguay, produced negative results (Kirchheimer, 1979).

At present, natural infection of nine-banded armadillos is a well-established fact. Its distribution is limited to some states in the US and Mexico. In Mexico, 1 of 96 armadillos was positive based on histopathology and mouse footpad inoculation (Amezcua *et al.*, 1984). In a study of armadillos found dead on the highways of Louisiana, 10 of 494 (2%) were positive based on histopathology and pyridine extraction (Job *et al.*, 1986a). The infection was also confirmed in an armadillo at the San Diego Zoo, California, and in another armadillo at the Centers for Disease Control and Prevention. The two armadillos originally came from Texas (Walsh *et al.*, 1981).

The ELISA method was adopted for serological study of leprosy in armadillos using phenolic glycolipid (PGL-1) antigen (Truman *et al.*, 1986), which is considered specific for *M. leprae* (Young and Buchanan, 1983). This test was conducted on armadillos captured in central Louisiana before being used in the laboratory (1960–1964). It was found that 17 of the 182 sera (9.3%) were serologically positive. This study was undertaken to refute the argument that free armadillos could have become infected by experimental armadillos through carelessness. The sera were collected at that time for a study on leptospirosis. Of 20 armadillos captured shortly before this study, four were positive.

Another study used ELISA and histopathological tests to examine 77 armadillos in an estimated population of 254 ± 60 animals in a defined area of Louisiana. Five of 67 (1.5%) sera tested with ELISA and 1 of 74 (1.3%) ears submitted for histopathological examination were positive (Stallknecht *et al.*, 1987).

On the Texas Gulf Coast, the presence of leprosy in armadillos was demonstrated (Smith *et al.*, 1983). More recently, 237 armadillo ears from 51 central Texas districts were examined; no positives were found upon histological examination (Clark *et al.*, 1987). A similar negative result was obtained for 853 ears from armadillos killed on the highways or captured for research purposes in five southeastern US states. The examination included microscopic and histopathological examination (Howerth *et al.*, 1990). An infected animal had previously been found in the state of Mississippi (Walsh *et al.*, 1986).

A spontaneous case of leprosy similar to the borderline or dimorphous form was described in a chimpanzee imported from Sierra Leone to the United States. Clinical and histopathologic characteristics (with invasion of dermal nerves by the agent) were identical to those of the human disease. Attempts to culture the bacteria were negative, and the chimpanzee did not respond to tuberculin or lepromin, just as humans infected with lepromatous or dimorphous leprosy give a negative reaction. As with *M. leprae* of human origin, experimental inoculation of rats with the iso-

lated bacillus produced neither disease nor lesions. The only differences with *M. leprae* of human origin were negative results to the dopa oxidation and pyridine tests. However, the dopa oxidation test sometimes fails in animals (armadillos) inoculated experimentally with human *M. leprae* (Donham and Leininger, 1977). Results obtained by inoculating mouse foot pads were similar to those derived with *M. leprae* of human origin, i.e., reproduction of the bacterium in six months up to a quantity similar to that of *M. leprae* without dissemination from the inoculation point (Leininger *et al.*, 1978).

Another case of naturally acquired leprosy was discovered in a primate, *Cercocebus atys* or sooty mangabey monkey (identified in one publication as *Cercocebus torquatus atys*), captured in West Africa and imported to the United States in 1975 (Meyers *et al.*, 1980, 1981). The clinical picture and histopathology were similar to man's and the etiologic agent was identified as *M. leprae* based on the following criteria: invasion of the host's nerves, staining properties, electron microscopy findings, inability to grow in mycobacteriologic media, positive dopa oxidation reaction, reactivity to lepromin, patterns of infection in mice and armadillos, sensitivity to sulfones, and DNA homology (Meyers *et al.*, 1985). Simultaneous intravenous and intracutaneous inoculation succeeded in reproducing the infection and disease in other *Cercocebus* monkeys. The early appearance of signs (5 to 14 months), varying clinical disease forms, neuropathic deformities, bacillemia, and dissemination to various cool parts of the body make the mangabey monkey potentially the most complete model for the study of leprosy. It is the third animal species reported to be able to acquire leprosy by natural infection (Walsh *et al.*, 1981; Meyers *et al.*, 1983, 1985).

The Disease in Man: The incubation period is usually 3 to 5 years, but it can vary from 6 months to 10 years or more (Bullock, 1982). Clinical forms of leprosy cover a wide spectrum, ranking from mild self-healing lesions to a progressive and destructive chronic disease. Tuberculoid leprosy is found at one end of the spectrum and lepromatous leprosy at the other. Between them are found the intermediate forms.

Tuberculoid leprosy is characterized by often asymptomatic localized lesions of the skin and nerves. Basically, the lesion consists of a granulomatous, paucibacillary, inflammatory process. The bacilli are difficult to detect, and can be observed most frequently in the nerve endings of the skin. This form results from active destruction of the bacilli by the undeteriorated cellular immunity of the patient. On the other hand, the humoral response generally involves low titers. Nerve destruction causes lowered conduction; heat sensibility is the most affected, tactile sensibility less so. Trophic and autonomic changes are common, especially ulcers on the sole and mutilation of limbs (Toro-González *et al.*, 1983).

Lepromatous leprosy is characterized by numerous symmetrical skin lesions consisting of macules and diffuse infiltrations, plaques, and nodules of varying sizes (lepromas). There is involvement of the mucosa of the upper respiratory tract, of lymph nodes, liver, spleen, and testicles. Infiltrates are basically histiocytes with a few lymphocytes. Cellular immunity is absent (negative reaction to lepromin) and antibody titers are high. In this form of the disease, as in the dimorphous, erythema nodosum leprosum (ENL) often appears.

The indeterminate form of leprosy has still not been adequately defined from the clinical standpoint; it is considered to be the initial state of the disease. The first

cutaneous lesions are flat, hypopigmented, and have ill-defined borders. If this initial form is not treated, it may develop into tuberculoid, dimorphous, or lepromatous leprosy. Bacilli are few and it is difficult to confirm their presence.

Finally, the dimorphous or borderline form occupies an intermediate position between the two polar forms (tuberculoid and lepromatous), and shares properties of both; it is unstable and may progress in either direction. Destruction of nerve trunks may be extensive. Bacilli are observed in scrapings taken from skin lesions.

A study group (WHO, 1985) has, primarily for practical treatment purposes, defined two types of the disease.

"a) *Paucibacillary*: This includes the categories described as indeterminate (I) and tuberculoid (T) leprosy in the Madrid classification, and the indeterminate (I), polar tuberculoid (TT) and borderline tuberculoid (BT) categories in the Ridley and Jopling classification, whether diagnosed clinically or histopathologically with a bacterial index of <2 according to the Ridley scale at all sites.

b) *Multibacillary*: This includes lepromatous (L) and borderline (B) leprosy in the Madrid classification and lepromatous (LL) and borderline lepromatous (BL) leprosy in the Ridley and Jopling classification, whether diagnosed clinically or histopathologically, with a bacterial index of ≥2 according to the Ridley scale at any site."

An estimated one-third of clinical cases become incapacitated, half of them completely. Nevertheless, these proportions are now changing, due to both prevention/control programs and early implementation of effective treatments.

There is evidence that inapparent infection may occur with a certain frequency among persons, especially family members, in contact with patients.

The Disease in Animals: The disease in armadillos (*Dasypus novemcinctus*) is similar to the lepromatous form in man. Infection in these animlas is characterized by macrophage infiltrates containing a large number of bacilli. Skin lesions range from mild to severe. The small dermal nerves are invaded by the etiologic agent. Many bacilli are seen in the macrophages of the lymph tissue, in the pulp of the spleen, and in Kupffer's cells in the liver.

M. leprae is known to prefer the coolest parts of the human or mouse body. For this reason, armadillos began to be used as experimental animals even before natural infection had been confirmed in these animals, since body temperature in nine-banded armadillos is between 30°C to 35°C. Experimental inoculation of armadillos with human leproma material reproduces the disease, characterized by broad dissemination of the agent, and involvement of the lymph glands, liver, spleen, lungs, bone marrow, meninges, and other tissues, in a more intense form than is usually observed in man (Kirchheimer *et al.*, 1972).

The disease in the chimpanzee appeared as a progressive, chronic dermatitis with nodular thickening of the skin on the ears, eyebrows, nose, and lips. Lesions of the nose, skin, and dermal nerves contained copious quantities of acid-fast bacteria (Donham and Leininger, 1977). The disease was histopathologically classified as dimorphous or borderline 12 months after the clinical symptoms were first observed, and as lepromatous in a subsequent biopsy (Leininger *et al.*, 1978).

In the case of the *Cercocebus* monkey, the initial lesion consisted of nodules on the face. Four months later, a massive infiltration and ulceration were seen on the face, and nodules on the ears and forearms. Sixteen months after cutaneous lesions

were first observed, the animal began to suffer deformities and paralysis of the extremities. Histopathologic findings indicated the subpolar or intermediate lepromatous form, according to the Ridley and Jopling classification. The disease was progressive, with neuropathic deformation of the feet and hands. It seemed to regress when specific treatment was administered. The animal apparently acquired the disease from a patient with active leprosy. Experimental infections carried out to date have indicated that these animals may experience a spectrum of different forms similar to those seen in man (Meyers *et al.*, 1985).

Source of Infection and Mode of Transmission: Man is the principal reservoir of *M. leprae*. The method of transmission is still not well known due to the extended incubation period. Nevertheless, the principal source of infection is believed to be lepromatous patients, in whom the infection is multibacillary, skin lesions are often ulcerous, and a great number of bacilli are shed through the nose; similarly, bacilli are found in the mouth and pharynx. Consequently, transmission might be brought about by contact with infected skin, especially if there are abrasions or wounds. Currently, particular importance is attributed to aerosol transmission. Nasal secretions from lepromatous patients contain approximately 100 million bacilli per milliliter. In addition, *M. leprae* can survive for about seven days in dried secretions. Another possible route of transmission is mother's milk, which contains a large number of bacilli in lepromatous patients (Bullock, 1990). Oral transmission and transmission by hematophagous arthropods are not discounted, but they are assigned less epidemiological importance.

Until recently, leprosy was believed to be an exclusively human disease. However, research in recent years has demonstrated that the infection and the disease also occur naturally in wild animals. Although some researchers (Kirchheimer, 1979) have expressed doubt that the animal infection is identical to the human, the accumulated evidence indicates that the etiologic agent is the same. The criteria (Binford *et al.*, 1982) used to identify the bacillus in animals as *M. leprae* were as follows: (1) selective invasion of the peripheral nerves by bacilli, since the only *Mycobacterium* known to date to invade the nerves is *M. leprae*, (2) failure to grow on common laboratory media for mycobacteria, (3) positive pyridine test to eliminate acid-fastness, (4) positive dopa test, (5) characteristic multiplication in mouse foot pads and in armadillos, and (6) reactivity of lepromin prepared with animal bacilli compared to that of standard lepromin.

The origin of the infection in animals is unknown. Some authors believe that armadillos contracted the infection from a human source, perhaps from multibacillary patients before the era of sulfones. In this regard, it should be pointed out that leprosy bacilli may remain viable for a week in dried nasal secretions and that armadillos are in close contact with the soil. The high prevalence in some localities would also indicate that armadillos can transmit the disease to each other, either by inhalation or direct contact. Another possible transmission vehicle is maternal milk, in which the agent has been detected (Walsh *et al.*, 1981). It has also been suggested that transmission among armadillos may be brought about by thorns penetrating the ears, nose, or other body parts (Job *et al.*, 1986b), as apparently armadillos use places with spiny plants to hide from their predators. These authors have found thorns in the ears of 25.5% of 494 armadillos captured in Louisiana, and in the nose of 36.6% of them.

It is difficult to demonstrate that armadillos are a source of infection for man because of the long incubation period and the impossibility of excluding a human source in an endemic area. In Texas, a case of human leprosy was attributed to a patient's practice of capturing armadillos and eating their meat (Freiberger and Fudenberg, 1981). Subsequently, another five cases with hand lesions were detected in natives of the same state who habitually hunted and cleaned armadillos but had no known contact with leprosy patients (Lumpkin III *et al.*, 1983). To determine if there was a significant association between contact with armadillos and human leprosy in Louisiana, a group of 19 patients was compared with another group of 19 healthy individuals from the same area. Of those with leprosy, four had had contact with armadillos, as opposed to five in the control group. Consequently, it was concluded that such an association did not exist (Filice *et al.*, 1977). However, this conclusion was questioned, since the only valid comparison would be between persons who have handled armadillos and those who have had no contact with them (Lumpkin III *et al.*, 1983).

The prevalence of leprosy in armadillos in Louisiana and Texas suggests that these animals could serve as a reservoir of *M. leprae.* However, nothing is known about the frequency of infection in nonhuman primates and the role they may play in transmission of the disease. The sources of the cases of leprosy in these animals were probably people with lepromatous leprosy.

Diagnosis: Clinically, an anesthetic or hypoesthetic cutaneous lesion raises suspicion of leprosy, even more so if the nerves are enlarged. Diagnosis is confirmed by biopsy of the skin lesion, which also permits classification of the form of the leprosy. For patients with lepromatous or borderline lepromatous leprosy, diagnosis can be made by using the Ziehl-Neelsen staining technique on a film of nasal mucosa scrapings or the interphase between erythrocytes and leukocytes from a centrifuged blood sample. Histopathologic preparations do not stain well using Ziehl-Neelsen and consequently a Fite-Faraco stain is recommended. Also used is the simplified staining method consisting of eliminating acid-fastness with pyridine in order to differentiate *M. leprae* (Convit and Pinardi, 1972). In tuberculoid and other paucibacillary forms of leprosy, it is difficult and at times impossible to confirm the presence of the etiologic agent; in any case, examination of many histologic sections is recommended in order to detect any bacteria present, especially in the nerve endings.

Skin tests have no diagnostic value, but they do serve as an aid to prognosis. Patients with tuberculoid leprosy or other paucibacillary forms react positively to the intradermal lepromin or Mitsuda test (with dead *M. leprae* bacilli and a reading after 28 days), since their cellular immunity is generally not affected. In contrast, lepromatous leprosy and other multibacillary forms give negative results to the Mitsuda test. The lepromin test has limited value for detecting infection in those in contact with patients or the general population in an endemic area (Jacobson, 1991). Serological tests are also of limited use.

The ELISA technique (Young and Buchanan, 1983) for measuring PGL-1 (phenolic glycolipid antigen) antibodies is a great step forward. The reactive titer depends on the patient's bacillary load and also serves to detect infection in those who are in contact with multibacillary patients, as well as in some people in endemic areas (Jacobson, 1991). In Malawi, Africa, where most cases are paucibacillary, the test was not sufficiently sensitive (unless its specificity were to be sacrificed), but it

was used to detect a high percentage of multibacillary patients (Burgess *et al.*, 1988). A variation of this test is the use of the synthetic disaccharide epitope of PGL-1 as an antigen (Brett *et al.*, 1986).

Control: Control is based on early detection and chemotherapy. Given the multiple confirmed cases of resistance to dapsone, combination of this medication with rifampicin is presently recommended for paucibacillary leprosy, and the same two medications in combination with clofazimine are recommended for multibacillary leprosy. Rifampicin has a rapid bactericidal effect and eliminates contagion in patients in one to two weeks. To achieve the objective of eliminating leprosy, all patients should receive polychemotherapy. This treatment has been successful in reducing general prevalence from 5.4 million in 1986 to 3.7 million in 1990. Widespread testing began in 1992 on a new oral treatment that was developed over the preceding five years and combines two antibiotics, rifampicin and ofloxacin. Ofloxacin inhibits an enzyme that controls the way that DNA coils inside the bacterium. It is hoped that this combination will be able to cure leprosy in the course of one month. If testing is successful, all patients should have access to this medication (WHO, 1992). The isolation of patients in leprosariums is no longer necessary, since medication is effective in suppressing infectiousness and thus interrupts transmission of the disease.

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LEPTOSPIROSIS

ICD-10 A27.0 leptospirosis icterohaemorrhagica; A27.8 other forms of leptospirosis

Synonyms: Weil's disease, swineherd's disease, rice-field fever, cane-cutter's fever, swamp fever, mud fever, and other local names; Stuttgart disease, canicola fever (dogs).

Etiology: Leptospires are spiral-shaped bacteria, with open, hooked ends; they are motile, aerobic, and culturable, and they measure some 6 to 20 microns long by 0.1 microns in diameter. They can be seen under a dark-field microscope and pass

through filters that block other bacteria. Two species are recognized: *Leptospira interrogans* and *L. biflexa*. *L. interrogans* is pathogenic for man and animals; *L. biflexa*, a free-living saprophyte found in surface waters, is seldom associated with infection in mammals.

The species of interest as a zoonotic agent is *L. interrogans*. It has more than 200 serologic variants, or serovars, which constitutes the basic taxon. Serovars are grouped for convenience into 23 serogroups (which is not a recognized taxon) on the basis of the predominant agglutinogenic components they share (Faine, 1982; Alexander, 1991). Through the use of ribosomal RNA gene restriction patterns, an attempt is being made to characterize *L. interrogans* serovars in order to establish the bases for molecular typing (Perolat *et al.*, 1990).

Geographic Distribution: Worldwide. There are universal serovars, such as *L. interrogans* serovar *icterohaemorrhagiae* and serovar *canicola*, and serovars that occur only in certain regions. Each region has characteristic serotypes, determined by its ecology. Leptospirosis has a high prevalence in tropical countries with heavy rainfall and neutral or alkaline soils.

Occurrence in Man: Incidence varies in different parts of the world. The disease may occur sporadically or in epidemic outbreaks. In general, outbreaks are caused by exposure to water contaminated by the urine of infected animals. Several occupational groups are particularly at risk, such as workers in rice fields, sugarcane plantations, mines, sewer systems, and slaughterhouses, as well as animal caretakers, veterinarians, and members of the military.

Occurrence in Animals: The infection is common in rodents and other wild and domestic mammals. Worldwide, the infection occurs in approximately 160 mammalian species (Alexander, 1991). Each serovar has its preferred animal host or hosts, but each animal species may be host to one or more serovars. Thus, for example, the serovar *pomona* has pigs and cattle as its principal hosts, but it may transitorily infect other host animals. Dogs are the principal reservoir of *canicola*, but it may occasionally be found in foxes, swine, and cattle.

The Disease in Man: Man is susceptible to a large number of serovars. The incubation period lasts from one to two weeks, although cases with an incubation period of only two days or more than three weeks are known. The disease is characterized by two phases, the bacteremic phase, lasting 7 to 10 days, and the leptospiruric phase, lasting from a week to several months. Clinical manifestations vary and have differing degrees of severity. In addition, numerous cases of infection occur inapparently or subclinically. In general, two clinical types are distinguished: icteric and anicteric. The serious icteric, or hepatonephritic, type (Weil's disease) is much less frequent than the anicteric type. Some authors estimate that this form occurs in approximately 10% of cases. It is often associated with infection caused by *icterohaemorrhagiae*, but this is not the only serovar that can produce it. On the other hand, numerous infections caused by *icterohaemorrhagiae* occur in anicteric form. In the classical form of Weil's disease, the onset of symptoms is sudden, with fever, headache, myalgias, conjunctivitis, nausea, vomiting, and diarrhea or constipation. Prostration may be severe. Petechiae on the skin, hemorrhages in the gastrointestinal tract, and proteinuria are common. Hepatomegaly and jaundice, renal insufficiency with marked oliguria or anuria, azotemia, and electrolyte imbalance develop

with the disappearance of leptospiremia and fever. If the patient's condition improves, diuresis is reestablished and jaundice decreases. Convalescence lasts one or two months, during which time fever, cephalalgia, myalgias, and general malaise may reappear for a few days.

In anicteric cases, the symptomatology is milder. The symptoms during leptospiremia, which occurs during the first week of the disease, are fever, myalgias (particularly in the calves), conjunctivitis, stiffness in the neck, nausea, and sometimes vomiting. Often, the disease resembles influenza. The anicteric form has a benign course and patients recover in about a month. Leptospiruria may continue for a week or several months after the disappearance of clinical symptoms.

Treatment should be started early in order to prevent tissue lesions. Penicillin G and amoxicillin were effective as late as one week after the onset of the disease (Benenson, 1990).

The Disease in Animals

CATTLE: At least 13 serovars have been isolated from cattle. In the Americas, the predominant serovars in cattle are *pomona*, *hardjo,* and *grippotyphosa*; at times, infections caused by *canicola* and *icterohaemorrhagiae*, as well as by other serovars, are found. The serovars *pomona* and *hardjo* are universal. As laboratory methods have improved, outbreaks caused by the latter have been confirmed with increasing frequency. In recent years, serovars belonging to the Hebdomadis group have been isolated more frequently. The importance of infection caused by some serovars is difficult to interpret. This is true of the serotype *paidjan* (Bataviae serogroup), isolated from the kidneys of cattle (obtained in an Argentine slaughterhouse), and the serotype *galtoni* (Canicola serogroup), isolated in Argentina and Colombia (Szyfres *et al.*, 1967; Tedesco *et al.*, 1969). To date, there are no known outbreaks caused by these serotypes in Argentina.

The infection may cause an acute or subacute disease or remain clinically inapparent. The disease manifests with a fever lasting four or five days, anorexia, conjunctivitis, and diarrhea. Leptospiremia begins to disappear when antibodies form, and the leptospires completely disappear from the bloodstream in approximately one week due to humoral immunity. The surviving leptospires are then harbored in the convoluted tubules of the kidneys and the infection enters a chronic phase. Leptospiruria sheds enormous quantities of leptospires to the outside environment, particularly during the first months of infection; later this decreases or ceases entirely. Leptospiruria caused by *hardjo* is much more prolonged than that caused by *pomona*. The *hardjo* serovar (Sejroe serogroup) in cattle is characterized by two syndromes: (a) agalactia, or a significant reduction in milk production, and (b) abortions or birthing of weak calves that die soon after birth. In infections caused by *hardjo*—but not by *pomona*—it was found that leptospires can reside in the genital tract (uterus and oviducts) in both pregnant and nonpregnant females (Ellis and Thiermann, 1986). Infection of the genital tract may indicate the possibility of sexual transmission (Prescott, 1991). *L. interrogans* is subdivided into two genotypes: *hardjo* hardjo-bovis and *hardjo* hardjo-prajitno. The first genotype is the most prevalent in the US.

Infertility may be a sequela of the infection. Serious cases include jaundice. However, the most notable symptoms in a certain proportion of the animals are abortion and hemoglobinuria. Abortions usually occur between one and three weeks after the onset of the disease. Up to 20% of aborting animals retain the placenta.

Cattle of all ages are susceptible. The course of the disease is more severe in calves, which experience stunted growth and variable mortality rates.

Quick-spreading epizootics are characterized by a high morbidity rate. It is possible that rapid passage of the leptospires from one animal to another intensifies their virulence. In slow-moving epizootics, the rate of inapparent infection varies from one herd to another.

Treatment with high doses of penicillin G or tetracycline is recommended for acute leptospirosis. Dihydrostreptomycin (12.5 mg/kg of bodyweight twice a day) may also be used, but due to its potential toxicity, treatment should be suspended after three days. Another suggested treatment is intramuscular sodium ampicillin (20 mg/kg of bodyweight twice a day). In the chronic disease caused by *pomona*, it has been repeatedly shown that a single intramuscular injection of dihydrostreptomycin (25 mg/kg of bodyweight) eliminates the infection from the kidneys of most animals treated. However, this treatment fails in the case of infection caused by *hardjo*, although the number of leptospires is apparently reduced (Ellis *et al.*, 1985).

SWINE: The serovars most often isolated from swine in the Americas and in the rest of the world are *pomona*, *tarassovi*, *grippotyphosa*, *canicola*, and *icterohaemorrhagiae*, as well as *bratislava* and *muenchen* of the Australis serogroup.

Swine are a very important reservoir of *pomona*, with abundant and prolonged leptospiruria. The clinical infection varies from one herd to another. In some cases, infection occurs subclinically, although the animals may exhibit a fever lasting a few days; in others, the infection produces such symptoms as abortion and birth of weak piglets. Stunted growth of piglets, jaundice, hemoglobinuria, convulsions, and gastrointestinal disorders have also been seen. At times, meningitis and nervous symptomatology are present. Abortion usually occurs between 15 and 30 days after infection. The principal serovars that cause abortions or stillborn piglets are *pomona*, *tarassovi*, and *canicola*. Infection that occurs during the last third of pregnancy is the most critical in interrupting gestation. Leptospires of the serovars *bratislava* and *muenchen* localize in the kidneys and in the genital tract of swine, as do *hardjo* leptospires in cattle.

As in cattle, a single intramuscular injection of dihydrostreptomycin (25 mg/kg of bodyweight) is recommended for chronic infections caused by *pomona*.

HORSES: Horses react serologically to many serotypes prevalent in the environment. *Pomona* has been isolated from these animals in the United States, and *hardjo* has been isolated in Argentina. In Europe, *icterohaemorrhagiae*, *sejroe*, and *canicola* have been isolated, as well as *pomona*. Most infections are inapparent. There may be photophobia, watery eyes, edema of the ocular conjunctiva, miosis, and iritis in the acute phase of the disease. In the chronic phase, there may be anterior and posterior adhesions, a turbid vitreous body, formation of cataracts, uveitis, and other ophthalmologic abnormalities (Sillerud *et al.*, 1987). Abortions may occasionally occur in infected mares (Bernard *et al.*, 1993).

Corneal opacity, which is frequently a sequela of the acute phase, can be reproduced through inoculation of inactivated leptospires from various serovars. An antigen relationship has also been demonstrated between *L. interrogans*, crystallin, and the cornea (Parma *et al.*, 1986). Often, the disease's sequela (periodic ophthalmia) is recognized instead of the acute, febrile phase. The onset of periodic ophthalmia occurs when the febrile phase has disappeared, after a latent phase that sometimes

lasts several months. Leptospires have been detected in eye lesions of affected animals, and a high concentration of antibodies can be found in the aqueous humor. However, it should be borne in mind that leptospirosis is not the only cause of periodic ophthalmia. One hundred horses from the Minnesota River valley (USA) were examined ophthalmologically and serologically. A statistically significant association was found between uveitis and serology positive for *pomona*. Not all the seropositive horses were affected by uveitis, possibly due to different levels of exposure, strains of varying virulence, or different routes of infection (Sillerud *et al.*, 1987). Serious cases of leptospirosis with hepatonephritic and cardiovascular syndromes have been described in Europe.

SHEEP AND GOATS: Epizootics in these species are not very frequent. Various serovars that appear to have come from other animal species in the same environment have been isolated from sheep and goats in different countries (Faine, 1982), for example, *hardjo* in Australia and New Zealand, *pomona* in the United States and New Zealand, *grippotyphosa* in Israel, and *ballum* in Argentina. In Western Australia (Australia), a persistent leptospirosis caused by the serovar *hardjo* was found in sheep that had no contact with cattle infected by the same serovar (Cousins *et al.*, 1989). The authors conclude that, in addition to cattle, sheep could be a maintenance host for *hardjo*.

As in other ruminant species, the disease is characterized by fever, anorexia, and, in some animals, by jaundice, hemoglobinuria, anemia, abortion, birth of weak or stillborn animals, and infertility. The virulence of the infecting serovar and the condition of the animal determine the severity of the clinical picture.

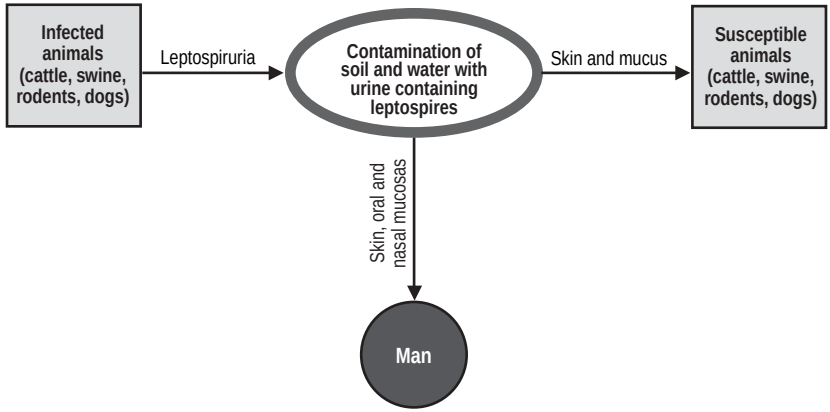
DOGS AND CATS: The predominant serovars in dogs throughout the world are *canicola* and *icterohaemorrhagiae*. In addition to these serovars, *pyrogenes*, *paidjan*, and *tarassovi* have been isolated in Latin America and the Caribbean, and *ballum*, *grippotyphosa*, *pomona*, and *bratislava* have been isolated in the United States (Nielsen *et al.*, 1991). Similar serovars predominate in Europe. The infection may range from asymptomatic to severe. The most serious form is the hemorrhagic, which begins suddenly with a fever that lasts from three to four days, followed by stiffness and myalgia in the hind legs, and hemorrhages in the oral cavity with a tendency toward necrosis and pharyngitis. In a subsequent stage, there may be hemorrhagic gastroenteritis and acute nephritis. Jaundice may occur with infection by *canicola* or by *icterohaemorrhagiae*, particularly in infection caused by the latter serovar. Case fatality is estimated at 10%.

The disease rarely occurs in cats.

WILD ANIMALS: Many wild animals, including rodents, are perfectly adapted to leptospires and show no symptoms or lesions.

Source of Infection and Mode of Transmission (Figure 12): After a week of leptospiremia, animals shed leptospires in their urine, contaminating the environment. The best reservoirs of the infection are animals that have prolonged leptospiruria and generally do not suffer from the disease themselves. For example, this is true of rats, which harbor *icterohaemorrhagiae* and rarely have lesions. The infection in man and animals is contracted directly or indirectly, through skin abrasions and the nasal, oral, and conjunctival mucosa. Indirect exposure through water, soil, or foods contaminated by urine from infected animals is the most common route. An

Figure 12. Leptospirosis. Synanthropic transmission cycle.



unusual case of transmission occurred in Great Britain, where an 11-year-old boy acquired the infection from a rat bite (Luzzi *et al.*, 1987).

People who work with livestock are often exposed to animal urine, directly or as an aerosol, which can contaminate the conjunctiva, nasal mucosa, or abrasions on exposed skin. They may also become infected indirectly by walking barefoot where animals have urinated. In many countries, domesticated animals, particularly swine and cattle, constitute important leptospire reservoirs and a frequent source of infection for man.

Rice-paddy workers are exposed to water contaminated by urine of rodents that infest the fields. Among agricultural workers, sugarcane harvesters are another high-risk group. Field mice nesting among crops are a source of infection for harvesters, particularly during the early morning hours, when workers' hands come into contact with dew mixed with urine.

Among pets, dogs are a common source of infection for man by serovars *canicola* and *icterohaemorrhagiae*.

Tropical regions are endemic areas of leptospirosis and the highest case rates correspond to areas with heavy rainfall. The highest number of cases occurs during the rainy season. Epidemic outbreaks erupt because of environmental changes, such as flooding, which cause rodents to move into cities. An example of this is the epidemics that occurred in the city of Recife (Pernambuco State, Brazil), in 1966 and 1970, with 181 and 102 cases, respectively. The predominant serovar was *icterohaemorrhagiae*. Humidity, high temperatures, and an abundance of rats were the principal factors that precipitated these outbreaks as well as others in tropical regions. Small epidemic outbreaks are also caused by recreational activities, such as swimming or diving in streams or ponds contaminated by the urine of infected animals. An outbreak occurred in a cattle- and swine-raising region of Cuba, where 21 cases were diagnosed in people who bathed in the Clavellina River and the Maniadero reservoir. The Pomona and Australis serogroups were predominant and two isolates of the latter were obtained from the river water (Suárez Hernández *et*

al., 1989). Epidemic outbreaks caused by several different serovars have occurred among soldiers wading in streams or camping by riverbanks during jungle maneuvers. Such epidemics have occurred in Panama and Malaysia; in these cases, the source of infection was the urine of infected wild animals.

Animals, either primary or secondary hosts, contract the infection in a similar way. The density of the host population and the environmental conditions in which it lives play important roles. On cattle ranches, the infection is usually introduced by a carrier animal with leptospiruria and, at times, by fields that flood with water contaminated at a neighboring establishment.

Pathogenic leptospires (*L. interrogans*) do not multiply outside the animal organism. Consequently, in addition to carrier animals, existence of a leptospirosis focus requires environmental conditions favorable to the survival of the agent in the exterior environment. Leptospires need high humidity, a neutral or slightly alkaline pH, and suitable temperatures. Low, inundated ground and artificial or natural freshwater receptacles (ponds, streams, reservoirs, etc.) are favorable to their survival, whereas salt water is deleterious. Soil composition, both its physiochemical and biological characteristics (microbe population), also acts to prolong or shorten life for leptospires in the environment. Temperatures in the tropics constitute a very favorable factor for survival of leptospires, but cases of leptospirosis may also occur in cold climates, although they are less frequent.

Role of Animals in the Epidemiology of the Disease: Wild and domesticated animals are essential for the maintenance of pathogenic leptospires in nature. Transmission of the infection from animals to man is effected directly or indirectly.

Human-to-human transmission is rare. Man is an accidental host and only in very special conditions can he contribute to the maintenance of an epidemic outbreak. Such was the case in an epidemic described in the forest northeast of Hanoi (Vietnam). The outbreak occurred among soldiers occupied in logging and transport of logs by buffalo through a swampy area. Leptospiruria was observed in 12% of 66 convalescent soldiers. In contrast, the rate of infection was insignificant among buffalo and rodents in the region. The pH of the surface water was neutral, the workers worked barefoot, and their urine had a pH that fluctuated around seven (their diet was vegetarian). Leptospiruria persisted in some of the soldiers for more than six months (Spinu *et al.*, 1963).

A case of transmission through mother's milk was described in the US (Songer and Thiermann, 1988). A female veterinarian continued nursing after being infected with the serovar *hardjo* while performing an autopsy on a cow. Twenty-one days after the appearance of clinical symptoms in the mother, the baby became ill with fever, anorexia, irritability, and lethargy. The serovar *hardjo* was isolated from the baby's urine and the baby recovered with antibiotic treatment.

Various cases of congenital infection have also been described (Faine, 1991).

Diagnosis: In man, the etiologic agent can be isolated from blood during the first week of the disease; afterwards, it can be isolated from the urine, either by direct culture or by inoculation into young hamsters. Repeated blood samples are necessary for serological examination. The patient has no antibodies during the first week; they appear in six to seven days and reach maximum levels in the third or fourth week. If the first sample is negative or low-titer and the second shows an appreciable increase in antibody titer (fourfold or more), leptospirosis is indicated.

The same diagnostic procedures are employed for animals as for man. Blood or urine may be used for the bacteriologic examination, depending on the stage of the illness. If a necropsy is performed on a sacrificed or dead animal, kidney cultures should be made. Examination of several tissue samples from the same individual is not always easily done in veterinary practice, but individual diagnosis of domestic animals is not as important as herd diagnosis. Discovery of high antibody titers in several members of a herd and a clinical picture compatible with leptospirosis indicate a recent infection.

Low titers may indicate residual antibodies from a past infection or recently formed antibodies that have not yet had time to reach a high level.

The serologic reference test that is used most for man as well as for animals is microscopic agglutination (MAT). This test should be carried out using representative serovars from different serogroups, especially those occurring in the region. It is necessary to bear in mind that cross-reactions are produced not only between different serovars of the same serogroup but, at the beginning of the infection (two to three weeks), also between serovars of different serogroups, and a heterologous serovar titer may predominate. Reaction to the homologous serovar becomes more pronounced with time. Cross-reactions are much more frequent in man than in animals.

The macroscopic plate test with inactivated antigens can be used as a preliminary or screening test for man and animals. It is fast and easy, and particularly useful for diagnosing disease in a herd.

Plate agglutination is a genus-specific test, which uses as an antigen the *patoc* strain of saprophytic leptospira (*L. biflexa*) to determine if the patient is suffering from leptospirosis (Mazzonelli *et al.*, 1974). Reaction to this test is marked during the acute phase of leptospirosis and then quickly becomes negative (Faine, 1982). Among more recent tests, those of interest are indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA). With both, the types of immunoglobulins (IgM or IgG) can be determined by using the corresponding antigens. IgM appears after the first week of the disease and IgG appears after several weeks. In some human cases, IgG antibodies cannot be detected for reasons as yet unknown.

The utility of ELISA for diagnosing infection due to *hardjo* was compared with MAT. It was found that a positive reaction can be obtained with MAT 10 days after the animal has been experimentally infected; ELISA does not give a positive reaction until 25 days after infection. In addition, there was a 90% concordance between both tests. Cross-reactions with sera from animals inoculated with other serotypes occurred in fewer than 1% (Bercovich *et al.*, 1990).

The serovar *hardjo* is subdivided into subserovars or genotypes: *hardjo* genotype hardjo-bovis and *hardjo* genotype prajitno. A DNA probe for genotype hardjo-bovis was developed by LeFebvre (1987). Three methods for detecting *hardjo* type hardjo-bovis were compared: with DNA hybridization, 60 of the 75 urine samples from cows experimentally exposed were positive; with immunofluorescence, 24 samples were positive; and with culturing, only 13 were positive. The DNA probe was shown to be much more sensitive than the other techniques in detecting the genotype hardjo-bovis (Bolin *et al.*, 1989a).

A very sensitive generic test is polymerase chain reaction (PCR), which can detect as few as 10 leptospires (Mérien *et al.*, 1992).

Control: In man, control measures include: (a) personal hygiene; (b) use of protective clothes during farm work; (c) drainage of lowlands whenever possible; (d) rodent-proof structures; (e) food protection and correct garbage disposal; (f) control of infection in domestic animals; (g) avoidance of swimming in streams and other fresh watercourses that may be contaminated, and (h) chemoprophylaxis of high-risk occupational groups (sugarcane harvesters, rice-paddy workers, or soldiers).

Human immunization has not been widely applied. It has been used with promising results in Italy, Poland, and the former Soviet Union. However, because of secondary, mainly allergic effects, its use did not spread. Tests of a vaccine made in a chemically defined, protein-free medium are under way (Shenberg and Torten, 1973). In China, a similar vaccine is being used on a wide scale.

The use of antibiotics in prophylaxis and treatment of human leptospirosis has yielded contradictory results. One study (Takafuji *et al.*, 1984) showed that doxycycline is effective in chemoprophylaxis; the same drug is probably also effective in treatment. Because leptospirosis caused many cases of disease among American soldiers training in Panama, a double-blind field test was undertaken to determine the efficacy of doxycycline in preventing the infection. Nine hundred forty soldier volunteers were randomly divided into two groups. One group was given an oral dose of 200 mg of doxycycline each week for three weeks, and the other group was given a placebo. After remaining in the jungle for three weeks, 20 cases of leptospirosis were diagnosed in the placebo group (attack rate of 4.2%) and only one case was diagnosed in the doxycycline group (attack rate of 0.2%), i.e., the drug was 95% effective (Takafuji *et al.*, 1984). It has been suggested (Sanford, 1984) that chemoprophylaxis would be justified in areas where incidence is 5% or higher. Mechanization of farm work has resulted in a decrease of outbreaks, for example, among rice-paddy workers.

Among domesticated animals, vaccination of pigs, cattle, and dogs is effective in preventing the disease, but it does not protect completely against infection. Vaccinated animals may become infected without showing clinical symptoms; they may have leptospiruria, although to a lesser degree and for a shorter time than unvaccinated animals. A few known human cases of leptospirosis were contracted from vaccinated dogs. There are bacterins to protect against the *pomona*, *hardjo*, and *grippotyphosa* serovars in cattle; against *pomona* in swine; and against *canicola* and *icterohaemorrhagiae* in dogs. Immunity is predominantly serovar-specific, and the serovar or serovars active in a focus must be known in order to correctly immunize the animals. Females should be vaccinated before the reproductive period to protect them during pregnancy. Young animals can be immunized after 3 or 4 months of age. Bacterins now in use require annual revaccination. For herds to which outside animals are being introduced, it is recommended that vaccination be repeated every six months. An effective measure is to combine vaccination with antibiotic treatment (Thiermann, 1984).

Vaccination against *hardjo* is not very satisfactory, not even if the prevalent genotype hardjo-bovis is used in combined vaccines (Bolin *et al.*, 1989b) or in monovalent vaccines (Bolin *et al.*, 1991).

It has been demonstrated that vaccination with bacterins initially stimulates the production of IgM antibodies, which disappear after a few months and are replaced by IgG antibodies. Vaccination generally does not interfere with diagnosis because of the quick disappearance of IgM antibodies, which are active in agglutination. IgG

are the protective antibodies and can be detected with serum protection assays in hamsters or with the growth inhibition test in culture media.

A vaccine derived from the outer membrane of leptospires has been obtained and has yielded very promising results in laboratory tests by conferring resistance not only against the disease but also against the establishment of leptospiruria. Chemotherapy is promising. Experiments have shown that a single injection of dihydrostreptomycin at a dose of 25 mg/kg of bodyweight is effective against leptospiruria in cattle and swine. The infection has been eradicated in several herds with antibiotic treatment and proper environmental hygiene. The combination of vaccination and chemotherapy for the control of swine leptospirosis has been proposed.

Proper herd management is important for control. It has been repeatedly demonstrated that swine can transmit the *pomona* serovar to cattle. Therefore, separation of these two species is important for prophylaxis.

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LISTERIOSIS

ICD-10 A32.1 listerial meningitis and meningoencephalitis; A32.7 listerial septicaemia; A32.8 other forms of listeriosis; P37.2 neonatal (disseminated) listeriosis

Synonyms: Leukocytosis, listerial infection, listeriasis, listerellosis, circling disease (in animals).

Etiology: The genus *Listeria* contains seven species, but only two are of interest in human and animal pathology: *L. monocytogenes* and *L. ivanovii* (formerly *L. bulgarica* or serovar 5 of *L. monocytogenes*). A notable difference between the two pathogenic species is their hemolytic ability.

The most important species for both man and animals is *L. monocytogenes*, a gram-positive, facultatively anaerobic bacillus 0.5 to 2 microns long and 0.5 microns in diameter that is motile at temperatures between 20°C and 25°C. It is beta-hemolytic in blood agar and forms a narrow band of hemolysis around the colonies (unlike *L. ivanovii,* which forms a wide band). A noteworthy characteristic of *L. monocytogenes* is its ability to grow at low temperatures; at a pH between 6 and 9, it can reproduce at temperatures from 3°C to 45°C. It is a facultative, intracellular parasite of the reticuloendothelial system. For purposes of epidemiological

research, *L. monocytogenes* is subdivided into 11 serovars. Most human (92%) and animal cases are caused by serovars 4b, 1/2b, and 1/2a (Bortolussi *et al.*, 1985). Therefore, serotyping is of limited usefulness for identifying a source of infection (Gelin and Broome, 1989).

Of 161 isolates serotyped in the US, 33% belonged to serovar 4b; 31.5%, to serovar 1/2b; 30%, to serovar 1/2a; 4%, to serovar 3b; 1%, to serovar 3a; and 0.5%, to serovar 1/2c (Gelin *et al.*, 1987). When 71 isolates were serotyped in Brazil, seven different serovars were recognized; 50% were 4b and 29.6% were 1/2a (Hofer *et al.*, 1984).

Although serotyping has been useful as a preliminary approach, other schemes had to be devised in order to be able to specify the source of infection. Subtyping was done primarily with two methods: phage typing and electrophoretic enzyme typing. In Great Britain, 64% of the strains could be typed using 28 phages; in France, 78% could be typed using 20 phages. In both cases, a sizeable percentage of strains could not be typed. All strains of *L. monocytogenes* can be typed using the isoenzymatic subtyping method (Selander *et al.*, 1986). Recently, ribosomal RNA typing (ribotyping) has been used with success.

Geographic Distribution: Worldwide. *L. monocytogenes* is widely distributed in vegetation, soil, and human and animal intestines.

Occurrence in Man: Incidence is low, but it is an important disease because of its high mortality. In many developing countries, listeriosis is rare. There is greater concentration of cases in European countries and the United States, perhaps because medical personnel in these countries are more on the lookout for the disease and because better laboratory support is available. In the former Federal Republic of Germany (West Germany), there were 296 cases of listeriosis between 1969 and 1985, 60% of which occurred in urban areas. Fifty percent of the strains isolated were from newborns and the most common serovar was 4b (Schmidt-Wolf *et al.*, 1987). In Great Britain, information was obtained from 722 cases occurring from 1967 to 1985. In 246 cases (34%), the infection affected the mother, the fetus, or the newborn. Neonatal infection was diagnosed within the first two days postpartum in 133 (54%) cases; 56 cases (23%) were diagnosed later than two days postpartum. There were 47 (19%) cases of intrauterine death. There were also 10 cases (4%) of mothers with bacteremia that did not affect the fetus. Overall case fatality was 50% (McLauchlin, 1990a). The author estimates that these data must include less than 50% of the total number of cases that occurred in the country. In adults and youth, 474 cases were recorded; 275 (58%) were men and 199 (42%) were nonpregnant women. Case fatality was 44%. Seventy-six percent of these patients had an underlying illness. An increase in incidence was noted in autumn (McLauchlin, 1990b).

There were an estimated 800 cases per year in the US between 1980 and 1982, with an incidence of 3.6 per million inhabitants and at least 150 deaths (19% case fatality). The highest attack rates were seen in newborns (4.7 per 100,000 live births) and in persons 70 years of age or older (11 per million) (Gellin and Broome, 1989). There are few recognized cases in developing countries. Sporadic cases have been seen in several Latin American countries. In a Mexican hospital, hemocultures were carried out during a three-month period on all children whose mothers showed signs of amniotic infection; *L. monocytogenes* was isolated from 4 out of 33 newborns examined (Pérez-Mirabate and Giono, 1963). In Peru (Guevara *et al.*, 1979),

serovars 4d and 4b of *L. monocytogenes* were isolated from three fatal cases of neonatal listeriosis and from five aborted fetuses. In Argentina, there are few data on the occurrence of human listeriosis. In Córdoba (Argentina), there are cases of neonatal listeriosis each year, and these constitute between 2% and 3% of bacteriologically confirmed sepsis (Paolasso, 1981). In a small town in the province of Buenos Aires, Manzullo (1981) isolated *L. monocytogenes* type 1a from a bovine fetus, the vaginal exudate of the woman who milked the cows, and from the household's female dog. In another town, Manzullo (1990) isolated the agent from a woman's vaginal exudate and from the woman's female cat. In a Buenos Aires medical center, nine cases of listeriosis were diagnosed in 15 years, two of them fatal. Only one patient was not immunocompromised (Roncoroni *et al.*, 1987).

Most cases occur sporadically, but epidemic outbreaks have occurred in several countries. In 1981, in a maternity hospital in Halifax (Canada), there were 34 perinatal cases and 7 cases in women without underlying illness or immunosuppression. Case fatality in the babies born live was 27%. There were five spontaneous abortions and four babies stillborn at term. The epidemic outbreak was attributed to coleslaw: *L. monocytogenes* serovar 4b was isolated from the cabbage as well as from the patients. On the farm where the cabbages were grown, two sheep had died from listeriosis the previous year; in addition, the farmer used sheep dung as fertilizer. It is also worth noting that the farmer kept the cabbage refrigerated at 4°C, which allowed the etiologic agent to multiply at the expense of other contaminant microorganisms (Schlech *et al.*, 1983).

An earlier outbreak occurred in 1979 in eight hospitals in Boston (USA); it affected 20 patients, 15 of whom acquired the infection in the hospital. Raw vegetables were assumed to be the source of infection.

In Massachusetts (USA), an epidemic outbreak caused by pasteurized milk was recorded in 1983. It affected 42 immunocompromised patients and seven immunocompetent patients; there were also perinatal cases. Case fatality was 29%. Of 40 isolates, 32 were type 4b. It is possible that the milk had been contaminated after pasteurization (Schuchat *et al.*, 1991).

The largest epidemic in the US was recorded in 1985 in Los Angeles, California (Linnan *et al.*, 1988). The epidemic affected pregnant women, their fetuses, and their newborns. Case fatality was 63% for the infected fetuses and newborns. The outbreak was due to a Mexican soft cheese; serovar 4b was isolated from the patients and the cheese. The incubation period was 11 to 70 days, with an average of 31 days (Schuchat *et al.*, 1991).

There have been epidemic outbreaks in Switzerland, Denmark, and France. In Switzerland, the 1987 outbreak that led to 64 perinatal cases and 58 nonperinatal cases was caused by a soft cheese. Case fatality was 28%. The strain of *L. monocytogenes* responsible was the same enzymatic type as the strain that caused the outbreak in California in 1985 (Gelin and Broome, 1989). One of the largest epidemics known to date occurred in France in 1992. It affected 691 persons and 40% of the cases were caused by serotype 4b. The epidemic strain was isolated from 91 pregnant women and their children. Of the remaining persons affected by the epidemic strain, 61% were immunodeficient. The phage type was the same as in California (1985), Switzerland (1983–1987), and Denmark (1985–1987). The epidemic strain was isolated from 163 samples of meat products, 35 cheese samples, and 12 other food samples. The epidemic lasted from 18 March to 23 December 1992 and caused

63 deaths and 22 abortions. The cause was attributed to pig's tongue in gelatin (WHO, 1993). In 1993 (January–August), 25 new cases occurred in France. This time the outbreak was again due to serogroup 4, but to a different lysotype than in the 1992 epidemic. Of the 25 cases, 21 were maternal-fetal, with 4 spontaneous abortions and 2 stillbirths at term. Most of the cases occurred in western France. The epidemiological investigation was able to attribute the infection to a pork product ("rillettes") distributed by a single commercial firm (*Bol Epidemiol Hebdom* No. 34, 1993).

There are various risk groups: pregnant women, fetuses, newborns, the elderly, and immunocompromised patients. However, there was some controversy regarding AIDS patients. Several authors maintained that AIDS patients were unlikely to contract listeriosis, even though their cellular immunity system was highly compromised. While it is true that listeriosis is not one of the principal conditions affecting AIDS patients, its incidence in those infected by HIV is 300 times higher than in the general population (Schuchat *et al.*, 1991).

Occurrence in Animals: Listeriosis has a wide variety of domestic and wild animal hosts. The infection has been confirmed in a large number of domestic and wild mammals, in birds, and even in poikilotherms. The most susceptible domestic species is sheep, followed by goats and cattle. The frequency of occurrence in these animals is not known.

Outbreaks in sheep have been described in several Latin American countries. The disease has been confirmed in alpacas in Peru, and in sheep, fowl, and cattle in Argentina and Uruguay.

The first epizootic outbreak (1924) was recognized in England in laboratory rabbits suffering from a disease characterized by mononucleosis, from whence the specific name of the agent, *monocytogenes*, comes. Mononucleosis rarely occurs in man or in animals other than rabbits and rodents.

Several outbreaks have been described in Great Britain and the US due to silage with a pH higher than 5, which favors multiplication of *L. monocytogenes*. As the use of silage increases, outbreaks, which occur when the quality of silage is poor and the pH high, increase as well.

The Disease in Man: The most affected group is newborns (50% of cases in France and 39% in the US), followed by those over age 50. The disease is very rare between 1 month and 18 years of age. According to data from two German obstetrical clinics, listerial infection caused 0.15% to 2% of perinatal mortality. Listerial abortion in women usually occurs in the second half of pregnancy, and is more frequent in the third trimester. Symptoms that precede miscarriage or birth by a few days or weeks may include chills, increased body temperature, cephalalgia, slight dizziness, and sometimes, gastrointestinal symptoms. These septicemic episodes may or may not recur before birth of a stillborn fetus or a seriously ill full-term baby. After delivery, the mother shows no disease symptoms, but *L. monocytogenes* can be isolated from the vagina, cervix, and urine for periods varying from a few days to several weeks. If the child is born alive but was infected *in utero*, it may show symptoms immediately after birth or within a few days. The symptomatology is that of sepsis or, less frequently, a disseminated granulomatosis (granulomatosis infantisepticum). There may also be symptoms of a respiratory tract disorder. Case fatality is high. The main lesion is a focal hepatic necrosis in the form of small, grayish-

white nodules. Some children born apparently healthy fall ill with meningitis shortly thereafter (a few days to several weeks). In these cases, the infection was probably acquired *in utero* or during birth. In the US, neonatal meningitis is the most common clinical form, while in Europe, perinatal septicemia prevails. Hydrocephalus is a common sequela of neonatal meningitis.

Meningitis or meningoencephalitis is the most common clinical form in adults, especially in those over 50. Listerial meningitis often occurs as a complication in debilitated persons, alcoholics, diabetics, in patients with neoplasias, or in elderly patients with a declining immune system. Before the existence of antibiotics, case fatality was 70%. Listerial septicemia also occurs among weakened adults, especially patients undergoing long-term treatment with corticosteroids or antimetabolites. In addition, listeriosis may result in endocarditis, external and internal abscesses, and endophthalmitis. A cutaneous eruption has been described among veterinarians who handled infected fetuses.

The recommended treatment for maternal-fetal listeriosis is ampicillin. Various antibiotics, such as ampicillin (alone or in combination with aminoglycosides), tetracycline (not for those under 8 years of age), and chloramphenicol, may be used for the other forms of the disease (Benenson, 1990).

The Disease in Animals

SHEEP, GOATS, AND CATTLE: Listeriosis manifests itself in ruminants as encephalitis, neonatal mortality, and septicemia. The most common clinical form is encephalitis. In sheep and goats, the disease has a hyperacute course, and mortality may vary from 3% to more than 30%. In cattle, listerial encephalitis has a chronic course, with the animals surviving for 4 to 14 days. In general, only 8% to 10% of a herd is affected.

A ruminant with encephalitis isolates itself from the herd and shows symptoms of depression, fever, lack of coordination, torticollis, spasmodic contractions and paralysis of facial muscles and throat, profuse salivation, strabismus, and conjunctivitis. The animal tries to lean against some support while standing and, if able to walk, moves in circles. In the final phase of the disease, the animal lies down and makes characteristic chewing movements when attempting to eat.

Listerial encephalitis can affect animals of any age, but it is more common in the first three years of life. Nevertheless, it does not appear before the rumen becomes functional. Septicemia is much more common in young animals than adults. Abortion occurs mainly during the last months of gestation and is generally the only symptom of genital infection, the dam showing no other signs of disease. If uterine infection occurs in the cow before the seventh month of pregnancy, the dead fetus is usually retained in the uterus for several days and has a macerated appearance, with marked focal necrotic hepatitis. In addition, the placenta may be retained and metritus may develop. If infection occurs in the final months of pregnancy, the fetus is practically intact and shows minimal lesions.

L. monocytogenes can also cause mastitis in cows. There are few described cases, either because the presence of this agent in cows has not been studied or because its occurrence really is rare. Mastitis caused by *Listeria* varies in severity from subclinical to acute and chronic. Elimination of the agent in milk occurs over a long period of time and may have public health repercussions, especially since pasteurization does not guarantee complete safety if the viable bacteria count is high before heat treatment (Gitter, 1980).

A study carried out in 1970–1971 in Victoria (Australia) (Dennis, 1975) showed that listeriosis is an important cause of perinatal mortality in sheep. In 94 flocks, fetuses and lambs that died during the neonatal period were examined, and *L. monocytogenes* was found in 25%. The disease caused by this agent occurs mostly in winter. It has been estimated that the rate of abortion in flocks affected by listeriosis in Victoria varies from 2% to 20%.

L. ivanovii, which differs from *L. monocytogenes* on the basis of several phenotypic characteristics, was associated in several countries with abortions in sheep and, occasionally, in cows (Alexander *et al.*, 1992).

OTHER MAMMALS: Listeriosis is rare in swine; when it does occur in the first few weeks of life, it usually takes the septicemic form. Few cases are known in dogs, in which the disease may be confused with rabies. In other domestic and wild species, the disease generally appears as isolated cases and in the septicemic form. Outbreaks have been described in rabbit and guinea pig breeding colonies.

FOWL: Young birds are the most affected. Outbreaks are infrequent and mortality may range from the loss of a few birds on one farm to a high rate of losses on other farms. The septicemic form is the most common, with degenerative lesions of the myocardium, pericarditis, and focal hepatic necrosis. On rare occasions, the meningoencephalitic form is found, with marked torticollis. Since the generalized use of antibiotics in poultry feed began, few cases of listeriosis in this species have been reported.

Source of Infection and Mode of Transmission: The causal agent is widely distributed in animals and man, as well as in the environment. *L. monocytogenes* has been isolated from different mammalian and avian species and from the soil, plants, mud, pasture, wastewater, and streams. The presence of virulent and avirulent (for mice) strains in animals and in the environment complicates clarification of the epidemiology, but serotyping can be of considerable help. Cattle, sheep, and many other animal species eliminate the agent in their feces. *L. monocytogenes* has also been isolated from the feces of patients and their contacts, as well as from a small percentage of the general human population. However, it has been isolated from the stools of some 20% to 30% of pregnant women, and has also been found in the female genital tract. In addition to untypeable strains, potentially pathogenic serotype 1 and serovar 4b have been isolated (Kampelmacher and van Noorle Jansen, 1980). Consequently, the natural reservoir is wide and the number of hosts is large. Despite this, few people contract the disease. Many women from whose stools the agent has been isolated give birth to healthy children. Concurrent conditions, such as stress and other predisposing causes (particularly diseases or treatments that depress the immune system), come into play in initiating the disease. Another predisposing cause is the decline in the immune system that occurs with aging, as well as endocrine changes during pregnancy and deficiencies in immunoregulation at the placental level.

The source of infection for the fetus and newborn is evidently the infected mother herself. It is believed that the almost inapparent disease course manifested by the mother is caused by a mild bacteremia. Airborne infection might play a role, as suggested by the influenza-like symptoms exhibited by the mother. The mother's genital tract is probably infected via the fecal route, while the fetus is infected via the

bloodstream or placenta. The discovery of the causal agent in the semen of a man whose wife's genitals were infected would indicate that, in some cases, the infection may be transmitted through sexual contact.

The oral route of transmission seems to be important, as indicated by the recent outbreaks occurring in the US, Switzerland, and France (see the section on occurrence in man), where some contaminated vegetables, milk and milk products, and meat were the vehicle of the infection. It is also interesting to note that the milk that led to one of the outbreaks came from establishments where listeriosis had been diagnosed in the animals. The disease affected two very susceptible groups: newborns and debilitated persons. Of 49 patients hospitalized with listerial septicemia or meningitis, 7 were newborns and 42 were adults. All the adults were suffering from other diseases or undergoing treatment with immunosuppressants.

A rise in listeriosis cases when animals feed on silage would indicate the digestive system as the portal of entry. The causal agent has been isolated from poorly prepared fodder that had a pH higher than 5. During an outbreak of encephalitis in sheep, the same serovar and phage type of *L. monocytogenes* was isolated from the silage and from the animals' brains. The silage contained 1 million listeriae per gram (Vázquez-Boland *et al.*, 1992).

L. monocytogenes is distributed in populations of healthy animals and the disease can be produced when stress lowers the host's resistance.

Although it has been demonstrated that food has been the source of infection in both human and animal outbreaks, the source of infection is not known with certainty in sporadic cases in man. However, it has been possible to confirm that a significant percentage of such cases were caused by the ingestion of a contaminated food (Schuchat *et al.*, 1992; Pinner *et al.*, 1992). Cases of listeriosis have been associated with ingestion of raw sausage and undercooked chicken (Schwartz *et al.*, 1988). It is likely that many cases with a food source cannot be detected because the extended incubation period makes it impossible for patients to associate a food with their infection (Gelin and Broome, 1989).

One case of listeriosis in a woman with cancer was associated with consumption of turkey franks. The investigation established that the franks in opened packages in her refrigerator were contaminated, but those in unopened packages were not. Cultures from other foods in the refrigerator also yielded positive results. The conclusion was that a cross-contamination was involved (CDC, 1989).

An interesting study was conducted in the US in 1992 (CDC, 1992). During the period 1988–1990, special epidemiological surveillance was conducted in four of the country's districts, with a population of 18 million inhabitants. There were 301 cases of listeriosis identified (7.4 per million inhabitants), 67 (23%) of whom died. The patients' food consumption histories indicated that the listeriosis patients ingested 2.6 times more soft cheeses than did the controls, or purchased 1.6 times more prepared foods. The patients' refrigerators were examined and it was found that 79 (64%) of 123 contained at least one food contaminated by *L. monocytogenes*; in 26 (33%) of the 79 refrigerators the same enzymatic strain as that found in the patients was isolated.

The wide distribution of *Listeria* spp. in nature and in animal feces explains why its presence in raw meats is almost inevitable. Prevalence in raw meats may vary from 0% to 68%. Pork is contaminated most often, but contamination is also frequent in uncooked chicken. There is little information regarding the virulence of *L. monocytogenes* strains isolated from meats (Johnson *et al.*, 1990).

There is no uniform criterion regarding when to reject foods according to the degree of contamination by *L. monocytogenes*. Several countries (France, US) require that there be no contamination at all, while others (Canada, Germany) have a certain tolerance. It is impossible to ensure the total absence of *Listeria* spp. in all foods (Dehaumont, 1992).

In California (USA), a six-month study was conducted on the prevalence of *Listeria* spp. in environmental samples from 156 milk-processing plants. *Listeria* spp. was isolated from 75 (12.6%) of the 597 environmental samples. Half of the isolates were identified as *L. monocytogenes*. Of the 156 plants, 46 gave positive samples for *Listeria* spp. and 19.9% of these isolates were identified as *L. monocytogenes* (Charlton *et al.*, 1990).

Role of Animals in the Epidemiology of the Disease: The epidemiology of sporadic listeriosis is still not well known. Most researchers consider it a disease common to man and animals and not a zoonosis *per se*. It is likely that animals contribute to maintenance of listeria in general in nature and especially to its distribution.

Studies conducted in recent years suggest that man and animals can contract the infection from many sources. Most cases in man occur in urban areas, where there is little contact with animals. Nonetheless, animals may be the source of the infection. In one case, infection was confirmed in a woman who drank raw milk; the same serotype of *Listeria* was isolated from the raw milk and from the woman's premature twins. The etiologic agent was isolated from 16% of cows that had listerial abortions. The previously described outbreaks caused by milk, meat, or vegetables contaminated by manure from listeria-infected animals demonstrate that animals may be an important source of infection.

There are indisputable cases of direct transmission of the infection from animals to man. A cattleman assisted during the delivery of a cow, inserting his arms in the uterus. Within the next 24 hours, a rash appeared on his hands and one arm and developed into pustules. He later experienced fever, chills, and generalized pain. The same phage type was isolated from the cow's vagina and from the cattleman's pustules (Cain and McCann, 1986). The veterinary profession is particularly at risk of contracting cutaneous listeriosis. Many veterinarians have become ill after attending cows that aborted, fetuses, or newborns, or after conducting autopsies of septicemic animals. The most frequent lesion is a papular exanthema (Owen *et al.*, 1960; Nieman and Lorber, 1980; Hird, 1987). Contact with sick birds may also cause human infection (Gray and Killinger, 1966).

Diagnosis: Diagnosis can be made only through isolation of the causal agent. If the sample is obtained from usually sterile sites, such as blood, cerebrospinal fluid, amniotic fluid, or biopsy material, seeding can be done directly in blood agar, with incubation at 35°C for a week and daily checks. Listeria can be isolated from any organ in septicemic fetuses.

In sheep, goats, or cattle with encephalitis, samples of the medulla oblongata should be cultured. In septicemic fowl, rodents, or neonatal ruminants, blood or internal organs should be cultured. The "cold enrichment" method is used especially in epidemiological investigations and is indicated for culturing highly contaminated specimens. However, this method has no diagnostic value for clinical cases because of the time it takes, since treatment with antibiotics (preferably ampicillin) should begin as soon as possible to be effective.

At present, contaminated samples as well as foods are cultured in an enrichment medium and then in a selective medium. One procedure is the US Department of Agriculture procedure; it uses nalidixic acid and acriflavin in broth to inhibit the growth of contaminating flora. The culture is incubated for 24 hours at 30°C and then a subculture is done in another broth of the same composition for another 24 hours at 30°C. Finally, a highly selective solid medium that contains lithium chloride and moxalactam is used (McClain and Lee, 1988).

A test has been developed to distinguish pathogenic from nonpathogenic strains of *L. monocytogenes*. This method is based on the potentiating and synergistic effect that the extrosubstance of *Rhodococcus equi* has for producing hemolysis in cultures of pathogenic strains of *L. monocytogenes* (Skalka *et al.*, 1982).

In general, serologic tests are confusing and not useful because of cross-reactions with enterococci and *Staphylococcus aureus,* especially by serogroups 1 and 3 of *Listeria*. DNA probes that specifically detect *L. monocytogenes* have been developed (Datta *et al.*, 1988).

Control: In regions where human neonatal listeriosis is common, a Gram stain can be made from the meconium of a newborn, and treatment with antibiotics can be rapidly initiated if bacteria suspected of being *Listeria* are found. Women who develop influenza-like symptoms in the final months of pregnancy should be carefully examined and treated, if necessary, with antibiotics. The limited arsenal of defense against the infection includes such measures as the pasteurization of milk, rodent control, and common practices of environmental and personal hygiene.

Special recommendations have been developed for food preparation (CDC, 1992): cook products of animal origin well, thoroughly wash vegetables that are eaten raw, keep raw meats separate from other foods, do not consume raw milk, wash utensils used in food preparation well, and reheat all food leftovers at a high temperature. Immunocompromised individuals must not eat soft cheeses and veterinarians must take precautions during delivery, and particularly during abortions and autopsies.

Animals with encephalitis or those that have aborted should be isolated and their placentas and fetuses destroyed. Recently acquired animals should only be added to a herd after undergoing a reasonable period of quarantine.

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LYME DISEASE

ICD-10 A69.2

Synonyms: Lyme borreliosis, Lyme arthritis, erythema migrans (formerly erythema chronicum migrans) with polyarthritis.

Etiology: The etiologic agent is a spirochete, transmitted by ticks of the *Ixodes ricinus* complex and named *Borrelia burgdorferi* in honor of the person who discovered it (Burgdorfer *et al.*, 1982; Steere *et al.*, 1983; Johnson *et al.*, 1984). The genus *Borrelia* belongs to the family *Spirochaetaceae* and is made up of spiral-shaped, actively motile bacteria. *B. burgdorferi* is 11 to 39 microns long and has 7 to 11 flagella. The strains of *B. burgdorferi* isolated in Europe have demonstrated some heterogeneity, particularly in the two principal plasmid-dependent surface proteins (Steere, 1990).

Geographical Distribution and Occurrence in Man: The human disease has been recognized in 46 states in the US. Areas with endemic foci in that country are the Atlantic coast (particularly in the Northeast), Wisconsin and Minnesota in the Midwest, and California and Oregon along the Pacific coast (Benenson, 1990). The natural foci of the infection are expanding. In New York State, the number of counties with recorded human cases increased from four to eight between 1985 and 1989 and the number of counties where the presence of the tick *Ixodes dammini*, the vector of the infection, was documented increased from 4 to 22 during the same period (White *et al.*, 1991).[1] In the US, more than 40,000 cases were recorded between 1982 and 1992, and it is currently the principal disease transmitted by ticks. The major vectors of the infection in the US are *Ixodes dammini* in the East and Midwest, and *I. pacificus* on the Pacific coast.

The etiological agent has also been isolated in Ontario (Canada). Many European countries record cases of Lyme borreliosis and the vector on that continent is *Ixodes ricinus*. The disease has also been recognized in Australia, China, Japan, and coun-

[1] A study indicates that *Ixodes dammini* and *I. scapularis* (a tick in the southern US) are geographic variants of the same species, which would correctly be named *I. scapularis* (Oliver *et al.*, 1993). Since there are differences in terms of ecology and the rate of infection (Kazmierczak and Sorhage, 1993), we feel it is advisable to retain the terminology commonly in use for both varieties in order to avoid confusion.

tries of the former Soviet Union. In the Asian countries, the tick that transmits the infection is *I. persulcatus*.

In the Northern Hemisphere, the disease has the highest incidence in summer during the months of June and July, but it may appear in other seasons depending on the tick life cycle in the region (Benenson, 1990).

Occurrence in Animals: In endemic areas and areas near to them, various species of domestic animals (dogs, horses, and cattle) are infected by *B. burgdorferi*.

In the natural foci of the infection, wild animals form the major part of the life cycle of the tick and of the agent it transmits. In these foci, high rates of reactors to the indirect immunofluorescence test, using antigens from the etiologic agent, have been found in several wild animal species. The prevalence of reactors among animals infested with *I. dammini* in eastern Connecticut from 1978 to 1982 was as follows (Magnarelli *et al.*, 1984): white-tailed deer (*Odocoileus virginianus*), 27%; white-footed mice (*Peromyscus leucopus*), 10%; eastern chipmunks (*Tamias striatus*), 17%; gray squirrels (*Sciurus carolinensis*), 50%; opossums (*Didelphis virginiana*), 17%; raccoons (*Procyon lotor*), 23%; and dogs, 24%. The spirochete was isolated from the bloodstream of 1 out of 20 white-footed mice examined (Anderson and Magnarelli, 1983; Bosler *et al.*, 1984).

Of 380 samples obtained from dogs from two locations selling animals in Wisconsin, 53% reacted positively to the immunofluorescence test and the pathogenic agent was isolated from the blood of 8 out of 111 dogs (Burgess, 1986). In Texas, the same test was used to examine 2,409 canine samples in 1988; of these, 132 (5.5%) yielded positive results. Many of the seropositive dogs were from the north-central part of the state, where most of the human cases are recorded (Cohen *et al.*, 1990).

It has been noted that horses are frequently bitten by *I. dammini*. In a serological study of 50 randomly selected horses in New England (USA), a known endemic area, 13 of the horses were reactive to the indirect immunofluorescence test.

In another serological survey using the enzyme-linked immunosorbent assay (ELISA) technique, 13 of 100 horses examined in the month of June tested positive and 6 of 91 (7%) tested positive in the month of October. The horses came from five eastern US states. The frequency of antibody responses was higher in horses from New Jersey than in horses from Pennsylvania (Bernard *et al.*, 1990). In contrast, no reactive horses were found in central Texas (Cohen *et al.*, 1992).

The Disease in Man: The characteristic cutaneous lesion, erythema migrans (EM), appears from 3 to 20 days after the tick bite. The lesion begins with a red macula or papule that widens. The borders are clearly delineated, the central lesion pales, and an annular erythema forms. The erythema may be recurrent, with secondary lesions appearing on other parts of the body. The cutaneous lesions may be accompanied for several weeks by malaise, fever, cephalalgia, stiff neck, myalgias, arthralgia, or lymphadenopathy. The EM constitutes the first stage or phase of the disease and lasts a few weeks, but may recur. In the second stage, after several weeks or months have passed and the agent has disseminated, some patients develop multiple EMs, meningoencephalitis, neuropathies, myocarditis, and atrioventricular tachycardia. Some suffer arthritic attacks in the large joints, which may recur for several years, at times taking a chronic course (Steere *et al.*, 1983). Months or years later, the third stage may occur in some patients; this stage sometimes includes acrodermatitis chronica atrophicans and neurological and articular changes.

It should be borne in mind that the connection between EM and arthritis might not be apparent, as several weeks or months transpire between the two episodes. Of 405 patients showing EM, 249 had later neurological, cardiac, and articular symptoms (Steere and Malawista, 1979). In Europe, cases with arthritis are rare, while neurological symptoms and acrodermatitis are more frequent.

Treatment for Lyme disease consists of giving the patient doxycycline for 10 to 30 days, or ceftriaxone, particularly if there is a neurological disorder (Benenson, 1990).

The Disease in Animals: The effect of the spirochete infection on wild animals is not known, but it may be asymptomatic. The predominant symptom in dogs is lameness due to arthritis in different joints, which may be migratory. Arthralgia is often accompanied by fever, anorexia, fatigue, and lymphadenitis. Arthritis is usually temporary, but may become chronic.

Different symptoms have been observed in horses, including arthritis, encephalitis, uveitis, dermatitis, edema of the limbs, and death of colts associated with natural infection in pregnant mares. However, the infection has not been confirmed in any of the cases described (Cohen *et al.*, 1992).

In cattle, infection caused by *B. burgdorferi* has also been associated with lameness. Serological analysis using Western blot, ELISA, and indirect immunofluorescence techniques on 27 milk cows from 17 herds in Minnesota and Wisconsin found that high serological titers were associated with arthritis (Wells *et al.*, 1993).

Source of Infection and Mode of Transmission: The etiologic agent is transmitted by a vector, which in the US is the tick *Ixodes dammini* on the Northeast Coast and northern states of the Midwest, but *I. pacificus* on the West Coast (Benenson, 1990). The vector is *I. ricinus* in Europe, possibly *I. holocyclus* in Australia (Stewart *et al.*, 1982), and *I. persulcatus* in Asia.

Isolation of the etiologic agent has made it possible to definitively establish the role of ticks as vectors. In fact, in the endemic area of Connecticut, a spirochete with the same antigenic and morphological characteristics as the one in Lyme disease patients was isolated from 21 (19%) of 110 nymphs and adult ticks (*I. dammini*). The high rate of infection of the vector was shown by direct immunofluorescence; in one locality, 30 (21%) of 143 *I. dammini* contained spirochetes, and in another, 17 (26%) of 66 contained spirochetes. These results were obtained only for nymphs and adults that had fed, while 148 larvae that had not fed were negative (Steere *et al.*, 1983). On Shelter Island, New York, more than 50% of ticks were infected (Bosler *et al.*, 1983). In contrast, only 2% of the *I. pacificus* ticks were infected.

The fact that the larvae were not infected prior to feeding on blood would indicate that the tick becomes infected from an animal reservoir. This reservoir would be small rodents and other wild mammals; among these the white-footed mouse (*Peromyscus leucopus*) is considered very important on the East Coast of the US. In Europe, the reservoir of the infection is also small, wild rodents, such as *Apodemus sylvaticus* and *Clethrionomys* spp. Tick larvae and nymphs feed on the blood of these small mammals and become infected with *B. burgdorferi*. The adult tick may transmit the etiologic agent to a very small percentage of the eggs, but there is a gradual loss of the agent when they go on to the larval and nymph stages until it disappears completely. The infection is renewed when larval and nymph ticks feed on rodents (Burgdorfer *et al.*, 1989). This fact is reflected in the high percentage of lar-

vae and nymphs found on these small wild mammals, as well as their high rate of infection by *B. burgdorferi*. The adult tick has a predilection for deer (*Odocoileus virginianus*) in the foci along the eastern coast of the US. This cycle is repeated in other areas of the world, with different animal species whose blood feeds the stages of various tick species. The biotope where these cycles develop is wooded areas or areas of dense vegetation that retain the moisture that is favorable to ticks (Madigan and Tleitler, 1988).

Adult ticks are abundant in spring and fall; nymphs, in spring and early summer; and larvae, in late summer and early fall. All stages in the development of ticks are parasitic in humans, but the nymph stage is primarily responsible for the transmission of *B. burgdorferi* to man (Anderson, 1989; Steere, 1990).

Role of Animals in the Epidemiology of the Disease: On the basis of current information, it can be asserted that wild animals are primarily responsible for maintaining the infection in natural foci. Dogs and birds may spread ticks and increase endemic areas. Man is an accidental host.

Diagnosis: Until recently, diagnosis was based exclusively on the clinical picture, especially a history of EM, and on epidemiological information.

Although now possible, isolation of the infective agent by culture is still not very practical. In 1983, Steere *et al.* isolated the agent in only three patients, using a total of 142 clinical samples taken from 56 patients. Barbour, Stoener, Kelly (BSK) medium is used for isolation and is incubated at 33°C; it is easier to isolate the agent from cutaneous lesions than from blood. The indirect immunofluorescence test with conjugated IgM and IgG sera was widely used. Patients with EM had elevated IgM antibody titers only between the EM phase and convalescence two to three weeks later. Patients with late manifestations of the disease (arthritis, cardiac, or neurological anomalies) had elevated IgG antibody titers (Steere *et al.*, 1983). It was later shown that indirect ELISA was more sensitive and specific than immunofluorescence (Steere, 1990). In serological tests, there may be cross-reactions with other spirochetes. Given that all serological tests have limited specificity and sensibility, their use is not recommended for asymptomatic individuals.

Diagnosis in animals is similar to that in humans. Early treatment with antibiotics shortens the duration of EM and may prevent or lessen late manifestations of the disease; it may also have an effect on reducing the level of antibodies.

Control: The only methods of prevention consist of avoiding endemic areas and tick bites. Persons entering natural foci should use protective footwear and clothing, though this is not always possible. Insect repellents may provide some protection. It is advisable to check the body frequently and remove attached ticks by pulling gently with tweezers pressed as closely as possible to the skin. It is recommended that gloves be used during this operation.

Dogs should be checked frequently and ticks should be removed as carefully as with humans. The use of tickicides in powder form or collars is a good preventive measure. There is currently an inactivated commercial vaccine available for dogs. It is administered in two doses at three week intervals and annually thereafter (Chu *et al.*, 1992). Widespread and indiscriminate use of this vaccine is a matter of discussion, although it is recognized that the bacterin has no side effects (Kazmierczak and Sorhage, 1993).

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MELIOIDOSIS

ICD-10 A24.1 acute and fulminating melioidosis; A24.2 subacute and chronic melioidosis; A24.3 other melioidosis

Synonyms: Whitmore's disease, rodent glanders.

Etiology: *Pseudomonas* (*Malleomyces*) *pseudomallei*, a small, aerobic, motile, gram-negative bacillus closely related to *P. mallei*, the agent of glanders. When stained with methylene blue or Wright stain, it shows bipolar coloration, in the shape of a safety pin. It is pleomorphic and sometimes forms chains. It is a saprophytic

bacteria that lives in surface waters and in soil. *P. pseudomallei* can survive in moist, clayey soil; under laboratory conditions; at ambient temperature; and in shade for 30 months (Thomas and Forbes-Faulkner, 1981).

P. pseudomallei has several possible virulence factors, including an endotoxin, an exotoxin, and various digestive enzymes that can attack tissue. The role that each of these virulence factors plays in pathogenesis is still unknown. The exotoxin is the most toxic substance produced by the bacteria and can inhibit intracellular protein synthesis (Dance, 1991; Ismail *et al.*, 1991).

Geographic Distribution: Most human and animal cases have been recorded in Southeast Asia (Indonesia, Malaysia, Myanmar [Burma], and Thailand), which is considered the main endemic area. The disease has also been diagnosed in northeastern Australia, Guam, Iran, Korea, Madagascar, Papua New Guinea, Sri Lanka, and Turkey. Cases have also occurred in Bangladesh, India, and Pakistan. In the Americas, the infection has been confirmed in Aruba, the Bahamas, Ecuador, El Salvador, Mexico, Panama, and Puerto Rico. More recent investigations have revealed the agent's presence in other areas (Brazil, Burkina Faso, Côte d'Ivoire, Haiti, and Peru) by isolating it from people, animals, or soil and water samples. Sporadic cases have also occurred in human in Kenya and the Gambia, in swine in Burkina Faso and Niger, and in goats in Chad. The agent's distribution is predominantly tropical. The epizootic that occurred in the "Jardin des Plantes," in Paris, is the first reported outbreak in a temperate climate. In Europe, in addition to France, there have been cases in horses in Spain (Benenson, 1990; Galimard and Dodin, 1982; Dance, 1991a).

Occurrence in Man: Clinically apparent infection caused by *P. pseudomallei* is not very common. During the war in Indochina, several hundred French, American, and Vietnamese soldiers became ill with melioidosis. From 1965 to 1969, three cases per month occurred among US Army soldiers in Vietnam (Piggott, 1976). According to a serological survey, 9% of the 3 million US personnel participating in the Vietnam conflict were exposed to the agent. Cases confirmed in the US during the 1970s were almost all military personnel or travelers returning from Southeast Asia (CDC, 1977).

The numerous cases that occurred among military personnel during the Vietnam War provoked interest in the disease among medical professionals in Thailand. Prior to 1965, only three cases of melioidosis had been recorded in that country, while there were a total of about 1,000 cases between 1967 and 1988 (Kanai and Dejsirilert, 1988).

Melioidosis is currently recognized as the most common cause of pneumonia occurring in the Top End region in the Northern Territory of Australia (Currie, 1993).

Occurrence in Animals: In endemic zones, sporadic cases have been reported in different animal species. Occasional outbreaks have occurred among sheep (in Australia and Aruba), in swine (Vietnam), in goats, cattle, horses, dogs, dolphins, tropical fish, and zoo animals, as well as in monkeys imported for laboratories. A case occurred in macaques of the species *Macaca fascicularis* imported to Great Britain from the Philippines. There were a total of 13 confirmed or suspected cases in 50 imported animals. Most had splenic abscesses, but their general condition was

not affected and infection was suspected on the basis of results from serological tests (Dance *et al.*, 1992).

The Disease in Man: The incubation period may be a few days, but in some patients the agent lies dormant for months, or even years, before clinical signs are seen. The infection may occur subclinically, as was shown by a serologic survey of war veterans, or the disease may take an acute and fulminant, or subacute and chronic form. In the acute form, the patient dies in a few days, after suffering fever, pneumonia, and gastroenteritis. The disease generally appears as a respiratory illness that varies from mild bronchitis to severe and fatal pneumonia. Case mortality is approximately 30% (Kanai and Dejsirilert, 1988).

In septicemic cases of short duration, the principal lesion consists of small abscesses distributed throughout the body. When septicemia is prolonged, larger, confluent abscesses are found, often localized in one organ.

Lasting from a few months to many years, the subacute and chronic form is characterized by localization in some organ, such as the lungs, lymph glands, skin, or bones. The lesion consists of a combination of necrosis and granulomatous inflammation. The central zone of necrosis contains a purulent or caseous exudate that can be confused with a tubercular lesion.

In endemic areas, such as Southeast Asia, seroepidemiological surveys indicate that latent or subclinical forms are common. In latent cases, *P. pseudomallei* may remain inactive for years and become activated when there is some other disease or an individual's defenses are lowered due to the administration of steroids or other immunosuppressant therapy (Kanai and Dejsirilert, 1988).

In northern Australian aborigines, a form of the disease has been observed in which primary localization is in the lower urogenital system. This localization was observed in 6 of 16 aborigines with melioidosis (Webling, 1980).

Although the infection may occur in healthy individuals, *P. pseudomallei* is largely an opportunistic bacteria. In Thailand, 70% of patients have some concurrent disease, particularly diabetes or renal deficiency (Dance, 1991b). The ratio between men and women affected is 3:2. Most cases occur during or after tropical rains.

Various beta-lactamic agents are bactericides for *P. pseudomallei*. One of these compounds, ceftazidime, reduced mortality by 50% among individuals with acute and severe melioidosis (White *et al.*, 1989).

The Disease in Animals: Many animal species are susceptible. Sporadic cases have been observed in sheep, goats, horses, swine, cattle, dogs, cats, nonhuman primates, wild and peridomestic rats, other wild animals, laboratory guinea pigs, and rabbits. The most susceptible species are sheep, swine, and goats, in which epidemic outbreaks have occurred.

As seen in Aruba, the disease in sheep consisted primarily of abscesses of the viscera, joints, and lymph nodes. In a few weeks, 25 of 90 sheep died from the disease and many survivors suffered weight loss and polyarthritis (Sutmöller *et al.*, 1957). In cases in Australian sheep, cough and nervous symptoms were also observed (Laws and Hall, 1964).

In swine, the symptomatology consists of fever, prostration, dyspnea, cough, and arthritis. In suckling pigs, the disease is often fatal. In addition, the disease may be found through necropsy or when meat is seized in slaughterhouses. In northern Queensland (Australia), melioidosis occurs sporadically in swine bred in contact

with the soil. In the southern part of the same state, which is not an enzootic area, veterinary inspection at a slaughterhouse uncovered cases in suckling pigs from eight intensive breeding facilities, during three successive years. These cases (159 out of 17,397 animals inspected) occurred after abundant rains and flooding. Abscesses were found in the bronchial ganglia of 40% and in the spleen of 34%. The outbreak was attributed to inhalation of aerosols from water (Ketterer *et al.*, 1986).

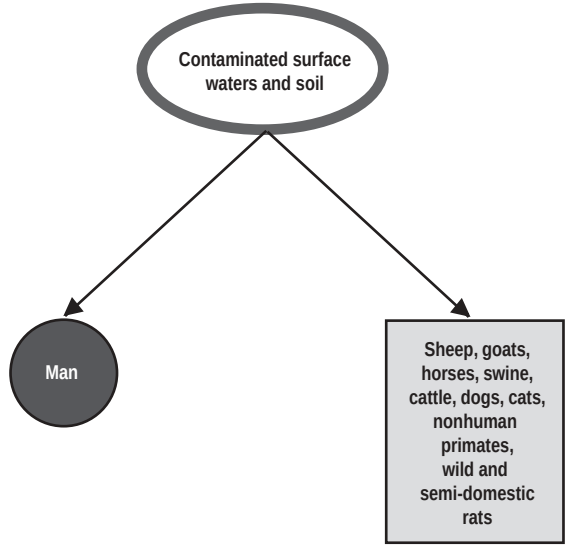
The disease is rare in cattle. The etiologic agent has been isolated from splenic abscesses, from the central nervous system, and from aborted fetuses.

In horses, the infection may become apparent due to the symptoms of septicemia, colic, diarrhea, and edemas in the legs.

The symptomatology is not very characteristic and the disease is difficult to diagnose in animal species in which it occurs sporadically. The lesions, which are similar to those in man, may suggest melioidosis and lead to its diagnosis.

Source of Infection and Mode of Transmission (Figure 13): Investigations have shown that the reservoirs of *P. pseudomallei* are surface waters and soil, as corroborated by sampling done in Southeast Asia. The highest isolation rates were obtained in rice fields and newly planted oil palm plantations (14.5%–33.3% of the isolations were from water samples). Seroepidemiologic studies also show that the highest reactor rates to the hemagglutination test came from workers or inhabitants of those areas. Human and animal infection occurs mainly during the rainy season. The etiologic agent can survive for many months in surface water and, with its low nutritional requirements, it can multiply in the hot, humid environment characteristic of endemic regions.

Figure 13. Melioidosis (*Pseudomonas pseudomallei*). Mode of transmission.



Transmission from animal to animal or from animal to man has not been proven, but it is thought that in some cases the infection may be passed from person to person. In addition to a case in Vietnam in which an American soldier with prostatitis seems to have transmitted the disease venereally to a woman, venereal transmission of the disease was also suspected among Australian aborigines with urogenital melioidosis. In accordance with tribal rituals, these aborigines smear their genitals with clay and coitus normally takes place in contact with the soil (Webling, 1980).

It is accepted that humans and animals acquire the infection through contact with contaminated water or soil, primarily through skin abrasions, but also through inhalation of dust and ingestion of contaminated water. During the war in Indochina, the number of recorded human cases climbed considerably due to contamination of war wounds with mud, traversal of flooded countryside, or prolonged stay in trenches.

The rat flea *Xenopsylla cheopis* and the mosquito *Aedes aegypti* are capable of transmitting the infection experimentally to laboratory animals. The etiologic agent multiplies in the digestive tract of these insects. The role of these possible vectors in natural transmission has not yet been evaluated, but it is thought to be of little importance.

Role of Animals in the Epidemiology of the Disease: Melioidosis seems to be a disease common to man and animals, with water and soil as reservoirs and sources of infection for both. Nevertheless, animals are believed to play a role as hosts in transporting the etiologic agent to new geographic areas.

Diagnosis: The only incontrovertible diagnostic method is isolation and identification of the etiologic agent, by either direct culture or inoculation of guinea pigs. *P. pseudomallei* can be isolated from abscesses, sputum, blood, urine, and various tissues.

The allergenic test using melioidin may be useful for diagnosis in animals, but gives many false negatives in swine and false positives in goats.

Of the serologic tests, indirect hemagglutination with melioidin-sensitized erythrocytes has proven to be sufficiently sensitive and specific in nonendemic areas. In endemic areas, titers of ≥ 1:160 would have to be considered significant reactions (Appassakij *et al.*, 1990). The indirect immunofluorescence and ELISA tests have proven to be more sensitive and specific (Dance, 1991). A latex agglutination test developed and evaluated by Smith *et al.* (1993) is considered highly sensitive and specific.

The ELISA test was used on Malaysian sheep to detect the anti-exotoxin. The antitoxin was confirmed in 49.3% of the sera taken from a sheep herd that had been naturally exposed to the infection. In sheep kept on a property without infection, the rate was 6% (Ismail *et al.*, 1991).

Control: Since it is an infrequent disease, specific preventive measures are not justified. In man, the use of boots during outdoor work can provide a certain amount of protection against the infection in endemic areas. Proper treatment of wounds and abrasions is important.

In animals, control of the infection is difficult, unless the environment is changed through such measures as drainage of low-lying, flooded fields.

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NECROBACILLOSIS

ICD-10 A48.8 other specified bacterial diseases

Synonyms: Schmorl's disease, calf diphtheria, foot rot.

Etiology: *Fusobacterium necrophorum*, a nonsporulating, obligate anaerobe that is a pleomorphic, gram-negative bacillus of the family *Bacteroidaceae*. In broth cultures, *F. necrophorum* varies from coccoid shapes to filaments with granular inclusions. Rod shapes are more common in agar cultures. This bacteria is a component of the normal flora of the mouth, gastrointestinal tract, and urogenital tract of man and animals. Strains have varied virulence categories: pathogenic for mice; slightly pathogenic or not at all, but hemolytic, like the first category; and a third category (formerly called *Sphaerophorus pseudonecrophorus*) that is neither hemolytic nor pathogenic. There may be mutation from one category (or phase) to another. The validity of the identification of this bacteria in works prior to 1970 is questioned (Holdeman *et al.*, 1984).

Different species of *Bacteroides* play an important pathogenic role in necrobacillosis. They may appear alone or in conjunction with other species of the same genus, particularly in man, or with *F. necrophorus* in animals. *Bacteroides* spp. is also a nonsporulating, gram-negative, obligate anaerobe. *Bacteroides nodosus* is of particular interest in sheep pathology. These bacteria are nonmotile, and take the shape of straight or slightly curved rods sized 1 to 1.7 by 3 to 6 microns. They appear singly or in pairs and often have thickened ends (Holdeman *et al.*, 1984). They have numerous pili (fimbriae), an important virulence factor. The pili likely play an important role in colonization of the epidermal matrix of hooves. These appendices also make it possible to sub-classify the agent serologically into 9 serogroups containing 16 to 20 serovars or serotypes, according to their determination in different countries (Gradin *et al.*, 1991).

The polymicrobial nature of most anaerobic infections in man makes it difficult to distinguish the true pathogen or pathogens from those that merely accompany the infection (Kirby *et al.*, 1980). Singly or acting jointly with other nonsporulating, anaerobic bacteria, *F. necrophorum* causes different diseases and pathological conditions in man and animals. Different species of the genus *Bacteroides*, which belong to the same family as *F. necrophorum*, cause disease either by themselves (in man) or in combination and at times in synergistic action with *F. necrophorum* (in man and animals).

Geographic Distribution: Worldwide.

Occurrence in Man: Advances in laboratory technology for the isolation of anaerobes have led to greater recognition of their role in human pathology and, consequently, to an increase in the number of recorded cases in medical facilities.

Occurrence in Animals: Some diseases, such as foot rot in sheep, occur frequently in all countries where sheep are raised. Others, such as calf diphtheria (necrobacillary stomatitis), are less common. Bovine hepatic necrobacillosis causes appreciable economic losses in many countries due to confiscation of animals in slaughterhouses; it is more frequent in areas where cattle are fed grain in feedlots (Timoney *et al.*, 1988).

The Disease in Man: *F. necrophorum* causes a wide variety of necrotic lesions, empyema, pulmonary abscesses, arthritis, and ovariosalpingitic sepsis. *Bacteroides fragilis* and *F. necrophorum* are important agents of cerebral abscesses and, occasionally, of meningitis, almost always as a consequence of an otitis media (Islam and Shneerson, 1980). The formerly high incidence of septicemia caused by *F. necrophorum* in children and adolescents who had suffered from tonsillitis (Lemierre's syndrome) has now diminished notably and constitutes only 1% to 2% of all bacteremias caused by anaerobes. Patients with septicemia usually exhibit exudative pharyngitis or a peritonsillar abscess, but these symptoms may disappear by the time some patients obtain medical attention (Seidenfeld *et al.*, 1982). In most human clinical specimens, only the genera *Bacteroides*, *Prevotella*, *Porphyromonas*, and *Fusobacterium* should be considered among the anaerobic bacilli (Jousimies-Somer and Finegold, 1991). Infections in man come from the normal flora of adjacent cavities.

The most effective antibiotics for treating infections caused by gram-negative anaerobes are metronidazole, chloramphenicol, and imipenem (Jousimies-Somer and Finegold, 1991).

The Disease in Animals: *F. necrophorum* is more important in animal than in human pathology and is the cause of several common diseases.

SHEEP: Foot rot is the most common cause of lameness in sheep. The disease begins with interdigital dermatitis, progresses to the epidermal matrix of the hooves, and then causes destruction of the interdigital skin and detachment of the hoof. Environmental factors, such as wet soil and grass that soften the feet, are involved in producing the disease, along with two bacterial agents, *F. necrophorum* and *Bacteroides nodosus*. *F. necrophorum* establishes itself first and causes inflammation and destruction of the epidermis before penetrating to deeper layers. Hoof degeneration is due to the proteolytic properties of *B. nodosus*. The disease may appear in several forms: benign, usually caused by less virulent strains of *B. nodosus*; virulent, with deformation and detachment of the hoof; and chronic, which may last years, with or without producing lameness.

Other hoof diseases affecting sheep are interdigital dermatitis and infectious bulbar necrosis. The former, caused by *F. necrophorum*, is characterized by an edematous and erythematous inflammation of the interdigital skin, which may be covered by a layer of moist, gray, necrotic material. Infectious bulbar necrosis is caused by *F. necrophorum* and *Corynebacterium pyogenes* and is characterized by abscesses and suppuration of the bulbar area of the hoof, particularly on the hind feet. The disease results from the interaction of both bacteria. *C. pyogenes* produces a factor that

stimulates proliferation of *F. necrophorum*, and the latter protects *C. pyogenes* from phagocytosis by producing a leukocidin (Cottral, 1978).

CATTLE: Calf diphtheria (necrobacillary stomatitis) is characterized by sialorrhea, anorexia, and necrotic areas in the oral cavity. Infection can spread to the larynx and, by inhalation, to the lungs, where it causes abscesses and pneumonia. The disease only occurs in animals under 2 years of age; mature animals seem immune. The disease is caused by *F. necrophorum* and is seen in dairy operations with deficient hygiene. The same disease also affects young goats.

Hepatic necrobacillosis is discovered by veterinary inspection in slaughterhouses and results in confiscation of carcasses. Lesions on the liver are characterized by well-delineated yellow areas with a firm consistency.

Foot rot in bovines is an acute or chronic necrotic infection of the interdigital skin and the coronary region. The chronic form frequently produces arthritis in the distal joint of the limb. *F. necrophorum* and *Bacteroides meleninogenicus* have been isolated from biopsy samples of foot rot lesions. A mixture of both bacteria administered by interdigital scarification or intradermal inoculation reproduced the typical lesions (Berg and Loan, 1975). Nevertheless, the etiology still has not been completely clarified, and it is possible that concurrent infection by *F. necrophorum* and other bacteria (*B. nodosus*, staphylococci) causes the disease (Timoney *et al.*, 1988). Mastitis caused by *Bacteroides fragilis* has also been described in cattle.

SWINE: Pathologies such as ulcerous stomatitis, necrotic enteritis, necrotic rhinitis, and abscesses have been described in this species.

OTHER ANIMAL SPECIES: Similarly to what happens in man, osteomyelitis in animals may be caused by anaerobes. Of a total of 39 anaerobic bacteria isolated from 19 marrow specimens, the most frequent genus was *Bacteroides* (18 isolates). *B. asaccharolyticus* was isolated from 26% of the specimens (Walker *et al.*, 1983).

Source of Infection and Mode of Transmission: *F. necrophorum* and *Bacteroides* spp. are part of the normal flora of several mucous membranes in humans and animals. The infection is endogenous, particularly in man. The relative infrequency of the disease in man indicates that predisposing factors are necessary for it to occur. These are usually traumas and debilitating illnesses. In sum, they are opportunistic agents. A lowered oxidation-reduction potential (E_h) resulting from insufficient blood supply, together with tissue necrosis and the presence of other facultative bacteria, creates a favorable environment for this and other anaerobic bacteria. Vascular disease, edema, surgery, and cold are some of the common factors favoring implantation and multiplication of anaerobes (Finegold, 1982). Most patients with anaerobic pulmonary infection (abscesses, necrotic pneumonia, pneumonitis, empyema) suffer from altered consciousness or dysphagia due to aspiration of the oropharyngeal content, which is rich in anaerobic flora. The underlying conditions are usually alcoholism, a cerebrovascular accident, general anesthesia, convulsions, and narcotics abuse, among others (Bartlett and Finegold, 1974).

An important predisposing factor in sheep and bovine foot rot is softening of the interdigital epidermis caused by moist ground, enabling *F. necrophorum* to implant itself and multiply. In addition, this bacteria abounds in humid environments (soil and grass contaminated by animal feces) and has been proved able to survive outside a host's body for several months. In contrast, *B. nodosus* is a parasite that can

live for only a short time in the environment and is introduced in establishments by sick or carrier animals. *F. necrophorum* creates conditions necessary for the multiplication of *B. nodosus*. Thus, both bacteria are required to cause the disease.

As mentioned above, under different conditions other bacteria, such as *Corynebacterium pyogenes* (which causes infectious bulbar necrosis), interact synergistically with *F. necrophorum*.

Bovine hepatic necrobacillosis, the agent of which is *F. necrophorum*, has an endogenous origin. The agent possibly penetrates by way of the portal circulation from epithelial lesions in the rumen, which in turn may be caused by excessive acidity due to provision of concentrated foods.

Calf diphtheria, or necrobacillary stomatitis, is prevalent in environments where hygienic practices are markedly poor.

Role of Animals in the Epidemiology of the Disease: None. Necrobacillosis is a disease common to man and animals.

Diagnosis: When a nonsporulating, anaerobic bacterium is suspected as the cause of infection in a human patient, specimens collected from the lesions for bacteriologic diagnosis must be free of contaminants from the normal flora, of which these anaerobes are natural components. Thus, for example, when anaerobic origin is suspected for human pulmonary infection, transtracheal aspiration with a needle or direct penetration of the lung must be used. By contrast, the patient's sputum is not a suitable material for examination. In the case of empyema or abscesses, obtaining pus under aseptic conditions is not a problem (Finegold, 1982).

In veterinary practice, diagnosis of hoof diseases in sheep and cattle is based on clinical characteristics. Samples for laboratory diagnosis of hepatic necrobacillosis can be collected without difficulty. In calf diphtheria, ulcerous, necrotizing lesions with a strong, putrid odor point to the disease; if a bacteriologic examination is attempted, epithelial samples from the edges of the ulcer should be used (Guarino *et al.*, 1982).

Control: Prevention in man consists primarily of avoiding and properly treating predisposing conditions. Specific control measures are neither known nor justified.

Control of sheep foot rot is the subject of continuing research. An important preventive measure is avoiding introduction of animals from places where the disease exists, since *B. nodosus* is considered an obligate parasite. As with other contagious diseases, a period of isolation is recommended for recently acquired animals before introducing them into the flock. Once the disease is introduced, transmission may be reduced by chemoprophylaxis using a foot bath of 5% formalin, 10% zinc sulfate, or 10% copper sulfate. To control the disease, it is recommended that damaged hooves be cut during the dry season in order to expose the necrotic parts, and that the animals be given foot baths or topical treatment with the preparations indicated above, in addition to intramuscular administration of antibiotics. Studies are still under way to perfect a vaccine made with *B. nodosus*, but the existence of serogroups and serotypes within this bacterium complicates this task (Ribeiro, 1980). One study indicates that in addition to 9 serogroups (A to H), there are 16 or more serotypes. More than one serogroup of *B. nodosus* may exist in a single flock, and several serogroups are sometimes isolated from the hoof of a single sheep. Vaccines made from purified pili (which contain the principal protecting immuno-

gen) of *B. nodosus* immunize satisfactorily against a homologous strain of the bacterium (Stewart *et al.*, 1983a). In addition to the pili, which only protect against homologous strains, there are two other immunogens that could give heterologous immunity. Vaccines made of whole cells tested against vaccines of purified pili (all having an equal pilus content) provided comparable protection. Although vaccines using whole cells are cheaper to produce and confer protection against heterologous strains, they are irritants and cause weight loss (Stewart, 1983b).

Control reduces but does not eliminate the problem. Some apparently healthy animals may harbor *B. nodosus* in their hooves and maintain the infection in the field.

Prevention of calf diphtheria is achieved principally by maintaining hygienic standards.

Chlortetracycline administered in feedlot foods helps to reduce the incidence of hepatic abscesses and allows the animals to gain weight normally (Timoney *et al.*, 1988). An important preventive measure is not allowing animals to change abruptly from their customary food to concentrated foods.

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NOCARDIOSIS

ICD-10 A43.0 pulmonary nocardiosis; A43.1 cutaneous nocardiosis; A43.8 other forms of nocardiosis

Etiology: Three pathogenic species, *Nocardia asteroides*, *N. brasiliensis*, and *N. otitidiscaviarum* (*N. caviae*). The first was proposed as the type species.

Nocardia belong to the order *Actinomycetales* and are higher bacteria that resemble fungi in many characteristics. They are aerobic, gram-positive, weakly acid-fast, and form long, branched filaments that fragment into coccoid and bacillary forms. This fragmentation is the way the bacteria multiply.

Geographic Distribution: Worldwide. *Nocardia* are common members of the soil flora and act to decompose organic matter. They are not part of the normal flora of man or other animals. There seems to be a difference in the distribution of the species. *N. asteroides* has been identified all over the world, while *N. brasiliensis* is present mainly in tropical and subtropical climates in North, Central, and South America (Pier, 1979; Land *et al.*, 1991). *N. otitidiscaviarum* predominates in the soil in the US, India, Japan, Mexico, and Tunisia (Land *et al.*, 1991).

Occurrence in Man: Nocardiosis is not a reportable disease and there is no reliable information on its frequency. Cases are sporadic. In the US (Beaman *et al.*, 1976), an estimated 500 to 1,000 cases occur each year. Between 1972 and 1974, 81.2% of the cases were due to *N. asteroides*, 5.6% to *N. brasiliensis*, 3% to *N. otitidiscaviarum,* and 10.2% to unspecified *Nocardia*. The majority of cases occurred in people between 21 and 50 years of age, and the male to female ratio was 3 to 1.

Occurrence in Animals: The frequency of animal nocardiosis is not well known. Different diseases due to *Nocardia* spp. have been described in cattle, sheep, monkeys, dogs, cats, wild animals, marine mammals, and fish. In New Zealand, where little attention had been paid to this disease previously, 34 cases were reported between 1976 and 1978, and 26 of these were manifested as bovine mastitis (Orchard, 1979).

The Disease in Man: The principal agent is *N. asteroides.* Nocardiosis is a suppurative infection whose course varies from acute to chronic, with a tendency

toward remission. The most common clinical form is pulmonary. Pulmonary nocardiosis may become chronic if not treated properly. Acute pneumonic forms occur primarily in immunodeficient patients (Lerner, 1991). The symptomatology is not specific: cough, respiratory difficulty, and hemoptysis when there is chronic cavitation. It usually begins with a primary pyogenous lesion in the lungs. Through hematogenous dissemination, the agent localizes in different organs and tissues. Cerebral abscesses are frequent. Between 20% and 38% of persons with nocardiosis show nervous symptoms. The case fatality rate in patients with cerebral abscesses is nearly 50%. A few cases of cerebral abscesses caused by *N. otitidiscaviarum* have been reported (Bradsher *et al.*, 1982). Other localizations include subcutaneous tissue, bones, and various organs.

Smego and Gallis (1984) analyzed 62 cases of infection caused by *N. brasiliensis* in the US, from their own files and from the literature. Of the 62 patients, 46 had both a cutaneous disease and a soft tissue disease. The cutaneous disease took the form of cellulitis, pustules, ulcers, pyoderma, subcutaneous abscesses, and mycetoma. Six patients had a pleuropulmonary disease and one of them also had a disease of the central nervous system. Dissemination of the disease, which is considered characteristic of *N. asteroides*, was seen in eight cases. Traumas were an important predisposing factor in cutaneous nocardiosis in 19 of 43 cases. All the patients with cutaneous or soft tissue disease recovered, as did 83% of the pulmonary patients. Case fatality was high in the cases of dissemination.

The recommended treatment is cotrimoxazole, sulfisoxazole, or sulfadiazine. It is important that treatment begin as soon as possible and continue for some time. In cases that are resistant to the sulfonamides, it is advisable to add amikacin or high doses of ampicillin (Benenson, 1990).

The incubation period is unknown. It most likely varies depending on the virulence and phase of multiplication of the *Nocardia* strain, as well as the host's resistance. Most (85%) cases of nocardiosis have occurred in immunologically compromised persons (Beaman *et al.*, 1976).

N. brasiliensis seldom causes pulmonary disease, but more frequently produces mycetomas.

The Disease in Animals: Cattle are the most affected species. *N. asteroides* and, more rarely, *N. otitidiscaviarum* are agents of bovine mastitis. The udder usually becomes infected one to two days after calving (Beaman and Sugar, 1983), but the disease may appear throughout lactation, frequently caused by unhygienic therapeutic infusions into the milk duct. The disease course varies from acute to chronic. The mammary gland becomes edematous and fibrotic. Fever is common and prolonged. Pus forms with small granules (microcolonies) as do fistulas to the surface. There may also be lymphatic or hematogenous dissemination to other organs. Among animals with acute infection, mortality is high.

Bovine nocardiosis may also manifest as pulmonary disease (especially in calves under 6 months of age), abortions, lymphadenitis of various lymph nodes, and lesions in different organs.

Canids are the second most affected group. The principal agent is *N. asteroides*, but infections caused by *N. brasiliensis* and *N. otitidiscaviarum* have also been described. The clinical picture is similar to that in man, and the most common clinical form is pulmonary. Dogs exhibit fever, anorexia, emaciation, and dyspnea.

Dissemination from the lungs to other organs is frequent and may affect the central nervous system, bones, and kidneys. The cutaneous form is also common in dogs, with purulent lesions usually located on the head or extremities. Nocardiosis is most frequent in male dogs under 1 year of age. The fatality rate is high (Beaman and Sugar, 1983).

Nocardiosis in cats is more unusual and is seen mostly in castrated males. Most cases are due to *N. asteroides*, but 30% have been attributed to *N. brasiliensis* or to other similar nocardias.

A disease with multiple pyogranulomatous foci in the liver, intestines, peritoneum, lungs, and brain was described in three macaque monkeys (*Macaca mulatta* and *M. menestrina*). *Nocardia* spp. was isolated in two cases. The assumption is that two monkeys were infected orally (Liebenberg and Giddens, 1985). Earlier references record five cases in monkeys, four of which had a localized infection. Pulmonary lesions were found in three of them. *N. otitidiscaviarum* was isolated from the hand of a baboon (*Papio* spp.) and a cynomolgus macaque (*M. fascicularis*) had lesions on the brain, jaws, lungs, heart, and liver (Liebenberg and Giddens, 1985).

The recommended treatment is prolonged administration of cotrimoxazole for some six weeks.

Source of Infection and Mode of Transmission: Nocardias are components of the normal soil flora. These potential pathogens are much more virulent during the logarithmic growth phase than during the stationary phase, and it is believed that actively growing soil populations are more virulent for man and animals (Orchard, 1979).

Man probably acquires the infection by inhaling contaminated dust. Predisposing causes are important in the pathogenesis of the disease, since most cases occur either in persons with deficient immune systems or those taking immunosuppressant drugs. An outbreak was confirmed among patients in a renal transplant unit and the strain of *N. asteroides* was isolated from the dust and air in the room (Lerner, 1991). Mycetomas caused by *N. brasiliensis* may be caused by a trauma to the skin. Wounds that come into contact with the soil may become infected by *Nocardia* spp. The most common route of infection by *N. brasiliensis* is through traumatic inoculation of the skin by thorns, nails, cat scratches, or burns (Smego and Gallis, 1984).

Animals probably contract pulmonary infections in the same way as man. Mastitis occurring later in the lactation period is produced by contaminated catheters. Mastitis at the beginning of lactation is more difficult to explain. It is possible that the focus of infection already exists in the nonlactating cow and that when the udder fills with milk, the infection spreads massively through the milk ducts and causes clinical symptoms (Beaman and Sugar, 1983). However, the origin of the initial infection remains an enigma, but it could also be due to the insertion of contaminated instruments. The multiple cases of nocardia-induced mastitis that are at times observed in a dairy herd are attributable to transmission of the infection from one cow to another by means of contaminated instruments or therapeutic infusions.

Role of Animals in the Epidemiology of the Disease: Nocardiosis is a disease common to man and animals; soil is the reservoir and source of infection. There are no known cases of transmission from animals to man or between humans.

Diagnosis: Microscopic examination of exudates can indicate nocardiosis, but only culture and identification of the agent provide a definitive diagnosis. In pulmonary nocardiosis, bronchoalveolar lavage and aspiration of abscesses or collection of fluids can be used, guided by radiology (Forbes *et al.*, 1990).

Various serological tests have been described. An enzyme immunoassay with an antigen (a 55-kilodalton protein) specific for *Nocardia asteroides* yielded good results in terms of both sensitivity and specificity (Angeles and Sugar, 1987). Serodiagnosis in immunodeficient patients—who currently suffer more frequently from nocardiosis—is very difficult. A more recent work (Boiron and Provost, 1990) suggests that the 54-kilodalton protein would be a good candidate as an antigen for a probe for detecting antibodies in nocardiosis.

Control: No specific control measures are available. Prevention consists of avoiding predisposing factors and exposure to dust (Pier, 1979). Environmental hygiene and sterilization of instruments are important.

For control of mastitis caused by *Nocardia* spp. in cows, it is recommended that udder hygiene practices be adopted as well as general hygiene rules for the dairy facility.

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PASTEURELLOSIS

ICD-10 A28.0

Synonyms: Shipping fever, bovine respiratory disease complex, fibrinous pneumonia (cattle); pasteurella pneumonia (lambs); hemorrhagic septicemia (cattle, lambs); fowl cholera; snuffles (rabbits).

Etiology: The genus *Pasteurella* was reclassified on the basis of DNA:DNA hybridization in order to determine the genetic relationship of the different accepted or proposed species (Mutters *et al.*, 1985). Based on the results of that study, the genus has been subdivided into 11 species. The species of interest here are: *Pasteurella multocida*, *P. dagmatis* sp. nov., *P. canis* sp. nov., and *P. stomatis* sp. nov. *P. caballi*, described more recently, should be added as well (Schater *et al.*, 1989). *P. haemolytica*, an important pathogen for animals and, occasionally, for man, is more related to the genus *Actinobacillus* and might receive its own generic name in the future (Mutters *et al.*, 1986). In addition, the DNA:DNA hybridization between strains of biotype A and biotype T ranges only from 3% to 13%, depending on the biotype used as the reference strain, and thus the two biotypes should be classified as separate species (Bingham *et al.*, 1990). The advantages of reclassification are not yet evident in epidemiological research, diagnosis, and treatment. Pasteurellae are small, pleomorphic, nonmotile, gram-negative, bipolar staining, nonsporulating bacilli, with little resistance to physical and chemical agents.

Subdivision of *P. multocida* and *P. haemolytica* into serotypes is important in the areas of epidemiology and control (vaccines). Subclassification of *P. multocida* into serotypes is based on its capsular (A, B1, D, and E) and somatic (1–16) antigens; the latter can occur in different combinations. *P. haemolytica* has been subdivided into two biotypes (A and T) and 15 serotypes.

Geographic Distribution: *P. multocida* and *P. haemolytica* are distributed worldwide. The distribution of the other species is less well-known, but based on their reservoirs they can be assumed to exist on all continents.

Occurrence in Man: Rare. It is not a reportable disease and its incidence is little known. According to laboratory records, 822 cases occurred in Great Britain from 1956 to 1965. A special survey in the US revealed 316 cases caused by *P. multocida* from 1965 to 1968. Data on the occurrence of human pasteurellosis in other countries are scarce. The disease caused by *P. haemolytica* is rare.

Occurrence in Animals: Common in domestic and wild species of mammals and birds.

The Disease in Man: The principal etiologic agent of human pasteurellosis is *P. multocida*. The other species make a lesser contribution to human disease. Fifty-six cultures from Göteborg University (Sweden), obtained from human cases of pasteurellosis, were reexamined. As a result, 26 strains were reclassified as *P. multocida* subspecies *multocida*; 11 as *P. multocida* ssp. *septica*; 12 as *P. canis*; 4 as *P. dagmatis,* and 1 as *P. stomatis*. Two strains were provisionally classified, one as *P. haemolytica* biogroup 2 (T) and another as belonging to the group that cannot be typed (Bisgaard and Falsen, 1986). The main clinical symptoms of the disease con-

sist of infected bites or scratches inflicted by cats or dogs (or occasionally by other animals), diseases of the respiratory system, and localized infections in different organs and tissues. Cases of septicemia are rare. The English-language literature records 21 cases of meningitis (Kumar *et al.*, 1990).

Various cases of pasteurellosis in pregnant women have been described. One primigravida who was carrying twins suffered from chorioamnionitis caused by *P. multocida* at 27 weeks, after her membranes had broken. The twin close to the cervix became infected and died shortly after birth, while the other twin did not become infected. It is believed that the infection rose upwards from the vagina, with asymptomatic colonization (Wong *et al.*, 1992). Two pregnant women with no history of concurrent disease received phenoxymethylpenicillin in an early phase of pasteurellosis. Despite the treatment, one of them became ill with meningitis and the other suffered cellulitis with deep abscess formation. Both of them had animals (dog and cat), but had not been bitten (Rollof *et al.*, 1992).

Most clinical cases arise from infected wounds. Most cats and dogs are normal carriers of *Pasteurella* and harbor the etiologic agent in the oral cavity. The microorganism is transmitted to the bite wound and a few hours later produces swelling, reddening, and intense pain in the region. The inflammatory process may penetrate into the deep tissue layers, reaching the periosteum and producing necrosis. Septic arthritis and osteomyelitis are complications that occur with some frequency. Septic arthritis often develops in patients suffering from rheumatoid arthritis. Cases have been described in which articular complications appeared several months and even years after the bite (Bjorkholm and Eilard, 1983). Of 20 cases of osteomyelitis with or without septic arthritis, 10 developed from cat bites, 5 from dog bites, 1 from dog and cat bites, and 4 had no known exposure (Ewing *et al.*, 1980).

P. multocida may also aggravate certain respiratory tract diseases, such as bronchiectasis, bronchitis, and pneumonia. In terms of case numbers, chronic respiratory conditions from which the agent is isolated are second in importance to infection transmitted by animal bite or scratch. Septicemia and endocarditis are extremely rare.

The age group most affected is persons over 40 years old, despite the fact that bites are more frequent in children and younger people.

P. multocida is sensitive to penicillin, but some resistant animal and human strains have been found; thus, it is advisable to do an antibiogram. *In vitro* tests have also shown excellent sensitivity to ampicillin, third-generation cephalosporins, and tetracycline (Kumar *et al.*, 1990).

The Disease in Animals: Pasteurellae have an extremely broad spectrum of animal hosts. Many apparently healthy mammals and birds can harbor pasteurellae in the upper respiratory tract and in the mouth. According to the most accepted hypothesis, pasteurellosis is a disease of weakened animals that are subjected to stress and poor hygienic conditions. In an animal with lowered resistance, pasteurellae harbored in the fauces or trachea may become pathogenic for their host. There is a marked difference in the level of virulence among different strains of *P. multocida*. In some diseases, *P. multocida* is the primary and only etiologic agent; in others, it is a secondary invader that aggravates the clinical picture.

A relationship exists between the serotype of *Pasteurella*, its animal host, and the disease it causes. Therefore, serologic typing is important for epizootiologic studies as well as for control (through vaccination).

Bovine hemorrhagic septicemia is caused by *P. multocida* serotype 6:B in Asia, and by 6:E and 6:B in Africa. In fibrinous pneumonia ("shipping fever") in cattle, serotype 1 of *P. haemolytica*, and serotype 2:A of *P. multocida* predominate.

CATTLE: Shipping fever, also called bovine respiratory disease complex, is a syndrome that causes large economic losses in the cattle industry of the Western Hemisphere. In the US, it causes annual losses estimated at more than US$ 25 million. Shipping fever is an acute respiratory disease that particularly affects beef calves and heifers as well as adult cows when they are subjected to the stress of prolonged transport. The symptomatology varies from a mild respiratory illness to a rapidly fatal pneumonia. Symptoms generally appear from 5 to 14 days after the cattle reach their destination, but some may be sick on arrival. The principal symptoms are fever, dyspnea, cough, nasal discharge, depression, and appreciable weight loss. The fatality rate is low.

The etiology of the disease has not been completely clarified, and it is noteworthy that the disease does not occur in Australia, even when animals are transported over long distances (Irwin *et al.*, 1979). Several concurrent factors are believed to cause the syndrome. Most prominent among these are such stress factors as fatigue, irregular feeding, exposure to cold or heat, and weaning. Viral infections, which occur constantly throughout a herd and are often inapparent, are exacerbated by factors such as overcrowding during transport. Moreover, susceptible animals suddenly added to a herd lead to increased virulence. The virus most often identified as the primary etiologic agent is parainfluenza virus 3 (PI3) of the genus *Paramyxovirus*. Infection by this virus alone usually causes a mild respiratory disease. However, the damage it causes to the respiratory tract mucosa aids such secondary invaders as *P. multocida* and *P. haemolytica*, which aggravate the clinical picture. On the other hand, virulent strains of *Pasteurella* can cause the disease by themselves. Pasteurellae frequently isolated in cases of shipping fever include *P. haemolytica* biotype A, serotype 1, and various serotypes of group A of *P. multocida*. The fact that treatment with sulfonamides and antibiotics gives good results also indicates that a large part of the symptomatology is due to pasteurellae. Another important viral agent that acts synergistically with pasteurellae is the herpesvirus of infectious bovine rhinotracheitis. Similarly, viral bovine diarrhea, chlamydiae, and mycoplasmas can play a part in the etiology of this respiratory disease.

An important disease among cattle and water buffalo in southern and southeastern Asia is hemorrhagic septicemia. In many countries, it is the disease responsible for the most losses once rinderpest has been eradicated. Hemorrhagic septicemia also occurs in several African countries, including Egypt and South Africa, and, less frequently, in southern Europe. The disease seems to be enzootic in American bison, and several outbreaks have occurred (the last one in 1967), without the disease spreading to domestic cattle (Carter, 1982). In tropical countries, hemorrhagic septicemia occurs during the rainy season. The main symptoms are fever, edema, sialorrhea, copious nasal secretion, and difficulty in breathing. Mortality is high. Surviving animals become carriers and perpetuate the disease. Cases of hemorrhagic septicemia have also been recorded in horses, camels, swine, yaks, and other species. It must be borne in mind that hemorrhagic septicemia is due to the specific *P. multocida* serotypes 6:B and 6:E. There is no evidence that the disease occurs in domestic cattle in the Americas.

P. multocida is also responsible for cases of mastitis.

SHEEP: *P. haemolytica* is the etiologic agent of two different clinical forms, pneumonia and septicemia. Biotype A serotype 2 is the most prevalent agent of pasteurella pneumonia among lambs in Great Britain (Fraser *et al.*, 1982). Pulmonary disease in sheep follows a viral infection (P13). Although *Pasteurella* is a secondary invader, it is the predominant pathogen. Occurrence of the disease is sporadic or enzootic. The main symptoms are a purulent nasal discharge, cough, diarrhea, and general malaise. Lesions consist of hemorrhagic areas in the lungs and petechiae in the pericardium. Pasteurella septicemia is caused by biotype T of *P. haemolytica* and appears in temperate climates in the fall, when the sheep's diet is changed (Gillespie and Timoney, 1981). In Mexico, 860 pneumonic lungs were examined, and 120 isolates of *P. haemolytica* type A were obtained from them. The most common serotypes were 1 (22%), 2 (16%), 5 (11%), and 9 (7%). Twenty-seven percent of the isolates could not be typed (Colin *et al.*, 1987). *P. haemolytica* is the only etiologic agent of sporadic sheep mastitis in the western US, Australia, and Europe (Blood *et al.*, 1979).

SWINE: Pasteurellosis also appears in the form of pneumonia and, more rarely, as septicemia. *Pasteurella* may be a primary or secondary agent of pneumonia, particularly as a complication of the mild form of classic swine plague (hog cholera) or mycoplasmal pneumonia. The anterior pulmonary lobes are the most affected, with hepatization and a sero-fibrinous exudate on the surface. Serotype 3:A of *P. multocida* is the most prevalent in chronic swine pneumonia (Pijoan *et al.*, 1983). Studies have revealed evidence of the etiologic role of toxigenic strains of *P. multocida* serotype D in atrophic rhinitis. *Bordetella bronchiseptica* acting synergistically with toxigenic strains of *P. multocida* probably causes this disease, the etiology of which has been the subject of much debate (Rutter, 1983).

Atrophic rhinitis is characterized by atrophy of the nasal turbinate bones, sometimes with distortion of the septum. Experiments have shown that the agents—*B. bronchiseptica* and toxigenic *P. multocida*—can cause the disease separately in 1-week-old gnotobiotic suckling pigs. However, turbinate atrophy is more severe and may become complete when the animals are inoculated with both agents (Rhodes *et al.*, 1987). Atrophic rhinitis could not be seen in some herds from which only *B. bronchiseptica* was isolated. The purified toxin of type D strains of *P. multocida*, inoculated intranasally, caused severe turbinate atrophy (Dominick and Rimler, 1986).

Various outbreaks of hemorrhagic septicemia caused by *P. multocida* 2:B have been reported in India. In one of these outbreaks, 40% of the herd died (Verma, 1988).

RABBITS: Pasteurellosis is common in rabbit hutches. The most frequent clinical manifestation is coryza. As in other animal species, the disease appears under stressful conditions. The principal symptoms are a serous or purulent exudate from the nose and sometimes from the eyes, sneezing, and coughing. The pathological process may spread to the lungs. Septicemia and death are not uncommon. Males that are kept together may show pasteurella-infected abscesses produced by bites. An atrophic rhinitis syndrome also occurs in rabbits. Autopsy of 52 adult rabbits revealed that 26 of them (50%) had turbinate atrophy. *P. multocida* and *B. bron-*

chiseptica were isolated from more than 70% of the rabbits. Six percent of those from which only *B. bronchiseptica* was isolated had the syndrome (DiGiacomo *et al.*, 1989).

WILD ANIMALS: Pasteurellosis occurs in many wild animal species, among which occasional epizootic outbreaks take place. The etiologic agent is *P. multocida; P. haemolytica* has not yet been isolated. Two disease forms are found: hemorrhagic septicemia, in which the whole animal body is invaded by pasteurellae, and the respiratory syndrome or pulmonary pasteurellosis.

FOWL: Fowl cholera is an acute septicemic disease with high morbidity and morality in all species of domestic fowl. Its incidence has diminished worldwide due to improved commercial poultry management practices. The disease usually appears on poultry farms where hygiene is deficient. Explosive outbreaks may occur two days after infected birds are introduced into a flock. Mortality is variable, at times reaching 60% of the poultry on a farm. Many of the survivors become carriers and give rise to new outbreaks. At the beginning of a hyperacute outbreak, fowl die without premonitory symptoms; mortality increases, but the only symptom seen is cyanosis of the wattle and comb. Later, the disease process slows down and respiratory symptoms appear. Cases of chronic or localized pasteurellosis may occur following an acute outbreak, or the disease may take this course from the outset of infection. The chronic disease is caused by attenuated strains of *P. multocida* and manifests itself mostly as "wattle disease" (edematization and later caseation of these appendages). Another localization can be the wing or foot joints. Fowl cholera is produced by *P. multocida* of serogroup A, predominantly serotypes 1 and 3 (Mushin, 1979); some strains of group D have also been isolated, but they seem to be less pathogenic. *P. multocida* causes outbreaks with high mortality among wild birds, especially waterfowl.

Source of Infection and Mode of Transmission: The reservoir includes cats, dogs, and other animals. The etiologic agent is harbored in the upper respiratory passages. Cats are the carriers of the agent 70% to 90% of the time, but dogs (20% to 50%), sheep, cattle, rabbits, and rats are also important carriers (Kumar *et al.*, 1990). The most common form of the disease (60% to 86% of cases) is a wound contaminated as the result of an animal bite. Cats are primarily responsible in 60% to 75% of the cases, followed by dogs. The mode of transmission for the pulmonary form is probably aerosolization of the saliva of cats or dogs. Some patients (7% to 13%) do not acknowledge having been bitten by or otherwise exposed to animals (Kumar *et al.*, 1990).

For human infections transmitted by animal bite or scratch, the source of the infection and the mode of transmission are obvious. Except in the case of bites, animal-to-man transmission is accomplished through the respiratory or digestive tract. An analysis of 100 cases of human pasteurella infections of the respiratory tract and other sites found that 69% of the patients had had contact with dogs or cats, or with cattle, fowl, or their products. Nevertheless, 31% of the patients denied all contact with animals; consequently, it is suspected that interhuman transmission may also occur.

Among fowl, where *P. multocida* is undoubtedly the primary agent of infection, the source of the outbreaks is carrier fowl, and transmission occurs predominantly

by means of aerosols. Dogs and cats rarely suffer from pasteurellosis (with the exception of wounds infected with pasteurellae in fights) and are healthy carriers. Other mammals acquire the disease from members of their own species either through the respiratory or digestive tract, or by falling victim to the pasteurellae in their own respiratory tracts when stress lowers their defenses. There is much evidence that stress factors play an important enabling role in unleashing the respiratory syndrome of shipping fever, and that these factors permit multiplication of serotype 2 of *P. haemolytica* (Frank and Smith, 1983). Serotypes 6:B and 6:E, which cause hemorrhagic septicemia in cattle and water buffalo, are perpetuated by means of carriers and chronically ill animals that serve as a source of infection for their kind.

Role of Animals in the Epidemiology of the Disease: Pasteurellae survive only a very short time in the environment. It is certain that animals constitute the most important reservoir of the pasteurellae that are pathogenic for man.

Diagnosis: In the case of human infection, diagnosis is made by isolating and identifying the etiologic agent from wounds or other sites.

In hemorrhagic septicemia or fowl cholera, the etiologic agent can be cultivated from the animal's blood or viscera. In pneumonia of domestic animals, a pure culture of pasteurellae may indicate their role in the pathology, but does not reveal whether these bacteria are primary or secondary agents of the disease.

Control: Measures to reduce the likelihood of bites, such as elimination of stray dogs, can prevent some cases of human infection.

Control in animals lies mainly in adequate management of herds or poultry farms. Bacterins as well as live attenuated vaccines are in use, or are being tested, against *P. multocida* and *P. haemolytica*. Protection against homologous serotypes is satisfactory, but protection is only partial or irregular against heterologous serotypes. In general, attenuated live vaccines give better immunity than bacterins. In Asia, extensive experimentation proved that a bacterin with an oil adjuvant can offer solid immunity against hemorrhagic septicemia. A single dose of live vaccine with a streptomycin-dependent mutant strain conferred immunity against hemorrhagic septicemia in 66.6% to 83.3% of calves and in 100% of young buffalo (De Alwis and Carter, 1980).

The use of PI3 vaccine has been recommended for the control of shipping fever. It is better to vaccinate against the principal viral agents before weaning or transporting animals. The bacterins of *P. haemolytica* and *P. multocida* have been questioned. Attenuated live vaccines or vaccines from subunits, such as the cytotoxin (leukotoxin) of *P. haemolytica* (Confer *et al.*, 1988), are more reliable. Attenuated live vaccines of *P. haemolytica* are being tested. A bacterin containing multiple antigens of the prevalent serotypes, incorporated into a polyvalent anticlostridial biological with aluminum hydroxide adjuvant, has been tested against *P. haemolytica* pneumonia in lambs and has given satisfactory results (Wells *et al.*, 1984). Several live vaccines are available against avian cholera, some of which can be administered in the drinking water. Selection of *Pasteurella* strains within the serotypes that cause the disease is important in immunization.

Bovine hemorrhagic septicemia should be considered an exotic disease and appropriate measures should be taken to prevent its spread to disease-free areas.

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PLAGUE

ICD-10 A20.0 bubonic plague; A20.2 pneumonic plague; A20.7 septicaemic plague

Synonyms: Black death, pestilential fever, pest.

Etiology: The etiologic agent of plague is *Yersinia pestis*, a gram-negative, nonmotile bacterium, coccobacillary to bacillary in form and showing bipolar staining that is not very resistant to physical and chemical agents. DNA hybridization studies demonstrated the close genetic relationship between *Yersinia pestis* and *Y. pseudotuberculosis* (Bercovier *et al.*, 1980). On the basis of this, the authors suggested calling the etiologic agent of plague *Y. pseudotuberculosis* subsp. *pestis* (International Committee on Systemic Bacteriology, List 7, 1981). However, the Committee's Judicial Commission (1985) decided to reject this nomenclature and retain the name *Y. pestis* in order, among other reasons, to avoid possible confusion. Three biological varieties are distinguished: *Orientalis* (oceanic), *Antiqua* (continental), and *Mediaevalis*. This distinction has a certain epidemiological significance, principally for nosography, but there is no difference in the biotypes' pathogenicity.

Some virulence factors of *Y. pestis* were defined in the 1980s. Apparently, the principal factor is a 45-megadalton plasmid. This plasmid encodes calcium dependency for growth at 37°C, but not at lower temperatures, as well as the virulence antigens V and W. The two proteins on the outer membranes that are assumed to be important in virulence (E and K) are also plasmid dependent. The precise role of each of these factors is not yet well defined (Butler, 1989).

Geographic Distribution: Natural foci of infection persist on nearly all continents; they do not exist in Australia, New Zealand, or New Guinea. In the Americas, sylvatic plague is maintained in rodents in the western third of the United States, the border region of Ecuador and Peru, southeastern Bolivia, and northeastern Brazil. Similarly, there are foci in north-central, eastern, and southern Africa, including Madagascar; the Near East; the border area between Yemen and Saudi Arabia; Kurdistan province (Iran); and central and Southeast Asia, in Myanmar (Burma) and Vietnam. There are also several natural foci in the former Soviet Union and in Indonesia (Benenson, 1990).

Occurrence in Man: Since the dawn of the Christian era, there have been three great pandemics: the first began in 542 (Justinian plague) and is estimated to have caused 100 million deaths; the second began in 1346, lasted three centuries, and claimed 25 million victims; and the last began in 1894 and continued until the 1930s. However, the data on incidence in the Middle Ages are very approximate and difficult to verify. As a result of the last pandemic, natural foci of infection were established in South America, West Africa, South Africa, Madagascar, and Indochina.

Urban plague has been brought under control in almost the entire world, and rural plague of murine origin is also on the decline. Nevertheless, epidemics have occurred in Indonesia, Nepal, and southern Vietnam. In this last country, there were 5,274 cases in 1967 due to contact with domestic rats and their fleas.

From 1958 to 1979, 46,937 cases of human plague were recorded in 30 countries; if Vietnam is excluded, the total number is reduced to 15,785. The large number of cases in Vietnam is attributed to military operations there and consequent ecologic changes. On the other hand, 16 of the 30 countries reporting plague cases were in Africa. However, incidence of the disease on that continent was very low, less than 6% of the world total (Akiev, 1982). Figure 14 shows the number of cases and deaths caused by human plague worldwide from 1971 to 1980.

The incidence of plague from 1977 to 1991 included 14,752 cases with 1,391 deaths distributed in 21 countries (WHO, 1993).

In 1991, there was a large increase of cases in Africa, with a total of 1,719 people affected, due primarily to an outbreak in Tanzania. In that country, there were 60 deaths among a total of 1,293 cases, 1,060 of which occurred in the Tanga region. There were also 137 cases reported in Madagascar and 289 in Zaire (WHO, 1993).

In Asia, there were 226 total cases, with 15 deaths. There were 100 cases in Myanmar, 94 in Vietnam, 29 in China (with 11 deaths), and the remainder in two other countries (WHO, 1993).

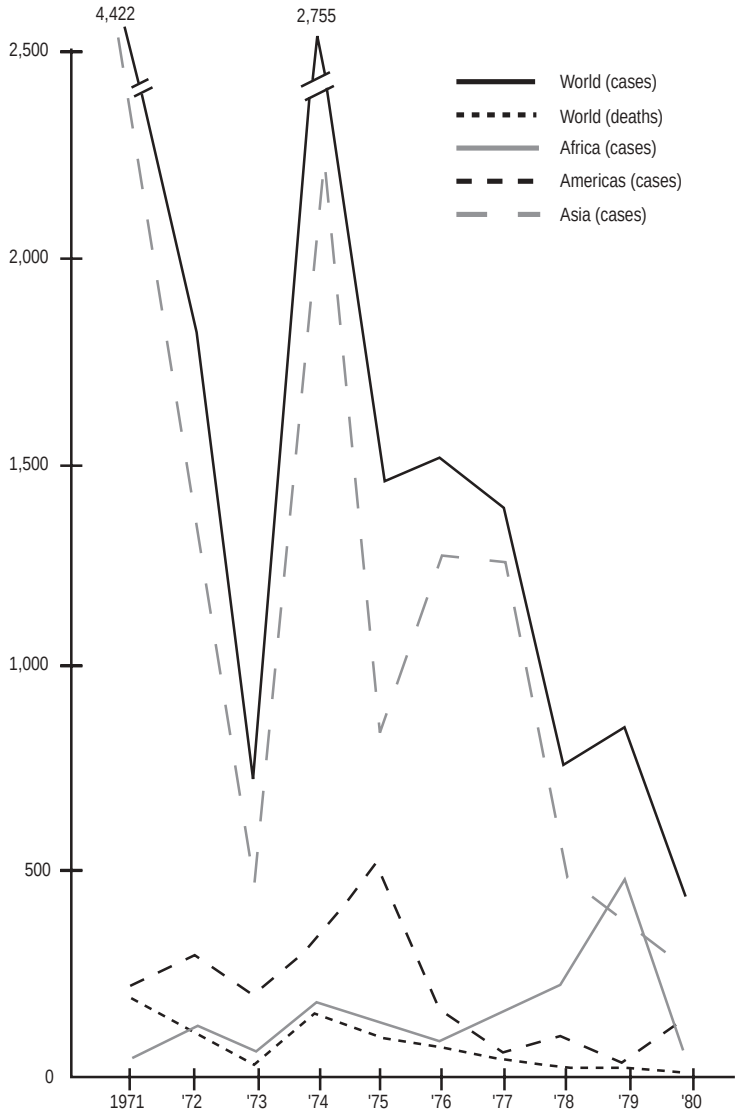
There are seven countries in the Americas with cases of plague: Bolivia, Brazil, Ecuador, Peru, the US, and occasionally, Colombia and Venezuela (Akiev, 1982). During the period 1971–1980, there were 2,312 cases in the Americas (Table 2), 1,551 of which occurred in Brazil, 316 in Peru, 247 in Bolivia, 123 in the US, and 75 in Ecuador (PAHO, 1981). In all the countries, the number of cases fluctuated greatly from year to year; at times, epidemic outbreaks have occurred. Plague continues to be a public health problem in the Americas because of the persistence of sylvatic plague and the link between domestic and wild rodents. In Ecuador, an outbreak of seven cases occurred in May 1976 in Nizac, Chimborazo Province, a settlement of 850 inhabitants. The outbreak was preceded by a large epizootic in rats and mortality among guinea pigs raised in homes for food. The worst outbreak since 1966 occurred in 1984 in northern Peru, with 289 cases reported in 40 localities. An association was presumed between this outbreak and a great abundance of rodents, possibly the result of ecologic changes due to flooding (Rust, 1985).

In the US, 35 cases were recorded from April to August 1983, the greatest number of cases since 1925. Almost all the cases occurred in five southwestern states.

Twenty-one cases of plague were reported in the Americas in 1991. Ten of these occurred in Brazil and 11 in the US, although there were no deaths (WHO, 1993). In 1992, there were 8 cases in Brazil (all in Bahia) and 13 in the US (4 in Arizona, 4 in New Mexico, and 1 each in five more states) (OPS, 1992). One of the cases in Arizona was primary pulmonary plague in a 31-year-old patient who died one day after being admitted to the hospital. Blood and urine cultures taken from the patient were negative. After the patient's death, *Y. pestis* was isolated from the sputum. The source of the infection was a sick cat. This is the third case in the US of primary pulmonary plague contracted from a cat. The incubation period is very short in these cases (two to three days) and the symptoms do not lead one to suspect plague (CDC, 1992). There have been no cases of direct human-to-human transmission in the US since 1924 (Benenson, 1990).

In October 1992, an outbreak of plague was reported in Cajamarca (Peru) which is still active. In nine localities affected, with an estimated at-risk population of 30,000, there were 547 cases and 19 deaths (up to mid-January 1994). The outbreaks were preceded by deaths among wild rodents and guinea pigs (*Cavia porcellus*) bred

Figure 14. Number of cases and deaths from human plague worldwide, 1971–1980.



Source: PAHO Epidemiol Bull 2(6):4–5, 1981.

Table 2. Number of cases and deaths from human plague in the Americas, 1971–1980.

Country	1971		1972		1973		1974		1975		1976		1977		1978		1979		1980	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
Bolivia	19	3	0	0	0	0	14	5	2	0	24	5	29	9	68	2	10	0	26	2
Brazil	146	2	169	13	152	...	291	...	496	5	97	...	1	...	11	...	0	0	98	0
Ecuador	27	0	9	0	1	1	0	0	0	0	8	1	0	0	0	0	0	0	0	0
Peru	22	5	118	15	30	2	8	2	3	0	1	0	0	0	6	1	0	0	0	0
United States of America[a]	2	0	1	0	2	0	8	1	20	4	16	3	18	2	12	2	13	2	18	5
Total	216	10	297	28	185	3	321	8	521	9	146	9	48	11	97	5	23	2	142	7

C = Cases
D = Deaths
… Data unavailable
[a]Plague found in rodents.
Source: PAHO Epidemiol Bull 2(6):4–5, 1981.

at home by the peasants. One factor that helped to increase the number of cases was that rodenticides were used without simultaneous or prior use of flea pulicides (Report from Dr. Alfonso Ruiz to the Pan American Health Organization, February 8, 1994).

Occurrence in Animals: Natural infection by *Y. pestis* has been found in 230 species and subspecies of wild rodents. In natural foci, sylvatic plague is perpetuated through the continuous circulation of the etiologic agent, transmitted by fleas from one rodent to another. It is generally believed that the survival of the etiologic agent in a natural focus depends on the existence of rodent species, or individuals within a species, with differing levels of susceptibility. The most resistant individuals are host to and infect the fleas, which in turn infect susceptible animals in the area and can spread to domestic rodents. Susceptible animals generally die, but they increase the population of infected fleas by means of their bacteremia. When the number of susceptible individuals is large and climatic conditions favorable, an epizootic may develop in which many rodents die. As the epizootic diminishes, the infection continues in enzootic form in the surviving population until a new outbreak occurs. Infection may remain latent in enzootic foci for a long time, and the absence of human cases should not be interpreted as a sign that the natural focus is eliminated.

During the period 1966–1982, 861 isolates were taken of *Y. pestis* in foci in northeastern Brazil. Of these, 471 were from rodents or other small mammals, 236 were from batches of fleas, 2 from batches of *Ornithodorus*, and 152 from patients. In the rodents, the highest number of isolates were taken from *Zygodontomys lasiarus pixuna*, which also provided the highest number of fleas, primarily of the genus *Polygenis*; on only one occasion was the agent isolated from cat fleas (*Ctenocephalides felis*). The agent was isolated from human fleas (*Pulex irritans*) found on the floor of dwellings on 10 occasions. Human flea infection suggests the possibility of human-to-human transmission through flea bites, usually after a fatal case in the family (Almeida *et al.*, 1985).

House cats that come into contact with rodents and/or their fleas can become infected and fall ill, and can transmit the infection to man. In the US and South Africa, several cases of the disease in cats have been described (Kaufmann *et al.*, 1981; Rollag *et al.*, 1981). In New Mexico (USA), 119 cases of plague were reported in domestic cats from 1977 to 1988 (Eidson *et al.*, 1991). There is also evidence that camels and sheep in enzootic plague areas can contract the infection and that, in turn, man can become infected when sacrificing these animals. Such cases occurred in Libya (Christie *et al.*, 1980).

The Disease in Man: The incubation period lasts from two to six days, though it may be shorter. Three clinical forms of plague are recognized: bubonic, septicemic, and pneumonic. The symptoms shared by all three are fever, chills, cephalalgia, nausea, generalized pain, diarrhea, or constipation; toxemia, shock, arterial hypotension, rapid pulse, anxiety, staggering gait, slurred speech, mental confusion, and prostration are also frequent.

Bubonic plague—the most common form in interpandemic periods—is characterized by acute inflammation and swelling of peripheral lymph nodes (buboes), which can become suppurative. There may be a small vesicle at the site of the flea bite. The buboes are painful and the surrounding area is usually edematous.

Bacteremia is present at the beginning of the disease. The fatality rate in untreated cases is from 25% to 60%. At times, the disease may take the form of a mild, localized, and short-lived infection (pestis minor). Another, less frequent form is meningitis, which occurs primarily after ineffective treatment for bubonic plague (Butler, 1988). In septicemic plague, nervous and cerebral symptoms develop extremely rapidly. Epistaxis, cutaneous petechiae, hematuria, and involuntary bowel movements are seen. The course of the disease is very rapid, from one to three days, and case fatality may reach nearly 100%.

Pneumonic plague may be a secondary form derived from the bubonic or septicemic forms by hematogenous dissemination, or it may be primary, produced directly by inhalation during contact with a pneumonic plague patient (primary pneumonic plague). In addition to the symptoms common to all forms, dyspnea, cough, and expectoration are present. The sputum may vary from watery and foamy to patently hemorrhagic. This is the most serious form.

Primary pneumonic plague, the origin of which is human-to-human transmission by aerosol and which has caused outbreaks and sometimes devastating epidemics, is rare. The pneumonic form seen in present times is the secondary form, resulting from septicemic dissemination. Since 1925, the US has recorded very few cases of primary pneumonic plague, all of which have resulted from exposure to a cat with secondary pneumonia. The first case occurred in California in 1980 (CDC, 1982). A similar case occurred more recently in Arizona (CDC, 1992). In total, there have been three cases of primary pneumonia with the same characteristics. Secondary invasion of the lungs (secondary pneumonic plague) occurs in untreated patients and approximately 95% of them die without becoming transmitters of the agent by aerosol. If left untreated, the small number of patients who do not die may give rise to other cases of pneumonic plague by airborne transmission (Poland and Barnes, 1979). In countries that maintain epidemiologic surveillance and where physicians and the general population are alert to the disease, the high fatality rates caused by all forms of plague have been largely arrested by early diagnosis and prompt treatment with antibiotics, such as streptomycin, tetracycline, and chloramphenicol.

The Disease in Animals: *Y. pestis* primarily infects animals of the order *Rodentia*; if affects wild as well as domestic rodents and, to a lesser degree, rabbits and hares (lagomorphs). The infection may be acute, chronic, or inapparent. Different species of rodents and different populations of the same species show varying degrees of susceptibility. In this regard, it has been observed that a population in an enzootic area is more resistant than another in a plague-free area, a phenomenon attributed to natural selection. Domestic (commensal) rats are very susceptible; *Rattus rattus* die in large numbers during epizootics. By contrast, susceptibility varies greatly between different species in natural foci and must be determined for each situation. In the western United States, prairie dogs (*Cynomys* spp.) and the ground squirrel *Citellus beecheyi* are very susceptible, while certain species of *Microtus* or *Peromyscus* are resistant.

Lesions found in susceptible animals dead from plague vary with the course of the disease. In acute cases, hemorrhagic buboes and splenomegaly are present without other internal lesions; in subacute cases the buboes are caseous, and punctiform necrotic foci are found in the spleen, liver, and lungs.

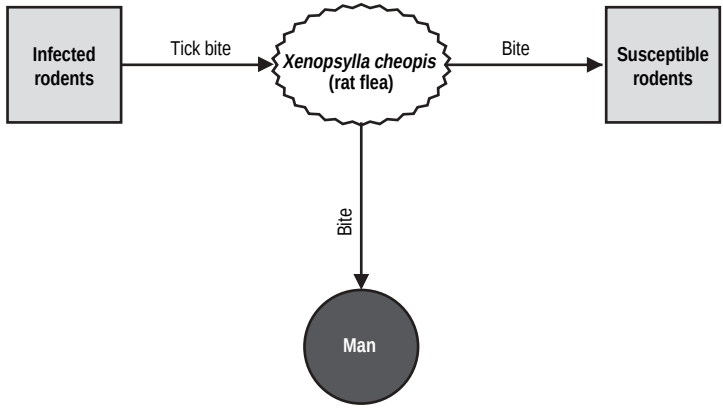
Natural infection in cats has come under close scrutiny, as they have been a source of infection for man in several instances. Feline plague is characterized by formation of abscesses, lymphadenitis, lethargy, and fever (Rollag *et al.*, 1981). Secondary pneumonia may also be present, as in the case at Lake Tahoe, California, where a kitten transmitted the infection to a man by aerosol. Fatality is over 50% in cats infected experimentally. In contrast, dogs inoculated with the plague agent react only with fever. Other carnivores are not very susceptible, with the exception of individuals with greater than normal susceptibility, as might be expected in any animal population.

Natural infection has been recorded in camels and sheep in the former Soviet Union and Libya (Christie *et al.*, 1980) and, more recently, in camels from Saudi Arabia (A. Barnes, personal communication).

Source of Infection and Mode of Transmission (Figure 15): Wild rodents are the natural reservoir. The maintenance hosts vary in each natural focus, but they are almost always rodent species with low susceptibility, i.e., the animals become infected but do not die from the disease. Very susceptible species, in which many animals die during an epizootic, are important in amplification and diffusion of the infection as well as in its transmission to man, but they cannot be permanent hosts. The epizootics that afflict prairie dogs (*Cynomys* spp.) are devastating. In one epizootic, only some animals survived in two of seven colonies. Another explosive epizootic annihilated an entire colony of 1,000 to 1,500 animals in two months. A third epizootic reduced the population by 85% (Ubico *et al.*, 1988). *R. rattus* is very susceptible, but the infection usually dies out rapidly in this species. Only in some circumstances, as occurred in India, can it serve as a temporary host, but not for many years. Consequently, the persistence of a focus depends on rodent species that have a wide spectrum of partial resistance.

In a natural focus, the infection is transmitted from one individual to another by fleas. Different species of fleas vary greatly in their efficiency as vectors. Biological

Figure 15. Plague. Domestic and peridomestic transmission cycle.



vectors are characterized by the blocking phenomenon. When *Y. pestis* is ingested with the septicemic host's blood, the agent multiplies in the flea's stomach and the proventriculum becomes blocked by the mass of bacteria. When a blocked flea tries to feed again, it regurgitates the bacteria into the bloodstream of the new host (this is the case with *Xenopsylla cheopis*, the domestic rat flea). Wild rodent fleas are generally less efficient and their capacity as biological vectors varies; it is believed that mechanical transmission may be important in natural foci. Also, these vectors are not very species-specific and can transmit the infection between different rodent species living in an enzootic area. The etiologic agent survives for a long time in fleas; some have remained infected for a period of 396 days. For this reason, fleas may be considered part of the natural reservoir, which would be an arthropod-vertebrate complex. More than 200 species of fleas have been implicated in the transmission of plague.

Infection from a natural focus may be passed to commensal rodents (domestic rats and mice) by members of the ubiquitous rodent species that approach human dwellings and can thus initiate an outbreak of plague within households. In the same way, peridomestic rodents may come into contact with wild rodents. Transmission is effected by means of fleas.

Other mammals (dogs, marsupials) may also serve as the link between the wild and domestic cycles by transporting fleas from one place to another. In northeastern Brazil, South American short-tailed gray opossums (*Monodelphis domestica*) naturally infected with the plague agent via *Polygenis bohlsi jordani* (a principal vector of sylvatic plague in this region) have been found to live near and enter houses. The natural plague foci can experience long periods of reduced activity, during which the proportion of infected rodents is small and no human cases occur. When these foci become active, epizootics among rodents and, at times, epidemic outbreaks can occur. Such could have been the case in the central Java (Indonesia) focus where no human plague had occurred since 1959, but where 100 cases were reported in 1968 and 40 in 1971.

When man enters a natural focus, he may contract the infection through bites of fleas of wild rodents or lagomorphs, or through skin abrasions or bites when handling these animals. Human cases are sporadic under these circumstances. When plague penetrates the domestic and peridomestic environment, man is infected via fleas of commensal rodents, and epidemic outbreaks may result. The domestic rat flea (*Xenopsylla cheopsis*) is the biological vector *par excellence* of plague. The name zootic plague has been given to plague transmitted by insects. Indirect interhuman transmission via human ectoparasites (*Pulex irritans* and *Pediculus humanis*) is rare and has only been observed in heavily infected environments. In some areas of the Andes, this mode of transmission occurs with some frequency, especially during wakes for those who have died of plague. These outbreaks almost always occur within families.

Secondary pneumonia as a complication of bubonic or septicemic plague may give rise to a series of primary pneumonic plague cases through interhuman transmission via the respiratory route. This is so-called demic plague. At present, bubonic plague is eminently zoonotic and occurs primarily in semi-arid areas.

Cats have transmitted the infection in a small proportion of cases (in the US, 2.2% from 1930 to 1979). Because buboes in cats are located in the head and neck region, it is thought that cats contract the infection by consuming infected rodents. Transmission from cat to man has resulted from direct contact, bites, or scratches.

Role of Animals in the Epidemiology of the Disease: Perpetuation of plague depends on the *Y. pestis*-rodents-fleas complex in natural foci. Plague in commensal rats is usually a collateral phenomenon to sylvatic plague, and so, by extension, is demic plague.

Diagnosis: Early diagnosis is essential to protect the patient and the community. Diagnosis is confirmed in the laboratory by puncturing the bubo and collecting fluid from gelatinous edemas, cerebrospinal fluid, and sputum for preparation of a Gram- or Giemsa-stained smear, and culturing in appropriate media. The culture can be identified rapidly using specific phagocytolysis or the immunofluorescence and agglutination tests.

An index case (the first case in a community), which may be the precursor of an outbreak, can be provisionally diagnosed with the rapid immunofluorescence test, using material from a bubo, and confirmed later by culture or inoculation in laboratory animals (guinea pigs or mice).

Hemoculture can be used in the initial, septicemic period of bubonic plague.

The serological tests most often used for human patients are passive hemagglutination and the fluorescent antibody test. The enzyme-linked immunosorbent assay (ELISA) procedure for detecting the F1 antigen (Fraction 1) of *Y. pestis* with monoclonal antibodies yields apparently satisfactory results, but does not eliminate the need for bacteriological confirmation (Williams *et al.*, 1986).

Inoculation of laboratory animals has proven superior to culture on culture media for plague research in rodents or fleas. Passive hemagglutination is of great value for epizootic studies of the infection, both in native rodent populations and in sentinel animals in natural foci. Resistant animals, such as dogs, can fulfill the latter surveillance function. During a plague episode in which one man in southeastern Utah (USA) died, the only evidence of the infection's activity was the discovery of positive titers in two of the family dogs. In the same country, coyotes have proved useful as sentinels. Coyotes rarely die of plague, but produce antibodies against the disease agent; in addition, since they feed on sick and dead rodents, examining a coyote is equivalent to examining several hundred rodents. A rapid serological test (an enzymatic immunoassay) has been perfected for testing these animals (Willeberg *et al.*, 1979). The passive hemagglutination test, employing specific Fraction-1 antigen (pesticin), is also useful in retrospective studies of plague in human communities in enzootic areas. A DNA probe has been developed that could prove useful in epidemiological surveillance of plague (McDonough *et al.*, 1988).

Control: Prevention of human plague is based on control of rodents and vectors of infection. Eradication of natural foci is a long-term, costly, and difficult task that can be achieved by changing the ecology of the foci and dedicating the enzootic area to agriculture. In general, the objectives of prevention campaigns are more limited and consist mainly of emergency programs in situations with a high potential for human infection. In all areas where natural plague foci exist, continuous surveillance must be maintained (dogs have been used very successfully as sentinel animals) and emergency measures set in motion if cases of the disease develop. Essentially, these measures consist of the use of insecticides and rodenticides. Insecticides should be employed before or at the same time as rodenticides, but never after, as fleas abandon dead animal hosts and seek out new hosts, including man. During outbreaks, the main effort should be directed toward flea control,

which is very effective and economical. If human plague cases occur, patients must be isolated (stringent isolation is required for pneumonic patients) and treated. All contacts should be disinfected and kept under surveillance; if deemed necessary, chemoprophylaxis (tetracycline and sulfonamides) should be given for six days; flea and rodent control should be continued. In such places as the Andes, where flea infestations on humans are prevalent, prophylactic measures are recommended for persons attending funerals of plague victims, along with strict control of these cases to prevent human-to-human transmission.

In the mountains of Tienshan (China), measures were taken to control the gray or Altai marmot (*Marmota baibacina*), a reservoir of plague. Between 1967 and 1987, the marmot population was reduced from 14.52 animals for every 10 hectares in 1967 to 0.91 in 1987. More recently, bacteriologic and serologic tests were performed on 5,000 marmots and 2,000 domestic dogs; with the exception of three dogs, the tests were negative. No more human cases were reported (Lu *et al.*, 1991).

The inactivated vaccine provides protection for no more than six months and vaccination is justified only for inhabitants of high-incidence areas, laboratory personnel who work with plague, and people who must enter a plague focus. It should be kept in mind that several doses are needed to obtain a satisfactory level of protection. The inactivated vaccine was used on US troops in Vietnam and is believed to have been very useful in protecting them.

Plague is subject to control measures established under the International Sanitary Code (World Health Organization).

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PSEUDOTUBERCULOUS YERSINIOSIS

ICD-10 A28.2 extraintestinal yersiniosis

Etiology: *Yersinia pseudotuberculosis* is a coccobacillary, gram-negative bacteria that is motile at 25°C, nonmotile at 37°C, and can live a long time in soil and water. It belongs to the family *Enterobacteriaceae*. DNA hybridization studies have confirmed the close relationship between the agent of plague and that of pseudotuberculous yersiniosis.

Y. pseudotuberculosis is subdivided on the basis of its biochemical properties into five biotypes and on the basis of somatic (O) antigens into six serogroups (1–6), types 1, 2, 4, and 5 of which are divided into subgroups (Schiemann, 1989). More recently, Tsubokura *et al.* (1993) expanded the serogroups to 11 and also added a subgroup to O:1 (O:1C).

Virulent strains of *Y. pseudotuberculosis* have a plasmid that determines the virulence factors, including a kinase that determines the pathogenicity of the strains (Galyov *et al.*, 1993).

Geographic Distribution: The distribution of the etiologic agent is probably worldwide. The greatest concentration of animal and human cases is found in Europe, the Russian Far East, and Japan.

Occurrence in Man: For many years, pseudotuberculous yersiniosis was considered a disease that almost exclusively affected animals. However, since the 1950s, cases of lymphadenitis were described in children who had been operated on for appendicitis. In slightly more than three years, 117 cases of the disease were reported in Germany, most of which were diagnosed serologically. Hundreds of cases were diagnosed in Europe in later years (Schiemann, 1989).

Outbreaks occur as well as sporadic cases, which are possibly more numerous. An epidemic outbreak with 19 cases occurred in Finland (Tertti *et al.*, 1984). In the

Russian Far East, a scarlatiniform form of the disease has been described, with several thousand cases (Stovell, 1980). Three outbreaks occurred in the period 1982–1984 in Okayama Prefecture (Japan). In one outbreak, serogroup 5a was isolated from 16 patients and the infection was tied to contaminated foods. The other two outbreaks occurred in remote mountainous regions and affected a large number of preschool- and school-aged children, as well as adults. In these two outbreaks, a common source of infection could not be found, although it may have been well or stream water. Serotype 2c was detected in the feces of one patient and in well water. In another case, serotype 4b was detected in the feces of the patient and of a wild animal (Inoue *et al.*, 1988).

Also in Japan, outbreaks occurred in 1991 in Aomori Prefecture in four primary schools and one secondary school. A total of 732 people became ill, including students, teachers, and administrative personnel; 134 were hospitalized. *Y. pseudotuberculosis* serotype 5a was isolated from 27 (81.8%) of the 33 samples examined. The strains isolated had the plasmid that determines various virulence factors, such as calcium dependence at 37°C and autoagglutination. The outbreak was attributed to food served in the schools, but no specific food could be pinpointed. The etiologic agent was also isolated from wastewater and the cooks' feces (Toyokawa *et al.*, 1993). Serotypes 1, 2, and 3 have been isolated in Asia, Europe, Canada, and the US; serotypes 4 and 5 have been isolated in Europe and Japan; and serotype 6 has been isolated in a few cases in Japan (Quan *et al.*, 1981).

Occurrence in Animals: Numerous species of domestic and wild mammals, birds, and reptiles are naturally susceptible to the infection. The disease occurs sporadically in domestic animals. In Europe, devastating epizootics have been described in hares. Epizootic outbreaks have occurred in guinea pigs, wild birds, turkeys, ducks, pigeons, and canaries. Serotype 1 predominates in animal disease.

The Disease in Man: The disease mainly affects children, adolescents, and young adults. In the past, the most recognized clinical form was mesenteric adenitis or pseudoappendicitis with acute abdominal pain in the right iliac fossa, fever, and vomiting. In the outbreaks in Okayama Prefecture, abdominal pains were accompanied by diarrhea. In another large outbreak in Japan, 86.4% of 478 patients had pyrexia, 73.8% had rashes, 66.7% had abdominal pain, and 63.4% experienced nausea and vomiting. Another frequent sign is strawberry tongue and painful pharyngeal redness. In the 19 patients studied in Finland (Tertti *et al.*, 1984), the disease lasted from one week to six months. Twelve of the patients had complications: six had erythema nodosum, four had arthritis, one had iritis, and one had nephritis.

The incubation period is still unclear, but is estimated to last from one to three weeks.

Septicemia caused by *Y. pseudotuberculosis* is rare and usually appears in weakened individuals, particularly in the elderly or immunodeficient.

In the Russian Far East, a scarlatiniform type of the disease has been described. This syndrome is characterized by fever, a scarlatiniform rash, and acute polyarthritis. The disease can be reproduced in volunteers using cultures of the agent isolated from patients (Stovell, 1980).

Y. pseudotuberculosis is sensitive to tetracycline. Ofloxacin proved very effective in treatment tested on infected rats, but the beta-lactams were not effective (Lemaitre *et al.*, 1991).

The Disease in Animals: Outbreaks of yersiniosis in guinea pig colonies have occurred in several parts of the world with some frequency. The course of the disease in these animals is usually subacute. The mesenteric lymph nodes become swollen and caseous, and sometimes there are nodular abscesses in the intestinal wall, spleen, liver, and other organs The animal rapidly loses weight and often has diarrhea. The disease lasts about a month. The septicemic form is rarer; the animal dies in a few days without showing significant symptoms. Mortality varies from 5% to 75%. Apparently healthy animals infected with *Y. pseudotuberculosis* that remain in the colony can perpetuate the infection and cause new outbreaks. Serotype 1 was isolated in an outbreak in a colony of guinea pigs in Argentina (Noseda *et al.*, 1987).

In cats, anorexia, gastroenteritis, jaundice, and often palpable mesenteric lymph nodes and hypertrophy of the spleen and liver are observed. Death can ensue two or three weeks after the onset of the disease.

Epizootics with abortions, suppurative epididymo-orchitis, and high mortality have been recorded in sheep in Australia and Europe. In Australian sheep, infection caused by serotype 3 of *Y. pseudotuberculosis* is common and occurs primarily in animals 1 to 2 years of age. The infection lasts up to 14 weeks during winter and spring (Slee and Skilbeck, 1992). Affected animals usually experience diarrhea and weight loss. Symptoms include characteristic microabscesses in the intestinal mucosa and increased thickness in the colonic and cecal mucosa (Slee and Button, 1990). Isolated cases with abortions and abscesses have been confirmed in sheep in several countries. Serotypes O:3 and O:1 have been isolated from goats in Australia. Diarrhea and loss of conditioning are the most notable symptoms (Slee and Button, 1990). Abortions and neonatal death were described in a herd of goats (Witte *et al.*, 1985).

The infection and disease in cattle have been recognized in several countries. In Australia, they are caused by serotype 3, which seems to prevail in the country's ruminants. In an episode of diarrhea in a dairy herd, 35 young animals died; in 20 of 26 examined histologically, the characteristic microabscesses were found in the intestinal mucosa. The disease occurred during the winter, spring, and early summer. In adult animals, there was a high rate of serologic reactors (Slee *et al.*, 1988). The disease has also been described in Australia in adult cattle in flooded fields, with diarrhea and death. Again, the serotype isolated was O:3 (Callinan *et al.*, 1988). More recently, the disease was described in two herds in Argentina. In one herd, 5.8% of the cattle became sick and 1.7% died. The symptoms consisted of cachexia, diarrhea, and lack of motor coordination. In the second herd, 0.6% of 700 animals died and deaths occurred suddenly without prior symptoms. The serotype responsible was also O:3 in Argentina (Noseda *et al.*, 1990). In Canada, there have also been cases in cattle, with abortions and pneumonia.

Cases of gastroenteritis have been observed in swine. *Y. pseudotuberculosis* has been isolated from the feces and particularly from the tonsils of apparently healthy animals.

Outbreaks in turkeys have been described in the US (Oregon and California) and England. An outbreak occurred on four farms in California (Wallner-Pendleton and Cooper, 1983). The main symptoms were anorexia; watery, yellowish-green diarrhea; depression; and acute locomotor impairment. The disease affected males 9 to 12 weeks old and had a morbidity rate of 2% to 15% and high mortality, principally due to cannibalism. Administration of high doses of tetracyclines in food seemed to

arrest the disease, but the birds were condemned in the postmortem inspection because of septicemic lesions. The principal lesions were necrotic foci in the liver and spleen, catarrhal enteritis, and osteomyelitis.

The pseudotuberculosis agent is the most common cause of death in hares (*Lepus europaeus*) in France and Germany. Rabbits (*Oryctolagus cuniculus*) and the ringdove (*Columba palumbus*) are also frequent victims of the disease. Epizootics have been described among rats (*Rattus norvegicus*) in Japan.

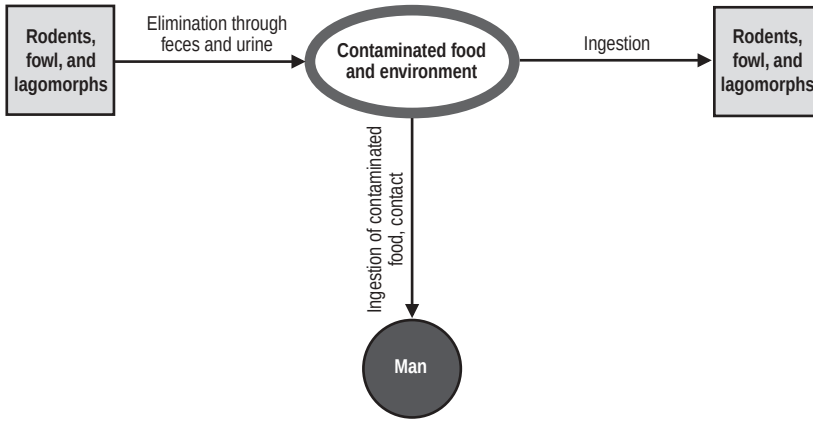
In captive animals, disease caused by *Y. pseudotuberculosis* occurs with some frequency. Serotype O:1 was isolated in farm-bred nutrias (*Myocastor coypus*); it affected both young animals and adults with acute or chronic symptoms. The principal symptoms were diarrhea, swelling of the lymph nodes, formation of nodules in various organs, cachexia, and paralysis of the hindquarters (Cipolla *et al.*, 1987; Monteavaro *et al.*, 1990). In two London zoos, there were several deaths across a broad band of mammalian and avian species. Disease and death occurred sporadically, particularly in winter. The most affected species was the Patagonian mara (*Dolichotis patagonum*). Death in captive animals due to *Y. pseudotuberculosis* represents 0.66% to 0.79% of deaths each year. The serotypes isolated were 1a and 1b, which are the predominant types in many European countries. Some strains of 2a were also isolated (Parsons, 1991).

The disease also occurs in captive monkeys. In one colony, one green monkey (*Cercopithecus aethiops*) and nine squirrel monkeys (*Saimiri sciureus*) became sick. The digestive system was most affected during the acute phase and the lymphatic tissues, spleen, and liver suffered severe alteration in the chronic phase (Plesker and Claros, 1992). In another colony of New World monkeys, two different serotypes were isolated (O:1 and O:2), depending on the group of origin (Brack and Gatesman, 1991; Brack and Hosefelder, 1992).

Source of Infection and Mode of Transmission (Figure 16): Many facets of the epidemiology of pseudotuberculous yersiniosis still need to be clarified. The broad range of animal and bird species that are naturally susceptible to the infection and are carriers of *Y. pseudotuberculosis* suggests that animals are the reservoir of the etiologic agent. In this enormous reservoir, researchers emphasize the role of rodents and various bird species. In mountainous areas of Shimane Prefecture (Japan), a bacteriological study was conducted of 1,530 wild mice of the genera *Apodemus* and *Eothenomys*, and moles (*Urotrichus talpoides*). *Y. pseudotuberculosis* was isolated from the cecum of 72 animals and 10 of the strains had virulence plasmids. The etiologic agent was detected only in the mice, more frequently during the mating season and in newborns (Fukushima *et al.*, 1990). Another study in the same prefecture cultured feces from 610 wild mammals and 259 wild birds. Thirty-seven strains of *Y. pseudotuberculosis* were isolated from 34 mammals (5.6%) and from 2 anserine fowl (0.8%). The serotypes isolated were the same as those isolated from humans in that region of Japan, thus the inference of an epidemiological connection between the human infection and the infection in wild animals. The highest rate of infection (14%) was obtained in an omnivorous canine, the raccoon dog (*Nyctereutes procyonoides*), which is common in Japan, China, and Korea (Fukushima and Gomyoda, 1991).

In studies conducted in Germany and Holland, the agent was isolated from 5.8% and 4.3% of the tonsils of 480 and 163 clinically health swine, respectively, indi-

Figure 16. Pseudotuberculous yersiniosis (*Yersinia pseudotuberculosis*). Probable mode of transmission.



cating that this animal is a healthy carrier (Weber and Knapp, 1981a). In Japan, 2% of pig tongues and 0.8% of chopped pork contained *Y. pseudotuberculosis*. When samples taken from retail pork were examined, two of the four strains isolated (corresponding to serotype 4b) had the same pathogenic properties as the human strains obtained from patients (Shiozawa *et al.*, 1988). One 4b strain was isolated previously from pork by Fukushima (1985). The agent was isolated in 0.58% of 1,206 samples of swine feces examined over 14 months. These isolations, as well as those from tonsils, were done in the cold months, corresponding to the season in which human cases occur (Weber and Knapp, 1981a). In New Zealand, the agent has frequently been isolated from deer. A study conducted in cattle in the same country isolated the agent from 134 (26.3%) of 509 fecal samples from 84% of 50 herds. Serotype 3 was the most prevalent (93.2%), followed by 1 and 2. None of the herds had prior history of disease due to *Y. pseudotuberculosis*, and thus were healthy carriers. The study was conducted in young animals during the winter (Hodges and Carman, 1985). The authors note that diagnosis should not rely solely on examination of feces.

Several authors believe the soil is the reservoir of the agent, but isolations from the soil in Europe have primarily yielded serotype 2, which is rarely found in the human disease (Aldova *et al.*, 1979). However, in the focus of scarlatiniform pseudotuberculosis in the Russian Far East, serotype 1 has been isolated from water and soil possibly contaminated by animal feces, which would explain the large number of cases. In Khabarovsk Kray, in the Asiatic northeast of the Russian Federation, the disease changed seasons in the period 1983–1989, going from winter to the middle of summer. This change could be explained by the early provision of vegetables in stores, which could be contaminated by the feces of wild and synanthropic

Muridae (Dziubak *et al.*, 1991). In any case, animals and wild fowl undoubtedly contribute to environmental contamination. An epizootic or epornitic in one animal species often has repercussions in other species due to the excretion of the agent in feces and contamination of the environment.

The mode of transmission is fecal-oral. The localization of the infection in the mesenteric lymph nodes indicates that the digestive tract is the bacteria's principal route of entry.

In repeated outbreaks of yersiniosis in guinea pig colonies in Great Britain, the infection was transmitted by vegetables contaminated with feces of the ringdove (*Columba palumbus*). In the outbreak of pseudotuberculosis in turkeys in California (USA) (Wallner-Pendleton and Cooper, 1983), two dead squirrels were found near the feeders. The etiologic agent was isolated from necrotic lesions in the liver and spleen of one of the squirrels. The immediate source of infection for man is often difficult to ascertain. A common source of infection was not found for the epidemic outbreak in 19 patients in Finland (Tertti *et al.*, 1984).

The vehicles of infection are pork and possibly meat from other species; water from contaminated wells and streams; and vegetables contaminated by feces of wild animals, rodents, and other mammals and birds.

In both man and animals, the disease is prevalent in the cold months. Two reasons are suggested for this phenomenon. The agent survives better at low temperatures and many animals are healthy carriers that become ill when stressed by cold, moisture, and poor nutrition, and eliminate the agent in their feces (Carniel and Mollaret, 1990). Parturition is another stress factor. Young animals are more susceptible. The infection is transmitted from animal to animal in contaminated pastures.

Role of Animals in the Epidemiology of the Disease: Wild mammals, rodents, and others, as well as domestic mammals (swine) and wild birds, constitute the reservoir. The most common route of transmission to man is perhaps indirectly through contamination of the environment and foods by feces. The agent can survive for a relatively long time on vegetables and inanimate objects. A case of transmission by dog bite is also known.

Diagnosis: Definitive diagnosis can only be obtained through isolation and identification of the causal agent. The most suitable material is the mesenteric lymph nodes. The agent can be isolated from contaminated samples in culture media used for enterobacteria. A selective agar called cefsulodin-irgasan-novobiocin (CIN) can be used for epidemiological studies. Enrichment with diluted alkalis has been used successfully for isolations from meat samples (Fukushima, 1985). Serotyping of isolated strains is important from an epidemiological perspective. Serological tests commonly used to determine infection by *Y. pseudotuberculosis* are agglutination, hemagglutination, complement fixation, and more recently, enzyme-linked immunosorbent assay (ELISA) with the corresponding serotype, which is considered most sensitive and specific. Results should be carefully evaluated, since *Y. pseudotuberculosis* and *Y. enterocolitica* give cross-reactions and various serotypes have antigens in common with other enterobacteria.

Control: The principal preventive measure consists of protecting food and water against fecal contamination by rodents and fowl. Controlling peridomestic rodent populations and limiting the number of birds in public places are also recommended.

Meats and other animal products should be well cooked. Only chlorinated water should be consumed or, in its absence, water should be boiled for several minutes. Vegetables should be washed well with chlorinated water.

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RAT-BITE FEVER

ICD-10 A25.0 spirillosis; A25.1 streptobacillosis

Etiology: *Streptobacillus moniliformis* and *Spirillum minus* (*S. minor*).

Rat-bite fever is caused by two different bacteria: *Streptobacillus moniliformis* and *Spirillum minus*. Their geographic distribution and clinical picture are different and thus they will be treated separately.

1. Infection due to *Streptobacillus moniliformis*

Synonyms: Haverhill fever, epidemic arthritic erythema, streptobacillary fever.

Etiology: *Streptobacillus moniliformis* is a gram-negative, pleomorphous, nonmotile, nonsporogenic, microaerophilic bacillus 1 to 5 microns long and 0.1 to 0.7 in diameter. It occurs in isolated form or in chains 10 to 150 microns long, depending on the culture medium. Isolation of *S. moniliformis* requires media with a 20% supplement of serum, blood, or ascitic fluid (Savage, 1984).

Geographic Distribution: Worldwide.

Occurrence in Man: Very rare. It generally occurs in sporadic cases. Almost half of all cases are due to bites from laboratory rats. There have also been outbreaks in the US and Great Britain. The name Haverhill fever derives from an outbreak of "epidemic arthritic erythema" that occurred in 1926 in Haverhill, Massachusetts (USA). The largest outbreak to date occurred in Great Britain. It affected 304 people at a girls' school in a rural area, representing 43% of all the students and personnel at the school (McEvoy *et al.*, 1987).

Occurrence in Animals: The agent is isolated from the nasopharynx of a high percentage of healthy rats. Epizootics have been described in wild and laboratory mice. There have been some outbreaks in turkeys and isolated cases in other animals.

The Disease in Man: The incubation period lasts from 2 to 14 days after the bite from a rat or other rodent. The disease begins with symptomatology similar to that of influenza: fever, headache, chills, and myalgia. The bite wound heals spontaneously without complications. A maculopapular rash on the extremities as well as migratory arthralgia and myalgia are common. Polyarthritis is seen in the most severe cases. After a short time, body temperature returns to normal, but the fever may recur. Endocarditis is a possible complication. Mortality reaches 10% in untreated cases.

Haverhill fever has been attributed to the ingestion of milk contaminated by rat feces. Its characteristics were the severity of vomiting and the incidence of pharyngitis, as well as the usual symptoms of rat-bite fever (Washburn, 1990).

The outbreak that affected so many people at the school in Great Britain was attributed to water contaminated by rats. Many girls were hospitalized for weeks, with severe arthralgia and frequent relapses. There were also complications, such as endocarditis, pneumonia, metastatic abscesses, and anemia (McEvoy *et al.*, 1987).

The recommended treatment is intramuscular administration of penicillin for two weeks. McEvoy *et al.* (1987) recommend treatment with erythromycin to prevent the spontaneous development of L forms during the disease.

The Disease in Animals: Laboratory and wild rats are healthy carriers and harbor the etiologic agent in their nasopharynx. Purulent lesions have sometimes been observed in these animals. *S. moniliformis* is pathogenic for rats and has produced epizootics among rats in laboratories and in their natural habitat. In one epizootic among laboratory rats, high morbidity and mortality rates were recorded, with such symptoms as polyarthritis, gangrene, and spontaneous amputation of members. In guinea pigs, the agent can produce cervical lymphadenitis with large abscesses in the regional lymph nodes. Some outbreaks have been described among turkeys in which the most salient symptom was arthritis.

Source of Infection and Mode of Transmission: Rats are the reservoir of the infection. They harbor the etiologic agent in the nasopharynx and transmit it to humans by biting. In the Haverhill epidemic, the source was milk. According to the epidemiological investigation conducted on the school in Great Britain, the source of infection was drinking water contaminated by rat feces.

All outbreaks are due to a common source, whereas sporadic cases are due to a bite from a rat or other rodent. It would seem that man is not very susceptible, since there are very few recorded cases. Personnel working with laboratory rodents are exposed to infection. People who live in rat-infested houses can become infected without contact with rodents (Benenson, 1990). Infection among turkeys has been attributed to rat bites. It is suspected that infection in mice and other rodents in laboratories can be caused by aerosols when these rodents are kept in the same environment as rats.

Role of Animals in the Epidemiology of the Disease: Rats are the reservoir of the infection and play an essential epidemiological role.

Diagnosis: Diagnosis is accomplished by isolating *S. moniliformis* from the bloodstream or articular lesions in blood- or serum-enriched media. Inoculation of guinea pigs or rats from colonies that are demonstrably free of infection can also be used.

A few laboratories use serological tests, such as tube agglutination, complement fixation, or immunofluorescence (Wilkins *et al.*, 1988).

Control: The principal means of prevention is control of the rat population. Other important measures are pasteurization of milk and protection of food and water against rodents. Laboratory rats, mice, and guinea pigs should be kept in separate environments and personnel charged with their care should be instructed in proper handling techniques.

2. Infection due to *Spirillum minus*

Synonyms: Sodoku, spirillary fever.

Etiology: The etiologic agent is *Spirillum minus*. These bacteria are not well characterized and there are no reference strains because it is difficult to culture the spirillum. The genus name is still uncertain and the species name *minor* is considered

incorrect. It is a spiral-shaped bacterium with two or three twists; it is motile, 3 to 5 microns long, and about 0.2 microns in diameter (Krieg, 1984).

Geographic Distribution: Worldwide, but more frequent in the Far East.

Occurrence in Man: Occasional.

Occurrence in Animals: The incidence of the infection in rats varies in different parts of the world. It affects 25% of rats in some regions.

The Disease in Man: It is similar to the disease caused by *S. moniliformis*. The most notable differences are that arthritic symptoms are rare and that four weeks after the bite there is a characteristic eruption with reddish or purple plaques. The incubation period is one to four weeks. Fever begins suddenly and lasts a few days, but it recurs several times over a period of one to three months. There is a generalized exanthematous eruption that may reappear with each attack of fever. Although the bite wound heals during the incubation period, it exhibits an edematous infiltration and often ulcerates. Similarly, the lymph nodes become hypertrophic.

Mortality is approximately 10% in untreated patients.

Treatment consists of intramuscular administration of procaine penicillin for two weeks.

The Disease in Animals: The infection is not apparent in rats.

Source of Infection and Mode of Transmission: The reservoir is rats and other rodents; their saliva is the source of infection for man. The infection is transmitted by bites.

Role of Animals in the Epidemiology of the Disease: Rats play the principal role. Human infections caused by bites from ferrets, dogs, cats, and other carnivores have also been described. It is presumed that these animals become contaminated while catching rodents and thus act as mechanical transmitters.

Diagnosis: Diagnosis is accomplished by dark-field microscopic examination of infiltrate from the wound, the lymph nodes, the erythematous plaques, and from the blood. The most reliable diagnosis is obtained by intraperitoneal inoculation of mice with blood or infiltrate from the wound, followed by microscopic examination of their blood and peritoneal fluid some two weeks after inoculation. The bacteria do not grow in laboratory culture media.

Control: Control is based on reduction of the rat population and on construction of rat-proof dwellings.

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RHODOCOCCOSIS

ICD-10 J 15.8 other bacterial pneumonia

Etiology: *Rhodococcus* (*Corynebacterium*) *equi* belongs to the order *Actinomycetales*; it has a coccoid or bacillary shape, is gram-positive, aerobic, nonmotile, encapsulated, and nonsporogenic. Its normal habitat is the soil; it is a saprophytic bacteria that requires few nutrients and multiplies abundantly in fecal matter from herbivores.

Most strains of *R. equi* belong to 4 serogroups, which in turn contain 14 serotypes. Approximately 60% of the strains in North America belong to capsular serotype 1, and 26% belong to capsular serotype 2. In Japan, capsular serotype 3 predominates in cultures isolated from foals (Timoney *et al.*, 1988).

R. equi is an opportunistic pathogen and is harbored in the macrophages in the animal organism, causing a granulomatous inflammation (Prescott, 1991). A 15- to 17-kilodalton antigen has been identified that is probably associated with the virulence of *R. equi* (Takai *et al.*, 1991a) and could be used as a marker for it.

Geographic Distribution: Worldwide. Since 1923, when the first case of rhodococcosis was described in foals in Switzerland, the disease has been reported on all continents. *R. equi* is frequently and abundantly isolated from soil where there have been sick horses, but also from areas where there was no rhodococcosis, and even from soil where there have been no horses or other domestic animals recently (Barton and Hughes, 1980).

Occurrence in Man: Very rare. From the first human case described in 1977 up to 1983, the literature records no more than 13 human cases (Van Etta *et al.*, 1983).

Cases are more frequent due to the AIDS epidemic and at least 20 more cases were reported from 1983 to 1990 (Prescott, 1991). In many parts of the world, particularly in developing countries, physicians and hospital microbiologists know little about this disease. Consequently, underreporting is possible.

Occurrence in Animals: Infection due to *R. equi* is recognized worldwide as an important cause of bronchopneumonia, ulcerative enteritis, and lymphadenitis in foals, and less frequently in other animal species (Barton and Hughes, 1980).

The Disease in Man: As in other animals, in man the lungs are the organ most often affected. The disease appears with a fever lasting several days to several weeks, discomfort, dyspnea, unproductive cough, and, frequently, chest pain. Initially, x-rays show infiltration with nodular lesions, particularly in the superior lobes of the lungs. If the patient is not treated, the granulomatous lesion can develop into suppuration and cavitation. Extrapulmonary cases, such as osteomyelitis, hemorrhagic diarrhea and cachexia, pleurisy, abscesses, and lymphadenitis occur rarely (Prescott, 1991).

The infection and the disease appear in immunocompromised patients. *R. equi* is an intracellular parasite of the macrophages, which explains the pyogranulomatous nature of the disease and the predisposition of patients with cell-mediated immune system defects. Currently, AIDS patients represent 88% of cases. The remaining cases are patients undergoing immunosuppressive treatment due to neoplasias or an organ transplant. HIV-infected patients have a higher incidence of simultaneous secondary infections and higher mortality (54.5% as compared to 20% for patients not infected with HIV).

Given the intracellular nature of rhodococcosis, the efficacy of the antimicrobial agent depends on its ability to penetrate the phagocytes. *R. equi* is sensitive to erythromycin, vancomycin, amikacin, gentamicin, neomycin, and rifampicin. Surgical resection of the lesion or lesions is an important part of treatment (Prescott, 1991; Harvey and Sunstrum, 1991). The survival rate was 75% when antibiotic treatment was combined with surgical resection of the infected tissue. The survival rate for those who received only antibiotics was 61% (Harvey and Sunstrum, 1991).

The Disease in Animals: Rhodococcosis is a disease that occurs primarily in foals from 2 to 6 months of age, and particularly from 2 to 4 months of age. This susceptibility of young foals could be because at that age the passive immunity conferred by the mother is in decline and the animal's own immune system is still immature. Foals older than 6 months are resistant, unless they have a defect in cellular immunity or another concurrent disease with a debilitating effect (Yager, 1987).

Equine rhodococcosis appears as a subacute or chronic suppurative bronchopneumonia. Formation of abscesses is extensive, accompanied by a suppurative lymphadenitis. The lesions progress slowly. The degeneration of the macrophages coincides with the lysis of pulmonary parenchyma. Formation of abscesses continues with expansion of the purulent center. The infection is spread through the lymphatic system and affects the regional lymph nodes. Despite bacteremia no lesions are found in the liver or spleen, which would indicate that fixed macrophages could destroy *R. equi* in the circulatory system. It is estimated that approximately 50% of foals with bronchopneumonia develop concomitant ulcerative colitis and typhlitis. A small number of foals develop only intestinal lesions (Yager, 1987).

In infection caused by *R. equi*, we find both subclinical cases discovered upon autopsy and a disease with a fatal outcome in less than one week (26% of 89 foals who died from rhodococcosis).

The disease usually begins with a fever, rapid breathing, and cough and then becomes more intense. Mucopurulent nasal discharge and dyspnea are also common.

Most cases occur in summer, when there are more foals at a susceptible age and the temperature favors growth of the bacteria.

The recommended treatment is a combination of erythromycin and rifampicin, which have a synergistic effect, for 4 to 10 weeks. The two drugs are liposoluble and can penetrate the phagocytes. In the case of diarrhea, fluids and electrolytes should be replaced.

In swine, rhodococcosis appears as cervical and submaxillary lymphadenitis. *R. equi* has also been isolated from normal lymph nodes. Infection is rare in other species. Some sporadic cases have been reported in cattle, goats, sheep, reptiles, and cats. In cattle, the few cases reported were pyometra, chronic pneumonia, and lymphadenitis (Barton and Hughes, 1980).

Source of Infection and Mode of Transmission: *R. equi* is a saprophyte in soil. Its concentration depends on the presence of horses and ambient temperature. Feces of herbivores greatly favor their growth. It is believed that one of the feces' components, acetic acid, is the principal factor in the agent's multiplication (Fraser *et al.*, 1991). The prevalence of virulent *R. equi* (isolated from the soil and the feces of foals) on a horse-breeding farm where rhodococcosis is endemic is much higher than on a farm that has no history of the disease. Foals bred on an endemic farm are constantly exposed to virulent strains of *R. equi* (Takai *et al.*, 1991b). In New Zealand, samples of fecal matter from different animals and from the environment have been examined. The most frequent isolates came from the feces of foals (82%), mares (76%), deer (89%), sheep (97%), goats (83%), pigeons (64%), and soil samples (94%) (Carman and Hodges, 1987). However, *R. equi* could only be isolated from 2 of 521 human fecal samples (Mutimer *et al.*, 1979).

The route of infection for man is through inhalation. The gastroenteritis caused by *R. equi* that a few patients suffer from may be caused by swallowing sputum. A possible animal source of infection was assumed in 12 of 32 human patients (Prescott, 1991).

The airborne route is also preponderant in foals that inhale dust from the soil. In contrast, in swine the route of infection is probably oral, as indicated by their lesions (cervical and submaxillary lymphangitis). *R. equi* colonizes in the intestine of foals in the first 2 months of life. The formation of antibodies and the increased rate of formation would indicate a subclinical infection, acquired orally (Takai *et al.*, 1986; Hietala *et al.*, 1985; Yager, 1987).

Role of Animals in the Epidemiology of the Disease: Although many non–HIV-infected patients suffering from rhodococcosis acknowledged some exposure to animals, it is still unclear whether animals represent a source of infection for man. Herbivores contribute with their feces to the rapid multiplication of *R. equi* in the warm months and sick foals seem to be responsible for spreading virulent strains. The reservoir of *R. equi* is the soil.

Diagnosis: Positive diagnosis can be obtained by isolating the etiologic agent. *R. equi* grows in common laboratory media. Sputum can be used for isolation, but it is

much more accurate to collect material from a bronchial sample obtained through percutaneous thoracic aspiration, or biopsy during a lobectomy. *R. equi* can sometimes be found in cultures with a variety of other bacteria and may be inadvertently discarded as "diphtheroid." The etiologic agent could be isolated from the blood of approximately one-third of human patients with pneumonia (Prescott, 1991).

Control: There are no practical measures for protecting humans or foals. It is more reasonable to prevent diseases that predispose humans to infection by *R. equi*, particularly AIDS. Another measure could be to reduce the dose of immunosuppressive medications whenever possible.

There are no preventive vaccines for equine rhodococcosis. On horse-breeding farms, the accumulation of feces and resulting multiplication of *R. equi* should not be permitted. Dusty conditions should be avoided in and around stables. On endemic farms, it is recommended that foals be examined frequently in the first months of life and that sick foals be treated (Fraser *et al.*, 1991).

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SALMONELLOSIS

ICD-10 A02.0 salmonella enteritis; A02.1 salmonella septicaemia; A02.8 other specified salmonella infections

Synonyms: Nontyphoid salmonellosis.

Etiology: The genus *Salmonella* belongs to the family *Enterobacteriaceae*. It is made up of gram-negative, motile (with a few exceptions), facultatively anaerobic bacteria. Salmonellae grow between 8°C and 45°C and at a pH of 4 to 8. They do not survive at temperatures higher than 70°C. Pasteurization at 71.1°C for 15 seconds is sufficient to destroy salmonellae in milk.

These bacteria can resist dehydration for a very long time, both in feces and in foods for human and animal consumption. In addition, they can survive for several months in brine with 20% salinity, particularly in products with a high protein or fat content, such as salted sausages; they also resist smoking. It has been indicated that they can survive for a long time in soil and water (WHO Expert Committee on Salmonellosis Control, 1988).

A study conducted in Great Britain showed that *S. typhimurium* can survive 4 to 14 months in the environment of facilities with infected calves, an important epidemiological factor (McLaren and Wray, 1991). It can survive in ripening cheddar cheese for 10 months at 7°C (el-Gazzar and Marth, 1992).

Le Minor and Popoff (1987) used DNA:DNA hybridization to show that they are genetically a single species. Various classification schemes have been proposed, leading to controversy and confusion. At present, the trend is to return to the scheme conceived by Kauffmann-White due to its simplicity and because it is clearer and more useful from a clinical and epidemiological standpoint. The nomenclature scheme of Edwards and Ewing that was frequently used, particularly in the Americas, is being abandoned (Farmer *et al.*, 1984). As a result, the serotype term is used directly as a species. Thus, *S. enterica* serotype *Typhimurium* according to one scheme or *Salmonella* subspecies I serotype *typhimurium* according to another scheme would currently be *S. typhimurium*.

The Kauffmann-White scheme divides salmonellae into serotypes. O somatic, H flagellar, and Vi capsular antigens are distinguished primarily on the basis of their antigenic structure. Currently, there are close to 2,200 serotypes.

Some serotypes have several different phenotypes, and their identification can be important in epidemiologic investigation. For example, biochemical tests were able to differentiate three biotypes of *S. typhimurium*, each of which was associated with a geographic and ecological region. *S. gallinarum* and *S. pullorum* are two nonmotile salmonellae adapted to birds. Some authors consider them a single species or serotype because they are antigenically identical. However, each of these serotypes causes a different disease (fowl typhoid and pullorum disease). They can be distinguished because, unlike *S. gallinarum, S. pullorum* does not use dulcitol or d-tartrate (D'Aoust, 1989).

Phage typing is also useful for some serotypes. The Scottish Salmonella Reference Laboratory studied 2,010 cultures of *S. typhimurium* and differentiated 137 different groups of phage types/biotypes. Four major epidemic clones were recognized that accounted for 52% of the cultures, with a predominance of bovine and

human strains. Epidemiological investigation shows that most salmonellosis outbreaks caused by *S. typhimurium* were caused by a lysotype/biotype that remained stable throughout the course of the epidemic (Barker *et al.*, 1980). Plasmid profiles and patterns of antibiotic resistance are also useful as epidemic markers.

Except for serotypes *S. typhi* and *S. paratyphi* A, and *S. paratyphi* C, which are strictly human and whose only reservoir is man, all serotypes can be considered zoonotic or potentially zoonotic.

Salmonellae have several virulence factors that contribute to causing diarrhea, bacteremia, and septicemia. These factors include the lipopolysaccharide of the outer wall, pili, flagella, cytotoxin, and enterotoxin (Murray, 1986).

Geographic Distribution: Worldwide. *S. enteritidis* is the most prevalent species, followed by *S. typhimurium*. Changes in the relative frequency of serotypes can be observed over short periods of time, sometimes within one or two years.

Only a limited number of serotypes is isolated from man or animals in a single region or country. The predominance of one or another can vary over time. Some serotypes, such as *S. enteritidis* and *S. typhimurium*, are found worldwide; in contrast, *S. weltevreden* seems to be confined to Asia.

Occurrence in Man: It is very common. Salmonellosis occurs both in sporadic cases and outbreaks affecting a family or several hundreds or thousands of people in a population. The true incidence is difficult to evaluate, since many countries do not have an epidemiological surveillance system in place, and even where a system does exist, mild and sporadic cases are not usually reported. In countries with a reporting system, the number of outbreaks has increased considerably in recent years; this increase is in part real and in part due to better reporting.

In 1980, *Salmonella* was isolated from slightly more than 30,000 people in the US (CDC, 1982). In 1986, 42,028 cases were isolated (Hargrett-Bean *et al.*, 1988). In the US and many other countries, the prevalent serotype was *S. typhimurium*. From 1976 to 1993, the rate of isolation of *S. enteritidis* increased (21% of all isolates) and overtook *S. typhimurium* as the most common serotype. During the period 1985–1991, 375 outbreaks caused by *S. enteritidis* were reported, with 12,784 cases, 1,508 hospitalized cases, and 49 deaths. Most of the cases were sporadic or small family outbreaks, and many of them were from the same phage type, indicating the possibility of a single source of infection (CDC, 1992a).

During a conference held in 1990 that was attended by 1,900 people from 30 states in the US, at least 23% became ill with gastroenteritis caused by *S. enteritidis*. The source of infection was a dessert prepared with eggs that were possibly undercooked (CDC, 1990).

In 1985, an outbreak occurred in Illinois (USA) that affected 20,000 people and was caused by pasteurized milk contaminated by *S. typhimurium* that was multiresistant to antibiotics (ampicillin and tetracycline).

Table 3 shows information on some outbreaks in the period 1981–1985 in various countries (WHO Expert Committee on Salmonellosis Control, 1988).

According to several authors' estimates, the number of human cases occurring each year in the US ranges from 740,000 to 5,300,000. In Canada, the data were similar (Bryan, 1981). Rates for reported cases are about 10 per 100,000 inhabitants in Denmark, 44 per 100,000 in Finland, and 43 per 100,000 in Sweden, one-third to two-thirds of which were probably contracted by international travelers (Silliker,

Table 3. Outbreaks of foodborne salmonellosis in selected countries, 1981–1985.

Year	Country	Food	Serotype	Approx. number of cases
1981	England	Chicken	montevideo	500
1981	The Netherlands	Cold buffet	indiana	700
1981	Scotland	Raw milk	typhimurium	654
1982	England	Chocolate	napoli	245
1982	Norway	Black pepper	oranienburg	126
1984	England	Cooked meat	virchow	274
1984	England	Cold roast beef	typhimurium	450
1984	Canada	Cheddar cheese	typhimurium	2,000
1984	Worldwide[a]	Meat gelatin	enteritidis	766
1985	England	Cooked meats	infantis	150
1985	England	Powdered milk for infants	ealing	60
1985	United States of America	Pasteurized milk	typhimurium	20,000

[a]Meals prepared in London for airlines.
Source: World Health Organization, 1988.

1982). In the former West Germany, 33,215 cases were reported in 1978, 40,717 in 1979, and 48,607 in 1980 (Poehn, 1982). In Australia, from 1980 to 1983, annual incidence was 32.2 per 100,000 inhabitants and in 1985 it was 27.0 per 100,000 (D'Aoust, 1989).

Seven of the 23 outbreaks of gastroenteritis that occurred on transatlantic flights to the US between 1947 and 1984 were due to salmonellosis (Tauxe *et al.*, 1987).

It is difficult to evaluate the situation of this disease in developing countries because of the lack of epidemiological surveillance data, but epidemic outbreaks are known to occur. In 1977, an extensive outbreak took place in Trujillo (Peru) among university students who lunched in the university dining hall. Of 640 students who ate regularly in the hall, 598 (93%) became ill and 545 were hospitalized, resulting in temporary overcrowding of community medical services. Serotype *S. thompson* was isolated from the patients' stools, and epidemiologic evidence pointed to eggs used in the food as the source of the infection (Gunn and Bullón, 1979). In the period 1969–1974, 3,429 cases of acute diarrhea in children in Buenos Aires (Argentina) and its environs were studied. Isolations of 932 strains of *Salmonella* were obtained from 3,429 stool samples. Between 1969 and 1972, isolation of *S. typhimurium* predominated, revealing the existence of an epidemic. The clinical picture was serious and the mortality rate reached 14% of the 246 children studied. After 1972, isolations of serotype *S. oranienburg* increased, and those of *S. typhimurium* decreased. Seventy-three percent of the children acquired the infection at home; 27% first showed symptoms in the hospital after being admitted for causes other than gastrointestinal disorders (Binsztein *et al.*, 1982). Starting in 1986, there was a notable increase in *S. enteritidis* in Europe, the US, South America, and some African countries. From 1986 to 1988, 39 outbreaks occurred in Argentina, affecting more than 2,500 people, with a serious clinical picture (Eiguer *et al.*, 1990; Rodrigue *et al.*, 1990).

Occurrence in Animals: It is very common. The rate of infection in domestic animals has been estimated at from 1% to 3%. In 1980, 16,274 strains of 183 serotypes of *Salmonella* were isolated in the former West Germany from animals, foods of animal origin, water, and other sources (Pietzsch, 1982). In 1985, *Salmonella* was isolated from 1.25% of 222,160 samples of meat obtained during veterinary inspection in slaughterhouses. In other examinations of animals and animal organs, *Salmonella* was isolated from 4.81% of 81,851 examined. Positive cultures were obtained from 4.59% of 141,827 bovine fecal samples. In the US, 2,515 cultures of nonhuman origin were obtained in 1980 (CDC, 1982). Several surveys have found the incidence of avian salmonellosis to be lower than 1% in Sweden, approximately 5% in Denmark, and approximately 7% in Finland. Its incidence in other countries is higher. In Great Britain, there were 3,626 isolations in 1980 and 2,992 in 1981. Epidemiologic surveillance of animals, including birds, is of the utmost importance, since the source of the large majority of nontyphoid salmonellosis cases is food of animal origin. There are no data from developing countries in this regard.

Some reports on pets indicate that salmonellosis occurs frequently. In the former West Germany between 1967 and 1983, different researchers isolated salmonellae from 8.4% to 12.8% of the dogs examined and from 9.8% to 11.2% of 908 cats. In the US, 0.04% of 124,774 dogs examined during the same time period gave positive cultures, as did 0.1% of 29,613 cats. In Iran, 7.7% of 672 dogs and 13.6% of 301 cats were positive (D'Aoust, 1989).

Infection caused by *Salmonella* is also spread among wild mammals, birds, amphibians, reptiles, and invertebrates.

The Disease in Man: With the exception of *S. typhi* and the paratyphoid serotypes (particularly A and C), which are species-specific for man, all other infections caused by *Salmonella* may be considered zoonoses. Salmonellosis is perhaps the most widespread zoonosis in the world.

Salmonellae of animal origin cause an intestinal infection in man characterized by a 6- to 72-hour incubation period after ingestion of the implicated food, and sudden onset of fever, myalgias, cephalalgia, and malaise. The main symptoms consist of abdominal pain, nausea, vomiting, and diarrhea. Salmonellosis normally has a benign course and clinical recovery ensues in two to four days. The convalescent carrier may shed salmonellae for several weeks and, more rarely, for a few months. Conversely, the carrier state is persistent in infections due to *S. typhi* or paratyphoid salmonellae. Although salmonellosis may occur in persons of all ages, incidence is much higher among children and the elderly. Dehydration can be serious.

Extraintestinal infections caused by zoonotic salmonellae are relatively infrequent. Of the 6,564 strains of *Salmonella* spp. isolated from 1969 to 1983 in a hospital in Liverpool (England), 3% were extraintestinal infections. Of the 194 extraintestinal cultures, 34% were from blood, 32% from urine, 23% from pus and inflamed tissues, 5% from bones, 5% from cerebrospinal fluid, and 3% from sputum (Wilkins and Roberts, 1988).

Serotypes adapted to a particular animal species are usually less pathogenic for man (*pullorum*, *gallinarum*, *abortus equi*, *abortus ovis*). An exception is *S. choleraesuis*, which produces a serious disease with a septicemic syndrome, splenomegaly, and high fever a few days to a few weeks after the onset of gastroen-

teritis. Bacteremia is present in more than 50% of patients with *S. choleraesuis* infections and the fatality rate may reach 20%. Serotypes *sendai* and *dublin* can also cause septicemia ("enteric fever") and often metastatic abscesses.

Zoonotic salmonellae usually heal without complications and the only treatment recommended is rehydration and electrolyte replacement. A small proportion of patients, particularly those weakened by other diseases (AIDS, neoplasias, diabetes, etc.), can suffer from bacteremia. There may also be different localizations, such as the lungs, pleura, joints, and, more rarely, the endocardium. Children under the age of 5 and the elderly are more susceptible to complications. Children younger than 2 months, the elderly, and patients with concurrent diseases should be given antibiotics (ampicillin, amoxycillin, cotrimoxazole, and chloramphenicol). Antibiotics should also be given to patients with a prolonged fever with extraintestinal complications (Benenson, 1990).

A high proportion of *Salmonella* strains with multiple antibiotic resistance has been seen in many countries. The main cause of this in industrialized countries has been the overuse of antibiotics in animal feed as a growth enhancer, as well as the indiscriminate prescription-drug treatment of people and animals. In Great Britain, the prophylactic use of antibiotics against bovine salmonellosis has resulted in the emergence of multiresistant strains of *S. typhimurium*, which have caused epizootics with high mortality. Outbreaks and epidemics of multiresistant strains of several serotypes have occurred in nurseries and pediatric clinics, with complications of septicemia or meningitis and high mortality. An epidemic caused by multiresistant strains of serotype *wien* originated in Algeria in 1969 and spread to several European and Asian countries; the source in the food chain was not discovered. Other epidemics spreading to several countries have been caused by *S. typhimurium* phage type 208 (WHO Scientific Working Group, 1980) and, in more recent years, by *S. enteritidis*. In developing countries, the principal cause of the emergence of multiresistant *Salmonella* strains may be self-medication, made possible by the public's easy access to antibiotics without a prescription.

The Disease in Animals: Salmonellae have a wide variety of domestic and wild animal hosts. The infection may or may not be clinically apparent. In the subclinical form, the animal may have a latent infection and harbor the pathogen in its lymph nodes, or it may be a carrier and eliminate the agent in its fecal material briefly, intermittently, or persistently. In domestic animals, there are several well-known clinical entities due to species-adapted serotypes, such as *S. pullorum* or *S. abortus equi*. Other clinically apparent or inapparent infections are caused by serotypes with multiple hosts.

CATTLE: The principal causes of clinical salmonellosis in cattle are serotype *dublin* and *S. typhimurium*. Other serotypes can sometimes be isolated from sick animals.

Salmonellosis in adult cattle occurs sporadically, but in calves it usually acquires epizootic proportions. The disease generally occurs when stress factors are involved. Serotype *dublin*, adapted to cattle, has a focal geographic distribution. In the Americas, outbreaks have been confirmed in the western United States, Venezuela, Brazil, and Argentina. It also occurs in Europe and South Africa.

In adult cattle, the disease begins with high fever and the appearance of blood clots in the feces, followed by profuse diarrhea, and then a drop in body tempera-

ture to normal. Signs of abdominal pain are very pronounced. Abortion is common. The disease may be fatal within a few days or the animal may recover, in which case it often becomes a carrier and new cases appear. Calves are more susceptible than adults, and in them the infection gives rise to true epidemic outbreaks, often with high mortality. Septicemia and death are frequent in newborns. The carrier state is less frequent among young animals and occurs primarily in adult cattle. The infection is almost always spread by the feces of a cow that is shedding the agent, but it may also originate from milk.

SWINE: Swine are host to numerous *Salmonella* serotypes and are the principal reservoir of *S. choleraesuis*. Serotypes that attack swine include *S. enteritidis*, *S. typhimurium*, and *S. dublin*. These serotypes are generally isolated from the intestine and from the mesenteric lymph nodes. *S. choleraesuis* is very invasive and causes septicemia; it may be isolated from the blood or from any organ. Swine are particularly susceptible and experience epidemic outbreaks between 2 and 4 months of age, but the infection also appears in mature animals, almost always as isolated cases.

Swine paratyphoid (*S. choleraesuis*) or necrotic enteritis occurs mostly in poorly managed herds living in poor hygienic conditions. It is frequently associated with classic swine plague (cholera) or with such stress factors as weaning and vaccination. The most frequent symptoms are fever and diarrhea. The infection usually originates from a carrier pig or contaminated food.

Infection by other serotypes may sometimes give rise to serious outbreaks of salmonellosis with high mortality.

Because of the frequency with which swine are infected with different types of salmonellae, pork products have often been a source of human infection.

SHEEP AND GOATS: Cases of clinical salmonellosis in these species are infrequent. The most common serotype found in gastroenteritis cases is *S. typhimurium*, but many other serotypes have also been isolated. Serotype *S. abortus ovis*, which causes abortions in the last two months of pregnancy and gastroenteritis in sheep and goats, seems to be restricted to Europe and the Middle East (Timoney *et al.*, 1988).

HORSES: The most important pathogen among horses is *S. abortus equi*, which causes abortions in mares and arthritis in colts. It is distributed worldwide. As in other types of salmonellosis, predisposing factors influence whether the infection manifests itself clinically. Pregnant mares are especially susceptible, particularly if other debilitating conditions are present. Abortion occurs in the last months of pregnancy, and the fetus and placenta contain large numbers of bacteria. This serotype is adapted to horses and is rarely found in other animal species.

Horses are also susceptible to other types of salmonellae, particularly *S. typhimurium*. Salmonella enteritis occurs in these animals, sometimes causing high mortality. Calves suffer from acute enteritis with diarrhea and fever; dehydration may be rapid. Nosocomial transmission has been seen in hospitalized horses. From April 1990 to January 1991, in an outbreak among hospitalized horses, 97.8% of the animals contracted the infection due to *S. typhimurium* var. *copenhagen* with the same plasmid profile. Other strains of *S. typhimurium* var. *copenhagen* with a different plasmid profile and *S. enteritidis* began to appear in February 1991 (Bauerfeind *et al.*, 1992).

DOGS AND CATS: In recent years, a high prevalence of infection caused by numerous serotypes has been confirmed in cats and dogs. These animals may be asymptomatic carriers or may suffer from gastroenteritic salmonellosis with varying degrees of severity.

Dogs can contract the infection by eating the feces of other dogs, other domestic or peridomestic animals, or man. Dogs and cats can also be infected by contaminated food. In addition, dogs can transmit the disease to man.

Treatment for these animals consists mainly of fluid and electrolyte replacement. Antibiotic treatment is reserved for septicemic cases and is effective if begun early in the course of the disease. The antibiotics indicated for invasive salmonellosis are ampicillin, chloramphenicol, and sulfamethoxazole with trimethoprim (Timoney *et al.*, 1988).

Multiresistant animal strains that can be transmitted to man are another problem. The indiscriminate use of antibiotics in animals often results in changes in flora in the colon, allowing rapid multiplication of resistant bacteria. In addition, the number of carrier animals in the group that shed the etiologic agent can increase (Timoney *et al.*, 1988).

FOWL: Two serotypes, *S. pullorum* and *S. gallinarum*, are adapted to domestic fowl. They are not very pathogenic for man, although cases of salmonellosis caused by these serotypes have been described in children. Many other serotypes are frequently isolated from domestic poultry; for that reason, these animals are considered one of the principal reservoirs of salmonellae.

Pullorum disease, caused by serotype *S. pullorum*, and fowl typhoid, caused by *S. gallinarum*, produce serious economic losses on poultry farms if not adequately controlled. Both diseases are distributed worldwide and give rise to outbreaks with high morbidity and mortality. Pullorum disease appears during the first 2 weeks of life and causes high mortality. The agent is transmitted vertically as well as horizontally. Carrier birds lay infected eggs that contaminate incubators and hatcheries. Fowl typhoid occurs mainly in adult birds and is transmitted by the fecal matter of carrier fowl. On an affected poultry farm, recuperating birds and apparently healthy birds are reservoirs of infection.

Salmonellae unadapted to fowl also infect them frequently. In the US, more than 200 serotypes of *Salmonella* spp. have been isolated from chickens and/or turkeys (Nagaraja *et al.*, 1991). Nearly all the serotypes that attack man infect fowl as well. Some of these serotypes are isolated from healthy birds. The infection in adult birds is generally asymptomatic, but during the first few weeks of life, its clinical picture is similar to pullorum disease (loss of appetite, nervous symptoms, and blockage of the cloaca with diarrheal fecal matter). The highest mortality occurs during the first 2 weeks of life. Most losses occur between six and ten days after hatching. Mortality practically ceases after a month. The clinically apparent form of the disease is rare after three weeks of life, but many birds survive as carriers (Nagaraja *et al.*, 1991).

The most common agent in ducks and geese is *S. typhimurium*. The infection may be transmitted from the infected ovary to the egg yolk, as in pullorum disease, or by contamination of the shell when it passes through the cloaca.

The most common agent of salmonellosis in pigeons is *S. typhimurium* var. *copenhagen*.

Salmonellosis is frequent in wild birds. In one species of seagull (*Larus argentatus*), it was found that 8.4% of 227 birds examined were carriers of salmonellae and that the serotypes were similar to those in man. Wild birds have also been implicated as vectors of outbreaks of serotype *S. montevideo* in sheep and cattle in Scotland (Butterfield *et al.*, 1983; Coulson *et al.*, 1983).

OTHER ANIMALS: Rodents become infected with the serotypes prevalent in the environment in which they live. The rate of wild animal carriers is not high. Rodents found in and around food processing plants can be an important source of human infection.

Of 974 free-living wild animals examined in Panama, 3.4% were found to be infected, principally by serotype *S. enteritidis* and, less frequently, by *S. arizonae* (*Arizona hinshawii*) and *Edwardsiella*. The highest rate of infection (11.8%) was found among the 195 marsupials examined. *Salmonella* was isolated from only 8 of 704 spiny rats (*Proechimys semispinosus*).

Outbreaks of salmonellosis among wild animals held in captivity in zoos or on pelt farms are not unusual.

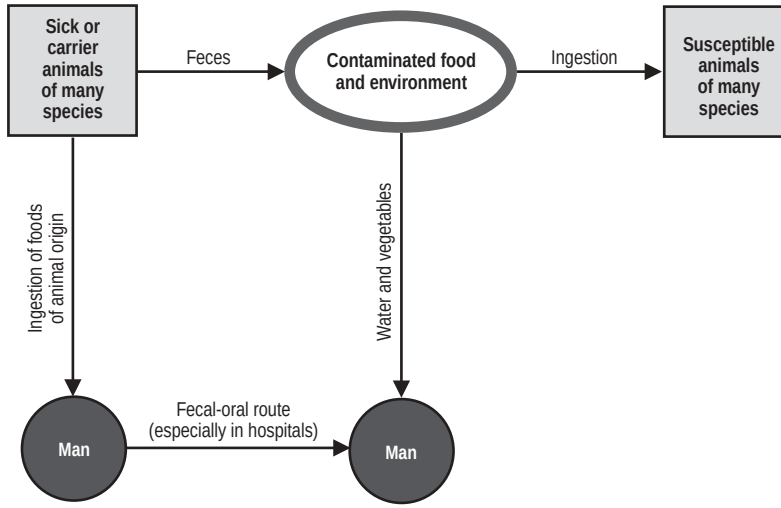
Salmonella infection in cold-blooded animals has merited special attention. Because of the high rate of infection among small turtles kept as house pets in the US, their import was prohibited and a certificate stating them to be infection-free was required for interstate commerce.

An infection rate of 37% was found in 311 reptiles examined live or necropsied at the National Zoo in Washington, D.C. The highest rate of infection was observed in snakes (55%) and the lowest in turtles (3%). The salmonellae isolated were 24 different serotypes formerly classified under the common name of *S. enteritidis*, 1 strain of *S. choleraesuis*, and 39 of *S. arizonae*. No disease in their hosts was attributed to these bacteria, but they may act together with other agents to cause opportunistic infections (Cambre *et al.*, 1980).

Source of Infection and Mode of Transmission (Figure 17): Animals are the reservoir of zoonotic salmonellae. Practically any food of animal origin can be a source of infection for man. The most common vehicles are contaminated poultry, pork, beef, eggs, milk, and milk and egg products. Foods of vegetable origin contaminated by animal products, human excreta, or dirty utensils, in both commercial processing plants and household kitchens, have occasionally been implicated as vehicles of human salmonellosis. An outbreak of enteritis occurred in June and July of 1991 in the US and Canada. It affected 400 people who ate melons contaminated by *S. poona*, a relatively rare serotype. It is assumed that the salmonellae penetrated the soft portion of the fruit from the rind when contaminated knives were used and the melons were left at ambient temperature in the summer (Publ Hlth News. Abst Hyg Comm Dis 60 (9): 210, 1991). Contaminated public or private water supplies are important sources of infection in typhoid fever (*S. typhi*) and, less frequently, in other salmonella infections. An outbreak caused by *S. typhimurium* occurred in 1965 in Riverside, California due to contaminated water. The causal agent was isolated from 100 patients examined, though it probably affected 16,000 people (Aserkoff *et al.*, 1970).

Fowl (chickens, turkeys, and ducks) represent the most important reservoir of salmonellae entering the human food chain (D'Aoust, 1989). In England and Wales from 1981 to 1983, 51.3% of 347 vehicles of human salmonellosis were associated with fowl; in 1984–1985, 32.2% of 177 vehicles were of avian origin (Humphrey *et*

Figure 17. Salmonellosis. Mode of transmission (except *Salmonella typhi* and the paratyphoid serotypes).



al., 1988). Another important source of salmonellae is raw or poorly cooked eggs, whether alone or as a component of various foods. An outbreak of *S. enteritidis* during a wedding celebration in a London hotel affected 173 people. The agent, phage type 4, was isolated from 118 of those affected and another 17 asymptomatic people. The source of infection was a sauce made from eggs imported from the continent. An unusual aspect of this outbreak was that some people fell ill only three hours after consuming the food. The percentage of eggs infected with *S. enteritidis* is low (an estimated 0.001%) but the risk increases when a large number of eggs is used to prepare a dish (Stevens *et al.*, 1989). Pork, beef, milk, and milk products (ice cream, cheeses) are other sources of human infection. Important contributing factors are inadequate cooking, slow cooling of the food, lack of refrigeration for many hours, and inadequate reheating before serving. Large outbreaks are invariably due to improper handling of food in restaurants and institutional dining facilities. Man can also contract the infection directly from domestic animals or house pets, such as dogs, turtles, monkeys, hamsters, and others. Young children are especially susceptible to salmonellae in reptiles, even without direct contact. In Indiana (USA), two cases were described in children; one child was less than 2 weeks old and the other less than 3 months. They were infected indirectly by *S. marina*. The source of the infection was iguanas kept in the house. These animals harbor a wide variety of serotypes and their rate of infection varies from 36% to 77% (CDC, 1992b). There are numerous reports from Asia, Canada, the US, and Europe on transmission from small turtles to humans, particularly children. This led several countries to prohibit their import. The serotypes isolated most frequently are *S. poona* and *S. arizonae* (D'Aoust *et al.*, 1990). The long period of survival (many months) of salmonellae in

fecal matter can explain why direct contact is not always necessary, as in the case of some reptiles kept in or near a house (Morse and Duncan, 1974). Interhuman transmission is particularly important in hospitals; children and the elderly are the principal victims. In Baden-Würtenberg (Germany), an outbreak of *S. enteritidis*, phage type 4, occurred in a home for elderly disabled persons. The same serotype and phage type was isolated from 95 residents and 14 employees. The source of infection was a dessert made of orange cream prepared with eggs with contaminated shells (WHO Surveillance Programme for Control of Foodborne Infections and Intoxications in Europe, 1991).

Institutional and nosocomial outbreaks are usually due to food that is undercooked and kept at the wrong temperature, or to a kitchen employee who is an asymptomatic carrier. Nosocomial cases require prompt epidemiological investigation because they can involve patients who, given their age or illness, can experience severe cases of salmonellosis (CDC, 1991).

Insects, particularly flies, may have some role as mechanical vectors in very contaminated environments.

Carrier animals perpetuate the animal-to-animal cycle by means of their excreta or, in the case of fowl, infected eggs. Feed contaminated by such ingredients as bone, meat, or fish meal plays an important role as a vehicle of infection.

Intensive cattle-raising in developed countries is a very important contributing factor in the epidemiology of salmonellosis. Close contact between animals and the use of concentrated feed or ingredients that may be contaminated create conditions favorable to outbreaks. In developing countries, the source of infection is mainly the contaminated environment and water sources where animals crowd together.

Animal-to-animal transmission occurs not only at the home establishment, but also during shipping, at auctions and fairs, and even at slaughterhouses prior to sacrifice. Meat can become contaminated in abattoirs by means of contaminated equipment and utensils during skinning and butchering. Contaminated water can be a source of infection for man and animals.

The cycle of infection in fowl begins with contaminated eggshells or yolks. Contaminated eggs spread the infection in the incubator. When the eggs hatch, the newborn chicks become infected and many of those that do not die become carriers. This is the most important mechanism at work when fowl in poultry yards become infected. Another vehicle of infection may be contaminated feed. Cannibalism and the ingestion of contaminated eggs also contribute to transmission of the infection.

Non–species-specific serotypes spread easily from one animal species to another and also to humans.

Role of Animals in the Epidemiology of the Disease: Since animals constitute the reservoir of salmonellae (except *S. typhi* and the paratyphoid serotypes), they play an essential role in its epidemiology.

Diagnosis: In humans, clinical diagnosis of gastroenteritis due to *Salmonella* is confirmed by isolation of the etiologic agent from the patient's stool, serologic typing, and, when necessary, phage typing and plasmid profiling. In the few cases of septicemia, the agent may be isolated from the blood during the first week of the disease, and from feces in the second and third weeks.

Diagnosis of animal salmonellosis is also made by culturing fecal material. For infections caused by *S. pullorum* and *S. gallinarum* in fowl, serologic diagnosis is

important to identify and eliminate individual carriers. Infection by *S. dublin* can be diagnosed serologically in a herd, but not in individual cattle. As a screening test, the *S. pullorum* antigen can also be used in detecting antibodies for the lipopolysaccharide of *S. enteritidis* in chickens. Seroagglutination with the *S. abortus equi* antigen can be used as a preliminary test prior to culture in mares that have aborted. Postmortem examinations of animals primarily use cultures from the mesenteric lymph nodes.

Surveillance of food processing requires that cultures be made from product samples at different stages of preparation, and from utensils and surfaces that come into contact with the food. Special sampling methods have been developed for different kinds of foods.

Control: Given current conditions under which cattle and poultry are raised, transported, marketed, and slaughtered, as well as existing food processing practices, it is impossible to obtain salmonellae-free foods of animal origin. Control is currently based on protecting man from infection and reducing its prevalence in animals. Veterinary meat and poultry inspection and supervision of milk pasteurization and egg production are important for consumer protection.

Another important control measure is the education of food handlers, both in commercial establishments and in the home, about correct cooking and refrigeration practices for foods of animal origin, and about personal and environmental hygiene.

Epidemiological surveillance by health authorities is necessary to evaluate the magnitude of the problem in each country, locate the origins of outbreaks, and adopt methods designed to reduce risks.

In animals, salmonellosis control consists of: (a) elimination of carriers, which is currently possible for pullorum disease and fowl typhoid by means of serologic tests; (b) bacteriologic control of foods, mainly of such ingredients as fish, meat, and bone meal; (c) immunization; and (d) proper management of herds and poultry farms.

Immunization may be an important method for preventing animal salmonellosis. Two types of vaccines are being used: bacterins and live attenuated vaccines. Bacterins are administered parenterally, usually in two doses two to four weeks apart. Commercially available bacterins act against *S. dublin*, *S. typhimurium*, and *S. abortus equi*. Live salmonellae vaccines are administered orally; they are usually genetically defective mutants. In the US, strains of *S. dublin* and *S. typhimurium* that are unable to synthesize aromatic amino acids are used. Vaccines that are unable to synthesize purines are used against these serotypes and *S. choleraesuis* in Germany. These vaccines are avirulent and do not revert to the virulent state.

In the US, a vaccine has been developed against *S. choleraesuis*, with a strain attenuated through repeated selection of a virulent strain with passes of neutrophils from salmonellosis-free swine. In this way, the vaccine strain lost the 50-kilobase plasmid, which is a virulence factor (Kramer *et al.*, 1992). Live vaccines stimulate a greater cell-mediated immune response than bacterins, which primarily promote a humoral response with little or no association with protection. Oral administration (whether of bacterins or live vaccines) has the advantage of producing local immunity in the intestine and reducing elimination of salmonellae in feces. Parenteral administration of live vaccines can sometimes cause adverse reactions due to endotoxins (WHO Expert Committee on Salmonellosis Control, 1988).

The results of many tests conducted to date indicate that immunization with vaccines and some bacterins can prevent the disease (particularly in its severe form), but not the infection or carrier status.

A control measure known as Nurmi's method originated in Finland. Salmonella-free cultures of fecal organisms from the cecum of adult birds are administered orally to newly hatched chickens and turkey chicks. The cecal flora (some 60 species of bacteria) from the adult birds compete with the salmonellae and thus protect the chicks against salmonellosis at their most susceptible age. Treated chicks resist high doses of salmonellae. It is believed to work by competitive exclusion.

Various countries have had success combating pullorum disease (*S. pullorum*) and fowl typhoid (*S. gallinarum*), reducing the rate of infection to a minimum. Several countries have undertaken control programs for *S. enteritidis* in fowl. Control is important to reduce both public health risk and economic losses. In general terms, the first step is to ensure that establishments that provide eggs for incubation and 1-day-old chicks are free of infection. Each group of egg layers must be examined serologically and bacteriologically to certify those that are disease-free and destroy those that are infected. After the surroundings and the installations are disinfected, they should be repopulated from a safe source. Once a reliable source of eggs and chicks is assured, clean-up of commercial farms should begin.

Some countries limit the control program to *S. enteritidis*, others to all invasive serotypes, including *S. typhimurium* and *S. hadar*. In Sweden, during the first year of control (1991–1992), infection was found in 6% of the layer establishments. This fell to 2% in the second year. An organization of broiler breeders in Northern Ireland had a successful program that eradicated infection by *S. enteritidis* in the establishments of their associates (McIlroy *et al.*, 1989).

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SHIGELLOSIS

ICD-10 A03.0 shigellosis due to *Shigella dysenteriae*;
A03.1 shigellosis due to *Shigella flexneri*;
A03.2 shigellosis due to *Shigella boydii*;
A03.3 shigellosis due to *Shigella sonnei*; A03.8 other shigellosis

Synonyms: Bacillary dysentery.

Etiology: The genus *Shigella* belongs to the family *Enterobacteriaceae*. Shigellae are small gram-negative, nonmotile, unencapsulated bacilli; they are anaerogenic (with a few exceptions) and non-lactose fermenting (or slow fermenters).

The genus *Shigella* may be considered genetically as a single species, closely related in DNA analyses to *E. coli*. However, it is divided into four species based on phenotype traits. Each species is a distinct serogroup: *Shigella dysenteriae* (serogroup A), *S. flexneri* (serogroup B), *S. boydii* (serogroup C), and *S. sonnei* (serogroup D). The four serogroups contain a total of 38 serotypes. Serotyping is important in epidemiological investigation. Diagnostic laboratories are generally limited to identifying the serogroup and sending cultures to a reference laboratory for identification of the serotype.

The primary virulence factor of a *Shigella* strain is its ability to invade cells of the intestinal mucosa. The invasive capacity depends on factors controlled by both chromosomic and plasmidic genes (Keusch and Bennish, 1991).

The invasive capacity of a strain can be demonstrated with the Sereny test, which consists of inoculating a culture in a guinea pig's conjunctival sac. Invasive strains produce keratoconjunctivitis in 24 to 48 hours. Cultures obtained from clinical cases always yield a positive Sereny test result. Shigellae also produce cytotoxins, particularly in the case of *S. dysenteriae* serotype 1 (Shiga toxin).

Geographic Distribution: Worldwide.

Occurrence in Man: Shigellosis can be either epidemic or endemic. Epidemic or pandemic shigellosis is usually caused by *S. dysenteriae* serotype 1 (Shiga bacillus), the most virulent and toxigenic strain. In 1969–1970, a widespread epidemic caused by *S. dysenteriae* serotype 1 occurred in Central America and Mexico, with high morbidity and mortality rates, particularly in children. More than 13,000 patients died as a result. The infection was introduced in the US, where 140 cases occurred from 1970 to 1972. The epidemic spread to Central Africa and Asia (India, Bangladesh, and Sri Lanka). Plasmid analysis demonstrated that the pandemic was not produced by a single bacterial clone. Thus, it is difficult to explain the appearance of the disease in such distant areas. The strains isolated in all areas proved to be multiresistant to antibiotics (WHO, 1987). In Guatemala, there were 112,000 cases with 10,000 deaths from 1969 to 1972. A new outbreak appeared in Guatemala in 1991 caused by *S. dysenteriae* serotype 1; it affected 540 people in the course of one month, both in Guatemala City and in Verapaz, a city of 10,000 inhabitants (CDC, 1991).

Endemic shigellosis is usually caused by *S. flexneri* and *S. sonnei*. The first occurs primarily in developing countries, the second, in economically advanced countries. Morbidity and mortality rates are high in developing countries, particularly in chil-

dren aged 1 to 5 years (WHO, 1987). Of 16,567 isolations done in the US during 1987, 67.7% were *S. sonnei*, 22.2% were *S. flexneri,* 2.1% were *S. boydii,* 1.4% were *S. dysenteriae*, and 6.6% were unidentified species (Keusch and Bennish, 1991).

It is very difficult to calculate the number of cases worldwide, but they are estimated at more than 200 million each year, 650,000 of whom die (WHO, 1991). In the US, there are an estimated 300,000 clinical cases (Bennett, cited in Wachsmuth and Morris, 1989).

An outbreak affecting large numbers of people occurred in 1987 during a mass "Rainbow Family" gathering in a forest in North Carolina (USA). It is estimated that more than 50% of the 12,700 participants were affected. The location's sanitary infrastructure was insufficient for so many people. The outbreak was caused by *S. sonnei*, which is resistant to many antibiotics (ampicillin, tetracycline, and trimethoprim with sulfamethoxazole), and which contained a 90-kilobase plasmid not found in strains not related to this epidemic. When the participants dispersed, they became the source of infection for outbreaks in three US states (Wharton *et al.*, 1990).

Those who suffer most from the disease are those who cannot follow personal hygiene rules, such as patients or residents confined in different institutions. Children are the principal victims of the disease in endemic areas. Resistance in adults is due to acquired immunity to the prevalent serotype. Adult travelers visiting endemic areas contract the disease because they have had no previous exposure. Similarly, when a new serotype is introduced into a susceptible population, the disease affects all age groups (Levine and Lanata, 1983).

Occurrence in Animals: It is common in captive nonhuman primates and rare in other animal species. All species of *Shigella*, including *S. dysenteriae* type 1 (Shiga bacillus), which is considered the most pathogenic form for man, have been isolated from nonhuman primates (L'Hote, 1980). In 1984, an epizootic caused by *S. flexneri* occurred at the National Zoo in Washington, DC (USA), and since then, shigellosis has become endemic. The infected species were gibbons (*Hylobates concolor* and *H. syndactylies*), macaques (*Macaca silenus*, *M. nigra*, and *M. sylvanus*), colobus monkeys (*Colobus guerzea*), and gorillas (*Gorilla gorilla*). From 1984 to 1988, the two species of gibbons (species in danger of extinction) had a high rate of infection and disease (Banish *et al.*, 1993a). *S. sonnei* was isolated from mangabey monkeys (*Cercocebus albigena*) and spider monkeys (*Ateles susciceps*) in the same zoological collection (Banish *et al.*, 1993a).

The Disease in Man: It is seen most often in preschool-aged children. When a new serotype is introduced in tropical areas in which the population is undernourished, the disease affects all age groups, particularly children, the elderly, and debilitated individuals. The incubation period is one to seven days, but usually four days.

The clinical picture may vary from an asymptomatic infection to a serious and fatal disease. The disease begins with fever and abdominal pains, as well as diarrhea that may be watery at first and later dysenteric with blood and mucus. The rectum and colon are the parts of the intestine most affected. In the final stages, there is an intense tenesmus with frequent elimination of small amounts of feces consisting almost entirely of blood and mucus. The disease is self-limiting in well-nourished individuals, but may last for weeks or months in undernourished persons (Keusch and Bennish, 1991). Convulsions are frequent in hospitalized children.

Shigellae rapidly acquire resistance to antimicrobials. The choice of an antimicrobial will depend on the antibiogram of the strain isolated or local patterns of susceptibility. Fluids and electrolytes must be replaced if dehydration occurs. Antiperistaltics are contraindicated, both for intestinal infections caused by shigellae and for other intestinal infections.

In many countries, strains of *Shigella* resistant to sulfonamides and to several antibiotics have been observed.

The Disease in Animals: It occurs in monkeys, with a clinical picture similar to that in man. In nonhuman primate colonies, strains resistant to many antibiotics are frequently found. As in man, an antibiogram must be done to identify the most appropriate antimicrobial. Enrofloxacine was used with good results at the National Zoo in Washington, DC (Banish *et al.*, 1993a).

Source of Infection and Mode of Transmission: The principal reservoir of the infection for man is other humans who are sick or carriers. The sources of infection are feces and contaminated objects. The most common mode of transmission is the fecal-oral route. Outbreaks with numerous cases have had their origin in a common source of infection, such as foods contaminated by hands or feces of carrier individuals. Insects, particularly flies, can also play a role as mechanical vectors.

There is a direct relationship between the frequency of shigellosis and a country's degree of economic development, as well as between poor and well-off classes within a country. Lack of health education, health infrastructure (potable water and sewer system), environmental hygiene, and personal hygiene habits are all factors that contribute to the spread of infection. Shigellosis is a disease of poverty.

Bacillary dysentery is a serious disease with high mortality in nonhuman primates in captivity, but there is doubt that monkeys can harbor the etiologic agent in their natural habitat. Monkeys probably contract the infection though contact with infected humans. The infection spreads rapidly in nonhuman primate colonies because the monkeys defecate on the cage floor and often throw their food there.

Role of Animals in the Epidemiology of the Disease: Of little significance. Cases of human bacillary dysentery contracted from nonhuman primates are known. The victims are mainly children. In highly endemic areas, dogs may shed *Shigella*, at least temporarily.

The etiologic agent has been isolated rarely from bats and rattlesnakes. Nevertheless, animals other than nonhuman primates play an insignificant role.

Diagnosis: Definitive diagnosis depends on isolation of the etiologic agent by culture of fecal material on selective media. There are several selective media, which are based on the suppression of lactose fermenters. One of these is MacConkey agar with bile salts, xylose, lysine, and deoxycholate (XLD). Serologic identification and typing, at least of the serogroup, are important for diagnosis and for epidemiological research.

Control: In man, control measures include: (a) environmental hygiene, especially disposal of human waste and provision of potable water; (b) personal hygiene; (c) education of the public and of food handlers about the sources of infection and modes of transmission; (d) sanitary supervision of the production, preparation, and preservation of foods; (e) control of flies; (f) reporting and isolation of cases and sanitary disposal of feces; and (g) search for contacts and the source of infection.

A live streptomycin-dependent vaccine, administered orally in three or four doses, provided good protection against the clinical disease for 6 to 12 months. However, it is currently not in use due to side effects such as vomiting in a small number of those who have been given the vaccine. Another undesirable and more serious effect of this vaccine is the instability of the strain and reversion to its original virulence (WHO, 1991). Different types of vaccines have been developed, including hybrids of *Shigella* and *E. coli*, and of *Shigella* and *Salmonella*; vaccines obtained through deletions and mutations; and oral vaccines of dead shigellae. All these vaccines are awaiting evaluation (WHO, 1991).

In two military camps in Israel, intensive measures (primarily bait and strategically located traps) were taken in the early summer of 1988 to control flies for 11 weeks. The test was repeated in the summer of 1989. The number of flies was reduced by 64% and clinic visits for diarrhea caused by shigellosis fell by 42% in the first year and 85% in the second. These results indicate that flies, acting as mechanical vectors, are an important factor in the transmission of shigellosis (Cohen *et al.*, 1991).

Indiscriminate use of antibiotics must be avoided in order to prevent the emergence of multiresistant strains and to ensure that these medications remain available for use in severe cases.

In animals, control consists of: (a) isolation and treatment of sick or carrier monkeys; (b) careful cleaning and sterilization of cages; (c) prevention of crowding in cages; and (d) prompt disposal of wastes and control of insects.

At the National Zoo in Washington, DC, carrier status for multiresistant *S. flexneri* was eliminated through intramuscular administration of enrofloxacine (5 mg/kg of bodyweight every 24 hours for 10 days). The large primates received the same medicine orally. In this way, it was possible to eradicate *S. flexneri* from a colony of 85 primates, although after 10 to 12 months *S. sonnei* was isolated from the feces of three animals (Banish *et al.*, 1993b).

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STAPHYLOCOCCAL FOOD POISONING

ICD-10 A05.0 foodborne staphylococcal intoxication

Synonyms: Staphylococcal alimentary toxicosis, staphylococcal gastroenteritis.

Etiology: It is caused by an enterotoxin preformed in food by *Staphylococcus aureus*. The overwhelming majority of outbreaks are due to coagulase-positive strains of *S. aureus*. Very few coagulase-negative strains are capable of producing enterotoxins. Some outbreaks may be due to *S. intermedius* and *S. hyicus*.

The genus *Staphylococcus* consists of gram-positive bacteria in the form of cocci grouped in clusters. The bacteria is not very heat-resistant, but the enterotoxin is. There are five known types of enterotoxins (A, B, C, D, and E), but enterotoxin A is most prevalent in outbreaks. Some strains of *S. aureus* can produce both the enterotoxins and toxic shock syndrome toxin-1.

Geographical Distribution: Worldwide.

Occurrence in Man: In some countries, the disease is an important cause of food poisoning. Most sporadic cases are not recorded. Outbreaks affecting several or many people are those that are primarily known and recorded.

In the US during the period 1977–1981, 131 outbreaks were reported, affecting 7,126 people. In the last three years of that five-year period, only enterotoxin A was incriminated. Milk (the most common source of toxins C and D) and commercially packaged foods are the least common causes of the disease in the United States (Holmberg and Blake, 1984). In Japan, the annual average of food poisoning outbreaks from 1976 to 1980 was 827. Of a total of 8,742 cases, 28.2% were caused by staphylococcal poisoning (Genigeorgis, 1989).

It has been suggested that a proportion of the intestinal disorders frequently observed in developing countries are caused by staphylococcal food poisoning. Evidence of this is the fact that titers of antibodies to enterotoxins are higher in residents of these countries than in travelers (Bergdoll, 1979).

Occurrence in Animals: Spontaneous cases of staphylococcal poisoning in domestic animals are not known. The rhesus monkey (*Macaca mulatta*) is susceptible to the enterotoxin through the digestive tract and is used as an experimental animal to show the presence of the toxin in implicated foods. Intravenous or peritoneal inoculation with the enterotoxin in cats and kittens has also been used for the same purpose. Dogs possibly suffer from gastroenteritis similar to that in man.

Mastitis in cattle caused by staphylococci is of interest from a public health perspective. In modern milking systems, *S. aureus* is a common pathogen in cows' udders. The agent is transmitted by means of milking machines or the milker's hands, and enters through the milk duct or superficial lesions on the teat. Mastitis caused by *S. aureus* in cattle may vary from the prevalent subclinical form of infection to a severe gangrenous form. Both forms are economically important because of the losses they cause in milk production (Gillespie and Timoney, 1981). Studies conducted in five northern European countries and in Japan have shown that a large proportion of the staphylococci isolated from cases of bovine mastitis are toxigenic. In Europe, 41.4% of 174 strains isolated produced enterotoxins, and of these, 48.6% produced A; 5.6%, B; 29.2%, C; and 33.3%, D; either singly or in combination. In Japan, 34.4% of 1,056 strains isolated from cows with subclinical mastitis were toxigenic, and of these 31.1% produced enterotoxin A; 54.3%, C; 27%, D; and 10.7%, B; either singly or in combination. Enterotoxins A, C, or D are the predominant types in staphylococcal poisoning in many countries (Kato and Kume, 1980). Nevertheless, the types of enterotoxins produced by strains isolated from milk seem to vary in prevalence in different countries; this may often be because an unrepresentative number of strains has been studied.

S. intermedius and *S. aureus* are the most common agents in canine skin infections and cause pyoderma, impetigo, folliculitis, and furunculosis. *S. aureus* is frequently a complicating agent of demodectic mange, producing cellulitis in the deep layers of the skin. Enterotoxigenic staphylococci were isolated from 13% of 115 domestic dogs in Japan. The strains isolated were producers of enterotoxins A, C, and D that can cause food poisoning in man (Kaji and Kato, 1980). A study conducted in Brazil in dogs with pyodermatitis confirmed that 13 of 52 isolates of *S. intermedius* and 6 of 21 of *S. aureus* produced enterotoxins. There were six isolates of enterotoxin C, seven of D, and six of E. Four strains produced toxic shock syndrome toxin-1 (Hirooka *et al.*, 1988).

In fowl, staphylococcal infection can cause diseases ranging from pyoderma to septicemia with different localizations (salpingitis, arthritis, and other disorders).

Purulent staphylococcal synovitis is a disease that causes appreciable losses in chickens and turkeys. In the former Czechoslovakia, one of the principal sources of staphylococcal food poisoning is thought to be infected poultry (Raska *et al.*, 1980). Staphylococcal strains isolated from poultry farms in that country and others produce enterotoxin D. Many researchers have isolated *S. aureus* from the nasal passages and skin of 100% of the birds examined, as well as from the nose and skin of 72% of swine (Genigeorgis, 1989). These data indicate that meat- and milk-producing animals may make a significant contribution to contamination of the food chain.

The Disease in Man: The incubation period is short, generally three hours after ingestion of the food involved. The interval between ingestion and the first symptoms may vary from 30 minutes to 8 hours depending on the amount of toxin ingested and the susceptibility of the individual.

The major symptoms are nausea, vomiting, abdominal pain, and diarrhea. Some patients may show low fever (up to 38°C). More serious cases may also show prostration, cephalalgia, abnormal temperature, and lowered blood pressure as well as blood and mucus in the stool and vomit. The course of the disease is usually benign and the patient recovers without medication in 24 to 72 hours.

There are patients who require hospitalization due to the severity of the symptoms. It is assumed that these are people who have ingested foods with high doses of the enterotoxin, who were not exposed to the enterotoxin in the past, or who may be debilitated due to other causes.

Source of Infection and Mode of Transmission: The principal reservoir of *S. aureus* is the human carrier. A high proportion of healthy people (30% to 35%) have staphylococci in the nasopharynx and on the skin. A carrier with a respiratory disease can contaminate foods by sneezing, coughing, or expectorating. Similarly, he may contaminate food he handles if he has a staphylococcal skin lesion. However, even if not sick himself, the carrier may contaminate food by handling different food ingredients, equipment, utensils, or the finished product. According to various authors, the proportion of enterotoxin-producing *S. aureus* strains of human origin varies from 18% to 75% (Pulverer, 1983). The proportion of toxigenic strains isolated from various sources (humans, animals, and food) is very high.

Strains of human origin predominate in epidemics, but animals are also reservoirs of the infection. Milk from cow udders infected with staphylococci can contaminate numerous milk products. Many outbreaks of staphylococcal poisoning have been caused by the consumption of inadequately refrigerated raw milk or cheeses from cows whose udders harbored staphylococci. The largest outbreak affected at least 500 students in California (USA) between 1977 and 1981 and was traced to chocolate milk (Holmberg and Blake, 1984). Another outbreak occurred in the US in which 850 students became ill after drinking chocolate milk. The average amount of enterotoxin A in the milk was 144 ng per half-pint carton (Evenson *et al.*, 1988).

Goat milk is implicated more rarely. A small outbreak occurred in Israel among Bedouin children who drank *semna*, goat milk that is skimmed, sweetened, and heated. The milk came from a goat with mastitis caused by *S. aureus* enterotoxin B (Gross *et al.*, 1988).

Small outbreaks and sporadic cases occurred in a town in Scotland between December 1984 and January 1985, in which cheeses made from sheep milk were implicated. Bacteriological examination of the various samples of the cheese was

unsuccessful in isolating *Staphylococcus*, but the presence of enterotoxin A was confirmed (Bone *et al.*, 1989). In various Mediterranean countries, *Staphylococcus* is one of the most important agents in ovine mastitis. Not only can ovine staphylococcus cause economic losses, it could also be a public health problem. Food poisoning is probably the most important foodborne disease in Spain and other countries of the region. The vehicle of poisoning could be cheese made from sheep's milk. In Spain, 46 of 59 isolates of *S. aureus* produced enterotoxin C; 2, enterotoxin A; 1, enterotoxin D; and 2, enterotoxins A and C (Gutiérrez *et al.*, 1982). In developing countries, where the refrigeration of milk after milking leaves much to be desired, it is possible that milk and milk products are an important source of staphylococcal intoxication.

According to recent studies, a high proportion of strains isolated from staphylococcal mastitis produce enterotoxin A, which causes many human outbreaks.

Several studies were successful in isolating the *S. aureus* phage type 80/81 from skin lesions and cow's milk, which is related to epidemic infections in man. One of the studies proved that phage type 80/81 produced interstitial mastitis in cows. The same phage type was found among animal caretakers, which indicates that the bacterium can be transmitted between man and animals and that the latter may reinfect man.

Infected fowl and dogs (see the section on occurrence in animals) may also give rise to and be a source of staphylococcal poisoning in man.

One subject that deserves special attention is the appearance of antibiotic-resistant strains in animals whose food contains antibiotics. There is concern regarding the possible transmission of these strains to man. On several occasions, resistant strains have been found both in animals (cows, swine, and fowl) and in their caretakers, with the same antibiotic resistance. Moreover, "human" strains (phage typed) have occasionally been isolated from the nostrils and lesions of other species of domestic animals.

A variety of foods and dishes may be vehicles of the toxin. If environmental conditions are favorable, *S. aureus* multiplies in the food and produces enterotoxins. Once made, the toxin is not destroyed even if the food is subjected to boiling for the usual cooking time. Consequently, the toxin may be found in food while staphylococci are not.

Poisoning is usually caused by primarily protein-based cooked foods that are contaminated during handling and left at room temperature. Red meat and fowl were responsible for 47.3% of the outbreaks in the US (ham was the most common source in that country) and 77.2% in England. In Spain, primarily mayonnaise and foods containing mayonnaise were implicated; in Germany, four outbreaks were due to meat and three to eggs and milk products (Genigeorgis, 1989). During a Caribbean cruise, 215 of 715 passengers were poisoned by cream-filled pastries served at two different meals on board. The remaining pastries were thrown out and could not be studied, but enterotoxigenic strains of *S. aureus* phage type 85/+ were isolated from the feces of 5 of 13 patients and from none of the controls. Isolates of the same phage were obtained from a perirectal sample and from a forearm lesion from two of seven members of the ship's crew who were in charge of pastry preparation (Waterman *et al.*, 1987).

An important causal factor in poisoning is keeping food at room temperature or inadequate refrigeration, practices which allow staphylococci to multiply. Lack of

hygiene in food handling is another notable factor. Outbreaks of food poisoning may often be traced to a single dish.

Role of Animals in the Epidemiology of the Disease: Most outbreaks are caused by human strains and, to a lesser degree, by strains from cattle or other animals.

Animal products, such as meat, milk, cheese, cream, and ice cream, usually constitute a good substrate for staphylococcal multiplication. Pasteurization of milk does not guarantee safety if toxins were produced prior to heat treatment, as the toxins are heat-resistant. Outbreaks have also been caused by reconstituted powdered milk, even when the dried powder contained few or no staphylococci.

Diagnosis: The short incubation period between ingestion of the food involved and the appearance of symptoms is the most important clinical criterion. Laboratory confirmation, when possible, is based mainly on demonstration of the presence of enterotoxin in the food. Biological methods (inoculation of cats with cultures of the suspect food, or of rhesus monkeys with the food or cultures) are expensive and not always reliable. As substitutes, serological methods, such as immunodiffusion, immunofluorescence, hemagglutination inhibition, enzyme-linked immunosorbent assay (ELISA), and reverse passive latex agglutination are used (Windemann and Baumgartner, 1985; Shinagawa *et al.*, 1990). These tests are useful in epidemiological research but not in daily practice (Benenson, 1990).

The isolation of enterotoxigenic staphylococcal strains from foods and typing by phage or immunofluorescence have epidemiological value. Quantitative examination of staphylococci in processed or cooked foods serves as an indicator of hygiene conditions in the processing plant and of personnel supervision.

Control: Control measures include the following: (a) education of those who prepare food at home and other food handlers, so that they will take proper personal hygiene measures; (b) prohibiting individuals with abscesses or other skin lesions from handling food; (c) refrigeration at 4°C or lower of all foods in order to prevent bacterial multiplication and the formation of toxins. Foods must be kept at room temperature for as little time as possible.

The veterinary milk inspection service should supervise dairy installations, the correct operation of refrigeration units and their use immediately after milking, and refrigerated transport of the milk to pasteurization plants.

The veterinary meat inspection service should be responsible for enforcing hygiene regulations before and after slaughter as well as during handling and processing of meat products. Control of hygiene conditions in meat retail establishments is also important.

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STREPTOCOCCOSIS

(*S. suis* and other species of interest)

ICD-10 A38 scarlet fever; G00.2 streptococcal meningitis; J 02.0 streptococcal pharyngitis

Synonyms: Streptococcal infection, streptococcal sore throat, scarlatina.

Etiology: The genus *Streptococcus* includes many species that display notable differences in their biological properties and their pathogenicity for man and animals. Streptococci are round, nonmotile, gram-positive bacteria that occur in pairs or long chains, particularly in fluid cultures. *Streptococcus* does not form spores and certain species, such as *S. suis*, have capsules that can be seen when cultured in serum media.

Lancefield's serological classification is very useful for identifying these bacteria. This scheme currently distinguishes 20 serogroups and identifies them with the letters A to V, excluding I and J. Many components of the serogroups have not been given specific names. Lancefield's classification is based on a precipitation test with antisera for the different dominant polysaccharide antigens located on the bacterium wall. Capsular species can in turn be divided into serotypes. This is true of *S. suis,* which is currently subdivided into 29 capsular serotypes (Higgins *et al.*, 1992). Several serogroups produce additional antigens that serve to identify serotypes. Serotyping is useful in epidemiology.

A single serogroup may include strains that are physiologically and biochemically different, thus classification cannot be based solely on serology (Timoney *et al.*, 1988). Moreover, some strains cannot be typed serologically in a serogroup and can only be identified on the basis of biochemical and physiological properties or by the combination of these characteristics plus serology (Kunz and Moellering, 1981).

A common technique for preliminary identification consists of dividing the streptococci into three categories according to their hemolytic reactivity: alpha (incomplete hemolysis and greenish discoloration on blood agar), beta (complete lysis of erythrocytes), and gamma (nonhemolytic). β-hemolytic streptococci are usually the cause of acute diseases and suppurative lesions, while α-hemolytic and Γ-streptococci cause subacute disease, with some exceptions.

S. suis serotype 2 is of particular interest in terms of zoonoses because transmission from swine to man has been confirmed. This agent belongs to Lancefield's

group D. There are other *Streptococcus* species that are common to both man and animals, but which may or may not have specific reservoirs for different animal species.

Geographic Distribution: Streptococci are distributed worldwide. *S. suis* is probably prevalent in all areas where swine are bred.

Occurrence in Man: Disease caused by *S. suis* in man is rare. Between 1968 and 1984, it was isolated from 30 cases of meningitis in the Netherlands; another 30 cases caused by this agent occurred outside that country from 1968 to 1985 (Arends and Zanen, 1988).

Infections caused by group A (*S. pyogenes*) are common in man, with an apparently higher prevalence in temperate climates. For a long time, streptococci belonging to serogroup B (*S. agalactiae*) were considered mainly pathogenic for animals. They are now recognized as one of the major causes of septicemia, pneumonia, and meningitis in human newborns. In addition, streptococci belonging to serogroup D (*S. bovis*) are a frequent cause of endocarditis and bacteremia in man. There are sporadic cases of disease caused by streptococci belonging to groups C, G, F, H, and others. In man, there have been rare cases due to *S. acidominimus*, which is found in milk and in the genital and intestinal tracts of cattle; to *S. uberis*, which causes mastitis in cows and is found in milk, the oropharynx, skin, and intestinal tract; to *S. lactis* and *S. cremoris*, which cause mastitis in cows and are found in cow milk; and to *S. equi* and its subspecies, *S. zooepidemicus*, which produce various diseases in animals. Finally, there is *S. canis*, groups G, L, and M (Gallis, 1990).

Occurrence in Animals: Some diseases are very common and economically important. These include mastitis in cows caused by *S. agalactiae* (group B) and strangles caused by *S. equi* (group C) in horses and *S. suis* in swine.

The Disease in Man: In the 60 cases recorded up to 1988, the clinically predominant form of infection caused by *S. suis* was meningitis. Most patients showed classic symptoms of meningitis: severe headache, high fever, confusion, and stiff neck. More than 50% experienced a loss of auditory acuity. Other complications were arthritis and endophthalmitis. Mortality was 7%. Most patients were employed in occupations involving the handling of swine or their products (swine breeders, slaughterhouse workers, butchers, swine transporters). Of the 30 patients in the Netherlands, 28 cases were caused by *S. suis* type 2, 1 by type 4, and 1 by a strain that could not be typed (Arends and Zanen, 1988). The same authors estimate that in that country the risks for slaughterhouse workers and swine breeders would be 3 per 100,000 inhabitants.

S. pyogenes is the principal pathogen among hemolytic streptococci. This agent frequently causes epidemics of septic sore throat and scarlet fever (streptococcal tonsillitis and pharyngitis), various suppurative processes, septicemias, puerperal sepsis, erysipelas, ulcerative endocarditis, and other localized infections. Streptococcal sore throat and scarlet fever are epidemiologically similar. The latter is differentiated clinically by the exanthema caused by strains producing an erythrogenic toxin. The disease is mild or inapparent in a high percentage of those infected. Rheumatic fever is a sequela of streptococcal sore throat or scarlet fever and may be caused by any strain of group A. Glomerulonephritis is another complication, produced only by certain nephritogenic strains of the same group.

Group B streptococci are important causal agents of neonatal disease. Group A streptococci and *Staphylococcus aureus* were replaced by *Escherichia coli* and serogroup B streptococci as the principal agents of neonatal infection. In infections caused by group B streptococci (*S. agalactiae*), two clinical syndromes are distinguished, depending on the age of the infant at the onset of disease. The acute or early-onset syndrome appears between the first and fifth day of life and is characterized by sepsis and respiratory difficulty. The delayed-onset syndrome generally appears after the tenth day and is characterized by meningitis, with or without sepsis. Affected children show lethargy, convulsions, and anorexia. Mortality is high in both forms, but higher in the early-onset syndrome.

In older children and adults, group B streptococci cause a variety of clinical syndromes: urinary tract infections, bacteremia, gangrene, postpartum infection, pneumonia, endocarditis, empyema, meningitis, and other pathological conditions (Patterson and el Batool Hafeez, 1976).

Disease caused by group C streptococci (*S. equi*) is sporadic and rare in man. However, in 1983, an epidemic outbreak occurred in New Mexico (USA), with 16 cases caused by the consumption of white cheese made at home with unpasteurized milk. The agent was identified as *S. zooepidemicus*, one of the four species that make up group C. The disease in these patients consisted of fever, chills, and vague constitutional symptoms, but five of them had a localized infection, which manifested in such varied symptoms as pneumonia, endocarditis, meningitis, pericarditis, and abdominal pains (CDC, 1983).

In England and Wales between 1983 and 1984, there were eight deaths during 32 outbreaks associated with milk and milk products contaminated by *S. zooepidemicus* (Barrett, 1986). There were 11 cases in Hong Kong between 1982 and 1990 in patients suffering from septicemia associated with a cardiovascular illness. Mortality was 22%. Five of the 11 patients had a predisposing disease. The source of infection was undercooked or raw pork (Yuen *et al.*, 1990).

In sporadic cases caused by streptococcus group C, the most common clinical manifestation is exudative pharyngitis or tonsillitis. With some exceptions, group C streptococci isolated from these cases belong to *S. equisimilis*, which produces septicemia in suckling pigs. An outbreak of pharyngitis caused by group C streptococci, due to the consumption of raw milk, was followed by a high incidence of glomerulonephritis (Duca *et al.*, 1969).

Both enterococcal and nonenterococcal group D streptococci cause serious diseases in man. *S. bovis* causes bacteremia and endocarditis, and enterococci cause urinary tract infections, abdominal abscesses, and a significant percentage of cases of bacterial endocarditis. *S. suis*, already described, belongs to group D.

Streptococci belonging to other serogroups, as well as those not serologically grouped, cause a wide variety of clinical manifestations, including dental caries and abscesses, meningitis, puerperal sepsis, wound infections, endocarditis, and other pathological conditions (Kunz and Moellering, 1981).

Nonhemolytic streptococci and "viridans" type (a-hemolytic) streptococci can cause subacute endocarditis.

The preferred antimicrobial for treatment is penicillin (Benenson, 1990).

The Disease in Animals: *S. suis* belongs to group D and can be β- or α-hemolytic (Timoney *et al.*, 1988). This agent frequently causes septicemia, meningitis, pneu-

monia, and arthritis. Less frequently, it causes endocarditis, polyserositis, encephalitis, and abscesses. Although the rate of infection in a herd can be high, it does not usually affect more than 5% (Clifton-Hadley, 1984). Of 663 strains isolated from sick swine in Canada, 21% belonged to type 2 (the most frequently occurring type in all countries), followed by types 1/2 (which has capsular antigens from 1 and 2) and 3, with 12% each. Types 20 and 26 were the only types not found (Higgins and Gottschalk, 1992). In Denmark, types 2 and 7 represented 75% of the isolates. Type 7 was isolated more frequently than in other countries, usually in suckling pigs younger than 3 weeks. Experimental inoculation with *S. suis* type 7 in suckling pigs under 7 days old caused severe disease (Boetner *et al.*, 1987). In Australia, type 1 has caused septicemia, meningitis, and polyarthritis in suckling pigs (Cook *et al.*, 1988). In weaned piglets from various regions of Australia, type 2 is predominant (Ossowicz *et al.*, 1989), although types 3, 4, and 9 have also been isolated and there are indications that they can produce the same disease picture. In another study in New South Wales and Victoria (Australia), type 9 was predominant (Gogolewski *et al.*, 1990).

In cattle, sheep, and goats, strains of types 5 and 2 were isolated from purulent lesions in the lungs and from other extramammary sites (Hommez *et al.*, 1988).

Most isolates of *S. suis* type 2 are sensitive to penicillin.

S. agalactiae (*S. mastitidis*), in Lancefield's group B, is the principal agent of chronic catarrhal mastitis in dairy cows. *S. dysgalactiae* (group C) and *S. uberis* (group E) cause sporadic cases of acute mastitis in bovines. *S. pyogenes*, a human pathogen, can infect the cow's udder, producing mastitis and leading to epidemic outbreaks in man.

Horse strangles, caused by *S. equi* (group C), is an acute disease of horses characterized by inflammation of the pharyngeal and nasal mucosa, with a mucopurulent secretion and abscesses of the regional lymph nodes.

S. equisimilis (group C) infects different tissues in several animal species. Group C streptococci that are adapted to animals and classified as *S. zooepidemicus* produce cervicitis and metritis in mares and often cause abortions. They also cause septicemia in colts. They are pathogenic for bovines, swine, and other animals, in which they produce various septicemic processes.

S. zooepidemicus (group C) is an opportunistic pathogen in many animal species. It is a commensal on the skin, the mucosa of the upper respiratory tract, and in the tonsils of many animal species. In horses, it is the common agent of wound infections and is a secondary disease agent after a viral infection in the upper respiratory tract of colts and young animals. It is also the agent of other infections in horses (Timoney *et al.*, 1988). In cows, *S. zooepidemicus* can cause acute mastitis when it enters a wound in the teat. A fatal case of septicemia was described in a chicken (Timoney *et al.*, 1988).

Streptococci belonging to other groups cause abscesses and different disease processes in several animal species. The many diseases caused by streptococci are clinically differentiated by the agent's portal of entry and the tissue it affects.

Source of Infection and Mode of Transmission: The reservoir of *S. pyogenes* is man. Transmission of this respiratory disease agent (septic sore throat, scarlet fever) results from direct contact between an infected person, whether patient or carrier, and another susceptible person. The disease is most frequent among children from 5 to 15 years old, but also occurs at other ages.

In Germany, Denmark, the US, Great Britain, and Iceland, important epidemics have had their origin in the consumption of raw milk or ice cream made with milk from cows with udders infected by *S. pyogenes*. These epidemics were due to infection in the cows' udders contracted from infected milkers. Between 1920 and 1944, 103 such epidemics of septic sore throat and 105 of scarlet fever were recorded in the US due to consumption of raw milk from cows with infected udders. In other instances, the milk was contaminated directly (without the udders' being infected by people with septic sore throat or localized infections). In several epidemic outbreaks, the milk became contaminated after pasteurization.

According to the WHO Expert Committee on Streptococcal and Staphylococcal Infections (1968), contamination of milk products has caused small outbreaks of streptococcal respiratory disease, but these are increasingly less frequent.

Pasteurization has been the most important factor in the reduction of streptococcal outbreaks resulting from milk. In Third World countries, much milk is still consumed raw, and even in developed countries, outbreaks are produced by products made with raw milk.

Special attention has been given to neonatal sepsis caused by group B streptococci (*S. agalactiae*). Research has shown that *S. agalactiae* colonizes a high percentage of women (7% to 30% or more) in different locations, such as the intestinal tract, the cervicovaginal region, and the upper respiratory tract. The agent is possibly transferred from the rectal region to the vaginal canal, since most of the bacteria are intestinal. Infants can become contaminated *in utero* or during childbirth. Only a small percentage of neonates (approximately 1%) become infected and fall ill; in most, the agent colonizes the skin and the mucosa without affecting their health. The principal victims of the infection, especially in the case of the early-onset syndrome, are premature infants, low birthweight babies, and those born after a difficult labor. The principal reservoir of group B streptococci causing neonatal disease is clearly the mother. The *S. agalactiae* serotypes isolated from mothers and sick newborns are always the same. Although *S. agalactiae* is an agent of bovine mastitis and has also been isolated from other animal species, there is no evidence that the infection is transmitted from animals to man. In general, human and animal strains differ in some biochemical, metabolic, and serologic properties. It has been experimentally shown that human strains of *S. agalactiae* can produce mastitis in bovines (Patterson and el Batool Hafeez, 1976). However, some studies have suggested that a percentage of human infections may have derived from a bovine source (Van den Heever and Erasmus, 1980; Berglez, 1981) or that there is reciprocal transmission between humans and bovines. Nonetheless, research findings seem to indicate that if such transmission occurs, its importance is probably limited.

The outbreak of disease caused by *S. zooepidemicus* (group C) in New Mexico (USA) (see the section on the disease in man) clearly indicates that raw milk and unpasteurized milk products can be the source of infection for man. The epidemiological investigation of this outbreak sampled milk from cows on the establishment where the cheese was made as well as samples of the cheese itself. *S. zooepidemicus* was isolated from many of the samples. In Europe, there have also been cases of *S. zooepidemicus* infection caused by ingestion of raw milk. A case of pneumonia caused by *S. zooepidemicus* in a woman who cared for a sick horse has been described (Rose *et al.*, 1980). The cases of disease caused by *S. zooepidemicus* that occurred in Hong Kong were attributed to the consumption of cooked or raw pork (Yuen *et al.*, 1990).

Infection caused by *S. suis* type 2 is a true zoonosis. It is a highly occupational disease among those who breed pigs or participate in slaughtering, processing, or marketing them. Man contracts the infection primarily through skin lesions.

The infection in swine is widespread in areas where these animals are bred. In an endemic herd, both sick and healthy pigs carry the agent in their nasal cavities and tonsils. The percentage of carrier animals can reach 50% or more of the herd during outbreaks and fall to only 3% when there are no clinical cases. Carrier status can last for at least 45 days and may persist in animals treated with penicillin (Clifton-Hadley and Alexander, 1980). Among swine, the infection is transmitted through the air and possibly through the digestive route as well. Pigs can also be carriers of *S. suis* in the vaginal canal and piglets can become infected during delivery (Robertson *et al.*, 1991).

Animals can also transmit groups G, L, and M to man, but the epidemiology of these cross-infections has not yet been elucidated.

Role of Animals in the Epidemiology of the Disease: Swine are the reservoir and source of *S. suis* infection in man. Animals do not act as maintenance hosts for *S. pyogenes*, but can sometimes cause important epidemic outbreaks by contracting the infection from man and retransmitting it by means of contaminated milk. There is no firm evidence that animals play any significant role in the transmission of group B streptococci causing neonatal sepsis. Raw cow milk can be a source of group C streptococcal infection in humans.

Diagnosis: If milk is suspected as the source of an epidemic outbreak in man, an attempt should be made to isolate the etiologic agent. Obviously, a correct identification of the agent is required. From either a human or animal source, it is advisable to identify the serogroup of streptococci involved, and to establish the species whenever possible. However, few laboratories have the human and material resources necessary for this task.

A method has been described for identifying pregnant women with heavy colonization of the genital tract by group B streptococci (Jones *et al.*, 1983). The goal of this procedure is to start treating the newborn with drugs immediately after birth to reduce morbidity and mortality due to neonatal sepsis caused by group B streptococci.

Infection by *S. suis* should be suspected if the patient presents the clinical manifestations described and his or her occupation involves contact with swine or their by-products. Culture, isolation, and typing can confirm the diagnosis.

In swine, definitive diagnosis also depends on isolation and identification of the agent. In endemic herds, the symptomatology may be sufficiently clear to make a clinical diagnosis during new outbreaks. In a study conducted in Quebec (Canada) with 1,716 weaned pigs belonging to 49 herds and 23 control herds, nasal and tonsil samples were taken with swabs. The samples were cultured in a brain-heart infusion broth, strengthened with a supplement selective for *Streptococcus* and 5% anti-*S. suis* type 2 serum developed in goats. After the diameter of the precipitation zone was measured in 539 isolates, serum plate agglutination was used to identify isolates of *S. suis* serotype 2. This method successfully identified 93.1% of the cultures isolated using the diameter of the precipitation zone as the sole criterion. Specificity was 94.5% and relative sensitivity was 88.7% (Moreau *et al.*, 1989).

Control: Those who work with swine or their by-products should pay attention to cuts or abrasions and treat them properly to prevent infection by *S. suis* type 2.

As for preventing the disease in swine, there are doubts regarding the efficacy of the bacterins used against *S. suis*. However, many veterinarians and breeders maintain that they prevent outbreaks of acute illness. Adding penicillin to feed when piglets are being weaned early can also control acute disease. The disadvantage is that penicillin becomes inactive in feed (Fraser *et al.*, 1991). Experimental tests showed that tiamulin administered in water was effective in reducing the effects of *S. suis* type 2 (Chengappa *et al.*, 1990).

Prevention of human infection transmitted through milk is achieved primarily by pasteurization. Infected persons should not participate in milking or handling milk or other foods.

The prevention of neonatal sepsis has been attempted by active immunization of pregnant women with capsular polysaccharides of group B streptococci, as well as by passive immunization with immunoglobulin preparations given intravenously. Both immunization methods are in the experimental stage. Promising results have been obtained with prophylactic intravenous administration of ampicillin to women in labor. In this way, a significant level of the antibiotic is obtained in the amniotic fluid and in samples of the umbilical cord. Among the newborns of obstetric patients receiving this treatment, only 2.8% were colonized by group B streptococci and none became ill, while in the control group, 35.9% of the newborns were colonized and four developed the early-onset syndrome (Fischer *et al.*, 1983).

To reduce the prevalence of mastitis caused by *S. agalactiae* in dairy herds, cows testing positive to the California Mastitis Test (CMT) are treated with penicillin by extramammary infusion. However, this procedure does not eradicate the infection, probably because of reinfection. Application of antiseptic creams to teat lesions can help to prevent mastitis caused by *S. dysgalactiae* and *S. zooepidemicus*. Bacterins have been tried for preventing equine strangles caused by *S. equi*. Although they confer satisfactory immunity, they produce a local and systemic reaction (Timoney *et al.*, 1988).

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TETANUS

ICD-10 A33 tetanus neonatorum; A34 obstetrical tetanus; A35 other tetanus

Synonyms: Trismus, lockjaw.

Etiology: *Clostridium tetani*; the pathology is produced by the neurotoxin of the infectious agent, since the bacterium does not invade the animal body. *C. tetani*, like all clostridia, is a gram-positive, anaerobic, motile bacillus, 2–2.5 microns long by 0.3–0.5 microns in diameter. It forms terminal ovoid spores, giving it the appearance of a tennis racket. While multiplying logarithmically, *C. tetani* amasses an intracellular neurotoxin called tetanospasmin, which is released when the cell lyses. Tetanospasmin is a very potent toxin. It is estimated that less than 2.5 ng/kg of bodyweight would be fatal for man and that 0.3 ng/kg of bodyweight would be fatal for a guinea pig (Orenstein and Wassilak, 1991). Production of the neurotoxin is determined by a plasmid gene (Finn *et al.*, 1984).

C. tetani spores are very resistant to environmental factors and can survive in the soil for many years.

Geographic Distribution: Worldwide. The etiologic agent is a soil microorganism that can also be found in the feces of animals and man. The spores of *C. tetani* are found primarily in cultivated land rich in organic matter, or in pastures. The disease occurs more frequently in the tropics than in temperate or cold climates.

Occurrence in Man: The incidence of the disease is low in industrialized countries; in developing countries, it still represents an important public health problem. In the decade 1951–1960, the mortality rate from tetanus was 0.16 per 100,000 inhabitants in the US and Canada and 8.50 per 100,000 in Latin America, excluding

Argentina and Brazil. In 1987, it was estimated that 1,680,000 cases and 1,030,000 deaths occurred worldwide. In 1973, 60% to 90% of cases occurred in newborns during the first month of life (Orenstein and Wassilak, 1991). Currently, the distribution of the disease by age group is completely different in the US. In the period 1989–1990, there were 117 cases of tetanus in 34 states, with an annual incidence of 0.02 per 100,000 inhabitants. In marked contrast to developing countries, 58% of the patients were 60 years of age or older and only one case occurred in a newborn. Case fatality bore a direct relationship to age: 17% in patients aged 40 to 49, and 50% in those aged 80 or older (CDC, 1993).

Inhabitants of rural areas are more exposed than those in urban areas. Case fatality is high despite improved treatment.

A study conducted in Paraguay demonstrated that tetanus is more frequent in men than in women, and more common in newborns and children than in adults (Vera Martínez *et al.*, 1976).

In Argentina, the annual rates of incidence for the period 1965–1977 were 1.2 to 1.7 per 100,000 inhabitants (except in 1967, when the rate was 3.1 per 100,000 inhabitants). The disease was more frequent in subtropical or temperate provinces than in the cold Patagonian provinces. Average hospital admissions for tetanus in Buenos Aires between 1968 and 1973 were higher during the hot months. Tetanus mortality in these municipal hospitals reached 35.8% and was eight times higher in children younger than 15 days than in other age groups (Mazzáfero *et al.*, 1981). Table 4 shows the morbidity distribution by climate for tetanus in Argentina during the period 1967–1977. In 1990, 49 cases were reported; in 1991, there were 38 cases of all ages; and in 1992, there were 7 neonatal cases. Underreporting is evident, since the number of deaths exceeds the number of patients, as indicated by the authorities in charge of the National Disease Surveillance System (Argentina, Ministerio de Salud y Acción Social, 1990, 1991, and 1992).

Occurrence in Animals: The disease is infrequent in animals. There are enzootic areas, particularly in the tropics. Horses are the most susceptible species. Cases also occur in sheep and cattle.

The Disease in Man: It is characterized by painful spasms of the masseter muscles (trismus) and neck muscles (rictus), but it frequently affects other muscles in the body. Although the average incubation period is 14 days, it may vary from less than two days to several months. If the disease is not complicated by other infections, temperature may be normal or only slightly elevated. Reflexes are exaggerated, and rigidity of the abdominal muscles, urine retention, and constipation are common. The case fatality rate is high, but varies from one country to another. In the US, fatality fell from 90% in 1947 to 60% in 1969. In 1989–1990, it was 17% in patients aged 40 to 49 and 50% in those aged 80 or older. The disease is much more severe when the incubation period is short and convulsions appear early. The longer, more frequent, and more intense the convulsions become, the worse the prognosis.

The symptomatology of neonatal tetanus is the same as that of the disease in adults; only the infection's portal of entry differs. In newborns, the infection usually enters through the umbilical stump. At other ages, the route of entry is a wound. Puncture wounds produced by contaminated objects or trauma wounds are especially dangerous. Surgical interventions and induced abortions performed without adequate asepsis have given rise to tetanus.

Table 4. Distribution of tetanus morbidity according to political division and climate, Argentina, 1967–1977.

Political division and climate	Average number of notified cases per year	Population at middle of reporting period (in thousands)	Rate per 100,000 inhabitants
Subtropical	168.8	4,221	3.9
Catamarca	3.4	175	1.9
Corrientes	19.2	587	3.3
Chaco	38.5	572	6.7
Formosa	14.2	248	5.6
Jujuy	6.7	323	2.1
Misiones	15.3	470	3.3
Salta	20.4	533	3.8
Santiago del Estero	15.7	519	3.0
Tucumán	32.6	794	4.1
Temperate	217.6	19,409	1.1
Federal District	18.5	2,974	0.6
Buenos Aires	111.9	9,289	1.2
Córdoba	20.9	2,177	0.9
Entre Ríos	16.5	838	1.9
La Pampa	3.4	177	2.2
La Rioja	0.6	139	0.4
Mendoza	4.5	1,025	0.4
San Juan	3.1	403	0.7
San Luis	1.5	187	0.8
Santa Fe	36.2	2,200	1.6
Cold	3.7	762	0.5
Chubut	0.6	202	0.3
Río Negro	1.3	281	0.4
Neuquén	1.6	170	0.9
Santa Cruz	0.2	94	0.2
Tierra del Fuego	—	15	0.0

Source: Bull Pan Am Health Organ 15:328, 1981.

C. tetani is not an invasive bacteria. The spores enter through a wound that may be an anaerobic medium, especially if there is tissular necrosis. Under such conditions, *C. tetani* enters a vegetative state, multiplies, and releases the neurotoxin as it lyses. The disease is due to tetanospasmin, a very potent neurotoxin (see the section on etiology). It enters the nervous system through the neuromuscular junctions of alpha motor neurons. Tetanospasmin inhibits the release of various neurotransmitters, allowing the lower motor neurons to increase muscle tone and produce convulsions simultaneously in the agonist and antagonist muscles (Cate, 1990).

The patient must be kept in an intensive care unit and treated with benzodiazepines to reduce anxiety, and to obtain a central anticonvulsive effect and muscular relaxation. It is often necessary to continue with tracheal intubation or a tra-

cheostomy. Simultaneously with these measures, human antitetanus immunoglobulin must be administered (intramuscular administration of 500 IU). Administration of penicillin or other antibiotics is recommended to reduce the toxin load (Cate, 1990).

The Disease in Animals: Horses are very susceptible to tetanus and usually acquire it from shoeing nails. They may also contract it from any other wound contaminated with *C. tetani* if anaerobic conditions favor its multiplication. Their symptoms are similar to those of human tetanus. Localized rigidity appears first, due to tonic convulsions of the masseter muscles, the neck muscles, and the hind legs, followed by generalized rigidity. Reflexes are increased and the animals are easily startled by noise, which causes general convulsions.

Postpartum cases are seen in cows, especially if the placenta is retained. Cattle have a high rate of neutralizing antibodies against the neurotoxin (tetanospasmin) of *C. tetani*, but the antibody level drops markedly after parturition, leaving the animal very susceptible to the disease. In calves and lambs, tetanus often follows castration, especially when rubber bands are used, since the necrotic tissue left by this operation favors anaerobiosis.

Dehorning, tail docking, and shearing may also give rise to the disease.

Iatrogenic tetanus sometimes occurs after surgical operations and vaccinations.

The incubation period lasts 2 to 14 days. The symptomatology is similar to that in man. Death occurs in 4 to 10 days.

Treatment consists of tranquilizers, curariform agents, and 300,000 IU of tetanus antitoxin every 12 hours. Good results can be obtained in horses if they are treated at the onset of the disease. The wound must also be cleaned and drained, and broad spectrum antibiotics administered (Fraser *et al.*, 1991).

Source of Infection and Mode of Transmission: The reservoir and source of infection is soil containing *C. tetani*. The etiologic agent is found in many soils, particularly cultivated soil rich in organic matter. Areas where the exposure risk is high are referred to as "telluric foci" of *C. tetani*.

The agent is commonly found in horse feces. It has also been found in other species, such as cattle, sheep, dogs, rats, and chickens; similarly, man may harbor *C. tetani* in the intestinal tract.

Transmission is effected through wounds. Scabs or crusts promote multiplication of the etiologic agent. Some cases are due to dog bites. Tetanospasmin is produced after the spores have germinated, i.e., by the vegetative form of the bacteria.

In Paraguay, of 2,337 cases studied from 1946 to 1972, the portal of entry was the umbilical stump in 31.7%, small wounds in 38.7%, wounds caused by removal of the chigoe flea *Tunga penetrans* in 7.7%, and the remainder followed induced abortions, surgical interventions, burns, and injections without proper asepsis (Vera Martínez *et al.*, 1976).

Role of Animals in the Epidemiology of the Disease: Tetanus is a disease common to man and animals, not a zoonosis. Some authors ascribe the role of reservoir to animals (McComb, 1980; Benenson, 1990), but it is more likely that the disease agent derives from the soil, and that it is present in the digestive tract of herbivores and omnivores only transitorily and does not multiply there (Wilson and Miles, 1975; Smith, 1975). Nevertheless, domesticated animals can disseminate

toxigenic strains of *C. tetani* by means of their feces, in cultivated as well as uncultivated areas.

Diagnosis: Prior existence of a wound and accompanying symptoms are the bases for diagnosis. Direct microscopic examination of wound material is useful. Given the urgency of diagnosis, the value of culturing *C. tetani* is doubtful. It is not always possible to isolate the etiologic agent from a wound.

Control: In man, given the soil origin of the infection, the only rational means of control is active immunization with toxoid. Children 2 to 3 months of age should receive three doses of the toxoid in the triple DPT vaccine (diphtheria, pertussis, tetanus) at intervals of one month to six weeks. They should then receive a booster, preferably administered 18 months after the last dose. An initial series of three doses induces protective titers of antitoxin for 5 to 13 years in 90% or more of those vaccinated. Booster shots ensure higher titers of the antitoxin and probably confer immunity throughout a woman's childbearing years (Halsey and de Quadros, 1983). Periodic boosters of tetanus toxoid every 10 years are recommended, particularly for population groups most at risk. The effectiveness of the toxoid was confirmed during World War II. US soldiers who were vaccinated with three doses of tetanus toxoid experienced one case of tetanus among 455,803 wounded, while in the unvaccinated Japanese army, the incidence was 10 cases per 100,000 wounded soldiers.

In developing countries, immunization is recommended for pregnant mothers to prevent tetanus mortality in newborns. The effectiveness of prenatal immunization with tetanus toxoid (anatoxin) has been demonstrated. Primary immunization consists of administering two doses, one at the start of pregnancy and another one month later, but not beyond three weeks before birth. If a pregnant woman has already been immunized, she only needs a booster and probably has enough antibodies to protect the children she bears over the next five years (Stanfield and Galazka, 1984).

Passive immunization with antitoxin should be reserved for persons with no previous active immunization who must undergo surgical operations, as well as for women after abortion or birth and for their newborn children in high-risk areas. The use of human antitoxin serum is preferable, but if unavailable, horse or bovine hyperimmune serum can be used after the patient is tested for a possible allergic reaction to the serum.

Wounds should be cleaned and debrided. Persons who have previously received basic toxoid treatment should be given a booster if the wound is small and more than 10 years have passed since the last dose. If the patient has a large, contaminated wound, a booster toxoid should be given if he was not vaccinated in the last five years. Persons who did not receive a full primary series of tetanus toxoid should receive a dose of toxoid and may require an injection of human tetanus immunoglobulin, if it is a major wound and/or is contaminated (Benenson, 1990).

Control procedures in animals are similar. Horses in particular should be vaccinated with toxoid; two doses given one to two months apart are sufficient. If the horse suffers from a potentially dangerous wound, another toxoid injection should be given. If the animal has not received toxoid previously, 2,000 to 3,000 IU of antitoxin should be given. At the same time, one dose of toxoid should be given and repeated one month later. The antitoxin confers passive immunity for approximately two weeks. Colts are given toxoid at 2 months of age and mares are given toxoid in

the last six weeks of pregnancy (Fraser *et al.*, 1991). Operations such as dehorning, castration, and tail docking should be done in the most aseptic conditions possible and antiseptics should be applied to surgical wounds.

Lambs in the first month of life can become passively immunized when the ewe is vaccinated with two doses of aluminum phosphate-adsorbed toxoid. The first injection should be administered eight weeks and the second, three or four weeks before the birth (Cameron, 1983).

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TICK-BORNE RELAPSING FEVER

ICD-10 A68.1

Synonyms: Endemic relapsing fever, spirochetosis, spirochetal fever, recurrent typhus, borreliosis.

Etiology: Spirochetes of the genus *Borrelia* (syn. *Spirillum*, *Spirochaeta*, *Spironema*). Given the close relationship of specificity between the tick species and the *Borrelia* strains it harbors, classification of the etiologic agent according to its vector has been proposed. Thus, the agent transmitted by *Ornithodoros hermsii* would be named *Borrelia hermsii*, the one found in *O. brasiliensis* would be *B. brasiliensis*, etc. Other borreliae derive their species name from their geographical region of origin. These include *B. hispanica*, transmitted by *O. erraticus*; *B. venezuelensi*, transmitted by *O. rudis*; and *B. caucasica,* transmitted by *O. verrucosus*.

However, not all researchers agree with this taxonomy. Some maintain that all the strains adapted to different *Ornithodoros* species are merely variants of a single species, *Borrelia recurrentis*, the agent of epidemic relapsing fever, transmitted by lice.

Borreliae are helical bacteria 3–20 microns long by 0.2–0.5 microns in diameter. They are gram-negative, have flagella between the external and internal membranes, are actively motile, and change direction frequently. Some species (*B. duttoni*, *B. parkeri*, *B. turicata*) grow in laboratory culture media (Kelly, 1984).

Geographic Distribution: Natural foci of *Borrelia* transmissible to man are found worldwide, with the exception of Australia, New Zealand, and Oceania.

Occurrence in Man: The incidence is low. Man contracts the infection only upon entering the natural foci where infected *Ornithodoros* are found. In some regions of Africa, the vector *O. moubata* has become established in dwellings, where it lives in dirt floors. In Latin America, *O. rudis* (*O. venezuelensis*) and *O. turicata* also have an affinity for dwellings.

In 1969, the number of cases in South America was 278, with one death. In 1976, 15 cases were reported in the US. Sporadic cases occur in the western US states, in

Canada (British Columbia), Mexico, Guatemala, Panama, Colombia, Venezuela, Ecuador, and Argentina.

Although endemic relapsing fever is usually sporadic, at times group outbreaks occur. In 1973, there was an outbreak with 62 cases (16 confirmed and 46 clinically diagnosed) among tourists at Grand Canyon National Park in Arizona (USA) who were lodged in rustic wooden cabins infested by rodents and their ticks. In 1976, an outbreak occurred under similar circumstances in California, with 6 cases among 11 tourists (Harwood and James, 1979).

A telephone and mail survey was conducted of 10,000 people who visited the Grand Canyon. The results showed that there were 14 cases of relapsing fever among the tourists, and that 7 of these had to be hospitalized. There was laboratory confirmation of 4 cases and clinical diagnosis of 10 cases. Rodent nests were found beneath the ceilings and underneath the floors of the cabins where the tourists were lodged. These nests may have sheltered the vectors of the infection, as frequently happens with *Ornithodoros* (CDC, 1991).

Occurrence in Animals: In natural foci, many wild animal species are infected, among them rodents, armadillos, opossums, weasels, tree squirrels, and bats.

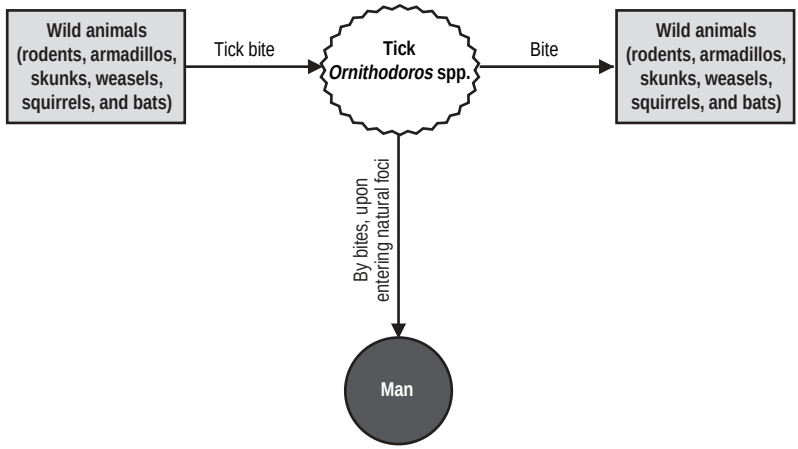
The Disease in Man: Epidemic relapsing fever (transmitted by lice) and endemic relapsing fever (transmitted by ticks) have similar clinical pictures. The average incubation period is 7 days after the tick bite, but may vary from 4 to 18 days. The disease is characterized by an initial pyrexia that lasts three to four days and begins and disappears suddenly. The fever, which may reach 41°C, is accompanied by chills, profuse sweating, vertigo, cephalalgia, myalgia, and vomiting. At times, erythemas, petechiae, epistaxis, and jaundice of varying degrees of severity may be observed. After several days without fever, the attacks of fever recur several times, lasting longer than in the first episode. The primary characteristic of the disease is the syndrome of periodic fevers. There are generally three to seven relapses of fever, with intervals of four to seven days (Barbour, 1990). Periodic recurrences are attributed to antigenic changes or mutations in the borreliae, against which the patient cannot develop immunity. Borreliae in the first attack are antigenically different from those isolated in relapses and there is no protective immunity among these serotypes. The variable antigens are proteins on the outer membrane and their variation is the result of a new DNA arrangement (Barbour, 1990).

Treatment is based on tetracyclines. Complications consist of meningitis and some other neurological disorders, but these occur in a small percentage of patients. Endemic fever is fatal in 2% to 5% of cases.

The Disease in Animals: Little is known about the natural course of the infection and its possible clinical manifestations in wild animals. As with many other reservoirs of infectious agents in natural foci, the hosts and borreliae are probably well adapted to each other, and the latter likely have little or no pathogenic effect on their hosts.

Borreliosis (spirochetosis) of fowl is a serious disease in geese, ducks, and chickens. It is caused by *B. anserina* and transmitted by *Argus persicus* and *A. miniatus*. The bovine infection in South Africa produced by *B. theileri* and transmitted by *Margaropus decoloratus* and *Rhipicephalus evertsi* causes a benign disease. These borrelioses affect only animals and are not transmitted to man.

Figure 18. Tick-borne relapsing fever (*Ornithodoros* spp.). Mode of transmission.



Source of Infection and Mode of Transmission (Figure 18): The borreliae that cause endemic relapsing fever have as their reservoir wild animals and ticks of the genus *Ornithodoros*; in addition, the latter are vectors of the infection. These ticks are xerophilic argasids that are long-lived and very resistant to dessication and long periods of fasting in environments with low humidity and high temperatures. Borreliae survive in the ticks for a long time. Depending on the species of *Ornithodoros*, transovarial transmission may vary from less than 1% to 100%. In the Western Hemisphere, the most important vectors of *Borrelia* are *O. hermsii*, *O. turicata*, *O. rudis*, and possibly *O. talaje*. The continuous circulation of borreliae in nature is ensured by the ticks' characteristics and their feeding on infected wild animals. *O. hermsii* lives at altitudes of over 1,000 meters, feeds on the blood of squirrels, and can be found in rodent burrows and wooden huts. *O. turicata* attacks sheep and goats, as well as other animals, and infests hides, rodent and snake burrows, and pigsties.

Transmission to humans is caused by a bite from an infected tick.

Role of Animals in the Epidemiology of the Disease: Several species of wild animals constitute the reservoir of the etiologic agent. The relative importance of ticks and wild animals as reservoirs is the subject of debate, but both undoubtedly play important roles in maintaining the infection in nature. An exception is infection by *B. duttoni* in Africa, which has not been found in animals and is transmitted directly to man by the tick *O. moubata*.

Diagnosis: Diagnosis is based on demonstrating the presence of the etiologic agent in the patient's blood during the febrile phase by dark-field microscopy using fresh smears or films stained by Giemsa or Wright techniques, or by inoculation in mice. The number of borreliae diminishes or disappears at the end of a fever attack;

thus, intraperitoneal inoculation of young mice and examination of their blood 24 to 72 hours after inoculation is advisable.

Control: Control measures are difficult to apply and are impractical, since cases in the Western Hemisphere are rare and usually widely dispersed. The principal recommendation is to avoid being bitten by ticks living in caves, burrows of rodents and other animals, or primitive huts.

Human dwellings should be built to keep out the hosts (rodents or others) of *Ornithodoros*. In addition, the storage of wood inside or near buildings should be avoided. People entering natural foci should examine themselves for ticks periodically, in addition to using protective footwear and clothing. Repellents provide partial protection; dimethyl phthalate is the most highly recommended.

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TULAREMIA

ICD-10 A21.0 ulceroglandular tularaemia; A21.1 oculoglandular tularaemia; A21.2 pulmonary tularaemia; A21.7 generaliz ed tularaemia; A21.8 other forms of tularaemia

Synonyms: Francis' disease, deer-fly fever, rabbit fever, Ohara's disease.

Etiology: *Francisella tularensis*, a highly pleomorphic, gram-positive, nonmotile bacillus; it has a fine capsule and can survive for several months in water, mud, and decomposing cadavers.

Two biovars are recognized: *F. tularensis* biovar *tularensis* (Jellison type A) and *F. tularensis* biovar *palaearctica* (Jellison type B). Names have also been suggested for some local biovars, such as *mediaasiatica* (Olsufjev and Meshcheryakova, 1982) and *japonica*. Classification into biovars is not based on antigenic differences, but on the agent's biochemical, virulence, and ecologic characteristics, and its nosography.

Geographic Distribution: Natural foci of infection are found in the Northern Hemisphere. In the Americas, the disease has been confirmed in Canada, the US, and Mexico. It is found in most European countries, Tunisia, Turkey, Israel, Iran, China, and Japan. In the former Soviet Union, there are extensive areas with natural foci.

F. tularensis biovar *tularensis* predominates in North America and causes 70% to 90% of human cases in that part of the world. The principal sources of infection by this biovar are lagomorphs (mainly those of the genus *Sylvilagus)* and ticks. Biovar *palaearctica* (syn. *holarctica*) causes 10% to 30% of human cases; its principal hosts are rodents. Biovar *tularensis* is more virulent than biovar *palaearctica* (Bell and Reilly, 1981).

Biovar *palaearctica* is found in western and northern Europe, Siberia, the Far East, in some parts of central Europe, and less frequently, in North America. Biovar *palaearctica* is distributed in natural foci among *Rodentia* spp. and *Lagomorpha* spp. In the Asian part of the former Soviet Union, where there are natural foci among *Lepus* and *Gerbilinae*, the name *F. tularensis* var. *mediaasiatica* has been suggested for the etiologic agent. This biovar, like *palaearctica*, is moderately virulent. Genetic studies have shown that the *mediaasiatica* and *japonica* varieties hybridize with *F. tularensis* var. *tularensis*, indicating the possibility of genetically related strains outside of North America. The strains of Central Asia differ from the two main biovars in their glucose fermentation properties (Sandström *et al.*, 1992).

Occurrence in Man: It is not an internationally reportable disease and its global incidence is hard to establish. The countries with the best data are the US and the former Soviet Union. In both, the number of human cases has apparently declined sharply. In the former Soviet Union, where in the 1940s some 100,000 cases were reported annually, the incidence has diminished to a few hundred cases per year. In the US, the average number of annual cases fell from 1,184 in the 1940s to some 274 cases between 1960 and 1969 and has continued to fall.

In the period 1977–1986, the average number of cases per year was 225. Many mild cases are not reported (Rohrbach, 1988). Current incidence is approximately

0.6 to 1.3 per million inhabitants (Boyce, 1990). The reduced incidence is attributed to, among other factors, limited demand for beaver (*Castor canadensis*) and muskrat (*Ondatra zibethicus*) skins and the resulting decline in hunting for these animals. In the US, 50% or more of the cases appear in a few states, such as Arkansas, Missouri, Oklahoma, Tennessee, and Texas. Although sporadic cases have occurred in all states except Hawaii, their numbers have fallen.

In areas where transmission is effected primarily by arthropods, incidence peaks in spring and summer. In contrast, in areas where cases of infection transmitted by wild rabbits predominate, the peaks occur in winter (Boyce, 1990), during the hunting season.

Epidemiological data on 1,026 human cases in the midwestern US states indicated that 63% involved an attached tick and 23% exposure to wild rabbits or other animals, such as squirrels, cats, and raccoons (Taylor *et al.*, 1991). In Canada, there were 31 cases between 1975 and 1979 (Akerman and Embil, 1982).

Occurrence in Animals: The disease affects a large number of vertebrates (more than 100 species of wild and domestic animals) and invertebrates (more than 100 species). Natural infection has been found in ticks, mosquitoes, horseflies, fleas, and lice that parasitize lagomorphs and rodents.

Epizootic outbreaks have been described in sheep, commercially bred furbearers (mink, beaver, and fox), and wild rodents and lagomorphs.

In Sweden, epizootics occur in hares (*Lepus timidus*), the principal source of human infection caused by *F. tularensis* biovar *palaearctica*. Between 1973 and 1985, 1,500 samples were submitted to the National Veterinary Institute in Uppsala, divided nearly equally into *Lepus europeus* and *L. timidus*. Tularemia was diagnosed by immunofluorescence in 109 samples of *L. timidus*, but in none of the *L. europeus* samples. The rate of animals infected varied by year; the highest rates occurred in autumn (Mörner *et al.*, 1988).

Few serological surveys have been conducted in domestic animals (Rohrbach, 1988). In endemic areas of Georgia and Florida, titers of ≥ 1/80 were found in 2 (6.2%) of 32 stray cats. As a result of an outbreak of 12 human cases of tularemia on the Crow Indian reservation in southern Montana (USA), 90 dogs were tested serologically. Of these, 56 had agglutination titers of ≥ 1/40, whereas in a nearby town, only 6 of 34 yielded similar titers (Schmid *et al.*, 1983).

A study conducted in western Georgia and northwestern Florida (USA) used the serum agglutination test on 2,004 mammals of 13 species; 344 animals of 10 species were positive with titers of ≥ 1/80 (McKeever *et al.*, 1958).

The Disease in Man: It is seen most commonly as sporadic cases, but epidemic outbreaks have occurred in the US and the former Soviet Union.

The incubation period usually lasts from three to five days, but may range from one to ten days. Several clinical forms of the disease are known; they are determined principally by the agent's route of entry. In all its forms, the disease is of sudden onset, with rising and falling fever, chills, asthenia, joint and muscle pain, cephalalgia, and vomiting. The most common clinical form is ulceroglandular, which represents 85% of all cases in the Western Hemisphere. A local lesion is seen at the site of entry (an arthropod bite, or a scratch or cut inflicted by contaminated nails or knife), which progresses to a necrotic ulceration accompanied by swelling of the nearby lymph node. The node frequently suppurates, ulcerates, and becomes scle-

rotic. In untreated cases, the disease course lasts three to five weeks and convalescence takes several weeks or months, with intermittent bouts of fever. A variety of this form is the glandular, in which there is no primary lesion; this is the most prevalent type in Japan. The oculoglandular form develops when contaminated material comes into contact with the conjunctiva. The primary lesion localizes on the lower eyelid and consists of an ulcerated papule; at the same time, the regional lymph nodes swell. The primary pulmonary form, caused by aerosols, affects rural and laboratory workers, and produces pneumonia in one or both lungs. The typhoidal form is rare; it is caused by ingestion of contaminated foods (usually infected wild rabbit meat) or water. It is a systemic disease that has very varied symptoms and is difficult to diagnose. It is sometimes expressed as gastroenteritis, fever, and toxemia. Pneumonia is frequent in typhoidal tularemia. If not treated early, the course of this clinical form may be short and fatal. Mortality in the pulmonary forms is high. Prior to the existence of antibiotics, mortality for all cases of tularemia in the US was close to 7%. Mortality outside of the Americas has rarely exceeded 1%. This difference is attributed to the greater virulence of the tick-transmitted strains of *F. tularensis* (biovar *tularensis*) in the US. In the former Soviet Union, untreated cutaneous infections (ulceroglandular form) are fatal for less than 0.5% of patients (biovar *palaearctica*).

The results of serologic and skin sensitivity tests carried out among exposed groups show that inapparent infections are common.

Streptomycin is the preferred antibiotic for all forms of tularemia. Recommended treatment is 15 to 20 mg/kg/day of streptomycin via intramuscular administration, divided into various doses over 7 to 14 days (Boyce, 1990). Laboratory tests with Scandinavian strains of *F. tularensis* biovar *palaearctica* obtained the lowest minimal inhibitory concentration with quinolones, as compared to other antibiotics. This result should be taken into account in clinical assays. In the Scandinavian countries, where most tularemia patients are ambulatory, quinolones have the additional advantage that they can be administered orally (Scheel *et al.*, 1993).

The Disease in Animals: In has been demonstrated experimentally that susceptibility to *F. tularensis* varies in different species of wild animals. Three groups have been established based on the infecting dose and the lethal dose. Group 1, the most susceptible, contains most species of rodents and lagomorphs, which generally suffer a fatal septicemic disease. Group 2 is composed of other species of rodents and birds, which though highly susceptible to the infection, rarely die from it. Group 3 consists of carnivores, which require high doses to become infected, rarely develop bacteremia, and only occasionally manifest overt disease.

Group 1 animals are an important source of infection for arthropods, other animals, man, and the environment. The clinical picture of the natural disease in these animals is not well known, since they are usually found dead or dying. Experimentally inoculated hares show weakness, fever, ulcers, abscesses at the inoculation site, and swelling of the regional lymph nodes. Death ensues in 8 to 14 days. The lesions resemble those of plague and pseudotuberculosis, with caseous lymph nodes and grayish white foci in the spleen.

High-mortality outbreaks have occurred in sheep in enzootic areas in Canada, the US, and the former Soviet Union. In addition to causing economic losses, tularemia in sheep is a source of infection for man. In the US, the infection is transmitted by

the tick *Dermacentor andersoni*, which during outbreaks is found in great numbers at the base of the sheep's ears and on the neck. Sick animals separate themselves from the flock and manifest fever, rigid gait, diarrhea, frequent urination, and respiratory difficulty. Most deaths occur among young animals. Pregnant ewes may abort. Reactions to serologic tests indicate that many animals have an inapparent infection. Sheep can be classified in group 2 based on their susceptibility to the infection. Autopsy reveals infarcts of the regional lymph nodes, mainly those of the head and neck, as well as pneumonic foci. In this species, tularemia is a seasonal disease, coinciding with tick infestations.

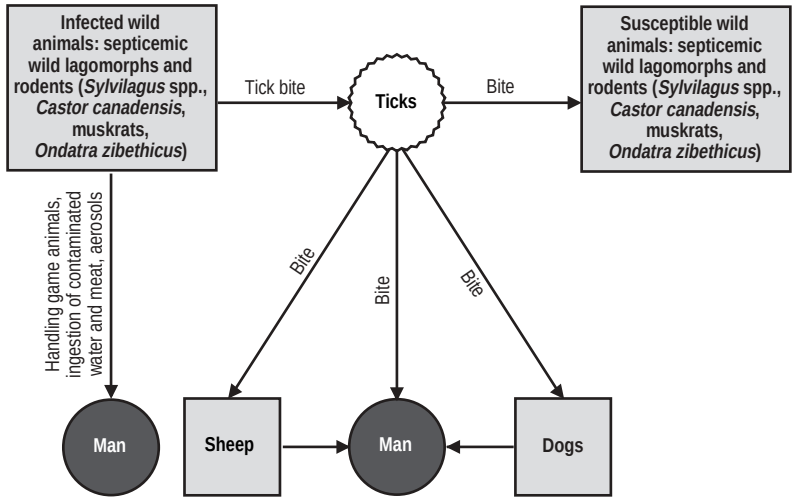
The disease has been confirmed on occasion in horses, with symptoms that include lack of coordination, fever, and depression. The animals were parasitized by a large number of ticks. Infected young swine can manifest fever, dyspnea, and depression. Cattle seem to be resistant (Rohrbach, 1988).

Cats can become infected and fall ill when hunting rodents in endemic areas or by consuming dead lagomorphs. Cats can, in turn, transmit the infection to man. In a case that occurred in Georgia (USA), a young man who contracted ulceroglandular tularemia had three Siamese cats that had fallen ill two weeks earlier. The cats had fever, anorexia, and apathy; the veterinarian prescribed streptomycin and penicillin. The animals were cared for by their owner, who developed a necrotic ulcerous lesion that started with a wound on his finger, although he did not recall having been scratched or bitten. The three cats died despite treatment. On autopsy, necrotic foci were found in the liver and spleen that contained coccobacilli positive for *F. tularensis* with immunofluorescence.

Another case was described in New Mexico (USA). The patient found his cat under the bed eating a dead wild rabbit. He tried to remove the cat and was bitten; four days later he fell ill with tularemia. The cat fell ill one day earlier, with apathy, anorexia, and fever, but no other symptoms. The veterinarian did not prescribe any treatment and the animal was found to be healthy when examined a week later. Serum agglutination yielded a titer of 1/160. The owner also recovered, after being treated with streptomycin (CDC, 1982). In Oklahoma (USA), a state considered endemic, a case of acute tularemia in three cats was diagnosed clinically and then confirmed by culture and immunofluorescence. The three animals showed signs of depression, lethargy, ulcerated tongue and palate, moderate lymphadenomegaly, hepatosplenomegaly, and panleukopenia, with a severe toxic change in the neutrophils. Upon necropsy, multiple necrotic foci were found in the lymph nodes, liver, and spleen, as well as severe enterocolitis. The diagnosis was confirmed by immunofluorescence and culture (Baldwin *et al.*, 1991). Although tularemia is rare in cats, it should be kept in mind in enzootic areas. Since 1928, only 51 human cases have been described that involve exposure to infected cats (Capellan and Fong, 1993).

Source of Infection and Mode of Transmission (Figure 19): In natural foci, the infection circulates among wild vertebrates, independently of man and domestic animals. Ticks are biological vectors of *F. tularensis*; not only do they transmit the etiologic agent from donor animals to other animals, they also constitute an important interepizootic reservoir. They are also responsible for transtadial and transovarial transmission of the bacteria. Each enzootic region has one or more species of vertebrate animals and of ticks that play the primary roles of transmitting and maintain-

Figure 19. Tularemia. Mode of transmission in the Americas.



ing the infection in nature. It is a matter of debate whether very susceptible lagomorphs and rodents (group 1) are true reservoirs or only amplifiers and the main source of infection for man. Less susceptible animals (group 2), together with ticks, are thought to be important reservoirs.

Domestic animals, such as sheep and cats, are accidental hosts, but they may also constitute sources of infection for man.

Humans contract the infection upon entering the natural foci of tularemia. The sources of infection and modes of transmission of the causal agent are many. In North America, the animals that most frequently serve as the source of infection for man are wild rabbits (*Sylvilagus* spp.), hares (*Lepus californicus*), beavers (*Castor canadensis*), muskrats (*Ondatra zibethicus*), meadow voles (*Microtus* spp.), and sheep. The biovar *tularensis* is generally transmitted by wild rabbits or by their ticks (*Dermacentor variabilis*, *D. andersoni*, *Amblyomma americanum*). The biovar *palaearctica* is more common among rodents, particularly aquatic rodents, but also in some species of lagomorphs, such as *Lepus europaeus* and *L. variabilis*. Tularemia in Sweden is transmitted from *L. variabilis* by means of mosquitoes. The European hare plays no role in Sweden, but it does in other European countries. Rodents such as beavers and muskrats are important in aquatic cycles. In different ecological areas, other ticks (e.g., *Ixodes* spp., *Haemophysalis* spp.) and arthropods are also involved. In many enzootic areas, the principal route of penetration is through the skin (by means of hematophagous arthropods, scratches, or knife cuts). Another portal of entry is the conjunctiva, which can be contaminated by materials splashed into the eyes or, in the case of hunters or sheep shearers, by hands soiled from handling sick animals. Infection via the oral route occurs as a result of ingesting water contaminated by dead animals or the urine and feces of infected animals, or by eating undercooked meat of lagomorphs or other infected animals. In addition,

the disease can be contracted through the respiratory system by inhaling aerosols contaminated in the laboratory or dust from fodder, grain, or wool contaminated with rodent excreta.

Some cases of human infection by cat scratches or bites have been described. It is assumed that these animals had recently hunted and captured sick rodents or had eaten dead lagomorphs. Another case occurred in a person exposed to a cat with an ulcer (CDC, 1982). The disease was also contracted by a Canadian zoo veterinarian who was bitten on the finger when treating a sick primate (*Sanguinus nigricollis*). In this zoo, four primates in adjacent cages died from tularemia, possibly transmitted by fleas from squirrels that often came near the cages. *F. tularensis* was isolated from one of the squirrels. The primate responsible for infecting the veterinarian had sialorrhea, ocular and nasal discharges, and ulcers on the tongue (Nayar *et al.*, 1979).

The highest incidence of cases occurs in the summer, when ticks are most active. Hunters are an especially vulnerable group, and the number of human cases increases in hunting season.

Role of Animals in the Epidemiology of the Disease: Human-to-human transmission has not been confirmed. Tularemia is a zoonosis that is transmitted to man (an accidental host) through contact with wild or domestic animals (of the latter, usually sheep), by a contaminated environment, or by such vectors as ticks, horseflies, and mosquitoes.

Diagnosis: In man, clinical diagnosis is based on the symptomatology and prior contact with a likely source of infection. Laboratory confirmation is based on: (a) isolation of the etiologic agent from the patient's local lesion, lymph nodes, and sputum by means of direct culture or inoculation into laboratory animals; (b) the immunofluorescence test on exudates, sputum, and other contaminated materials; (c) the skin test with bacterial allergen, which gives delayed hypersensitivity reactions (these reagents can give a diagnosis during the first week of illness); and (d) serologic tests, such as tube agglutination or microagglutination (Snyder, 1980; Sato *et al.*, 1990). An enzyme-linked immunosorbent assay with sonicated antigen has been perfected (Viljanen *et al.*, 1983). This test has the advantage of permitting an early diagnosis, which is important for treatment; it can also detect IgM, IgA, or IgG antibodies. However, the microagglutination test is used more often due to its simplicity and reliability; other tests are used only in case of doubt (Syrjälä *et al.*, 1986). In the agglutination test, a four-fold increase in titer is significant. Antibodies appear in the second week of illness and may persist for years. Cross agglutination with *Brucella* antigen can occur, but at a lower level than with the homologous antigen. Absorption of the patient's serum with *Brucella* antigen removes all doubt.

In sheep, laboratory confirmation is obtained by isolating the causal agent or by serologic tests.

Due to the risk to laboratory personnel, methods to isolate the causal agent should only be used at reference laboratories that have the required safety measures.

Control: To prevent the disease in man, general and individual protective measures may be taken. General measures include reducing the source of infection, controlling vectors, changing the environment, and educating the public. Except for the last one, these control measures are costly and difficult to apply. In the former Soviet

Union, where tularemia was an important health problem, anti-tularemia institutes have been established in epizootic regions to carry out these control activities.

An important protective measure consists of immunizing at-risk individuals, populations, or occupational groups with attenuated live vaccines. In the former Soviet Union, the drastic reduction achieved in human morbidity is attributed to this single activity. In the US, there is an attenuated vaccine for high-risk groups (Burke, 1977) that has proven effective in reducing the incidence of the typhoidal form and attenuating the ulceroglandular form (Rohrbach, 1988). Other protective measures consist of using insect repellents and protective clothing to avoid tick infestation and bites of other arthropods, promptly removing ticks from the body, using gloves to handle and skin wild animals, avoiding consumption of untreated water in areas where contamination by *F. tularensis* is suspected, and thoroughly cooking wild animal meat in enzootic areas.

Controlling the infection in sheep involves applying tickicides by spray or dip, and administering antibiotics (streptomycin, tetracyclines) in case of an outbreak.

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ZOONOTIC TUBERCULOSIS

ICD-10 A16 respiratory tuberculosis, not confirmed bacteriologically or histologically; A18 tuberculosis of other organs

Etiology: The etiologic agents of mammalian tuberculosis are *Mycobacterium tuberculosis*, the main cause of human tuberculosis; *M. bovis*, the agent of bovine tuberculosis; and *M. africanum*, which causes human tuberculosis in tropical Africa. This last species has characteristics halfway between those of *M. tuberculosis* and *M. bovis*. *M. microti*, which causes tuberculosis in rodents, should be added to these agents, although it is not of zoonotic interest (nontuberculous mycobacteria are presented in the chapter, "Diseases Caused by Nontuberculous Mycobacteria").

The principal agent of zoonotic tuberculosis is *M. bovis*; the agent in man and other primates is *M. tuberculosis*, which is the type species of the genus.

Tuberculous mycobacteria are alcohol- and acid-resistant, nonsporogenic, gram-positive bacilli. These mycobacteria are resistant to many disinfectants, desiccation, and other adverse environmental factors because the cell wall has a high lipid content.

Phage typing is being used in epidemiological research on *M. tuberculosis*, and the API ZIM system divides the genus into seven biovars (Casal and Linares, 1985; Humble *et al.*, 1977). The use of phage typing was not widespread and the method practically fell into disuse. It has been replaced by DNA hybridization.

Analysis of DNA fragments obtained through the digestive action of one or more restriction endonucleases is useful for identifying strains of both *M. tuberculosis* and *M. bovis* (Collins and De Lisle, 1985; Shoemaker *et al.*, 1986).

Many authors prefer to refer to a single species (*M. tuberculosis*) and human and bovine types.

Geographic Distribution: The distribution of *M. bovis* and *M. tuberculosis* is worldwide. *M. africanum* is prevalent in Africa, but it has also been isolated in Germany and England. *M. africanum* strains phenotypically related to *M. tuberculosis* are nitrase positive and are found in western Africa; those that are similar to *M. bovis* are nitrase negative and are isolated more frequently in eastern Africa (Grange and Yates, 1989).

Occurrence in Man: The prevalence of human tuberculosis of animal origin has diminished greatly in countries where mandatory pasteurization of milk has been implemented and where successful campaigns to control and eradicate the bovine infection have been carried out. The British Isles, where the incidence of human infection due to *M. bovis* is currently low and is limited to the elderly, were once the most affected area due to the consumption of raw milk. However, despite the great reduction in rates of human infection by bovine strains in Great Britain, tuberculosis originated by these strains continues to occur. From 1977 to 1979 in southeast England, isolations from 5,021 tuberculosis patients revealed 63 patients (1.25%) infected with "classic bovine strains" (*M. bovis*), 53 of which were Europeans and 10, immigrants. Of these cases, 27 (42.85%) had pulmonary tuberculosis and 36 (57.14%) had extrapulmonary tuberculosis. There was a marked difference in the frequency of renal tuberculosis caused by *M. bovis* (23.8%) and *M. tuberculosis*

(8.2%). Commenting on these results, Collins *et al.* (1981) suggested the possibility of human-to-human transmission, given that bovine tuberculosis had practically disappeared from Great Britain, that milk is pasteurized, and that some cases occurred in young people. Also in southeast England, human cases caused by *M. bovis* continued to occur nearly 30 years after the program to eradicate bovine tuberculosis ended in 1960. From 1977 to 1987, there were 201 new confirmed human cases caused by *M. bovis*, or 1.20% of all isolations of tuberculous mycobacteria (Yates and Grange, 1988). Most cases occurred in the elderly, who may have acquired the infection when it was still prevalent in cattle (in 1935, before the start of the eradication program, 40% of cattle were positive to tuberculin). The pulmonary and genitourinary forms are currently the most common forms in humans infected by *M. bovis* (Yates and Grange, 1988). In Slovakia, 52 human cases caused by the bovine bacillus were recorded during the period 1979–1983, 10 to 15 years after the eradication of bovine tuberculosis. The average age of the patients was 61. Of these, 88% suffered from pulmonary tuberculosis; 17% of these were relapses and 71% were new cases (Burjanova and Nagyova, 1985). In the Czech Republic, 47 patients infected by *M. bovis* were reported during the period 1981–1983 (Kubin *et al.*, 1985). In Germany during the period 1953–1957, when the prevalence of tuberculosis in cattle was still high, 45% of tuberculous adenitis cases in children were caused by *M. bovis*. Later, as prevalence declined in cattle, this form of tuberculosis as well as cutaneous tuberculosis declined notably. In the US at the beginning of the 20th century, up to 20% of human tuberculosis was attributed to *M. bovis*; in 1980, barely 0.1% of human tuberculosis was so attributed (Good and Snider, 1980). In the Netherlands, where bovine tuberculosis had been eradicated, 125 people were infected by *M. bovis* from 1972 to 1975 (Schonfeld, 1982). More than 80% of these patients were born when transmission of *M. bovis* via milk was still possible. The five patients younger than 20 years, who were born after the bovine infection was eradicated, were presumed to have contracted the infection outside the Netherlands. Interhuman transmission is still a matter of controversy, but it is undeniable that eradication campaigns against bovine tuberculosis have drastically reduced the incidence of human cases of this origin. For example, in Great Britain in 1945, 5% of all fatal tuberculosis cases and 30% of cases of the disease in children under 5 years old were due to bovine strains (Collins and Grange, 1983).

In countries where milk is routinely boiled, as in Latin America, the incidence of infection by *M. bovis* has always been low. Nevertheless, pulmonary and extrapulmonary forms of human tuberculosis of animal origin continue to be a problem in areas where the prevalence of infection in cattle is high, because not all milk consumed is boiled, many products are prepared from unpasteurized milk, and cases of infection are contracted via aerosols. In Peru, a study of 853 strains of pulmonary tuberculosis identified 38 (4.45%) as *M. bovis* (Fernández Salazar *et al.*, 1983). Several laboratories in Argentina studied a total of 7,195 strains, primarily between 1978 and 1981. Most of the strains were isolated from adult pulmonary tuberculosis patients, and 82 (1.1%) were classified as *M. bovis* (Argentina, Comisión Nacional de Zoonosis, 1982).

Occurrence in Animals: In industrialized countries, bovine tuberculosis has been eradicated or is in an advanced stage of control, while in several developing countries the situation has not improved or prevalence is increasing. Almost all Western

European countries report a prevalence of bovine infection lower than 0.1%. In the Western Hemisphere, Canada and the US have reduced the infection rate to very low levels. In the US in 1969, 0.06% of 4.5 million cattle examined reacted to tuberculin (most of the reactors showed no evident lesions when slaughtered). In 1989, 33.5 million cattle were slaughtered in the US (excluding reactors to tuberculin), of which only 143 had tuberculous lesions (0.0004%). In Latin America, Costa Rica, Cuba, Jamaica, Panama, Uruguay, and Venezuela have national control programs. Cuba is already in the post-eradication surveillance phase. The rate of infection is very low in several Central American and Caribbean countries. The highest infection rates are found in the milk-producing regions near large cities in South America. In South American countries in which hogs are fed unpasteurized milk products, the infection rate in swine is similar to or higher than in cattle, judging by records of confiscations at slaughterhouses. However, it should be kept in mind that these figures include a large percentage of lesions caused by nontuberculous mycobacteria (see the chapter, "Diseases Caused by Nontuberculous Mycobacteria").

Bovine tuberculosis is important not only because it is a source of human infection, but also because of the economic losses it causes.

Mycobacterium africanum, isolated for the first time from a human patient in Senegal and described in 1969 (Castets *et al.*, 1969), is capable of infecting nonhuman primates and causing pulmonary, lymph node, and renal lesions. Thorel (1980) isolated these strains from chimpanzees and from a *Cercopithexus* monkey of African origin that were found in experimental stations in Europe. These animals had probably contracted the infection from man. There is a potential danger of retransmission to those who work with them. There is also a report on bovine infection in Malawi caused by *M. africanum* (Berggren, 1981), but it fails to provide details on typing (Pritchard, 1988).

Man can transmit *M. tuberculosis* to monkeys, dogs, cats, and psittacine birds (see the section on the disease in animals).

The Disease in Man: *M. bovis* can cause the same clinical forms and pathologic lesions as *M. tuberculosis* (the agent of human tuberculosis). Historically, the most prevalent forms caused by *M. bovis* were extrapulmonary, and children were among those most affected. The reason for extrapulmonary localization of the bovine bacillus is not that it has an affinity for other tissues, but that it is most commonly transmitted by consumption of raw milk or raw milk products. Thus, in those countries where the prevalence of bovine tuberculosis was high and raw milk was consumed, many cases of extrapulmonary tuberculosis, such as cervical adenitis, genitourinary infections, tuberculosis of the bones and joints, and meningitis, were caused by *M. bovis*. According to data on typing of tuberculosis bacilli in the British Isles prior to control of bovine infection, 50% or more of cervical adenitis cases were caused by *M. bovis*. Pulmonary tuberculosis caused by the bovine bacillus occurs less frequently, but its incidence is significant in occupational groups in contact with infected cattle or their carcasses, particularly in countries where animals are stabled. This form cannot be distinguished clinically or radiologically from the disease caused by *M. tuberculosis*. Transmission occurs by aerosol droplets micromillimeters in diameter. In countries where the incidence of the human infection caused by *M. tuberculosis* has declined and the bovine infection has not been controlled, it is believed that *M. bovis* could assume a principal role in human pulmonary tubercu-

losis. Although Denmark was declared free of bovine tuberculosis in 1952, 127 cases of human infection caused by *M. bovis*, 58% of which were pulmonary tuberculosis, were detected between 1959 and 1963 in middle-aged and elderly persons.

In countries where the control of bovine tuberculosis is advanced, human cases caused by *M. bovis* are observed mainly in the elderly, who were exposed to the pathogenic agent in their youth or childhood.

Reduction or elimination of *M. bovis* in cattle and compulsory pasteurization of milk have helped reduce the incidence of infection in man. At the same time, the clinical picture of human infection caused by the bovine agent has changed. Currently, pulmonary tuberculosis predominates, followed by urogenital tuberculosis.

Interhuman transmission of *M. bovis* is possible, but few cases have been satisfactorily confirmed. As is the case with most zoonoses, man is generally an accidental host of *M. bovis* and human infection depends on the animal source. Since *M. tuberculosis* and *M. bovis* are very similar in their pathogenic effect on man, it is not understood why large-scale interhuman transmission of the bovine infection does not occur. A possible explanation is that pulmonary patients infected by *M. bovis* shed fewer bacteria in their sputum than do those infected by *M. tuberculosis* (Griffith, 1937).

Inhabitants of Latin America have been assumed to be protected from infection by the bovine bacillus because of the widespread custom of boiling milk. Undoubtedly, if this practice were not followed, the rate of human infection by *M. bovis* would be much higher there, considering the infection's wide distribution and the rate of infection in dairy cattle in many Latin American countries. However, some people in rural areas do drink raw milk and frequently consume products (cream, butter, soft cheese) made at home from raw milk. In Latin America and other parts of the world, children are the main victims, as indicated by typing data from Brazil, Peru, and Mexico. These data also confirm that some children are fed milk or milk products that are not heat-treated.

Although it is not customary to stable cattle in Latin America, cases of pulmonary tuberculosis caused by *M. bovis* have been recorded, with rural laborers and employees of abattoirs and locker plants being the most exposed groups. In Argentina, the bovine bacillus was isolated from 8% of 85 pulmonary patients from rural areas, while only 1 case due to *M. bovis* was found among 55 patients in the capital.

People suffering from pulmonary tuberculosis of bovine origin can, in turn, retransmit the infection to cattle. This occurrence is particularly evident in herds from which tuberculosis has been eradicated and which later become reinfected, the source of exposure often being a ranch hand with *M. bovis* tuberculosis. Such episodes have occurred in the US and in several European countries. Between 1943 and 1952, 128 herds containing more than 1,000 head of cattle were reinfected in Denmark by 107 individuals with tuberculosis. Similar occurrences continued in Denmark until 1960, despite advances made in the eradication of bovine tuberculosis. Huitema (1969) reports on 50 herds that were infected by people with tuberculosis caused by *M. bovis*; 24 of the patients suffered from renal tuberculosis. It is possible that this phenomenon (retransmission of the infection from man to cattle) also occurs in the Southern Hemisphere, but goes unnoticed due to high rates of tuberculosis in cattle.

In regions where bovine tuberculosis has been eradicated, cattle cease to be a source for human infection, but man may continue to be a potential source of infection for cattle for years.

Persons with pulmonary or genitourinary tuberculosis due to the human type species (*M. tuberculosis*) can temporarily infect and sensitize cattle. Cattle are very resistant to *M. tuberculosis*; the agent does not cause a progressive tuberculosis in these animals, but the bacillus can survive for some time in their tissues, especially the lymph nodes, sensitizing the animal to mammalian tuberculin and confusing the diagnosis. Sensitization can persist for some six to eight months after the human source of infection is removed. Elimination of *M. tuberculosis* in milk has occasionally been confirmed, but tuberculous lesions of the udder were not present. Man can transmit the human bacillus to several other animals, principally monkeys and dogs, in which it produces a progressive tuberculosis.

In many countries, direct or indirect exposure of man to bovine tuberculosis is an important source of sensitization to tuberculin. In Denmark, a relationship was found between the prevalence of bovine tuberculosis and the rate of reactors to tuberculin in the human population. In the same country, statistical data indicate that a third of the population between the ages of 30 and 35 owes its tuberculin sensitization to infection by *M. bovis*. The same study suggests that the risk of developing pulmonary tuberculosis later is much smaller among those sensitized by the bovine bacillus than by the human bacillus, perhaps because *M. bovis* infection is contracted mainly through the digestive tract and not via aerosols. Another interesting conclusion is that less calcification occurs in pulmonary tuberculosis resulting from *M. bovis* than from *M. tuberculosis.*

The treatment for humans infected by *M. bovis* is the same as for those infected by *M. tuberculosis* (isoniazid, rifampicin, ethambutol), except that pyrazinamide should be excluded, as it is not active against the bovine bacillus.

The Disease in Animals: Many mammalian species are susceptible to the agents of tuberculosis. Bovine tuberculosis is the most important form in economic terms and as a zoonosis. Tuberculosis in swine also causes substantial economic losses.

CATTLE: The principal etiologic agent for cattle is *M. bovis*. As in man, the bacillus enters the body mainly by inhalation. The intestinal tract is an important route of infection in calves nursed on contaminated milk. The most common clinical and pathological form is pulmonary tuberculosis. The causal agent enters the lungs and multiplies there, forming the primary focus; this is accompanied by tuberculous lesions in the bronchial lymph nodes of the same side, thus producing the primary complex. These lesions can remain latent or develop further, depending on the interaction between the agent and the host's body. If the animal's resistance to tuberculosis bacilli breaks down, the infection will spread to other organs via the lymph or blood vessels, giving rise to early generalization of the infection. If the immune system is unable to destroy the bacilli, they will cause tubercles to form in organs and tissues where they lodge. New foci are produced, mainly in the lungs, kidneys, liver, spleen, and their associated lymph nodes. Dissemination may also give rise to acute miliary tuberculosis.

In most cases, tuberculosis has a chronic course, with effects limited to the lungs. The disease process is slow and may remain clinically inapparent for a long time. In fact, some animals spend their entire useful lives without any evident symptomatology, although they constitute a potential threat for the rest of the herd. Other animals develop chronic bronchopneumonia, accompanied by coughing and reduced milk production. In advanced cases, when the lungs are largely destroyed, there is pronounced dyspnea.

Pearl disease, a tuberculous peritonitis or pleurisy, is another form sometimes observed in infected herds in countries with no tuberculosis control program.

It is estimated that about 5% of tuberculous cows, especially in advanced cases, have tuberculous uterine lesions or tuberculous metritus, and that 1% to 2% have tuberculous mastitis. This clinical form not only has public health repercussions, but also serves as a source of infection for calves nursed naturally or artificially. One of the main signs of tuberculosis acquired by the oral route is swelling of the retropharyngeal lymph nodes. In calves, the primary lesion is usually located in the mesenteric lymph nodes and the intestinal mucosa is not affected.

The disease appears more frequently in older animals because the disease is chronic and because older animals have had more time to be exposed to the infection. The infection is more prevalent among dairy cattle than among beef cattle, not only because their useful economic life is longer, but because dairy cattle are in closer contact with one another when gathered for milking or when housed in dairy sheds.

Cattle are resistant to the *M. avium* complex (MAC) and rarely suffer progressive tuberculosis due to these agents. Nevertheless, they are very important in control programs because cattle can become paraspecifically sensitized to mammalian tuberculin, leading to difficulties in diagnosis. *M. avium* infects cattle through the digestive tract. When lesions are present, they are generally limited to the intestine and mesenteric lymph nodes. However, lesions can occasionally be found in the lungs and regional lymph nodes but not in other tissues, indicating that the entry route may sometimes be the respiratory tract. Lesions tend to heal spontaneously. Bovine-to-bovine transmission of *M. avium* infection does not occur (see the chapter, "Diseases Caused by Nontuberculous Mycobacteria").

Cattle are very resistant to *M. tuberculosis*, and rarely develop anatomicopathologic lesions. In several countries, *M. tuberculosis* has been isolated from the lymph nodes of some positive reactors to tuberculin that showed no lesions in postmortem examination. Again in this instance, the infection's importance lies in sensitizing these animals to tuberculin.

An experiment comparing the pathogenicity of *M. africanum*, *M. bovis*, and *M. tuberculosis* for calves inoculated intravenously showed that *M. africanum* (at least the strain used in this experiment) was as pathogenic for calves as *M. bovis* (de Kantor *et al.*, 1979).

SWINE: This species is susceptible to the following agents: *M. bovis*, *M. avium* complex, and *M. tuberculosis. M. bovis* is the most pathogenic and invasive for swine and is the cause of most cases of generalized tuberculosis.

The principal route of infection is the digestive tract through consumption of contaminated milk or milk products, kitchen and abattoir scraps, and excreta from tuberculous fowl and cattle. The primary infection complex is found in the oropharynx and the submaxillary lymph nodes, or in the intestines and the mesenteric lymph nodes. The lesions are usually confined in the primary complex. Chronic lesions are not found in single organs, as they often are in cattle. Prevalence is lower in young animals than in adults, but the former show a greater tendency toward generalization of the infection. Eradication programs for bovine tuberculosis directly help to reduce the infection rate among swine. In the US in 1924, tuberculous lesions were found in 15.2% of hogs butchered, while in 1989, they were found in only 0.67%.

Most cases of swine tuberculosis are due to the *M. avium* complex. Thus, the reduction of avian tuberculosis has also helped lower the rate of infection in swine. In Great Britain, as tuberculosis of bovine origin declined, infections caused by MAC increased proportionally (Lesslie *et al.*, 1968). The total number of confiscations due to generalized tuberculosis was reduced even more drastically. In some Latin American countries, *M. bovis* is the cause of 80% to 90% of tuberculous lesions in swine. The relative proportions of *M. bovis* and MAC as the cause of swine tuberculosis are reversed when *M. bovis* infection is controlled in cattle, as it has been in several European countries and in the US.

MAC usually causes adenitis of the digestive tract and, more rarely, a generalized disease (see the chapter, "Diseases Caused by Nontuberculous Mycobacteria").

Swine are also susceptible to the human bacillus (*M. tuberculosis*), which produces an infection of the lymph nodes that drain the digestive system and, more rarely, generalized tuberculosis. The main sources of infection are kitchen scraps and leftovers from tuberculosis sanatoriums. This infection has been confirmed in several countries in the Americas, Europe, and Africa.

Swine-to-swine transmission of the infection is insignificant. Intestinal lesions are hyperplastic, and ulcers that would cause the agent to be shed are not observed. However, swine may transmit the infection to other swine when they have pulmonary, uterine, or mammary lesions (Thoen, 1992).

If there is generalization of the infection caused by MAC, the lesions appear in diffuse form and there is little tendency toward encapsulation. The cutaway view of a lesion generally shows a smooth surface and there may be foci of caseation, but calcification is minimal. Lesions caused by *M. bovis* or *M. tuberculosis*, in contrast, are caseous and well-circumscribed by fibrosis with pronounced calcification (Thoen, 1992). Other bacteria, for example *Rodococcus equi*, can produce lesions similar to tuberculous lesions.

SHEEP AND GOATS: Tuberculosis in sheep is generally rare and sporadic. In the few cases described, the most important agent was *M. avium*, followed by *M. bovis*. Only two cases involved *M. tuberculosis*. In research in New Zealand stemming from a program to eradicate bovine tuberculosis, multiples cases of infection by *M. bovis* were confirmed among sheep sharing the same pasture with infected cattle. In one area, 597 sheep were given the tuberculin test on the inner thigh and 108 (18%) reactors were discovered. Lesions, mostly in the lymph nodes, were found in 43 (61%) out of 70 necropsies. The lungs were affected in eight sheep (Davidson *et al.*, 1981). A similar result was observed in another region of New Zealand, on land where the prevalence of tuberculosis in cattle and opossums (*Trichosurus vulpecula*) was high. The tuberculin test yielded positive results in 11% of the sheep, and was judged to have a sensitivity of 81.6% and a specificity of 99.6% (Cordes *et al.*, 1981).

Prevalence in goats seems to be low. In countries with advanced programs to eradicate bovine tuberculosis, the infection in goats is monitored, since this species is susceptible to *M. bovis*, frequently suffers from pulmonary tuberculosis, and can reinfect cattle. Nannies also suffer from tuberculous mastitis and their milk may constitute a danger to the consumer. In addition, goats are susceptible to *M. avium* and *M. tuberculosis*, and the latter agent sometimes causes generalized processes. Little is known about the disease's occurrence in goats in developing countries, since these animals are generally slaughtered without veterinary inspection.

HORSES: Tuberculosis is infrequent in horses. In countries where the incidence of bovine infection is high, the principal agent of the disease in horses is *M. bovis*. The infection's predominant route of entry is the digestive system. Lesions are generally confined to the lymph nodes of the digestive tract, where they produce a tissue reaction that resembles tumors. Some cases of generalized infection, caused by both *M. bovis* and *M. avium*, have been described. Often, no lesions are found in infections produced by *M. avium*. In Germany, the avian bacillus was isolated from 30% of 208 horses with no apparent lesions.

M. tuberculosis is seldom isolated from horses. In a study carried out some time ago, only 13 of 241 typed strains corresponded to the human bacillus (Francis, 1958).

The disease is very rare in asses and mules.

It is interesting to note that horses are hypersensitive to tuberculin, and thus the allergenic test does not give reliable results.

DOGS AND CATS: Dogs are resistant to experimental tuberculosis infection. Recorded cases in dogs are probably due to massive and repeated exposure brought about by living with humans with tuberculosis or frequently eating contaminated food. Infection may be produced by aerosols, or by ingestion of sputa, milk, and viscera. Almost 75% of the cases are due to the human bacillus and the rest to the bovine. The clinical picture is not characteristic. The only symptoms found in eight tuberculous dogs in New York City were anorexia, weight loss, lethargy, vomiting, and leukocytosis. Radiology revealed pleural and pericardial effusion, ascites, and hepatomegaly. Granulomatous lesions in soft tissues were similar to those observed in neoplasias (Liu *et al.*, 1980). Infection mainly localizes in the lungs or mesenteric lymph nodes; intestinal ulcers and renal lesions are sometimes found as well. Consequently, dogs can shed bacilli by coughing and in their saliva, feces, and urine. It has also been demonstrated that the etiologic agent can be present in the pharynx and feces of dogs living in the same house with tuberculous patients, even when the animals show no tuberculous lesions. Although few cases of transmission from dog to man have been confirmed, a tuberculous dog (or even an apparently healthy animal living with a tuberculous patient) represents a potential risk and should be destroyed. A dog infected with *M. bovis* can, in turn, be a potential source of reinfection for cattle.

Cats also have a great natural resistance to tuberculosis. *M. bovis* is the most common pathogen in cats, and has been isolated in 90% of the cases. The agent gains entry via the digestive tract when milk or viscera containing tuberculosis bacilli is consumed. Cat-to-cat transmission of *M. bovis* in a scientific institution in Australia has been described (Isaac *et al.*, 1983). In countries where bovine tuberculosis has been brought under control, infection in cats is rare, and the few recorded cases have been caused by *M. tuberculosis* and occasionally MAC.

Destructive lesions are sometimes found; pneumonitis and cutaneous tuberculosis are frequent. In urban areas of Buenos Aires, a cooperative study was conducted by the Pasteur Institute and the Pan American Institute for Food Protection and Zoonoses (INPPAZ). *M. bovis* was isolated from the lesions of 10 of approximately 150 cats studied (I.N. de Kantor. Personal communication). In New Zealand between 1974 and 1986, *M. bovis* was isolated from 57 cats. With the exception of six animals, all came from suburban and rural areas where tuberculosis is also pres-

ent in wild animals, particularly the opossum (*Trichosurus vulpecula*). Cutaneous lesions were observed in 58% of the cats, with a pyogranulomatous reaction and coagulative necrosis. These lesions had not been described earlier in other geographic areas, where the prevalence of tuberculosis among cats was 2% to 13% before successful control and eradication programs were implemented. Presumably the cats acquired the infection when feeding on tuberculous wild animals (De Lisle *et al.*, 1990). Several cases of reinfection of cattle herds by tuberculous cats have been described.

WILD, CAPTIVE, AND DOMESTIC ANIMALS: Animals living in the wild, far from man and domestic animals, generally do not contract tuberculosis. On the other hand, captive animals in zoos, on pelt farms, in laboratories, and in family homes may be exposed to infection. Monkeys are susceptible to *M. tuberculosis* as well as *M. africanum* and *M. bovis*. Almost 70% of the isolations from these animals are strains of the human bacillus, some are *M. africanum*, and the rest are *M. bovis*. The disease is contracted via the respiratory or digestive route. The infection can be propagated from monkey to monkey and constitutes a grave problem for colonies kept in scientific institutions and zoos. These animals can retransmit the infection to man. It is not unusual to find tuberculous pet monkeys that may have been infected before their acquisition or through contact with a family member. In France, infection due to *M. africanum* has been described in three chimpanzees and a *Cercopithexus* monkey. Three of these animals belonged to a scientific center and one of the chimpanzees belonged to a zoo. Since *M. africanum* has properties intermediate between those of *M. bovis* and *M. tuberculosis*, it is possible that infection by *M. africanum* was not described earlier in nonhuman primates because the species type of strains isolated previously was misidentified. It still has not been determined whether the infection was transmitted to the primates by man or acquired in their natural forest habitat (Thorel, 1980).

Tuberculosis is a problem in cervids, particularly now that deer farming has become popular in several countries. Tuberculosis in deer is caused primarily by *M. bovis*. This presents the possibility of retransmission of the infection to cattle in countries that are practically free of bovine tuberculosis. It is also a potential risk for people who are in contact with these animals. *M. bovis* has been found in free-roaming deer, probably living near cattle operations in Canada, the US (Hawaii), Great Britain, Ireland, and Switzerland. Deer most exposed to the disease are captive animals in zoos or deer on farms.

The first report on infection in farmed deer comes from New Zealand, in a region where the disease exists in cattle and opossum (*Trichosurus vulpecula*). An outbreak of bovine tuberculosis was recorded on farms in England that imported red deer (*Cervus elaphus*) from an eastern European country. Upon necropsy of 106 deer, 26 were found to be infected and 19 had visible lesions. The tuberculin test had 61.3% specificity and 80% sensitivity (Stuart *et al.* 1988). In a case of this type, the test would be used primarily to determine whether or not tuberculosis exists on a farm. An eradication program has been established in New Zealand based on the tuberculin test and slaughter of reactors, but the high percentage of false negatives hampers success.

In South Australia, an outbreak was reported in 1986 in three herds of another deer species (*Dama dama*). Upon necropsy, 47 of 51 animals were found to have

bovine tuberculosis (Robinson *et al.*, 1989). In eight US states, the infection was found in 1991 in ten herds of deer. This caused concern because information from Canada indicated the possibility of human infection from this source (Essey *et al.*, 1991).

Outbreaks have been described in farmed fur-bearing animals, such as mink and silver fox; the source of infection was meat or viscera of tuberculous cattle or fowl. Tuberculosis has been found in wild species of ungulates and carnivores in zoos and some nature preserves, and the infection has been confirmed in several animal species in zoos in Latin America and other parts of the world.

Two wild species are reservoirs of and sources of infection by *M. bovis* in cattle. An opossum (*Trichosurus vulpecula*) from Australia—where tuberculous infection has not been found in this species—was introduced into New Zealand, where it contracted bovine tuberculosis. Currently, opossum are attributed a major role in maintaining infection caused by *M. bovis* in cattle in the region of New Zealand where they are found. DNA restriction endonuclease analysis demonstrated that *M. bovis* isolates from cattle and opossum in Upper Hutt (the region where the eradication program encountered difficulties) belong to the same restriction category (Collins *et al.*, 1988).

In southwestern England, reinfection of cattle herds has been attributed to the high rate of *M. bovis* infection found in badgers (*Meles meles*). When the badger population was eliminated from certain areas and prevented from repopulating them, transmission to cattle was halted, thus proving the causal relationship between infection in these species (Wilesmith, 1983).

There is abundant literature on the infection in badgers and cattle. It is estimated that the badger population in Great Britain is approximately 250,000 animals and that infection by *M. bovis* is endemic on the island, regardless of the density of the colonies. A total of 15,000 badgers, most of them killed on roadways, were examined and 3.9% were positive for *M. bovis* (Cheeseman *et al.*, 1989). These researchers and others (Wilesmith *et al.*, 1986) consider the badger an ideal maintenance host or natural reservoir that acts as a source of infection for cattle, although a low level source. In Ireland, it was demonstrated that destroying badger colonies reduced the prevalence of the disease in cattle. The highest incidence of tuberculosis in cattle was found in areas with a high population density of cattle and badgers (McAleer, 1990). Although these researchers admit that badgers may be partially responsible for tuberculosis in cattle, there are other questions that must be investigated and clarified. As badgers scour pastures in search of worms, they excrete *M. bovis* in their feces, urine, and sputum and in pus when they have open abscesses. It is not clear how the cattle become infected, as they suffer primarily from pulmonary tuberculosis, which has a respiratory route of infection, except in the case of calves, many of which become infected by mouth through contaminated milk. Badger colonies with tuberculosis may also coexist with cattle for some time without transmitting the infection to these animals (Grange and Collins, 1987).

In Argentina in 1982 and 1983, 4 million hares (*Lepus europaeus*) were slaughtered under veterinary inspection and 369 animals were confiscated for various causes. *M. bovis* was isolated from only five hares and histopathological examination showed a tuberculous granuloma with significant caseation and little calcification, with the presence of alcohol- and acid-resistant bacilli (de Kantor *et al.*, 1984). Alpacas imported from the Andean highlands to Europe were the cause of small outbreaks of tuberculosis (Veen *et al.*, 1991).

In South Africa, tuberculosis has been diagnosed in many wild species: the Cape buffalo (*Syncerus caffer*), the greater kudu (*Tragelaphus strepsiceros*), and the forest duiker (*Cephalophus grimmia*), among others (Pastoret *et al.*, 1988).

Source of Infection and Mode of Transmission (Figure 20): The main reservoir of *M. bovis* is cattle, which can transmit the infection to many mammalian species, including man. Man contracts the infection primarily by ingesting the agent in raw milk and milk products, and secondarily by inhaling it.

Tuberculosis is transmitted among cattle mainly via aerosols. The digestive tract is an important route of transmission prior to weaning.

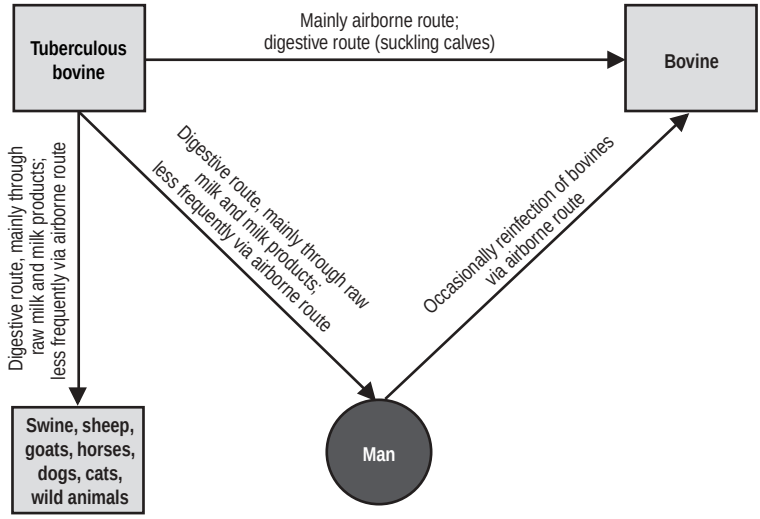
A human infected by *M. bovis* who suffers from the pulmonary or urogenital form of tuberculosis can retransmit the infection to cattle. This phenomenon becomes particularly evident during the final stages of bovine tuberculosis eradication.

Tuberculosis in swine, goats, and sheep has as it principal source of infection cattle, fowl, and occasionally man. Swine are infected enterogenously, and retransmission to other swine, other species, and man is thought to be rare. Goats can constitute a source of infection for man and for cattle.

Dogs often contract the infection from humans and, less frequently, from cattle. They may in turn retransmit it to man and cattle. Dogs become infected via the digestive and respiratory tracts. The principal source of infection for cats is cattle and, to a lesser degree, man. The route of entry is mainly oral. At times, cats can be a source of infection for cattle and humans.

Among wild animals in captivity, monkeys are particularly interesting because of their susceptibility to *M. tuberculosis* and *M. bovis*. They contract the infection from man by inhaling the agent. Tuberculous primates constitute a health risk for humans.

Figure 20. Tuberculosis (*Mycobacterium bovis*). Mode of transmission.



Domestic cattle are the source of infection for wild animals. Once the agent is introduced among wild animals that share pasture with cattle, it can spread among them and represent a risk for domestic animals and for man. This is true of deer and badgers (*Meles meles*) in Great Britain and of opossum (*Trichosurus vulpecula*) in New Zealand.

Role of Animals in the Epidemiology of the Disease: Human-to-human transmission of animal tuberculosis is rare. The infection depends on an animal source.

Diagnosis: Since the human infections caused by *M. tuberculosis* and *M. bovis* are clinically and radiologically indistinguishable, definitive diagnosis can only be achieved by isolating and typing the etiologic agent. In this regard, it should be noted that *M. bovis* grows poorly in media containing glycerin, such as Löwenstein-Jensen culture, which are generally used for culturing *M. tuberculosis*.

For routine diagnosis of bovine tuberculosis, the only approved method for eradication programs is the tuberculin test. The most appropriate tuberculin is the purified protein derivative (PPD), since it is specific and not very costly to produce. It has been made from both human and bovine strains, but research has shown that tuberculin produced with an *M. bovis* strain is more specific. In most countries, only a PPD tuberculin is used in eradication campaigns, and the comparative test (simultaneous application of mammalian and avian tuberculin) is reserved for problem herds in which paraspecific sensitization is suspected. The test is carried out by intradermal inoculation of 0.1 ml of tuberculin into the skin of the caudal fold or the wide part of the neck, depending on standards established in each country. It should be borne in mind that the skin of the neck is much more sensitive than that of the caudal fold. The amount of tuberculin used varies from 2,000 to 10,000 IU in different countries. The test will be more sensitive but less specific when larger doses are used. The test's effectiveness depends not only on the tuberculin and its correct application, but on the response capability of the infected animal. Some herds include anergic animals, which are usually old and have very advanced tuberculosis. Clinical examination and knowledge of the herd's history can help to complete the diagnosis.

The tuberculin test may also be applied to goats, sheep, and swine with satisfactory results. In swine, the preferred inoculation site is the base of the ear, with 2,000 IU of mammalian and avian tuberculin; in goats and sheep, the tuberculin can be applied to the eyelid, the fold of the tail, or the inner thigh.

The tuberculin test is unsatisfactory for horses, dogs, and cats. Some research has suggested that the test using BCG might give better results in dogs. For monkeys, the intrapalpebral test is recommended, as well as radiography in advanced cases.

The tuberculin test has several disadvantages. These include waiting time (reading at 72 hours in cattle) and the need for the veterinarian to visit the herd twice (once to inject the tuberculin and the other to read the test). Similarly, human patients require two medical visits. Old cows with advanced tuberculosis are anergic. This can also happen if there is an intercurrent febrile disease. As an eradication program progresses, the percentage of reactor animals without visible tuberculosis lesions increases at slaughterhouses. These disadvantages have led many researchers to seek serologic tests than can replace or at least complement tuberculin tests.

The enzyme-linked immunosorbent assay (ELISA) using bovine PPD was evaluated in five different groups of cattle, including 53 animals with positive cultures

and 101 animals from a tuberculosis-free area. Sensitivity of 73.6% and specificity of 94.1% were obtained (Ritacco *et al.*, 1990). The authors note that ELISA was able to detect IgG against *M. bovis* in the sera of cattle with active tuberculosis, but not in those with a clinically inapparent infection (e.g., at the onset of infection or in the latent state). There was little coincidence between the results from the tuberculin test and results from ELISA. Antibodies were detected in almost three out of four bovines with active tuberculosis. In contrast to what happens with anergic animals, which lose cellular reactivity to the hypersensitivity test with tuberculin, antibodies are more abundant when there is a strong antigenic discharge. Thus, ELISA could be useful as a complement to the intradermal test in detecting anergic tuberculous animals that represent a risk for the rest of the herd (Ritacco *et al.*, 1990). The results obtained in humans infected by *M. tuberculosis* are not unlike those obtained in cattle infected by *M. bovis*. Specificity was 93% in adults and 98% in children; sensitivity was 69% in adults and 51% in children. The conclusion is that enzyme immunoassay can be useful for detecting patients with nonbacilliferous, extrapulmonary, and pediatric tuberculosis (de Kantor *et al.*, 1991).

The enzyme immunoassay can also be used to detect circulating antigens or to diagnose tuberculosis in homogenized animal tissues (Thoen *et al.*, 1981). For a program to eliminate infected badgers, a serological procedure is being sought that could detect individual infected animals and thus prevent indiscriminate slaughter.

In Australia, a simple test has been developed to measure *in vitro* the cell-mediated immune response to bovine PPD tuberculin. The test is based on detecting—using a sandwich enzyme immunoassay—gamma-interferon produced by incubation (for 24 hours) of whole bovine blood in the presence of tuberculin (Rothel *et al.*, 1990). A field study conducted of a large number of cattle compared the anal-caudal test with PPD tuberculin and the gamma-interferon assay. Specificity with gamma-interferon was 96% to 98%, while sensitivity was 76.8% to 93.6% (depending on the method of interpretation). If the two diagnostic tests are combined, it is possible to obtain sensitivity of 95.2% (Wood *et al.*, 1991; Wood *et al.*, 1992). The sandwich enzyme immunoassay to detect gamma-interferon in whole bovine blood proved to be more sensitive and specific than the direct enzyme immunoassay for detecting IgG in serum. In a study conducted in Argentina, the gamma-interferon test was positive in 9 of 19 animals that had tuberculous lesions limited to the lymph nodes and no antibodies in the ELISA test. In contrast, cattle with disseminated lesions had a high antibody titer and little or no gamma-interferon production (Ritacco *et al.*, 1991).

Control: Prevention of human infection by *M. bovis* consists of the pasteurization of milk, vaccination with BCG, and above all, control and eradication of bovine tuberculosis.

The only rational approach to reducing and eliminating losses produced by the infection in cattle and preventing human cases caused by *M. bovis* consists of establishing a control and eradication program for bovine tuberculosis. Eradication campaigns are usually carried out by administering tuberculin tests repeatedly, until all infected animals are eliminated from the herd. Application of the tuberculin test and slaughter of reactors has given excellent results in all countries that have undertaken eradication campaigns. At present, many developed countries are free or practically free of bovine tuberculosis. In developing countries, the inability of governments to

compensate owners for the destruction of reactors hinders establishment of eradication programs and makes it necessary to find other incentives, such as a surcharge on milk. Campaigns should be begun in regions of low prevalence, where replacing reacting animals is easier, and later extended to areas of higher prevalence. The success of a program depends on the cooperation of the meat inspection agencies so that tuberculosis-free herds are correctly certified, activities are evaluated, and appropriate epidemiologic surveillance is maintained. The cooperation of the health services is also important to prevent persons with tuberculosis from working with animals and either infecting or sensitizing them.

Controlling tuberculosis caused by *M. bovis* in its principal reservoir, cattle, is the best method of preventing transmission to other species, including man.

Several vaccines have been tested for preventing bovine tuberculosis, among them BCG, but none have proved effective. Treatment with anti-tuberculosis drugs, particularly isoniazid, takes many months, is costly, can produce drug-resistant *M. bovis* strains, and the result is uncertain.

Data on the status of bovine tuberculosis in Latin America and the Caribbean, with a summary on other countries, have been compiled and tabulated by de Kantor and Alvarez (1991) and de Kantor and Ritacco (1994).

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Part II

MYCOSES

ADIASPIROMYCOSIS

ICD-10 B48.8

Synonyms: Adiaspirosis, haplomycosis, haplosporangiosis.

Etiology: *Chrysosporium (Emmonsia) parvum* var. *crescens* and *C. parvum* var. *parvum*, saprophytic soil fungi that characteristically form large spherules (adiaspores) in the lungs. In the tissular phase, the fungus does not multiply. *C. crescens* is the most common agent in man and animals. *C. parva* occurs primarily in animals and forms smaller spherules than *C. crescens*. *C. parvum* var. *crescens* and *C. parvum* var. *parvum* differ in size. In the lungs, *C. crescens* measures 200 to 700 microns, whereas *C. parvum* measures 40 microns. In addition, *C. parvum* is mononuclear, even when it reaches its maximum size, while *C. crescens* eventually has hundreds of nuclei.

Geographic Distribution: Worldwide. In the Americas, the infection has been confirmed in Argentina, Brazil, Canada, Guatemala, Honduras, the United States, and Venezuela.

Occurrence in Man: Rare. Eleven human cases have been reported in Asia, Europe, South America, and the United States (Englund and Hochholzer, 1993). According to Moraes *et al.* (1989) there were 23 cases, four of which were extrapulmonary.

Occurrence in Animals: Frequent in small wild mammals. The disease has been confirmed in at least 124 mammalian species or subspecies (Leighton and Wobeser, 1978). Among other mammals, the disease has been diagnosed in skunks (*Mephitis mephitis*) in Argentina, Canada, and the United States.

The Disease in Man and Animals: The only clinically significant form, in man as well as animals, is pulmonary adiaspiromycosis. The few human cases have been diagnosed through biopsy or autopsy specimens. The fungus causes light gray to yellowish lesions in the lungs, without greatly affecting the animal's overall health. The number of spherules (adiaspores) in the lung tissue depends on the number of conidia (spores) inhaled. In the lungs, the fungus increases significantly in size. If few conidia are inhaled, usually only one lung is affected. If the inoculum is large, both lungs are likely to be affected. Adiaspiromycosis usually disappears spontaneously but requires surgical resection if it persists (Englund and Hochholzer, 1993). The etiologic agent may also be found in other organs, though rarely. One case of disseminated adiaspiromycosis was described in an AIDS patient. The most significant clinical characteristic was disseminated osteomyelitis. The fungus, *Chrysosporium parvum* var. *parvum*, was isolated during surgery from the pus of a wrist lesion, as well as from the sputum and bone-marrow aspirate. The mycotic infection was controlled with amphotericin B (Echeverría *et al.*, 1993). A fatal case of adiaspiromycosis was recorded in Brazil in a 35-year-old rural worker who had complained of generalized weakness, dry cough, afternoon fever, and a weight loss of 8 kg during the four weeks prior to hospitalization. Clinical symptoms and radiography were similar to miliary tuberculosis. The fungus was detected in the specimens obtained during autopsy (Peres *et al.*, 1992). Another similar fatal case had occurred previously in Brazil (Moraes *et al.*, 1989).

The disease is generally asymptomatic, but resection of the affected tissue may be necessary if it persists and symptoms appear.

In 7 out of 25 skunks (*Mephitis mephitis*) captured and autopsied in Alberta, Canada, lesions were found that varied from slight and only visible microscopically to severe with grayish-white nodules in the pulmonary parenchyma that spread to the bronchotracheal and mediastinal lymphatic ganglia. Histologically, the lesions were characterized by a centrally located spherule surrounded by granulomatous inflammation (Albassam *et al.*, 1986).

Source of Infection and Mode of Transmission: The great preponderance of pulmonary localizations indicates that the infection is contracted through inhalation. *C. crescens* has been isolated from the soil. Differences in the infection rates for three very similar species of squirrels indicate that the fungus may be present in certain habitats (Leighton and Wobeser, 1978), possibly linked to the root microflora of certain plants. Other authors (cited by Mason and Gauhwin, 1982) suggest that predator-prey interactions affect its distribution: upon ingesting infected animals, carnivores eliminate adiaspores in their feces, where the spores germinate and develop. This was demonstrated in cats, in a mustelid (*Mustela nivalis*), and in birds of prey. Thus, predators could play a role in disseminating the etiologic agent.

Under very windy conditions, both animals and humans may inhale airborne conidia released from the soil.

Role of Animals: The soil is the reservoir for the fungus and the source of infection in humans and other animals. It is believed that some animals may play a role in disseminating the agent.

Diagnosis: Diagnosis may be made by observation of spherules in lung tissue, by stained histological preparations, and by culture and inoculation into laboratory animals. The most effective method for detecting adiaspores in the lungs of animals is tissue digestion with a 2% sodium hydroxide solution (Leighton and Wobeser, 1978). The spherules are stained with acid-Schiff and Gomori methenamine silver nitrate reagents (Englund and Hochholzer, 1993).

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ASPERGILLOSIS

ICD-10 B44.0 invasive pulmonary aspergillosis;
B44.1 other pulmonary aspergillosis;
B44.7 disseminated aspergillosis; B44.8 other forms of aspergillosis

Synonyms: Pneumonomycosis, bronchomycosis (in animals).

Etiology: *Aspergillus fumigatu*s and occasionally other species of the genus *Aspergillus*, such as *A. flavus*, *A. nidulans*, *A. niger*, and *A. terreus*. These saprophytic fungi are common components of the soil microflora; they play an important role in the decomposition of organic matter.

Aspergillus flavus and *A. parasiticus* are known for their production of aflatoxins in oleaginous grains and seeds such as corn, rice, peanuts, and cottonseeds stored under damp conditions. Aflatoxin B_1 is hepatotoxic and carcinogenic for humans and animals. These fungi do not produce the aflatoxin in animal tissue. Thus, this chapter covers only infection by *Aspergillus* spp.

Geographic Distribution: The fungus is ubiquitous and distributed worldwide. The disease has no particular distribution.

Occurrence in Man: Aspergillosis occurs sporadically and is uncommon. Its incidence, as is that of other opportunistic mycoses[1] (candidiasis, zygomycosis), is increasing due to the growing use of antibiotics, antimetabolites, and corticosteroids. It occurs frequently in advanced cases of cancer. Small nosocomial outbreaks have also been reported (see section on the disease in man).

In Mexico, aspergillosis lesions were found in 1.2% of more than 2,000 random autopsies performed in a general hospital (González-Mendoza, 1970).

Occurrence in Animals: Sporadic cases have been described in many species of domestic and wild mammals and birds. The disease in fowl and cattle has economic

[1] Mycoses that attack debilitated persons or those treated over a long period with antibiotics, antimetabolites, or corticosteroids.

implications. The incidence is low in adult domestic fowl, but outbreaks in chicks and young turkeys can cause considerable losses on some farms.

The Disease in Man: Aspergillosis establishes itself in patients debilitated by chronic diseases (such as diabetes, cancer, tuberculosis, deep mycoses) and diseases of the immune system, as well as in persons treated with antibiotics, antimetabolites, and corticosteroids for prolonged periods. Persons occupationally exposed for long periods to materials contaminated by fungus spores (grain, hay, cotton, wool, and others) run a greater risk.

A study group on aspergillosis in AIDS patients conducted a retrospective review of 33 patients with invasive aspergillosis in different medical facilities in France. Of this group of 33 patients, 91% were recorded from 1989 to 1991, suggesting that invasive aspergillosis is an emerging complication of AIDS. *Aspergillus* spp. cultures were obtained from bronchopulmonary lavage of 28 patients, and no other pathogenic agents were found. Of 15 patients who underwent biopsy or autopsy, 14 were histologically positive. The clinical and radiological symptoms were comparable to aspergillosis in non-AIDS patients with neutropenia, though the AIDS patients had a higher incidence of neurological complications (Lortholary *et al.*, 1993).

There are two differentiated clinical forms of the disease: localized and invasive. Aspergillosis is essentially a respiratory system infection acquired through inhalation of *Aspergillus* spp. conidia. Patients with pronounced granulocytopenia may contract an acute and rapidly progressing pneumonia. The symptoms are high fever, pulmonary consolidation, and cavitation. Normal children who inhale a large number of conidia may develop fever, dyspnea, and miliary infiltration (Bennett, 1990). Allergic bronchopulmonary aspergillosis (ABPA) occurs in patients with preexisting asthma who present eosinophilia and intermittent bronchial obstruction (Bennett, 1990). Eosinophilia, precipitant antibodies, and high serum IgE concentration are found in these patients; the intradermal [skin prick] test produces an immediate reaction to *Aspergillus* antigens, with papules and reddening. Despite recurring exacerbations, some patients do not experience any permanent loss of pulmonary function. Other patients, however, suffer corticoid-dependent asthma or permanent obstructive disease (Bennett, 1990). ABPA patients may expectorate bronchial plugs in which hyphae of the fungus can be detected microscopically. Even during remission, 33% of patients evidenced circulating immune complexes, primarily involving IgG (Bhatnagar *et al.*, 1993).

Allergic bronchopulmonary aspergillosis is more common than was thought in the past. The disease may begin during childhood and continue without being clinically recognized for many years or decades, until the patient begins to suffer from fibrotic pulmonary disease. In this regard, it must be noted that aspergillosis infection may be asymptomatic and suspected only due to a significant increase in serum IgE. Often the diagnosis comes too late for chemotherapy treatment to be effective. When corticoids are discontinued, dyspnea and wheezing occur, requiring a return to medication with prednisolone (Greenberger, 1986). A later study concluded that inhaled beclomethasone dipropionate may be more effective in treating ABPA than traditional prednisolone by mouth (Imbeault and Cormier, 1993).

Another form of the disease is the fungus ball or aspergilloma, which occurs when the fungus colonizes respiratory cavities caused by other preexisting diseases (bron-

chitis, bronchiectasis, tuberculosis). This form is relatively benign, but it occasionally produces hemoptysis.

Other clinical forms are otomycosis (often caused by *A. niger*) and invasion of the paranasal sinuses by the fungus. Though rare, the cutaneous form of the disease may appear in immunodeficient patients.

The invasive form is usually very serious. The fungi penetrate the blood vessels and can spread throughout the body. Cases of pulmonary aspergillosis have also been described in patients who are not immunodeficient. There is general insistence that the invasive form of the disease occurs only in patients with neutropenia. Neutrophil polymorphonuclear leukocytes are very important in the defense against aspergillosis or in those who have serious defects in cell-mediated immunity (Karam and Griffin, 1986). Karam and Griffin describe three cases over five years in a university hospital and cite 32 cases found in the literature. Of the 32 cases cited, 14 had no underlying disease.

Surgical intervention in the case of pulmonary or pleuropulmonary aspergillosis may be indicated to treat pleural empyemas and bronchopleural fistulae. In these cases, myoplasty, thoracomyoplasty, and omentoplasty are the procedures most recommended (Wex *et al*., 1993). Surgical removal is also justified in the case of invasive aspergillosis in the brain and paranasal sinuses, as well as in noninvasive colonization of the paranasal sinuses (Bennett, 1990). When colonization is invasive, it is advisable to discontinue or reduce the use of immunosuppressants and to start treatment with intravenous amphotericin B or itraconazole.

Several small outbreaks have occurred during the renovation, expansion, or remodeling of hospitals and the construction of highways near hospitals. During these projects, large numbers of conidia are made airborne, and may become concentrated due to ventilation systems with defective filters. Between July 1981 and July 1988, 11 immunodeficient patients in a military hospital contracted disseminated aspergillosis and died as a result. The hospital's project involved the renovation of the intensive care unit and several other rooms. The infection spread no further after several simultaneous measures were taken, such as installing floor-to-ceiling partitions in the construction area, negative pressure in the same area, antifungal decontamination using copper 8-hydroxyquinoline, and high-efficiency particulate air (HEPA) filters in air conditioning units and in rooms with immunodeficient patients (Opal *et al.*, 1986). However, a certain percentage of patients with lymphoma who received bone marrow transplants and were located in single-occupancy rooms with positive air pressure and high efficiency air filters did acquire aspergillosis. Of 417 lymphoma patients studied, 22 (5.2%) contracted invasive aspergillosis. These 22 patients were treated with amphotericin B, 17 of them prior to being diagnosed with aspergillosis; seven survived. All of the patients with disseminated aspergillosis died (Iwen *et al.*, 1993).

The Disease in Animals: Although aspergillosis occurs sporadically in many animal species, where it primarily causes respiratory system disorders, the following discussion only deals with the disease in cattle, horses, dogs, and fowl.

CATTLE: It is estimated that 75% of mycotic abortions are due to *Aspergillus*, particularly *A. fumigatus*, and 10% to 15% to fungi of the order *Mucorales*. As brucellosis, campylobacteriosis, and trichomoniasis are brought under control, the relative role of fungi as a cause of abortions increases. Mycotic abortion is seen mainly in

stabled animals; thus, it occurs during the winter in countries with cold or temperate climates. Generally, only one or two females in a herd abort.

The pathogenesis of the disease is not well known. It is thought that the fungus first localizes in the lungs or the digestive system, where it multiplies before invading the placenta via the bloodstream and causing placentitis. Most abortions occur during the third trimester of pregnancy. The cotyledons swell and turn a brownish gray color. In serious cases, the placenta becomes wrinkled and leathery. The fungus may invade the fetus as well, causing dermatitis and bronchopneumonia. Retention of the placenta is common. Other forms of the infection are the pulmonary forms, also due primarily to *A. fumigatus*, and skin aspergillomas, caused by *A. terreus* (Schmitt, 1981).

HORSES: Invasive pulmonary aspergillosis is relatively rare in horses. As in cattle, the disease is generally associated with abortion. There is also an association between enterocolitis (*Salmonella, Ehrlichia ristici*) and invasive pulmonary aspergillosis (Hattel *et al.*, 1991).

DOGS: Aspergillosis in dogs is generally confined to the nasal cavity or paranasal sinuses. *A. fumigatus* is the most common fungus. Disseminated aspergillosis is rare and has been found in dry, warm regions. In Australia, 12 cases due to *A. terreus* were recorded during 1980–1984. Eleven of the 12 dogs were German Shepherds. The disease was characterized by granulomas in several organs, particularly in the kidneys, spleen, and bones. Lumbar diskospondylitis and focal osteomyelitis were common, generally in the epiphysis of the long bones (Day *et al.*, 1986). Six cases of disseminated aspergillosis were recorded in the United States with characteristics similar to those in Australia (Dallman *et al.*, 1992).

FOWL: Outbreaks of acute aspergillosis occur in chicks and young turkeys, sometimes causing considerable losses. The symptoms include fever, loss of appetite, labored breathing, diarrhea, and emaciation. In chronic aspergillosis, which occurs sporadically in adult birds, the clinical picture is varied and depends on the localization. The affected birds may survive for a long time in a state of general debilitation. Yellowish granulomas of 1 to 3 mm (or larger, if the process is chronic) appear in the lungs. Plaques develop in the air sacks and may gradually cover the serosa; the same lesions or a mucoid exodate are found in the bronchial tubes and the trachea. Granulomatous lesions are also found frequently in different organs, as either nodules or plaques. The principal etiologic agents are *A. fumigatus* and *A. flavus*. Many species of domesticated and wild birds are susceptible to the disease. Captive penguins frequently are victims (Chute and Richard, 1991).

Clinical forms other than the pulmonary form occur in birds. These are dermatitis, osteomycosis, ophthalmitis, and encephalitis. Osteomycosis and encephalitis are probably spread through the bloodstream (Chute and Richard, 1991).

Source of Infection and Mode of Transmission: The reservoir is the soil. The infecting element is the conidia (exospores) of the fungus, which are transmitted to man and animals through the air. The causal agent is ubiquitous and can survive in the most varied environmental conditions. Despite this, the disease does not occur frequently in man, indicating natural resistance to the infection. This resistance may be undone by the use of immunosuppressant medications or factors that impair the immune system (see the section on the disease in man for other details on predis-

posing factors and diseases). In domestic mammals and birds, as well as in people who work with them, an important source of infection is fodder and bedding contaminated by the fungus, which releases conidia upon maturing. Apparently, exposure must be prolonged or massive for the infection to become established. Airborne conidia are found in incubators, hatcheries, incubation rooms, and air ducts; these may be the source of infection for chicks or young turkeys (Chute and Richard, 1991).

Role of Animals in Epidemiology: The source of infection is always the environment. The infection is not transmitted from one individual to another (man or animal).

Diagnosis: Due to the ubiquitous nature of the agent, isolation by culture is not a reliable test, since the agent may exist as a contaminant in the environment (laboratory or hospital) or as a saprophyte in the upper respiratory tract. A conclusive test may be obtained by simultaneously conducting a histological examination using biopsy material and confirming the presence of the fungus in the preparations. The agent may also be isolated by culturing aseptically obtained specimens from lesions not exposed to the environment. The species can only be identified by means of a culture. The immunodiffusion test has yielded very good results, as have counterimmunoelectrophoresis and enzyme-linked immunosorbent assay (ELISA). Serological tests are useful for diagnosing aspergillomas and in allergic bronchopulmonary aspergillosis, but not in invasive aspergillosis (Bennett, 1990). High levels of *A. fumigatus*-specific IgE and IgG are detected in the sera of ABPA patients, while IgG alone is detected in aspergillomas (Kurup, 1986). In fowl, it is enough to confirm the presence of the fungus through direct observation or by culturing materials from lesions of sacrificed birds.

Control: Due to the ubiquitous nature of the fungus, it is impossible to establish practical control measures. Prolonged treatment with antibiotics or corticosteroids should be limited to cases in which such therapy is essential. It is advisable to take special precautionary measures to avoid nosocomial outbreaks and to protect immunodeficient patients when construction work is done inside or near hospitals. Patients with lymphoma who receive bone marrow transplants should receive prophylactic treatment with amphotericin B (Iwen *et al.*, 1993). Moldy bedding or fodder should not be handled or given to domestic mammals and birds. Hygienic conditions in incubators and incubation rooms are important in preventing avian aspergillosis.

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BLASTOMYCOSIS

ICD-10 B40.0 acute pulmonary blastomycosis; B40.1 chronic pulmonary blastomycosis; B40.3 cutaneous blastomycosis; B40.7 disseminated blastomycosis; B40.8 other forms of blastomycosis

Synonyms: North American blastomycosis, Chicago disease, Gilchrist's disease.

Etiology: *Blastomyces dermatitidis*, a dimorphic fungus existing in mycelial form in cultures and as a budding yeast in the tissues of infected mammals. The fungus also exists as yeast in enriched culture media at 37°C. The mycelial form in culture media at 25°C is cottony white, turning to brown over time.

Sandy, acidic soil close to rivers or other freshwater reservoirs is the microecosystem most favorable to *B. dermatitidis*. It remains in an infective sporulated state in this biotope, as its spores (conidia) can detach and become airborne. High ambient humidity seems to favor the release of spores.

B. dermatitidis is subdivided into two serotypes (1 and 2) based on the presence of an exoantigen, called A and recognized by a specific precipitin. Strains examined from India, Israel, and the United States, and one strain examined from Africa all contained A antigen (serotype 1). Eleven of 12 African strains examined were type 2. The African strains are deficient in A antigen, but contain K antigen (Kaufman *et al.*, 1983).

Geographic Distribution: The disease has been observed in eastern Canada, India, Israel, South Africa, Tanzania, Tunisia, Uganda, the United States, and the former Zaire. Autochthonous cases have also occurred in some Central and South American countries (Klein *et al.*, 1986). In the United States, endemic areas are located along the Mississippi, Missouri, and Ohio rivers, and in parts of New York State. In Canada, they are located along the St. Lawrence River and near the Great Lakes.

Occurrence in Man: Predominantly sporadic. Most of the cases have been recorded in the United States, with the highest prevalence in the Mississippi and Ohio river basins. From 1885 to 1968, there were 1,573 cases in that country (Menges as cited by Selby, 1975). Klein *et al.* (1986) summarized from the literature the incidence in different endemic U.S. states: from 0.1 to 0.7 cases per 100,000 inhabitants per year in Arkansas from 1960 to 1965; 0.61, 0.44, and 0.43 cases per 100,000 inhabitants per year in Mississippi, Kentucky, and Arkansas, respectively, from 1960 to 1967; and 0.48 cases per 100,000 inhabitants per year in Wisconsin from 1873 to 1982. Hyperendemic areas in these states have an incidence of 4 cases per 100,000 per year. These data do not include slight cases of the disease that do not generally receive medical attention.

In Louisiana (USA), an attempt was made to identify all cases that occur in the state and to study one district in detail (Washington Parish) that is considered endemic. The average annual incidence for the entire state during 1976–1985 was 0.23 cases per 100,000 inhabitants, while the incidence for Washington Parish was 6.8 cases per 100,000. In 30 cases studied in this district, the patients' ages ranged from 3 weeks to 81 years. Five people died, and one of these was probably infected *in utero* (Lowry *et al.*, 1989).

In Canada, about 120 cases of blastomycosis were recorded up until 1979. Most of the cases occurred in Quebec, followed by Ontario and the maritime provinces. More recently, 38 cases were reported in Ontario, as was a new focus to the north and east of Lake Superior that accounted for 20 of the patients (Bakerspigel *et al.*, 1986).

The disease also occurs in the form of outbreaks. Klein *et al.* (1986) reported seven of them, mainly in the northern part of the mid-western United States. The largest outbreak affected 48 people in Wisconsin who traveled to a beaver pond and also visited their dens and dams. Only one outbreak occurred in an urban area (near Chicago), and in nine months affected five people living close to a highway under construction. Another outbreak in a wooded, marshy area of Virginia simultaneously affected four raccoon hunters and their four hunting dogs (Armstrong *et al.*, 1987). The disease occurs more frequently among males and the highest rate of infection is found in men over 20 years of age. Most cases occur in winter (Klein *et al.*, 1986).

Occurrence in Animals: Sporadic. Canids are the most affected, and the greatest concentration of cases is seen in Arkansas (USA). A study was conducted on the accumulated data of 20 university veterinary hospitals in terms of the risk factors for blastomycosis in dogs. From 1980 to 1990, 971 cases were recorded. The prevalence of blastomycosis in dogs was 205 per 100,000 hospital admissions. The highest incidence of the disease occurred in autumn. The principal victims were hunting dogs weighing between 23 and 45 kg and aged 2 to 4 years. The endemic areas were the same as for man. Hunting dogs generally cover large distances and can enter endemic areas with ecological niches of the fungus (Rudmann *et al.*, 1992). Cases have also been described in cats, a horse, a captive sea lion (*Eumetopias jubata*), an African lion (*Panthera leo*) in a zoo, a dolphin, and a ferret. Cats follow dogs in terms of numbers of cases, but the total number of cats affected is small. In a university hospital in Tennessee (USA), 5 out of 5,477 cats treated presented blastomycosis (Breider *et al.*, 1988).

The Disease in Man: The incubation period is not well known, but is estimated to be from 21 to 106 days (an average of 43 days) (Klein *et al.*, 1986). Blastomycosis may develop insidiously and silently, or acutely with symptoms of a febrile disease, arthralgia, myalgia, and pleuritic pain. It may start with a dry cough that becomes productive with hemoptysis, chest pain, and weight loss. Fever, cough, dyspnea, and diffuse pulmonary infiltration indicated by chest x-ray were seen in a description of acute respiratory distress syndrome in 10 adult patients. Six of the patients had no underlying disease associated with a change in immunity and two had no recent exposure to environmental reservoirs of *B. dermatitidis*. Microscopic examination of tracheal secretions showed budding yeasts. Five of the 10 patients died, despite intravenous treatment with amphotericin B (Meyer *et al.*, 1993). However, in most cases, the disease is asymptomatic at the outset and is diagnosed in a chronic state. The principal clinical form is pulmonary blastomycosis. It is a systemic disease with a wide variety of pulmonary and extrapulmonary manifestations. The pulmonary form has the symptoms of chronic pneumonia. The lesions are similar to those produced by other granulomatous diseases (Chapman, 1990).

The extrapulmonary forms are attributed to dissemination from the lungs. The cutaneous form is the form most commonly seen in patients. Some patients do not present simultaneous pulmonary involvement. The disease is evidenced by verruci-

form lesions on exposed parts of the body or by an irregularly shaped scabby ulcer with raised borders. A single patient may present both types of cutaneous lesions (Chapman, 1990). Other forms consist of subcutaneous nodules and particularly lesions in the joints, long bones, vertebrae, and ribs. The lesions are osteolytic and well defined, with abscesses forming in the soft tissue. A large number of patients may have prostate and epididymis lesions (Chapman, 1990).

Of 15 AIDS patients in six endemic and four nonendemic areas, seven suffered from a localized pulmonary blastomycosis and eight from disseminated or extrapulmonary blastomycosis. Localization in the CNS was frequent (40% of cases). Six of the patients died in the first 21 days after admission to the medical facility with a clinical picture of blastomycosis, two of them with fulminant pneumonia (Pappas *et al.*, 1992). The authors conclude that blastomycosis is a late and often fatal complication that occurs in a small number of AIDS patients.

The preferred medication for disseminated cases is intravenous amphotericin B; ketoconazole is preferred for patients with more limited lesions, as it does not have the amphotericin B side effects.

The Disease in Animals: The highest incidence is seen in dogs around two years of age. Symptoms consist of weight loss, chronic cough, dyspnea, cutaneous abscesses, fever, anorexia, and, with some frequency, blindness. The lesions localize in the lungs, lymph nodes, eyes, skin, and joints and bones. Of the 47 clinical cases described, 72% occurred in large males. Lesions were present in the respiratory tract in 85% of the cases (Legendre *et al.*, 1981). The number of cases in dogs is increasing in the United States; between January 1980 and July 1982, 200 cases of canine blastomycosis were recorded in Wisconsin alone. Cases also have been reported east of the Mississippi River (Archer *et al.*, 1987). The preferred treatment is the same as for man—intravenous amphotericin B. A large percentage of sick dogs are euthanized due to the high cost of treatment and the possible side effect of nephrotoxicity (Holt, 1980).

Source of Infection and Mode of Transmission: The reservoir is environmental. Epidemiologic studies conducted in recent years reveal that the optimum microecosystem is sandy, acidic soil along waterways, and probably around artificial reservoirs as well (see the section on etiology). When environmental conditions change, the agent isolated once often cannot be isolated again. Exposed men and dogs are those who come into contact with the foci in endemic areas (see the section on geographic distribution), for work or recreation, particularly hunting. Transmission to man and animals is via the airborne route; fungal conidia are the infecting element.

Role of Animals in the Epidemiology of the Disease: None. It is a disease common to man and animals. There are no known cases of transmission from one individual to another (man or animal).

Diagnosis: Diagnosis is based on direct microscopic examination of sputum and material from lesions, on isolation of the agent in culture media, and on histological preparations. *B. dermatitidis* grows well in Sabouraud's culture medium or another suitable culture medium. It is most distinctive in its budding yeast form, and thus the inoculated medium should be incubated at 37°C (the mycelial form of the fungus is obtained at ambient temperature). *B. dermatitidis* in its yeast form (in tissues or cul-

tures at 37°C) is characterized by a single bud attached to the parent cell by a wide base from which it detaches upon reaching a size similar to that of the parent cell. In contrast, *Paracoccidioides brasiliensis*, the agent of paracoccioidomycosis ("South American blastomycosis"), has multiple buds in the yeast-forming phase. A commercial DNA probe can be used to confirm the identity of the *B. dermatitidis* culture (Scalarone *et al.*, 1992).

Serological tests used are complement fixation and gel immunodiffusion; the latter yields the best results. Sensitivity is much greater in disseminated than in localized blastomycosis. An antigen-capture ELISA test proved to be more specific than the conventional enzymatic immunoassays: of eight serum samples obtained from patients in an early stage of the disease, seven tested positive with this method, whereas three tested positive with gel immunodiffusion and three with complement fixation. There were no cross reactions with sera from patients with histoplasmosis or coccidioidomycosis (Lo and Notenboom, 1990), though it should be borne in mind that cross reactions with *Histoplasma* and *Coccidioides* may occur. At present, the intradermal test is considered to have no diagnostic value. In dogs, serological tests have not yielded reliable results.

Control: There are no adequate control measures.

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CANDIDIASIS

ICD-10 B37.0 candidal stomatitis; B37.1 pulmonary candidiasis; B37.2 candidiasis of skin and nail; B37.3 candidiasis of vulva and vagina; B37.4 candidiasis of other urogenital sites; B37.5 candidal meningitis; B37.6 candidal endocarditis; B37.7 candidal septicaemia

Synonyms: Moniliasis, candidosis, thrush, candidomycosis.

Etiology: *Candida albicans (Monilia albicans, Oidium albicans)* is the most common species in man and animals. Other less frequent species are *Candida tropicalis*, *C. parapsilosis*, *C. krusei*, *C. guillermondi*, *C. pseudotropicalis*, and *C. lusitaniae*.

C. albicans in young cultures measures approximately 3 x 5 microns. It is gram-positive and reproduces by budding. In Sabouraud's medium it forms creamy white, convex colonies. Old cultures have septate hyphae and sometimes chlamydospores (enlarged spherical cells with thick walls). *C. albicans* forms part of the normal flora in the human and animal digestive system, mucosa and, to a lesser extent, the skin. It is also found in the soil, in plants, and in fruits. In its normal habitat, *Candida* takes the form of a budding yeast. In infected tissue, it can produce hyphae or pseudohyphae (filaments consisting of elongated budding cells that did not detach from the parent cell). Odds and Abbott (1980, 1983) developed a biotyping method for *Candida albicans*, later modified by Childress *et al.* (1989). This method consists of

evaluating the growth of the strain in nine agar plates with various biochemical compositions in order to differentiate the strains for epidemiological purposes.

Geographic Distribution: Worldwide. There are no delimited endemic zones.

Occurrence in Man: It is the most frequent opportunistic mycosis. Its incidence has increased in recent years due to the increase in prolonged treatments with antibiotics and corticosteroids. Candidiasis is a sporadic disease; epidemics have occurred in nurseries, particularly among premature babies in intensive care units; some epidemics are due to the use of contaminated medicinal solutions or parenteral feeding fluids. It is estimated that the disease is responsible for nearly one-quarter of mycotic deaths. In a general hospital in Mexico, candidiasis lesions were found in 5.4% of random autopsies conducted (González-Mendoza, 1970).

Occurrence in Animals: The disease has been confirmed in numerous mammalian and avian species. Moniliasis in chicks and poults is common and sometimes has economic implications. Outbreaks have been described in various parts of the world.

The Disease in Man: *Candida* is found as a commensal in the digestive tract and vagina of a high percentage of healthy individuals. Diaper rash and cheilitis (lip sores) are often caused by *Candida*. In adults, candidiasis is always associated with debilitating diseases or conditions, such as diabetes (which particularly favors superficial candidiasis), AIDS, tuberculosis, syphilis, cancer, obesity, and others. The agent often is responsible for intertrigo of large skin folds, balanitis, and onychia with paronychia (especially in women whose work frequently requires them to immerse their hands in water).

The most frequent form of the mucosal infection presents clinically as a mycotic stomatitis (thrush) characterized by lightly adhering white plaques on the tongue and other parts of the mouth that can leave a bloody surface when removed. Some have observed that this clinical form increased in asthmatic children treated with inhaled steroids. The infection often heals spontaneously (Edwards, 1990).

The high incidence of thrush in cancer or AIDS patients should lead a physician treating a patient with thrush to test for these diseases (Syrjanen *et al*., 1988).

Another form of mucosal infection is esophageal candidiasis, which may or may not be an extension of oral thrush. It is particularly frequent in patients receiving treatment for malignant processes of the hematopoietic or lymphatic system. The most common symptoms of esophagitis are pain upon swallowing and substernal pain (Edwards, 1990).

Gastrointestinal candidiasis follows the esophageal form in frequency among cancer patients. The small intestine is the third most frequent site of infection. Ulcers are the most common lesions in the stomach and intestine.

Mucosal candidiasis recently has been surpassing *Trichomonas* as a cause of vulvovaginitis. This form is commonly accompanied by vaginal discharge of varying intensity and pruritus vulvae.

Although candidiasis is usually limited to mucocutaneous forms, systemic infection can occur through hematogenous transmission, particularly in very weak patients who are treated with antibiotics over a long period. These cases often develop as a result of lesions caused by medical explorations using catheters, insertion of these instruments in the urethra, or surgical interventions. Though localiza-

tion may occur in any organ, it is most frequent in the eyes, kidneys, lung, spleen, and the CNS, as well as around a cardiac value prosthesis or in the bones.

The antimycotic recommended for mucosal and skin candidiasis is nystatin; clotrimazole is also effective. Amphotericin B or fluconazole are used to treat other sites.

A cooperative study in 18 medical centers in Europe evaluated the efficacy, harmlessness, and tolerance of oral fluconazole (50 mg/day in a single dose) and of polyenes (oral amphotericin B at 2 g/day or nystatin at 4 million units/day in four or more doses) in preventing mycotic infection. The study included 536 patients hospitalized with a malignant disease who were about to receive chemotherapy, radiotherapy, or bone marrow transplants, including patients who already had neutropenia or who were expected to develop it. Treatment was administered for approximately 30 days. Oral fluconazole proved to be more effective than the oral polyenes in preventing buccopharyngeal infection and was equally effective in preventing infections in other parts of the body in patients with neutropenia. Side effects were recorded in 5.6% of 269 patients in the group treated with fluconazole and 5.2% of 267 patients treated with polyenes. These reactions led to a discontinuation of treatment in seven patients in each group (Philpott-Howard *et al.*, 1993).

The Disease in Animals: Candidiasis in chicks, poults, and other fowl is usually sporadic. Epidemic outbreaks sometimes occur, particularly in poults, with mortality ranging from 8% to 20%. Avian candidiasis is an infection of the upper respiratory system. In young birds it sometimes has an acute course, with nervous symptoms. However, the disease is generally asymptomatic and diagnosis occurs postmortem. The most frequent lesion is found in the crop and consists of plaques that resemble curdled milk and adhere lightly to the mucosa. In adult birds, candidiasis has a chronic course and causes thickening of the crop wall, on which a yellowish necrotic material accumulates. In Israel, a strange epidemic of a venereal disease in geese that affected many farms was described. The disease began with reddening and tumefaction of the mucosa of the penis or cloaca; the lesion later became gangrenous and a portion of the penis was lost. Examinations indicated a mixed flora of bacteria and *C. albicans*. Experimental inoculation of the bacterial flora did not affect the birds; in contrast, it was possible to reproduce the disease with *C. albicans* isolated from the lesions.

Oral candidiasis occurs sporadically in calves, colts, lambs, swine, dogs, cats, laboratory mice and guinea pigs, as well as in zoo animals. *Candida* spp. can, on rare occasions, lead to mastitis and abortions in cattle. A systemic disease due to *C. albicans*, with lesions in various organs, was reported in calves that underwent prolonged treatment with antibiotics. Skin lesions and thrush have been described in cats.

Source of Infection and Mode of Transmission: *C. albicans* occurs as a component of the normal flora in the digestive system of a high percentage of healthy individuals and animals. The yeast is also found in nature.

In young fowl, *C. albicans* is probably a primary etiologic agent, while in man candidiasis is almost always associated with other diseases. Prolonged treatment with antibiotics, cytotoxic agents, and corticosteroids is a predisposing factor. The use and abuse of antibiotics over an extended period is an important factor in the proliferation of and later infection by *Candida* and other fungi, in that they alter the natural flora of the mucosal surfaces.

Most infections have an endogenous source. The infection can be spread through contact with oral secretions, skin, vagina, and feces of sick individuals or carriers. A mother with vaginal candidiasis can infect her child during childbirth. Balanitis may in some cases be due to sexual relations with women suffering from vaginitis caused by *C. albicans*. In nurseries, particularly in units for premature infants, the infection may have an environmental source (see the section on occurrence in man). An exogenous infection probably occurred due to indirect contact between patients in a hospital bone marrow transplant unit and an intensive care unit (Vázquez *et al.*, 1993).

Role of Animals in the Epidemiology of the Disease: It is a disease common to man and animals. There are no known cases of transmission from animal to animal, but human-to-human transmission has occurred, as in the case of mothers who infect their children during childbirth.

Diagnosis: Given the ubiquitous nature of the yeast, laboratory diagnosis must be conducted with great care. Direct examination of lesions in the nails, skin (in potassium hydroxide) or the mucous membranes (in lactophenol-cotton blue), or microscopic observation of gram-stained films, is diagnostically significant if the microorganism is found in great numbers. The examination should be carried out with fresh specimens. The presence in lesions of the budding yeast form together with forms with hyphae or pseudohyphae has diagnostic value. Isolation of the agent from blood, pleural or peritoneal fluid, cerebrospinal fluid, or biopsy material obtained aseptically from closed localized foci permits diagnosis of disseminated candidiasis. However, it should be kept in mind that fungemia may be transient and is not always indicative of systemic infection. Hemocultures can detect candidemia in 35% to 44% of patients with disseminated candidiasis. *C. albicans* grows well in a medium of blood agar and Sabouraud agar at 25°C and 37°C. It can be identified by demonstrating the presence of chlamydospores upon seeding in depth a plate of corn meal agar and observing it at 24 and 48 hours. Since another characteristic of this species is the production of germinating tubes, identification can be performed by adding a small amount of culture to a small amount of serum and incubating the mixture at 37°C for two to four hours (Carter and Chengappa, 1991). The other species of *Candida* can be identified by their biochemical properties of carbohydrate fermentation and assimilation. A labeled anti-*C. albicans* globulin for immunofluorescence testing of smears of pathologic or cultured materials is available.

The most widely used serologic test to diagnose systemic candidiasis is immunodiffusion or double diffusion in ouchterlony agar gel, which cumulative experience has shown to be highly sensitive and specific. The immunoelectrophoresis test correlates well with the immunodiffusion test and results are obtained in only two hours. Nonetheless, serologic diagnosis of systemic candidiasis presents serious difficulties and an increase in patients' titers should be confirmed. Immunosuppressed patients have a poor humoral response, and thus an attempt has been made to use techniques that detect antigenemia rather than circulating antibodies. To date the results have not been very encouraging. Sensitivity is low (Lemieux *et al.*, 1990; Bougnoux *et al.*, 1990). Tube agglutination, indirect immunofluorescence, and indirect hemagglutination are also useful tests if the antibody level detected is above that prevalent in the normal population. The predominant or sole antibodies in healthy individuals are IgM. In contrast, with systemic candidiasis there is an initial rapid increase of IgM and then IgG, with subsequent reduction of IgM and persistence of IgG.

Control: Neonatal candidiasis can be prevented by treating the mother's vaginal candidiasis with nystatin during the third trimester. This antimycotic antibiotic can also be used in patients undergoing prolonged treatment with broad-spectrum antibiotics. Plastic catheters should be avoided. Generalized thrush in weakened patients can be halted by treating the oral lesions. To prevent epidemics in nurseries, patients with oral thrush should be isolated and strict hygiene measures established. As a preventive measure, nutritional deficiencies should be corrected, given that candidiasis occurs with greater frequency in patients with vitamin deficiencies or inadequate diets (Ajello and Kaplan, 1980).

Recommended control measures in case of a moniliasis outbreak among fowl include destroying all sick birds and administering copper sulphate (1:2,000) in the drinking water and nystatin (110 mg/kg) in the feed.

To date there is no vaccine.

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COCCIDIOIDOMYCOSIS

ICD-10 B38.0 acute pulmonary coccidioidomycosis; B38.1 chronic pulmonary coccidioidomycosis; B38.3 cutaneous coccidioidomycosis; B38.7 disseminated coccidioidomycosis; B38.8 other forms of coccidioidomycosis

Synonyms: Posada's disease, San Joaquin Valley fever, desert fever.

Etiology: *Coccidioides immitis*, a diphasic fungus that exists in the mycelial phase when it is a soil saprophyte, and in the spherule phase in organic tissues and fluids.

The life cycle of *C. immitis* is unique among pathogenic fungi. The fungus occurs in one phase in the natural environment, i.e., the soil of semiarid regions, and in another when it is parasitic in the mammalian host. In the soil, *C. immitis* develops as a mycelium (a mass of filamentous hyphae that make up the fungus). The cycle begins with the arthroconidium, or arthrospore (spore formed in the hyphae), which in a suitable medium germinates and forms a branching, septate mycelium. When the mycelium fragments, it releases into the air arthroconidia 2 to 5 microns in size. The parasitic phase begins with the inhalation of arthroconidia by man and animals. Arthroconidia grow to form thick-walled spherules 10 to 80 microns in diameter. The cytoplasm of the spherules divides to produce hundreds of endospores which, when released, disperse into the surrounding tissue and give rise to new spherules. The parasitic cycle lasts from four to six days (Drutz and Huppert, 1983) and can revert to the saprophytic or mycelial phase if the endospores reach the soil upon the death of the infected animal or through bodily excretions. The endospores give rise to hyphae and renew the cycle (Stevens, 1990). However, the mycelial cycle does not depend on this reversion as the hyphae contain large amounts of arthroconidia that are dispersed by the wind and colonize new sites in the soil.

Geographic Distribution: Limited to the Americas. The fungus is found in arid and semiarid areas of the United States Southwest, northwestern Mexico, Argentina,

Colombia, Guatemala, Honduras, Paraguay, Venezuela, and probably Bolivia. The endemic area in Latin America is estimated to cover 1.5 million km^2, more than 1 million km^2 of which are in Mexico (Borelli, 1970).

Occurrence in Man: In some endemic areas the rate of infection seems to be very high and it is estimated that in some of these areas in the United States nearly 100% of the population could contract the infection within a few years (Fiese, cited by Ajello, 1970). There are an estimated 25,000 to 100,000 cases in the US each year. Approximately 20% of the cases involve people who live outside endemic areas and become infected while visiting them (Drutz and Huppert, 1983). Some cases have also been described in Europe (the former Czechoslovakia, Great Britain, and Denmark). The rate of reactors to the skin test in different endemic areas varies from 5% to more than 50% of the population. There is a significant increase in cases in the United States. In 1991, 1,208 new cases were recorded in California as compared to 450 cases per year on average in the previous five years. Of these cases, 80% came from Kern County, a known endemic area. Sixty-three percent of the cases were reported from October through December. The outbreak in California could have been associated with prolonged drought, followed by occasional heavy rains. Another important factor could be migration to California of people not previously exposed to the fungus. In the United States, endemic areas are found in Arizona, California, Nevada, New Mexico, Texas, and Utah (CDC, 1993). The data on South America are more fragmentary, but the rate of infection appears to be lower in this region.

Occurrence in Animals: Natural infection has been found in many species of mammals. Infection is very frequent in cattle and dogs in endemic areas. Veterinary inspection has discovered coccidioidomycosis lesions in 5% to 15% of the cattle slaughtered in abattoirs in central Arizona (USA). Several million cattle are thought to be infected in the endemic areas of the southwestern United States. Infection has also been demonstrated in sheep, horses, swine, and wild rodents.

Several studies were carried out on animals in the endemic region of Mexico. In the state of Sinaloa, sera from 100 hogs and 200 cattle were examined by immunoelectrophoresis and reactions were found in 12% and 13%, respectively (Velasco Castrejón and Campos Nieto, 1979). In the state of Sonora, when the intradermal test using coccidioidin was conducted on 459 cattle, 6.75% tested positive. Another study performed histological examinations of granulomatous lesions discovered in 3,032 slaughtered cattle and found that the lesions in 77 (44%) of 175 animals confiscated for suspected tuberculosis were actually caused by *C. immitis*, indicating a rate of infection of 2.5% in all the animals (Cervantes *et al.*, 1978).

The Disease in Man: The incubation period lasts from one to four weeks. An estimated 60% of infections occur asymptomatically and are only recognizable with the intradermal test. The remaining 40% present as a respiratory disease with acute symptoms similar to those of influenza and that generally pass without sequelae. About 5% of primary infections develop either an erythema multiforme or an erythema nodosum arthralgia. What is more common, however, is a light erythroderma or maculopapular eruption. Chest pain can be strong and pleuritic. The radiological picture is varied, but hilar adenopathy with alveolar infiltrates and infiltrates that change area are indicative of coccidioidal pneumonia (Ampel *et al.*, 1989). When

the primary respiratory disease does have sequelae, these consist of fibrotic or cavernous lesions in the lungs. Pneumonia may persist in some patients for six to eight weeks, accompanied by fever, chest pain, cough, or postration (persistent coccidioidal pneumonia). Mortality in these cases is high in immunocompromised patients. Another disease form is the chronic form, which can be confused with tuberculosis (Drutz, 1982).

Extrapulmonary dissemination generally occurs following the primary disease in approximately 0.5% of infections (CDC, 1993). Thoracic radiography may or may not show abnormalities. The most common localization is in the cutaneous and subcutaneous tissues. Cutaneous lesions generally consist of verruciform granulomas (usually on the face), erythromatous plaques, and nodules. Sometimes there are subcutaneous abscesses. Osteomyelitis occurs in 10% to 50% of disseminated cases and may affect one or more bones. Meningitis cases are frequent (33% to 50% of patients) and generally fatal within two years. Eosinophilic pleocytosis is frequent in coccidioidal meningitis and has diagnostic value (Ragland *et al.*, 1993). Other manifestations are thyroiditis, tenosynovitis, and prostatis (Drutz, 1982). Clinical coccidioidomycosis is more frequent among migrant workers and soldiers transferred to endemic zones. In endemic areas of *C. immitis* the symptomatic form of the disease is frequent in individuals infected by the human immunodeficiency virus. Immunodeficiency is an important risk factor for developing the disease (Ampel *et al.*, 1993).

Treatment is difficult and often unpredictable. Fungicides that were effective in some cases were not in other similar cases. It is estimated that less than 5% of those infected need treatment. Those who are suffering from a progressive illness, patients with severe primary pulmonary disease, and those who have disseminated infection should be treated. Treatment should also be considered for patients with a compromised immune system. Amphotericin B and ketoconazole are the medications most frequently used (Ampel *et al.*, 1989). The administration of 400 mg of fluconazole daily for up to four years to 47 patients with coccidioidal meningitis produced a favorable result in 37 patients (Galgiani *et al.*, 1993).

The Disease in Animals: The infection is asymptomatic in cattle. Lesions are generally limited to the bronchial and mediastinal lymph nodes. On rare occasions, small granulomatous lesions are found in the lungs and the submaxillary and retropharyngeal lymph nodes. Macroscopic lesions resemble those seen in cases of tuberculosis.

Ziemer *et al.* (1992) conducted a retrospective study of 15 cases of coccidioidomycosis in horses recorded from 1975 to 1984 in a university hospital in California, with diagnosis confirmed by culture or histopathology. The most common symptom in 53% of the horses was chronic weight loss, which ranged from 45.5 kg to 91 kg in three horses. One of the horses lost 24% of its body weight in three months. Thirty-three percent of the horses had a persistent cough. Sixty percent of the animals had respiratory abnormalities detected through auscultation. Other symptoms were depression and superficial abscesses.

Various cases have been described in sheep, with lesions similar to those in cattle.

In the same university hospital in California, 19 cases of coccidioidomycosis were recorded in llamas (10 from Arizona and 9 from California). Eighteen of the animals had disseminated mycosis, with pyogranulomas in the lungs, thoracic ganglia, liver,

and kidneys. The llama seems to be highly susceptible to infection by *C. immitis*. It is not known whether there are unapparent or slight infections in this species (Fowler *et al.*, 1992).

After man, the dog is the species most affected. In addition to the lungs, granulomatous lesions are found in nearly all organs. The disseminated form of the disease is frequent in dogs and the disease advances progressively until death (Timoney *et al.*, 1988).

Source of Infection and Mode of Transmission: *C. immitis* is a soil saprophyte in arid and semiarid regions. Its distribution in endemic zones is not uniform. The infection is transmitted to man and animals through inhalation of wind-borne arthrospores of the fungus; it occurs more frequently after dust storms. The infection can be contracted in the laboratory by inhaling the spores from fungus cultures.

Exposure to soil with a high concentration of the agent increases the risk of a symptomatic and severe disease. This was probably the case with two archeology students on a dig in southern California (Larsen *et al.*, 1985; Ampel *et al.*, 1989).

Those most exposed to contracting the infection are individuals without a history of the infection who visit or migrate to endemic areas.

Coccidioidomycosis is currently increasing in the United States due to significant growth in population and tourism in endemic areas.

In recent decades, due to the great increase in the use of immunosuppressant drugs for transplants, oncology, and rheumatology, as well as to AIDS, the severe form of the disease is seen more frequently (Ampel *et al.*, 1989).

Role of Animals: The soil is the common source of infection for man and animals. The fungus is not transmitted from one individual to another, because man and other infected animals do not produce arthroconidia, the infecting agent. An exceptional case due to aerosolization of endospores occurred during the autopsy of a horse with disseminated coccidioidomycosis. The veterinarian who performed the autopsy contracted the infection by inhaling the endospores (Kohn *et al*., 1992).

Diagnosis: Diagnosis is based on confirmation of the fungus's presence by means of: (1) direct microscopic examination that reveals spherules with endospores in sputum, pus, pleural fluid, or gastric juices (treated with a 10% solution of potassium hydroxide); (2) culture of clinical material; and (3) histopathology. Cultures should not be prepared in Petri dishes but in closed tubes so as to avoid infection of the handler and laboratory personnel. Appropriate biosafety equipment should also be used.

The skin test using coccidioidin or spherulin (considered to be more sensitive) is very valuable in epidemiologic studies. It is administered in the same way as tuberculin. The test should be read at 24 and 48 hours. A reaction of 5 mm or more is considered positive. This test is very useful for delimiting endemic areas. In infections by *C. immitis* there may be cross-reactions with other fungal antigens, especially histoplasmin. In clinical diagnosis, the intradermal test with a positive result is only significant if the patient had no reaction at the beginning of the illness. In a study comparing the tests with coccidioidin (prepared from the mycelial phase fungus) and spherulin (parasitic phase fungus) in patients with coccidioidomycosis, one preparation could not be shown superior to the other for diagnosis. Forty-three percent of the patients reacted positively to both preparations, another 43% reacted

negatively to both, and 14% has contradictory results. The lack of reaction in a high percentage of patients is perhaps due to defects in immune function, particularly in the case of advanced disease (Gifford and Catanzaro, 1981). Serologic tests in use are complement fixation (CF), precipitation, immunodiffusion, and latex agglutination. The combination of immunobiological tests provides useful information for both diagnosis and prognosis. In the first two weeks of the disease, IgM antibodies predominate, as can be demonstrated by the tube precipitation, latex agglutination, and immunodiffusion tests. IgG antibodies appear somewhat later and may be detected through CF or immunodiffusion. A persistent high CF titer with loss of reactivity to the skin test indicates dissemination of the infection. In 75% to 95% of meningitis cases, antibodies can be detected with the CF test (Drutz, 1982). Radioimmunoassay is useful for diagnosis and prognosis of the pulmonary disease. As patients improve, the test titer decreases (Catanzaro and Flataner, 1983). The CF test also indicates the efficacy of the treatment.

Control: It is recommended that persons from nonendemic areas not work in endemic areas, since they lack immunity against coccidioidomycosis. In the United States, dust control measures (paving roads, seeding lawns, sprinkling dust with oil) have been used successfully to protect military personnel.

People at risk of contracting disseminated coccidioidomycosis (pregnant women, immunocompromised patients) should be advised to avoid endemic areas. Trials of a vaccine made from formalin-inactivated spherules are being conducted in California and Arizona (USA). Animal tests have shown that the vaccine does not prevent the infection, but does arrest its progress and prevent dissemination of the disease (Drutz and Huppert, 1983). A test conducted from 1980 to 1985 with 1,436 vaccinated subjects and 1,431 subjects given a placebo showed a slight but statistically insignificant reduction in the incidence of coccidioidomycosis in the vaccinated group as compared to the group receiving the placebo. There was no difference between the two groups in the severity of the disease (Pappagianis, 1993). Treatment with antifungal drugs may be useful to prevent dissemination in high-risk patients with primary coccidioidomycosis.

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CRYPTOCOCCOSIS

ICD-10 B45.0 pulmonary cryptococcosis; B45.1 cerebral cryptococcosis; B45.2 cutaneous cryptococcosis; B45.3 osseous cryptococcosis; B45.7 disseminated cryptococcosis; B45.8 other forms of cryptococcosis

Synonyms: Torulosis, European blastomycosis, Busse-Buschke's disease.

Etiology: *Cryptococcus neoformans (Saccharomyces neoformans, Torulopsis neoformans, Torula histolytica)*, a saprophytic yeast growing in certain soils. The agent has a spheroid or ovoid shape, is encapsulated, ranges from 4 to 7 microns in diameter, and is gram-positive. It reproduces by means of buds attached by a delicate base to the parent cell. Research in recent years has demonstrated that *C. neoformans* has a sexual form and is a basidiomycete.

Of epidemiological interest is *C. neoforman*'s subdivision into four serotypes (A, B, C, and D) on the basis of capsular polysaccharide antigens. In turn, the serotypes are categorized in two varieties: *C. neoformans* var. *neoformans* (serotypes A and D) and *C. neoformans* var. *gattii* (serotypes B and C). In addition to biochemical, serological, and genetic differences, serotypes A and D are different in their perfect (sexual) state from serotypes B and C. Although a few A and D strains can be conjugated with B and C, their survival is short-lived (Diamond, 1990).

Geographic Distribution: Worldwide. In the Americas the disease has been confirmed in Argentina, Brazil, Canada, Colombia, Mexico, the United States, and Venezuela. Serotype A is prevalent throughout the world. Serotype D is common in some European countries (Denmark, Italy, and Switzerland), but rare in the United States. In contrast, serotypes B and C are more localized and are recognized as disease agents, particularly in southern California, southeastern Oklahoma, and some other areas of the United States, as well as in Asia (Kaplan *et al.*, 1981; Fromtling *et al.*, 1982). In some regions of Australia, a high percentage of isolated strains have the characteristics of the *gattii* strain, as in the case of the indigenous population in the Northern Territory. In one study, 25 of 26 isolates (24 of them from meningitis patients) corresponded to *gattii*. In another study, 21 of 22 strains (95.5%) were also of the *gattii* variety. In South Australia, which has a primarily urban population, 65.2% of 23 strains were classified as *gattii* (Ellis, 1987). Other sites with a high prevalence of *gattii* var. are Brazil (10 of 31 strains) and southern California (30 of 73) (Kwon-Chung and Bennett, 1984). In Argentina, 101 of 105 isolates from 1981–1990 were classified as *C. neoformans* var. *neoformans* and 4 as var. *gattii* (serotype B). These data are similar to those found in the United States (Bava and Negroni, 1992).

Occurrence in Man: Cases are sporadic, with a higher incidence in men than in women. From 1965 to 1997, 1,264 cases of cryptococcosis were documented in the United States. Of 848 cases confirmed between 1973 and 1997, 608 patients had meningitis and 240 had extrameningeal localizations. These data indicate a great increase as compared to earlier periods (Kaufman and Blumer, 1978). There were 85 cases in Malaysia between 1974 and 1980, predominantly among ethnic Chinese (Pathmanathan and Soo-Hoo, 1982). In the United States and Europe, cryptococcosis occurs primarily in patients with immune system defects (especially AIDS) or who are undergoing immunosuppressant treatment. The prevalence of the disease

has grown worldwide as the number of AIDS patients has increased. In Argentina, the annual number of cases ranged from four to eight until 1987, began to increase in 1988, and reached 35 cases in 1990. The age group most affected was 20- to 39-year-olds. More men were affected than women, particularly when the underlying disease was AIDS (Bava and Negroni, 1992). It is estimated that the male-female ratio was 3:1. The percentage of AIDS patients who contracted cryptococcosis in Argentina increased from 12.5% in 1990 to 25.9% in 1991. This percentage is similar to the incidence of cryptococcosis in AIDS patients in central Africa and southeast Asia (20% to 35%), but greater than that in Europe and the United States (6% to 10%). In greater Buenos Aires, cryptococcosis is second among the tracer diseases of AIDS, after esophageal candidiasis (Bava *et al.*, 1992). In Malaysia, on the other hand, only 14% of the patients studied had AIDS.

Epidemiologic studies based on the intradermal test indicate that many individuals exposed to the agent show no symptoms of the disease.

Occurrence in Animals: Rare, sporadic cases. Some epizootic outbreaks of mastitis and cryptococcal pneumonia have been described in cattle. The disease has been described in goats, horses, and cats.

The Disease in Man: The large majority of cases are meningitis or meningoencephalitis. This form is preceded by a pulmonary infection, which is often asymptomatic or, if symptomatic, may resolve spontaneously. In most cases of localization in the CNS, pulmonary invasion is not evident (Diamond, 1990). The initial pulmonary infection can resolve spontaneously, give rise to a granulomatous mass ("cryptococcoma"), or disseminate via the bloodstream. The pulmonary form manifests with fever, cough, chest pain, and hemoptysis. Radiography shows single or multiple nodules or large cryptococcomas. The course is usually chronic. When dissemination from the original pulmonary focus occurs, the infection localizes primarily in the meninges, spreading to the brain. The most obvious symptoms of the meningeal form of the disease are headache and visual disturbances. Other symptoms may include confusion, personality changes, agitation, and lethargy. Cryptococcal meningoencephalitis can follow a course lasting for weeks or months and is almost always fatal if not properly treated. The characteristic lesion in the brain is comprised of groups of fungal cysts without inflammation. This lesion can also be found in other sites (Diamond, 1990). Asymptomatic meningitis sometimes occurs when there are other locations and the disease is discovered through lumbar puncture and culture of the cerebrospinal fluid (Liss and Rimland, 1981). The lesion can affect the skin, the mucosa, and the bones, as well as various other organs. Cutaneous infection is characterized by the formation of papules and abscesses and subsequent ulceration.

Man is resistant to *C. neoformans*. There are cryptococcosis patients who show no obvious predisposing factors. However, the fungus is to a large extent an opportunistic pathogenic agent. The number of cases increased significantly with the HIV epidemic. In the United States, cryptococcosis is the fourth potential leading case of death in AIDS patients, after *Pneumocystis carinii*, cytomegaloviruses, and mycobacteria. A retrospective study of AIDS patients was conducted in a hospital in Porto Alegre, Brazil to determine the diseases that could affect the CNS. Between 1985 and 1990, 138 autopsies were performed and all the brains were examined macro- and microscopically. According to the results, 29 (21%) suffered from

cerebral toxoplasmosis; 17 (12%), from cryptococcosis; 2 (1%), from tuberculosis; and 1 (0.7%), from candidiasis. In addition, there were cadavers with vascular lesions and gliosis; 5% had encephalopathy due to HIV (Wainstein *et al*., 1992).

Cryptococcosis often appears in patients weakened by other diseases (reticuloendothelial system disorders, particularly Hodgkin's disease) and by corticosteroid treatment. The incubation period is unknown. Pulmonary lesions may precede cerebral lesions by months or years. It is estimated that some 100 deaths per year in the United States are due to cryptococcosis.

Intravenous amphotericin B in doses of 0.4–0.6 mg/kg per day for six weeks can be effective in many cases. Recently, the preferred therapy is a combination of intravenous amphotericin in reduced doses and oral flucytosine. This combination is not indicated for AIDS patients due to the early development of signs of flucytosine poisoning. Fluconazole is useful for preventing relapses after administering amphotericin B (Diamond, 1990; Benenson, 1990).

The Disease in Animals: The disease has been recognized in cattle, horses, sheep, goats, dogs, cats, nonhuman primates, and several species of wild animals (in zoos), but not in birds. Various cases have been described in sheep and goats with pulmonary disease and mastitis. Of four cases described in goats in Western Australia, the pulmonary form predominated in two animals; one had accumulated fluid in the pleural and peritoneal cavities, atelectatic lungs, and dark red plaque in the trachea from which *C. neoformans* was isolated; the fourth animal had an alopecic lesion on the head from which a yellow exudate seeped, which showed *Cryptococcus* spp. upon microscopic examination (Chapman *et al.*, 1990). The disseminated form of the disease is the form most commonly diagnosed in dogs and cats. Of 21 cases in dogs with a clinical history, 13 manifested the meningeal form, 4 the nasal form, and 1 osteoarticular involvement; the remaining animals had lesions in other organs. Six cases described in Australia all had the meningeal form (Sutton, 1981). The primary diagnosis in cats has been a disorder of the central nervous system, with granulomas in the eyes and nasal passages, as well as the cutaneous form. Of 29 cats with cryptococcosis, 24 (83%) had the nasal form and 15 had the cutaneous and subcutaneous form. One cat with a significant involvement of the nasal cavity developed meningoencephalitis and optical neuritis. Antibodies to feline immunodeficiency virus were detected in eight cats. These animals suffered from advanced or disseminated cryptococcosis. *C. neoformans* var. *neoformans* was isolated from 21 cats and *C. neoformans* var. *gattii* was isolated from 6 cats. Treatment with oral fluconazole yielded very good results. All the cats were cured except for one that died four days after treatment began (Malik *et al.*, 1992). Nasal and pulmonary tumors with a myxomatous consistency have been observed in various animal species. Several outbreaks of mastitis have been confirmed in cows, with visible abnormalities in the udder and changes in the milk. A few cases of meningoencephalitic and pulmonary cryptococcosis, cases affecting the frontal sinuses and para-orbital area, and abortions have been described in horses.

Source of Infection and Mode of Transmission: Serotypes A and D (*C. neoformans* var. *neoformans*) are ubiquitous and have been isolated from various environmental sources, such as soil, certain plants, bird feces, raw milk, and fruit juices. The causal agent is found frequently in pigeon roosts and in soil contaminated by pigeon feces. The creatinine in pigeon fecal matter serves as a source of nitrogen for *C. neo-*

formans, favoring its development and prolonging its survival in the soil. Pigeons do not become ill with cryptococcosis.

The environmental source of *C. neoformans* var. *gattii* was unknown until a few years ago. A study conducted in Australia succeeded in isolating var. *gattii* from 35 samples of bark and plant remains accumulated under the foliage of a species of eucalyptus, *Eucalyptus camaldulensis*. Attempts to isolate samples from other eucalyptus species were unsuccessful. *E. camaldulensis* has been exported to various countries in the Americas, Africa, and Asia. The air sample taken from beneath the foliage demonstrated that the presence of the agent in the air coincided with the eucalyptus' blooming season in late spring. These findings would explain the high incidence of *C. neoformans* var. *gattii* among the aborigines in Australia's Northern Territory, where these trees are abundant and the indigenous population lives in close contact with them (Ellis and Pfeiffer, 1990). Man and animals become infected by inhaling dust containing the causal agent. *C. neoformans*, which has no capsule in nature, becomes encapsulated in the lungs, allowing it to resist phagocytosis. Although all researchers agree that the infection is contracted through inhalation, there is still debate regarding the infecting element. Some believe it is the yeast form of the agent while others believe it is the basidiospores of the agent's sexual phase. It has also been pointed out that the yeast form would be too large (4 to 7 microns) to enter the alveoli, while basidiospores measure only about 2 microns (Cohen, 1982).

Role of Animals in the Epidemiology of the Disease: There are no known cases of transmission of the disease from animal to animal, from animal to man, or from man to man, except in the case of a corneal transplant (Beyt and Waldman, 1978).

Diagnosis: Diagnosis can be made through microscopic observation of encapsulated *C. neoformans* in tissues and body fluids, and can be confirmed by culture. The use of culture media to differentiate serotypes A and D from serotypes B and C now facilitates serotyping (Salkind and Hurd, 1982; Kwon-Chung *et al.*, 1982). The direct immunofluorescence test can be used for the same purpose for cultures and for some histological preparations (Kaplan *et al.*, 1981).

As the etiologic agent multiplies in the human host, the capsular polysaccharide of *C. neoformans* neutralizes antibodies. Excess antibodies can be detected in blood and urine, as well as in cerebrospinal fluid in cases in which the central nervous system is affected. Cases that come to receive medical attention are frequently far advanced. Consequently, better results are obtained if the medical examination is directed toward detecting the specific antigen rather than the antibodies. The plate latex agglutination test with particles sensitized by anticryptococcal globulin is used to detect the cryptococcal antigen. The enzyme-linked immunosorbent assay (ELISA) test is also available to detect the capuslar polysaccharide antigen of the etiologic agent. This test is much more sensitive than latex agglutination and permits earlier diagnosis (Scott *et al.*, 1980). In patients with meningoencephalitis, a sample of the cerebrospinal fluid is used for direct microscopic examination and a cell count, another examination with India ink to detect encapsulated fungus cells, and culture in Sabouroud's dextrose agar with incubation at 30°C to 37°C to isolate the fungus. The antigen is sought in serum and cerebrospinal fluid.

In England, 828 HIV-positive patients with fever were examined (in the United Kingdom, 85% of cases occur in immunodeficient individuals, while in the United States, 50% of patients apparently have a normal immune system). Sixty-nine of the

828 patients had meningitis. The cryptococcal antigen detection test was performed using the latex technique for the capsulated polysaccharide antigen. The test was positive in 16 of 17 patients with meningitis and with positive cultures (Nelson *et al*., 1990).

A study conducted on 20 cats with cryptococcosis and 184 uninfected animals used the latex agglutination test. The latex particles were sensitized with rabbit antibodies to *C. neoformans* to detect the antigen in the cats' serum. The test was positive in 19 of the 20 cats with cryptococcosis and in none of the controls (Medlean *et al*., 1990). According to some authors, the test has prognostic value in humans, in that a progressive disease is accompanied by a rise in titer, whereas there is generally a decline in the agglutinating titer when there is clinical improvement.

Control: There are no specific measures for preventing the disease. It is important to control underlying diseases and to reduce prolonged treatment with corticosteroids as much as possible.

Controlling the pigeon population might prevent some cases. Human exposure to accumulations of pigeon excrement should be avoided, particularly on windowsills, in roosts, perches, and nests. Removal of pigeon excrement should be preceded by chemical decontamination or by wetting down with water or oil to prevent aerosolization (Benenson, 1990).

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DERMATOPHYTOSIS

ICD-10 B35

Synonyms: Tinea, dermatomycosis, ringworm.

Etiology: Several species of *Microsporum* and *Trichophyton* and the species *Epidermophyton floccosum*. Ecologically and epidemiologically, three groups of species are distinguished according to the reservoir: anthropophilic, zoophilic, and geophilic. This discussion will consider only zoophilic species transmissible to man.

Dermatophytes were formerly considered imperfect fungi, *Fungi imperfecti* or *Deuteromycotyna.* However, several species have been shown to reproduce sexually. The most important zoophilic species are *Microsporum canis* (whose perfect state received the name *Nannizzia otae*), *Trichophyton mentagrophytes (Arthroderma benhamiae*), and *T. verrucosum*. Species of more limited interest are *M. equinum, T. equinum, M. gallinae, M. nanum, M. persicolor*, and *T. simii*. The species *T. mentagrophytes* is subdivided into two varieties: *T. mentagrophytes* var. *erinacei* and var. *quinckeanum.*

The infecting element is the arthrospore (an asexual spore formed in the hyphae and released when these break down) of the parasitic phases. Conidia that form in organic material substrates (where the fungus may form sexual and asexual spores) may also be infective.

A notable characteristic is that the hyphae and spores are highly resistant in desquamated epithelium, where they may remain viable for several months or even years if they don't dry up.

Geographic Distribution: Among the zoophilic species, *M. canis, T. verrucosum, T. equinum*, and *T. mentagrophytes* are distributed worldwide. *T. mentagrophytes* var. *erinacei* has limited distribution (France, Great Britain, Italy, and New Zealand) and *T. simii* is limited to Asia. The geographic distribution of these fungi depends on the dispersion of the host animals. The host hedgehog of *T. mentagrophytes* var. *erinacei* exists only in Europe and in New Zealand, where it was introduced from Europe. The abundance or rarity of a dermatophyte species depends largely on the rural or urban habitat and the relationship between man and animals. *M. canis* is a fungus that occurs primarily in urban areas where its natural hosts, the dog and cat, are abundant and in close contact with humans. In contrast, *T. verrucosum* is found in rural areas, particularly among stabled cattle, i.e., generally in areas with cold or temperate climates.

Occurrence in Man: Dermatophytic infections are common, but their exact prevalence is unknown. The disease is not notifiable and, moreover, many people with minor infections do not see a doctor. Most of the data come from dermatologists, mycology laboratories, and epidemiologic investigations. Economically advanced countries have experienced a marked reduction in some species of anthropophilic dermatophytes. This is true of *M. audouinii*, which causes epidemic outbreaks of tinea capitis. In such countries, zoophilic dermatophytes are now much more significant. A study conducted in England on 23 families to evaluate the prevalence of the infection among family members who were in contact with clinically or sub-clinically infected young cats found that 46 (50%) out of 92 individuals contracted the infection due to

M. canis. The percentage of adults infected was 44.2% and that of children and young people was 80% (12 out of 15) (Pepin and Oxenham, 1986). A retrospective study of 1,717 Ministry of Agriculture veterinarians in the United Kingdom found that dermatophytosis was the most common zoonosis, with a prevalence of 24% (Constable and Herington, cited by Pepin and Oxenham, 1986). In northeast Madrid (Spain), the annual incidence of dermatophytosis was found to be 84 cases per 10,000 inhabitants, and the most frequent agents in 135 patients were *Epidermophyton floccosum*, an anthropophilic dermatophyte (35.5%), *Microsporum canis* (26.6%), and *Trichophyton mentagrophytes* (20.7%) (Cuadros *et al.*, 1990). A retrospective study conducted in Argentina on 1,225 samples of superficial mycoses (95% adult patients and 5% children) indicated that 60% were dermatophytes. The most common agent was *T. rubrum* (66.6%), followed by *T. mentagrophytes* (20%), *M. canis* (8%), and others (Canteros *et al.*, 1993). In Peru, it is likely that zoophilic species are responsible for 21% of human dermatomycoses (Gómez Pando and Matos Díaz, 1982). A study conducted in India found that *T. verrucosum* and *T. mentagrophytes* var. *mentagrophytes* were responsible for 56 (38.6%) of 145 human isolates and for 50 (53.8%) of the 93 human cases in the rural area (Chatterjee *et al.*, 1980).

Many human cases originated in Hungary, in a nursery of 5,500 rabbits. Over the course of six months, all the rabbits were infected by *T. mentagrophytes* var. *mentagrophytes* (var. *granulosum*) and 38 human cases appeared among workers and their families (Szili and Kohalmi, 1983).

Occurrence in Animals: In recent years, epidemiologic studies have demonstrated that dermatophytic infection in animals is very common. Tinea occurs more frequently among stabled animals than those kept in open pastures throughout the year.

Infection by *M. canis* is very common in cats and dogs and is often asymptomatic. In Lima (Peru) and its environs, *M. canis* was found in 12 (15%) of 79 cats without apparent lesions examined and *T. mentagrophytes* in 8 (10%). *M. canis* was isolated from 17 (3.9%) of 432 samples from dogs, and *T. mentagrophytes* from 22 (5%) (Gómez Pando and Matos Díaz, 1982). In the United Kingdom, in 1,368 dermatophytes isolated between 1956 and 1991, *Microsporum canis* was diagnosed in 92% of infected cats and in 65% of dogs (Sparkes *et al.*, 1993). Long-haired cats and dogs under one year of age were most affected (Sparkes *et al.*, 1993).

The cat is the most common host and reservoir of *M. canis*. Some studies have found infection in between 6.5% and 88% or more of the cats examined. These studies were conducted in areas where the cats were in contact with other cats. A completely different picture was obtained in a study conducted at the University of Wisconsin (USA). Fifteen genera of fungi, 13 of which were considered saprophytes, were isolated from the skin of 172 cats that lived alone with their owners. *T. rubrum*, considered an anthropophilic dermatophyte, was isolated from 14 cats; *T. gypseum* and *M. vanbreuseghemii*, both geophilic, were isolated from 1 cat each; but *M. canis* was isolated from none. *T. rubrum* is a common agent in human dermatophytosis, but the role that cats might play in its transmission to man is unknown (Moriello and De Boer, 1991).

The Disease in Man: Dermatophytosis, or tinea, is a superficial infection of the keratinized parts of the body (skin, hair, and nails). As a general rule, zoophilic and geophilic dermatophytes produce more acute inflammatory lesions than the anthro-

pophilic species, which are parasites better adapted to man. The *Microsporum* species cause most cases of tinea capitis and tinea corporis, but are rarely responsible for infection of the nails (onychomycosis) or skin folds (intertrigo). However, the *Trichophyton* species can affect the skin in any part of the body.

There are two varieties of *T. mentagrophytes*: an anthropophilic variety (var. *interdigitale*) that is relatively nonvirulent in humans and localizes in the feet (athlete's foot), and a zoophilic variety (morphologically granular) that causes a very inflammatory dermatophytosis on different areas of the human body. The zoophilic variety is usually found in rodents, cats, dogs, and other animals. Transmission to man is probably caused by contamination of his habitat by hair from infected animals. Several epidemic outbreaks of inflammatory dermatophytoses on different parts of the body among the U.S. troops in Vietnam were caused by *T. mentagrophytes* var. *mentagrophytes* (var. *granulosum*). About one-fourth of the rats trapped in the vicinity of military camps were infected with strains of the same variety of fungus. Among the inhabitants of the region, the disease was seen only in children, suggesting that adults were probably immunized by infections contracted during childhood.

Currently, *M. canis* is one of the principal etiologic agents of tinea and, in many countries, has displaced the anthropophilic species *M. audouinii* as the cause of tinea capitis. In South America, *M. canis* is the most common of the microspora.

The incubation period of the disease is one to two weeks. Tinea of the scalp is most frequent among those aged 4 to 11 years and its incidence is higher among males. The disease begins with a small papule, the hair becomes brittle, and the infection spreads peripherally, leaving scaly, bald patches. Suppurative lesions (kerions) are frequent when the fungus is of animal origin. Tinea caused by *M. canis* heals spontaneously during puberty.

Suppurative tinea barbae, which affects rural populations, is caused by *T. mentagrophytes* of animal origin. However, in the United States dry tinea barbae is caused by *T. mentagrophytes* of human origin and by *T. rubrum* (Silva-Hunter *et al.*, 1981).

Tinea corporis is characterized by flat lesions that tend to be annular. The borders are reddish and may be raised, with microvesicles or scales.

Tinea corporis in children is usually an extension of tinea capitis to the face and is caused by *M. canis* or *M. audouinii*. Active lesions may also appear on the wrists and neck of mothers or young adults who have contact with the infected child. Tinea corporis in adults, occurring primarily on the limbs and torso, is chronic in nature and usually is caused by the anthropophilic dermatophyte *T. rubrum* (Silva-Hunter *et al.*, 1981).

Tinea pedis (athlete's foot), the incidence of which is increasing worldwide, is caused by anthropophilic species of *Trychophyton* and, to a lesser extent, by *Epidermophyton floccosum* (also anthropophilic).

In AIDS patients, mycosis caused by *T. mentagrophytes* and *M. canis* can be cutaneous and disseminated (Lowinger-Seoane *et al.*, 1992). AIDS patients may suffer from extensive dermatophytosis caused by a fungus as rare in humans as *M. gallinae*, a zoophilic dermatophyte; there are only seven known cases, all of them localized (del Palacio *et al.*, 1992).

The recommended treatment is topical application of antimycotics. The azoles (miconazole, clotrimazole, econazole, bifonazole, oxiconazole, tioconazaole, and others) are used most frequently. These antimycotics produce good results in all forms of dermal tinea caused by zoophilic dermatophytes.

Topical treatment should continue for two to four weeks. Naftifine is another powerful antimycotic (Hay, 1990).

The Disease in Animals: The most important species considered reservoirs of dermatophytes transmissible to humans are cats, dogs, cattle, horses, and rodents.

CATS AND DOGS: The most important etiologic agent in these animals is *M. canis*. This dermatophyte species is very well adapted to cats and approximately 90% of infected animals manifest no apparent lesions. When lesions do occur, they appear primarily on the face and paws.

Lesions are frequent and apparent in dogs and may appear on any part of the body in the form of tinea circinata (ringworm).

Dogs and cats may also be infected by other dermatophytes, particularly *T. mentagrophytes*.

CATTLE: The principal etiologic agent of tinea in cattle is *T. verrucosum* (*T. faviforme, T. ochraceum, T. album*, and *T. discoides*). The disease is more common in countries where animals are kept in stables during winter, and its incidence is higher in calves than in adults. Lesions may be as small as 1 cm in diameter or may cover extensive areas; they are most frequently located on the face and neck, but lesions are also found with some frequency on other parts of the body, such as the flanks and legs. The lesion is initially characterized by grayish white, dry areas with a few brittle hairs. The lesion then thickens and resembles a light brown scab. The scab falls off, leaving an alopecic area. The condition clears up spontaneously within two to four months.

HORSES: Dermatophytosis in horses is caused by *T. equinum* and *M. equinum*; the latter is rare in the Americas. Lesions are usually found in areas where the harness causes friction. They are dry, bald, covered with scales, and the skin is thickened. Colts are the most susceptible. Infections caused by *Trichophyton equinum* are usually more severe, with pruritus and exudative lesions causing the hair to stick together in clumps. When they drop off, they leave alopecic areas. Infections due to *M. equinum* cause less serious lesions with small scaly areas with brittle hairs.

RODENTS AND LAGOMORPHS: Tinea favus of mice, caused by *T. mentagrophytes* var. *quinckeanum*, is widely distributed throughout the world and is transmissible to domestic animals and man. The lesion is white and scabby and localized on the head and trunk. *T. mentagrophytes* (var. *mentagrophytes*) is another dermatophyte common to rodents. Laboratory mice and guinea pigs are mostly infected by *T. mentagrophytes*, and may not have apparent lesions; the agent's presence is often detected when humans contract the infection. It is also transmissible to dogs.

Dermatophytosis in rabbits is also caused by *T. mentagrophytes* and usually occurs in animals that have recently been weaned. Scabby areas of alopecia are seen clinically around the eyes and nose. Secondary lesions appear on the feet. This disease is self-limiting.

SHEEP AND GOATS: Tinea is rare in these species. The lesions localize on the head and face. The most frequent agent is *T. verrucosum*. The lesions are limited to areas of the head covered by hair; they are circular, balding, and have thick scabs. Two outbreaks of dermatophytosis caused by *M. canis* were described in Australia. In the first outbreak, transmission was attributed to cats and to the use of contaminated shearing implements. In the second, with 20% of 90 sheep infected, it was not pos-

sible to determine how the infection had been introduced, but its spread throughout the establishment was undoubtedly due to shearing implements and close contact among the animals immediately after being sheared (Jackson *et al.*, 1991).

SWINE: The most common agent of swine tinea is *M. nanum*. Infection has been confirmed in Australia, Canada, Cuba, Kenya, Mexico, New Guinea, New Zealand, and the United States. This dermatophyte was isolated in only a few human cases. The lesion is characterized by a wrinkled area covered by a thin, brown scab that detaches easily. *M. nanum* lives as a soil saprophyte in areas where swine are raised and is classified as geophilic.

FOWL: Tinea favus in hens occurs sporadically throughout the world and is rarely transmitted to man. Its agent is *T. gallinae*.

Source of Infection and Mode of Transmission: The natural reservoirs of zoophilic dermatophytes are animals. Transmission to man occurs through contact with an infected animal (either sick or a carrier) or indirectly through spores contained in the hair and dermal scales shed by the animal. Dermatophytes remain viable in shed epithelium for several months or even years. The same animal can infect several people within a family, but a zoophilic dermatophyte does not usually spread from person to person and, unlike the anthropophilic dermatophytes, does not cause epidemic tinea. Cases of human-to-human transmission of *M. canis* have been observed, but the agent loses its infectiveness for man after a few intermediaries (Padhye, 1980). A nosocomial infection was described in a nursery for newborns. Although tinea of the scalp is common among children, it is rarely found in newborns. The common source of the infection turned out to be a nurse who had an indolent infection due to *M. canis* (Snider *et al.*, 1993). *T. verrucosum*, whose principal reservoir is cattle, is found in infections in rural populations. A study conducted in Switzerland found that 14% of those working with infected cattle contracted dermatophytosis caused by *T. verrucosum* (Haub, as reported to Gudding *et al.*, 1991). This mycosis also has economic consequences, in that skins from the infected animal depreciate in value. It is a reportable disease in Norway. In contrast, *M. canis* is transmitted by cats and dogs to urban and rural populations. The cat is considered the principal source of infection for humans due to the custom of picking up and petting a cat, as well as to its high rate of infection. Cats can also host the anthropophilic dermatophyte, *T. rubrum*, in their hair, but it has not been demonstrated that they can transmit it to man. Infection due to *T. mentagrophytes* var. *mentagrophytes* (var. *granulosum*) and *T. mentagrophytes* var. *quinckeanum* is indirectly transmitted from rodents to man via residues of shed epithelium in the environment. Cats and dogs can also become infected by these dermatophytes in the same way or by direct contact when they hunt rodents and can, in turn, transmit the infection to man.

Animal-to-animal transmission occurs in the same ways. Crowding and reduced organic resistance influence the incidence of infection.

Role of Animals in the Epidemiology of the Disease: Animals are the reservoir of zoophilic dermatophytes and the source of infection for man. As in other zoonoses, human-to-human transmission is rare. Transmission of anthropophilic dermatophytes from humans to animals is also rare.

The dermatophyte *M. gypseum* is the causal agent of sporadic cases of tinea in humans and animals; its reservoir is the soil (geophilic).

Diagnosis: Clinical diagnosis can be confirmed by the following methods: a) microscopic observation of hair and scales from lesions; this method can provide a diagnosis at the genus level, since the spores surround the hair shaft in an irregular mosaic when infection is due to *Microsporum* and are arranged in chains when infection is due to *Trichophyton*; b) the use of Wood's light (filtered ultraviolet light), under which hair infected by many species of *Microsporum* exhibits a bright blue-green fluorescence; c) isolation in culture media, the only method that permits identification of the species.

Control: Prevention of human dermatophytoses caused by zoophilic species should be based on controlling the infection in animals, although this is difficult to accomplish. Avoiding contact with animals that are obviously sick can prevent a certain percentage of human cases. These animals should be isolated and treated with topical antimycotics or griseofulvin administered orally. Remains of hair and scales should be burned and rooms, stables, and all utensils should be disinfected. Apparently healthy cats can be examined with Wood's light. Controlling the rodent population is a useful measure.

In cold climates where animals are stabled over long periods of time, dermatophytoses can be a problem in cattle and horses. Man and animals respond to infection with a humoral and cellular immunity, as has been demonstrated by experiments as well as by the observation that animals once infected are protected against reinfection. Two vaccines were developed in the former Soviet Union: one for cattle, made from an attenuated strain of *T. verrucosum*, and another for horses, made from *T. equinum*. Both vaccines yielded satisfactory results in preventing dermatophytoses. The vaccine was used in Norway in 200,000 cattle with very good results (Aamodt *et al.*, 1982). An eradication program was established in Gausdal, Norway; vaccination was required for all cattle for a period of six years, followed by voluntary vaccination thereafter. The prevalence of infected herds was 70% and eradication was achieved in 1987. A live attenuated vaccine was used (two doses with an interval of 14 days) along with disinfection of stables, isolation of infected animals, and other hygiene methods (Gudding *et al.*, 1991).

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HISTOPLASMOSIS

ICD-10 B39.0 acute pulmonary histoplasmosis capsulati; B39.1 chronic pulmonary histoplasmosis capsulati; B39.3 disseminated histoplasmosis capsulati; B39.5 Histoplasma duboisii

Synonyms: Reticuloendothelial cytomycosis, cavern disease, Darling's disease.

Etiology: *Histoplasma capsulatum*, a dimorphic fungus that has a yeast form in the parasitic phase and develops a filamentous mycelium in the saprophytic phase, producing macroconidia and microconidia. The yeast form may also be grown in the laboratory by culturing the fungus in an enriched medium at 37°C. The perfect (or sexual) state of the fungus is also known and has been given the name *Emmonsiela capsulata*.

There are two known varieties of the agent: *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii*. They are indistinguishable in the mycelial phase but in infected tissue the yeast-form cells of var. *duboisii* are much larger (7–15 microns) than those of var. *capsulatum* (2–5 microns). The tissue reactions they produce are also different. In regions in which the two varieties of the fungus coexist, the use of monoclonal antibodies in the ELISA or Western blot tests has been suggested for differentiating them in the yeast phase (Hamilton *et al.*, 1990).

Geographic Distribution: Distribution of var. *capsulatum* is worldwide and more abundant in the Americas than other continents. Autochthonous human cases are rare in Europe and Asia. The var. *duboisii* is known only in Africa between 20° S and 20° N (there are known cases in Madagascar) (Coulanges, 1989), where the other variety is known to exist as well. Distribution of the fungus in the soil is not uniform, as some regions are more contaminated than others and microfoci exist where the agent is highly concentrated. The assumption is that endemic areas would be determined by the number of microfoci. As for the *duboisii* variety, efforts to determine its habitat in the environment have been unsuccessful.

Occurrence in Man: Judging from the results of the histoplasmin intradermal test, the rate of infection is very high in endemic areas. It has been estimated that in the United States, where the infection is concentrated in the Missouri, Ohio, and Mississippi river basins, 30 million inhabitants have been infected by *Histoplasma* and some half million people become infected each year (Selby, 1975). The disease appears sporadically or in epidemic outbreaks. Isolated cases frequently elude diagnosis. There was an outbreak in 1980 with 138 cases of acute pulmonary disease

among workers in a lime quarry in northern Michigan, an area not considered endemic (Waldman *et al.*, 1983). Another outbreak occurred in 1978–1979 at the Indianapolis campus of Indiana University, affecting 435 people. Again in 1980–1981, an outbreak in an area close to the same university affected 51 people (Schlech *et al.*, 1983). Histoplasmosis is considered the most common systemic mycotic infection in the United States (Loyd *et al.*, 1990). There are also endemic regions in Latin America. Although prevalence varies from region to region, it has been claimed that the entire population of Latin America lives within or near areas where the infection can be contracted (Borelli, 1970). In Mexico, epidemic outbreaks or isolated cases of the disease have been recorded in all but two states. There was a study of 11 outbreaks affecting 75 people in 1979, with mortality at 5.3%, and 12 outbreaks affecting 68 people in 1980. Most of the cases occurred in people who for occupational, educational, or recreational reasons had visited caves, abandoned mines, and tunnels in which bat droppings had accumulated. More than 2,000 large mines have had to be abandoned because of the presence of *H. capsulatum* due to large bat colonies (OPS, 1981). There are also endemic areas in Guatemala, Peru, and Venezuela (Ajello and Kaplan, 1980). In Cuba, three outbreaks, one of which affected 521 people, occurred between 1962 and 1963. In 1978 there was an outbreak among students who visited a cave in the province of Havana; more recently, in a cave in the city of Morón, seven of eight spelunkers contracted the disease (González Menocal *et al.*, 1990).

Although the infection is common, the clinical disease is much less so. Radiography revealed pulmonary calcifications in a high percentage (about 25%) of people reacting to histoplasmin. Approximately 90% of those who have a positive reaction to the histoplasmin hypersensitivity skin test are clinically normal.

In Africa, there are some 200 known cases of histoplasmosis due to the *duboisii* variety (Coulanges, 1989).

Occurrence in Animals: Many species of domestic and wild mammals are susceptible to the infection. Surveys using the histoplasmin test have shown that infection is frequent in cattle, sheep, and horses in endemic areas. Dogs are the animal species in which the infection appears most frequently with clinical symptoms. Of 14,000 dogs admitted to the University of Ohio clinic (USA) over the course of four years, histoplasmosis was diagnosed in 62 (0.44%) (Cole *et al.*, 1953).

The Disease in Man: When conidia are inhaled, they can lodge in the bronchioles and alveoli. After a few days, they germinate and produce yeasts that are phagocytized by macrophages where they proliferate. The macrophages move toward the mediastinal lymph nodes and the spleen. When immunity develops, the macrophages acquire the ability to destroy the phagocytized yeasts, and the infiltrates in the nodes and other infection sites disappear (Loyd *et al.*, 1990). Most infections occur asymptomatically. The development of the disease depends on the number of conidia inhaled and on the individual's cellular immunity. The incubation period lasts from 5 to 18 days. There are essentially three clinical forms of the disease: acute pulmonary, chronic cavitary pulmonary, and disseminated. The acute pulmonary form is the most frequent and resembles influenza with febrile symptoms that may last from one day to several weeks. A high percentage of patients also experience cough and chest pain. In most patients, chest radiographs show no changes, but in other cases small infiltrates and an increase in the hilar and

mediastinal nodes can be seen. Erythema nodosum or multiforme, diffuse eruption, and arthralgia may be present. This form of the disease often goes unnoticed. In mild cases, recovery occurs without treatment, with or without pulmonary calcification. The chronic form of the disease occurs most frequently in people over the age of 40, with a high prevalence among males, and almost always with a preexisting pulmonary disease (particularly emphysema). Its clinical form resembles pulmonary tuberculosis, with cavitation. The course may vary from months to years and cure may be spontaneous. The disseminated form of the disease is the most serious and is seen primarily in the very young or elderly, where it can take an acute or chronic course. The acute course occurs primarily among nursing babies (immature immunity) and small children and is characterized by different degrees of hepatosplenomegaly, fever, and prostration. It is often confused with miliary tuberculosis and is highly fatal if the patient is not treated. Leukopenia, thrombocytopenia, and anemia are frequent. The agent can be isolated from blood and bone marrow. Between 1934 and 1988, the medical literature recorded only 73 pediatric cases of disseminated histoplasmosis (Miranda Novales *et al.*, 1993). The symptomatology in the chronic disseminated form depends on the localization of the fungus (pneumonia, hepatitis, endocarditis, etc.). There is frequently ulceration of the mucosa and hepatosplenomegaly in these cases. It usually occurs in adults, who may survive for many years, but it can be fatal if the patient is not treated.

Disseminated histoplasmosis occurs in immunodeficient patients, including patients with AIDS. It is sometimes the first manifestation of the syndrome and in some endemic areas it is the most common infection in AIDS (Johnson *et al.*, 1988). The forms of the disease and their symptoms are very varied. The most frequent clinical symptoms in 27 patients (23 men and 4 women) were fever, weight loss, anemia, cutaneous lesions, micronodules in the lungs, hepatosplenomegaly, and adenomegaly (Negroni *et al.*, 1992). Some cases follow a fulminant course with respiratory insufficiency; other cases involve encephalopathy (AIDS dementia), gastrointestinal histoplasmosis with intestinal perforation, and cutaneous histoplasmosis with papules on the limbs, face, and torso.

Fifty radiographs of AIDS patients suffering from disseminated histoplasmosis indicated no changes in 27 patients and different abnormalities (nodular opacities and irregular or linear opacities) in 23 patients. Radiographic results in these patients were varied and nonspecific (Conces *et al.*, 1993).

In the United States, an annual average of only 68 deaths due to histoplasmosis was recorded for 1952–1963, despite the high prevalence of the disease in endemic areas. This confirms that the disease is usually benign.

In African histoplasmosis caused by var. *duboisii*, lesions occur most frequently on the skin, in subcutaneous tissue, and bones. Skin granulomas appear as nodules or ulcerous or eczematous lesions. Abscesses can be observed in subcutaneous tissue. Isolated or multiple lesions are found in osseous histoplasmosis, sometimes asymptomatically (Manson-Bahr and Apted, 1982). When the disease is progressive and severe, giant cell granulomas may form in many internal organs.

Treatment of acute pulmonary histoplasmosis is justified only in severe and prolonged cases. Short-term treatment with intravenous amphotericin B for three or four weeks is generally sufficient. Patients with disseminated histoplasmosis should usually be treated for a longer period with intravenous amphotericin B or oral ketoconazole (Loyd *et al.*, 1990).

Twenty-seven AIDS patients with disseminated histoplasmosis were given oral itraconazole (200 mg per day to 24 patients and 400 mg per day to 3 patients) for six months. Patients who were considered cured continued to take 100 mg per day. A total of 23 patients responded well to the treatment, three showed questionable results, and one had a negative result (Negroni *et al.*, 1992). Forty-two patients with AIDS and disseminated histoplasmosis who successfully completed treatment with amphotericin B for 4 to 12 weeks (15 mg/kg of body weight) were given itraconazole (200 mg twice a day) to prevent relapses, with satisfactory results (Wheat *et al.*, 1993).

The Disease in Animals: Dogs manifest clinical symptoms most often but, as in man, most infections are asymptomatic. The primary respiratory form of the disease almost always heals by encapsulation and calcification. In disseminated cases, the dogs lose weight and have persistent diarrhea, anorexia, and chronic cough; hepatosplenomegaly and lymphadenopathy may also be observed.

Cats follow dogs in terms of frequency of clinical histoplasmosis. The symptoms of feline disseminated histoplasmosis are anemia, weight loss, lethargy, fever, and anorexia. In chest radiographs, the lungs of 7 of 12 cats indicated anomalies. Kittens one year of age or younger were most affected (Clinkenbeard *et al.*, 1987).

H. capsulatum has also been isolated from the intestinal contents and various organs of bats. High rates of reactors have been found in different domesticated species (cattle, horses, sheep) in endemic areas and the agent has been isolated from the lymph nodes of dogs and cats as well as from a wild rodent (*Proechimys guyanensis*) and a sloth in Brazil. Birds are not susceptible to histoplasmosis, perhaps because their high body temperature does not allow the fungus to develop.

Source of Infection and Mode of Transmission: The reservoir of the agent is the soil, where it lives as a saprophyte. Its distribution in the soil is not uniform and depends on various factors such as humidity, temperature, and others yet to be determined. Microfoci that have led to sporadic cases and epidemic outbreaks have usually been associated with soils in which excreta from certain species of bird or bats have accumulated over some time. These excreta apparently allow the fungus to compete with other microorganisms in the soil, ensuring its survival. In contrast to birds, which are not infected by *H. capsulatum* and whose role in the epidemiology is limited to the enabling function of their excreta, certain bat species, particularly species that live in colonies, do become infected and eliminate the fungus in their droppings, thus contributing to its dissemination. Humans frequently become infected when they visit caves, tunnels, and abandoned mines and other places where there are large populations of bats and much accumulated guano. Most infections in Mexico were due to exposure to bat droppings; cases occurred among explorers, tourists, spelunkers, geologists, biologists, and others entering such places for work or study.

Man and animals acquire the infection from the same source (the soil) through inhalation. Microconidia of the fungus are the infecting element. The infection usually starts when natural foci are disturbed by activities that scatter the etiologic agent in the air, such as bulldozing, cleaning or demolishing rural structures (especially henhouses), and visits to caves inhabited by bats.

Histoplasmosis occurs predominantly in rural areas, but outbreaks have also occurred among urban dwellers, particularly construction workers. This was the

case in outbreaks on the Indianapolis campus of Indiana University, where building demolition and excavation led to many human cases (see the section on occurrence in man).

In dogs, the disease appears more frequently in working and sporting breeds.

Role of Animals in the Epidemiology of the Disease: Both man and animals are accidental hosts of the etiologic agent and do not play a role in maintaining or transmitting the infection. Only certain bat species are thought to play an active role in disseminating the infection, in addition to contributing to its development by means of their droppings. However, further study is needed to assess the role of bats in spreading the agent from one roost to another, and to determine the susceptibility of certain species to histoplasmosis (Hoff and Bigler, 1981).

Diagnosis: Laboratory diagnosis can be performed through microscopic examination of stained smears; immunofluorescence using clinical specimens such as sputum, ulcer exudate, and other materials; isolation in culture media; inoculation of mice; and examination of histopathologic sections (bone marrow, lung, liver, and spleen). In the acute pulmonary form, radiological findings of pulmonary infiltrates and hilar adenopathy, combined with data indicating that the patient comes from an endemic area and has symptoms compatible with histoplasmosis, are enough to establish a presumptive diagnosis.

Disseminated histoplasmosis is diagnosed by culturing the blood, bone marrow, urine, or other extrapulmonary tissues, or through biopsy and histopathology. Severe acute, but not chronic, histoplasmosis can be diagnosed using a peripheral blood smear with Wright or Giemsa stain. Biopsy material from the liver or material from oropharyngeal ulcers stained with silver methenamine yields good results (Loyd *et al.*, 1990).

The histoplasmin test is administered like the tuberculin test and read at 24 and 48 hours. Sensitivity is established one to two months after infection and lasts for many years. Although this test is extremely value for epidemiological research, its usefulness is limited in clinical diagnosis. It is advisable to administer the test together with the coccidioidin and blastomycin tests because of cross-reactions. A negative test in a patient can indicate that the infection is recent or that the disease has a different etiology.

Serological tests (complement fixation, immunodiffusion, radioimmunoassay, enzyme immunoassay, precipitation, latex agglutination) are useful for diagnosis but not very sensitive or specific. Tests for blastomycosis and coccidioidomycosis should be performed at the same time. It should be kept in mind that a histoplasmin test can produce antibodies; thus, it is recommended that the blood sample be taken when the allergy test is conducted. It is expected that a test that detects *H. capsulatum* antigen in serum and urine will give more specific results (Wheat *et al.*, 1986).

Control: The principal protection measure consists of reducing people's exposure to dust by spraying with a 3%–5% formalin solution on the ground when cleaning henhouses or other potentially contaminated sites. The use of protective masks has been recommended. Control of natural foci is difficult. During one outbreak, it was possible to eradicate the fungus from its natural foci by spraying the soil with formol.

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MYCETOMA

ICD-10 B47.0 eumycetoma; B47.1 actinomycetoma

Synonyms: Maduromycosis, Madura foot, maduromycotic mycetoma, eumycotic mycetoma, actinomycetoma.

Etiology: Mycetomas may be caused by many species of fungi (eumycetoma) or by bacterial agents (actinomycetoma). The principal agents of eumycetoma are *Madurella mycetomatis, M. grisea, Leptosphaeria senegalensis* (all of which produce black granules), *Pseudallescheria (Petriellidium, Allescheria) boydii*, various species of *Acremonium* (white or yellow granules), *Exophiala jeanselmei*, and other species of fungi. Actinomycetomas are caused by *Nocardia brasiliensis, N. asteroides*, and *N. otitidiscaviarum, Streptomyces somaliensis, Actinomadura madurae*, and *A. pelletieri*. The principal agents of animal mycetomas are *P. boydii, Curvularia geniculata, Cochliolobus spicifer, Acremonium* spp., and *Madurella grisea*.

Both the fungi and the actinomycetes are soil saprophytes that accidentally enter the host's tissues, where they form granules (colonies). Eumycetoma granules contain thick hyphae whereas actinomycetoma granules contain fine filaments.

Geographic Distribution: The agents of maduromycosis are distributed worldwide but occur primarily in the tropics. In tropical areas of Africa and India, infection is most frequently caused by *Madurella mycetomatis* and *Streptomyces somaliensis*. In Mexico, Central America, and South America, mycetomas are caused primarily by *Nocardia brasiliensis* and *Actinomadura madurae*; in Canada and the United States, they are caused primarily by *Pseudallescheria boydii*; and in Japan they are due to *Nocardia asteroides* (Mahgoub, 1990).

Occurrence in Man: Infrequent. It is more common in tropical and subtropical zones, particularly where people go barefoot.

Most cases occur in Africa. In Sudan, 1,231 patients required hospitalization in a two-and-a-half-year period. In many African countries, such as Cameroon, Chad, Kenya, Mauritania, Niger, Senegal, Somalia, and Sudan, mycetoma is considered

the most frequent deep mycosis (Develoux *et al.*, 1988). The responsible agents in Africa vary by geographic area. In India, mycetoma is endemic in many areas. In the Americas, it occurs most frequently in Mexico and Central America (due primarily to *Nocardia brasiliensis*) (Manson-Bahr and Apted, 1982). In São Paulo (Brazil) there were 154 cases between 1944 and 1978; 73.4% of these were actinomycetomas and 26.6% were eumycetomas. In Niger, men are infected more frequently than women (4:1). The disease occurs in rural areas.

Occurrence in Animals: Rare.

The Disease in Man: Mycetoma is a slow-developing, chronic infection that usually localizes on the foot, the lower leg, sometimes the hand, and rarely on some other part of the body. The incubation period is several months from the time of inoculation. The lesion may begin as a papule, nodule, or abscess. The mycetoma spreads to deep tissue and the foot (or hand) swells to two or three times its normal size. Numerous small abscesses form, as well as fistulous tracks in the subcutaneous tissue that branch out to the tendons and may reach the bones. Pus discharged to the surface contains characteristic granules (microcolonies) that may be white or another color depending on the causal agent. The skin does not lose sensitivity nor does the patient generally feel any pain. Actinomycetomas almost always respond to treatment with antibacterial antibiotics (streptomycin, co-trimoxazole), but eumycetomas are quite resistant (ketoconazole, myconazole) and often lead to amputation. Oral dapsone is preferred for cases of *Actinomadura madurae*. The same treatment is recommended for patients affected by *Streptomyces somaliensis* but should be changed to trimethoprim/sulfamethoxazole tablets if no improvement is seen after one month. The latter treatment is also used for infections caused by *Nocardia* spp. (Mahgoub, 1990).

The Disease in Animals: Almost all confirmed cases have occurred in the United States. In animals (dogs, cats, horses), eumycetomas are localized in the feet, lymph nodes, abdominal cavity, and other areas of the body. The most common agents of eumycetoma in animals are *Curvularia geniculata* and *Pseudallescheria boydii*. Mycetomas are frequently preceded by traumas. Intra-abdominal infections have been described in dogs in association with ovariohysterectomies or a surgical incision that had opened up, with surgery occurring two years prior to the appearance of clinical symptoms. Lesions seen in animals are similar to those in humans. They generally start with a small subcutaneous nodule that grows gradually for months or years. They may become deeper and destroy underlying tissues (McEntee, 1987).

Cases of keratomycosis and other ophthalmic conditions due to *Pseudallescheria boydii* have been described in humans as well as horses and dogs (Friedman *et al*., 1989).

Source of Infection and Mode of Transmission: The etiologic agents of this disease are saprophytes in soil and vegetation. The fungus is introduced into subcutaneous tissue of humans and animals through wounds. Contaminated thorns or splinters may be the immediate source of the infection. In animals, there are cases of post-operative wounds being infected by *P. boydii*.

Role of Animals in the Epidemiology of the Disease: None.

Diagnosis: Microscopic examination of pus or material from curettage or biopsy can distinguish eumycetoma granules from actinomycetoma (nocardiosis) granules. The agent is identified through isolation in culture media such as Lowenstein-Jensen medium for actinomycetoma granules and blood agar for eumycetoma granules. Sabouraud's agar is used for subculturing with antimicrobial antibiotics. It is recommended that biopsy material, rather than material from the fistulae, be used to obtain the granules aseptically (Mahgoub, 1990). It is advisable to determine the agent's sensitivity to different medications in order to ensure correct treatment.

In a study conducted in Sudan, specific diagnosis was achieved for 78% of the specimens by using histologic methods, and for 82% of the cases by immunodiffusion (Mahgoub, 1975). The choice of strains for serological testing is very important.

Control: Humans can avoid becoming infected by wearing shoes.

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PROTOTHECOSIS

Synonyms: Algal infections.

Etiology: In recent years, mycologists have called attention to infections in humans and animals caused by microorganisms of the genus *Prototheca*, the nature and taxonomy of which have not yet been clearly defined. Most authors believe they are unicellular algae, but others describe them as algae-like fungi.

The cells of *Prototheca* spp. are round or oval and measure between 2 and 16 microns in diameter. The species of interest are *P. wickerhamii* and *P. zopfii*. These microorganisms reproduce asexually. Hyaline cells, called sporangia when mature, produce from 2 to 20 endospores in their interior that increase in volume and repeat the reproductive cycle when they reach maturity.

Geographic Distribution: The agents are distributed worldwide.

Occurrence in Man: Slightly more than 30 cases of protothecosis have been described, 60% of them in men. With the exception of one case due to *P. zopfii*, the causal agent in all other cases in which the species was identified was *P. wickerhamii*. Recently, an infection caused by green algae was described (Jones, 1983).

Occurrence in Animals: Protothecosis occurs in many animal species, but above all in cattle and dogs. Numerous isolations have been recorded (McDonald *et al*., 1984). Most infections are due to *P. zopfii*. Occurrence is sporadic. Nevertheless, 23 infected animals were found in one dairy herd of 90 cows.

Mastitis caused by *P. zopfii* in cattle is more frequent than was formerly thought. In the United States, there were 400 reported cases in 1982 in New York State alone (Mayberry, 1984, cited in Pore *et al*., 1987). In Australia, mastitis due to *P. zopfii* was diagnosed in 17 of the 120 cows in a herd (Hodges *et al*., 1985). There were 10 cases in a herd of 192 cows in Denmark and 5 cases in a herd of 130 cows in Great Britain (Pore *et al*., 1987).

The Disease in Man: The incubation period is unknown. Protothecosis manifests itself in two principal clinical forms (Kaplan, 1978). One is progressive ulcerative or verrucous lesions of the cutaneous and subcutaneous tissue on exposed skin. The other is chronic olecranon bursitis, with pain and swelling. In one case of dissemination, intraperitoneal and facial nodules were observed.

Treatment consists of surgical excision of the lesion. Antibacterial medications are ineffective. Of the antimycotics, amphotericin B has produced satisfactory results.

The Disease in Animals: The predominant form of protothecosis in cattle is mastitis, which at times may affect all four quarters of the udder. Temperature and appetite may remain normal. Inflammation of the udder is mild in comparison with bacterial mastitis, but it is invasive and chronic. The etiological agent causes pyogranulomas in the mammary gland and the regional lymph nodes (Pore *et al*., 1987). Milk production in the affected quarter diminishes, and small clots may be found in the milk. The disease was reproduced experimentally using a small number of *P. zopfii* (McDonald *et al*., 1984).

Protothecosis in dogs is usually a systemic disease, with dissemination of the infection to many internal organs. The severity of the disease varies according to the

organs affected. Weakness and weight loss were observed in all cases of dissemination (Kaplan, 1978).

Approximately one-half of the cases in dogs are caused by *P. wickerhamii* and the other half by *P. zopfii* (Dillberger *et al.*, 1988). Other animal species in which protothecosis has been diagnosed are Atlantic salmon and cats. In salmon, *P. salmonis* causes a disseminated and fatal disease (Gentles and Bond, 1977). The clinical manifestation of protothecosis in cats more closely resembles the cutaneous disease in humans and does not tend to disseminate as it does in dogs. The infection in cats is caused by *P. wickerhamii* (Dillberger *et al.*, 1988).

Source of Infection and Mode of Transmission: *Prototheca* spp. and green algae are saprophytes found in nature, primarily in stagnant or slow-moving waters. Humans acquire the infection, possibly through skin lesions, when they come into contact with contaminated water or other habitats of these agents. The profusion of these agents in the environment, as well as the few cases described in humans, indicate that they are not very virulent and that lowered host resistance is required for them to act as pathogens. In fact, five of nine patients with cutaneous or subcutaneous protothecosis had a preexisting or intercurrent disease. Similarly, seven of eight patients with the olecranon bursitis form had previously sustained a trauma to the elbow (Kaplan, 1978). Cattle contract mastitis caused by *P. zopfii* in the environment itself; the portal is probably the teat. *P. zopfii* is abundant in dairies, in cow feces as well as in drinking troughs, feed, and mud. A study conducted on various dairy cows, some with mastitis caused by *Prototheca* and others without any history of the disease, isolated the agent (94% *P. zopfii* and 6% *P. wickerhamii*) in 48 (25.3%) of 190 samples (Anderson and Walker, 1988). Little is known of the predisposing conditions in dogs, which almost always manifest systemic protothecosis.

In cattle, the retropharyngeal and mandibular lymph nodes affected by green algae indicate that the infection is possibly contracted by ingestion of contaminated water. The few cases described in cattle and sheep suggest that these species are not very susceptible to green algal infection.

Diagnosis: Special stains such as Gomori, Gridley, and PAS (periodic acid-Schiff) applied to histological sections from affected tissues permit detection of *Prototheca* in all developmental stages. To determine the species, cultures or the immunofluorescence test with species-specific reagents must be used. The immunofluorescence technique can be used for cultures as well as for histological sections stained with hematoxylin-eosin, but not for those stained with the methods mentioned above.

Control: Treatment of underlying conditions or diseases in humans.

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RHINOSPORIDIOSIS

ICD-10 B48.1

Etiology: *Rhinosporidium seeberi*, a fungus that in tissue forms sporangia containing a large number of sporangiospores. Its environmental habitat is unknown and its taxonomy uncertain.

Geographic Distribution: The disease has been confirmed in the Americas, Asia (endemic zones in India and Sri Lanka), Africa, Europe, Australia, and New Zealand.

Occurrence in Man and Animals: The disease is rare throughout the world. Up to 1970, data from Latin America show 108 cases in humans. Most occurred in Paraguay (56), Brazil (13), and Venezuela (13) (Mayorga, 1970). According to more recent data, more than 50 cases have occurred in Venezuela, mainly in the states of Barinas and Portuguesa. In addition to the Latin American countries already cited, the disease has been confirmed in Argentina and Cuba. In the United States, some 30 cases have been recorded, primarily in the south. Five cases have been reported in Trinidad (Raju and Jamalabadi, 1983), four of them affecting the conjunctiva. Most of the cases in Africa were recorded in Uganda. A retrospective study (1948–1986) of 91,000 biopsies was conducted at the Central Hospital of Maputo, Mozambique; rhinosporidiosis was diagnosed in 33 (0.036%) (Moreira Díaz *et al.*, 1989). Some 1,000 cases have occurred in India and Sri Lanka, and 72 occurred in Iran over a 30-year period.

The disease is seen mostly in children and young people, predominantly in males (Mahapatra, 1984).

Rhinosporidiosis in animals occurs in cattle, horses, dogs, cats, and geese. More than 90% of the cases occur in males (Carter and Chengappa, 1991). The disease occurs sporadically, as it does in humans. An unusual case occurred in a province in northern Argentina where an outbreak was described in a herd of cattle that was kept in a flooded field for two years. Twenty-four percent of the animals examined had polyps (Luciani and Toledo, 1989).

The Disease in Man and Animals: Rhinosporidiosis is characterized by pedunculated or sessile polyps on the mucous membranes, particularly of the nose and eyes. The polyps are soft, lobular, and reddish with small white spots (the sporangia). These excrescences are not painful but they do bleed easily. In humans, these granulomatous formations can also be found in the pharynx, larynx, ear, vagina, penis, rectum, and on the skin. Cases of dissemination to internal organs are rare.

The clinical picture in animals consists of a chronic polypoid inflammation that may cause respiratory difficulty and sneezing if the disease lodges in the nasal mucosa and if the lesion is sufficiently large. Another common symptom is epistaxis.

Treatment for humans and animals consists of surgical excision of the polyp. Recurrence is rare. Successful treatment with dapsone has been described in three patients (Job *et al*., 1993).

Source of Infection and Mode of Transmission: The natural habitat of the agent is unknown. It is suspected that the infection enters the body with soil particles through lesions of the mucous membranes. Those affected almost always live in rural areas, thus the assumption that the agent lives in the soil. In India and Sri Lanka, where most cases have been recorded, the source of infection has been associated with stagnant waters, but it has not yet been possible to demonstrate the presence of the fungus in such waters or in aquatic animals. The route of infection and the mode of transmission are also unknown.

Role of Animals in the Epidemiology of the Disease: Rhinosporidiosis is a disease common to humans and animals, contracted from an as yet unknown environmental source. It is not transmitted from one individual to another.

Diagnosis: Since the fungus cannot be cultured, diagnosis depends on the clinical appearance of the lesions and demonstration of the agent's presence in tissues. Best results are obtained by using stained histological preparations.

Control: No practical control measures are available.

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SPOROTRICHOSIS

ICD-10 B42.0 pulmonary sporotrichosis; B42.1 lymphocutaneous sporotrichosis; B42.7 disseminated sporotrichosis; B42.8 other forms of sporotrichosis

Etiology: *Sporothrix schenckii* (*Sporotrichum schenckii, Sporotrichum beurmanni*), a saprophytic fungus that lives in soil, plants, wood, and decaying vegetation.

S. schenckii is a dimorphic fungus that occurs in a mycelial form in nature and a yeast form in infected animal tissues or on enriched culture media (such as blood agar) at 37°C. The latter form generally produces multiple buds and occasionally a single bud.

Geographic Distribution: Worldwide; more common in tropical regions.

Occurrence in Man: Sporadic; its frequency varies from region to region. The disease has been confirmed in all Latin American countries except Bolivia, Chile, and Nicaragua. It is more frequent in Asia, Brazil, the Central American countries, Mexico, South Africa, and Zimbabwe than in other countries. Although it is a relatively rare disease, an epidemic affecting 3,000 workers was recorded in South African gold mines. One group of cases also occurred in the United States among forestry workers who contracted the disease while planting pine trees, and another group of cases occurred among students who came in contact with contaminated bricks (Mitchell, 1983). The largest outbreak in the United States, encompassing 15 states, occurred in the spring of 1988 and affected 84 people. The outbreak was due to *S. schenckii* in sphagnum moss that was used to pack young plants for shipment

(Coles *et al.*, 1992). In the area around Ayerza Lagoon in Guatemala, 53 cases were seen between 1971 and 1975 (Mayorga *et al.*, 1979). Results of skin hypersensitivity tests using *S. schenckii* and *Ceratocystis stenoceras* (a closely related species) antigens indicated that asymptomatic infection is probably frequent among people who work with plants. The study done in the Ayerza Lagoon region (Mayorga *et al.*, 1979) found that cutaneous hypersensitivity was at least 10 times higher among local inhabitants than among residents of Guatemala City.

The disease is much more frequent in males than in females.

Occurrence in Animals: Occasional. Horses are the most frequently affected. Cases have been recorded in dogs, cats, rodents, cattle, swine, camels, birds, and wild animals.

The Disease in Man: The incubation period can range from three weeks to three months. The most common clinical form is the cutaneous form; it begins with a nodule or pustule at the point where broken skin allowed inoculation. The primary lesion is usually located on exposed extremities. The infection may remain confined to the entry site or may eventually spread and produce subcutaneous nodules along the enlarged lymph nodes. The nodules may ulcerate, and a gray or yellowish pus appears. The patient's general state of health is usually not affected. There are also vegetative and verrucous dermal and epidermal forms.

Disseminated forms, which are rare, may give rise to localizations in different organs, especially the bones and joints (80% of extracutaneous forms) as well as the mouth, nose, kidneys, and subcutaneous tissue over large areas of the body. Of more than 3,000 miners who contracted cutaneous sporotrichosis, only five developed systemic infections and none developed the pulmonary form (Lurie, 1962). Some researchers have concluded that dissemination occurs via the bloodstream or the lymphatic system from the inoculation site on the skin, while others believe that a primary focus in the lungs is involved.

Pulmonary sporotrichosis, a rare form of the disease, results from inhalation of the fungus. Its course may be acute, but in general it is chronic and can be confused with tuberculosis. The number of cases described is probably less than 90, and most patients lived in states bordering the Mississippi and Missouri rivers in the United States. Many of them had underlying diseases, such as alcoholism and tuberculosis. The most common symptoms are cough (69%), expectoration (59%), dyspnea, pleuritic pain, and hemoptysis. Patients frequently complain of weight loss, fatigue, and a slight rise in body temperature. The most frequent lesion in the lungs occurs in the upper lobe, and radiography shows cavitation, surrounded by parenchymatous densities (Pluss and Opal, 1986).

Oral potassium iodide may be used to treat the cutaneous form. Extracutaneous cases have been treated successfully with ketoconazole and itraconazole, or with the new oral triazole, saperconazole. Treatment with this last antimycotic requires a dose of 100 to 200 mg per day for a period of three-and-a-half months (Franco *et al.*, 1992).

Because of their occupation, farmers, gardeners, and floriculturists are the persons most exposed to the infection.

The Disease in Animals: The disease in horses and mules is similar to that in humans; it must be differentiated from epizootic lymphangitis caused by

Histoplasma farciminosum (Cryptococcus farciminosum). The skin covering the spherical nodules becomes moist, the hair falls out, and a scab forms. The ulcers heal slowly and leave alopecic scars. The affected extremity swells due to lymphatic stasis. No cases of dissemination have been described in horses.

The disease in dogs may manifest as the cutaneo-lymphatic form, but it frequently affects the bones, liver, and lungs.

The disease in cats is of particular interest because it has often served as the source of infection for humans. One of these epizootic episodes occurred in Malaysia, where four veterinary students became infected when caring for cats with sporotrichosis on their forelegs and faces. Five cats with lesions inflicted during fights in the clinic of the Veterinary School were treated with antibacterial medications for two weeks, but the wounds did not heal. During this period, various ulcerative nodules appeared on the eyes, behind the ears, and in the nose. *S. schenckii* was isolated from these lesions. The four students who treated the cats contracted sporotrichosis, as did the owner of one of the cats (Zamri-Saad *et al*., 1990). Three members of a family caught the infection from their cat and became ill with cutaneous sporotrichosis, which disappeared completely after two weeks of treatment with ketoconazole (Haqvi *et al*., 1993). Other cases of zoonotic transmission occurred in Brazil (Larsson *et al.*, 1989) and the United States (Dunstan *et al.*, 1986). Reed *et al*. (1993) described the case of a veterinarian who contracted the infection from a cat; the authors also reviewed the relevant literature.

Source of Infection and Mode of Transmission: The reservoirs of the fungus are soil and plants. Humans and animals almost always become infected through a cutaneous lesion. The infection can be contracted from handling moss, wood splinters, firewood, or dead vegetation on which the fungus has developed. The source of infection in a gold mine epidemic in the Transvaal (South Africa) was timber on which *S. schenckii* was growing. Nevertheless, the source of infection is not always easily recognized. Out of the 53 cases of sporotrichosis that occurred in the Ayerza Lagoon area of Guatemala, 24 (45.3%) patients attributed the wound and subsequent ulceration to handling fish, 6 (11.3%) attributed it to wood splinters, and 20 (37.7%) could not remember any trauma. An attempt to isolate *S. schenckii* from 58 environmental samples yielded negative results (Mayorga *et al*., 1979).

Inhalation provides another entry route for the fungus and is responsible for the small number of pulmonary sporotrichosis cases that have been recorded.

Feline sporotrichosis is known for its ability to transmit the infection to humans. Of 19 people who contracted the disease from a cat in the United States, none had experienced any traumatic lesion at the site of infection. Transmission occurred through direct contact with the ulcerous lesions on the cats' skin, which contained a large amount of fungus. The principal victims of zoonotic sporotrichosis are veterinarians. Of the 19 zoonotic cases, 12 involved veterinarians or their assistants (Dunstan *et al*., 1986). Outside the United States, transmission was attributed to cat scratches or bites.

Cats (usually male) may carry decaying vegetation containing the fungus between their nails and may transmit the infection to other cats when they fight.

Role of Animals in the Epidemiology of the Disease: Sporotrichosis is a disease common to man and animals. Feline sporotrichosis is zoonotic.

Diagnosis: Diagnosis can be confirmed by culture and identification of the fungus. A specific and rapid method is direct immunofluorescence applied to biopsy samples from affected tissues or smears from sputum and bronchial lavages. Serological tests (latex agglutination, immunodiffusion, indirect immunofluorescence) are useful for patients with extracutaneous sporotrichosis. The disadvantage of serological tests is that antibodies may take some time to develop or may disappear after a while even though the disease persists (Pluss and Opal, 1986).

Control: It is recommended that wood in industries where cases occur be treated with fungicides. Moss must be wetted only immediately prior to packing plants so as to keep the fungus from developing.

Veterinarians and their assistants should use gloves to handle and treat cats with cutaneous legions suspected of being sporotrichosis.

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ZYGOMYCOSIS

ICD-10 B46.0 pulmonary mucormycosis; B46.1 rhinocerebral mucormycosis; B46.2 gastrointestinal mucormycosis; B46.3 cutaneous mucormycosis; B46.4 disseminated mucormycosis; B46.8 other zygomycoses

Synonyms: Mucormycosis, entomophthoromycosis.

Etiology: Zygomycosis denotes a group of diseases caused by several genera and species of fungi belonging to the class *Zygomycetes*, orders *Entomophthorales* and *Mucorales*. Consequently, the etiologic agents are numerous; the principal ones are mentioned below in connection with the different diseases they cause, which can be subdivided into entomophthoromycoses and mucormycoses (CIOMS, 1982).

All the zygomycetes develop as hyphae and appear in the environment as well as in tissue as filamentous fungi. Sabouraud's agar is an excellent culture medium for these fungi, in which they develop at ambient temperature. The sporangiophores (specialized hyphae that support sporangia) contain many asexual spores (Carter and Chengappa, 1991).

Geographic Distribution: Worldwide. Mucormycosis has no defined geographic distribution. Entomophthoromycosis predominates in the tropics, particularly in Africa and Asia.

Occurrence in Man: It occurs sporadically, particularly in patients weakened by other diseases. However, in the 1970s there was an epidemic of cutaneous zygomycosis in the United States caused by contamination of elastic bandages with the fungus. The clinical manifestation was cellulitis, caused by direct inoculation of the fungus through the bandages. The infection was invasive in some patients and affected muscles and internal organs (Sugar, 1990). At present, the incidence of zygomycosis is increasing because of the longer survival of diabetics and the growing number of immunosuppressed patients. Despite its broad diffusion in nature and the likelihood that humans will come into contact with spores, this is not a very frequent mycosis.

It is possible that the incidence of mucormycoses is higher in the developed countries, given the higher survival rate of diabetics and the number of immunosuppressed patients. In a hospital in Washington, D.C., 730 cases of mucormycoses were recorded between 1966 and 1988. Of 170 cases of entomophthoromycosis caused by *Basidiobolus haptosporus* described up to 1975, 112 occurred in Africa. To these cases should be added 75 cases in Uganda that became known later (Kelly *et al.*, 1980). This disease also occurs in Southeast Asia and Latin America. Entomophthoromycosis due to the genus *Conidiobolus* also occurs in the tropics and is more common among men (CIOMS, 1982).

Occurrence in Animals: It occurs sporadically in many animal species, such as domestic and wild mammals (including marine mammals), birds, reptiles, amphibians, and fish. There was a significant epizootic outbreak in New South Wales and Queensland, Australia, affecting 52 sheep farms; 700 sheep died in three months. The causal agent was *Conidiobolus incongruens* of the order Entomophthorales (Carrigan *et al.*, 1992).

The Disease in Man: The agents of mucormycoses are potential pathogens that are classified as opportunistic, since they invade the tissues of patients debilitated by other diseases or treated for a long time with antibiotics or corticosteroids. About 40% of the cases have been associated with diabetes mellitus. In contrast, in Africa and Asia entomophthoromycoses occur in individuals without histories of preexisting illness (Bittencourt *et al.*, 1982).

The mucormycoses are caused by fungi of the genera *Absidia, Mucor, Rhizopus, Cunninghamella, Rhizomucor*, and several others. The infection begins in the nasal mucosa and paranasal sinuses, where the fungi may multiply rapidly and spread to the eye sockets, meninges, and brain. The clinical forms caused by these fungi are rhinocerebral, pulmonary, gastrointestinal, disseminated, cutaneous, and subcutaneous mucormycoses. The rhinocerebral form appears mainly in diabetes mellitus patients with acidosis and in leukemia patients with prolonged neutropenia. Patients have fever, facial pain, and headache. As rhinocerebral mucormycosis progresses, there may be loss of vision, ptosis, and pupillary dilatation. This form of the disease is highly fatal. Patients with a malignant blood disease and those receiving immunosuppressants primarily suffer from pulmonary or disseminated mucormycoses and, less frequently, from the rhinocerebral form. The gastrointestinal form has occurred in a few cases in malnourished children and in adult patients with advanced malnutrition; it is generally diagnosed postmortem. The cutaneous and subcutaneous form may be due to deep burns, injections, and application of contaminated bandages. Mucormycosis is characterized by vascular occlusion with fungal hyphae, thrombosis, and necrosis.

Localized mucormycosis may disseminate (disseminated mucormycosis) to various organs and systems. The underlying diseases are generally leukemia, solid neoplasias, chronic renal deficiency (dialysis treatment with deferoxamine seems to predispose the patient to mucormycosis, particularly to *Rhisopus* spp.), hepatic cirrhosis, organ transplants (particularly bone marrow transplants), and diabetes. The largest group of disseminated mucormycoses involves cancer patients (51% of 185 cases analyzed) (Ingram *et al.*, 1989).

Treatment consists of controlling the underlying disease, controlling hyperglycemia and acidosis in diabetics, and reducing immunosuppressant use in other cases. Surgical intervention and systemic administration of amphotericin B yielded favorable results in pulmonary and rhinocerebral mucormycosis when diagnosis occurred early. In primary cutaneous mucormycosis, débridement and topical treatment with amphotericin B are indicated. Generally, the earlier the infection is detected, the smaller the amount of dead tissue that will have to be removed and the greater the chances for avoiding major tissue damage (Sugar, 1990).

Treatment of entomophthoromycosis consists primarily of surgical excision of the subcutaneous nodules (*Basidiobolus*) or corrective surgery (*Conidiobolus*) of the nose and other parts of the face. It is advisable at the same time to treat the patient

with ketoconazole or some other oral antimycotic azole derivative (Yangco *et al.*, 1984).

Entomophthoromycoses due to *Basidiobolus haptosporus* are characterized by the formation of granulomas with eosinophilic infiltration in subcutaneous tissues. Generally, the region affected is the buttock or thigh, with hard tumefaction of the subcutaneous tissue and a clear delimitation from the healthy tissue. The disease is usually benign, but can sometimes be invasive and cause death (Greenham, 1979; Kelly *et al*., 1980).

Entomophthoromycoses due to *Conidiobolus coronatus* and *C. incongruens* generally originate in the lower nasal conchae and invade the subcutaneous facial tissues and paranasal sinuses. Lesions in the pericardium, mediastinum, and the lungs have also been described (CIOMS, 1982).

The Disease in Animals: Zygomycosis in animals is usually found during necropsy or postmortem inspection in abattoirs. Few cases are confirmed by isolation and identification of the causal agent. Lesions are granulomatous or ulcerative. Zygomycosis in cattle, sheep, and goats usually appears as ulcers of the abomasum. A 10-year study of gastrointestinal mycoses in cattle was conducted in Japan. Of 692 cattle autopsied, 45 had systemic mycosis, 38 of them in the gastrointestinal tract. The large majority (94.7%) of stomach infections were due to mucormycoses and the lesions consisted of focal hemorrhagic necroses. Many of the cattle were affected by predisposing factors for ruminal acidosis, such as ruminal atony (Chihaya *et al*., 1992). In cattle, lesions can also be found in nasal cavities and bronchial, mesenteric, and mediastinal nodes (Carter and Chengappa, 1991). In some countries, these fungi are an important cause of mycotic abortions. In Great Britain, they account for 32% of abortions caused by fungi, and in New Zealand for 75%.

In horses, zygomycosis takes the form of a chronic, localized disease that causes the formation of cutaneous granulomas on the extremities. A clinical study of 266 cases of zygomycosis conducted in tropical Australia found that 18% involved *Basidiobolus haptosporus* and 5.3% involved *Conidiobolus coronatus*.

In the disease caused by *B. haptosporus* (*B. ranarum*), lesions are found primarily on the trunk and face. In contrast, lesions due to *C. coronatus* are located in the nasal region (Miller and Campbell, 1982). Pulmonary infection, disease of the guttural pouch, systemic infection, and some mycotic abortions have also been described in horses.

Zygomycosis in piglets produces a gastric ulceration and appears in adult animals as a disseminated infection. Gastroenteritis with diarrhea, dehydration, and some deaths attributed to zygomycosis have been described in suckling pigs (Reed *et al*., 1987). Disseminated zygomycosis appears as granulomas in the submaxillary, cervical, and mesenteric nodes, and in the abdominopelvic organs. Three herd animals weighing between 50 and 80 kg were found with very swollen submandibular nodes; systemic dissemination was confirmed postmortem in three of them (Sanford *et al*., 1985).

An epidemic occurred in 52 sheep farms in Australia, leading to the death of 700 sheep within a period of three months. The affected animals had marked, asymmetrical swelling of the face, extending from the nostrils to the eyes. They were depressed, without appetite, and had marked dyspnea and frequent bloody discharge from the nose. The animals would die between 7 and 10 days later. Necropsy con-

firmed severe necrogranulomatous rhinitis that went as deep as the palate. Lesions were also confirmed in the lymph nodes and thorax. *Conidiobolus incongruens* was isolated from the nasal lesions, parotid gland, submandibular glands, and the lungs. The most important histopathological change was a severe granulomatous inflammation that contained small eosinophilic foci of coagulative necrosis. There were fungal hyphae in the center of these foci.

To explain an outbreak of this magnitude, the authors assume that the infection was influenced by environmental factors. After a rainy winter, grass grew plentifully; it was cut, and the cuttings began to decompose. Additional rain, heat, humidity, and the presence of decomposing plants created conditions favorable to proliferation of the etiologic agent (Carrigan *et al*., 1992).

In dogs and cats, the disease usually affects the gastrointestinal tract and mortality is very high. Lesions of the stomach or small intestine are accompanied by vomiting, and lesions in the colon are accompanied by diarrhea and tenesmus (Ader, 1979).

Source of Infection and Mode of Transmission: Zygomycetes are ubiquitous saprophytes that produce a large number of spores; they are common inhabitants of decomposing organic material and food, and are found in the gastrointestinal tract of reptiles and amphibians. Humans contract the infection through inhalation, inoculation, and contamination of the skin by spores, and sometimes through ingestion. The common route of entry is the nose, by inhalation of spores. Debilitating diseases, such as diabetes mellitus, and prolonged treatment with immunosuppressants and antibiotics, are important causal factors of mucormycosis. *Mucoraceae* spores probably do not germinate in individuals with intact immune systems, judging from experimental tests in laboratory animals. However, some cases have been described in apparently normal people with no known underlying disease. Subcutaneous entomophthoromycosis due to *Basidiobolus* develops as a result of direct inoculation by thorns, and the disease caused by *Conidiobolus* spp. is contracted through inhalation.

Entomophthoromycosis generally occurs in healthy individuals with no preexisting disease.

In domestic animals, the digestive route of infection seems to be more important than inhalation.

Role of Animals in the Epidemiology of the Disease: Humans and animals contract the infection from a common source in the environment. The infection is not transmitted from one individual to another (man or animal).

Diagnosis: Diagnosis is based on confirmation of the agent's presence in scrapings or biopsies of lesions by means of direct microscopic examination or by culture. Zygomycetes in tissue can be identified by their large nonseptate hyphae. The species of fungus can only be determined by culture and spore identification (Ader, 1979). An indirect ELISA test with a homogenate of *Rhizopus arrhizus* and *Rhizomucor pusillus* can be useful for diagnosing mucormycosis. This test was able to detect 33 of 43 cases of mucormycosis. The sensitivity of the test is 81% and the specificity is 94%. It cannot determine the genus or the species of the causal agent (Kaufman *et al*., 1989).

Control: Human zygomycosis can be prevented in many cases by proper treatment of metabolic disorders, especially diabetes mellitus. Prolonged treatment with antibiotics and corticosteroids should be limited to those cases in which it is absolutely necessary. Animals should not be allowed to consume moldy fodder.

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ZOONOSES AND COMMUNICABLE DISEASES COMMON TO MAN AND ANIMALS

Third Edition

Volume II

Chlamydioses, Rickettsioses,
and Viroses

Scientific and Technical Publication No. 580

PAN AMERICAN HEALTH ORGANIZATION
Pan American Sanitary Bureau, Regional Office of the
WORLD HEALTH ORGANIZATION
525 Twenty-third Street, N.W.
Washington, D.C. 20037 U.S.A.

2003

Also published in Spanish (2003) with the title:
Zoonosis y enfermedades transmisibles comunes al hombre y a los animales: clamidiosis, rickettsiosis y virosis
ISBN 92 75 31991 X (3 volume set)
ISBN 92 75 31992 8 (Vol. 2)

PAHO HQ Library Cataloguing-in-Publication
Pan American Health Organization
Zoonoses and communicable diseases common to man and animals: chlamydioses, rickettsioses, and viroses
3rd ed. Washington, D.C.: PAHO, © 2003.
3 vol.—(Scientific and Technical Publication No. 580)

ISBN 92 75 31991 0—3 volume set
ISBN 92 75 31992 9—Vol. 2
I. Title II. Series
1. ZOONOSES
2. VIROSES
3. RICKETTSIA INFECTIONS
4. COMMUNICABLE DISEASE CONTROL
5. FOOD CONTAMINATION
6. PUBLIC HEALTH VETERINARY
NLM WC950.P187 2003 V.2 En

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PROLOGUE

In recent years, zoonoses and communicable diseases common to man and animals have gained increasing attention worldwide. Human diseases that have their origins in infected animals, such as AIDS or Creutzfeldt-Jakob, have highlighted the need for a better understanding of animal diseases in terms of their epidemiology, mechanism of transmission to man, diagnosis, prevention, and control. Social and demographic changes have also contributed to the importance of gaining and disseminating knowledge about zoonoses. For instance, as people encroach further and further on ecological areas with which they had little contact and whose fauna may not be well known, their exposure to animals—and the infections they transmit—has increased. New knowledge is also being developed in the area of urban ecology. The ease and speed of modern travel also facilitates the spread of diseases once confined to specific geographic areas, as recently occurred with severe acute respiratory syndrome (SARS). Animal migration and trade pose a similar threat, as was shown by the outbreaks in the United States of West Nile fever, and most recently, monkeypox—two diseases not previously known in the Western Hemisphere. Each of these examples highlights the need for improved knowledge and surveillance of and response to zoonoses.

The negative effects of zoonoses are far reaching. High incidence rates continue to cause significant morbidity and mortality in both humans and animals. Their economic impact is seen in lost labor productivity due to illness; reduced travel and tourism to affected areas; reduced livestock and food production; death and destruction of affected animals; and restrictions on and reductions in international trade. Zoonoses can be a serious drain on a country's economy, which in turn can have wide repercussions for a society's health.

To help solve these problems, the Pan American Health Organization (PAHO)—an international public health organization that has devoted itself to improving the health and living conditions of the people of the Americas for over one hundred years—established the Veterinary Public Health Unit. The Unit's overall objective is to collaborate with PAHO's Member Governments in the development, implementation, and evaluation of policies and programs that lead to food safety and protection and to the prevention, control, or eradication of zoonoses, among them foot-and-mouth disease.

To this end, PAHO's Veterinary Public Health Unit has two specialized regional centers: the Pan American Foot-and-Mouth Disease Center (PANAFTOSA), created in 1951 in Rio de Janeiro, Brazil, and the Pan American Institute for Food Protection and Zoonoses (INPPAZ), established on November 15, 1991, in Buenos Aires, Argentina. INPPAZ's precursor was the Pan American Zoonoses Center (CEPANZO), which was created through an agreement with the Government of Argentina to help the countries of the Americas combat zoonoses, and which operated from 1956 until 1990.

Since its creation in 1902, PAHO has participated in various technical cooperation activities with the countries, among them those related to the surveillance, prevention, and control of zoonoses and communicable diseases common to man and

animals, which cause high morbidity, disability, and mortality in vulnerable human populations. PAHO has also collaborated in the strengthening of preventive medicine and public health through the promotion of veterinary health education in learning, research, and health care centers. An example of this work is the preparation of several publications, among which the two previous Spanish and English editions of *Zoonoses and Communicable Diseases Common to Man and Animals* stand out.

Scientific knowledge has progressed since the last edition was published in 1986. Also, the countries of the Americas have modified their livestock production strategies in recent years, which has affected the transmission of zoonotic infections and their distribution. The publication of this third edition is an attempt to address these changes. The third edition is presented in three volumes: the first contains bacterioses and mycoses; the second, chlamydioses, rickettsioses, and viroses; and the third, parasitoses.

We believe that this new edition will continue to be useful for professors and students of public health, medicine, veterinary medicine, and rural development; workers in public health and animal health institutions; and veterinarians, researchers, and others interested in the subject. We also hope that this publication is a useful tool in the elaboration of national zoonosis control or eradication policies and programs, as well as in risk evaluation and in the design of epidemiological surveillance systems for the prevention and timely control of emerging and reemerging zoonoses. In summary, we are confident that this book will contribute to the application of the knowledge and resources of the veterinary sciences for the protection and improvement of public health.

MIRTA ROSES PERIAGO
DIRECTOR

PREFACE TO THE FIRST EDITION

This book considers two groups of communicable diseases: those transmitted from vertebrate animals to man, which are—strictly speaking—zoonoses; and those common to man and animals. In the first group, animals play an essential role in maintaining the infection in nature, and man is only an accidental host. In the second group, both animals and man generally contract the infection from the same sources, such as soil, water, invertebrate animals, and plants; as a rule, however, animals do not play an essential role in the life cycle of the etiologic agent, but may contribute in varying degrees to the distribution and actual transmission of infections.

No attempt has been made to include all infections and diseases comprised in these two groups. A selection has been made of some 150 that are of principal interest, for various reasons, in the field of public health. The number of listed zoonoses is increasing as new biomedical knowledge is acquired. Moreover, as human activity extends into unexplored territories containing natural foci of infection, new zoonotic diseases are continually being recognized. In addition, improved health services and better differential diagnostic methods have distinguished zoonoses previously confused with other, more common diseases. A number of diseases described in this book have only recently been recognized, examples of which include the Argentine and Bolivian hemorrhagic fevers, angiostrongyliasis, rotaviral enteritis, Lassa fever, Marburg disease, and babesiosis.

The principal objective in writing this book was to provide the medical professions a source of information on the zoonoses and communicable diseases common to man and animals. Toward that end, both medical and veterinary aspects, which have traditionally been dealt with separately in different texts, have been combined in a single, comprehensive volume. As a result, physicians, veterinarians, epidemiologists, and biologists can all gain an overview of these diseases from one source.

This book, like most scientific works, is the product of many books, texts, monographs, and journal articles. Many sources of literature in medicine, veterinary medicine, virology, bacteriology, mycology, and parasitology were consulted, as were a large number of reports from different biomedical disciplines, in order to provide up-to-date and concise information on each disease. It is expected that any errors or omissions that may have been committed can, with the collaboration of the readers, be corrected in a future edition.

Where possible, explanations were attempted with special emphasis on the Americas, particularly Latin America. An effort was made, one which was not always successful, to collect available information on diseases in this Region. Data on the incidence of many zoonoses are fragmentary and frequently not reliable. It is hoped that the establishment of control programs in various countries will lead to improved epidemiologic surveillance and disease reporting.

More space has been devoted to those zoonoses having greatest impact on public health and on the economy of the countries of the Americas, but information is also included on those regionally less important or exotic diseases.

The movement of persons and animals over great distances adds to the risk of introducing exotic diseases that may become established on the American continent given the appropriate ecologic factors for existence of the etiologic agents. Today,

public health and animal health administrators, physicians, and veterinarians must be familiar with the geographic distribution and pathologic manifestations of the various infectious agents so that they can recognize and prevent the introduction of exotic diseases.

We, the authors, would like to give special recognition to Dr. Joe R. Held, Assistant Surgeon-General of the United States Public Health Service and Director of the Division of Research Services of the U.S. National Institutes of Health, who gave impetus to the English translation and reviewed the bacterioses sections.

We would also like to express our utmost appreciation to the experts who reviewed various portions of this book and offered their suggestions for improving the text. These include: Dr. Jeffrey F. Williams, Professor in the Department of Microbiology and Public Health, Michigan State University, who reviewed the chapters dealing with parasitic zoonoses; Dr. James Bond, PAHO/WHO Regional Adviser in Viral Diseases, who read the viroses; Dr. Antonio Pío, formerly PAHO/WHO Regional Adviser in Tuberculosis and presently with WHO in Geneva, and Dr. James H. Rust, PAHO/WHO Regional Adviser in Enteric Diseases, both of whom reviewed the bacterioses; and Dr. F. J. López Antuñano, PAHO/WHO Regional Adviser in Parasitic Diseases, who read the metazooses.

We would like to thank Dr. James Cocozza, PAHO/WHO Veterinary Adviser, for his review of the translation and Dr. Judith Navarro, Editor in the Office of Publications of PAHO, for her valuable collaboration in the editorial revision and composition of the book.

PEDRO N. ACHA
BORIS SZYFRES

PREFACE TO THE SECOND EDITION

The fine reception accorded the Spanish, English, and French versions of this book has motivated us to revise it in order that it still may serve the purpose for which it was written: to provide an up-to-date source of information to the medical profession and allied fields. This book has undoubtedly filled a void, judging by its wide use in schools of public health, medicine, and veterinary medicine, as well as by bureaus of public and animal health.

The present edition has been considerably enlarged. In the seven years since the first edition was published, our knowledge of zoonoses has increased broadly and rapidly, and new zoonotic diseases have emerged. Consequently, most of the discussions have been largely rewritten, and 28 new diseases have been added to the original 148. Some of these new diseases are emerging zoonoses; others are pathologic entities that have been known for a long time, but for which the epidemiologic connection between man and animal has been unclear until recently.

The use this book has had outside the Western Hemisphere has caused us to abandon the previous emphasis on the Americas in favor of a wider scope and geomedical view. Moreover, wars and other conflicts have given rise to the migration of populations from one country or continent to another. A patient with a disease heretofore known only in Asia may now turn up in Amsterdam, London, or New York. The physician must be aware of these diseases in order to diagnose and treat them. "Exotic" animal diseases have been introduced from Africa to Europe, the Caribbean, and South America, causing great damage. The veterinary physician must learn to recognize them to be able to prevent and eradicate them before they become entrenched. It must be remembered that parasites, viruses, bacteria, and other agents of zoonotic infection can take up residence in any territory where they find suitable ecologic conditions. Ignorance, economic or personal interests, and human customs and needs also favor the spread of these diseases.

Research in recent years has demonstrated that some diseases previously considered to be exclusively human have their counterparts in wild animals, which in certain circumstances serve as sources of human infection. On the other hand, these animals may also play a positive role by providing models for research, such as in the case of natural leprosy in nine-banded armadillos or in nonhuman primates in Africa. Of no less interest is the discovery of *Rickettsia prowazekii* in eastern flying squirrels and in their ectoparasites in the United States, and the transmission of the infection to man in a country where epidemic typhus has not been seen since 1922. A possible wild cycle of dengue fever is also discussed in the book. Is Creutzfeldt-Jakob disease a zoonosis? No one can say with certainty, but some researchers believe it may have originated as such. In any case, interest is aroused by the surprising similarity of this disease and of kuru to animal subacute spongiform encephalopathies, especially scrapie, the first known and best studied of this group. Discussion of human and animal slow viruses and encephalopathies is included in the spirit of openness to possibilities and the desire to bring the experience of one

field of medicine to another. In view of worldwide concern over acquired immunodeficiency syndrome (AIDS), a brief section on retroviruses has also been added, in which the relationship between the human disease and feline and simian AIDS is noted. Another topic deeply interesting to researchers is the mystery of the radical antigenic changes of type A influenza virus, a cause of explosive pandemics that affect millions of persons around the world. Evidence is mounting that these changes result from recombination with a virus of animal origin (see Influenza). That this should occur is not surprising, given the constant interaction between man and animals. As a rule, zoonoses are transmitted from animal to man, but the reverse may also occur, as is pointed out in the chapters on hepatitis, herpes simplex, and measles. The victims in these cases are nonhuman primates, which may in turn retransmit the infection to man under certain circumstances.

Among emerging zoonoses we cite Lyme disease, which was defined as a clinical entity in 1977; the etiologic agent was found to be a spirochete (isolated in 1982), for which the name *Borrelia burgdorferi* was recently proposed. Emerging viral zoonoses of note in Latin America are Rocio encephalitis and Oropouche fever; the latter has caused multiple epidemics with thousands of victims in northeast Brazil. Outstanding among new viral disease problems in Africa are the emergence of Ebola disease and the spread of Rift Valley fever virus, which has caused tens of thousands of human cases along with great havoc in the cattle industry of Egypt and has evoked alarm around the world. Similarly, the protozoan *Cryptosporidium* is emerging as one of the numerous agents of diarrheal diseases among man and animals, and probably has a worldwide distribution.

As the English edition was being prepared, reports came to light of two animal diseases not previously confirmed in humans. Three cases of human pseudorabies virus infection were recognized between 1983 and 1986 in two men and one woman who had all had close contact with cats and other domestic animals. In 1986, serologic testing confirmed infection by *Ehrlichia canis* in a 51-year-old man who had been suspected of having Rocky Mountain spotted fever. This is the first known occurrence of *E. canis* infection in a human. These two diseases bear watching as possible emerging zoonoses.

The space given to each zoonosis is in proportion to its importance. Some diseases that deserve their own monographs were given more detailed treatment, but no attempt was made to cover the topic exhaustively.

We, the authors, would like to give special recognition to Dr. Donald C. Blenden, Professor in the Department of Medicine and Infectious Diseases, School of Medicine, and Head of the Department of Veterinary Microbiology, College of Veterinary Medicine, University of Missouri; and to Dr. Manuel J. Torres, Professor of Epidemiology and Public Health, Department of Veterinary Microbiology, College of Veterinary Medicine, University of Missouri, for their thorough review of and valuable contributions to the English translation of this book.

We would also like to recognize the support received from the Pan American Health Organization (PAHO/WHO), the Pan American Health and Education Foundation (PAHEF), and the Pan American Zoonoses Center in Buenos Aires, Argentina, which enabled us to update this book.

We are most grateful to Dr. F. L. Bryan for his generous permission to adapt his monograph "Diseases Transmitted by Foods" as an Appendix to this book.

Mr. Carlos Larranaga, Chief of the Audiovisual Unit at the Pan American Zoonosis Center, deserves our special thanks for the book's artwork, as do Ms. Iris Elliot and Mr. William A. Stapp for providing the translation into English. We would like to express our most sincere gratitude and recognition to Ms. Donna J. Reynolds, editor in the PAHO Editorial Service, for her valuable collaboration in the scientific editorial revision of the book.

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INTRODUCTION

This new edition of *Zoonoses and Communicable Diseases Common to Man and Animals* is published in three volumes: I. Bacterioses and mycoses; II. Chlamydioses and rickettsioses, and viroses; and III. Parasitoses. Each of the five parts corresponds to the location of the etiologic agents in the biological classification; for practical purposes, chlamydias and rickettsias are grouped together.

In each part, the diseases are listed in alphabetical order to facilitate reader searches. There is also an alphabetical index, which includes synonyms of the diseases and the etiologic agents' names.

In this edition, the numbers and names of the diseases according to the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), are listed below the disease title. However, some zoonoses are not included in ICD-10 and are difficult to classify within the current scheme.

In addition, for each disease or infection, elements such as synonyms; etiology; geographical distribution; occurrence in man and animals; the disease in man and animals; source of infection and mode of transmission; role of animals in the epidemiology; diagnosis; and control are addressed. Patient treatment (for man or other species) is beyond the scope of this work; however, recommended medicines are indicated for many diseases, especially where they are applicable to prophylaxis. Special attention is paid to the epidemiological and ecological aspects so that the reader can begin to understand the determining factors of the infection or disease. Some topics include simple illustrations of the etiologic agent's mode of transmission, showing the animals that maintain the cycle of infection in nature. Similarly, other graphics and tables are included to provide additional information on the geographical distribution or prevalence of certain zoonoses.

The data on the occurrence of the infection in man and animals, along with data on the geographical distribution, may help the reader judge the relative impact that each disease has on public health and the livestock economy in the different regions of the world, given that the importance of different zoonoses varies greatly. For example, foot-and-mouth disease is extremely important from an economic standpoint, but of little importance in terms of public health, if animal protein losses are not considered. In contrast, Argentine and Machupo hemorrhagic fevers are important human diseases, but their economic impact is minimal, if treatment costs and loss of man-hours are not taken into account. Many other diseases, such as brucellosis, leptospirosis, salmonellosis, and equine encephalitis, are important from both a public health and an economic standpoint.

Finally, each disease entry includes an alphabetical bibliography, which includes both the works cited and other relevant works that the reader may consult for more information about the disease.

Part I

CHLAMYDIOSES & RICKETTSIOSES

RICKETTSIACEAE

This family includes the tribes Rickettsieae *and* Ehrlichieae*. When human ehrlichiosis was recognized in 1986, the disease was considered to be a zoonosis caused by* Ehrlichia canis*. However, findings in 1991 established that the human agent, although similar to* E. canis*, is actually a distinct species (Dawson et al., 1991). For this reason, ehrlichiosis falls outside the scope of the present volume.*

Rickettsiae, like bacteria, are prokaryotic intracellular organisms. However, because they lack certain enzymes, they are dependent on a eukaryotic cell of the host. An exception within the tribe Rickettsieae *is the genus* Rochalimaea*, which can be cultured in an axenic environment. Rickettsiae reproduce by binary fission within the cells of an arthropod or a human or animal host; both their DNA and RNA can be synthesized, and they are sensitive to antibiotics. They measure approximately 0.5 by 0.3 microns and may be either rod-shaped or spherical. They show up well with Gimenez and Macchiavellos stains but not as well with Gram stain (Weiss and Moulder, 1984; Mettler, 1991).*

In addition to the genus Rickettsia*, within the tribe* Rickettsieae *the genera* Coxiella *and* Rochalimaea *are also of interest.*

Organisms of the genus Rickettsia *may be divided into the following three groups: spotted fevers, typhus, and scrub typhus.*

The diseases in the spotted fever group are clinically similar and caused by related rickettsiae, and they are all transmitted by ticks.

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ASIAN IXODO-RICKETTSIOSIS

ICD-10 A77.2 Spotted fever due to *Rickettsia sibirica*

Synonyms: North Asian tick fever, Siberian tick typhus.

Etiology: *Rickettsia sibirica* (*Dermacentroxenus sibiricus*). This agent belongs to the spotted fever group of rickettsiae. *Dermacentor marginatus*, a variety of *R. sibirica* that was isolated from ticks in the former Czechoslovakia, is serologically distinct from *R. slovaca*, although the differences may not be sufficient to warrant establishing a separate species (Weiss and Moulder, 1984).

Geographic Distribution: Armenia, Kazakhstan, Kyrgyzstan, northern China, Mongolia, Siberia, and various islands in the Sea of Japan. *R. sibirica* has also been isolated from ticks and mammals in the former Czechoslovakia and in Pakistan.

Occurrence in Man: Sporadic. The disease occurs mainly in farmers, hunters, forestry workers, and people who enter the disease's natural foci in steppe and montane regions. Ticks may be carried from natural foci to populated areas via the fur of domestic animals, firewood, or by other means, and thus increase the possibility of infection.

Occurrence in Animals: The etiologic agent has been isolated from at least 18 wild rodent species that live in the disease's natural foci.

The Disease in Man: This is an acute, febrile, benign disease clinically similar to boutonneuse fever. It may also resemble the serious or moderate forms of Rocky Mountain spotted fever. It has an incubation period of two to seven days, and is treated with tetracycline.

The Disease in Animals: No information is available on the natural course of the disease in wild rodents or other species from which the rickettsia has been isolated; it is probably asymptomatic.

Source of Infection and Mode of Transmission: Man contracts the infection through tick bites. The principal vectors are ticks of the genera *Dermacentor*, *Haemaphysalis*, and *Rhipicephalus*. Nine species of naturally infected ticks have been found, and transovarial transmission has been confirmed in seven of them. The etiologic agent survives in the tick during hibernation. The continuous circulation of rickettsiae in natural foci is ensured by transovarial transmission from one arthropod generation to the next and by the presence of the infection in a wide variety of small mammal species.

At the end of hibernation and before egg laying, the ticks attach themselves to large domestic and wild mammals, and, accidentally, to humans who enter their habitat. Accordingly, the highest incidence of human disease occurs in spring, which is the period of greatest adult tick activity. It is usually the adult tick that attacks man, but larvae and nymphs of *Dermacentor nuttalli* and *Haemaphysalis concinna* may do so as well. The larvae and nymphs usually feed on small mammals, especially rodents, thus ensuring an additional reservoir and source of infection. Autumn brings a new generation of adult ticks, which may attach themselves to humans and produce cases of the disease.

Role of Animals in the Epidemiology of the Disease: Man is an accidental host; the reservoir consists of wild rodents and ticks. The latter play a key role in maintaining and transmitting the infection. Transstadial and transovarial transmission of *R. sibirica* has been confirmed in *D. marginatus* over a period of at least five years (Harwood and James, 1979). Domestic animals (cattle, horses, dogs) can serve as hosts for adult ticks.

Diagnosis: As with other spotted fevers, laboratory confirmation is obtained using such serological tests as complement fixation and microimmunofluorescence. The agent can be isolated in embryonated eggs or by inoculation in laboratory animals (guinea pigs, rats, hamsters).

Control: Control measures are directed against the vectors. They include the use of tickicides on domestic animals and in their environment, as well as the reduction of rodent populations, since rodents are the principal hosts of larvae and nymphs. Individuals who enter natural foci should wear protective clothing and use tick repellents.

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BOUTONNEUSE FEVER

ICD-10 A77.1 Spotted fever due to *Rickettsia conorii*

Synonyms: Marseilles fever, Mediterranean spotted fever, Mediterranean tick fever, African tick typhus, Kenya tick typhus, India tick typhus.

Etiology: *Rickettsia conorii* (*Dermacentroxenus conorii*). This microorganism belongs to the spotted fever group of rickettsiae. It can be differentiated from others in the group by serological and cross-immunity tests.

Geographic Distribution: The disease occurs in much of Africa, Southeast Asia, India, and areas of Europe and the Middle East adjacent to the Caspian, Mediterranean, and Black Seas.

Occurrence in Man: Sporadic. This is the most common rickettsial disease in South Africa. In Spain, the endemic area of Talavera de la Reina had 85 diagnosed cases in 1982 (España, Ministerio de Sanidad y Consumo, 1983). In Soria (Spain), 5% of 298 human sera samples were serologically positive for *R. conorii.* More than 90% of the cases were from the eastern part of the province, and 20% of the positive cases were found in a small area (Saz *et al.*, 1993). Similar results were obtained in Croatia on the Adriatic coast. The number of human cases in the Mediterranean basin has increased since the early 1980s, especially in Spain, France, Israel, and Italy. The number of cases in Italy rose from only 87 in 1974 to 1,128 in 1993 (personal communication, G. Federico, cited in Mansueto *et al.*, 1985). Most of the cases in the Mediterranean basin occur in summer, when ticks are most active.

Occurrence in Animals: In some areas, such as Kenya, serological studies have revealed a high proportion of reactors in several species of wild rodents (Heisch *et al.*, 1962). *R. conorii* has been isolated from many rodent species in South Africa and Kenya. Antibodies for spotted fever group rickettsiae were detected in a small sampling of sheep and goat sera examined in Ethiopia (Philip *et al.*, 1966) and also in nonhuman primates at the Kruger Reserve in South Africa (Kaschula *et al.*, 1978). The dog, principal host of the ixodid tick *Rhipicephalus sanguineus* (brown dog tick), has been the subject of seroepidemiological studies because the tick is both reservoir and vector of *R. conorii* disease in man. In western Sicily (Italy), where there are several endemic areas of boutonneuse fever, 81.5% of dogs examined were reactors in the indirect immunofluorescence test (Tringali *et al.*, 1986). In the south of France, this same test was used to examine the sera of 481 dogs; 80% were positive at a dilution of 1:32, and 45% at 1:128. The lower titers may indicate an old infection, and the higher titers, a recent infection. These data confirm that the disease is endemic in the south of France (Raoult *et al.*, 1985). In Israel, when sera from 92 dogs were examined using both the immunofluorescence and enzyme-linked immunosorbent assay tests on each sample, 30% were found to be positive. The prevalence of antibodies in dogs from two small communities where there had been cases of human disease caused by *R. conorii* was 2.8 times higher (82%–84%) (Keysary *et al.*, 1988).

The Disease in Man: Boutonneuse fever is usually benign. It is characterized by a primary lesion at the site where the tick was attached. The lesion consists of a small reddish ulcer covered by a small black scab (*tâche noire*), which may last throughout the course of the illness. Localized lymphadenitis is often seen. The fever appears 5 to 7 days after the tick bite and is accompanied by severe headaches and muscle and joint pain. A generalized eruption, at first macular and then maculopapular, appears on the fourth or fifth day of fever and lasts about a week. The disease takes a serious turn in approximately 5% of the cases. Of 142 cases treated at hospitals in Marseilles (France), 7 developed disease with purpuric exanthema, confusion, renal failure, hypoxemia, thrombocytopenia, hyponatremia, and hypocalcemia. Two patients died. Predisposing factors were advanced age, tobacco use, alcoholism, and respiratory insufficiency (Raoult *et al.*, 1986). Three fatal cases in children have been described in Israel. The

disease was characterized by irreversible shock, encephalopathy, renal failure, hemorrhagic tendency, and death within 24 hours of hospital admission. None of the children were known to have been bitten by a tick, nor was the black scab (*tâche noire*) observed. One child had no cutaneous eruption, and two had no antibodies. The diagnosis was based on isolation of *R. conorii* in the patients' blood or tissues, either by cell culture or inoculation in laboratory animals. These cases show that there is a grave form of boutonneuse fever in Israel (Yagupsky and Wolach, 1993).

Some investigators have attributed the spotted fever in Israel to a different species, *Rickettsia sharonii*, which would be antigenically different from the other rickettsiae in the spotted fever group and also from *R. conorii* (Goldwasser *et al.*, 1974). A clinical difference has also been pointed out, namely, the absence of the black scab in the Israeli patients.

The recommended treatment is tetracycline.

The Disease in Animals: Dogs infested with *R. sanguineus*, the main vector in the Mediterranean region, may have rickettsemia but show no clinical infection. Elsewhere, in wild rodents from which the agent has been isolated, the natural course of infection is unknown, but it is probably asymptomatic.

Source of Infection and Mode of Transmission: The vector of the infection in the Caspian, Mediterranean, and Black Sea basins is *R. sanguineus*. This tick is responsible for the focal nature of boutonneuse fever. All the human cases in this region correspond to the distribution of *R. sanguineus*. The tick completes its entire life cycle near human dwellings. *R. sanguineus* always prefers a dog as its host and only occasionally bites man, which would explain the small number of human cases of the disease despite the abundance of infected ticks. The causal agent is transmitted trans-ovarially from one tick generation to the next, so that the arthropod serves as both vector and reservoir. Dogs and their ticks are the main source of infection in man; wild rodents and their ticks are the reservoir in natural foci. In South Africa, the dog ticks *Haemaphysalis leachi* and *R. sanguineus* are the principal vectors of human infection. The agent has been isolated from many other tick species in their natural habitat, and they are probably involved in its primary life cycle in the wild. Studies carried out in Kenya and Malaysia confirm that in natural foci the agent circulates in a basic cycle between small wild animals and ticks. When ticks are crushed with the hand, the agent can penetrate via the conjunctival mucosa or the skin.

Role of Animals in the Epidemiology of the Disease: Man is an accidental host. The infection is maintained in nature by wild rodents and their ticks. Dogs play a very important role by introducing infected ticks into the human environment.

Diagnosis: Serologic tests are used for laboratory confirmation; the test used most often is microimmunofluorescence. A technique that could be performed easily is latex agglutination with *R. conorii* antigen, in much the same way as laboratories in the US use *R. rickettsii* antigen to diagnose Rocky Mountain spotted fever.

Cell culture (chick embryo fibroblasts, mouse L-cells, BHK-21, etc.) can be used to isolate *R. conorii* as well as other rickettsiae in the group. Recent infections can be distinguished from past ones by using specific anti-IgM and anti-IgG sera in the immunofluorescence test (Edlinger, 1979). A nested polymerase chain reaction assay on serum and tissue samples is useful for diagnosis, particularly in fatal cases (Leitner *et al.*, 2002).

Control: Control measures are directed against the vector and consist of using tickicides on dogs and their environment.

It is recommended that ticks not be crushed when they are detached.

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FLEA-BORNE TYPHUS

ICD-10 A75.2 Typhus fever due to *Rickettsia typhi*

Synonyms: Murine typhus, endemic typhus, urban typhus.

Etiology: *Rickettsia typhi* (*R. mooseri*), which belongs to the same group as *R. prowazekii*, the agent of endemic louse-borne typhus, and *R. canada* (not pathogenic to man), isolated from the tick *Haemaphysalis leporispalustris*. DNA:DNA hybridization between *R. typhi* and *R. prowazekii* is 70% to 79% (Myers and Wisseman, 1980). *R. typhi* is more virulent than *R. prowazekii* in guinea pigs. While some of the antigens are common to both species, others are species-specific. Immunologically, the two species can be differentiated by a cross-challenge of vaccinated guinea pigs or by the toxin neutralization test in mice (Weiss and Moulder, 1984).

Geographic Distribution: There are endemic areas throughout the world.

Occurrence in Man: Sporadic. Between 1963 and 1967, the average number of cases reported annually in the Americas was 241. Countries that reported cases during this period were Argentina, Brazil, Chile, Colombia (more than one-third of the total number of cases), Costa Rica, Ecuador, Mexico, Peru, USA, and Venezuela. In the US, there were some 42,000 cases between 1931 and 1946; after 1946, the incidence began to decline. There are fewer than 80 cases a year (Chin, 2000). Occurrence of the disease is associated with rat infestation. Although incidence of the disease has fallen sharply, especially in the developed countries, enzootic areas continue to exist on all the continents. In Texas (USA), there were 200 human cases between 1980 and 1984: 74% of the patients lived in the southern part of the state, and 85% had to be hospitalized (Taylor *et al.*, 1986). The island of Evia (Greece) is an endemic area; 49 cases were diagnosed at the general hospital in its capital city in 1985 (Tselentis *et al.*, 1992). A case of murine typhus appeared in Australia, after 30 years with no diagnosis of the disease (Graves *et al.*, 1992). In Kuwait, there were 254 cases between April and August 1978, most of them among the poorest members of the population, 80% of whose homes were rat-infested (Al-Awadi *et al.*, 1982). In southeast Asia, flea-borne typhus is an urban disease, since it is in the cities that man and rats, along with their fleas, share the same habitat. Scrub typhus, on the other hand, is endemic in rural areas. In Thailand, where murine typhus is endemic, a refugee camp was set up in 1985 to accommodate Khmers fleeing the civil war in neighboring Cambodia. Only eight months after the camp was constructed, 170 cases, including some of scrub typhus, were diagnosed at the camp hospital within a period of four months. At the same time, there was a sharp increase in the population of the rat *Rattus exulans* (Brown *et al.*, 1988). In Africa, Ethiopia is an endemic country, as is Myanmar (Burma) in Asia.

The incidence is greatest in summer and fall, when rat fleas are most active.

Occurrence in Animals: The most important reservoirs of infection are the domestic rats *Rattus norvegicus*, *R. rattus*, and *R. exulans*. The principal vector is the eastern rat flea *Xenopsylla cheopis*. The basic transmission cycle of the infection is rat-flea-rat and, accidentally, rat-flea-man. Many other species of wild and domestic animals, as well as some of their ectoparasites, have been found to be naturally infected or experimentally susceptible, but their role in the epidemiology of endemic

typhus does not appear to be important. Nevertheless, there are indications that there may be an independent cycle of the agent in addition to the basic cycle. Such would be the case of infestation of the cat and opossum by the flea *C. felis*. This flea often parasitizes the opossum in suburban and rural areas of southern California (USA), where the classic vector *X. cheopis* is absent and rats are serologically negative.

The infection rate in rats varies greatly from one enzootic focus to another.

The Disease in Man: The incubation period is 6 to 14 days. The symptomatology of the disease is similar to that of epidemic louse-borne typhus, but its course is shorter and more benign. It begins with fever, severe cephalalgia, and generalized pains. Five or six days after the onset of fever a macular eruption appears, first on the trunk and then on the extremities, but it does not affect the palms of the hands, the soles of the feet, or the face. The symptomatology also includes coughing, nervousness, nausea, and vomiting. In the refugee camp in Thailand, the main symptoms were persistent fever, retroorbital cephalalgia, and myalgia. In the 200 cases that occurred in southern Texas, only 58.1% of the patients manifested a cutaneous eruption, and only 44.9% experienced nausea. Complications are rare. When patients are not treated, convalescence can last several months. Case fatality increases with age; in the US, the rate is currently under 1% for all ages.

Treatment consists of administration of tetracycline or its long-acting analogs, such as doxycycline or minocycline. With this treatment, the fever subsides in a few days.

The Disease in Animals: Rickettsemia occurs in rats during the first week of infection. The agent remains viable in the brain and other organs for long periods. The infection is asymptomatic.

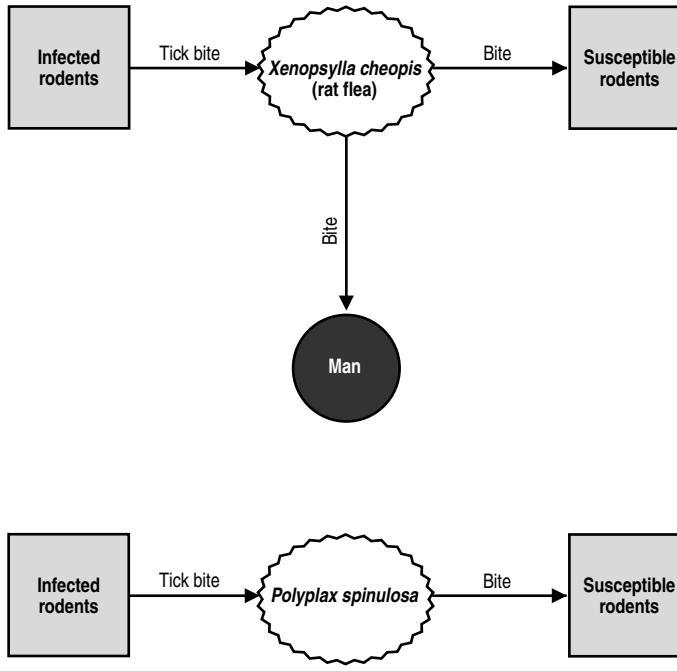
Source of Infection and Mode of Transmission (Figure 1): The most important reservoir of *R. typhi* is the rat, and the main vector is its flea, *X. cheopis*. Fleas become infected by feeding on the host when it has rickettsemia. The agent multiplies in the flea's intestine and Malpighian tubules without causing any apparent damage. The vector eliminates *R. typhi* in its feces throughout its lifetime, but not in its saliva. *X. cheopis* does not transmit the infection to its progeny, and the infection of new generations of fleas requires that they feed on a rickettsemic host. In other species of fleas, the infection follows the same pattern.

The infection is transmitted from rat to rat by means of the flea *X. cheopis* and the louse *Polyplax spinulosa*. The agent can survive for a long time in flea feces and in contaminated rodent burrows. The infection can be produced by contact with the mucous membranes of the conjunctiva and the mouth, or by inhalation.

Man becomes infected when the rat flea, or another flea, such as *C. felis,* bites him and defecates on his skin. When he scratches himself, he can introduce the contaminated fecal matter through the bite or some other skin abrasion. He exposes himself to the same process if he swats a flea against his skin. Man can probably acquire the infection by other routes as well, such as the conjunctiva or by inhalation, though these modes of transmission are of little importance.

The spread of the disease in man depends on the extent of the enzootic in rats and the degree of contact he has with these animals and their fleas. Although the disease used to occur primarily in rat-infested buildings in urban areas, it is now seen in rural areas as well.

Figure 1. Flea-borne typhus *(Rickettsia typhi)*. Transmission cycle.



Role of Animals in the Epidemiology of the Disease: This is an infection in rats that is accidentally transmitted to man by fleas. Cats and opossums can also carry the infected flea *C. felis* into the human environment. The infection is not transmitted from one person to another.

Diagnosis: The agent can be isolated by inoculating the blood of a febrile patient into male guinea pigs and embryonated eggs. In guinea pigs, the infection produces the Neil-Mooser reaction (adhesion of the tunica vaginalis testis that prevents reintroduction of the testicles into the abdomen). This reaction occurs both with the agent of murine typhus and also with those of the spotted fever group.

The complement fixation and indirect immunofluorescence tests are both very useful, though the latter is employed more often. The disadvantage of the complement fixation test is the appearance of anticomplementary sera. Also, the immunofluorescence test has the advantage that it can be adapted to distinguish IgM and IgG antibodies (Wisseman, 1982). The antibodies appear at the end of the second week of the disease, reach their peak two weeks later, and then gradually decline (Elisberg and Bozeman, 1979). Group specificity is good, although with human patients it is difficult to distinguish murine typhus from epidemic typhus, which is not the case in rodents. This distinction can be made with the complement fixation test if washed species-specific antigens are used.

Control: Control measures should be directed first against the vector and then against rodents. To decrease the number of fleas on rats, residual action insecticides are applied to rat runs, nests, and holes. Once the fleas have been dealt with, the next step is to control the rat population through the application of raticides. In addition, environmental sanitation measures can be taken, such as the elimination of rat holes and possible sources of food, as well as the construction of rat-proof buildings.

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INFECTIONS CAUSED BY *BARTONELLA HENSELAE*

Etiology: *Bartonella henselae* is a recently described species belonging to the family Rickettsiaceae. The genera *Rickettsia* and *Bartonella* are genetically related, as demonstrated by the fact that there is 25% to 33% DNA hybridization between *B. henselae* and *Rickettsia prowazekii*. The type species of the genus *Bartonella* is *B. quintana*, the agent of trench fever, which affected approximately 1 million soldiers in World War I and reemerged to a more limited extent in World War II. Some sporadic cases still occur. It is believed that the primary reservoir of *B. quintana* was a vole, probably *Arvicola terrestris,* which became independent of the zoonotic cycle and began to circulate between man and the louse *Pediculus humanus* (Weiss and Moulder, 1984).

The genus *Bartonella* currently includes four species: *B. quintana*, *B. vinsonii*, *B. elizabethae*, and *B. henselae* (Groves and Harrington, 1994). The species of greatest interest as an emerging agent of new zoonotic diseases is *B. henselae*. This rickettsia is bacilliform, curved slightly inward, and measures 1 to 2 microns long by 0.5 to 0.6 microns in diameter. It is gram-negative and stains well with Gimenez stain. The genus *Bartonella* differs from the genus *Rickettsia* most notably by the fact that it does not need eukaryotic cells in order to develop. It can be grown in noncellular culture media such as tryptose soy agar or brain-heart infusion agar containing 5% sheep's blood incubated at 35°C in a humidified stove in an atmosphere of 5% carbon dioxide. The first culture develops slowly and may take as long as five weeks (Welch *et al.*, 1992; Regnery *et al.*, 1992a).

The reservoir of *B. henselae* is the domestic cat, and the diseases that it causes are bacillary angiomatosis, bacillary parenchymatous peliosis, cat-scratch disease (CSD), and recurrent rickettsemia.

Geographic Distribution: Unknown, except for CSD, which appears to occur worldwide (Benenson, 1990).

Occurrence in Man and Cats: It is estimated that in the US, some 22,000 cases of CSD are diagnosed each year, and that more than 2,000 patients are hospitalized (Jackson *et al.*, 1993). The etiologic agent of CSD is not yet known for certain, but there is definite evidence that *B. henselae* plays an important role. It is still difficult to determine the relative role played by *B. henselae* and *Afipia felis* in the etiology of the disease (see "Cat-scratch Disease" in Volume I: Bacterioses and Mycoses). However, research points to *B. henselae* as the causative agent. In one serologic study, 88% of 41 patients were positive for *B. henselae* in the indirect immunofluorescence test, whereas only 25% of the same group reacted positively to *Afipia felis* (Regnery *et al.*, 1992b).

The number of cases of bacillary angiomatosis is unknown. Bacillary peliosis has been observed in isolation and in association with angiomatosis. As of 1982, there were approximately 100 cases of this condition on record (García *et al.*, 1982).

Researchers at the University of California at San Francisco (USA) conducted an epidemiologic study of four patients with bacillary angiomatosis in an effort to discover the source of infection. The four patients had been in contact with seven cats, and *B. henselae* was isolated from both the cats' blood and their fleas. Blood samples were taken from 61 cats in the San Francisco metropolitan area, living both in homes and at an animal shelter, and *B. henselae* was isolated from 41% of the samples.

The Disease in Man: *B. henselae* infection produces a broad range of clinical and pathological varieties: CSD (see "Cat-scratch Disease" in Volume I: Bacterioses and Mycoses), recurrent rickettsemia, bacillary angiomatosis, and bacillary peliosis.

Bacillary angiomatosis is a vasoproliferative reaction observed in histological sections taken from lesions of the skin, bones, lymph nodes, and brain. The presence of a large number of bacillary forms in the lesions can be detected with Warthin-Starry argentic stain or an electron microscope. Although the disease is seen most often in immunodeficient patients, especially those infected with the human immunodeficiency virus (HIV), it also occurs in immunocompetent patients. The most common skin lesions are painful, angiomatous papules, which can be mistaken for Kaposi's sarcoma, but which histologically resemble epitheloid hemangiomas. In the disseminated form of bacillary angiomatosis, patients experience fever, weight loss, discomfort, and increased volume of the affected organs (Koehler *et al.*, 1992; Groves and Harrington, 1994). The etiology of bacillary angiomatosis is apparently shared between *B. henselae* and *B. quintana*. Koehler *et al.* (1992) isolated *B. quintana* from three patients with cutaneous and osseous lesions of bacillary angiomatosis. A DNA:DNA hybridization assay with the type species demonstrated 99% to 100% relatedness (strains with over 70% relatedness are considered to belong to the same species) (Koehler and Brenner, 1993).

Bacillary peliosis is a pathological entity specific to the solid internal organs (liver, spleen, abdominal lymph nodes, and bone marrow), which is expressed in the form of small blood-filled cysts. In some cases it can also affect the kidneys, pancreas, and lungs. Most cases are seen in individuals who are weak and chronically ill, such as HIV-infected tuberculosis patients, those with cancer, and those on systemic anabolic steroids. The clinical symptoms are fever, weight loss, nausea, diarrhea, abdominal pain, and lymphadenopathy.

In a group of 48 patients with bacillary angiomatosis or peliosis studied by Tappero *et al.* (1993), 42 were HIV-positive.

Another clinical form is recurrent rickettsemia, which is rare. In immunocompetent individuals, the rickettsemia is recognized clinically by its sudden onset, fever, muscle and joint pains, and sometimes, headache, meningism, and photophobia (Lucey *et al.*, 1992). In immunodeficient patients, the disease develops slowly, with manifestations of fatigue, asthenia, discomfort, and weight loss. In AIDS patients, *B. henselae* can cause inflammatory disease without angiomatosis or peliosis, which can be demonstrated using immunocytochemical techniques on autopsy specimens of infected tissue (Slater *et al.*, 1994). The authors describe three cases of AIDS patients without neoangiogenic lesions on their organs but whose pathological changes were caused by *B. henselae*, as was demonstrated by immunocytochemistry.

The recommended treatment for bacillary angiomatosis, bacillary peliosis, and recurrent rickettsemia is the administration of erythromycin, rifampicin, or doxycycline for six weeks. In bacillary angiomatosis, if the lesions are limited to the skin, surgical excision alone is sufficient. With recurrent rickettsemia, the recommended treatment is intravenous gentamicin and ceftriaxone, followed by oral ciprofloxacin (Groves and Harrington, 1994). For the treatment of CSD, see "Cat-scratch Disease" in Volume I: Bacterioses and Mycoses.

The Infection in Cats: Although cats are the reservoir of *B. henselae*, they are asymptomatic, except for persistent and prolonged rickettsemia. This may be because of the agent's long adaptation to the animal host.

Source of Infection and Mode of Transmission: The reservoir is the domestic cat. In a study carried out in California (USA), *B. henselae* was isolated from blood in 25 (41%) of 61 cats from family homes and animal shelters (Koehler *et al.*, 1994). It was also demonstrated that the rickettsemia is prolonged: the agent was isolated from a naturally infected cat for 18 weeks after the infection was first detected serologically (Regnery *et al.*, 1992b). These data indicate that immunocompetent individuals are not very susceptible to *B. henselae* infection and that other factors lower their resistance and contribute to the development of bacillary angiomatosis or peliosis. On the other hand, the agent was not observed to be opportunistic in CSD.

In CSD, the causal link to the scratch or bite of a cat, especially one under 12 months old, is a salient fact in the epidemiology of this disease. With other human diseases caused by *B. henselae*, except for recurrent rickettsemia, it is clear that they are contracted directly from the scratch or bite of a young cat, or via their fleas (Groves and Harrington, 1994). Little is known about cat-to-cat transmission, but it is assumed to be through fleas, bites and scratches during play among young cats, or fights between tomcats.

Diagnosis: The most certain method of diagnosis is isolation of the agent in culture media (see the section on etiology), but this technique takes too long; serological methods are more practical. An indirect immunofluorescence test (Regnery *et al.*, 1992b) has been developed for diagnosis of CSD. The test showed that CSD patients had high titers to *B. henselae* antigens. Of 41 CSD patients, 88% tested positive, whereas in a group of 107 controls only 3% were positive. A diagnosis can also be obtained using immunocytochemistry on pathological specimens (Slater *et al.*, 1994).

Control: The epidemiology of diseases caused by *B. henselae* is just beginning to be understood and there are still many areas to explore before any rational foundation can be established for their prevention and control. Transmission to man could be reduced by controlling cat fleas and perhaps by treating infected cats with antibiotics. Any wound inflicted by a cat should be promptly washed with soap and water and disinfected.

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Q FEVER

ICD-10 A78

Synonyms: Pneumorickettsiosis, Balkan influenza, coxiellosis, abattoir fever, Australian Q fever, hiberno-vernal bronchopneumonia, nine-mile fever, quadrilateral fever, infection due to *Coxiella burnetii*.

Etiology: *Coxiella burnetii* (*Rickettsia burnetii*). The agent differs from other rickettsiae in its filterability and high degree of resistance to physical and chemical agents (it is more resistant than most nonsporogenic microorganisms). It does not produce agglutinins in the Weil-Felix test, nor does it cause a cutaneous rash in man, and it can be transmitted without the intervention of a vector.

C. burnetii is bacilliform and measures 0.4–1 by 0.2–0.4 microns. In order to develop, it requires the presence of eukaryotic cells, where it tends to take up residence in the phagolysosomes, rather than the cytoplasm or the nucleus as the *Rickettsia* species do. It shows up well with Gimenez stain (Weiss and Moulder, 1984). It has been found to have several different plasmids, the functions of which are not yet understood.

C. burnetii can be highly pleomorphic when it reproduces inside the phagolysosomes of an invaded host cell. Two different forms can be distinguished under an electron microscope: one, large and bacilliform, and the other, coccoid, which develops from the former and has greater electronic density (McCaul and Williams, 1981). A third form appears in the large cells after passage through embryonated eggs or BGM cell cultures when they have been kept in suboptimal temperature conditions or fresh medium has not been added. These small, high-density forms are similar to spores (Aitken *et al.*, 1987). The morphogenesis is comparable, but not identical, to cell differentiation in the formation of endospores. These small forms are responsible for the high resistance of the Q fever agent to environmental factors and many disinfectants.

C. burnetii has two antigenic phases (I and II), much like the S-to-R variation in salmonellae or brucellae. When harbored in the animal or tick organism, it is in phase I. After several passages through the yolk sac of embryonated eggs, it converts to phase II, which is avirulent. This antigenic variation is important for diagnosis and prophylaxis.

Geographic Distribution: Worldwide. The infection is endemic in many areas and its presence has been confirmed in at least 51 countries. Although the Nordic countries were previously believed to be free of Q fever and that the few cases seen there were imported, in the 1990s, the disease was recognized as endemic in Sweden.

Occurrence in Man: Q fever appears in the form of sporadic cases or outbreaks. The human infection is often asymptomatic, and its mild form can be mistaken for other febrile diseases. For this reason, sporadic cases often go undiagnosed and the true incidence of the disease is unknown. Moreover, the indiscriminate use of antibiotics in febrile patients hampers the clinical identification of Q fever as well as other rickettsioses and bacterioses. In Australia, which is considered an endemic area, there were some 2,000 cases in 1979–1980 (Hunt *et al.*, 1983), and the United Kingdom has at least 100 laboratory-confirmed cases each year (Heard *et al.*, 1985).

Several epidemic outbreaks have occurred in abattoirs and wool-processing plants. In Uruguay, 310 of 630 workers and veterinary inspection personnel in a meat-packing plant fell ill in a single month in a 1976 epidemic. Cases were most concentrated among workers involved in bone-milling and the collection of animal wastes, such as placentas, fetuses, and viscera. The outbreak was attributed to aerosols, probably generated by the handling of placentas and amniotic fluid. Three more outbreaks occurred, apparently in that same meat-packing plant, in August and October 1981 and in 1984, with 25, 17, and 46 cases, respectively. Most of the affected personnel worked in slaughtering and deboning (Ortiz Molina *et al.*, 1987). According to the same authors, there have been 15 more outbreaks in abattoirs since 1976, mostly involving cattle. Epidemics have occurred among slaughterhouse workers in other parts of the world as well. In Quebec (Canada), an outbreak in the 1950s affected 62 employees (36.5% of the company's total workforce) within a

period of 18 days (Pavilanis *et al.*, 1958. Cited in Lang, 1989). In Australia, 110 workers contracted the disease in a rural goat slaughterhouse (Buckley, 1980), and in Romania, 149 workers in a municipal abattoir contracted the infection (Blidaru *et al.*, 1982).

Other high-risk groups are ranch hands and persons living on farms where cattle, sheep, and goats are raised. A sudden outbreak on a dairy cooperative in Romania during the calving season affected 45 persons. The source of infection was traced to cows that had been acquired elsewhere to open up a new dairy establishment (Blidaru *et al.*, 1980). Q fever outbreaks have also occurred in scientific institutes that use sheep as models for the study of human diseases. In addition to outbreaks at two universities in 1969 and 1971, four other outbreaks affected a large number of persons, many of whom were not working directly with animals (Spinelli *et al.*, 1981; Meiklejohn *et al.*, 1981; Hall *et al.*, 1982). In 1992, there were 86 cases of Q fever in Berlin (Germany), which mainly affected staff and students at a veterinary clinic. The infection was traced to sheep that had been brought to the clinic with nonspecific symptoms. That was the largest outbreak in Germany in 28 years (Schneider *et al.*, 1993). There was also an outbreak in a human pathology institute at a German university following the autopsy of a patient; all the people involved in the autopsy were affected, plus seven others who worked in other buildings (Gerth *et al.*, 1982). During World War II, there were numerous Q fever epidemics, both large and small, among German and Allied troops stationed in southern and southeastern Europe. Major epidemics also occurred in the postwar years in the civilian population in Germany, with 2,000 confirmed cases, and in Italy, where an estimated 20,000 cases occurred in a two-year period (Babudieri, 1959).

Hundreds of serologically confirmed cases of Q fever have been reported in Bulgaria since the beginning of the 1990s. The increase in the number of cases is thought to be linked to the tripling of the number of goats in the country and to increased contact between the animals and their owners, as well as increased consumption of raw goat milk and its products (Serbezov *et al.*, 1999). Raoult *et al.* (2000) recorded 1,070 acute and 313 chronic cases of Q fever in a retrospective study conducted in France.

In addition to cattle, sheep, and goats, which are the principal sources of the infection in man, parturient cats and newborn kittens can also cause outbreaks. In Canada, an outbreak in a truck repair shop affected 16 of 32 employees. One of them had kept a cat in the shop that gave birth to kittens two weeks before the animal's owner got sick. The wife and son of the cat's owner also developed the disease. The authors assume that the outbreak started with the employee's contaminated clothing (Marrie *et al.*, 1989).

There have also been epidemics that were not linked to any direct contact with animals or their viscera. In Switzerland, an outbreak in the fall of 1983 produced 415 confirmed cases of acute Q fever (21% of the population of the towns involved) along a route that had been followed by 12 herds of 850 to 900 head each descending from alpine pastures to the valley below. Five of the herds had seropositivity rates ranging from 46% to 93%. The infection was transmitted to man by inhalation of dust in the road, which was no doubt contaminated with excreta from the animals (Dupuis *et al.*, 1987). Because it is so highly resistant, the agent can cause an outbreak far away, as occurred in Switzerland, where the disease was contracted by 19 workers who unpacked a machine from the US that had been packed in contaminated straw (Stoker

and Marmion, 1955). A similar outbreak occurred among art students in Great Britain who unpacked sculptures packed in straw (Harvey *et al.*, 1951). Another example of indirect transmission was reported among British air force personnel who cleaned a shed that had been occupied by sheep (Holland *et al.*, 1960).

Occurrence in Animals: The infection has been found in almost all species of domestic animals and many wild animals, including birds. In India, the agent was also isolated from amphibians (Kumar and Yadav, 1981) and a python. From the public health standpoint, the most important sources of infection for man are cattle, sheep, and goats.

Serologic surveys conducted in some endemic areas have revealed a sizable proportion of reactors in the bovine, ovine, and caprine population. In a seroepidemiologic study in Colombia, 57% of 482 dairy cows produced antibodies in the complement fixation test (Lorbacher and Suárez, 1975). In California (USA), serologic studies of 2,097 sheep and 1,475 goats from different sources gave reactor rates of 24% and 57%, respectively, for the two species (Ruppaner *et al.*, 1982). Serologic surveys in France revealed reactor prevalence rates of 15% for cattle and 20% for sheep and goats in some departments. In Ontario (Canada), infection rates in dairy cattle have risen sharply, from 2.4% in a 1964 serologic survey to 67% in 1984 (Lang, 1989). Of 103 flocks of sheep in Ontario, 22 had one or more serologic reactors (Lang *et al.*, 1991).

In the Upper Nile province of southern Sudan, where the prevalence of serologic reactors in the human population was 39%, a survey of the animal population showed that 40.4% of 52 sera from cattle were positive, as were 53% of 42 sera from goats, and 62.5% of 32 sera from sheep (Reinthaler *et al.*, 1988). In New Brunswick and Prince Edward Island (Canada), a survey was conducted of the cat population, since it is believed that these animals play a role in the transmission of *C. burnetii* to man. In New Brunswick, 19.2% of 104 cats, and on Prince Edward Island, 6.2% of 97 of them, reacted positively in the immunofluorescence test (Higgins and Marrie, 1990).

It is also common to find antibodies to *C. burnetii* in wild animals. In a series of sera from 759 rodents (representing 15 species) that were examined by microagglutination, 3% were seropositive, and 20% of 538 free-living birds were reactors (Riemann *et al.*, 1979). In India, 1.2% of 342 birds and 14.3% of 91 wild land animals tested positive (Yadav and Sethi, 1980). In Bialowieza National Park (Poland), microagglutination testing of sera from 47 aurochs (wild oxen) showed that 76.5% were reactors. Of 39 people working in the forest, 10.2% were positive as well (Ciecierski *et al.*, 1988).

The Disease in Man: The incubation period ranges from two weeks to 39 days, with an average of 20 days. The disease has a sudden onset, with fever, chills, profuse sweating, malaise, anorexia, myalgia, and sometimes nausea and vomiting. The fever is remittent and usually lasts from 9 to 14 days. A prominent symptom of the disease is severe cephalalgia, and retroorbital pain is common. In about half the patients, X-ray examination reveals pneumonitis, which manifests itself clinically in the form of a slight cough, mild expectoration, and, occasionally, chest pain. About 50% of patients have gastrointestinal problems, such as nausea, vomiting, or diarrhea. Acute hepatitis can also occur. In contrast to the other rickettsioses, Q fever does not cause a cutaneous rash. The disease ranges in severity, but in most cases it is benign. Many human infections are mild and inapparent and thus go undetected.

Q fever rarely attacks children under 10 years old. However, in the Netherlands, 18 cases in children under 3 years old were reported within a 16-month period (Richardus *et al.*, 1985). The disease is more serious in adults over 40. The case fatality rate for acute Q fever is less than 1%. A retrospective study of Q fever patients in France (1,070 acute cases during 1985–1998) found that different clinical forms of acute Q fever were associated with different patient statuses. Isolated fever occurred more frequently in females, hepatitis occurred among younger patients, and pneumonia occurred in older or immunocompromised patients (Raoult *et al.*, 2000).

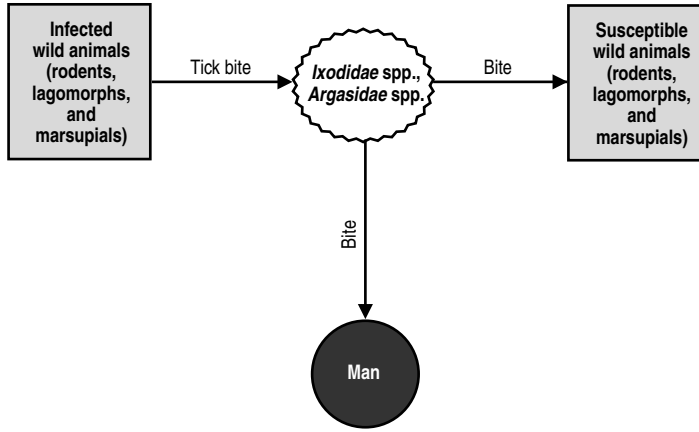
When the disease takes a chronic course, it mainly affects the cardiovascular system. The case fatality rate for chronic Q fever is approximately 65%. In Great Britain, out of 839 confirmed cases of Q fever, 92 (11%) had endocarditis and 10 had liver disease (Palmer and Young, 1982). Of the 313 chronic Q fever patients in the retrospective study in France, 259 had endocarditis; most patients had previous valvulopathy (Raoult *et al.*, 2000). Endocarditis is the most serious complication and is often fatal. It most often occurs among adults, with males being more frequently affected than females. Endocarditis develops slowly and usually manifests between 1 and 20 years after the acute disease. Sawyer *et al.* (1987) have summarized the characteristics of 28 cases from several different countries: 89% of the patients had a history of valve disease; the aortic valve alone was the site in 46% of the 28 cases; and the clinical signs were fever (86%), hepatomegaly (60%), splenomegaly (68%), and microscopic hematuria (80%). One study estimated the risk of developing endocarditis to be 39% among Q fever patients with valvular defects (Fenollar *et al.*, 2001).

Most cases of acute disease heal spontaneously; nevertheless, given the possibility that it could become chronic, treatment is recommended. It consists mainly of the administration of tetracycline or one of its derivatives, particularly doxycycline for two to three weeks (Chin, 2000). Several regimens have been tried for the treatment of chronic Q fever—for example, tetracycline combined with trimethoprim-sulfamethoxazole and rifampicin with doxycycline. Chronic Q fever endocarditis requires prolonged treatment (several years) with tetracycline, or doxycycline in combination with quinolones or hydroxychloroquine.

The Disease in Animals: As a general rule, the infection in domestic animals is clinically inapparent. In ruminants, after *C. burnetii* has invaded the bloodstream, it becomes localized in the mammary glands, the supramammary lymph nodes, and the placenta. Many cows get rid of the infection after a few months, but others become carriers, with the agent localized in the mammary glands and eliminated throughout many lactation periods. During calving, a large number of rickettsiae are shed with the placenta, and, to a lesser degree, the amniotic fluid, feces, and urine. The agent's strong resistance to environmental factors ensures its survival, as well as the infection of new susceptible animals and man. Activation of the infection during calving, with massive shedding of the agent in various secretions and excretions, explains why many sporadic outbreaks in man coincide with that period. Usually, neither milk production nor development of the fetus or the newborn animal is affected by the infection.

In Cyprus, there was an epizootic of Q fever-related abortions in sheep and goats during hostilities on the island in 1974. Twenty-one outbreaks of abortions in these

Figure 2. Q fever. Transmission—wildlife cycle.



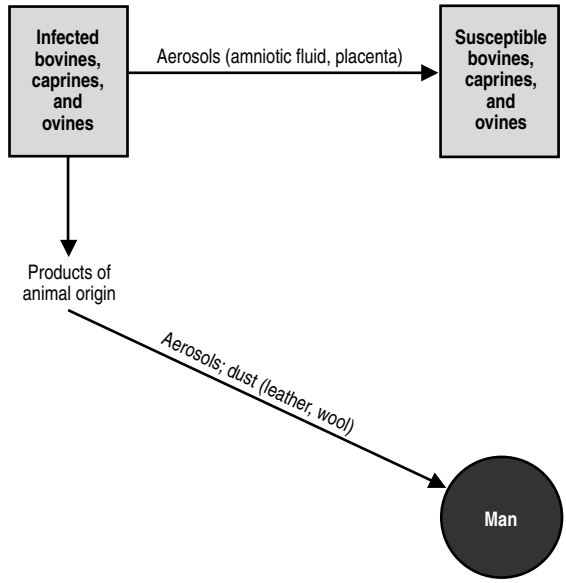
animals were recorded, all in the southeastern part of the island. At the same time, there were also 78 cases of Q fever among British soldiers stationed at the Eastern Sovereign Base Area. It is quite probable that the large concentration of livestock in this part of the island and the shortage of proper feed were factors contributing to the abortions (Crowther and Spicer, 1976). In the US, abortion in domestic animals is rarely associated with *C. burnetii* infection, and it has been observed that dairy cows with heavily infected placentas have given birth to normal calves. In Europe, on the other hand, especially in France, *C. burnetii* is thought to be responsible for 2% to 7% of all abortions in cattle and a similar proportion in sheep. So far no explanation has been offered to account for this difference between the US and Europe.

In Canada, there was an outbreak of abortions in a goat herd between January and April 1992. The fetuses appeared normal. The most remarkable lesion was a purulent inflammation of the cotyledons. Eleven of 33 pregnant goats aborted. *C. burnetii* was isolated, and 34 of the 40 adult female goats reacted positively in the enzyme-linked immunosorbent assay (ELISA). An epidemiological investigation to track down the origin of the infection revealed that 8 of the 11 goats that aborted had been at a livestock fair. Moreover, it was learned that at least six persons developed Q fever in the 12 months following the fair (Sanford *et al.*, 1993). Also, Canada has seen an increase in the rate of abortions and stillbirths in infected domestic ungulates (Marrie, 1990), and it is possible that this trend is occurring in other countries as well.

Little is known about the course of the natural infection in wild animals.

Source of Infection and Mode of Transmission (Figures 2 and 3): Two cycles of infection can be distinguished in nature: one in domestic animals (mainly cattle, sheep, and goats), and the other in natural foci, where the agent circulates between wild animals and their ectoparasites, especially ticks.

Figure 3. Q fever. Transmission—domestic cycle.



Many wild animal species, including marsupials, rodents, and lagomorphs, have been found to be infected. The natural infection has also been observed in more than 40 species of ticks from the families Ixodidae and Argasidae, as well as other arthropods that feed on animals. However, even if infected, not all tick species are able to serve as vectors and transmit the infection to vertebrates.

The relationship between the two cycles of infection is not well studied. There are indications that domestic animals may contract the infection through infected ticks coming from natural foci, but the infection in domestic animals is not dependent on this mechanism; it can be perpetuated independently. The most common mode by which the infection is transmitted between domestic animals is through the inhalation of aerosols from contaminated placental material, amniotic fluid, and excreta. The placenta of infected animals can contain as much as 10^9 g of the causative agent, which can be transported long distances via inert material (see the section on the disease in man for information about other outbreaks). Because of its strong resistance, the agent can be isolated from the soil as long as six months after infected animals have left the area. New foci of infection are created when an infected animal joins a disease-free herd.

The main sources of human infection are domestic animals and their contaminated products (leather and wool). In abattoirs, aerosols are generated by the handling of fetuses, placentas, uteruses, hide, and wool. The main mode of transmission is by aerosols. People who are in close contact with infected animals or their products because of their occupation or residence are most likely to be affected. Although the agent is shed in milk, there are few reported cases of human infection stemming from the consumption of contaminated milk. It seems that man can be infected via the digestive tract, but infection by that route is seldom clinically appar-

ent, probably because of the high titer of antibodies found in milk. Although humans can acquire the infection by entering a natural focus and getting bitten by an infected tick, such cases are rare.

Role of Animals in the Epidemiology of the Disease: Human-to-human transmission is rare. However, an outbreak of 38 cases at a hospital in Frankfurt (Germany) was traced to a staff member who worked with *C. burnetii* and was confirmed by isolation of the microorganism from his sputum. A similar episode originating in an autopsy room has been recorded.

As a general rule, man acquires the infection from domestic animals. Q fever is a zoonosis.

Diagnosis: Few laboratories have adequate installations and equipment to safely isolate *C. burnetii*, and it is therefore preferable to rely on serologic tests. Diagnosis is based on the difference between the titer of a sample taken during the acute stage of the disease and that of a sample taken during the convalescent stage. With serology it is important to take into account the differences between the phases. Strains of *C. burnetii* that have been recently isolated or maintained by passage in laboratory animals are in phase I. After a (varying) number of passages in embryonated eggs, the strains convert to phase II. The tests used most often are complement fixation and indirect immunofluorescence. Comparison studies have shown that with the complement fixation test, the highest titers are obtained at three months, while with indirect immunofluorescence, similar titers are reached at one or two months and maintained for at least a year. A disadvantage of complement fixation is that anticomplementary sera can sometimes develop. This does not happen with the indirect immunofluorescence test, which is also more versatile because it can distinguish several immunoglobulin isotypes. Specific IgM antibodies indicate a recent infection and can be detected the second week after the disease's onset. However, care should be taken to remove the rheumatoid factor before performing the test (Sawyer *et al.*, 1987). High IgA and IgG titers against phase I antigens are indicative of chronic disease (endocarditis) (Aitken *et al.*, 1987).

Use of the complement fixation test with phase II antigens will detect the infection in about 65% of the patients during the second week and about 90% of them by about the fourth week. When there are no complications, patients rarely react to the complement fixation test with phase I antigens. On the other hand, because phase I titers are high in cases of endocarditis, this test is useful for discovering possible complications during convalescence.

Various agglutination tests are also available: standard agglutination, microagglutination, agglutination-resuspension, and capillary agglutination. In about 50% of the patients, the presence of agglutinins can be detected at the end of the first week of the disease, and in 92%, during the second week. The Luoto capillary agglutination test, which uses phase I antigens stained with hematoxylin, is especially useful for epizootiologic studies because it can be used on milk samples. When serum from the acute stage of the disease is not available to test for seroconversion and compare with serum obtained during convalescence, the indirect immunofluorescence test for IgM antibodies, which uses both phase I and II antigens, can be useful. In an experiment carried out in Australia, all Q fever patients reacted positively at about two weeks after onset of the disease, and thus it was possible to obtain a diagnosis using only one serum sample (Hunt *et al.*, 1983).

The agent can be isolated from febrile blood and sometimes from sputum and urine in humans, as well as from substances such as milk, placentas, and amniotic fluid from animals. These materials are inoculated into laboratory animals (guinea pigs and mice) and embryonated eggs. However, as pointed out earlier, isolations should only be performed in laboratories that have high-safety equipment and supplies.

Control: Several vaccines have been developed to protect high-risk occupational groups such as workers in laboratories, abattoirs, wool-shearing sheds, and on farms, as well as patients with heart valve implants and immunodeficient individuals. One of these vaccines was tested on volunteers with good results (Ascher *et al.*, 1983). The most well-known vaccine is a formalin-inactivated whole-cell preparation made with phase I antigens, which confers much greater protection than those made with phase II antigens. The disadvantage of using whole-cell vaccines with phase I antigens is that they can cause undesirable side effects, such as local erythema, induration, granulomas, sterile abscesses, and systemic reactions in persons previously exposed to *C. burnetii* infection. The whole-cell vaccine should not be used in persons who have had a positive serologic or cutaneous reaction. To address these problems, a phase I cell chloroform:methanol residue vaccine (CMRV) has been developed (Williams *et al.*, 1992). Though the whole-cell and CMRV vaccines are not commercially available in the US, persons at risk can request vaccination. A Q fever vaccine is commercially available in Australia.

In a clinical trial in Australia, a whole-cell formalin-inactivated vaccine was administered to 4,000 abattoir workers and related groups over the period 1981–1984. The side effects observed were erythema and pain at the inoculation site and, sometimes, a passing headache. The protection conferred by the vaccine was very satisfactory and lasted for five years. Eight cases of Q fever were observed, but they were all in persons who were already incubating the illness before they were vaccinated, so that there was no time to establish immunity. On the other hand, there were 97 cases in unvaccinated individuals who worked or visited the participating abattoirs (Marmion *et al.*, 1990). In a random double-blind trial conducted at three abattoirs in Queensland (Australia) the formalin-inactivated vaccine was administered to 98 persons and an influenza vaccine to 102 persons; 15 months later, there were 7 cases in the group vaccinated against influenza and none in the group vaccinated against Q fever (Shapiro *et al.*, 1990). A Q fever vaccine is licensed in Australia.

Sheep used for experimental purposes should undergo serologic testing before they are accepted at research institutes. Measures aimed at combating infection in the animal reservoir (domestic animals) are difficult to implement because Q fever does not cause obvious economic losses and livestock owners are reluctant to invest in prophylaxis. When practicable, it is recommended to separate gravid females before they give birth and to bury or burn the placenta and all material surrounding the fetus.

Raw milk should not be consumed.

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QUEENSLAND TICK TYPHUS

ICD-10 A77.3 Spotted fever due to *Rickettsia australis*

Etiology: Despite its name, this disease belongs to the spotted fever group, and its agent is *Rickettsia australis*. A new agent from the same group was isolated on Flinders Island, northeast of Tasmania. The genetic difference between this rickettsia and *R. australis* is significant (Baird *et al.*, 1992).

Geographic Distribution: The original disease is limited to the area between Queensland and Sydney, in New South Wales (Australia), while the new spotted fever has been found on Flinders Island, Tasmania, and in Gippsland, Victoria, in southeastern Australia (Graves *et al.*, 1993).

Occurrence in Man: The disease caused by *R. australis* is sporadic. The disease caused by the new agent is not fully understood. On Flinders Island (population 1,000), annual incidence is nearly 1%. Between October and December 1989, there were 17 new cases. In all, 24 cases have been diagnosed on Flinders Island and in southeastern Australia (Graves *et al.*, 1993).

Occurrence in Animals: A serological study of wild animals in an area of Queensland revealed reactors in several species of marsupials and rodents. In southeastern Australia, where the Flinders variant of *R. australis* predominates, a study using indirect immunofluorescence showed that 11.2% of 312 domestic and farm dogs had antibodies to *R. australis*. While control dogs in New Zealand were negative, 15% of the dogs on Flinders Island were positive.

In a set of serum samples from species of native vertebrates captured in Gippsland, Victoria, particularly the rat *Rattus fuscipes*, 89% were positive in the competitive enzyme-linked immunosorbent assay (ELISA). On Flinders Island, the same test was used to examine sera from 37 wild animals (placental and marsupial mammals), and 8 (22%) proved to be positive (Graves *et al.*, 1993).

The Disease in Man: *R. australis* produces a benign macular disease similar to boutonneuse fever and Asian ixodo-rickettsiosis. An eschar is often seen at the site where the larval or adult tick was attached. Painful regional adenopathy is also observed. The eruption, which appears during the first week of the disease, disappears soon after the fever subsides. The clinical aspects of Flinders Island spotted fever (FISF) differ very little from those of Queensland tick typhus. Only a small proportion of patients have an eschar left by the tick, and the frequency of lymphadenopathy is also low.

Treatment consists of administering of tetracycline or doxycycline.

The Disease in Animals: Little is known about how the infection develops in marsupials or rodents, nor have signs of the disease been observed in dogs bitten by infected ticks. In the case of a dog inoculated experimentally with *R. australis*, a series of tests failed to reveal rickettsemia (Sexton *et al.*, 1991).

Source of Infection and Mode of Transmission: The natural history of *R. australis* is not well understood. In a focus in southeastern Queensland, either *R. australis*, the new variant, or the agent that produces FISF was isolated from two species of ticks: *Ixodes holocyclus* and *I. tasmani*. Another tick associated with the infection is *I. cornuatus*. No infected ticks from these species have been found on Flinders Island. A patient from the island with laboratory-confirmed rickettsiae had been bitten by *Aponomma hydrosauri* nine days before the onset of his illness, but it is not certain that this tick was the vector. The human infection has long been associated with the bite of *I. holocyclus*, a species that feeds on a large variety of vertebrate animals and often bites man.

Diagnosis: The disease must be distinguished from scrub typhus (*R. tsutsugamushi*), endemic murine (flea-borne) typhus (*R. typhi*), and Q fever, which also occur in Australia.

R. australis can be isolated by inoculating the blood of febrile patients into suckling guinea pigs and mice. In the complement fixation test, sera from convalescent mice inoculated with material containing *R. australis* had species-specific antibodies that could be distinguished from antibodies to other rickettsial antigens of the spotted fever group. Seeding the agent on plaques of Buffalo green monkey kidney cells has yielded satisfactory results after a month of incubation in carbon dioxide at 34.5°C.

Control: Control measures are similar to those used against infections caused by other spotted fever group rickettsiae.

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RICKETTSIALPOX

ICD-10 A79.1 Pustular rickettsiosis due to *Rickettsia akari*

Synonyms: Vesicular rickettsiosis, Kew Garden fever, gamaso-rickettsiosis varicelliformis.

Etiology: *Rickettsia akari* (*Dermacentroxenus murinus*). This microorganism belongs to the group of rickettsiae that produce spotted fever. *R. akari* is a small coccobacillus that can be seen in the nucleus and cytoplasm in stained histological sections of infected mouse tissue.

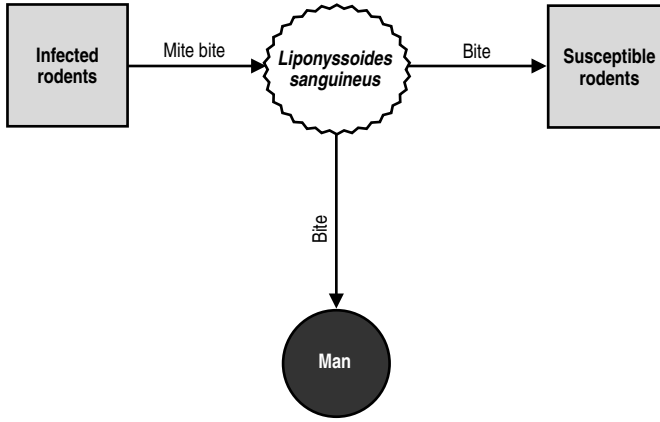
Geographic Distribution: The disease has been found in New York City and other cities in the US. A similar disease has also been reported in Ukraine, where the agent was also isolated from household rats. On the basis of clinical observations, it is suspected that this rickettsiosis occurs among natives of equatorial Africa and in South Africa (where there is serologic evidence as well). In addition, a serologic study conducted in Central America suggests that the disease has occurred in Costa Rica. In Korea, *R. akari* has been isolated from a vole (*Microtus fortis pelliceus*). The agent was isolated from a patient in Croatia, too (Radulovic *et al.*, 1996).

Occurrence in Man: Occasional. In 1946, an outbreak affected 144 persons in Kew Gardens, a neighborhood in New York City. For a while thereafter, about 180 cases were reported each year in the US, but then the incidence dropped off sharply. In 1979, there was a small outbreak of five cases in New York among persons living in two apartments in the same mouse-infested building (Brettman *et al.*, 1981). Also in Ukraine, where the infection was once widespread in the Donets basin, there has been a marked decline in the incidence of the disease.

Occurrence in Animals: The natural host of *R. akari* in the US is the house mouse (*Mus musculus*), and in Ukraine it is the rat (*Rattus* spp.). The infection is transmitted by the mite *Liponyssoides sanguineus* (*Allodermanyssus sanguineus*). The frequency of infection in rodents is unknown.

The Disease in Man: The disease has a benign course. It starts with a cutaneous lesion at the site of the mite bite (*L. sanguineus*) and continues with a week of

Figure 4. Rickettsialpox *(Rickettsia akari)*. Transmission cycle.



fever accompanied by a varicelliform eruption. Symptoms appear 9 to 24 days after the bite. The initial cutaneous lesion, a small papule that develops a vesicle in the center and later forms a dark crust, appears about one week before the fever and leaves a small scar. The febrile period is characterized by chills, profuse sweating, intermittent fever, cephalalgia, and myalgia. Some patients may experience nasal discharge, cough, nausea, vomiting, or abdominal pain. A maculopapular eruption appears between the first and the fourth day of the fever and then becomes a maculovesicular eruption that disappears at the end of the week, leaving no scars. The eruption is painless and can appear on many parts of the body, but it does not affect the palms of the hands or the soles of the feet. Leukopenia and mild lymphocytosis are present during the early days of the febrile period (Brettman *et al.*, 1981).

Although the disease has a benign course and is eventually self-limiting, antibiotics are recommended to reduce the duration of the symptoms. The preferred treatment is 250 mg of tetracycline every six hours for two to five days (Brettman *et al.*, 1981).

The Disease in Animals: The natural course of the infection in mice and other rodents is unknown. Laboratory mice are highly susceptible to artificial infection. Intranasal inoculation causes a pneumonia that is often fatal. Intraperitoneal inoculation causes peritonitis with a sanguinolent exudate, lymphadenitis, and splenomegaly. Death occurs between 9 and 18 days postinoculation. Strains of *R. akari* vary in terms of virulence.

Source of Infection and Mode of Transmission (Figure 4): The main reservoirs are the domestic mouse and the mite *L. sanguineus*, which can pass on the rickettsia by transovarial transmission. In the US, the nymphs and adult mites feed on domestic mice and may attack other animals and man (Weiss and Moulder, 1984). It is possible that there is also a wild cycle, as suggested by isolation of the agent from a wild

rodent in Korea. The disease is also believed to occur in the "bushveld" of South Africa (level, steppe-like grassland with abundant shrubs and thorny vegetation).

Both in the US and in the Russian Federation, rickettsialpox has occurred in cities and affected people living in rodent-infested dwellings. The etiologic agent is transmitted from one mouse to another by the mite *L. sanguineus* and, accidentally, to man. This mite is probably the main reservoir of the agent. Thus, *L. sanguineus* would be the vector of the infection and also serve as its reservoir. Although house mice are the preferred hosts, the vector also feeds on rats and other rodents. *L. sanguineus* does not remain permanently on the host; it only stays for one or two hours in order to feed. Large numbers of nymphs and adult mites are found in buildings located near rodent nests and paths (Harwood and James, 1979; Bell, 1981).

Role of Animals in the Epidemiology of the Disease: The infection is perpetuated by rodents and by the mite *L. sanguineus*; man is an accidental victim.

Diagnosis: Laboratory confirmation is accomplished by isolating the agent from blood taken during the febrile period and inoculating it in mice, then performing the complement fixation test using sample sera obtained during the acute phase of the disease, and then again three to four weeks later. The indirect immunofluorescence test is also useful in diagnosing the disease.

Control: Control measures target the vector and the rodents. They consist of applying acaricides in the infested area, followed by rodenticides. Trash should be incinerated to eliminate mice and rat havens in buildings. The sharp drop in incidence among persons in New York City is attributed to changes in waste-handling practices (Benenson, 1990).

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ROCKY MOUNTAIN SPOTTED FEVER

ICD-10 A77.0 Spotted fever due to *Rickettsia rickettsii*

Synonyms: Spotted fever, petechial fever, macular fever (Brazil), tick-borne typhus, New World spotted fever, North American tick typhus, São Paulo fever, Choix fever, pinta fever (Mexico).

Etiology: *Rickettsia rickettsii* (*Dermacentroxenus rickettsii*). This microorganism is the prototype of the spotted fever group rickettsiae. Although it is the most pathogenic of the group, its strains differ in terms of their virulence. Some of its antigens are shared by the entire group, and it also has species-specific antigens, which can be demonstrated by applying the microimmunofluorescence test to mouse sera. The agent penetrates human skin through a tick bite and travels through the body via the bloodstream and lymphatic system, attaching to endothelial cells along the way and eventually involving the lungs. It enters the cells by phagocytosis and then moves from the phagosome to the cytoplasm, and sometimes the nucleus, where it reproduces by binary fission (Raoult and Walker, 1990).

Geographic Distribution: The disease has been found in Brazil (states of Minas Gerais, Rio de Janeiro, and São Paulo), western Canada, Colombia, Costa Rica, the western and central areas of Mexico, Panama, and the US. In the US, it occurs everywhere except in the states of Alaska, Hawaii, Maine, and New Hampshire. The infection has not been identified outside the Americas.

Occurrence in Man: Sporadic. In the US, where the disease is the subject of epidemiological surveillance, there were 528 cases a year on average from 1970 to 1973. This figure rose considerably over the rest of the decade, and during 1977–1980, there were 4,411 cases, for an annual average of 1,103. However, the trend reversed in the next decade, falling from 1,170 cases in 1981 to 603 in 1989, with an incidence of 0.25 per 100,000 population. At the same time, the case fatality rate fell from 4.7% in 1982 to a low of 1.1% in 1989 (CDC, 1990). In 1990, a total of 649 persons contracted the disease, and case fatality increased by 7.6% (CDC, 1991).

In the US, which is the country most affected, there has been a notable eastward shift in the distribution of case incidence. From 1910 to 1930, the largest numbers of cases (between 100 and 600 a year) were reported in the Rocky Mountain region, where the tick *Dermacentor andersoni* is found. Today, however, the highest numbers are reported from the southeastern seaboard and the central southwest (the region corresponding to the dog tick *Dermacentor variabilis*). Of the 603 cases reported in 1989, 224 (37.1%) were from the southeastern seaboard and 100 (16.6%) from the central southwestern states. The incidence was highest in the state of Oklahoma (1.9 per 100,000 population), followed by North Carolina and Montana (1.8 per 100,000 population) (CDC, 1990). The cases occur mainly in the spring and summer, when the ticks are most active. In a series of 487 cases, 63% of the patients were males. The rate was highest in children 5 to 9 years old and lowest in persons age 20 and over (CDC, 1990). Geographically, overall national incidence was 5.2 cases per 1,000,000 population, and the highest incidence was in the southeast. Most cases occur between mid-April and mid-September, and are mainly seen in children and young adults, with males predominating (Bernard *et*

al., 1982). No recent figures are available on the incidence of this zoonosis in Latin America.

Occurrence in Animals: In Brazil, *R. rickettsii* has been isolated from dogs, opossums, and wild rabbits (*Sylvilagus* spp.). In the endemic areas of the US, it has been found, as elsewhere, in dogs, opossums, and wild rabbits, and also in many species of wild rodents. Rickettsemia is short-lived in wild animals (Weiss and Moulder, 1984; Raoult and Walker, 1990).

Serological studies in the US have confirmed that many species of wild mammals have antibodies for *R. rickettsii*. Since dogs infested with the tick *D. variabilis* are an important link in transmission of the infection to man, it is of interest to know the extent to which they are exposed to infected ticks. Several serological studies have found a high rate of reactors among dogs in endemic areas. The highest prevalence of seroreactors was reported in Columbus, Ohio, where 45.2% of 73 dogs tested by microimmunofluorescence were positive (Smith *et al.*, 1983).

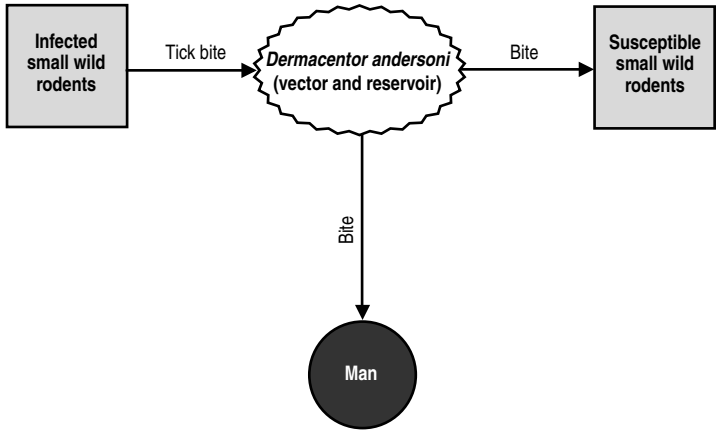
The disease occurs sporadically in both dogs and humans. An outbreak was reported among a group of Siberian huskies kenneled in a makeshift building on a high pasture where ticks were known to be present. Within five days, 7 of the 12 dogs had fallen sick (Breitschwerdt *et al*., 1985).

The Disease in Man: Clinical symptoms appear 2 to 14 days after the tick bite. The disease has a sudden onset and is characterized by fever, chills, headache, and pain in the muscles, joints, and bones. Fever of about 40°C lasts until the end of the second week of illness. Also, before the skin rash develops, there is often a phase of gastrointestinal upset with nausea, vomiting, and diarrhea (Raoult and Walker, 1990). A generalized macular rash appears three to six days after the onset of fever; at first it resembles measles, but it often becomes petechial. This rash, which starts around the wrists and ankles, is the most characteristic sign of the disease and is present in more than 80% of the cases. Involvement of the nervous system, with such symptoms as agitation, insomnia, delirium, or even coma, may develop at the end of the first week. During the second week there may be circulatory and pulmonary complications. Also, gangrene was reported in about 30 patients, a number of whom had to have a limb and/or digit amputated (Kirkland *et al*., 1993). The period of convalescence can be short for patients who receive treatment, but when the disease is allowed to progress untreated, it can last for weeks or months. In the US, case fatality declined from 4.5% to 1.2% (CDC, 1990).

The Disease in Animals: The infection is inapparent in most of its wild hosts. Dogs infected either experimentally or in nature may have clinical symptoms. In a group of four dogs that had been diagnosed serologically, three had high fever, abdominal pain, depression, and anorexia. Two of them displayed lethargy and nystagmus, and the third had conjunctivitis and petechial hemorrhages in the oral mucosa. The fourth dog had no clinical symptoms. It is possible that dogs in endemic areas are exposed to *R. rickettsii* at an early age and that maternal antibodies protect them from a severe form of the disease. Thus, by the time they are re-exposed later on, they may have become actively immune and therefore resistant to clinical infection (Lissman and Benach, 1980).

In an outbreak described by Breitschwerdt *et al.* (1985), the following symptoms of the disease were observed: lethargy, anorexia, ocular and nasal discharges, inco-

Figure 5. Rocky Mountain spotted fever. Transmission cycle in the US.

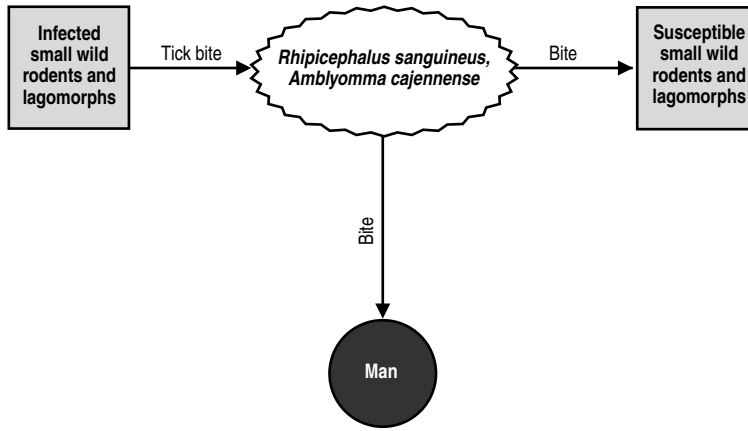


ordination, scleral blood vessel injection, fever, lymphadenomegaly, splenomegaly, and increased bronchovesicular sounds. In a report of four cases, in addition to suffering from various signs of the disease, the dogs developed necrotic skin lesions in such areas as the scrotum, earflap, nose, nipples, and the limbs (Weiser and Green, 1989). In 11 dogs with a serologically confirmed diagnosis, 9 had mild ophthalmic lesions that healed after the dogs were given parenteral oxytetracycline or oral tetracycline for a minimum of two weeks (Davidson *et al*., 1989). Since dogs have much more exposure to ticks than humans do, they can serve as an indicator of the prevalence and location of disease foci (Feng *et al*., 1979).

Source of Infection and Mode of Transmission (Figures 5 and 6): The natural reservoir is a complex of ticks of the family *Ixodidae* and small wild mammals. In the US, there are two main vectors and reservoirs: *D. andersoni* in the Rocky Mountain region, and the dog tick *D. variabilis* in the east and southeast. Currently, *D. variabilis* is much more important as a vector because most of the human cases occur in the eastern part of the country. In the endemic areas of Latin America, the principal vector is *Amblyomma cajennense*. This tick attaches to humans at any stage in its development, whereas *D. andersoni* and *D. variabilis* do so only as adults. In Mexico, the brown dog tick *Rhipicephalus sanguineus* is also a vector. In Costa Rica, the agent was isolated from *Haemaphysalis leporispalustris*, which infests the wild rabbit *Sylvilagus braziliensis*. This tick has no special preference for man and is not believed to be a vector for human disease (Fuentes *et al.*, 1985).

The agent circulates in natural foci via ticks, which transmit it to small rodents when they attach themselves in order to feed. Uninfected ticks, in turn, can then acquire the infection by taking a blood meal from infected wild animals (field mice, squirrels, etc.). Although wild rabbits (*Sylvilagus* spp.) were once thought to be a primary reservoir, doubts have been raised about how readily they can transmit the

Figure 6. Rocky Mountain spotted fever. Transmission cycle in Latin America.



NOTE: Transovarial transmission of *Rickettsia rickettsii* in ticks may possibly perpetuate the infection by itself.

infection to ticks (Burgdorfer *et al.*, 1980). Ticks play an important role not only as biological vectors but also as reservoirs, because they can pass *R. rickettsii* to their offspring by transovarial transmission.

The rate of infection in ticks is low, even in highly endemic areas, and it varies from year to year. Nevertheless, the infection can be maintained in nature by transovarial transmission alone. In this situation, ticks would be the main reservoir of the infection, and animals to which they attach would serve only to feed them.

The role of other animals as reservoirs capable of maintaining the infection in nature has not been established, since the rickettsemia that they experience is brief. As for dogs, even though they play a very important role in the epidemiology of the disease by introducing infected ticks into the human environment, it is doubtful that they can infect ticks under natural conditions.

Man becomes infected through the bite of a tick, which must remain attached to the body for at least four to six hours in order for the rickettsiae to "reactivate" (pass from the avirulent to the virulent stage). It is also possible, though less common, for rickettsiae in a tick's feces, or in pieces of its tissue that rupture at the time it is detached, to enter the body through a break in the skin.

Humans contract the infection either by entering tick-infested areas or through contact with ticks carried by dogs to suburban homes. The human infection is seasonal, coinciding with annual periods of greatest tick activity.

Role of Animals in the Epidemiology of the Disease: Man is an accidental host. The dog is a key link in the transmission of the infection to man because it introduces infected ticks into the human environment—specifically, such species as *D. variabilis*, *A. cajennense*, and *Rhipicephalus sanguineus*.

Diagnosis: Laboratory confirmation of the clinical diagnosis is based on isolation of *R. rickettsii* from the patient's blood during the first week of fever and inoculation of a coagulated blood suspension into male guinea pigs or embryonated eggs. Stained smears of the tunica vaginalis testis can be examined microscopically four to six days after inoculation. Although isolation of the agent is the most reliable way to diagnose the disease, due to the risk of contaminating the environment and exposing personnel to the infection, it is imperative that the test be performed only in reference laboratories equipped for the procedure.

It is very important to have an early presumptive diagnosis. If the disease is suspected because of the clinical signs and epidemiological antecedents, treatment should be started immediately without waiting for laboratory results. The Weil-Felix test is no longer used because of its low sensitivity and specificity. The main tests now used are indirect immunofluorescence and indirect hemagglutination. Complement fixation, latex agglutination, and microagglutination are specific but not sufficiently sensitive. The tests are performed on acute- and convalescent-stage sera. A four-fold rise in titer is considered positive. Sometimes *R. rickettsii* antigen can be detected in eruptive skin lesions using direct immunofluorescence (50%–70% sensitivity) (CDC, 1990). Diagnosis was obtained using polymerase chain reaction to amplify ribosomal DNA of *R. rickettsii* in blood clots from four of five patients, but in three of the cases reamplification was needed. This would indicate that the test is not sufficiently sensitive and has limitations for clinical diagnosis (Sexton *et al.*, 1994). Moreover, the value of serological tests for diagnosing *R. rickettsii* is limited by the fact that seroconversion cannot be demonstrated until at least six days after onset of the disease (Clements *et al.*, 1983a).

Control: Control measures include the application of tickicides in limited areas to exterminate or reduce the vector population, use of protective clothing and repellents (diethyltoluamide and dimethylphthalate) for individual protection, inspection of clothing twice a day to get rid of unattached ticks, and careful removal of attached ticks. It is also important to apply residual tickicides to dogs, kennels, and dwellings at two-week intervals.

Vaccines to protect individuals at high risk of exposure (laboratory workers and ecologists) have not given very satisfactory results. An improved, chick embryo cell-derived formalin-inactivated vaccine was tested on volunteers and evaluated. The vaccine conferred only partial protection (25% efficacy), but the volunteers who did become ill had a milder form of the disease (Clements *et al.*, 1983b).

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SCRUB TYPHUS

ICD-10 A75.3 Typhus fever due to *Rickettsia tsutsugamushi*

Synonyms: Tsutsugamushi disease, mite-borne typhus fever, tropical typhus, and various local names.

Etiology: *Rickettsia tsutsugamushi* (*R. orientalis*) belongs to the typhus group. In Greek, the word *typhos* means "stupor caused by a fever." There is a high degree of antigenic heterogeneity among the different strains. Eight antigenic prototypes are recognized, and there may even be more. Immunity against the homologous strain is long-lasting, but against the heterologous strains it is only temporary. Where several serotypes coexist in an endemic area, one of them may predominate (Shirai and Wisseman, 1975). In a series of 168 isolations obtained from various species of *Leptotrombidium* mites in Malaysia, 68.5% contained only one type, with the Karp prototype predominating (Shirai *et al.*, 1981). The different strains of *R. tsutsugamushi* vary in their virulence.

R. tsutsugamushi, a bacillus, is one of the smallest rickettsiae, averaging 1.2 microns in length. It can be seen with Giemsa stain or a modified version of Gimenez stain. It grows well in cell cultures and in the viteline sac of embryonated eggs. It is found in the perinuclear region of eukaryotic cells (Weiss and Moulder, 1984).

Geographic Distribution: From Primorski Krai, in the far eastern part of the Russian Federation, to southeast Asia, India, Afghanistan, Pakistan, northern Australia, and islands of the eastern Pacific. In these areas, the infection is found in a wide range of ecological conditions: primary jungle, semidesert, mountainous desert, and the alpine meadows of the Himalayas. Its distribution is uneven, since it depends on the presence of the agent and the vector/reservoir complex, the latter consisting of trombiculid mites and the small mammals, especially rodents, on which they feed. When all these elements come together, they form "typhus islands." Focalization occurs when the vector's larvae and the reservoir *Leptotrombidium* spp. are found in the same place.

Occurrence in Man: During World War II, scrub typhus was a serious problem for both the Allied and the Japanese forces in the southwestern Pacific and the India-Burma-China theater of operations. It is estimated that the Allied troops had some 18,000 cases. Case fatality in the various outbreaks ranged from 0.6% to 35.3%, depending on the area. The disease continues to be a public health problem in some

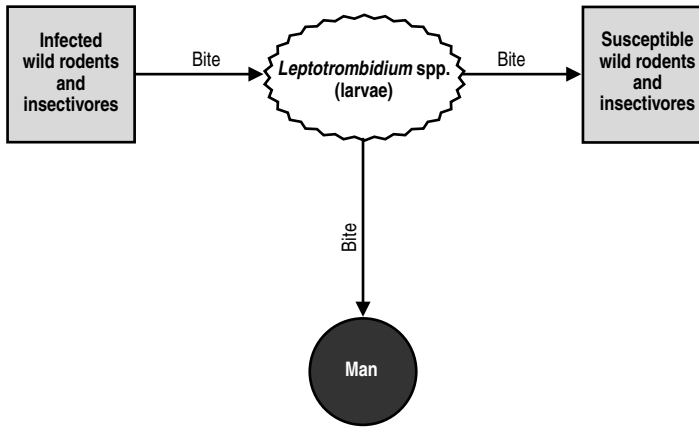
endemic areas. In most cases it occurs sporadically. Although the recorded incidence of clinical cases in Malaysia between 1967 and 1974 was very low (averaging about 55 a year), the real incidence of the disease was thought to be much higher. In a study conducted in two communities of peninsular Malaysia, the monthly incidence of infection was estimated at 3.9% in one community and 3.2% in the other. The lack of adequate laboratories in rural areas makes it difficult to distinguish scrub typhus from other febrile diseases (Brown *et al.*, 1978). In some areas, the disease in humans can disappear and then reappear many years later. That was what happened in Chiba Prefecture (Japan), where it was first recognized in a patient in 1950, and then disappeared, only to appear again in 1982 and resume its upward climb. A total of 152 cases were recognized in 1989, and the following year the number increased to 157. Ninety percent of these cases occurred in November and December. Of six isolations typed with monoclonal antibodies, five were of the Kawasaki type and one was Kuroki (Kaiho *et al.*, 1993). In recent years, new disease foci have been found in Korea and Australia's North Territory. Of 113 isolations from Korean patients, which were typed using polyclonal and monoclonal sera, 88 had an antigenic determinant that was not found in the Karp, Kato, and Gilliam prototype strains, and they also had antigens in common. The authors (Chang *et al.*, 1990) concluded that a new serotype, related to the Karp type, is prevalent in Korea.

The rate of serologic reactors can be very high in areas of great endemicity. For example, an indirect immunofluorescence study conducted in a Thai village revealed that 77% of the adults in the community were reactors. Similar results were found in Malaysia, especially among jungle aborigines, with much lower rates among the people living in villages. No doubt the population in endemic areas is constantly exposed to the infection.

Occurrence in Animals: Natural infection has been observed in many mammal species. Rats (*Rattus* spp.) and, in some regions, voles and field mice (*Microtus* spp. and *Apodemus* spp.), as well as arboreal shrews, are of particular interest. The species of infected mammals vary depending on the zoogeographic region in which the natural foci of infection are found.

The Disease in Man: One to three weeks after being bitten by a larval mite of the genus *Leptotrombidium*, the patient develops a fever, headache, conjunctival congestion, and generalized aches coupled with lymphadenopathy that is painful to the touch. Interstitial pneumonitis is also common. The temperature can rapidly rise to 40–40.5°C within the first few days (Saah, 1991). A skin ulceration with a black scab at the site of the bite is often found among patients of the Caucasian race but rarely among Asians. A macular eruption occurs at the end of the first week of fever and can last from just a few hours to as long as a week, in which case it assumes a maculopapular form and turns dark purple. Convalescence is long. The severity of the disease depends on the infecting strain and, above all, the amount of inoculum received. Within these parameters, the clinical picture can range from very mild to very severe. Some patients may experience delirium, tremor, psychomotor excitation, hypoacusis, and stiffness of the neck. In a group of 87 American soldiers who developed the infection, only 30 (34%) had a cutaneous eruption, and for 85% of them, the most common sign was adenopathy (Berman and Kundin, 1973; Saah, 1991). In untreated patients, pulmonary, encephalic, or cardiac complications can occur, often with fatal results. As with the other rickettsioses, the basic pathologic

Figure 7. Scrub typhus *(Rickettsia tsutsugamushi)*. Transmission cycle.



lesions may be found in the smaller blood vessels. The case fatality rate can range from 0% to 30% (Wisseman, 1982), and is much higher in older persons.

The classic treatment consists of oral tetracyclines: a high initial dose, followed by four daily doses over the course of a week. If the treatment is started during the first three days of the disease, a relapse may occur. In Malaysia and the Pescadores Islands (Taiwan), administration of a single dose of 5 mg/kg of doxycycline on the seventh and fifth days, respectively, was found to be effective (Benenson, 1990).

The Disease in Animals: In natural hosts, the infection is inapparent or relatively mild.

Source of Infection and Mode of Transmission (Figure 7): The most important vectors of *R. tsutsugamushi* are several mite species of the genus *Leptotrombidium,* most notably *L. akamushi*, *L. arenicola*, *L. deliense*, *L. fletcheri*, *L. pallidum*, and *L. pavlovsky*. The vector species differs depending on the particular ecosystem. For example, in Japan *L. akamushi* is found in partially cultivated fields that flood in spring and early summer, whereas *L. deliense* is associated more with jungles. The mites are often found in tightly circumscribed foci (belts or islands) in areas of scrub vegetation, hence the name of the disease. Only the larvae of these mites attach themselves to vertebrate hosts for feeding, and in the course of this act transmit the infection. During its other phases of development (egg, nymph, and adult), the mite lives in the surface layers of the soil. *Leptotrombidium* species serve not only as the vector but also as the reservoir, since they pass the agent to their offspring by transovarial transmission. This occurs at a very high rate and perpetuates the infection from one generation to the next. Another indication that *Leptotrombidium* species are probably the principal reservoir is that the larvae feed on animals or man only once (Saah, 1991). Shortly after the eggs emerge, the six-legged larvae remain on top of the soil or climb a few centimeters up a plant and wait for an animal or person to pass by so that they can attach to its skin. Once they have fed, the larvae return to the soil, where

they continue their life cycle (Weiss and Moulder, 1984). Wild vertebrates are also a possible reservoir, but their main role is that of food source for the mites.

The mite larvae transmit the infection to wild vertebrates (rodents and insectivores) and, accidentally, to man. The latter becomes infected when he enters the natural foci of infection. The highest incidence has been found among soldiers participating in military operations and farmers who enter the ecological niches of the agent. Military operations conducted in brush and jungle areas have led to epidemics affecting 20% to 50% of the troops over periods of several weeks or months.

It is suspected that some bird species that are frequently parasitized by the larvae of trombiculid mites may serve as transporters thereof, thereby giving rise to new foci of infection. Otherwise it would be difficult to explain how the infection has managed to spread to islands that are separated from other land areas by large bodies of water.

Role of Animals in the Epidemiology of the Disease: Man is only an accidental host of *R. tsutsugamushi*. In natural foci, the infection is circulated among small mammals by the trombiculid vector. However, there is some doubt as to whether these animals are indispensable to maintaining the infection in nature, since the mite alone could perform this role.

Diagnosis: A presumptive diagnosis, based on a rise in the titer during the course of the disease, may be obtained using the Weil-Felix test with *Proteus* OX-K as the antigen. However, this technique is not very sensitive and gives negative results for approximately half the cases.

The indirect immunofluorescence and immunoperoxidase tests are more sensitive and specific than the Weil-Felix test. The difficulty with the first is that a fluorescent microscope is not always available in rural hospitals. In such circumstances, the indirect peroxidase test is more practical (Yamamoto and Minamishima, 1982; Kelly *et al.*, 1988). Using the polymerase chain reaction combined with microplate hybridization, a system has been developed that yields a diagnosis within six hours (Sugita *et al.*, 1993). The etiologic agent can be isolated from blood by inoculating it in mice.

Control: Control measures consist of applying residual acaricides on land to be used for agriculture or military operations. Individual protection can be achieved by using clothes impregnated with acaricides (benzyl benzoate) in conjunction with repellents. When camps are set up in endemic areas, it may be helpful to burn the vegetation or apply herbicides.

There is no effective vaccine available, mainly because of the agent's wide antigenic heterogeneity. However, in a study conducted among 1,125 soldiers destined for the Pescadores Islands of Taiwan, a hyperendemic area, chemoprophylaxis with 200 mg of doxycycline per week proved to be effective (Olson *et al.*, 1980).

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ZOONOTIC CHLAMYDIOSIS

ICD-10 A70 *Chlamydia psittaci* infection

Synonyms: Psittacosis (in birds of the family Psittacidae), parrot fever, ornithosis (in other birds).

Etiology: Within the genus *Chlamydia* the following three species are currently recognized: *C. trachomatis*, *C. pneumoniae* (formerly TWAR strain), and *C. psittaci*. A fourth species, *C. pecorum* (Fukushi and Hirai, 1992; Kuroda-Kitagawa *et al.*, 1993), has been proposed. Chlamydiae are intracellular microorganisms with a characteristic reproductive cycle that goes through two phases, only one of which is infectious. It is now agreed that they are bacteria, but with certain exceptional characteristics—e.g., strict intracellular parasitism, metabolic and structural differences, and a distinct evolutionary cycle.

The infectious element is the elementary body, which binds to and is internalized by susceptible cells in the columnar epithelium of the mucosa. At six to eight hours, the internalized elementary body differentiates into a noninfectious reticulate body. The reticulate body then divides by binary fission, and after another 18 to 24 hours the new bodies undergo another reorganization, which condenses them and turns them into elementary corpuscles 0.2 to 0.3 microns in diameter. Hence, the intracellular inclusion bodies contain not only the elementary bodies (0.2 to 0.3 microns), but also the reticulate bodies, which are more than twice as large (0.8 microns). When the host cell disintegrates, the elementary bodies are released and the infection cycle starts anew. The elementary body is metabolically inert; the reticulate body is active, but parasitizes the host animal's cell because it cannot synthesize high-energy compounds, such as adenosine triphosphate and guanosine triphosphate.

C. trachomatis is the causative agent of trachoma (a keratoconjunctivitis) and the human genital tract infection. The agent of pneumonitis in mice is a biotype of this chlamydial species. *C. pneumoniae* causes human pulmonary disease. *C. psittaci* is the agent of psittacosis/ornithosis in birds and of several diseases in mammals, and it can accidentally infect humans. The new species, *C. pecorum*, has been isolated from cases of bovine encephalitis, pneumonia, and enteritis, and also from ovine polyarthritis. All *Chlamydia* species share a common antigen which, as in the case of gram-negative bacteria, is a lipopolysaccharide.

This chapter will deal only with *C. psittaci*, which can be transmitted from animals to humans. *C. psittaci* strains fall into two broad groups with very different characteristics, namely, the agents of avian psittacosis, and those of mammalian psittacosis.

According to endonuclease restriction analysis, *C. psittaci* has at least five biotypes, and the avian biotype has at least four serotypes. One of these avian serovars is responsible for infection and disease in psittacine birds and another one causes psittacosis in turkeys. The latter has been associated with outbreaks in both turkeys and humans (Andersen and Tappe, 1989). The avian strains of *C. psittaci* have varying degrees of virulence. The more virulent strains, usually isolated from turkeys (turkey serovar), can cause outbreaks in turkeys, with mortality ranging from 5% to 30%. These strains have also been isolated from asymptomatic wild birds. Humans, especially if they work with or are otherwise exposed to these birds, can also be victims of the disease. The less virulent strains are mainly isolated from pigeons and ducks, and occasionally from turkeys and free-living birds (Grimes and Wyrick, 1991). The virulence factors have yet to be determined.

There is even greater diversity among *C. psittaci* strains in mammals. One study (Spears and Storz, 1979) divides the mammalian strains into eight groups. The proposed species, *C. pecorum*, is an offshoot of the mammalian strains. It shares less than 15% DNA:DNA homology with other members of *C. psittaci*, *C. trachomatis*,

and *C. pneumoniae*, compared with 88% homology with the members of the proposed new species. Three serotypes of the species have been identified (Fukushi and Hirai, 1992).

Geographic Distribution: Worldwide.

Occurrence in Man: Generally sporadic. Most human cases of *C. psittaci* are transmitted by birds; cases transmitted by mammals are rare. Between 1929 and 1939, there was an epidemic that spread to 12 countries (in North Africa, Argentina, the US, and a large part of Europe) and caused some 1,000 cases and 200 to 300 deaths. The outbreaks were attributed to the importation of psittacines from South America (Schachter, 1975). The epidemic is believed to have originated in the province of Córdoba (Argentina). Since then, several outbreaks have also occurred among workers in turkey-processing plants. In the US, there were four outbreaks in the state of Texas in 1974, followed in 1976 by an outbreak in Nebraska that affected 28 out of 98 workers, and another in Ohio in 1981 that affected 27 out of 80 workers (CDC, 1982). A 1978 outbreak affecting 21 people at The College of Veterinary Medicine, in New York, is believed to have been associated with the autopsying of turkeys (Filstein *et al.*, 1981). Another outbreak occurred among workers engaged in turkey slaughtering and processing in central Minnesota. Between June and November 1986, a total of 186 suspected cases were identified, of which 122 (66%) were confirmed by serology (complement fixation) (Hedberg *et al.*, 1989). Another area in which workers are at risk is the raising, slaughtering, and processing of ducks. Between 1949 and 1963, a total of 1,072 human cases were identified in the former Czechoslovakia (Caffarena *et al.*, 1993). In 1985, an outbreak in a duck-processing plant in England affected 13 out of 80 workers (16%) (Newman *et al.*, 1992). At present, *C. psittaci* infection in the US is largely an occupational disease related to working with turkeys, whereas in central and eastern Europe it is found among employees who work with ducks.

In the UK, there were 150 suspected cases of psittacosis in Cambridgeshire County (population 300,000) between 1975 and 1983 (Nagington, 1984). The US had 1,136 cases and 8 deaths between 1975 and 1984 (Williams, 1989). Many sporadic cases go undiagnosed or are attributed to other diseases.

In Argentina, there were 26 cases in 1976, followed in 1977 by an outbreak of 180 suspected cases (of which 71 were confirmed), with 3 deaths. Between 1977 and 1981, there were 949 suspected cases of psittacosis, of which 387 (41%) were confirmed by complement fixation. Among these cases, there were two in which human-to-human transmission could be assumed, and 25% of the confirmed cases apparently had no connection with birds (Planes *et al.*, 1986). A 1989 outbreak of 12 cases in the city of Necochea originated at a store where psittacines were sold (Caffarena *et al.*, 1993). During 1992–1993 and the first three months of 1994, the Francisco Javier Muñiz Hospital for Infectious Diseases in Buenos Aires registered 55 cases of psittacosis, all of them serologically confirmed by indirect immunofluorescence, with 2 fatalities. In Uruguay, 22 cases were reported during 1962–1970 and 6 during 1987–1988 (Caffarena *et al.*, 1993).

Few human cases have been traced to the disease in mammals. In 1969, a man acquired acute follicular keratoconjunctivitis from his cat, which had pneumonitis (Schachter *et al.*, 1969). A cat was also linked to a human case of endocarditis with associated glomerulonephritis (Regan *et al.*, 1979). In Great Britain, some 10 cases

of severe infection in pregnant women were traced to *C. psittaci*, which causes enzootic abortions in sheep (Hadley *et al.*, 1992). Also, a case occurred in a pregnant woman in France who had assisted in birthing in a herd of goats, one-third of which had aborted (Villemonteix *et al.*, 1990).

Occurrence in Animals: Natural chlamydial infection has been found in 130 species of domestic and wild birds, more than half of them from the family Psittacidae. For practical purposes, all avian species may be considered potential reservoirs of chlamydiae. In addition to psittacines, the disease is common in fringillids, pigeons, turkeys, and ducks, and somewhat less frequent in chickens. Between 1960 and 1987, more than 20 outbreaks, mainly among turkeys, were reported in the US (Grimes and Wyrick, 1991). The infection rate is generally lower in wild birds. In the state of Florida, *C. psittaci* was isolated from 20% of 287 pet birds (250 of them psittacines) that had died (Schwartz and Fraser, 1982). A similar study of dead and dying birds in Japan yielded *C. psittaci* isolations in 19 (24.7%) of 77 psittacines and 12 (26.1%) of 46 passerines (Hirai *et al.*, 1983). On the other hand, among wild pigeons in Japanese residential areas, the agent was only isolated from 6 (0.8%) of 716 birds, even though 37% of 568 specimens yielded antibodies in the complement fixation test (Fukushi *et al.*, 1983). *C. psittaci* also parasitizes many wild and domestic mammalian species. It is difficult to determine the frequency of *C. psittaci* and *C. pecorum* in mammals. Some of the diseases have been diagnosed in only a few countries, for example, placentopathy and ovine enzootic abortion have only been known to occur in Germany, the US, France, Great Britain, and Hungary; sporadic bovine encephalomyelitis, only in the US and Spain; and ovine polyarthritis, only in the US (Timoney *et al.*, 1988). However, estimates have been received from Great Britain regarding two diseases of zoonotic interest. In a study of enzootic abortion in sheep conducted in Scotland in 1987–1991, specimens from ovine abortions were received from 30.7% of the herds; 28% of the reporting herds had evidence of *C. psittaci* infection, for an estimated prevalence of 8.6% (Leonard *et al.*, 1993). The prevalence of *C. psittaci* infection in cats from different habitats was also studied in Great Britain. Among pet cats, the agent was found in 30% of 753 conjunctival swabs collected; among feral cats, the infection was enzootic in 2 of 3 colonies studied; and cats living on sheep-raising farms were serologically positive at 10 of 22 establishments (Wills *et al.*, 1988).

The Disease in Man: The incubation period lasts one to two weeks, and sometimes longer. Many infections evolve asymptomatically, while with others the symptoms can vary widely in severity. Mild forms of psittacosis may be mistaken for common respiratory illnesses and often go unnoticed. The disease can have a sudden onset, with fever, chills, sweating, myalgia, loss of appetite, and headaches. In the 1986 outbreak in Minnesota, the symptoms of a large number of patients were quantified: 91% had headaches; 80%, chills; 88%, fever; 83%, weakness; 69%, coughing; and 58%, sweating (Hedberg *et al.*, 1989). On the other hand, there are cases in which the disease's onset is more insidious. The symptoms last for 7 to 10 days. When atypical pneumonia is present, radiography shows infiltrations at first, and less often, patches of consolidation in the lower part of the lungs, which may develop into bronchopneumonia. At first there may be a dry cough; later there is some expectoration of mucoid sputum that becomes mucopurulent. The most acute forms of the disease are seen in patients over the age of 50. The most serious cases

may have enlargement of the liver and spleen, vomiting, diarrhea, constipation, insomnia, disorientation, mental depression, and even delirium. The infection contracted from mammals almost always produces systemic disease, but fortunately these cases are rare. Pregnant women, at any point in the pregnancy, are susceptible to contracting the infection from sheep in countries where enzootic abortion occurs in these animals, or in goats infected with *C. psittaci* (see the section on occurrence in animals). In the cases described in Great Britain, all patients but one aborted and experienced fever, kidney and/or liver dysfunction, and disseminated intravascular coagulation. In two of the cases in England, the women had had no direct contact with sheep, but lived on a sheep farm (Hadley *et al.*, 1992).

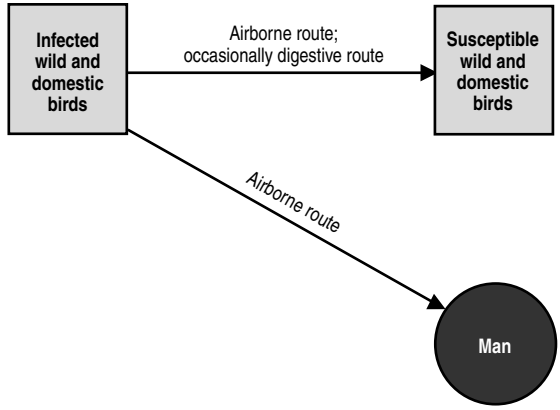
Early treatment is important in order to shorten the duration of the disease and prevent complications. Tetracycline should be given as long as the patient has fever and for 10 to 14 days thereafter. Erythromycin may be used with pregnant women or children under the age of 8, for whom tetracyclines are contraindicated (Benenson, 1990). Case fatality is less than 1% when patients receive proper treatment.

The Disease in Animals: Most infections in birds are latent and inapparent. The disease usually appears when the birds' overall resistance has been lowered because of stress (brought on by such factors as overcrowding, concurrent infections, unsanitary conditions, nutritional deficiencies, prolonged transport, etc.). Outbreaks have occurred in establishments that sell pet parrots and parakeets, or, more often, during the shipment of these animals, and the disease has also been reported in pigeons, turkeys, and ducks. The symptoms—fever, diarrhea, loss of appetite, emaciation, and respiratory distress—are uncharacteristic. Conjunctivitis is common, with severity ranging from mere conjunctival congestion to necrotic obstruction of the orbit. Autopsy may reveal inflamed serous membranes with fibrinous exudate, edematous or hyperemic areas in the lungs, and an enlarged and striated liver. Enlargement of the spleen is common in psittacine birds, and epicarditis and myocarditis are seen in turkeys. In chickens, however, the infection is almost always inapparent.

C. pecorum, the proposed new species, causes encephalitis, pneumonia, and enteritis in bovines and polyarthritis in sheep. The mammalian strains of *C. psittaci* are the strains that cause abortion, keratoconjunctivitis, and other diseases. Trials with parenteral inoculation of chlamydiae from ovine polyarthritis have reproduced the disease in turkeys, while chlamydiae associated with ovine enzootic abortions have been fatal for sparrows and have caused infection in pigeons. However, when chlamydiae from domestic mammals were given orally to several species of wild birds, no seroconversion was observed, nor was the agent detected in feces (Johnson and Grimes, 1983). The avian strains are not transmitted to domestic mammals, nor are mammalian strains communicable to birds. However, a case was described of conjunctivitis in a cat which had probably been contracted from a macaw (*Ara ararauna*) that its owner had acquired a month earlier, from which *C. psittaci* was isolated in a conjunctival scraping and also in a sample taken from the cloaca (Lipman *et al.*, 1994). Human infection from mammalian strains is accidental.

Source of Infection and Mode of Transmission (Figure 8): Wild and domestic birds are the natural reservoirs of *C. psittaci*. Except for the strains of *C. trachomatis* that are proper to man, the *C. trachomatis* biotype that causes pneumonitis in mice, and *C. pneumoniae*, also proper to man, the chlamydiae found in mammals belong to the species *C. psittaci* and *C. pecorum*. The mammalian strains of *C.*

Figure 8. Zoonotic chlamydiosis (psittacosis, ornithosis). Transmission cycle.



psittaci that cause enzootic abortion in sheep and goats are shed in large quantities through the feces and the placenta. Pregnant women can become infected by handling these materials at birthing stations or in abattoirs. The infection is probably also present in women who are not pregnant and persons who come in contact with these animals in the course of their work, which could be demonstrated in seroprevalence studies done by veterinarians. In the case of feline pneumonitis, large amounts of the agent are shed through the conjunctiva and the nose. This infection, which causes conjunctivitis and rhinitis, is common in cats, but human cases of the disease (conjunctivitis), despite frequent exposure, are rare (Schachter, 1989). The mammalian strains of *C. psittaci* are seldom pathogenic for man; only a few cases of human infection from this source have been contracted in the laboratory or in nature (Schachter and Dawson, 1979).

Humans contract the infection from birds by inhaling the airborne agent in contaminated environments. Sporadic human cases have been associated mainly with psittacines and other companion or decorative birds. However, in some places turkeys or ducks may outrank psittacines and pigeons as the main source of infection. Chlamydiosis of avian origin is largely an occupational disease of workers in turkey-processing plants, duck and geese pluckers, pigeon breeders, and employees at establishments that trade in exotic and pet birds. In the former Czechoslovakia and the former East Germany, there were more than 1,000 cases of infection (one-third of them with clinical disease) among workers engaged in plucking ducks and geese. Other occupational groups at risk are laboratory personnel and veterinarians.

In birds, the infection is primarily gastrointestinal and the agent is shed through the feces. Sick birds frequently suffer from diarrhea and release large quantities of chlamydiae into the environment through their feces, which give off aerosols as they dry. Chlamydiae are also spread through contamination of the plumage. The strains isolated from birds vary widely in terms of their virulence, and this fact, coupled

with variations in the extent of exposure to the agent, accounts for the range in severity of human disease.

Transmission between birds can also take place by inhalation, and in some cases via the digestive tract (coprophagy, cannibalism). Domestic fowl—turkeys, ducks, geese, and sometimes chickens—may be infected by wild birds, which represent a large reservoir of the infectious agent. Migrating birds can give rise to new foci of infection (Grimes, 1978). Little importance has been given to transovarial transmission, which has been confirmed in ducks, or to mechanical transmission by arthropod vectors.

Role of Animals in the Epidemiology of the Disease: Human *C. psittaci* infection is a zoonosis, and, as with most zoonoses, man is an accidental host. Human-to-human transmission is rare and has only been seen in a few nurses who had cared for psittacosis patients.

Diagnosis: The following serological techniques are regularly used: direct complement fixation (DCF), modified complement fixation (MCF), and latex agglutination (LA). The advantages of DCF are its relative sensitivity and the fact that it can be used for a large number of species, though not all of them. The most common technique is microprocedure. However, this test does not distinguish between IgM and IgG, and it is therefore necessary to resort to paired samples. The MCF test adds 5% (v/v) normal chick serum to guinea pig complement. By increasing the sensitivity of the test in this way, it is possible to use it for sera from birds that would not normally fix guinea pig complement (Grimes and Wyrick, 1991). The latex agglutination test is easy to perform, specific, and detects IgM only; a positive result indicates that the bird has an active infection. The LA test also makes it possible to assess the efficacy of treatment: if it is successful, the titer falls rapidly. The disadvantages of the method are its low sensitivity and that apparently it cannot be used with all avian species (Grimes, 1989). In the case of individual birds, it is best to use more than one method. The complement fixation test is generally used for the diagnosis of chlamydiosis in humans. Diagnosis can also be confirmed by isolating the agent from sputum or blood taken during the febrile stage of the disease and inoculating it in embryonated eggs, mice, or cell cultures. Several passages may be necessary. Early treatment of the patient with tetracyclines may interfere with isolation and with the formation of antibodies.

To isolate the agent it is best to use several organs at once—for example, the spleen, the liver, and intestinal contents. Serotyping can be done using a panel of 10 serovar-specific sera in the indirect immunofluorescence test (Andersen, 1991a).

A quick preliminary diagnosis can be obtained with samples taken from serous membrane exudate, spleen, liver, and lung, and stained by the Macchiavellos, Gimenez, or Giemsa method.

Isolations, whether from humans or animals, should only be performed in laboratories that adhere to the highest safety standards.

Control: Eradication cannot be considered due to the large number of hosts, including many free-living birds, nor are there effective vaccines for controlling the disease. The control strategy that has yielded the best results is giving tetracycline-based chemoprophylaxis to psittacine and other birds—specifically, 1% chlortetracycline and up to 0.7% calcium included in their feed. In the event of a chlamydio-

sis outbreak in an establishment where birds are sold, their sale should be suspended until the appropriate measures have been taken. Chlortetracycline should be added to the birds' feed for 45 days, and the cages and premises should be cleaned and disinfected with quaternary ammonium chloride. In the case of imported birds, chlortetracycline should be added to their feed for 45 days as a preventive measure, either in the country of origin or upon arrival at their destination. Mass treatment has also been given on turkey farms. Epidemiological surveillance is necessary. This should include serological screening to identify infected farms, placing the establishments under quarantine, and administering tetracycline in the turkeys' feed for a period of four weeks.

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ZOONOTIC TYPHUS CAUSED BY *RICKETTSIA PROWAZEKII*

ICD-10 A75.0 Epidemic louse-borne typhus fever due to *Rickettsia prowazekii*

Synonyms: *R. prowazekii* wild typhus, louse-borne typhus, classic typhus fever, typhus exanthematicus.

Etiology: *Rickettsia prowazekii.* The agent was isolated from the eastern flying squirrel, *Glaucomys volans volans*, in Florida (USA). This rickettsia is not distinguishable antigenically or by the toxin neutralization test from the classic strains of the etiologic agent of epidemic louse-borne typhus (Bozeman *et al.*, 1975).

Geographic Distribution: Worldwide, but as a cause of zoonosis, the agent is of greatest interest in the US. It has been isolated from flying squirrels or their ectoparasites in Florida, Maryland, and Virginia (USA). However, the geographical origin of the human cases that have been seen would suggest that the distribution is much wider. The distribution of the natural host, the flying squirrel, reaches across the entire eastern part of the US and northward into southern Canada (McDade *et al.*, 1980).

Occurrence in Man: Sporadic. Between 1976 and 1979, a total of 1,575 sera specimens were tested for antibodies to rickettsiae at the US Centers for Disease Control and Prevention (CDC). Of these sera, 1,349 (85.7%) were negative for all rickettsial antigens and 226 (14.3%) were positive for various rickettsial diseases. Of the latter, eight (3.5%) were positive for *R. prowazekii*—five from the state of Georgia and one each from Massachusetts, Pennsylvania, and Tennessee. These patients had not been parasitized by human lice, nor did any of their contacts become ill; therefore, the classic transmission cycle of man-louse-man did not apply. Two of the patients reported having had contact with flying squirrels (McDade *et al.*, 1980). Between July 1977 and January 1980, seven more sporadic cases were diagnosed in the states of North Carolina, Virginia, and West Virginia, none of which were associated with human lice (Duma *et al.*, 1981).

Occurrence in Animals: Serological studies carried out between 1972 and 1975 showed that 54.2% of 557 flying squirrels captured in Florida, Maryland, and Virginia were positive for the agent. The highest seroconversion rates for these animals were seen in the autumn and early winter, when the ectoparasites are in greatest abundance on the squirrels. The infection spreads rapidly among the young animals in autumn, when they begin to congregate in nests in which the vector is present. No other infected animal species were found in these habitats (Sonenshine *et al.*, 1978).

The Disease in Man: The disease has a sudden onset, with fever, headache, muscular aches, and rash. Except in a few severe cases, the disease appears to be more benign than classic louse-borne epidemic typhus (Duma *et al.*, 1981). Some patients also experience nausea, vomiting, and diarrhea. Four of eight patients in a study had a rash. The disease lasted two to three weeks in patients who did not receive appropriate treatment, while its course was shorter for those who received tetracycline or chloramphenicol (McDade *et al.*, 1980).

The Disease in Animals: The natural course of the infection in flying squirrels is unknown. Rickettsemia lasted two to three weeks in animals infected experimentally (Bozeman *et al.*, 1981). Animals inoculated intraperitoneally with high doses of the agent died on the seventh day.

Source of Infection and Mode of Transmission: The last outbreak of epidemic louse-borne typhus in the US was in 1922. A laboratory-confirmed case in 1950 was contracted outside the country. Recrudescent typhus (Brill-Zinsser disease) has been observed only in concentration camp survivors and immigrants from Eastern Europe (McDade *et al.*, 1980).

Unlike classic epidemic louse-borne typhus, the recent cases of human *R. prowazekii* infection have been zoonotic in character.

The reservoir (probably unique) of wild typhus is the flying squirrel, *Glaucomys volans volans*, which has a high rate of infection and rickettsemia lasting several weeks. Experiments have shown that cohabitation is not a factor in the transmission of infection among these animals. Of the many ectoparasites that infest them, the louse *Neohaematopinus sciuropteri* is the vector responsible for transmission. The mode of transmission to man is not yet fully understood. The squirrel louse*, N. sciuropteri,* does not feed on man. On the other hand, the squirrel flea, *Orchopeas howardii,* which can become infected, cannot transmit the infection to susceptible squirrels. It is possible that this flea, which bites man, may transmit the infection if it is squashed against broken skin, or that man may become infected via aerosols originating from the feces of the squirrel louse, especially during more intense epizootic periods (Bozeman *et al.*, 1981).

The cases described up to now have occurred largely among rural inhabitants, some of whom said they had had contact with flying squirrels. The time of the year when the human cases occurred (November to March) coincides with the period of heaviest transmission among squirrels.

Diagnosis: So far, human cases have been diagnosed using such laboratory tests as complement fixation, indirect immunofluorescence, toxin neutralization, and cross-absorption.

Control: Given the small number of confirmed human cases, no special measures are warranted.

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Part II

VIROSES

ARGENTINE HEMORRHAGIC FEVER

ICD-10 A96.0 Junín hemorrhagic fever

Synonyms: Junín hemorrhagic fever, Junín disease, stubble disease, O'Higgins disease, northwestern Buenos Aires hemorrhagic virosis, endemic-epidemic hemorrhagic virosis.

Etiology: Junín virus, a segmented single-strand RNA genome virus belonging to the genus *Arenavirus*, family Arenaviridae. The virions of this family, the prototype of which is the lymphocytic choriomeningitis virus, are ovoid or pleomorphic, measuring 110 to 130 nm in diameter (or as much as 300 nm in rare cases), and have a lipoprotein envelope. A characteristic of the family, from which it derives its name, are the sand-like particles seen in the interior of the virion with electron microscopy. The particles come from ribosomes of the parasitized cell which are engulfed by the virion when they are released from the cell.

The Junín virus belongs to the Tacaribe complex (New World arenaviruses), which is composed of the following viruses: Allpahuayo, Amapari, Bear Canyon, Cupixi, Flexal, Guanarito, Junín, Latino, Machupo, Oliveros, Paraná, Pichindé, Pirital, Sabiá, Tacaribe, Tamiami, and Whitewater Arroyo (Charrel *et al.,* 2002). Junín virus, Machupo virus (the agent of Machupo, or Bolivian, hemorrhagic fever) (Weissenbacher and Damonte, 1983), Guanarito virus (the agent of Venezuelan hemorrhagic fever), and Sabiá virus (the agent of Brazilian hemorrhagic fever) are pathogenic for humans. Laboratory infections have been produced with the Pichindé and Tacaribe viruses (Johnson, 1981).

Viruses of the Tacaribe complex share an antigenic affinity with the Old World arenaviruses, genus *Arenavirus*, which include the agents of Lassa fever in Africa and lymphocytic choriomeningitis in the Americas and Europe.

With the exception of Tacaribe virus, for which bats are the reservoir, the reservoirs of the arenaviruses are rodents, which carry a persistent infection.

Geographic Distribution and Occurrence: Argentine hemorrhagic fever (AHF) is found over a large area of Argentina's humid pampas, where the main agricultural crops are corn and other grains. The endemic area is inhabited by a population of more than 1 million and covers approximately 120,000 km^2 in portions of the following provinces: Buenos Aires (northwest), Córdoba (southeast), Santa Fe (south), and La Pampa (east). Recent studies have shown that the virus is active outside its

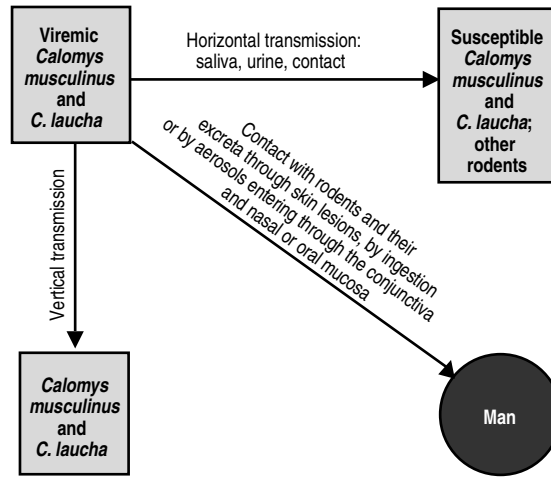
known endemic areas, as indicated by the fact that it was isolated from the field mouse *Akodon azarae* in the village of Pila located in southwest Buenos Aires Province. Antibodies were also found in 2 of Pila's 449 inhabitants, although no human cases of the disease were confirmed (Weissenbacher *et al*., 1983a). The first epidemics occurred in 1953 and 1954, and the etiologic agent was first isolated in 1958. Since then there have been annual epidemics of varying intensity. Over a 23-year period (1958–1980) more than 18,000 clinically confirmed cases of Argentine hemorrhagic fever were reported, with a case fatality rate of between 10% and 15% in untreated cases. The number of cases peaked every two or three years, and the largest epidemic was in 1964. The last four years of this period saw a downward trend, from 989 cases in 1977 to 161 in 1980 (Pan American Sanitary Bureau, 1982). During the 1981–1983 period, there was an average of 302 cases a year (Argentina, Ministry of Social Welfare, 1981–1983). In 1990, there were 727 cases; in 1991, 154 cases; and in 1992, only 2 cases. More of these cases occurred in the province of Córdoba than in the province of Buenos Aires (Argentina, Ministry of Public Health and Social Action, 1992). In a survey of the rural population in these two provinces conducted 14 years after the first appearance of AHF, neutralizing antibodies were found in 12% of the Córdoba inhabitants (7.6% with clinical disease and 4.4% with subclinical infection) and 11.6% of those in the province of Buenos Aires (9.7% with clinical disease and 1.9% with subclinical infection) (Weissenbacher *et al*., 1983b).

The disease mainly affects the rural population, and in particular those involved in the harvesting of corn and other grains, who are mostly male migrant workers. This trend coincides with the higher incidence of AHF in adult males. Most of the cases occur in autumn, between April and July, with the highest number usually in May. This seasonal distribution coincides with an increase in agricultural activities that facilitate contact with the rodent reservoirs of the virus, whose population also peaks at the same time of year.

The Disease in Man: The incubation period is from 10 to 16 days. The symptoms are similar to those of Machupo hemorrhagic fever, and their severity varies. The disease has an insidious onset. Its clinical manifestations are fever, malaise, chills, fatigue, dizziness, cephalalgia, and dorsalgia. Most patients experience conjunctival congestion, retro-orbital pain, epigastralgia, halitosis, nausea, vomiting, and constipation or diarrhea. Other symptoms are increased vascularization of the soft palate, axillary and inguinal adenopathy, petechiae on the skin and palate, and a congestive halo on the gums. Leukopenia, thrombocytopenia, albuminuria, and cylindruria are always present. The fever is constant and lasts for five to eight days. The symptoms that appear after day four include epistaxis, gingival hemorrhaging, slowed mental response, unsteady gait, hypotension (in 75% of patients), bradycardia, muscular hypotonia, and osteotendinous hyporeflexia.

In its mild form, the disease lasts about six days. In contrast, serious hemorrhagic cases are marked by hematemesis and melena, as well as more pronounced epistaxis and gingival hemorrhaging. When neurologic symptoms are predominant, the patient manifests muscular tremors in the tongue and hands, confusion or excitability, and sometimes tonic-clonic convulsive seizures. The intermediate forms are the most common and are seen in about 60% of patients. Convalescence lasts for several weeks, and sequelae are rare. After an apparent recovery, some patients develop

Figure 9. Argentine hemorrhagic fever. Probable transmission cycle of the Junín virus.



a cerebellar syndrome, which clears up after several days without further consequences. In a group of 130 laboratory-confirmed patients, 12 (9%) died (Argentina, Ministry of Social Welfare, 1971–1974). In untreated cases, the administration of human plasma made it possible to reduce the case fatality rate from 15%–20% to less than 3% (Carballal *et al*., 1991).

The Disease in Animals: As with the other arenavirus infections, rodents are the reservoir for maintenance of the Junín virus in nature (the exception is Tacaribe virus, for which bats are the reservoir). The main hosts of the Junín virus are the cricetid rodents *Calomys musculinus*, *C. laucha*, and *Akodon azarae.* Experimental inoculation of *C. musculinus* and *C. laucha* with field strains of Junín virus showed that the infection in those animals was asymptomatic, regardless of the age of the animal, the route of administration, or the amount of virus injected (Sabattini *et al*., 1977). Experimental infection with *Akodon* produced symptoms only when this animal was inoculated during the first week of life (Weissenbacher and Damonte, 1983).

Source of Infection and Mode of Transmission (Figure 9): The risk is not the same throughout the endemic area. Between 1965 and 1974, a total of 8,728 cases were reported, and 3,075 (35%) of these were from the parish of Pergamino in the province of Buenos Aires. The vicinity within which most of these 3,075 cases were contracted represents a very small portion of the entire area affected by hemorrhagic fever. The disease is more prevalent in males than females (4:1) and it occurs especially among rural laborers. The seasonal changes parallel the variations in the rodent population and also the degree to which workers are exposed to the predominant rodent species. A sizable outbreak occurred in this same area in 1977; from April to June, more than 300 cases were reported (Bond, 1977).

As mentioned earlier, the epidemic curve follows the variation in the density of the rodent population: the highest incidence occurs in autumn (April to July), which corresponds to the peak number of rodents, and the drop in human cases during the winter coincides with the sharp decline in the rodent population.

The Junín virus has been isolated from several species of cricetids, including *A. azarae*, *A. obscurus*, *C. musculinus*, *C. laucha*, and *Oryzomys nigripes*. These rodents tend to live in tall brush along fences enclosing cultivated fields, roadsides, stream banks, and railroad tracks. The various rodent species respond differently to the Junín virus, which may suggest their relative importance in maintaining the agent in nature. Persistent viremia was observed in specimens of *C. musculinus* that were captured, released, and then recaptured twice or three times at intervals of up to 55 days. It was verified that under natural conditions they shed the virus through their urine. Experimental inoculation of newborns confirmed that this rodent is chronically infected; although it does not manifest clinical symptoms, it has persistent viremia and sheds the virus through buccopharyngeal secretions and urine. When complement-fixing antibodies are present in adult animals, the infection produces viremia and viruria of shorter duration. These findings are similar to observations with *C. callosus*, which is considered the main reservoir of Machupo virus, the agent of Machupo hemorrhagic fever. It has also been demonstrated that the infection in *C. musculinus* is transmitted both vertically and horizontally (Sabattini *et al*., 1977). Although the population of this cricetid declines sharply in winter, the virus survives in nature because of the persistent viremia that is characteristically seen in this species. From the trapping of rodents in the endemic areas of Córdoba Province, it was learned that *C. musculinus* was the most abundant species, and the virus was isolated from a very high proportion of the specimens caught. In a study involving the capture, release, and recapture of *C. musculinus* in the south of Santa Fe Province and the north of Buenos Aires Province, it was shown that the animals which were antigen-positive in the enzyme-linked immunosorbent assay (ELISA) were predominantly males (76%). In light of the greater mobility of males and their increased likelihood of being wounded, this result suggests that the primary route of virus transmission is horizontal (Mills *et al*., 1992). Since *C. musculinus* prefer to live along the borders of cultivated fields, researchers contend that humans contract the infection in these areas more frequently than in the fields as such. The virus was also isolated from 4 out of 40 captured *Akodon*, but their scant numbers in cultivated fields would indicate that this rodent plays a limited role in the epidemiology of AHF (Sabattini *et al.*, 1977).

It is believed that the emergence and subsequent expansion of AHF has been due to disruptions in the environment generated by the cultivation of grains that favor the *Calomys* populations (Villafañe *et al*., 1977).

The type of crop under cultivation is also an important factor in the ecology of the virus. Rodent densities, especially those of *Calomys* populations, are lower in soybean fields compared with corn and sunflower fields. In areas where the cultivation of soybeans has increased, there has been a reduction in the cases of AHF (Kravetz *et al*., 1981, cited in Weissenbacher and Damonte, 1983).

Although the virus has been isolated from mites found on the rodents, it has not been shown that these parasites can transmit the virus, and so far they are not considered to play a role in the ecology of the virus or the epidemiology of the disease. The fact that the virus can be isolated from oral swabs and the urine of *Calomys*

indicates that these secretions are the main sources of the virus in the transmission of infection to other members of the species, and perhaps to other rodent species with which they come in contact. It has also been possible to demonstrate transmission from a mother to her litter and between animals placed in the same cage. There is no doubt that *Calomys* plays an important role in the natural cycle of the virus.

Man becomes infected by contact with infected rodents and their excreta. The routes of penetration in man may be through skin lesions, the ingestion of contaminated products, or the inhalation of aerosols that come in contact with the conjunctiva and the oral or nasal mucosa. These portals of entry have been corroborated in the laboratory. Human-to-human transmission is uncommon, but precautions should be taken. As in the case of Machupo hemorrhagic fever, intimate contact may lead to contagion, since viremic patients can have hemorrhages, and the virus has been isolated from pharyngeal swabs and the urine of patients.

Diagnosis: At one time, AHF was known as the "rubber stamp disease" because its signs and symptoms made it easy to diagnose. However, subsequent studies have shown that only 60% of cases can be correctly diagnosed on the basis of clinical examination alone. Presumptive diagnosis is based on the patient's epidemiologic history (i.e., occupation as a migrant worker or residence in an endemic area) and laboratory analyses, which consist of identifying leukoplaquetopenia, round cells in the urine, and inversion of the ratio of $CD4^+$ ("helper") lymphocytes to $CD8^+$ cytotoxic suppressors (Carballal *et al*., 1991). Up until 1965, virologic diagnosis of the disease was only attempted in a few of the cases identified. During the period 1965–1974, diagnosis was confirmed by virologic studies in 64% of the cases reported. Specific diagnosis is accomplished by isolating the virus or using serologic tests on acute- and convalescent-phase sera. It can also be isolated by inoculating the blood of febrile patients or autopsy material intracerebrally in suckling mice, or intraperitoneally or intramuscularly in guinea pigs, and observing whether the animals develop hemorrhagic lesions similar to those seen in man. The virus can also be isolated by culturing patient blood on monolayer Vero cells, in which case the virus produces a cytopathogenic effect, and by demonstrating the presence of viral antigen with immunoperoxidase stain (Lascano *et al*., 1981). This procedure, which gives results in two to eight days, is more rapid than inoculation in laboratory animals. The serologic tests used most often are complement fixation, serum neutralization, and indirect immunofluorescence. The complement fixation test is the least sensitive, and the antibodies that it detects appear late and disappear rapidly. The serum neutralization test is the most specific, detecting antibodies at three to four weeks after onset of the disease, while the indirect immunofluorescence test gives the earliest results and is rapid, economical, and simple to perform (Samoilovich *et al*., 1983). In a group of 50 individuals who had had AHF between 1 and 14 years earlier, the indirect immunofluorescence test detected antibodies in 88% and the serum neutralization test in 96%, while the complement fixation test found antibodies in only 30% of the persons studied (Damilano *et al*., 1983).

The most commonly used tests are ELISA and indirect immunofluorescence, because they are capable of detecting IgM and IgG (Carballal *et al*., 1991). Reverse-transcription–polymerase chain reaction (RT-PCR) techniques for diagnosing AHF have also been developed (Lozano *et al.*, 1993; Lozano *et al.*, 1995).

Control: In Bolivia, it was shown that an urban epidemic of hemorrhagic fever caused by the Machupo virus could be checked by controlling rodents that had

acquired peridomestic habits. However, application of this measure would be very difficult and costly in the agricultural areas of Argentina. Instead, hopes are directed toward the development of a safe and effective vaccine. The effort to obtain an inactivated vaccine appears to have been abandoned, and greater attention is now being given to live attenuated vaccines. Vaccines based on attenuated strains of XJCl3, XJO, and Candid #1 have been developed and tested in laboratory animals. The preparation based on the XJCl3 strain was administered to a total of 636 human volunteers, in which it induced a subclinical infection or mild clinical symptoms, and neutralizing antibodies lasted from seven to nine years in 90% of the subjects. Intracerebral inoculation of the strain in guinea pigs and *Cebus* monkeys produced neurovirulence, but in the marmoset *Callithrix jacchus*, which is considered a reliable animal model for AHF, the strain provided good protection (Weissenbacher and Damonte, 1983).

The vaccine based on the attenuated Candid #1 strain offers the greatest promise in terms of being both safe and effective. Trials conducted in laboratory animals have shown high seroconversion titers, very good protection against virulent strains, and no neurovirulence in monkeys. When this vaccine was given to human volunteers, there were no complications whatsoever and the levels of seroconversion were satisfactory (Barrera Oro, J., personal communication, March 1986; Barrera Oro and McKee, 1991; McKee *et al*., 1993). This vaccine was the subject of a cooperative international project. Starting with larger-scale preclinical trials, its safety and immunogenicity were confirmed in 300 volunteers in Argentina and the United States. Next, a random, double-blind, placebo-controlled prospective study was undertaken in 1988–1990 with 6,500 volunteers from 41 localities in the endemic area. When the results clearly demonstrated the efficacy of the vaccine, the immunization project was extended to 100,844 persons. No adverse reactions have been observed; the duration of immunity and persistence of antibodies have yet to be determined (World Health Organization, 1993).

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BOVINE PAPULAR STOMATITIS

ICD-10 B08.8 Other specified viral infections characterized by skin and mucous membrane lesions

Synonyms: Granular stomatitis, proliferating stomatitis.

Etiology: The bovine papular stomatitis (BPS) virus, a double-stranded DNA genome virus, belongs to the genus *Parapoxvirus* in the family Poxviridae, which also includes the viruses that cause contagious ecthyma and milkers' nodules (pseudocowpox). Like all the parapoxviruses, the virion of bovine papular stomatitis is large, measuring 125–150 nm by 207–215 nm. Its envelope may be composed of one or two membranes (Timoney *et al.*, 1988).

Geographic Distribution: BPS has been observed in Argentina, Australia, Canada, Kenya, Mexico, Nigeria, the US, and various European countries. Its distribution may therefore be assumed to be worldwide.

Occurrence in Man: There have been very few confirmed cases of BPS. Between 1953 and 1972, a total of 19 cases were recorded in Australia, Europe, and the US (Schnurrenberger *et al.*, 1980). However, the occurrence of five cases in students and professors at a school of veterinary medicine in the US who contracted the infection while tube-feeding a bull would indicate that it may be more frequent than previously believed. Surveillance for two years following the veterinary school

cases revealed three isolated cases (Bowman *et al.*, 1981). In Mexico, a human case originated from the handling of experimentally infected calves (Aguilar-Setien *et al.*, 1980). Since this disease is manifested as a mild clinical illness, it is likely to be overlooked by both the patient and the physician.

Occurrence in Animals: Little is known about the incidence of the disease. A survey conducted at a slaughterhouse in Australia revealed that about 5% of the young cattle had "erosive stomatitis" lesions. The morbidity rate may be quite high on some ranches, as suggested by the fact that 31 out of 120 calves were found to be affected on one establishment in Mexico (Aguilar-Setien *et al.*, 1980). The veterinary school cases mentioned above (see the section on occurrence in man), in which the persons acquired the infection from animals that had no apparent lesions at autopsy, would suggest that inapparent infection and the carrier state may be more common than had been thought (Bowman *et al.*, 1981).

Although the disease can cause developmental delay in calves because the lesions in the mouth interfere with eating, it is usually not considered to have economic repercussions. Its importance arises from the fact that it can be mistaken for vesicular diseases.

The Disease in Man: The incubation period lasts from three to eight days. Typically, the lesion is on a finger or hand, corresponding to the agent's point of penetration. It usually takes the form of a papule or verrucous nodule 3–8 mm in diameter, which begins to decrease in size after two weeks and disappears in approximately one month. In one case, there was an erythematous eruption on the patient's arm that lasted three days, and in another case, there was axillary adenopathy and myalgia. Sometimes the papule becomes vesiculated. All the cases described have been afebrile.

The lesions in man are similar to those of contagious ecthyma or milkers' nodule (pseudocowpox).

The Disease in Animals: Cattle are the only susceptible species. In the Western Hemisphere, the disease was first recognized in 1960 in the US. It was a mild illness observed primarily in young cattle and characterized by proliferative lesions in and around the mouth with no systemic reaction. In other outbreaks, the animals have had fever, profuse salivation, diarrhea, and lesions on the teats. Most of the time, however, the infection is clinically inapparent or causes a mild and benign afebrile disease. It begins with hyperemic foci 2–4 mm in diameter in the nostrils, on the palate, or on the inner surface of the lips, which rapidly become papules with a hyperemic border. Some of the lesions turn into wrinkled papular plaques, which can last from one day to three weeks. During the course of the disease, the lesions can be found in any stage of evolution, from new papules to yellow or reddish-brown spots left by those that have healed. The disease may continue in this way for several months. Morbidity can be very high in some herds.

Source of Infection and Mode of Transmission: Cattle are the natural host of the infection. The disease has not been confirmed in other domestic species. The epidemiology of BPS is still unclear. Transmission is believed to be by direct and indirect contact. Man contracts the infection from infected cattle. The agent enters through pre-existing skin abrasions and lacerations, or an accidental bite from an animal whose mouth is being examined.

Diagnosis: The virus can be isolated in cell cultures from such bovine organ sites as the testicle and the kidney, in which it produces a cytopathic effect. Histopathology and electron microscopy are useful for diagnosis.

In terms of differential diagnosis, it is important to distinguish this disease from bovine viral diarrhea, vesicular stomatitis, foot-and-mouth disease, bovine plague, bovine infectious rhinotracheitis, and mycotic stomatitis (Tripathy *et al.*, 1981).

Control: Current knowledge of the epidemiology of this disease is insufficient to establish effective control measures. It is important that feeding troughs and utensils used for feeding and watering be kept clean. Persons who handle animals with BPS should take the necessary precautions to avoid infection.

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BRAZILIAN HEMORRHAGIC FEVER

ICD-10 A96.8 Other arenaviral hemorrhagic fevers

Etiology: Sabiá (SABV) virus, a single-stranded RNA genome virus, is a new member of the genus *Arenavirus*, family Arenaviridae (see the chapter on Argentine hemorrhagic fever). This virus belongs to the Tacaribe complex. In a comparison of Sabiá virus with five other viruses in the complex (Guanarito, Junín, Machupo, Pichindé, and Tacaribe), sequence analysis of 250 nucleotides of the small genomic segment revealed a divergence of 56% with respect to the Guanarito, Junín, and Machupo viruses.

Geographic Distribution and Occurrence: So far, little is known about the distribution and occurrence of this disease. The first case was recognized in 1994 in the Brazilian state of São Paulo, in the small town of Sabiá. A secondary case developed in a laboratory technician who was working on characterization of the virus, and a third case occurred in a researcher at Yale University in the US when a receptacle containing a suspension of the virus broke in the ultracentrifuge.

The Disease in Man: The index case was in a 25-year-old agronomy technician who was admitted to the hospital 12 days after coming down with fever, cephalalgia, myalgia, nausea, vomiting, and asthenia. When the patient was examined at admission, she was very ill, somnolent, and mildly dehydrated, with pronounced reddening of the oropharynx. Analyses showed leukopenia and slightly elevated aspartate aminotransferase. Despite treatment with fluids, electrolytes, and antibiotics, the patient worsened and for the next three days presented hematemesis, vaginal hemorrhaging, conjunctival petechiae, difficulty in walking, tremors, and convulsions. On the third day, she lapsed into coma and shock, and on the following day she died. Autopsy revealed diffuse pulmonary edema, congestion with intraparenchymatous hemorrhaging, focal hemorrhages and necrosis in the liver, and a massive gastrointestinal hemorrhage. The laboratory technician working on isolation of the virus developed a fever of between 38°C and 40°C, chills, malaise, sore throat, headache, myalgia, conjunctivitis, nausea, vomiting, epigastric pain, diarrhea, bleeding gums, and leukopenia. The patient recovered, and paired sera samples showed seroconversion for the Sabiá virus. In the third case, the patient had a fever of 39.5°C and was given an experimental antiviral drug that enabled him to recover.

Source of Infection and Mode of Transmission: The source of transmission of the index case is unknown, but it is believed that rodents were involved. The patient did most of her work in an office, but 10 days prior to developing the disease she had visited two cities in São Paulo State. The other two cases were probably acquired from the inhalation of aerosols containing the virus in the laboratory.

The reservoir of the virus will be the subject of future research.

Diagnosis: The researchers who reported on this disease emphasized the difficulty of diagnosing it in the presence of several diseases in the area that have a similar clinical picture and in the absence of any precedent of hemorrhagic fever caused by a new arenavirus. Isolation and identification of the virus is the only way to arrive at a definitive diagnosis.

Prevention: The only recommendation that can be made at this point is to ensure that work on isolating this virus, as well as all the other arenaviruses that are pathogenic for humans, is performed in laboratories that meet the highest standards of safety.

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CALIFORNIA ENCEPHALITIS

ICD-10 A83.5

Synonym: La Crosse encephalitis.

Etiology: The California encephalitis antigenic group comprises 14 viruses, 10 of which occur in the US. The viruses in this group belong to the genus *Bunyavirus*, Bunyaviridae family, and they are mosquito-borne. Members of the *Bunyavirus* genus are spherical RNA genome viruses, measuring 90–100 nm in diameter.

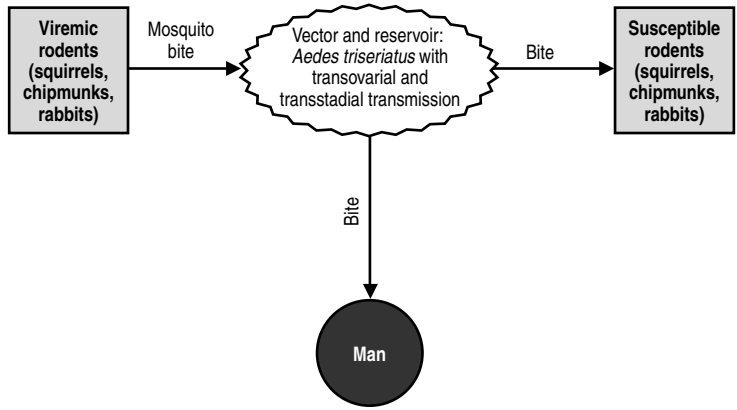
Of the California encephalitis virus group, the La Crosse (LAC) virus is the most important pathogen for man. The Jamestown Canyon (JC) virus in this same complex has been recognized as a human pathogen since 1980 (CDC, 1982). However, the original California encephalitis (CE) virus has not been observed since 1945, when three human cases were serologically diagnosed in that state, giving the disease its name. In Canada, four cases of this type of encephalitis were probably caused by the Snowshoe virus (McFarlane *et al.*, 1982). A febrile illness in man has been attributed to the Tahyna virus in several European countries, and to the Inkoo virus in Finland. The infection also occurs in Africa, and a case of human disease attributable to the Snowshoe virus was reported in China (White, 1989).

Geographic Distribution and Occurrence: The viruses that cause encephalitis in man, especially the LAC virus, are found mainly in the north-central region of the US, and their distribution extends to the midwestern and eastern states. As with other arboviruses, the rate of subclinical infection caused by the California viruses is much higher than the rate of clinical cases. During 1960–1970, a total of 509 human cases were recorded in the central and eastern US (most of them in Minnesota, Ohio, and Wisconsin). In 1978, there were 109 diagnosed cases in the country (CDC, 1981). California encephalitis is usually the most prevalent of the encephalitides in the US (Work and Work, 1991). In 1992, there were 29 reported cases of LAC encephalitis in Illinois, Minnesota, North Carolina, Ohio, West Virginia, and Wisconsin. This was the lowest number of reported cases since epidemiologic surveillance began in 1964 (CDC, 1993); the number of cases usually ranges from 60 to 130, but is probably much higher (Johnson, 1990). Serologic surveys in various parts of the US revealed that from 6% to more than 60% of resident rural workers had antibodies for the California group viruses. It has also been established that approximately 75% of the Indians in southern Florida have antibodies by the time they are 50 years old. The disease occurs in summer.

Antibodies have been found in several European countries in proportions ranging from 5% to 60% of the individuals examined using the serum neutralization test. In one study area, 24 of 103 febrile patients had positive serologic responses to the Tahyna virus.

The Disease in Man: The disease caused by the LAC virus occurs primarily in children and adolescents under 15 years of age. The symptomatology ranges from benign, aseptic meningitis to severe encephalitis. Nevertheless, it is likely that many cases pass as mild, undifferentiated fevers. The onset is insidious. Common symptoms include fever, headache (localized in the frontal lobes), nausea, vomiting, and a stiff neck; in more severe cases, lethargy and convulsions are observed. The nerv-

Figure 10. California encephalitis (La Crosse virus). Transmission cycle.



ous symptoms usually appear on the third day of illness and disappear in a week, although in more severe cases they last longer. Most patients recover, but one-third of them may have such sequelae as learning difficulties and behavioral changes (Work and Work, 1991). Support measures are important in patients with severe California encephalitis. Approximately half the children who develop an illness caused by the LAC virus have convulsions and should be treated, preferably with phenytoin (Johnson, 1990).

In five cases that occurred in New York (USA), presumably caused by the JC virus, the fatality rate in adults was high. Isolated cases attributed to this same virus have also been seen in Indiana and in Ontario (Canada) (CDC, 1982).

In Europe, the Tahyna virus has been observed to cause clinical pneumonia and pleurisy, acute arthritis, pharyngitis, undifferentiated fever, and sometimes central nervous system involvement.

The Disease in Animals: The natural hosts of the LAC virus, such as the eastern chipmunk (*Tamias striatus*) and arboreal squirrels, develop viremia when infected experimentally, but the infection is asymptomatic in inoculated adult animals (Thompson, 1981).

Source of Infection and Mode of Transmission (Figure 10): The LAC virus has been isolated from many species of mosquitoes. According to the frequency of isolations, the main vector is *Aedes triseriatus*, which breeds inside holes in trees and in other places where water collects, both in forests and near homes, particularly in abandoned tires. This virus is transmitted by the vector to rodents found in oak forests. A high prevalence of neutralizing antibodies has been seen in chipmunks and squirrels (*T. striatus*, *Sciurus carolinensis*, and *S. niger*), and lower rates have been observed in wild rabbits (*Sylvilagus floridans*). In experiments with the LAC virus, the eastern chipmunk (*T. striatus*) and the gray squirrel (*S. carolinensis*) developed viremia 2–5 days postinoculation, and vectors (*A. triseriatus*) feeding on these

mammals transmitted the infection to suckling mice at 15–17 days after ingesting the viremic blood.

The LAC virus has been isolated from the larvae of *A. triseriatus*, which indicates that the agent is transmitted transovarially. In addition, it has been possible to recover the LAC virus from eggs, larvae, and adults produced from experimentally infected *A. triseriatus*. The F_1 females transmitted the virus by biting suckling mice and squirrels. These experimental observations were subsequently confirmed when the virus was found in field-collected eggs and larvae of the vector. The LAC virus can also be transmitted sexually in *A. triseriatus*. It may be concluded, therefore, that *A. triseriatus* serves not only as vector but also as a reservoir, since it can transmit the infection transovarially for several generations. The virus overwinters in infected mosquito eggs that are in diapause (a state of inactivity with greatly lowered metabolism). When summer comes, adult mosquitoes begin to feed on the eastern chipmunk (*T. striatus*) and the gray squirrel (*S. carolinensis*), infecting them with the virus and thus widening the reservoir of the agent. Serologic testing of these rodent species has demonstrated high levels of neutralizing antibodies. According to studies in endemic areas, the red fox (*Vulpes fulva*) may serve as an amplifying and disseminating host of the LAC virus (Amundson and Yuill, 1981).

Another mosquito that would appear to be an important vector is *Aedes albopictus*. In light of the spread in the US of *Aedes albopictus*, introduced from Asia, an experimental study was conducted to evaluate it as a possible vector of LAC virus. The mosquito, infected either by mouth or transovarially, proved to be efficient in transmitting the infection to chipmunks (*T. striatus*) and vice versa. The chipmunks developed viremia in one to four days. After feeding on viremic chipmunks, the *A. albopictus* mosquitoes became infected and transmitted the LAC virus at a rate similar to the native vector, *A. triseriatus.* Unlike this latter vector (which, according to Patrican *et al.*, 1985, would not produce infected eggs until the second oviposition), *A. albopictus* transmitted the virus transovarially in the first oviposition (Cully *et al.*, 1992).

In the US, the period of highest LAC virus activity starts in July and lasts through the end of September. The human infection occurs primarily in deciduous oak forests during occupational or recreational activities. The virus is transmitted to man by mosquito bite.

The other viruses in the California group have different vectors and hosts, depending on distribution of the particular virus type and the ecological characteristics of the area. In Europe, the hare is an important reservoir of the Tahyna virus, and the vectors are various mosquitoes of the *Aedes* genus (*A. vexans*, *A. caspius*, and others). Antibodies to various viruses of this group have been found in equines, pigs, cattle, and deer, but not in birds.

The JC virus is transmitted by the mosquito *Culiseta inornata* and also those of the group *A. communis*. This vector transmits the infection vertically (transovarially) to its progeny and horizontally to vertebrates, especially white-tailed deer (*Odocoileus virginianus*) (CDC, 1982). The Snowshoe virus has been isolated from the hare *Lepus americanus*, which had a high rate of serologic reactors, as did the moose (*Alces alces americana*). The vectors are probably *A. communis* and *A. canadensis* (McLean *et al.*, 1975; McFarlane *et al.*, 1982). The virus was isolated from the larvae of *Aedes* spp. mosquitoes in the Yukon Territory in Canada, thus demonstrating that the virus survives the extreme winter conditions at those latitudes by means of transovarial transmission (McLean *et al.*, 1975).

Role of Animals in the Epidemiology of the Disease: *A. triseriatus* is the main vector of the LAC virus and also serves as its reservoir by virtue of transovarial transmission of the agent. By means of this mechanism, both the LAC virus and others of the California complex are able to overwinter in temperate or even the coldest climates (Snowshoe virus). Vertebrates serve as amplifiers of the virus in summer, and these hosts are important in the ecology of the disease, since both transovarial and venereal transmission of the virus in mosquitoes are relatively inefficient to ensure the endemicity of California encephalitis in the affected regions (Amundson and Yuill, 1981). Man is an accidental host who contracts the disease in natural foci.

Diagnosis: Laboratory confirmation can be achieved by serologic diagnosis. A four-fold or greater rise in titer between serum samples from the acute and the convalescent phases of the disease is considered significant. The tests most often used are hemagglutination inhibition (HI), complement fixation (CF), and virus neutralization (VN). The VN test is the most sensitive and is preferred, but it can only be performed in a few laboratories. The disadvantage of the CF test is that it detects antibodies later than the other tests, and with the HI test there are difficulties in producing the necessary antigens. An indirect immunofluorescence technique has been developed which is as sensitive as the VN or HI test and easier to perform (Beaty *et al*., 1982). Another technique that has been proposed is the use of enzyme immunoassay to detect IgM antibodies in sera and cerebrospinal fluid. This technique permits rapid and early diagnosis of the disease during its acute phase (Dykers *et al.*, 1985). It is difficult to isolate the virus from the blood of a febrile patient because of the short duration of viremia. The virus has been isolated from the brain in fatal cases.

Control: Individual prevention measures consist of the use of protective clothing and repellents. Control of wild *Aedes* species over extensive areas is difficult. Repeated and generous use of insecticides within and around camps for children and adolescents is recommended.

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CHIKUNGUNYA VIRUS DISEASE

ICD-10 A92.0

Synonyms: Chikungunya fever, Chikungunya hemorrhagic fever.

Etiology: Chikungunya (CHIK) virus is a single-stranded RNA genome virus belonging to the genus *Alphavirus* (group A arboviruses), family Togaviridae. There is an antigenic relationship between this agent and the Mayaro (see Mayaro Fever), O'nyong-nyong,[1] and Semliki viruses.[2] The spherical and icosahedrally symmetrical virions measure 50–60 nm in diameter and have an envelope.

Geographic Distribution: CHIK virus occurs widely in sub-Saharan Africa, India, and in many areas of Asia.

Occurrence in Man: There are extensive rural areas in which the infection is endemic, and epidemics, often explosive in nature, occur in the cities when there is a sufficiently large susceptible population. In South Africa, there were epidemics in 1975, 1976, and 1977 (Brighton *et al*., 1983). Ibadan, Nigeria, saw its first epidemic in 1969, with isolated cases seen in children before that year and afterwards. This epidemic was followed by a second one five years later. In both cases the highest morbidity rates were in children under 5 years of age, which would seem to indicate that the population in the older age groups had acquired immunity. During the interval between the two epidemics, the rate of neutralizing antibodies observed in children seen in a pediatric hospital declined significantly (Tomori *et al*., 1975). Elsewhere the intervals between urban epidemics have tended to be much longer. These periods of epidemic dormancy have been especially prolonged in India, where it was thought that CHIK virus disease had actually disappeared (Pavri, 1986). In Myanmar, where the last outbreak had occurred in 1975, the disease reappeared in 1984, when 1,548 children with symptoms of hemorrhagic fever were admitted to the children's hospital in Rangoon. By use of the enzyme-linked immunosorbent assay (ELISA) to detect IgM, it was possible to demonstrate the conversion of antibody titer for the CHIK virus in 86 out of 110 paired sera (Thein *et al*., 1992).

The disease is not always recognized, and it is often mistaken for dengue, which is clinically similar. In a survey conducted in northern Malaysia, it was found that 33% of the population examined had neutralizing antibodies to the virus, even though the disease had not been reported in the country. The high prevalence of reactors would suggest that the disease had probably been present but not correctly diagnosed (Tesh *et al*., 1975). In Nigeria, application of the hemagglutination inhibition

[1] O'nyong-nyong (ONN) virus was responsible for one of the most extensive epidemics in Africa, affecting 2 million people between 1959 and 1963. After that period, ONN was isolated once, in 1978 (Johnson *et al*., 1981). The clinical picture is similar to that of CHIK virus disease. The virus is transmitted by the *Anopheles funestus* mosquito, which is the most efficient vector, and by *A. gambiae*. The only known reservoir is man; the virus has not been found in other vertebrates.

[2] Semliki (Semliki Forest) is an alphavirus that has been isolated in Africa from several species of mosquitoes, birds, and mammals. A high percentage of the human population has antibodies to this virus. No disease attributable to this virus has been confirmed in man or animals.

test to 477 random serum samples from different ecological areas revealed that 14.3% of these contained antibodies to the CHIK virus. The highest seroprevalence rate was in the inhabitants of the rainforest (Adesina and Odelola, 1991). In Yunnan, China, the hemagglutination inhibition test revealed a seroprevalence of 10% in 273 healthy individuals (Zhang *et al*., 1991).

Occurrence in Animals: In South Africa, antibodies to the CHIK virus have been repeatedly found in primates—specifically, the African green monkey *Cercopithecus aethiops* and the baboon *Papio ursinus*. The virus circulates at high titer levels in both these species (McIntosh, 1970). A serologic survey conducted in the Kruger National Park reserve, South Africa, revealed antibodies to the CHIK virus in nearly 50% of the African green monkeys tested (Kaschula *et al*., 1978). Elsewhere in Africa reactors have been found in other species, including the colobus monkey *Colobus abyssinicus*, the chimpanzee, and the baboon *P. dogueri*. In Nigeria, seroprevalence was only 2.3% in 220 serum samples from domestic animals. In China, serologic tests indicate that bats, swine, birds, and monkeys are probably important hosts of the virus in the province of Yunnan (Zhang *et al*., 1991).

The Disease in Man: The CHIK virus was first isolated in 1955, and for a long time the disease was mistaken for dengue. The incubation period is four to seven days, following which the disease has a sudden onset, with fever, chills, cephalalgia, anorexia, lumbago, and conjunctivitis; adenopathy is also common. Many patients (60% to 80%) have a morbilliform rash, occasionally with purpura, on the trunk and limbs. The cutaneous eruption may recur every three to seven days. Other symptoms reported in the Myanmar children were coffee-colored vomit (52%), epistaxis (9%), and petechiae (8%) (Thein *et al*., 1992). A prominent symptom, seen especially in adult patients in Africa, is arthropathy, from which the disease gets its name (in Swahili, *chikungunya* means "walking hunchbacked"). The arthropathy is manifested by pain, swelling, and stiffness, especially of the metacarpophalangeal, wrist, elbow, shoulder, knee, ankle, and metatarsal joints (Kennedy *et al*., 1980). It appears between three and five days after the onset of clinical symptoms, and it can persist for many months and even years (Brighton *et al*., 1983). In this sense, CHIK virus disease is similar to Ross River, Mayaro, Sindbis, and O'nyong-nyong fevers (Tesh, 1982). No deaths have been attributed to CHIK virus disease.

The Disease in Animals: Clinically apparent infection has not been verified in animals.

Source of Infection and Mode of Transmission: The disease occurs in the rainy season, when the mosquito vector population is at its peak. Research on the subject suggests that the virus has a wild cycle, similar to that of yellow fever, operating between jungle primates and mosquitoes, including *Aedes africanus* and members of the *A. furcifer-taylori* group. The wild primates *C. aethiops* and *P. ursinus* develop a high-titer viremia, and under experimental conditions, it was demonstrated that the mosquitoes transmitted the virus to African green monkeys (McIntosh, 1970). Epizootics occur in monkeys when nonimmune individuals represent a significant portion of their population and when the human population in areas bordering the jungle is exposed to the infection.

In a study conducted over a period of five years (1964–1969) in an epidemic area of northern Natal, South Africa, during the first year a high percentage (54%) of the

wild primates, including young animals, were found to have antibodies, but by the end of the period the only serologic reactors were animals over 4 years of age. After 1964, at no point was it possible to isolate the virus from mosquitoes, nor could viral activity be confirmed in sentinel monkeys during the later period. The authors concluded that there had been an epizootic in the primate population shortly before the study and that it abated when the virus disappeared. At least in this particular ecosystem, the wild primates did not serve as maintenance hosts, and it is likely that the epizootics were started by a virus introduced from some other area that was more favorable to perpetuation of the agent (McIntosh, 1970). A study carried out between 1977 and 1981 on a ranch in Transvaal, South Africa, sought to determine whether virus persisted in the mosquito *Aedes furcifer*, which had been the vector during the 1976 epidemic, and whether this mosquito was capable of transmitting the agent transovarially. In the 11,293 male and female specimens collected, the virus could not be isolated from the first postepidemic population. In addition, 13,029 specimens of five other *Aedes* species were studied and the same negative result was obtained (Jupp and McIntosh, 1990). From these studies it would appear that the virus maintains itself only in very special ecosystems, the ecology of which is not yet fully understood.

In urban outbreaks the main vector is *A. aegypti*, and, given the high titers of viremia observed in febrile patients, a cycle involving mosquito-man-mosquito is likely. Since the extrinsic incubation in *A. aegypti* is relatively long, it is possible that the sudden nature of some of the outbreaks may come from mechanical transmission by mosquitoes that have interrupted a blood meal on viremic patients and gone on to feed on susceptible individuals (Halstead, 1981).

In Yunnan, China, the virus was isolated from the bat *Rousettus leschenaulti*, the mosquitoes *A. albopictus* and *Culex taeniorhynchus*, and a febrile patient (Zhang *et al*., 1991).

Diagnosis: The virus can be isolated from the blood of febrile patients by intracerebral inoculation in suckling mice or on VERO cells.

In serologic diagnosis, which is the approach most commonly used, seroconversion is demonstrated by comparing acute- and convalescent-phase sera in the hemagglutination inhibition, serum neutralization, or complement fixation test. The enzyme-linked immunosorbent assay (ELISA) is used to detect IgM (Thein *et al*., 1992). A reverse-transcription–polymerase chain reaction (RT-PCR)/nested PCR technique has also been shown to be useful in rapidly diagnosing CHIK virus disease (Pfeffer *et al.,* 2002).

If O'nyong-nyong fever is present in the same area, it may be difficult to identify the virus and make a serologic diagnosis because the two viruses are antigenically related. Differentiation is based mainly on higher titers in the homologous sera and higher antibody titers for the homologous antigens (Filipe and Pinto, 1973).

Control: The prevention of urban epidemics should focus on combating the *A. aegypti* vector. In Luanda, Angola, two simultaneous epidemics of yellow fever and Chikungunya fever were successfully interrupted thanks to an intensive campaign to control mosquitoes (Filipe and Pinto, 1973). However, major difficulties stand in the way of completely eradicating *A. aegypti* from Africa or Asia. A promising live attenuated vaccine is under evaluation (Turell and Malinoski, 1992).

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COLORADO TICK FEVER

ICD-10 A93.2

Synonym: Mountain fever.

Etiology: Colorado tick fever virus is a double-stranded RNA genome virus composed of 12 segments, belonging to the genus *Coltivirus*, family Reoviridae. The 12 segments distinguish this virus from the taxonomic genus to which it was previously assigned, *Orbivirus,* whose species have only 10 segments. The virion measures 60–80 nm in diameter and is not enveloped. It is closely related to Eyach virus, which has been isolated from the tick *Ixodes ricinus* in Germany and France.

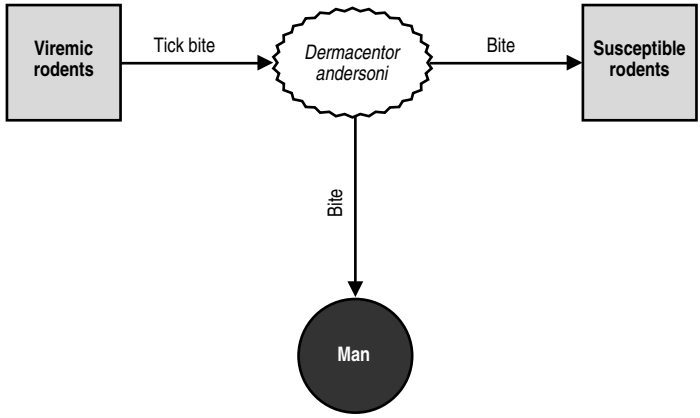
Geographic Distribution: The distribution of the virus corresponds to that of its vector, *Dermacentor andersoni*, in the mountainous areas of 11 western states of the US and the Canadian provinces of Alberta and British Columbia.

Occurrence in Man and Animals: In the US there are between 200 and 400 laboratory-confirmed human cases each year. Incidence of the disease is not fully known because reporting it is not compulsory. The infection always originates in endemic areas and affects both residents and visitors to these locations. It is seen most often in Colorado and Wyoming, which together account for more than 80% of all cases. Over the period 1970–1977 Colorado had an average of 174 cases per year (McLean *et al.*, 1981). In Canada, there have been no reports of human cases; the virus has been isolated from the vector only (Artsob and Spence, 1979).

The Disease in Man: The incubation period is three to six days. The patient's clinical history invariably reveals exposure to ticks. Since the *Dermacentor* bite is not painful, the patient tends to be unaware of the attached tick and must look for it in order to find it. Onset of the disease is sudden, with fever, chills, cephalalgia, retro-ocular pain, and severe muscular pain. Slightly more than 10% of patients have a cutaneous eruption. The disease is biphasic in approximately 50% of patients and similar in its symptomatology to dengue. The symptoms last for about 2 days, disappear for a few days, and then reappear for a slightly longer period. Leukopenia is observed on the fourth or fifth day of fever, with an increase in immature leukocytic forms. There may also be slight anemia and passing, but marked, thrombocytopenia, presumably the cause of the rare hemorrhages that can occur. The disease is also characterized by prolonged viremia due to persistence of the virus in mature or maturing erythrocytes. Since these cells enter the peripheral circulation, where they live for an average of 4 months, the virus remains in the bloodstream after the patient has recovered and developed antibodies (Emmons, 1988). Exacerbation of the symptoms can recur as many as 3 or 4 times. The disease is benign in adults. It was once thought that about 10% of children under 10 years old who contract the disease develop hemorrhagic complications or encephalitis, but subsequent reports indicated that such complications are less frequent (Emmons, 1988). Case fatality is very low. Treatment consists of providing care in response to the symptoms.

The Disease in Animals: The virus has been isolated from several species of squirrels, as well as other rodents and small mammals. Experimental inoculation produces prolonged viremia without clinical symptoms.

Figure 11. Colorado tick fever. Transmission cycle.



Source of Infection and Mode of Transmission (Figure 11): The disease occurs in spring and early summer, during the peak activity of *Dermacentor* species. Several species of squirrels constitute the main reservoir of the virus. A survey conducted in Rocky Mountain National Park (USA) revealed that the most important hosts were the species *Eutamias minimus* and *Spermophilus* (*Citellus*) *lateralis*, which were the principal source of the virus for the immature stages (larva and nymph) of the main vector, *D. andersoni* (elsewhere *Citellus colombianus* and *Eutamias amoenus* are also important). The prevalence of infection in these rodents was constant from April to July, and 5% to 6% of the specimens collected had viremia (Bowen *et al*., 1981). Viremia in squirrels lasts from 15 to 20 days, with sufficiently high titers to infect the vector. Transstadial transmission was verified in the main vector, but not transovarial transmission. Experimental studies with the squirrel *S. lateralis* have shown that the virus can overwinter in these rodents (Emmons, 1966). Thus it is possible that the virus may have two different mechanisms for surviving in winter: persistence in the vector nymphs and persistence in the host during hibernation.

Although other species of infected ticks have been found, their role in the ecology of the virus is still not fully understood. Moreover, these ticks are less inclined than *D. andersoni* to attack man. Their lifespan is usually two years, but it can vary depending on environmental conditions and the availability of animals to feed on. The larvae and nymphs feed on small mammals, while the adult prefers larger animals such as deer, porcupines, and man (Emmons, 1988). In areas not infested by *D. andersoni*, the virus is capable of circulating between hosts and vectors other than those found in the endemic area. In California this virus (or one very similar to it) has been isolated from the jackrabbit *Lepus californicus* and the western gray squirrel *Sciurus griseus* outside the endemic area and in the absence of *D. andersoni* (Lane *et al*., 1982). Antibodies to the virus were also found in Ontario, Canada, in the snowshoe hare *Lepus americanus*, indicating that the agent circulates in nature

in the eastern part of the country. However, no human cases of the disease have been observed outside the range of *D. andersoni*.

The infection is transmitted to humans when they enter an enzootic area and are bitten by the adult *D. andersoni* tick. In some enzootic areas, located at altitudes of about 1,300 meters, the rates of infection in this species of tick in the springtime range from 14% to 40%. Viremia in man is very prolonged, sometimes lasting up to 110 days after onset of the disease, and a case of human-to-human transmission via blood transfusion has been confirmed (CDC, 1975a).

The Role of Animals: Small mammals that renew their generations frequently are important reservoirs of the virus. Together with the tick *D. andersoni*, which transmits the agent transstadially, they ensure the stability of the virus in natural niches. The virus is transmitted through the tick's saliva when it feeds on the blood of one of the hosts. Man is an accidental host.

Diagnosis: Clinical diagnosis can be confirmed by isolation of the virus from the patient's blood. Best results are obtained from a combination of intracerebral and intraperitoneal inoculation of the blood in suckling mice and cell cultures, and use of the immunofluorescence test on washed erythrocytes from the patient. In addition, viral antigen can be detected using the direct immunofluorescence test on smears of the patient's blood. Serologic diagnosis is also possible with the neutralization, indirect immunofluorescence, and complement fixation tests using acute- and convalescent-phase sera to demonstrate a rise in antibody titer. A fourfold or greater increase in titer is significant.

Control: Individual prevention measures consist of avoiding tick habitats or, if one must go into such places, using protective clothing and a repellent, and afterwards, inspecting the body and eliminating any ticks that are found before they become attached. An attached tick should be removed by gently grasping the tick with fine-tipped tweezers as close to the skin as possible and pulling it away from the skin in a steady motion; after, cleanse the area with an antiseptic.

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CONTAGIOUS ECTHYMA

ICD-10 B08.0 Other orthopoxvirus infections

Synonyms: Orf virus disease, contagious pustular dermatitis, contagious pustular stomatitis.

Etiology: DNA genome virus, genus *Parapoxvirus* (family Poxviridae), which also includes the viruses that cause milker's nodule (pseudocowpox) and bovine papular stomatitis. The virion measures 160 by 260 nm. It is very resistant to environmental conditions, and it is highly epitheliotropic.

Geographic Distribution: The disease is found in all sheep-raising countries. In the United States, it occurs more frequently in western states.

Occurrence in Man: Rare. In New Zealand, which is a major sheep-producing country, an increase in human cases has been noted. Only two cases were recorded in 1975, but by 1979 the number had risen to 143, primarily affecting workers in packinghouses (Robinson and Balassu, 1981). To learn more about incidence of the disease, a surveillance program was undertaken among workers at 18 slaughterhouses in New Zealand. In the course of a year, 231 cases were found, representing an incidence of 1.4%. The most affected group were the workers who handled wool and hides. Reinfection occurred in 18 individuals (Robinson and Petersen, 1983, cited in Timoney *et al.*, 1988).

Occurrence in Animals: The disease occurs in sheep, goats, alpacas, camels, and sometimes dogs. There are enzootic areas all over the world where there are annual outbreaks on ranches with a history of infection. It has also been detected in several wild species.

A study was carried out in New Zealand to determine the rate of infection among lambs slaughtered at two packinghouses. Of 6,300,000 lambs killed over a period of three years, 0.5% had contagious ecthyma lesions, with the proportion peaking at 2.2% in the early summer. By extrapolation, it is estimated that lesions affect 1,250,000 lambs in the country's slaughterhouses every year (Robinson, 1983). In Namibia, 1,150 out of 4,350 goats developed contagious ecthyma and 13 of them died during 1985; in 1986, 3,492 out of 8,823 goats developed the disease and 240 of them died. The disease affected an even higher proportion of sheep, but the case fatality rate (1.1%) was lower than in the goats (Munz *et al.*, 1991).

The Disease in Man: Contagious ecthyma occurs among persons who have close contact with affected animals (herders, slaughterhouse workers, veterinarians, butchers, sheep-shearers). The incubation period is three to seven days. The lesion usually occurs on a finger, hand, or other exposed part of the body that has been in contact with infective matter. A papular lesion develops at the virus penetration site, and this lesion soon becomes a vesicle or pustule, which may or may not be accompanied by adenopathy. If there is no secondary infection, the lesion heals in two to four weeks. The scab falls off and leaves no scar. Occasionally, there is a generalized vesiculopapular eruption with pronounced pruritus. In one study, multiple lesions were seen in 21 of a total of 60 patients, and in another series they were observed in 6 out of 19 patients (Johannessen *et al.*, 1975; Leavell *et al.*, 1968). Although rare, ocular lesions can also occur. There is no specific treatment for the disease in man.

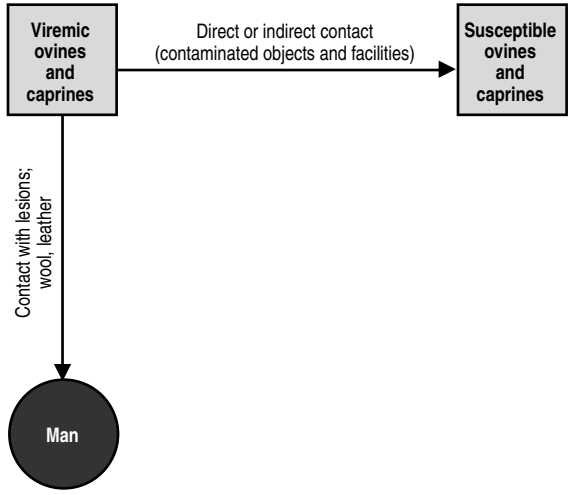
The Disease in Animals: Sheep and goats of any age are susceptible, but the disease is seen primarily in animals less than 1 year old, since adult animals on infected ranches tend to be immune as a result of previous exposure. The incubation period is two to three days. The lesions turn into papules, vesicles, and pustules. After about 11 days, thick brown scabs begin to form, and these last for one or two weeks, after which they loosen and fall off. The lesions occur on the lips, mouth, nostrils, eyelids, and ears. If there are only a few of them, the animal does not suffer greatly, but if they are numerous and are confluent, the intense pain interferes with eating. Ewes that are nursing infected lambs may also develop lesions on the teats and udder. The infection may also affect the animals' feet (the skin at the top of the hoof or between the hoof claws) and cause limping.

Morbidity can be very high, but mortality is low and is usually due to complications from secondary infections. One important complication is myiasis caused by larvae from the fly *Cochliomyia hominivorax*.

It is recommended that repellent be applied to keep flies away from the wounds and that larvicides be used in the event of myiasis. If there is a bacterial superinfection, antibacterial drugs are indicated.

Source of Infection and Mode of Transmission (Figure 12): Sheep and goats are the natural hosts of the virus. During an outbreak the disease may be transmitted by direct contact or indirectly by contaminated objects and facilities. The virus is resistant to desiccation and survives in the scabs for many months. The seasonal recurrence of outbreaks, at the time of year when there are susceptible young animals, can result from contamination of pasture with scabs and from contact with infected animals. Rough pasture can injure the epithelium of the mouth, facilitating penetration of the virus and infection.

Figure 12. Contagious ecthyma. Transmission cycle.



Man is infected accidentally by contact with animals with contagious ecthyma lesions, and transmission occurs through abrasions or other broken skin. For slaughterhouse workers, another possible source of infection is sheep wool and hides, where the virus can persist for approximately one month after the lesions have disappeared (Robinson, 1983). Personnel who vaccinate lambs with live vaccine are also exposed to the infection.

Role of Animals in the Epidemiology of the Disease: Contagious ecthyma is a zoonosis of low incidence in man.

Diagnosis: Clinical symptomatology in sheep and goats is usually sufficient to establish the diagnosis. In differential diagnosis, sheep-pox (with intense systemic reaction) and ulcerative dermatosis (with ulcers and scabs on the skin of the face, feet, and genital organs) should be taken into account.

In humans, laboratory confirmation is important and may be accomplished by use of the following procedures: (a) the complement fixation test, to confirm the presence of the viral antigen (in vesicular fluid or a suspension of scabs) and antibodies (in sera), and (b) cell culture (embryonic sheep kidney) and the immunofluorescence test to isolate the virus. Other tests used are agar gel immunodiffusion, virus neutralization, and capillary agglutination. A polymerase chain reaction technique useful in diagnosing the disease has also been developed (Torfason and Gunadottir, 2002). Another method is experimental inoculation of unvaccinated lambs from a disease-free flock.

Control: Control is accomplished by the vaccination of lambs on infected ranches. The most commonly used vaccine is a suspension of pulverized virulent scabs in a glycerinated solution and, therefore, application of such a vaccine should be restricted

to flocks with a history of infection. Observations in Great Britain indicate that lambs can be vaccinated when they are 1 or 2 days old by scarifying the axilla. The absence of a local reaction indicates that the vaccine was inactive, and vaccination should be repeated with a fresh vaccine. Immunity is established three weeks after application of the vaccine and lasts for more than two years. A major drawback of the vaccines currently in use is that they perpetuate the infection in the environment (Robinson and Balassu, 1981). Also, vaccination failures can occur for unknown reasons (Buddle *et al.*, 1984). An attenuated cell-culture vaccine administered subcutaneously has been developed in Germany, and according to its developers, it has given good results both in the laboratory and in field tests (Mayr *et al.*, 1981).

Prevention of the infection in humans consists of protecting skin wounds when working with sick animals and using gloves when vaccinating sheep.

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COWPOX

ICD-10 B08.0 Other orthopoxvirus infections

Synonym: Natural cowpox (as distinguished from the disease produced by the vaccinia virus).

Etiology: DNA genome virus belonging to the genus *Orthopoxvirus*, family Poxviridae. The type species of the genus *Orthopoxvirus* is the vaccinia virus. The virions of this genus are brick-shaped, measuring approximately 300 by 240 by 100 nm, and have an irregular arrangement of tubules on the outer membrane. The orthopoxviruses are the largest known viruses. This same genus includes the human smallpox (variola), vaccinia, and monkeypox viruses, among others. Antigenically, the cowpox agent is closely related to the vaccinia virus, from which it can be differentiated using the complement fixation, agar gel diffusion, and antibody absorption tests. The cowpox virus does not cause the development of pustules on chorioallantoic membrane when it is incubated at temperatures above 40°C. The virus has been isolated from zoo animals such as elephants and wild felids in Berlin, London, and Moscow. The isolations can be distinguished from one another only by using a combination of biological tests (Baxby *et al.*, 1979). The infection in domestic cats in Great Britain has attracted particular attention because of their close contact with humans and therefore the possibility of transmission. These viruses were said to be "cowpox-like." However, biological and genetic analyses of the two orthopoxviruses in question showed that the virus from the domestic cats is identical to that of cowpox and that there is no justification for designating a feline variant or subspecies (Naidoo *et al.*, 1992).

Geographic Distribution: The cowpox (CP) virus has been isolated in Great Britain and a few Western European countries. Suspected human cases of cowpox have also been reported in Egypt (Amer *et al*., 2001). The Americas, Australia, and New Zealand are probably free of the disease (Odend'hal, 1983).

Occurrence in Man and Animals: Little information is available on the frequency of the disease. CP is recognized only when many cases show up in bovines or when the disease occurs in man. Serologic surveys conducted in Great Britain demonstrated that the disease is not enzootic among bovines there, as it was once believed: low antibody titers were found in only 7 of 1,076 sera examined. Bank voles (*Clethrionomys glareolus*), wood mice (*Apodemus sylvaticus*), and short-tailed field voles have been shown to be the main reservoir of the virus in Great Britain (Hazel *et al*., 2000; Chantrey *et al*., 1999). In the Netherlands, 17 isolations were obtained within the period of a single year at 36 livestock-raising establishments in the province of Friesland, which might indicate that CP is enzootic in that area (Baxby, 1977; Baxby and Osborne, 1979).

In Great Britain, CP is rare in man, estimated at one or two cases a year. Only 20 cases were reported during the 13-year period 1969–1981, and in the next 12 years (1982–1993), there were only 23 cases. The apparent increase in cases may be the result of greater interest in the disease than a real increase in its incidence (Baxby, 1994), though the decline and discontinuation of smallpox vaccinations and the rise in the number of individuals taking immunosuppressant drugs or with HIV may also be factors (Blackford *et al*., 1993, cited in Amer *et al*., 2001).

Cases of cowpox in domestic cats have increased, and it is believed that these animals have become more important than cattle as a source of human infection. In the late 1980s, there were at least 30 cases of cowpox a year among cats in Great Britain (Bennett *et al.*, 1990). In Austria, 4% of 200 serum samples from cats produced positive orthopoxvirus reactions in the hemagglutination inhibition test, with titers ranging from 16 to 520. A study of 217 sera collected from domestic cats in western Norway found 10.1% to have antibodies to orthopoxvirus (Tryland *et al*., 1998).

Outbreaks caused by the CP virus occurred among felines and insectivores at a Moscow zoo in 1973–1974, and a female zoo employee also became ill (Marennikova *et al.*, 1977). The outbreaks originated from white rats being fed to the wild cats and pumas. Serologic investigation showed that 42% of these rats had antibodies to the virus. During that same period, two pox outbreaks caused by the virus occurred in a colony of white rats, 30% of which died. In addition, two of the colony's caretakers developed cutaneous eruptions on the hands, shoulders, knees, and head (Marennikova *et al.*, 1978). In Turkmenistan, an identical virus was isolated from two wild rodent species, the great gerbil (*Rhombomys opimus*) and the fulvous ground squirrel (*Citellus fulvus*). CP-like viruses have also been isolated from zoo or circus animals in Germany (elephantpox), Great Britain, and the Netherlands (Baxby *et al.*, 1982). During the elephantpox episode in Germany, there were several cases of human infection. In Europe, the spectrum of affected animal species is very broad. A serologic survey conducted in Germany using the indirect immunofluorescence test revealed antibodies to the CP virus in 218 of 303 wild rodents representing 5 species, but it was not possible to isolate the virus. In the same study, 202 of 277 cats examined at 67 different localities in the country were positive reactors, as were 61 of 106 cattle and 13 of 38 elephants from zoos and circuses (Jacoby, 1992).

The Disease in Man and Animals: The incubation period in humans and cattle is approximately five days. In cattle, after an incubation period of three to six days, the disease begins with a mild fever. Papules that progress to vesicles and then to pustules are observed on the teats. Upon breaking, the pustules form red scabs, which, in turn, can leave ulcerations that may take as long as a month to heal (Tripathy *et al.*, 1981).

In man, lesions occur on the hands and sometimes on the face and arms. In most cases, there is fever, local edema, and lymphadenitis. The human disease is quite severe and usually does not go unnoticed. It can even be fatal if the patient is immunocompromised. The experience of an 18-year-old in Germany is a case in point. The source of infection was a cat. The patient had been suffering from atopic dermatitis and allergic bronchial asthma for a number of years and was being treated with steroids. The CP infection began with a mild fever and multiple vesicles on the face, arms, and trunk. Later, he developed a spiking fever and his entire body became covered with cutaneous lesions. The hemorrhagic scabs left ulcerations, and the lesions extended to the respiratory mucosa. Despite intensive care, the patient died from cardiac arrest caused by a massive pulmonary thromboembolism (Eis-Hubinger *et al.*, 1990).

In the outbreaks among zoo animals in Great Britain and Moscow, two clinical forms were observed: a fulminating pulmonary form without cutaneous lesions, and a dermal form with long-lasting eruptions. Many animals died as a consequence of

the disease (Baxby *et al.*, 1982; Marennikova *et al.*, 1977). In domestic cats, the disease is characterized by scabby skin lesions or erythematous papules 5 to 7 mm in diameter, distributed over the entire body. In some cases, signs of respiratory difficulty are observed. Although most cats recover from the disease, some of them die (Hoare *et al.*, 1984). Eight kittens, 6 to 8 weeks of age, that were inoculated by various routes with an orthopoxvirus isolated from a wild root vole (*Microtus oeconomus*), manifested severe disease over a period of two to three days. Five of the eight kittens developed papules at the site of scarification and died. The lungs were the internal organs most affected. The authors of the study suggest that the domestic cat may serve as an intermediate host in transmission of the cowpox virus from rodents to man (Zhukova *et al.*, 1992).

Source of Infection and Mode of Transmission: It has been established that in Great Britain the infection is not enzootic in cattle, and that contact with cows accounts for only some of the human cases reported there and in other countries. Cowpox infection is endemic in European rodents (Hazel *et al*., 2000), and while several rodent-to-human cases of infection are suspected, only one has been proven (Wolfs *et al*., 2002). Domestic cats have also been shown to carry the virus and thus represent a source of infection for humans who have close contact with these animals. The infection is thought to be transmitted to humans from rodents and cats through a scratch or bite.

In cats, the primary lesion often originates in the vicinity of a bite, which would suggest that they might have acquired the infection from an infected rodent.

Although it has not been possible to discover the source of infection of a number of pox outbreaks in zoo or circus animals, in the Moscow zoo, the outbreaks clearly originated with the white rats that were fed to the wild cats and pumas. The human clinical cases that occurred in Moscow, as well as those in other outbreaks, were presumably the result of direct contact with sick animals.

Diagnosis: The virus can be isolated in various tissue culture and chick embryo systems. Cowpox virus can be differentiated from vaccinia virus using serologic tests (see the section on etiology). The appearance and histology of the focal lesions on chorioallantoic membrane and rabbit skin facilitate differential diagnosis. The CP virus can be distinguished from other pox viruses through a combination of biological tests (Baxby *et al.*, 1979) and through polymerase chain reaction (Schupp *et al.*, 2001; Wienecke *et al.*, 2000).

Control: Current knowledge does not allow for the establishment of preventive measures. Experiments indicate that the vaccinia MVA strain may protect man and other animals against the cowpox virus (Munz *et al.*, 1993), but it is doubtful that such intervention is justified.

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Addendum

BUFFALOPOX

An orthopoxvirus that affects the water buffalo (*Bubalus bubalis*) and man is the buffalopox virus, which is very similar to the vaccinia virus. The disease occurs in Egypt, India, and Indonesia. The lesions on the animals are similar to those caused by cowpox. In calves it can produce generalized disease. In an outbreak in India, 3.8% of 650 buffaloes had lesions on the udder and teats. The six milkers responsible for these animals developed a disease similar to milker's nodule, with a high fever that lasted for about two days prior to the appearance of lesions.

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CRIMEAN-CONGO HEMORRHAGIC FEVER

ICD-10 A98.0

Synonyms: Central Asian hemorrhagic fever, Congo fever.

Etiology: A three-segment RNA genome virus belonging to the genus *Nairovirus*, family Bunyaviridae. The virions are spherical, measure approximately 85–105 nm in diameter, and have a bilayered lipid envelope. Epidemiologically, this virus

belongs to the group of tick-borne hemorrhagic fever viruses, together with the agents of Omsk hemorrhagic fever and Kyasanur forest disease.

Geographic Distribution: The virus has been isolated in the Balkans, the southern region of the former Soviet Union, and former Soviet Republics in Asia. The disease also occurs in Afghanistan, China, Iran, Pakistan, Syria, and the United Arab Emirates. In Africa, it has been reported in the Central African Republic, Democratic Republic of the Congo, Ethiopia, Kenya, Madagascar, Mauritania, Nigeria, Senegal, South Africa, Uganda, and Zimbabwe. Seroepidemiologic surveys in humans and animals suggest that its geographic distribution may be far wider and that enzootic foci may exist both with and without human cases. Outside the known endemic areas, the virus has been isolated, or antibodies have been detected, in France, Hungary, India, and Turkey.

Occurrence in Man: Crimean-Congo hemorrhagic fever (CCHF) almost always occurs as isolated cases, and its distribution and incidence are scattered in terms of both space and time. During the Second World War, between 92 and 200 cases were reported among the military and civilian population in Crimea, Ukraine, in 1944, followed by about 100 additional cases in 1945. In Astrakhan, the Russian Federation, 104 cases and 18 deaths were reported between 1953 and 1963, reaching an annual high of 44 cases in 1963. In most of the villages and agricultural cooperatives where the disease occurred there was only one case a year. In Rostov Province, in the Russian Federation, there were 323 cases between 1963 and 1969, with a peak of 131 cases and a 16% case fatality rate in 1968. Bulgaria had 717 cases during the period 1953–1965, with a morbidity rate of 0.7% and a case fatality rate of 17%. Between 1968 and 1972, there were 121 confirmed cases in that country. In 79% of the foci, the disease occurred only once (Hoogstraal, 1979). An outbreak appeared in Bachu, Xinjiang Province, China, in 1965, in which 80% of the cases were fatal (Yen *et al*., 1985). In terms of prevalence, the complement fixation test proved positive in 16 of 135 persons examined. In Mauritania, tests for the presence of IgG antibodies using the enzyme-linked immunosorbent assay (ELISA) on samples taken from 99 family members or contacts of patients hospitalized with CCHF revealed a seroprevalence level of 36% (Gonzalez *et al*., 1990).

In several rural areas of South Africa, it was shown that seroprevalence increased with age and was related to the handling of sheep (Fisher-Hoch *et al*., 1992). Epidemics of the disease have always been related to some change in the environment, either from the effects of war, as in Crimea, or the expansion of cultivated land areas, as a result of collectivization in Bulgaria and the former Soviet Union. The incidence of cases parallels the population density of adult ticks belonging to the *Hyalomma marginatum* complex: it starts out low in early spring, reaches its peak in the first part of summer, and then declines until it disappears at the beginning of autumn.

Familial and nosocomial outbreaks—sometimes with numerous cases and high fatality rates—have been recorded in several countries of Africa, Asia, and Europe, arising from direct contact with a patient during the hemorrhagic period of the disease.

Occurrence in Animals: The main natural hosts of the CCHF virus are hares and hedgehogs (hosts for immature ticks) and cattle, sheep, goats, horses, and swine (hosts for adult ticks). Seroepidemiologic surveys of the endemic areas have shown widely varying reactor rates depending on the region, the time of year, and the animal species.

The periodic changes in the population of the tick vectors make for notable differences in the rates of infected animals. As a rule, the rate of animals with antibodies is null or very low in places where human cases have not occurred and high wherever there have been reports of the disease. In sheep experimentally infected with the virus, it was possible to detect IgM by the antibody-capture ELISA test at 5 to 21 days postinoculation. The competitive ELISA test, without distinguishing the antibody type, demonstrated the presence of antibodies up to 70 days postinoculation. In 5 of 11 experimentally infected cattle it was not possible to demonstrate the presence of IgM, but in the other 6, antibodies were detected between 7 and 49 days after they were inoculated. Total antibodies detected by the competitive ELISA test were diagnostic from day 6 onward, and they were still present at day 55.

In a group of 960 wild animals living on a natural reserve in South Africa, the highest prevalence was observed in large vertebrates such as the rhinoceros, giraffe, and buffalo, which are the preferred hosts of adult *Hyalomma* tick species, the vector of the virus (Burt *et al*., 1993). Researchers have demonstrated that IgM antibodies can be detected in sheep and cattle for only three to seven weeks, whereas in man they remain for three to five months. This difference may be due to the low susceptibility of these animals to the virus. Other studies conducted in different geographical areas confirm that IgM antibodies, which are indicative of recent infection, are only present for a short time and that the IgG antibodies persist much longer. The examination of 1,219 sheep from 14 different sites in southern Mauritania revealed prevalence rates ranging from 4.9% to 43%, depending on the herd (Gonzalez *et al*., 1990).

The Disease in Man: The period of intrinsic incubation, from the tick bite until the appearance of symptoms, lasts 5 to 12 days. The disease has a sudden onset, with high fever, chills, headache, vertigo, and diffuse myalgia. The fever lasts about eight days and may be continuous or biphasic. Abdominal pain, nausea and vomiting, diarrhea, and bradycardia are frequent; also common are hyperemia and edema of the face and neck, and conjunctival congestion. Leukopenia and thrombocytopenia are almost always present, and proteinuria is frequent. Hemorrhages begin on day four of the illness. Petechiae in the mouth and on the skin vary in frequency and intensity, and some patients have a distinct hemorrhagic purpura. The most common hemorrhagic manifestations are epistaxis, gingival hemorrhaging, hematuria, and hemorrhaging of the gastric mucosa. Convalescence is characterized by asthenia, headaches, malaise, and sometimes neuritis and temporary alopecia. When death occurs, it is usually due to shock brought on by the loss of blood or to neurological complications, pulmonary hemorrhages, or intercurrent infections. Hepatosplenomegaly is reported in about one-third of the patients. The case fatality rate is estimated at about 30%.

The infection in man does not always take such a severe course. It was once believed that the disease was more serious in Eurasia than in Africa, but studies have since shown that there is no difference in this regard. Of 31 cases reported in Africa, there were 11 deaths (Swanepoel *et al*., 1987). There are also mild febrile cases without hemorrhaging and even asymptomatic cases.

For patients without hemorrhagic complications, treatment with analgesics and antipyretics is usually sufficient. However, with patients that have complications, care should be taken to maintain the balance of fluids and electrolytes. When the hemorrhaging is severe, consideration should be given to using fresh platelets, fresh

frozen plasma, or concentrated coagulation factors. Heparin can be useful in the treatment of intravascular coagulation, but great care should be taken in its administration and use. Peritoneal dialysis may be used for the treatment of renal insufficiency (World Health Organization, 1985).

The Disease in Animals: In experimentally inoculated cattle and sheep, the infection was asymptomatic or produced a mild illness, even though viremia has been confirmed in various animal species. Other trials have shown that newborn rodents may succumb to the infection.

Source of Infection and Mode of Transmission: The natural foci of the virus are located mainly in the steppes, savannahs, semidesert areas, and foothill biotopes (World Health Organization, 1985). The virus has been isolated by immunofluorescence in 19 species and subspecies of ticks in Eurasia, and in 9 species in Africa. These ticks belonged mainly to the genera *Hyalomma*, *Dermacentor*, *Rhipicephalus,* and *Boophilus*. Several species of *Hyalomma* play a prominent role as vectors and reservoirs of the CCHF virus. Most of the cases in Bulgaria and the former Soviet Republics were transmitted by *Hyalomma m. marginatum*. The larvae and nymphs of these ticks feed on hares, hedgehogs, and birds, while the adult ticks feed on large wild and domestic animals and are easily attracted to man. The main vectors are the tick species that predominate on domestic animals in the particular enzootic area. The CCHF epidemics correspond closely to an abundance of *Hyalomma* species in the different ecologic areas (Hoogstraal, 1979).

Studies with specimens of *Hyalomma m. marginatum*, *Rhipicephalus rossicus*, and *Dermacentor marginatus* have shown that the survival mechanism of the virus during the rigorous winters of the former Soviet Union has been both transstadial and transovarial transmission in the ticks. Domestic animals, hares (*Lepus europaeus* and *L. capensis*), hedgehogs (*Erinaceus albiventris* and *Hemiechinus auritus*), and possibly some other animals may serve as amplifiers of the virus and a food source for the ticks. When infected by the vectors, all these animals present viremia for at least a week and serve, in turn, as the source of infection for uninfected ticks. High serologic reactor rates have been found among mammals in the enzootic areas. Birds do not become infected, but they play an important role as a food source for immature ticks and as a vehicle for the long-distance dispersion of these vectors (Hoogstraal, 1979).

The human disease occurs in rural areas, and the most vulnerable occupational groups are agricultural and livestock workers. Humans acquire the infection from the bite of an infected tick and can also become infected by crushing a tick with their hands if the virus happens to gain entry through a lesion on the skin. Humans may also be directly infected during the slaughter and skinning of viremic animals, as suggested by episodes that occurred in Kazakhstan and Uzbekistan. In South Africa, however, it was not possible to demonstrate that contact with the blood or raw flesh of animals poses an infection risk for man (Fisher-Hoch *et al*., 1992). There have been numerous cases, the majority of them fatal, of person-to-person transmission among family members and hospital personnel exposed to the hemorrhagic discharges of CCHF patients (Hoogstraal, 1979).

The Role of Animals in the Epidemiology of the Disease: There is a question as to whether vertebrates actually serve as a reservoir, or whether they are simply a food source for the vector ticks. The ticks, however, are not only vectors but also

reservoirs, because they can transmit the infection transovarially and transstadially. It is not known how long the cycle can be maintained in this way because the transmission rate is low. In a study in which uninfected *Hyalomma* larvae and nymphs and infected adult ticks were allowed to feed together on an uninfected guinea pig, the immature ticks became infected. After feeding, 3 (0.8%) of the 370 *H. truncatum* larvae became infected. The virus was transmitted transstadially to 15 (1.2%) of the 1,253 nymphs and to 12 (0.5%) of the 2,049 adult specimens. With another tick species (*H. impalatum*), the virus was transmitted to the nymphs but not the adults. The authors of this study concluded that a small proportion of larvae or nymphs may become infected when they feed together with infected adult ticks on a host without detectable viremia. These results suggest that many more vertebrates can serve as amplifiers of the virus than was originally believed (Gordon *et al*., 1993).

Diagnosis: The diagnosis can be confirmed from isolation of the virus by inoculating the blood of acute-phase patients or autopsy material intracerebrally in newborn mice, or by propagating it on Vero or CER cell cultures. Serologic diagnosis can be made with the following tests: complement fixation, serum neutralization (with newborn mice), indirect hemagglutination inhibition, radial gel diffusion, reverse-transcription–polymerase chain reaction (RT-PCR), ELISA, and immunofluorescence. The sensitivity of most of these tests is low. The ELISA test is considered more sensitive and specific, as well as faster and more readily reproducible (Donets *et al*., 1982). In addition, the ELISA test can detect IgM or global antibodies (Burt, 1993).

Control: The measures recommended are the same as for other tick-borne infections. In Bulgaria and the former Soviet Union there have been trials with an inactivated vaccine, but the results have not been satisfactorily evaluated. It is important to isolate patients, especially those with hemorrhages, in order to prevent contagion. Blood from patients should be treated with heat or chlorinated disinfectants. Personnel responsible for the patient should be provided with protective clothing.

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DENGUE

ICD-10 A90 Dengue fever [classical dengue]; A91 Dengue hemorrhagic fever

Etiology: Dengue (DEN) virus is an RNA genome virus of the genus *Flavivirus* (formerly arbovirus group B), family Flaviviridae. Four serotypes (1–4) are recognized. Immunity against the homologous type is complete and prolonged, but for the heterologous types it is partial and of short duration. The virus is transmitted by mosquitoes.

Geographic Distribution: Tropical Asia, eastern and western Africa, Polynesia and Micronesia, the Caribbean, Central America, much of South America, and Australia. The *Aedes aegypti* mosquito is the main vector of all four serotypes and the only one that has been identified so far in the Americas and Australia. *Aedes albopictus* may be the only vector in some parts of southeast Asia. This mosquito was accidentally introduced in Brazil (4 states), the United States (16 states), and Mexico. *A. albopictus* and *A. aegypti* are the principal vectors of the virus in rural and urban Malaysia, but not in the deep jungle. *Aedes niveus*, which feeds on humans and monkeys, is believed to be the vector of the wild cycle in Malaysia (Varma, 1989).

Occurrence in Man: Every year, millions of people contract the infection in Asia, Africa, the Pacific islands, and the Americas. The disease can occur both endemically (in which case it often goes undetected) and as an epidemic. Four epidemics occurred in the Americas in the space of two decades. The first (1963) was caused by DEN-3 and affected the Caribbean islands and Venezuela. The second (1969), due to DEN-2, affected the Caribbean islands and Colombia. The third (1977), caused by DEN-1, started in Jamaica, where it affected more than 60,000 persons, and spread to other Caribbean islands, Mexico, Central America, and Venezuela (Figueroa *et al.*, 1982). The fourth epidemic (1981), due to DEN-4, started in Saint Barthélemy, French Antilles, and spread to other Caribbean islands and Belize (PAHO, 1982). Puerto Rico was severely affected in all four epidemics. Following relatively high dengue activity in 1981 and 1982, when Brazil had its first dengue epidemic in 50 years, most countries reported only sporadic cases in 1983. The exceptions were Mexico, Colombia, and El Salvador, which had sizable localized outbreaks that year (PAHO, 1984). A significant outbreak of DEN-1 affected the city of Rio de Janeiro in 1986. The infection also flared up in countries that did not have any history of the disease or had not had an epidemic in several decades, with DEN-1 epidemics in Bolivia (1987), Paraguay (1988), Ecuador (1988), Peru (1990), and Costa Rica and Panama (1993) (PAHO, 1993).

A serologic survey carried out in Honduras established that there had been at least 134,000 cases in the 1978–1980 epidemic. Some population areas of the country, including the capital, were affected very little, if at all, probably because of the low density of the *Aedes aegypti* vector (Figueroa *et al.*, 1982). Serologic tests conducted in the endemic areas of Asia and Africa revealed high reactor rates. In a study carried out in four ecologic areas of Nigeria to determine the prevalence and distribution of immunity to the dengue virus, the serum-neutralization test showed that 45% of 1,816 persons were immune to DEN-2, and that the prevalence was higher in

adults than in children, and higher in urban than in rural populations (Fagbami *et al.*, 1977). Similar rates can be found in tropical Asia. In Malaysia, dengue is common not only in the cities and rural areas, but also among the indigenous peoples of the jungle.

Occurrence in Animals: Dengue is essentially a human disease transmitted by mosquitoes of the genus *Aedes*. However, there are strong indications that, in addition to the human cycle, there is a wild cycle involving nonhuman primates and *Aedes niveus* mosquitoes (Varma, 1989), which inhabit the forest canopy. The virus has also been isolated from naturally infected monkeys (WHO, 1985). In Malaysia, of approximately 600 sera collected from wild monkeys living far from human populations, 62.8% were positive for arbovirus group B and 8% exclusively for dengue (Rudnick, 1966a). Studies in jungle areas of Nigeria also point to the existence of a wild cycle that circulates independently of man (Monath *et al.*, 1974; Fagbami *et al.*, 1977).

The Disease in Man: In its common form, dengue fever is an acute and benign febrile disease. The incubation period (from the mosquito bite to the onset of clinical symptoms) lasts from five to eight days. Onset is sudden, with fever, chills, cephalalgia, retroocular pain, photophobia, and muscle and joint pain. There can also be nausea, vomiting, and sore throat. A general erythema is common at the beginning of the febrile period; a maculopapular or scarlatiniform rash may appear on the trunk three or four days after onset of the disease and spread to other parts of the body. The lymph nodes become enlarged and palpable. The fever itself, which is sometimes diphasic, lasts five to seven days. Convalescence, with fatigue and depression, may take several weeks. Case fatality is very low (Benenson, 1990; Tesh, 1982).

A serious and often fatal form of the disease, known as hemorrhagic dengue or dengue hemorrhagic fever (DHF), has been observed in at least 12 countries of tropical Asia. This form occurs mainly in children and can be caused by any of the four serotypes. The disease may start out as ordinary dengue, but then, after several days of fever, the signs of dengue hemorrhagic shock syndrome (DSS) appear—i.e., hemorrhaging, circulatory insufficiency, and hypotension. The pathogenesis and the risk factors associated with the development of DHF/DSS are not yet fully understood and have been the subject of some debate.

In Cuba, there was an explosive epidemic of DHF in May 1981, with severe cases of hemorrhage, shock, and even death. By the end of the epidemic in October 1981, a total of 344,203 cases had been reported: 9,203 were considered severe, 1,109 were critical, and there were 159 deaths from hemorrhagic dengue in children and adults. Serologic studies and virus isolations suggested that DEN-2 was the cause of the epidemic (Kourí *et al.*, 1983; Guzmán *et al.*, 1984). Cases of DHF and DSS have occurred in a number countries in the Americas: during the period 1981–1992, laboratory-confirmed cases were reported every year except 1983. Among the affected countries and territories were Aruba, Brazil, Colombia, Cuba, Dominican Republic, El Salvador, French Guiana, Honduras, Mexico, Nicaragua, Puerto Rico, Saint Lucia, Suriname, US Virgin Islands, and Venezuela. Cuba and Venezuela had major outbreaks of DHF/DSS (PAHO, 1993).

In children, the characteristics of DHF/DSS are abnormal vascular permeability and subsequent hypovolemia, as well as problems with blood coagulation. Patients

with these symptoms should be given oxygen along with electrolytes and fluids to replenish what they have lost. In severe cases of shock, plasma and plasma expander should be given.

In adults, the main characteristics of severe dengue are hemorrhage, disseminated petechiae, ecchymoses, and, less often, epistaxis, petechial rash, and bleeding gums; intestinal hemorrhage is rare and indicative of a grave prognosis. Blood transfusions are indicated only when there is a significant drop in the hematocrit index (Benenson, 1990).

The Disease in Animals: In nonhuman primates, experimental infection with the dengue virus is clinically inapparent. No signs of the disease were observed in sentinel monkeys in the jungle canopy.

Source of Infection and Mode of Transmission: The basic cycle takes place between humans and *Aedes* mosquitoes. The mosquito's source of infection is the human patient during the viremic period, which typically lasts five to six days. When the insect feeds on the blood of a febrile patient, it ingests the virus, which multiplies and infects the insect's salivary glands. After about 10 days, the mosquito can transmit the infection to persons who are not immune to the serotype in question. The principal vector is *Aedes aegypti*, which breeds in containers near or inside houses, is highly anthropophilic, and feeds in the daytime. Outside the Americas, the vectors are *A. albopictus* and several species of the *A. scutellaris* complex. Dengue occurs most often during the rainy season, when *A. aegypti* are in abundance, but in hyperendemic areas and places where there is no specific rainy season, it may occur throughout the year.

The epidemics described in the Americas (see the section on occurrence in man) occurred because of the infestation or reinfestation of *A. aegypti* in the countries of the Region. Currently, almost all the countries except Bermuda, Canada, Cayman Islands, Chile, and Uruguay have infestations of *A. aegypti*.

Isolation of the virus from naturally infected monkeys (WHO, 1985), coupled with high neutralizing titers for serotypes 1 and 2 in these animals, would suggest that the infection has a wild transmission cycle which is independent of the human-*Aedes*-human cycle, and which has monkeys as its reservoir. In addition to the fact that the dengue virus has been isolated from monkeys that were born in and remained in the jungle, seroconversion has also been demonstrated in sentinel monkeys. The vector is believed be a mosquito from the group *Aedes niveus*, which is present in large numbers in the jungle. So far, however, it has not been possible to isolate the virus from this or any other jungle species of mosquito. *A. aegypti* is not found in the Malay jungle. The connection, if any, between the dengue that occurs in the jungle and dengue as it is known in rural and urban areas is unknown.

It is generally accepted that dengue originated in southeast Asia and that *A. aegypti* comes from Africa. If this is true, then *A. albopictus*, which is native to Asia, should have a long-standing association with the dengue virus. The data available on both natural and experimental infection with the dengue virus from *A. albopictus* establish beyond any doubt the efficiency of this mosquito as a vector for epidemic dengue and its hemorrhagic complications. In the same way that *A. aegypti* is found in urban areas, *A. albopictus* is found in rural areas. A few years ago *A. albopictus* was responsible for a DEN-2 outbreak in Seychelles. In the southwest Pacific, the *A. scutellaris* complex is the principal, if not the only, vector (Varma, 1989).

Transovarial transmission has been demonstrated in both *A. aegypti* and *A. albopictus*, and the virus has been isolated from *A. aegypti* larvae collected in the field, which would indicate that there is natural transovarial transmission. This mode of transmission would be one of the virus' mechanisms for survival during interepidemic periods.

Diagnosis: Laboratory diagnosis can be obtained by seeding blood from the febrile patient onto mosquito tissue culture media; the presence of the virus is then detected by immunofluorescence using mono- and polyvalent sera from the four serotypes, or by the intrathoracic inoculation of mosquitoes. Serologic tests (hemagglutination inhibition, complement fixation, serum neutralization, indirect immunofluorescence, and ELISA, for both IgM and IgG antibodies) may be useful for verifying seroconversion. It is often difficult to interpret the results if the patient has been previously infected with another dengue serotype or another flavivirus.

Control: The most logical preventive measure would be a program for control and eradication of the *A. aegypti* vector. The countries of the Americas have had long experience in combating the mosquito in connection with the eradication of urban yellow fever. The campaign was conducted at the hemispheric level, since all the countries except Canada had had *A. aegypti* infestations. The hemisphere-wide program was initiated in 1942, and by 1962 the mosquito had been eradicated from 18 countries of the Americas. However, some of the countries that did not reach this objective at the time became the source of reinfestation for those that were *A. aegypti*-free. The problem is much more serious now than in the previous campaign because there has been an enormous increase in the urban population, for which planning and the necessary sanitation infrastructure are lacking. *A. aegypti* has become resistant to DDT, while at the same time organophosphorus insecticides are more expensive, their residual activity is shorter, and the vector is developing resistance to them. An important reason for not undertaking a vertical campaign is that many countries lack the necessary resources. In 1985, the Pan American Health Organization resolved that initiatives should be limited to programs aimed at reducing *A. aegypti* populations to the point that they will no longer pose a public health problem (PAHO, 1991).

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DISEASES CAUSED BY HANTAVIRUSES

ICD-10 A98.5 Hemorrhagic fever with renal syndrome; ICD-10 J12.8 Other viral pneumonia

Hantaviruses cause human disease throughout much of the world. The two types of hantaviral diseases are hemorrhagic fever with renal syndrome (HFRS), an Old World disease, and hantavirus pulmonary syndrome (HPS), a New World disease.

Synonyms: HFRS—Balkan hemorrhagic fever; epidemic hemorrhagic fever; Hantaan virus disease; hemorrhagic nephrosonephritis; Korean hemorrhagic fever; Russian hemorrhagic fever; epidemic nephropathy; nephropathia epidemica; Songo

fever. HPS—hantavirus adult respiratory distress syndrome; hantavirus cardiopulmonary syndrome.

Etiology: Hantaviruses belong to the genus *Hantavirus*, family Bunyaviridae. The virions in this family are spherical, measuring approximately 90–100 nm in diameter, and have a bilayered lipid envelope that contains three symmetrically helicoidal nucleocapsids. The single-strand RNA genome is composed of three segments which have been designated large (L), medium (M), and small (S).

This genus includes several viruses that differ antigenically from the Hantaan prototype (see Table 1). The virion envelope has two glycoproteins that are specific for each virus. Each of the viruses has a different rodent as its main reservoir, and they each have different clinical and pathological effects on man. Table 1 lists the main hantaviruses known to cause human disease and indicates their respective reservoirs, the diseases they produce, and their geographic distribution.

Geographic Distribution: Hantaviruses are widely distributed throughout the world (see Table 1).

Occurrence in Man and Animals: A) ASIA. Between 1950 and 1953, during the Korean War, HFRS was a serious medical and military problem for the United Nations troops, particularly the US soldiers. During this period, 3,000 soldiers were stricken with the disease, with general fatality ranging from 6%–8% to over 33% in some of the small outbreaks (Traub and Wisseman, 1978).

Korea and Russia both report between several hundred and several thousand cases of HFRS each year (Lee, 1996, cited in Schmaljohn and Hjelle, 1997). During 1978–1992, there were 2,706 cases reported in the eastern area of the former USSR, most of them severe cases clinically similar to the disease found in rural areas of the Republic of Korea; fatality ranged from 10% to 15%.

In a study of 300,000 small mammals representing 63 species from all the ecological zones of the region, 45 species proved to be positive for the viral antigen. In addition, 13 species of birds were positive.

China accounts for over half of the 150,000–200,000 hospitalizations due to HFRS that occur each year (Lee, 1996, cited in Schmaljohn and Hjelle, 1997). HFRS occurs in 18 provinces of the country, with an annual incidence ranging from 0.03 to 13 cases per 100,000 population in the different administrative divisions (Cohen, 1982). A total of 90,936 cases were reported in China in 1984, and 103,778 in 1985, with a case fatality rate of approximately 7%.

Although HFRS tends to occur in rural and forested areas, in the city of Osaka, Japan, there were a total of 100 cases and 2 deaths between 1960 and 1972. Outbreaks of the disease contracted from laboratory rats have been reported in laboratory personnel since 1976, with more than 100 cases and 1 death (Sugiyama *et al*., 1984). There have also been isolated cases among the rural population in Japan (Umenai *et al*., 1981). The viral antigen was detected in the large Japanese field mouse (*Apodemus speciosus*) and the Japanese grass vole (*Microtus montebelli*) (Umenai *et al*., 1981). In a group of 2,791 *R. norvegicus* specimens captured in Hokkaido, Japan, an infection rate of 73.4% was observed in the animals 6 months of age and older, compared with a rate of 15.2% in the younger ones. It was also found that the rats had persistent infection with neutralizing antibodies (Arikawa *et al*., 1994).

TABLE 1. Members of the genus *Hantavirus*, family Bunyaviridae, associated with human disease.

Species	Disease	Principal reservoir(s)	Distribution of virus
Hantaan (HTN)	HFRS[a]	*Apodemus agrarius* (striped field mouse)	China, Russia, Korea
Dobrava-Belgrade (DOB)	HFRS	*Apodemus flavicollis* (yellow-neck mouse) *Apodemus agrarius* (striped field mouse)	Balkans, Central & Northeastern Europe
Seoul (SEO)	HFRS	*Rattus norvegicus* (Norway rat)	Worldwide
Puumala (PUU)	HFRS	*Clethrionomys glareolus* (bank vole)	Europe, Russia, Scandinavia
Sin Nombre (SN)	HPS[b]	*Peromyscus maniculatus* (deer mouse)	US, Canada
New York (NY)	HPS	*Peromyscus leucopus* (white-footed mouse) *P. maniculatus*	US
Black Creek Canal (BCC)	HPS	*Sigmodon hispidus* (cotton rat)	US
Bayou (BAY)[c]	HPS	*Oryzomys palustris* (rice rat)	US
Andes (AND)	HPS	*Oligoryzomys longicaudatus*[e] (long-tailed pygmy rice rat)	Argentina, Chile, Uruguay
Araraquara (ARA)	HPS	Unknown	Brazil
Bermejo (BMJ)	HPS	*Oligoryzomys chacoensis*[e]	Bolivia
Choclo	HPS	*Oligoryzomys fulvescens*	Panama
Lechiguanas (LEC)	HPS	*Oligoryzomys flavescens*	Argentina
Laguna Negra (LN)	HPS	*Calomys laucha* (vesper mouse)	Bolivia, Paraguay
Oran (ORN)	HPS	*Oligoryzomys longicaudatus*[e] (long-tailed pygmy rice rat)	Argentina
HU39694	HPS	Unknown	Argentina
To be named[c,d]	HPS	*Calomys laucha* (vesper mouse)	Paraguay

[a] Hemorrhagic fever with renal syndrome (HFRS).
[b] Hantavirus pulmonary syndrome (HPS).
[c] Not yet isolated in cell culture.
[d] Viruses for which incomplete characterization is available, but for which there is clear evidence indicating that they are unique.
[e] Suspected host, but not confirmed.

Source: Adapted from Schmaljohn, C., B. Hjelle. Hantaviruses: A global disease problem. *Emerg Infect Dis 3*(2):95–104, 1997. [Table 1].

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B) EUROPE. During 1978–1992, there were a total of 65,906 cases of HFRS (most of them mild) in the European former USSR, with a fatality rate of between 1% and 2%. Puumala virus, the agent of nephropathia epidemica, is the predominant hantavirus in continental Europe. There was an outbreak of 88 cases of nephropathia epidemica in Germany in 1990. In the Ardennes region along the France-Belgium border, 133 cases in at least 9 foci, were reported in densely forested areas between September 1992 and September 1993. More than 80% of the patients had to be hospitalized (Clement *et al*., 1994).

The main reservoir of Puumala virus is the bank vole *C. glareolus*, which inhabits river banks. In Belgium, 44 out of 210 of these animals were found to have antibodies to the virus, and a number of seroconversions were observed in the course of capturing, releasing, and recapturing them (Verhagen *et al*., 1986). In an endemic area in northern Sweden, a study determined that the annual incidence of the disease was 2.858 men and 0.777 women per 1,000 population. The incidence was highest in the 20–39 age group. Serologic prevalence increased with age, reaching 40% among men and 15% among women in those aged 60 and over (Niklasson *et al*., 1987). Of 276 *C. glareolus* captured in various regions of northern Sweden, 41 were serologically positive, and antigen to the virus was detected in 22 of them. By contrast, in southern Sweden only 1 out of 181 specimens examined had antibodies (Niklasson and Le Duc, 1987).

In the Balkans, the mild illness associated with Puumala virus yields predominance to disease caused by two other viruses: Hantaan virus, the prototype of the genus, and Dobrava-Belgrade, which causes severe hemorrhagic fever with renal syndrome. This latter virus is found in Albania, Austria, Bosnia and Herzegovina, Germany, Slovakia, Slovenia, and several parts of Serbia. A study of *A. flavicollis* in northeastern Slovenia revealed antigen to Dobrava-Belgrade virus in the lung in 20% of the animals examined (Avsic-Zupanc *et al*., 1992; Taller *et al*., 1993). *A. agrarius* has also been identified as a reservoir for Dobrava-Belgrade virus in Central Europe (Sibold *et al*., 2001), and has been found to carry the virus in northeast Europe also (Nemirov *et al.*, 1999).

c) North America. Prior to 1993, the only hantavirus recognized as a human pathogen in North America was the Seoul virus. Studies were conducted in Baltimore, Maryland (USA) and several other ports to determine the prevalence of antibodies to the virus in the rat population. In Baltimore, the infection was found to be widespread, and both the prevalence and the antibody titer increased with the age of the animals (Childs *et al.*, 1985). In research carried out by Childs and several other authors, antibodies were also detected in humans, with highly variable prevalence. However, the disease was not recognized clinically. In Baltimore, to explore the possible correlation between hantavirus infection and kidney disease, a group of 8,080 persons were examined serologically. The overall serologic prevalence of hantavirus was 0.25%; in patients with proteinuria, the rate was 1.46%, while in those undergoing hemodialysis it was 2.76%. Hantavirus infection was consistently associated with the diagnosis of hypertensive renal disease in both groups. The authors also found that 6.5% of patients with terminal hypertensive renal disease were positive for the virus (Glass *et al*., 1993).

In 1993, a new disease appeared in the southwestern US. Unknown to public health authorities, it was initially referred to in the press as "the mystery disease," but came to be called "hantavirus pulmonary syndrome." The etiologic agent turned out to be a new virus belonging to the genus *Hantavirus*, which was given the name Sin Nombre. Its reservoir was found to be the deer mouse (*Peromyscus maniculatus*), from which the virus was isolated (CDC, 1994). Rodents trapped during the investigation into the outbreak revealed an overall hantavirus antibody prevalence rate of 30.4% in *P. maniculatus*. Retrospective studies subsequently found evidence of infection in humans prior to this outbreak (CDC, 2000a).

Since then, the presence of several new hantaviruses causing human disease in the US has been confirmed, including Bayou virus, Black Creek Canal virus, and New York virus (CDC 2000a). As of 15 January 2003, a total of 333 cases of HPS had been reported, of which 38% ended in death. The age of the patients ranged from 10 to 75 years (mean age 37 years); 61% were males and 39% were females. HPS has been reported in 31 states, including most of those west of the Mississippi River as well as in some eastern states (CDC, 2003).

The first case of HPS in Canada was recognized in 1994 in British Columbia; other cases were identified retrospectively, with the earliest dating back to 1989 in Alberta. By 31 December 1999, 32 cases of HPS had been reported in Canada, 12 (38%) of which were fatal (Health Canada, 2000).

d) Central America and the Caribbean. An outbreak of 12 cases of an HPS-like disease occurred in Panama in 1999–2000. The causative agent was found to be a novel hantavirus, Choclo virus (Vincent *et al.*, 2000). By the end of 2001, a total of 29 cases of HPS had been reported in Panama (PAHO, 2002). Rodents carrying hantaviruses similar to Sin Nombre virus have been found in Costa Rica and Mexico, but these viruses have not been associated with disease in humans (CDC, 2000b). Serologic evidence of hantavirus infection in humans and rodents has also been found in Barbados; *R. norvegicus* may be the host (Groen *et al*., 2002).

e) South America. Although HPS was first described in North America, it is now known to be more common in South America, with Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay all reporting cases. Table 2 shows the number of cases reported during 1993–2001 in South America.

TABLE 2. Reported cases of hantavirus pulmonary syndrome (HPS) in South America, 1993–2001.

	Year									
Country	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**Total**
Argentina	—	—	—	—	47	61	76	52	74	310
Bolivia	—	—	—	—	1	1	1	3	5	11
Brazil	3	—	1	3	—	11	26	54	69	167
Chile	—	—	1	3	30	35	26	31	78	204
Paraguay	—	16	15	5	4	5	4	15	27	91
Uruguay	—	—	—	—	2	3	12	6	4	27

Source: Adapted from Pan American Health Organization. [VII. Viral Diseases, 2nd Meeting of the Surveillance Network for Emerging Diseases in the Amazon and Southern Cone Regions (Atlanta, Georgia, 23–24 March 2002)]. Washington, D.C.: PAHO; 2002.

According to one study conducted in Argentina, in 1987, subclinical infections due to a hantavirus were detected in 12.5% of laboratory personnel having contact with rodents. Hantavirus antibodies were found in 3 out of 4 laboratory animal colonies, with a prevalence of 22.5%. In a group of 17 corn mice (*Calomys musculinus*), 4 were serologically positive. In the port of Buenos Aires, 31 rats were examined and all proved to be negative (Weissenbacher *et al*., 1990).

f) Africa. There is little information about hantavirus infections in this continent. In Gabon, antibodies were detected in 1 out of 30 specimens of human sera. In Kabrousse, Senegal, surveys revealed seroprevalence rates of 16.5% in the human population and 31% among rats. Since 1985, in the Central African Republic, patients with renal dysfunction of unknown etiology have been tested serologically for Hantaan virus. Of 305 patients, 4 demonstrated seroconversion and 10 had significant IgG titers. Efforts to isolate the virus were unsuccessful. Some patients had temporary renal insufficiency concomitant with hepatitis of imprecise etiology/pathology and eventually recovered (González *et al*., 1988). A study conducted in forested areas of that country between 1994 and 1997 found the prevalence of IgG antibodies to Hantaan virus to be 2% among the sera samples of 1,762 individuals screened by enzyme immunoassay (Nakounne *et al.*, 2000). In Madagascar, antibodies were found in rats and also in some individuals who had had contact with them. A 1989 study among schoolchildren from four villages in an area of the Nile River delta revealed a 9% (28/315) prevalence of antibodies to Hantaan virus (Corwin *et al.*, 1992).

The Disease in Man: The incubation period is usually two to three weeks. Table 3 provides an overview of the distinguishing characteristics of the human diseases caused by the most important hantaviruses. The following section provides more specific information regarding the characteristics of the diseases caused by the various hantaviruses.

a) Hemorrhagic Fever with Renal Syndrome (HFRS). The most severe forms of HFRS are caused by Hantaan virus and Dobrava-Belgrade virus. Authors Lee and Van der Groen have divided the course of HFRS into five phases: febrile, hypotensive, oliguric, diuretic, and convalescent. The febrile phase lasts three to seven days, during which the patient can have a fever of 40°C or higher, chills, and generalized discomfort and myalgia. There may be extensive edema of the peri-

TABLE 3. Distinguishing clinical characteristics for hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS).

Disease	Pathogens	Distinguishing characteristics[a]
HFRS (moderate-severe) Death rate 1%–15%	HTN, SEO, DOB	hemorrhage +++ azotemia/ proteinuria +++/++++ pulmonary capillary leak +/++ myositis +/+++ conjunctival injection ++/++++ eye pain/myopia ++/++++
HFRS (mild) Death rate <1%	PUU	hemorrhage + azotemia/ proteinuria +/++++ pulmonary capillary leak –/+ myositis + conjunctival injection + eye pain/myopia ++/++++
HPS (prototype) Death rate >40%	SN, NY	hemorrhage + azotemia/ proteinuria + pulmonary capillary leak ++++ myositis – conjunctival injection –/+ eye pain/myopia –
HPS (renal variant) Death rate >40%	BAY, BCC, AND	hemorrhage + azotemia/ proteinuria ++/+++ pulmonary capillary leak +++/++++ myositis ++/++++ conjunctival injection –/++ eye pain/myopia –

[a] Minimum/maximum occurrence of the characteristic: – rarely reported; + infrequent or mild manifestation; ++, +++, ++++ more frequent and severe manifestation.

Source: Schmaljohn, C., B. Hjelle. Hantaviruses: A global disease problem. *Emerg Infect Dis* 3(2):95–104, 1997.

toneum due to increased permeability of the capillaries, which accounts for the severe abdominal and lumbar pain. Characteristic symptoms are flushing of the face, neck, and thorax, and congestion of the conjunctiva, palate, and pharynx. At the end of this phase, petechiae are noted on different parts of the body and there is pronounced proteinuria. The hypotensive phase comes on abruptly and may last from a few hours up to two days. Soon the classic signs of shock may be observed. One-third of the deaths are caused by irreversible shock. Capillary hemorrhage is common. Oliguria may then develop, at which point the patient's blood urea and creatinine levels become elevated. The oliguric phase lasts three to seven days, and many patients become hypertensive; nausea, vomiting, and hemorrhaging are common. Approximately 50% of the deaths occur during this phase. Recovery begins with the onset of diuresis. Convalescence takes two to three months. The other forms (mild and moderate) have more varied and less pronounced symptomatology, and lower case fatality rates.

HFRS caused by Seoul virus is usually milder than that caused by Hantaan virus, but some cases can be severe. The clinical characteristics are high fever, fatigue, anorexia, vomiting, dorsalgia, myalgia, abdominal pain, petechiae on the soft palate, hepatomegaly, proteinuria, thrombocytopenia, and lymphocytosis. Mild renal and hepatic dysfunction are also observed.

In HFRS caused by Puumala virus (nephropathia epidemica) renal dysfunction is predominant and hemorrhaging is much less frequent; 90% of the cases are mild. The main symptoms are sudden onset, cephalalgia, fever, elevated serum creatinine, proteinuria, and/or hematuria. Clinical differences have been observed in different geographic areas and countries.

The treatment of patients with hemorrhagic fever with renal syndrome is supportive. During the febrile phase, the patient must remain in bed; sedation, the administration of analgesics, and the maintenance of fluid balance are indicated. Hypotension, when it occurs, should be corrected. In the oliguric phase, fluids should be restricted to the volume necessary to compensate for losses, and hypocalemia, when it occurs, should be treated. In severe cases, hemodialysis may be required. In the diuretic phase, the fluid and electrolyte balances should be monitored and treated if necessary (WHO, 1985).

B) HANTAVIRUS PULMONARY SYNDROME (HPS). HPS, usually the most severe disease of the diseases due to hantaviruses, particularly affects the lungs. In the prodromal febrile phase, the symptoms are chills, myalgia, headache, and abdominal pain; in the pulmonary phase that follows there is coughing and rapid development of respiratory insufficiency. Death comes from bilateral pulmonary (noncardiogenic) edema caused by the increased permeability of alveolar capillaries. In some cases there is marked hypotension. In several cases described in South America, infection with Andes virus was asymptomatic or caused only mild disease (C. Johnson, unpublished data, cited in Toro *et al.*, 1998).

For hantavirus pulmonary syndrome, early pulmonary ventilation is recommended, along with careful monitoring of fluid and electrolyte balance and arterial pressure. Experiments with intravenous administration of the antiviral drug ribavirin have met with apparent success, especially when it is given early in the course of the disease, but its usefulness has since been questioned.

The Disease in Animals: Rodents, which are the natural reservoirs of the virus, do not have a symptomatic infection. However, studies have shown that many rats inoculated within 24 hours of birth died about 30 days later; those that survived continued to maintain the virus in persistent form for up to 25 weeks postinoculation and it could be isolated from almost all the organs. On the other hand, when 6-week-old rats were inoculated with the virus, even though it could be isolated from several organs, its concentration gradually decreased. In the rats infected a few hours after birth, IgM antibodies predominated; however, even a high, long-lasting titer failed to keep the animals from becoming infected (Yamanouchi *et al*., 1984; Tanishita *et al*., 1986). Another study found that the viremia in rodents lasts 7 to 10 days, but the agent persists in tissue for at least 100 days (the length of observation time in the experimental infection of *A. agrarius coreae*) without producing clinical symptoms (Lee *et al.*, 1981).

Source of Infection and Mode of Transmission: The disease is manifested in various ecological environments, such as cultivated fields, forests, homes, and gar-

dens. Man contracts the infection upon entering the habitat of the rodents or when the rodents invade the dwellings, gardens, and food stores of humans. Some epidemics start in the autumn and winter months, when rodents invade people's homes and gardens. The disease predominantly affects adult males when the infection is contracted in forests or cultivated fields, but in urban epidemics the incidence by sex and age does not show any remarkable pattern.

The reservoirs for maintenance of the virus in nature are rodents. Each of the hantaviruses has its own particular rodent reservoir (see Table 2).

The duration of viremia in infected rodents, and the persistence of the virus in tissue, would indicate that these animals can contaminate the environment with their excretions and secretions for a long time (Lee *et al*., 1981). Detection of the virus in the brown fat of *C. glareolus* and other rodents suggests that this may be an important overwintering site for the virus (Gavrilovskaya *et al*., 1983).

Humans contract the infection through contact with the rodents and their excreta, primarily via the aerosol route, though rodent bites may also result in infection (Dournon *et al*., cited in Schmaljohn and Hjelle, 1997). Cases of person-to-person transmission of HPS have occurred in Argentina and Chile, though this route of transmission is considered rare and has only been documented with Andes virus (Padula *et al.*, 1998; Toro *et al.*, 1998; Wells *et al*., 1997).

It is suspected that epidemics are started in cities primarily by the contamination of food with the excreta of rodents that invade homes and larders. The most likely portal of entry of the etiologic agent would be the respiratory tract, followed by the digestive tract.

Diagnosis: Serologic diagnosis of hantavirus infection is accomplished by the demonstration of seroconversion in the indirect immunofluorescence or neutralization tests. The immunofluorescence test detects group-specific antibodies for hantaviruses. To determine the virus that caused the disease, it is necessary to use the plaque-reduction neutralization test with the different viruses of the genus. A differential diagnosis can also be obtained using the Western blot test. Antibodies appear during the first week of the disease and persist for many years. The enzyme-linked immunosorbent assay (ELISA) can distinguish IgM and IgG antibodies. In autopsy specimens, immunohistochemical analysis can be used to detect viral antigen. Very good results have been obtained with autopsy material using RNA sequence amplification in the polymerase chain reaction technique. In formalin-fixed specimens of lung and kidney tissue, it was possible to show the hantavirus that caused the disease through monoclonal antibody histochemical analysis.

The virus can be isolated in Vero E6 cells with blood and serum taken during the first phase of the disease. Hantaviruses are difficult to isolate. It is often necessary to make several blind passages before being able to detect the antigen. The virus is not cytopathic.

Control: Rodent control measures in towns and villages have reduced the severity of outbreaks. It is important to eliminate the food sources and refuges for rodents in houses and their surroundings and to use traps and rodenticides. In areas where plague is endemic, insecticides should be used first. Proper precautions should be taken when cleaning rodent-infested areas with large amounts of disinfectant. Dead mice should not be touched with bare hands; plastic or rubber gloves should be used.

Occupational groups frequently exposed to rodents should use protective face masks and gloves when handling rodents or traps containing rodents, and should disinfect the gloves prior to removing them (Mills *et al*., 2002).

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EASTERN EQUINE ENCEPHALITIS

ICD-10 A83.2

Synonyms: Eastern equine encephalomyelitis, eastern encephalitis.

Etiology: Single-strand RNA genome virus belonging to the genus *Alphavirus* (formerly arbovirus group A), family Togaviridae. The virion is spherical, measuring 50 to 60 nm in diameter. It belongs to the complex of mosquito-borne viruses. In nature, the virus has antigenic variants. The modified hemagglutination-inhibition test has established that the strains found in North America, Jamaica, and the Dominican Republic are different from those found in Panama, Trinidad and Tobago, and South America. Analysis of the RNA sequences and mapping of the oligonucleotides has made it possible to divide the virus found outside North America (known as the South American virus) into two groups, one corresponding to isolations from the Amazon basin and Peru, and the other covering the strains from Argentina, Ecuador, Guyana, Panama, Trinidad, and Venezuela (Weaver *et al.*, 1994). According to these authors, the split between the North American and South American antigenic varieties occurred about 1,000 years ago. A subtype of the North American variety of the eastern equine encephalitis (EEE) virus was isolated from the cerebrospinal fluid of a 6-year-old boy with meningitis. This is considered the first appearance of a subtype, since all the other EEE viruses isolated in the United States have been identical (Calisher *et al.*, 1990).

Geographic Distribution: The virus has been isolated in Argentina, Brazil, Canada (eastern), Colombia, Cuba, Dominican Republic, Guatemala, Guyana, Haiti, Jamaica, Mexico, Panama, Peru, Trinidad and Tobago, US (Atlantic and Gulf coasts), and Venezuela. The equine encephalitides (eastern, western, and Venezuelan) occur exclusively in the Americas. Reported isolations of the EEE virus in European and Asian countries have not been confirmed.

The South American strain of the EEE virus has also been isolated from migratory birds in the southern United States, but there is no evidence that infection cycles were started in local bird and vector populations or that enzootic foci were established (Calisher *et al.*, 1981).

Occurrence in Man: Eastern equine encephalitis (EEE) is less frequent than western equine (WEE) or Saint Louis equine encephalitis, but it is more serious and causes high mortality.

In the US, there were only 136 clinical cases between 1955 and 1978. In the period 1977–1997, there were an estimated 106 confirmed and probable cases in the US (CDC, 2002). The largest epidemic outbreak on record occurred in Massachusetts in 1938, when 38 cases were reported. Thanks to surveillance measures and campaigns to control the mosquito vectors, the incidence of human disease has declined. Fewer than five cases a year are reported in the US. Case fatality rates as high as 30% in past epidemic years are indicative of the severity of this infection in humans (CDC, 1990). In 1991, five cases were reported in older persons living in Florida (USA); two of these patients died, two lapsed into a coma, and one recovered partially. Heavy spring rains in north Florida had resulted in exceptionally large populations of *Culiseta melanura*, the main vector of the wild enzootic cycle. In

1992, Florida and Massachusetts each reported one human case, while there were 88 equine cases (54 of them in Florida).

While in the US, the incidence of human cases is low, in Central and South America it is even lower (or else the cases go undetected). This difference is attributed to the distinct habits of the vectors that transmit the virus outside the natural foci. In North America, *Aedes sollicitans* is anthropophilic and active in daylight, whereas *Culex taeniopus*, which has been indicated as a vector in Brazil, Panama, and Trinidad and Tobago, is for the most part a jungle mosquito; it is active at twilight and stays outdoors, so it is only an enzootic vector. During the 1973 epizootic in Panama, which affected 100 horses (40 of which died), no reactors were found in 1,700 human sera samples from the areas in which the virus had been active (Dietz *et al.*, 1980).

The epidemic outbreaks in man occur in late summer, at the same time as the epizootics in equines, which usually begin one or two weeks before the appearance of human cases. The age groups most affected are persons under 15 and over 50 years of age. Subclinical infection is less frequent than with western equine or St. Louis encephalitis. In the Dominican Republic, two or three months after an epidemic in 1948–1949, antibodies were detected in 32 of 827 persons examined. In New Jersey (USA), after an outbreak in 1959, a survey of 1,600 residents revealed that 69 of them had antibodies. During this latter outbreak, it was estimated that for each recognized case of encephalitis there were 16 to 32 clinically inapparent infections.

Occurrence in Animals: EEE manifests itself clinically in horses, and also in pheasants, turkeys, and other birds. The true incidence of EEE will only be known when a surveillance system is instituted and an effort is made to establish specific diagnoses for all encephalitis cases among horses. During the epidemiologic surveillance initiated in the US in 1971 as a result of the large epizootic of Venezuelan equine encephalitis (VEE), the EEE virus was isolated from 67 of 1,551 sick and healthy horses living on the same properties. Even though 1971 had not been considered an epizootic year for the EEE virus, these results showed that the disease occurs every year with similar frequency (Maness and Calisher, 1981). In several areas there have been high-mortality equine epizootics, both with and without outbreaks in the human population. According to the US Department of Agriculture, between 1956 and 1970, there were a total of 26,468 cases of encephalitis, but specific diagnoses were only available for 2,620 of them; of this figure, 605 were attributed to the EEE virus and 2,015 to western equine encephalitis. The most serious epizootic occurred in Louisiana (USA) in 1947, when an estimated 11,927 horses died (Dietz *et al.*, 1980). This epizootic was unusually large. Also in the US, outbreaks have occurred fairly often at farms where pheasants, ducks, and turkeys are raised.

Cuba recorded a series of extensive epizootics and smaller outbreaks in horses in 1914–1915 and in 1972. Mortality began to decline in 1971 and dropped to zero when vaccination coverage reached 86.7%. By 1973, with immunization coverage at 94%, the population of susceptible horses was practically eliminated. A 1973 outbreak in Panama coincided with a particularly high density of *Aedes taeniopus* mosquitoes. Within a three-week period (June-July), 40 equine deaths were reported. In an outbreak in the Dominican Republic in 1978, an estimated 3,600 horses were infected, and the case fatality rate was on the order of 34 per 1,000. There were no human cases (Calisher *et al.*, 1981). In Argentina, there was an EEE outbreak in 1981 which was localized in four districts of the province of Santiago del Estero. In

that area, the incidence of EEE was estimated at 17%, with a case fatality rate of 61% and a ratio of infection to disease of 2.9:1. There were no human cases, and neither the vectors nor the reservoirs were identified (Sabattini *et al.*, 1991). EEE has been recognized in Brazil for many years, but the infectious agent was isolated only recently, obtained from the brains of two animals in regions where mortality in horses was high (Kotait *et al.*, 1992). In one of the regions (Hapetininga) where the brain samples came from, an epidemiological study had been under way for about 20 years, and 16 strains of EEE virus were isolated from sentinel animals, mosquitoes, and wild birds (de Souza Lopes and de Abreu Sacchetta, 1974). The virus has been isolated from mosquitoes and sentinel animals in various states of Brazil. In Colombia, EEE was diagnosed serologically in a horse from Puerto Boyacá in 1991.

The Disease in Man: EEE is characterized by high mortality (about 65% of clinical cases, reduced in recent years to 30%) and a high frequency of permanent sequelae in patients who survive. The incubation period is from 5 to 15 days. Onset is sudden, with fever, cephalalgia, conjunctivitis, vomiting, and lethargy, and the disease progresses rapidly to delirium and coma. The neurological signs consist primarily of stiffness of the neck, convulsions, spasticity in the muscles of the extremities, and altered reflexes. A biphasic course is common in children, beginning with fever, vomiting, and headache for one or two days, followed by apparent recovery, and then finally taking the form of fulminant encephalitis. In children under 5 years of age who survive the disease, neurologic sequelae such as mental retardation, convulsions, and paralysis are frequently observed. The cell count in cerebrospinal fluid can show a predominance of lymphocytes, ranging from 600 to 2,000/mm^3. The number of polymorphonuclear cells may be elevated at the beginning of the disease (Monath, 1991).

There is no specific treatment. As with the other encephalitides, support measures, alleviation of symptoms, and intensive nursing care are recommended (Monath, 1991).

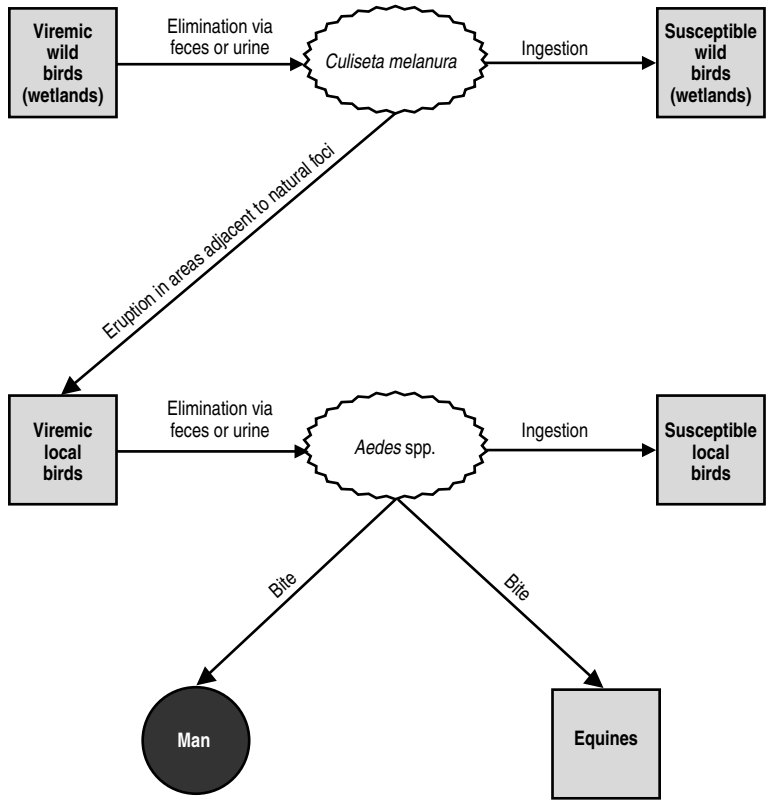
The Disease in Animals: The clinical symptomatology in equines is similar to that of western equine encephalitis (see chapter on western equine encephalitis), but the course of EEE is shorter and more likely to be fatal. The disease follows a biphasic febrile course. Fever appears 18 to 24 hours after the animal becomes infected and lasts for about one day. A second febrile period begins four to six days after initial infection and lasts from one to four days. It is during the second febrile period that the nervous symptoms appear. The animal suffers profound depression, stands with its legs splayed, keeps its head close to the ground, and has flaccid lips. Diarrhea or constipation and significant weight loss are also common. Some animals become excitable, walk around in circles, and stumble over obstacles. Eventually they fall and cannot get up. In fatal cases, death occurs 5 to 10 days after infection (Walton, 1981). Mortality in horses with signs of encephalitis is approximately 75% to 90%, and brain damage is common in those animals that survive.

In the eastern US, there have been numerous outbreaks of EEE in pheasants, with case fatality rates of 5% to 75%. The symptomatology in these birds consists of fever, depression, profuse diarrhea, voice changes, ataxia, tremors, partial or complete paralysis of one or both legs, or involuntary circular movements. Some pheasants suffer paralytic effects for several weeks. Mortality from EEE has also been seen in other domestic fowl, such as ducks. In North Carolina (USA), the disease

was reported in turkeys. The most important clinical sign was a 40% reduction in egg production. The eggs of the affected birds were small and white, and some of them had soft shells (Wages *et al.*, 1993). In Louisiana, an outbreak of EEE was diagnosed in a flock of emus (*Dromaius novaehollandiae*). The attack rate was 76% and the case fatality rate was 87%. Death was preceded by depression, hemorrhagic diarrhea, and blood-tinged vomiting. This outbreak coincided with one among horses during a period of unseasonably heavy rainfall when the mosquito vectors were abundant (Tully *et al.*, 1992). The high virulence of the EEE virus in these species contrasts with the clinically inapparent infection or benign course of the disease in native wild birds.

Source of Infection and Mode of Transmission (Figure 13): The basic infection cycle takes place between wild birds and mosquitoes. The arthropod vectors feed on the blood of viremic birds, and the virus reproduces in their middle intestine (extrinsic incubation). When the mosquito then bites a susceptible bird, it transmits

Figure 13. Eastern equine encephalitis. Transmission cycle in the US.



the infection and the virus starts to reproduce in this new host (intrinsic incubation), eventually invading its circulatory system (viremia). Ambient temperature affects reproduction of the virus in the mosquito vectors: low temperatures inhibit replication of the virus, whereas high temperatures activate it. The EEE virus has been isolated from the blood of a large number of wild bird species, both resident and migratory. The infection rate is low in wild birds during interepidemic years, but in epidemic periods it is very high.

In the eastern US, the virus circulates continuously between birds (especially passeriforms) and mosquitoes in many natural foci, typically in freshwater swamps. In this region the vector is *Culiseta melanura*, an ornithophilous mosquito. It has been observed that this vector sometimes feeds on horses, but rarely on humans. A similar role is attributed to *C. morsitans* (Morris and Zimmerman, 1981). When the virus breaks out into areas adjacent to its natural endemic foci, a new cycle starts between the local birds and mosquitoes. On the US Atlantic coast, *Aedes sollicitans*, a mosquito commonly found in brackish marshes that feeds on the blood of birds, equines, and man, is believed to be the main vector in outbreaks among both humans and equines. A study of mosquito food sources in southeastern Massachusetts (USA) suggests that *Coquilletidia perturbans*, *Aedes canadensis*, and *A. vexans* could be the vectors of the virus for equines and man (Nasci and Edman, 1981). In Florida, 14 strains of EEE virus were isolated in 1991 from 9,350 *A. albopictus* mosquitoes from 96 pools. It was also possible to identify the origin of the blood that they had fed on: 31% came from cattle, 19% from humans, 2% from passeriform birds, and the rest from other animals (CDC, 1992).

The initial infection in pheasants follows the same pattern as in humans or equines, but later the disease can spread horizontally from one bird to another, without the intervention of vectors, through pecking and cannibalism.

In the tropical countries of the Americas, the main vectors appear to be *Culex nigripalpus*, *C. taeniopus*, *Aedes taeniorhynchus*, and probably some other mosquito species. In a study conducted in the Venezuelan Guajira during an interepizootic period, multiple virus isolations were obtained from the mosquitoes *C. panacossa* and *C. dunni* (Walder *et al.*, 1984). This finding would seem to indicate that such vectors play an important role in maintenance of the virus in enzootic foci. These mosquitoes feed on marsupials and rodents, and they breed in swamps and jungles. In the Brazilian northeast, in the area around Belém, it has been demonstrated that EEE is enzootic in the rainforest, but the basic cycle of the virus is unclear.

Since the infection produces a low-titer viremia in humans and equines, it is thought that these species do not play a role in maintaining the agent in nature. The EEE virus was once isolated from the larvae of *C. melanura*, which suggested the possibility of transovarial transmission, but subsequent attempts at isolation were unsuccessful. On the other hand, the virus has been isolated from rodents in winter, indicating that these animals might play a role in maintaining the agent during harsh weather. In the Venezuelan Guajira, hemagglutination-inhibiting antibodies were found in 7.4% of 54 opossums (*Didelphis marsupialis*), with titers of 1:20 or higher, which suggests that these animals might serve as natural hosts for the EEE virus (Walder *et al.*, 1984).

It is still unclear whether the outbreaks in the Caribbean are due to autochthonous enzootic foci or to introduction of the virus by migratory birds from the US. Autumn conditions in the Caribbean, when birds migrate south from the US, would favor cir-

culation of the virus. However, outbreaks in Cuba, the Dominican Republic, and Jamaica caused by the North American strain of the virus, have preceded or coincided with EEE outbreaks in the southeastern US (Calisher *et al.*, 1981).

Role of Animals in the Epidemiology of the Disease: Humans, equines, and pheasants are accidental hosts. Wild birds are the reservoirs, and the infection is propagated among them by mosquitoes.

Diagnosis: Specific diagnosis can be made by isolating the virus from the brain of humans or equines that have died from the disease. In human patients, serologic diagnosis is based on rising titers in serial blood samples. Since inapparent infections are not very common, serologic diagnosis in equines can be based on a single blood sample, especially when there is an outbreak of the disease in the area. The serologic tests available for diagnosis are hemagglutination inhibition, complement fixation, indirect immunofluorescence, serum neutralization, and enzyme-linked immunosorbent assay (ELISA). Because of the rapid course of the disease, blood samples should be taken at short intervals.

Control: In man, the only practical measure for individual prophylaxis is the prevention of mosquito bites through the use of protective clothing and repellents, coupled with the installation of mosquito netting and screens in dwellings. Control of specific vectors in the region may help to reduce transmission. In endemic areas it is necessary to maintain active surveillance using sentinel birds such as chickens. Also, when there is a risk of human cases and epizootics in equines, the viral infection rate should be measured in the vectors and steps should be taken to reduce their population.

For the protection of equines, there are monovalent and bivalent inactivated vaccines available for the eastern and the western virus, prepared in chick embryo and in cell culture. Also, a trivalent inactivated vaccine has been developed for the EEE, WEE, and VEE viruses. In regions of the Americas where mosquito activity is practically constant, colts should be vaccinated at 3, 4, and 6 months and annually thereafter. In temperate or cold regions, the vaccine should be given one month before the mosquito season. In a study conducted during an epizootic outbreak in Panama, questions were raised about the efficacy and duration of protection conferred by the North American EEE strain against the South American strain (Dietz *et al.*, 1980). This deserves to be studied in greater detail.

It should be kept in mind that although the vaccination protects equines against the disease, it does not alter the risk of exposure for humans.

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EBOLA DISEASE

ICD-10 A98.4 Ebola virus disease

Synonyms: Ebola hemorrhagic fever, African hemorrhagic fever.

Etiology: Ebola (EBO) virus, an enveloped RNA genome virus, belongs to the genus *Filovirus*, family Filoviridae. It is morphologically similar to the other member of that genus, Marburg (MBG) virus, but is antigenically different. The virions of the Filoviridae family are threadlike and very long, measuring 80 nm in diameter and 800 to 1,000 nm in length. The capsomer-covered nucleocapsid is helicoid in shape. Strains of Ebola virus from the Democratic Republic of Congo (formerly Zaire), Gabon, Ivory Coast, and Sudan are associated with illness in both humans and animals, though some human carriers of the virus may be asymptomatic. The Reston strain, reported in Italy, the Philippines, and the United States, causes fatal hemorrhagic disease in animals, but has been asymptomatic in the few individuals that have been infected (CDC, 2000).

Geographic Distribution and Occurrence: The EBO virus has only been isolated from human cases that have occurred in Africa. The disease first appeared in southwestern Sudan in June 1976. The epidemic, which lasted until November of that year, affected 284 persons and had a case fatality rate of 53%. At the end of July 1976, a second epidemic erupted in northwestern Democratic Republic of the Congo and ended in November of that year. The latter outbreak, which occurred in 55 of the 250 villages in the epidemic area, affected 318 persons and had a case fatality rate of 88%. The attack rate was 10 to 14 per 1,000 inhabitants. Most cases occurred in adults and very few were seen in children under 10 years old; 56% of the cases were in women (Johnson, 1982).

A single case occurred in the Democratic Republic of the Congo in 1977. A second outbreak occurred in Sudan during August and September 1979, with 33 confirmed clinical cases and 22 deaths.

It was originally believed that the 1976 epidemics in the Democratic Republic of the Congo and Sudan were epidemiologically related. However, the distance of 850 km between the two areas, coupled with the lack of communication between them, indicated that the epidemics were independent in origin. This conclusion was confirmed when laboratory studies demonstrated that two different biotypes of the virus were involved (see the section on etiology).

The 1977 case of hemorrhagic Ebola in the Democratic Republic of the Congo occurred 325 km west of the area of the 1976 epidemic; its location suggests that the virus is endemic, and possibly enzootic, in the Congo River basin (Heymann *et al.*, 1980). In 1980, a case was serologically confirmed in Kenya.

In addition to those mentioned above, several other outbreaks of Ebola virus disease among humans occurred in Africa: 34 cases in Sudan in 1979, 49 cases in Gabon in 1994, 315 cases in the Republic of the Congo in 1995, 31 and 60 cases in two outbreaks in Gabon in 1996, and 425 cases in Uganda in 2000–2001. Of these, the lowest mortality rate was seen in the Uganda outbreak (53%) and the highest in the 1995 outbreak in the Republic of the Congo (81%). Yet another outbreak occurred in Gabon and the Republic of the Congo in 2001–2002. One case was reported in Ivory Coast in 1994 in a scientist who fell ill after conducting an autopsy on a chimpanzee. Two cases were reported from South Africa in 1996, the first in a medical professional who had treated Ebola patients in Gabon, and the second, in the nurse who cared for him (CDC, 2002).

A number of serologic surveys have been conducted using the indirect immunofluorescence test in an effort to determine the prevalence of the infection in the general population. In Sudan, 19% of the patient contacts had antibodies to the EBO virus, and in the Democratic Republic of the Congo, the seroprevalence rate was 1% outside the epidemic area (WHO, 1978a). Surveys in several countries of central Africa yielded an average reactor rate of 8% (Bouree and Bergmannn, 1983). The specificity of the indirect immunofluorescence test for titers of 1:4 to 1:64 was questioned when "antibody" levels in this range were found in 4 of 200 sera from Kuna Indians on San Blas Island, Panama, who were unlikely to have been infected by the EBO virus. Several surveys in Africa have shown very high titers (between 1:512 and 1:1,024) in the general population (Ivanoff *et al.*, 1982; Knobloch *et al.*, 1982). These results are indicative of either recent infections or of virus activity outside areas in which epidemics have occurred; they also suggest that the virus is endemic or enzootic in several African countries.

In a survey conducted in the Central African Republic to determine the seroprevalence of various viruses, including the Ebola and Marburg filoviruses, the immunofluorescence test was used to examine 4,295 samples from five different ecological areas. The prevalence of filoviruses was 24.4% in the study population (21.3% positive for EBO virus and 3.2% for MBG virus), and there were positive reactors to both viruses in all the areas. Since the infection does not always produce clinical symptoms, it may be that in equatorial Africa there are nonpathogenic filovirus strains that cross-react with pathogenic ones (Johnson *et al.*, 1993a). The same authors studied different ethnic groups living in the tropical rainforest and found a large difference in seroprevalence between Aka Pygmies (37.5%), who are hunter-gatherers, and two other ethnic groups (13.2%) who engage in subsistence agriculture (Johnson *et al.*, 1993b). An epidemiologic and serologic study conducted in five gold-panning villages in northeastern Gabon found a prevalence of 10.2% among individuals tested (Bertherat *et al*., 1999).

The Disease in Man: Several instances of human infection without manifestation of the disease or its symptoms have been documented (WHO, 2002; Leroy *et al*., 2000b). When the disease does manifest, the clinical symptoms range from a mild illness to a swift and fatal disease. The incubation period lasts about a week and onset is sudden, with fever and headache. A large proportion of patients experience thoracic pain, diarrhea, vomiting, dry and sore throat, and an erythematous maculopapular eruption on the trunk, which rapidly spreads to other parts of the body and tends to become confluent. The erythema may not be noticed on dark-skinned individuals. Desquamation ensues after three or four days (WHO, 1985). The high fever continues for a week, after which it gradually subsides. Data from past cases show that more than 90% of the patients who died, as well as 48% of those who recovered, had hemorrhagic symptoms. Among the latter, melena was the most common, and hematemesis, epistaxis, and bleeding in other organs and tissues were also frequently observed. Convalescence was slow and in some cases took up to two months (WHO, 1978b). Four or five days after onset of the disease, the patients develop extreme lethargy and changes in their mental state; gravely ill patients exhibit restlessness and confusion, and then lapse into a deep coma before they die (WHO, 1985). The hemorrhagic manifestations are less severe at the end of the outbreak than they are at the beginning (Sureau, 1989). Pregnant women usually abort their fetus and have copious hemorrhaging.

There are no known cases of human disease caused by the Reston strain of the virus.

The Disease in Animals: When inoculated experimentally in various monkey species, the EBO virus causes severe disease, characterized at first by fever and depression, followed by diarrhea, petechiae, languor, shock, and finally death (Fenner *et al.*, 1993). In the cynomolgus macaques imported into Italy and the US from the Philippines, the infection caused by the Reston strain of the virus produced disease and a high case fatality rate. Antibodies have also been found in other Old World primate species (Peters *et al.*, 1992).

Source of Infection and Mode of Transmission: The reservoir of the virus in nature is unknown. In studies conducted in Sudan and the Democratic Republic of the Congo, the virus could not be isolated and antibodies could not be detected in more than 1,000 captured animals, most of them mammals.

In 1980, a high titer for the virus was detected in a domestic rabbit from the same region of the Democratic Republic of the Congo where the isolated human case of the disease had occurred in 1977 (Johnson *et al.*, 1981). Subsequently, 3 of a group of 184 baboons in Kenya were found to have titers ranging from 1:64 to 1:128 with the indirect immunofluorescence test. Even though the experimental infection is always fatal in nonhuman primates, the investigators considered the possibility that in some circumstances there might be a subclinical form of the infection (Johnson, B.K. *et al.*, 1982). However, none of the findings suggest that these animals are the principal hosts for maintaining the virus in nature. Epidemiologic studies in the Democratic Republic of the Congo and Sudan point to the conclusion that most humans who developed the disease acquired the infection through close contact while providing care for a prior acute case, and that in several instances there was an amplification of cases in the hospital because of the failure to sterilize needles and syringes and other improper practices. Several of the outbreaks originated from one or a few isolated cases for which the source of infection is unknown and then successive cases

occurred as a result of person-to-person transmission. In Nzara, Sudan, the site of the first cases in the 1976 epidemic, 14 of the 67 patients had not had any contact with a primary case. Of these 14 patients, 9 had worked at a cotton mill, and it is possible that they introduced the infection to the human population in the area (WHO, 1978b).

Person-to-person transmission of the virus occurs by direct contact with blood, secretions, organs, or semen (up to seven weeks after clinical recovery) of infected individuals. Humans contract the virus from nonhuman primates by handling ill or dead infected animals (WHO, 2000). Antibodies to the Ebola-Reston virus were detected in eight individuals in the US who had been taking care of monkeys imported from the Philippines, but none of them exhibited any signs of the disease (CDC, 2000).

Diagnosis: The virus can be isolated from the blood of acute patients, but this procedure is extremely hazardous and should be performed only in laboratories that have maximum-security installations (biosafety level 4) in order to ensure that laboratory personnel and the general population are not exposed to infection.

Several techniques have been described for the rapid identification of EBO and related filoviruses. One involves the use of indirect immunoelectron microscopy on fluid specimens (sera, fluid from tissue cultures) with guinea pig polyclonal homologous antiserum (Geisbert *et al.*, 1991). Enzyme-linked immunosorbent assay (ELISA) and indirect immunoflourescence can also be used to detect virus-specific IgG antibody (Saijo *et al*., 2001a; Ksiazek *et al*., 1999; Saijo *et al*., 2001b; Ikegami *et al*., 2002). A reverse-transcription polymerase chain reaction (RT-PCR) method has also been shown to detect EBO virus during the acute phase of the disease (Drosten *et al.*, 2002; Leroy *et al*., 2000a).

Control: Prevention measures should be directed above all toward avoiding interhuman transmission. It is necessary to isolate the patient and take immediate steps to institute strict containment nursing practices. In addition, all samples taken for diagnostic purposes, excreta, and any other materials that may have been in contact with the patient should be regarded as infectious and handled or decontaminated using the appropriate procedures. To prevent the spread of infection to their partners, males should not engage in sexual intercourse until three months after clinical recovery, or until semen is shown to be free of the virus (CDC, 2000).

The number of health workers assigned to the patient's care should be restricted, and all such individuals should be duly trained and provided with complete protective gear, including gowns, gloves, masks, goggles, caps, and overshoes (Simpson, 1978). Deceased victims should be promptly cremated or buried, preferably in a plastic bag, by persons wearing protective clothing.

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ENCEPHALOMYOCARDITIS

ICD-10 B33.8 Other specified viral diseases

Synonyms: Columbia-SK disease, meningoencephalomyelitis, MM virus infection, three-day fever.

Etiology: Encephalomyocarditis (EMC) virus, a single-strand RNA genome virus of the genus *Cardiovirus*, family Picornaviridae. The viruses in the Picornaviridae family measure 25 to 30 nm in diameter and have an icosahedrally symmetric capsid; there is no envelope. Other members of this family include the genera *Enterovirus*, *Rhinovirus*, *Aphthovirus* (agents of foot-and-mouth disease), and *Hepatovirus* (hepatitis A virus).

Geographic Distribution: The virus is ubiquitous and has been isolated in Australia, Belgium, Brazil, Canada, Colombia, Cuba, former Czechoslovakia, Germany, Great Britain, Greece, India, Italy, the Netherlands, New Zealand, Panama, South Africa, Suriname, Uganda, and the United States.

Occurrence in Man: Rare. In addition to sporadic cases, in 1945–1946, there was an epidemic outbreak of "three-day fever" among US troops stationed in the Philippines. Diagnosis was based on the fact that 38.6% of 44 sera samples taken from convalescing soldiers were positive for EMC virus in the serum neutralization test.

The virus has been isolated from children in Germany and the Netherlands and from a laboratory worker in Uganda.

In surveys based on neutralization studies of human sera from various regions of the world, antibodies for the EMC virus were found at rates ranging from 1% to 33.9% in children and from 3.2% to 50.6% in adults. These findings indicate that infection with this virus is common and that most cases of infection are asympto-

matic or go unrecognized (Tesh, 1978). In the US, seroprevalence surveys in human populations have given results ranging between 3.5% (33/947) and 19.8% (26/131) (Zimmerman *et al.*, 1991).

Occurrence in Animals: EMC virus has numerous animal hosts and has been isolated from various species of rodents and monkeys, as well as mongooses, raccoons, horses, cattle, swine, elephants, and several species of wild birds.

In Australia, Cuba, New Zealand, Panama, and the US (Florida), epizootic outbreaks have occurred in swine and produced high fatality rates. In Cuba, the disease in swine was reported in nine provinces during the period 1975–1981, with high rates of morbidity and fatality (Ramos *et al.*, 1983).

In the state of Iowa, US, the serum neutralization test was used to survey 2,614 pigs from 104 herds, and it was found that 89.4% of the herds had one or more reactors. Seroprevalence was 13.8% among breeding animals and 8.5% among market hogs (Zimmerman *et al.*, 1991). In Italy, a seroprevalence rate of 6.9% was found in 635 pigs from 42 herds (Gualandi *et al.*, 1989). The high seroprevalence found in other countries indicates the broad diffusion of this infection.

The Disease in Man: The symptomatology varies. In 14 cases of the disease in children, fever and central nervous system involvement were observed, with lymphocytic pleocytosis and, in some cases, paralysis. In the outbreak among US troops in the Philippines, the disease had a sudden onset with intense cephalalgia and fever that lasted two to three days. Other frequently observed symptoms were pharyngitis, stiffness of the neck, and impaired reflexes. Pleocytosis was constant. All the patients recovered in four or five days without sequelae.

Unlike the disease in swine, myocarditis is not observed in humans.

The Disease in Animals: Swine are the animals most affected. In this species, the disease is characterized by sudden death with no warning signs. It can also occur in a less acute form with varying clinical manifestations, which may include fever, anorexia, and progressive paralysis. Most of the deaths in swine are seen in suckling pigs 3 to 20 weeks old. The pathological anatomic lesions are hydrothorax, hydropericarditis, lesions of the myocardium, and ascites. The heart muscle is pale, with small white or yellowish foci. Histopathological examination reveals degeneration of the myocardial fibers. Meningitis and areas of neuron degeneration may also be found (Murnane, 1981). In a 1970 epizootic that affected 22 farms in Australia and produced 277 deaths in swine, the predominant lesion was focal or diffuse necrosis of the myocardium, especially pronounced in the right ventricle, which corresponded to pale areas in the muscle observed at autopsy. In one outbreak, there were 42 deaths in a herd of 57 swine. In the outbreaks in Cuba, mortality ranged between 6.6% and 47.7% on the various farms affected (Lavicka *et al.*, cited by Gómez *et al.*, 1982).

Another important clinical manifestation is an impaired reproduction pattern characterized by early embryonic death, mummification of the fetus, and stillbirth. During an outbreak reported in a herd in New South Wales, Australia, 23 (17%) of 135 sows gave birth during the months of August and September, and 69 of their fetuses, or an average of 3 per litter, were mummified. Nine of the 23 sows produced full-term stillbirths and liveborn piglets. Six fetuses died at near full term and had multifocal necrosis of the myocardium (Links *et al.*, 1986). In an outbreak that

occurred in four swine-raising establishments in Quebec, Canada, the predominant clinical picture was reproductive failure in the sows and respiratory deficiency in suckling and weaned piglets. Autopsy revealed that the lesions were limited to the lungs and consisted of congestion and varying degrees of pulmonary edema. Histopathology showed lesions characteristic of pneumonia, ranging from interstitial to the proliferative form. The authors suggested that the swine may have had a pneumotropic variant of the EMC virus (Dea *et al.*, 1991). In several countries, the disease, including fatal cases, has been described in nonhuman primates.

The disease in cattle and monkeys is also characterized by myocardial lesions; mild encephalitis has also been observed in monkeys. A nine-month outbreak in a colony of 3,060 baboons produced approximately 80 deaths. The disease affected animals ranging in age from 1 day to 22 years. Sudden death occurred frequently. The most common symptom was respiratory difficulty associated with acute cardiac insufficiency. The most significant histological lesion was a non-suppurative necrotizing myocarditis. Placental infection and fetal loss were also reported (Hubbard *et al.*, 1992).

Experimentally infected mice and hamsters develop signs of encephalitis and die. Myocarditis is frequent.

Source of Infection and Mode of Transmission: The natural history of the EMC virus is still not fully understood. The agent has been isolated from a large number of mammalian and wild avian species. It has been suggested that rats and mice are the principal reservoir of the virus, with transmission between the rodents and other vertebrates presumably via the oral route. This hypothesis is based on the high rates of seroreactors among rodents, coupled with the large number of isolations of the virus. However, it is also argued that there may be some statistical bias involved in this conclusion, since the samplings from other animal species have been much smaller. Also, researchers have had contradictory experiences concerning whether the virus is carried in the rodents' intestine or transmission occurs through contact. Although the virus has been isolated from the feces of rodents, swine, and humans, transmission by contact has only been demonstrated on a few occasions. Accordingly, some investigators have questioned the capacity of rodents to serve as the reservoir, suggesting that the serological findings may merely be indicative of viral activity (Tesh and Wallace, 1978). Most of the outbreaks that have occurred in recent years have coincided with plagues of rats or mice.

The virus has also been isolated from several species of mosquitoes in Brazil, Uganda, and the US, and from ticks in India. However, there is no conclusive evidence that the infection is transmitted by arthropods.

The mode of transmission is probably oral, since many species are susceptible to being infected by that route (Tesh and Wallace, 1978).

Much greater amounts of virus are found in the tissue of rodents than in their feces, and it is possible that swine become infected from the ingestion of rodent cadavers. But that scenario would still not explain the mechanism of outbreaks in which large numbers of animals become infected, unless the feces of symptomless adult swine serve as the source of infection for suckling pigs. However, in Australia the experimental infection of 6- to 8-week-old suckling pigs showed that with high doses of the virus or with rodent-derived virus these animals were able to transmit the infection orally, but they could not transmit the infection to contacts, even when feces were left in the cages (Littlejohns and Acland, 1975). Thus it is still not known

with certainty what animal reservoir maintains the virus in nature, what the sources of infection are, or what circumstances give rise to outbreaks in swine and cases in humans. Since the virus is widespread in nature, there is reason to wonder why outbreaks in swine are not more frequent, why they do not occur in other regions, and why there are not more cases in humans.

Man only contracts the infection occasionally. It is possible that transmission occurs by the oral route, but the source of infection is still unknown.

Diagnosis: The virus can be isolated from serum and cerebrospinal fluid obtained from patients at the beginning of the illness and inoculated intracerebrally in mice, embryonated eggs, or tissue cultures (BHK-21, Vero, or HeLa). Serologic diagnosis can be done with the serum neutralization and hemagglutination-inhibition tests using acute- and convalescent-phase sera. Given the pantropic nature of the virus, it can be isolated from many organs (heart, spleen, brain, lungs, intestines, lymph nodes) of wild and domestic animals that have died from the disease or been sacrificed. The organ of choice is the heart. The virus has also been isolated from the feces of swine and rats.

Control: In Florida (USA), where there has been an especially large number of outbreaks in swine, the development of a vaccine for this species is considered necessary. An inactivated adjuvant vaccine has been developed that produces good antibody titers, but its efficacy in providing protection during an outbreak remains to be evaluated. Recommended control measures are to control rodents and not introduce animals from infected herds (Joo, 1992).

Because of the small number of human cases on record and the many gaps in knowledge about the epidemiology of the disease, control measures to protect humans are not warranted.

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EPIDEMIC POLYARTHRITIS

ICD-10 B33.1 Ross River disease

Synonyms: Ross River fever, epidemic polyarthritis and exanthema.

Etiology: Ross River (RR) virus, an RNA genome virus belonging to the genus *Alphavirus* (group A arboviruses), family Togaviridae. Antigenic differences have been found between the strains from northern Queensland and coastal New South Wales in Australia (Woodroofe *et al.*, 1977). As with all the alphaviruses, the RR virion is spherical; it measures 60 to 70 nm in diameter, and it has a bilayered lipid envelope with an icosahedral capsid.

The RR virus belongs to the Semliki complex, which also includes the Mayaro, Chikungunya, O'nyong-nyong, Bebaru, and Getah[1] viruses.

Geographic Distribution: The virus was only known in Australia, New Guinea, and the Solomon Islands until 1979, but starting in that year it spread to Fiji, American Samoa, New Caledonia, and the Cook Islands in the South Pacific.

[1] Getah virus has been isolated from equines and swine. It caused an epizootic among equines in Japan with manifestations of febrile exanthem and edema in the rear legs. The virus is mosquito-borne and active in the northern part of Australia, Cambodia, Japan, Malaysia, and the former Union of Soviet and Socialist Republics. It has been isolated repeatedly from *Aedes vexans* and other mosquitoes.

Occurrence: Epidemic polyarthritis is the most common arbovirus infection in Australia and cases of the disease have been reported in all its states. There were 47,059 cases reported in that country over the period 1991–2000, averaging 4,705 per year and ranging from a low of 2,571 cases in 1995 to a high of 7,750 cases in 1996 (Communicable Diseases Network Australia, National Notifiable Diseases Surveillance Network System, as of 8 December 2002. Available at www.health.gov.au/pubhlth/cdi/nndss/year002.htm). However, the largest epidemic occurred in the Pacific islands, where the virus appeared for the first time in 1979 in a population that was totally susceptible. In Fiji, there were an estimated 50,000 clinical cases, and serologic surveys showed that about 300,000 of the island group's 630,000 inhabitants were infected (Miles and Mataika, 1981). In American Samoa, the virus affected some 13,500 individuals in a total population of 31,000 (Tesh *et al.*, 1981), and in Rarotonga, the most populous of the Cook Islands, it affected the majority of the inhabitants (Rosen *et al.*, 1981). In Australia, an epidemic that started in early 1992 and lasted through part of 1993 had 5,516 reported cases and an adjusted incidence of 36.4 per 100,000 population. Queensland, the state most affected, had an annual incidence of 139.6 per 100,000; the rate in the Northern Territory was 134.1 per 100,000. The seasonal pattern of the infection was very pronounced: at its peak in March there were 1,602 cases, compared with only 123 in July (World Health Organization, 1994).

The epidemics tend to occur after heavy rains, when density of the mosquito vectors is high.

With a view to evaluating the immune status of the population in New South Wales and northern Victoria, which are areas at high risk for arboviruses such as RR and the agents of the Australian encephalitides (Murray Valley and Kunjin encephalitis), a survey was undertaken in 1991 in which 2,873 sera were submitted to the hemagglutination inhibition test. The prevalence of reactors ranged from 25% in one district to 72% in another. The rates were higher than they had been in 1981. Seroconversion during the period 1981–1991 had been 8.5% (Hawkes *et al.*, 1993). The disease is not common in children; it mainly affects persons in the 30- to 39-year age bracket.

In all areas where the virus is active, high rates of serologic reactors have been found in domestic and wild mammals.

The Disease in Man: The average incubation period is 9 days, but it ranges from 3 to 21 days or more. The symptomatology varies from an episode of a few days of fever, often no higher than 38ºC, to classic polyarthritis. The arthritic form is not seen in children, and it tends to be more severe and persistent in older persons. It mainly attacks the ankles, knuckles, knees, and wrists, but it can affect other joints as well. Some patients have arthralgia for several months. Arthritis is the most common sign of the disease and gives it the name "epidemic polyarthritis." Another sign that occurs in 40% to 70% of the cases, both in children and in adults, is a maculopapular cutaneous eruption. The eruption can last as long as five months, although it usually disappears within a shorter time (Mudge and Aaskov, 1983; Fraser, 1986). The average period of incapacity is estimated to be about six weeks, based on a review of 1,196 laboratory-diagnosed cases that occurred during a large epidemic in New South Wales in 1983–1984 (Hawkes *et al.*, 1985). The disease is self-limiting.

The clinical picture of polyarthritis is shared with five other alphaviruses: Barmah Forest, Mayaro, Chikungunya, O'nyong-nyong, and Sindbis.

The Disease in Animals: In Australia, the RR virus is thought to affect the central nervous system in equines and also to cause arthritis and muscular complications. Although there is some serologic evidence in this regard, virologic confirmation is lacking (Gard *et al.*, 1977).

On the other hand, RR virus infections are present in subclinical form in domestic animals, including in most equines (if one assumes the few cases of disease in horses were in fact caused by this agent). Signs of the disease have not been observed in marsupials, although they are suspected to be the vertebrate reservoirs of the virus.

Source of Infection and Mode of Transmission: The infection is transmitted by mosquitoes. In Australia, the main vectors are *Aedes vigilax* and *Culex annulirostris*, while in the Cook Islands, Fiji, and American Samoa, the most probable vector is *A. polynesiensis*. A low degree of vertical transmission (1.6%) has been demonstrated experimentally in *A. vigilax* (Vale *et al.*, 1992). The possibility of vertical transmission is also suggested by the fact that the virus was isolated from a female adult *A. normanensis* captured in Western Australia at the beginning of the rainy season, possibly before it fed on a vertebrate animal.

A. normanensis lays eggs that are resistant to desiccation and can therefore survive the dry season in northern Australia (Broom *et al.*, 1989).

In the arid parts of Western Australia, the epidemics occur when the rains get heavy or the rivers overflow. Lindsay *et al.* (1993) were able to isolate the virus from eight species of mosquitoes prior to an outbreak of epidemic polyarthritis. The large number of isolations from *A. vigilax* point to this species as the main vector in the region. The RR virus has been isolated from male *A. vigilax* and *A. tremulus* mosquitoes, two species whose females lay eggs that are highly resistant to desiccation and are able to survive periods of drought. Isolation of the virus from males is the first strong evidence of vertical transmission: since they do not feed on blood, transmission must have occurred via infected eggs laid by the previous generation.

The reservoirs of the virus have still not been identified. The frequency with which antibodies are found in wild and domestic animals suggests that they may serve as either reservoirs or amplifying hosts of the virus. In Australia, large marsupials, especially the macropods, are believed to play an important role, and in New South Wales, a local mouse species has been implicated. Experimentally infected lambs have been shown to produce high-titer viremia, and it is therefore believed that they may serve as amplifying hosts of the virus.

In Australia, the disease occurs mainly in rural areas. The RR virus is enzootic and probably circulates among wild animals by means of vectors. Man would be an accidental host.

There are several epidemiologic differences between the disease in Australia and that which occurs in the South Pacific islands. In the latter areas, it has been explosive and has affected urban populations. Another interesting difference is the ease with which the RR virus has been isolated from human patients in the islands. Whereas in Australia the agent has been very difficult to isolate, in the islands the opposite is true: in the Cook Islands, for example, the virus was isolated from almost half of a group of 100 patients suffering from arthritis who had not yet developed antibodies (Rosen *et al.*, 1981). The reasons for these differences are not fully understood, but it is thought that they may be due to a biological change in the virus which

would cause relatively high-titer viremia in man, as has been amply demonstrated. This explanation would account for the intensity of the epidemics on the islands, in which the disease is thought to be transmitted from person to person through the vectors (Rosen *et al.*, 1981). The hypothesis that man can serve as an amplifying host for the virus is also supported by the fact that in American Samoa the proportion of animals with antibodies has been found to be relatively low compared with that observed in the human population (Tesh *et al.*, 1981). Another interesting discovery has been evidence of transplacental transmission of the virus in the Fiji Islands: IgM antibodies were detected in the cord blood of 11,368 babies born to mothers who were pregnant during the 1979 epidemic. Since IgM antibodies normally do not cross the placenta, this finding would suggest an immune response to an intrauterine infection. The babies did not show any signs of the disease (Aaskov *et al.*, 1981).

Another question still unanswered is how the virus came to be introduced in the Pacific islands. It could have been carried there by a viremic person or animal or by infected mosquitoes, but there is no evidence to support this conclusion. Lindsay *et al.* (1993) think it is almost certain that the virus was introduced in the Pacific islands by man, who has the capacity to cover great distances in a short time. This would be feasible if a person had traveled to the islands while in a viremic state and then been exposed to mosquitoes. It is also not known whether the virus has become established as an enzootic on these islands (Miles and Mataika, 1981).

Role of Animals in the Epidemiology of the Disease: It would appear that in Australia the virus circulates enzootically between wild animals and mosquitoes, whereas during the epidemics in the Pacific islands the main host was probably man. There is evidence that various species of mosquitoes could be responsible for survival of the virus during the dry season and possibly also during winter in the temperate regions of Australia.

Diagnosis: The detection of IgM in an acute-phase serum specimen through enzyme-linked immunosorbent assay (ELISA) provides a presumptive diagnosis of recent infection (Mackenzie *et al.*, 1993, and McIntosh, 1996, cited in Harley *et al*., 2001). Testing of acute-phase serum (collected within 7 days of onset of illness) and convalescent-phase serum (taken within 8 to 28 days of onset) is necessary to confirm diagnosis (Mackenzie *et al.,* 1993, cited in Harley *et al*., 2001). The diagnostic standard is a fourfold or greater change in antibody titer as determined by hemagglutination inhibition, complement fixation, or serum neutralization (Mackenzie *et al*., 1993, and Calisher and Karabatsos, 1988, cited in Harley *et al*., 2001).

During the epidemics on the Pacific islands, the virus was isolated easily from the blood of patients in the acute phase of the disease before antibodies had developed, but in Australia isolations were difficult to obtain.

Newborn mice can be used to isolate the virus, which can then be replicated in cell cultures such as C6/36 (from *A. albopictus*), Vero, or PS/EK (swine kidney cells).

Control: In the event of an epidemic, measures should be taken to control the vectors. For individual protection, repellents and other antimosquito measures can be used. No vaccines are available.

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FEVER CAUSED BY GROUP C BUNYAVIRUSES

ICD-10 A93.8 Other specified arthropod-borne fevers

Etiology: The viruses in this serogroup belong to the genus *Bunyavirus*, family Bunyaviridae. The virion is round, measures approximately 90 to 100 nm, and has a bilayered lipid envelope.

The letter C was originally assigned to this serogroup to distinguish it from mosquito-borne arbovirus groups A and B. Table 4 gives the classification of the group C viruses and indicates their geographic distribution. The list should also include the Bruconha virus subsequently isolated in São Paulo, Brazil, from the mosquito *Culex* (*Melanoconion*) *sacchettae* (Calisher *et al*., 1983).

Geographic Distribution: The group C viruses have been isolated only in the Americas and are native to tropical America. Although most of the isolations have been made in Pará, Brazil, human cases have also been reported in Central America, French Guiana, Mexico, Panama, Peru, Suriname, Trinidad and Tobago, and the US (in the state of Florida).

Table 4. Classification of the group C bunyaviruses.

Complex	Virus	Subtypes	Distribution
Caraparu	Caraparu (CAR)	Ossa (OSSA)	Panama to Brazil
	Apeu (APEU)		Brazil
	Madrid (MAD)		Panama
Marituba	Marituba (MTB)	Murututucu (MUR)	Brazil
		Restan (RES)	Trinidad to Brazil
	Nepuyo (NEP)	Gumbo Limbo (GL)	South Florida (USA), Mexico, and Central America
Oriboca	Oriboca (ORI)		French Guiana to Brazil
	Itaqui (ITQ)		Brazil

Source: Berge, T.O., ed. *International Catalogue of Arboviruses Including Certain Other Viruses of Vertebrates*, 2nd ed. Atlanta: Centers for Disease Control; 1975. (DHEW Publ. CDC 75-8301). Table reproduced in Scherer *et al.*, 1983.

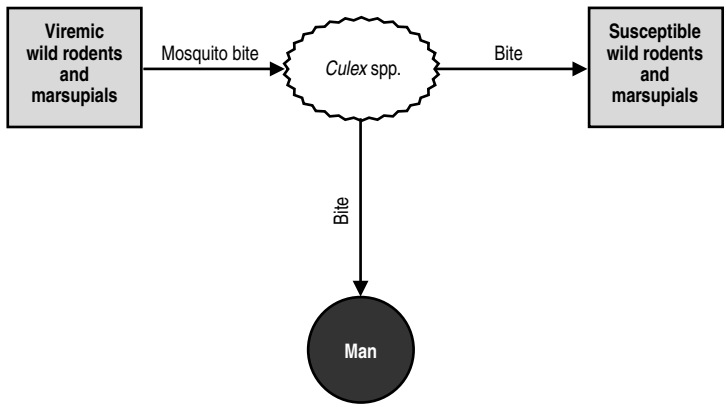
Occurrence: Approximately 50 cases have been reported, most of them caused by the Caraparu and Oriboca viruses. According to a serologic survey conducted in Belém, Brazil, inapparent infections are common: 102 of the 534 persons examined had a positive reaction in the hemagglutination inhibition test to one or more of three viruses: Caraparu, Murutucu, and/or Oriboca. In the Ribeira valley region in the southern part of the state of São Paulo, Brazil, blood samples were taken from 83 workers living near the jungle and 12 of them were positive for the Caraparu virus in the hemagglutination inhibition test. In addition, women and children living in the region's small villages were also positive. A biologist who worked in the jungle for nine months in this region developed an undifferentiated fever; acute- and convalescent-phase blood samples demonstrated seroconversion to the Caraparu virus. The results from the serologic surveys suggest that there may be an antigenic difference between the strains of Caraparu virus isolated in Pará and those isolated in São Paulo, since the latter are more closely related to the Bruconha virus (Iversson *et al*., 1987).

The Disease in Man: The incubation period is estimated to be less than two weeks. The infection produces an undifferentiated fever that lasts two to six days. The symptoms include pyrexia, cephalalgia, dorsalgia, and myalgia, and some patients have chills, malaise, photophobia, vertigo, and nausea. Recovery is complete, but convalescence can take several weeks. The patient should be given an antipyretic and remain in bed for a few days.

The Disease in Animals: The virus has been isolated from several species of rodents, marsupials, sloths, and bats. The disease is usually asymptomatic even in the presence of confirmed viremia.

Source of Infection and Mode of Transmission (Figure 14): The reservoirs are rodents and marsupials of the jungle. In Pará, Brazil, the main hosts are the species *Proechimys guyannensis* and *Oryzomys capito*, and in Bush Bush, Trinidad and Tobago, species of *Oryzomys* and *Zygodontomys*. The vectors are *Culex* mosquitoes, especially *C.* (*Melanoconion) vomerifer* in Belém and *C. portesi* in Trinidad and Tobago. Rodents have high viremic titers, and mosquitoes are easily infected when

Figure 14. Fever caused by group C bunyaviruses. Transmission cycle.



they bite them. The virus replicates in mosquitoes, which then transmit the infection to other susceptible rodents.

Humans become accidental hosts when they go into the jungle for occupational reasons and contract the infection from the bite of an infected mosquito.

Diagnosis: The virus may be isolated from patient blood by intracerebral inoculation in mice. Newborn mice die in one to three days. The tests used for serologic diagnosis are hemagglutination inhibition, complement fixation, and neutralization in VERO cell cultures.

Control: Preventive measures are the same as for other mosquito-borne arboviruses and are difficult to apply in the tropical jungles of the Americas.

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FOOT-AND-MOUTH DISEASE

ICD-10 B08.8 Other specified viral infections characterized by skin and mucous membrane lesions

Synonyms: Aphthosis, aftosa, hoof-and-mouth disease, aphthous fever, epizootic aphthae, contagious aphthae.

Etiology: Nonsegmented single-strand RNA genome virus belonging to the genus *Aphtovirus*, family Picornaviridae. The viruses in this family are very small, measuring 20–30 nm, and have an icosahedrally symmetric capsid with no envelope. The virions are resistant to solvents and detergents. The capsid is composed of 60 capsomers, each of which contains the proteins VP1, VP2, VP3, and VP4. The first three are located on the surface of the mature virion and constitute its antigenic determinants. Purified VP1 preparations produce neutralizing antibodies. The VP4 protein is located inside the virion, near or adjacent to the nucleoid.

Seven different types of aphthoviruses have been recognized: A, O, C, SAT_1, SAT_2, SAT_3 , and ASIA1. The agent has a high degree of antigenic plasticity and a tendency to mutate, which gives rise to numerous subtypes. When new subtypes emerge in a region, vaccinations cease to confer immunity and outbreaks occur.

Geographic Distribution: Virus types A, O, and C have the widest distribution in the world and have caused epizootics of foot-and-mouth disease (FMD) in Africa, Asia, Europe, and South America. The SAT virus types are found in Africa, and in 1962, there was an outbreak of SAT_1 that spread through Greece, the Middle East, and Turkey, but the disease was contained, and after 1970, it was no longer seen outside Africa. The ASIA1 type has also appeared in Africa; in 1973, it emerged in the Middle East and since then has spread as far as Turkey (Pereira, 1981), Greece, and Georgia; in 1984, it gave rise to outbreaks in Israel (FAO, 1985).

The first appearance of serotype O Pan Asia was reported in an isolated focus in northern India in 1990. It spread to Saudi Arabia and Turkey due to the movement of small animals, and from there, to Greece and Bulgaria. From 1996 to 1998, the serotype was reported in foci in Iran, Iraq, Israel, Jordan, Lebanon, Syria, and the Arabian peninsula. It was also identified in outbreaks in China, Nepal, and Taiwan. In March 2000, the strain was isolated in foci in South Korea and Japan, which had not been affected since 1934 and 1908, respectively. This strain also affected animals in South Africa, near Durban, and was traced to pigs that were fed contaminated meat scraps from Asian ships.

The FMD situation in Africa, Asia, Europe, and South America in 2000–2001 was troubling. Though several countries had made considerable progress in controlling FMD and had been declared FMD-free, outbreaks in 2000 and 2001 revealed weaknesses in control programs and highlighted the need for continued epidemiologic surveillance and rapid response capacity.

The first focus in the United Kingdom since 1981 was diagnosed on 20 February 2001 in pigs in Brentwood, Essex, and was related to another establishment at which the animals were fed contaminated food scraps from Haddon, Northumberland, the presumed source of the epidemic that occurred earlier that month. From there, the agent is believed to have spread to sheep farms that supplied several markets, thus widely propagating the infection. In addition to the 2,026 foci in the UK, the disease spread to France (2 foci) and the Netherlands (26 foci). The eradication effort in the UK, essentially based on slaughtering sick animals and their contacts, affected some 6 million animals, including cows, sheep, and pigs. Also, a seroepidemiologic study was undertaken around the depopulated areas (prevention and surveillance zones), and a total of 1.9 million samples from 27,000 herds were tested; this includes a variable number of samples taken due to the movement of animals for commercial and repopulation purposes. The results as of 22 October 2001 demonstrated that

99.8% of the herds and 99.96% of the animals did not have positive results that would indicate past infection.

The effective response of the EU countries, where vaccination was suspended in 1992, allowed them to control the epidemic there, and those that had foci were able to recover their FMD-free status. As of January 2003, all the countries of the European Union are officially listed as free of FMD, as are Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Hungary, Iceland, Latvia, Lithuania, the former Yugoslav Republic of Macedonia, Malta, Norway, Poland, Romania, Slovakia, Slovenia, Switzerland, and Ukraine (OIE, 2003).

In the Americas in the 1990s, the expansion of the Hemispheric Plan for Eradication of Food-and-Mouth Disease contributed to the decline in the clinical presence of FMD in South America and, by the end of the decade, the annual average number of FMD foci diagnosed in national laboratories had fallen to 161 from the high of 766 seen earlier during that period. Although Argentina had been recognized as FMD-free without vaccination in 1999, and Uruguay had been free of the disease since 1990 and discontinued vaccination and vaccine production in 1994 (PAHO, PANAFTOSA, 2000), outbreaks occurred in both countries in 2000 and 2001; Bolivia and the south and central regions of Brazil were affected as well.

The FMD situation in South America in 2001 was: 2,126 foci due to virus A in Argentina; 7 foci due to virus O and 81 to virus A in Bolivia; 15 foci due to virus A in Brazil; 5 foci due to virus O in Colombia; 15 foci due to virus O in Ecuador; and 4 foci in Venezuela. Peru reported no foci during the previous 61 weeks and Uruguay reported its last focus in August 2001. According to the World Organization for Animal Health, as of January 2003, Chile and Guyana are officially listed free of FMD without vaccination; the area of Argentina situated below the 42nd parallel South and the northwest region of Choco Department in Colombia were also FMD-free zones without vaccination. In Brazil, the zones covered by the states of Santa Catarina and Rio Grande do Sul recovered their status as free of FMD with vaccination, joining the states of Bahia, Espírito Santo, Goiás, Mato Grosso, Mato Grosso do Sul, Minas Gerais, Paraná, Rio de Janeiro, São Paulo, Sergipe, Tocantins, and the Federal District (OIE, 2003). French Guiana and Suriname are also FMD-free. In November 2002, Paraguay's status of FMD-free with vaccination was suspended following isolation of the FMD virus from bovine samples collected in Canindeyú Department (OIE, 2003).

The countries of North and Central America are officially listed as free of FMD without vaccination as of January 2003 (OIE, 2003); the Caribbean islands are also free of FMD (FEDESA, 2001).

Outbreaks of type O1 virus and of type A22 virus have been reported in the region of the Caucasus. Outbreaks of types O1 and A22 occurred for some time in Turkey, and though incidence had declined considerably since 1991–1992, outbreaks occurred again in 2000 and 2001.

In northern Africa, there have been sporadic outbreaks of type O1. In Tunisia, despite mass vaccination, it has not been possible to eradicate the infection because of the Maghreb open-border policy. In the rest of Africa, many of the countries have experienced outbreaks of types O, A, SAT_1, and SAT_2, although information on the epizootiologic situation in specific countries tends to be sparse. An area of Namibia is recognized as FMD-free (OIE, 2003).

In Asia, FMD is endemic from Iran to Southeast Asia, and the virus types that are active are A, O, C, and ASIA1. As of January 2003, Indonesia, Japan, the Republic of Korea, and Singapore (OIE, 2003) are officially listed as FMD-free without vaccination; the Democratic People's Republic of Korea and the Pacific Island nations, as well as Australia and New Zealand, are also FMD-free.

Occurrence in Man: Rare. Despite high incidence of the disease among domestic animals in many countries and countless opportunities to be exposed to the infection in the field and in the laboratory, man has proved to be quite resistant to the FMD virus. The question of whether or not humans are susceptible to the virus was debated for many years; however, there is no longer any doubt that FMD is a zoonosis, even though its incidence in man is very low. The virus has been isolated and typed in more than 40 human patients. Other cases have been diagnosed without typing the virus by reproducing the disease in animals or on the basis of serologic tests. The infection in man can cause a clinically apparent disease, and it can also be asymptomatic. It is believed that in order to acquire the infection humans need to be exposed to massive amounts of the virus or have some predisposing condition that makes them more susceptible. The scarcity of laboratories in the developing countries constrains their capacity to diagnose the disease in man, while the industrialized countries, which have good diagnostic services, are now free of the disease.

Occurrence in Animals: FMD causes heavy economic losses, both due to the disease itself and because of the disruption it causes in the marketing of cattle and their products at the national and international levels. The infection is common in many countries, where several different epizootiologic situations may prevail: the entire country may be FMD-free; a given area may be FMD-free; an area may have sporadic infections; and, finally, the area may be enzootic. Control programs have made considerable progress toward reducing the number of outbreaks, the attack rates, and the severity of the disease in infected animals.

From time to time extensive epizootics and panzootics may affect several countries, caused either by the accidental introduction of an exotic virus type or by a "domestic" subtype emerging in an area in which the infection had been relatively inactive. The spread of an epizootic depends on the density of the animal population, its susceptibility to the particular virus strain involved, and various environmental factors.

There are now only occasional outbreaks in Europe. In South America, the number of outbreaks has diminished in some countries but increased in others. Vaccination programs in South America have reduced the rate of affected herds as well as overall case-fatality (Casas Olascoaga *et al.*, 1982). However, an endemoepidemic situation continues to prevail in many countries.

The Disease in Man: Foot-and-mouth disease is a minor zoonosis that is rarely seen in man and produces a benign, self-limiting disease. The incubation period is usually two to four days, but it can be as long as eight days. The course of the disease is similar to that in animals. Symptoms in the initial phase are pyrexia, cephalalgia, anorexia, and tachycardia. The primary vesicle appears at the site where the virus penetrated, be it through a break in the skin or via the oral mucosa. From that point the disease becomes generalized and forms secondary aphthae on the mouth, hands, and feet. However, not all the symptoms or lesions are necessarily present.

When there is no secondary bacterial contamination of the aphthous ulcers, the patient recovers fully in about two weeks. The clinical symptoms of FMD may be mistaken for those of other vesicular diseases that affect man, especially infections caused by serotypes of the Coxsackie A viruses, which also produce lesions on the hands, feet, and mouth. Because of the similarity of FMD symptoms to those of other stomatitides, clinical diagnosis without laboratory confirmation is insufficient.

Confirmed cases of the disease have occurred mainly in individuals who had been in close contact with infected animals or with the virus in the laboratory. Pilz *et al.* (1962) described four cases in persons who had been handling infected bovine tongues in the preparation of vaccines, a method that is no longer being used. In all these cases, aphthae or vesicles appeared on the hands. Presence of the virus was demonstrated in three of the cases by the inoculation of material from the vesicles in young mice or on bovine tongue. In addition, the serum neutralization test was positive in all four patients. One of them, who had contracted the disease from the type C virus two years earlier, was sickened by type O when the institute where he worked began to handle the latter type. The virus type was determined by the complement fixation test based on an LD_{50} titer of $10^{-3.3}$/ml in suckling mice using epithelial material from the vesicles, and on a titer of $10^{-6.5}$/ml using material from lymph nodes. A second patient, who had been treated for neurodermatitis three times in the last nine years, developed aphthae on the hands and feet from which the type O virus was isolated (Pilz and Garbe, 1965). In total, these authors confirmed seven human cases of FMD between 1960 and 1965.

In another case, reported in the German literature, a veterinarian developed a fever of 38°C and vesicles on one hand and the feet five days after collecting fluid from a vesicle on a pig. A sample of vesicular material proved negative in the complement fixation test, but inoculation of the same material in 3-day-old mice, using mouse tissue as antigen, gave a positive result for the type C virus. The patient was also positive for the type C virus in the serum neutralization test (Eisner *et al.*, 1967).

Brooksby (1967) and Armstrong *et al.* (1967) described a case in a patient who lived on a ranch but apparently had no contact with the livestock. The animals had been slaughtered during the course of an FMD outbreak, and four days later the patient complained of a mild sore throat. Vesicles appeared on the palm and the back of the hand on day six, and in the next few days they also appeared on the feet, along with tumefaction of the tongue. The lesions disappeared two weeks after the date on which the animals were slaughtered, but they reappeared three days later and again after a lapse of five months. The lesions in these secondary attacks also cleared up in two weeks. When a suspension of epithelium from the vesicles on the hands was seeded on bovine thyroid tissue culture, cytopathic changes were observed, and fluid from the culture reacted positively in the complement fixation test using typo O antiserum. Titration of the epithelium yielded $10^{6.8}$ ID of virus and $TCID_{50}$ at a level of 50%, indicating that the disease could not have been the result of casual contamination. In the serum agglutination test the titers continued to rise for 30 days after onset of the disease, after which they began to fall. Efforts to isolate FMD virus during the second and third attacks were unsuccessful, and there was no increase in the neutralizing titer. It was therefore concluded that the attacks were caused by some other agent.

In Chile, an assistant at the Bacteriological Institute who had been working on FMD-related duties for more than 10 years suddenly developed vesicles on one

hand. Fluid extracted from one of the vesicles 36 hours after their appearance and inoculated on bovine kidney tissue cultures proved to be cytopathogenic. It was possible to inhibit virus activity in the presence of type O antisera obtained from guinea pigs. Inoculation of the strain in guinea pigs and mice produced typical FMD lesions. Application of the Reed and Muench method (Meléndez, 1961) showed that convalescent-phase serum protected against 416,000 TCID, whereas acute-phase serum conferred protection against only 61 ID.

The virus type isolated most frequently from human patients is type O, followed by type C, and rarely, type A. In a group of 21 cases of FMD it was possible to type 15 of them, and of these, 13 were type O, 1 was type C, and 1 was type A (Wetterlein, 1954).

The Disease in Animals: FMD is a disease of cloven-hoofed animals, especially cattle, swine, sheep, and goats. It has also been found in several species of wild animals. Solipeds and carnivores are resistant.

Some of the FMD virus strains have a strong affinity for a particular animal species. Thus there have been strains that caused serious outbreaks in swine but had little effect on cattle and strains isolated from cattle that proved difficult to reproduce in swine. This host adaptation is relative, however; after maintaining itself for a number of years in a given animal species, the virus can increase in virulence and attack other species.

The disease is very important economically because it spreads rapidly and causes high morbidity, production losses, and obstacles for the marketing of livestock and products of animal origin. Its greatest impact is on cattle.

The incubation period ranges from 48 hours to 4 days.

CATTLE: After penetrating the epithelium, almost always in the upper respiratory tract and the pharynx, the virus replicates and produces a primary aphtha which is clinically unnoticeable. From this point of entry, the virus invades the bloodstream and causes a viremia which is coincident with the febrile state, the first observable symptom of the disease. The febrile period lasts one or two days and is followed by the appearance of secondary vesicles in the mouth, snout, interdigital spaces, coronary band of the foot, and, fairly often, on the teats, udder, and other sites where the epidermis is thin. Other observable symptoms are anorexia, delayed rumination, champing sounds, and profuse salivation. There have also been abortions presumably induced by the fever. The foot lesions can cause varying degrees of lameness, and in some cases the lesion on the coronary band can cause the hoof to come off. The animal does not eat sufficiently and loses weight. The milk production of cows declines, and some of them dry up during the latter half of lactation.

The vesicles burst after one to three days and leave moist painful red erosions which after a few days are covered with new epithelium. Dark yellow spots remain in the mouth, and on the feet the vesicle sites may develop scabs while new epithelial tissue is being formed underneath. Pain and swelling of the feet last from one to two weeks. The most frequent complications are secondary bacterial infections of the open aphthae on the mouth and feet, myiasis, and mastitis.

Case fatality tends to be low: between 1% and 2% in adult animals, and between 4% and 5% in calves, except in an epizootic of "malignant aphthosis," which causes lesions of the myocardium and can result in very high case fatality, especially in calves.

SWINE: Claudication is the first noticeable symptom in swine. The ungual lesion begins with red spots on the rear of the plantar cushion, near the heel. In other cases, vesicles may appear on the coronary band, causing extensive inflammation of the surrounding skin and detachment of the hoof, especially in very heavy swine that are forced to move around. Since the formation of a hoof usually takes several months, during this period the swine remain prone and have difficulty procuring food. Vesicles are seen fairly often on the animal's snout, and sometimes on the mouth.

SHEEP AND GOATS: In these species, FMD is usually much milder and more benign than it is in cattle. Nevertheless, several epizootics have been recorded in which sheep and goats were more severely affected than cattle. In these ruminants, vesicles in the mouth may be small and go unnoticed, but the foot lesions are clinically noticeable because of the vesicles and consequent lameness. Secondary bacterial infections of the foot lesions are common. Abortions have also been observed in goats.

WILD ANIMALS: Natural infection has been confirmed in a large number of free-living animal species, as well as captive wild animals in zoos. During the FMD eradication campaign in California in 1924, lesions typical of the disease were found in 10% of 22,000 sacrificed deer. In addition to wild cervids, the infection occurs naturally in several species of bovids, suids, and elephants. Aphthous lesions have also been found in European hedgehogs (*Erinaceus europaeus*) in Great Britain, near a bovine focus of FMD. It has been demonstrated that the virus can overwinter in these animals. Outbreaks in zoos have been reported in Buenos Aires, Paris, and Zurich (Hedger, 1981).

Special attention has been given to study of the disease in wild animals in Africa, where free-roaming biungulates share pastureland with domestic animals. Of special interest are cases of infection in the free-living African buffalo (*Syncerus caffer*), most of which are completely asymptomatic. This bovid can maintain the infection independently of domestic animals (Hedger, 1981) and can remain a carrier for as long as five years.

Source of Infection and Mode of Transmission: Cloven-hoofed animals are the natural hosts of the FMD virus. An infected animal sheds the virus in all its secretions and excretions. The peak period of viral shedding occurs during three to five days between the final phase of the prodromal state and the appearance of aphthae, when the sick animal becomes a prime source of infection. At that point, the virus shedding begins to abate, and after 8 to 10 days the animal poses only minimal risk as a source of infection. The highest titers of the virus are found in the vesicular fluid and the epithelium of the lesion. The sick animal sheds large quantities of virus through its profuse salivation, which contaminates the environment and leaves virus-containing droplets in suspension. Smaller amounts of virus are shed in the urine and feces. The virus replicates itself in the mammary glands, and high titers can be found in the milk, from which it has been isolated between one and four days before the appearance of clinical symptoms. The semen of infected animals contains the virus and can be a potential source of infection via artificial insemination.

There are several modes of transmission, both direct and indirect. The infection is transmitted mainly by aerosols, and the pharynx is probably the most common site of virus penetration. When relative humidity in the environment is high, the FMD

virus can survive in aerosols for a long time and be transported to distant sites by inanimate vehicles and mechanical vectors. Other sites of virus penetration are the lower respiratory tract, the nasal passages, and the udder. The profuse secretions and excretions of a sick animal contaminate the environment and probably cause indirect transmission of the disease, especially in endemic areas (Brooksby, 1982). The virus is resistant to environmental factors and can survive for a long time outside the host organism. It has been demonstrated that preparations of the virus protected by organic matter are capable of retaining limited infective capacity even after four hours at 85ºC (Callis, 1979).

Man is regarded as one of the mechanical carriers of the virus, especially when the individual's occupation involves daily visits to several different farms. It is also likely that dogs carry contaminated material from one place to another. Meat and other products of animal origin such as milk, hides, and offal can be the source of outbreaks in distant places. Swine often contribute to the start of an outbreak and serve as amplifiers of the infection because of their great susceptibility and their high rate of viral shedding.

The asymptomatic carrier state has been confirmed in cattle, sheep, and goats, but not in swine. This state, which can last from several months to more than two years (Brooksby, 1982), can be demonstrated by collecting esophagopharyngeal secretions with a probang. Animals that have had clinical disease or a subclinical infection, and even vaccinated animals that have been in contact with the virus in the field, can become carriers. However, the role of carriers in the epizootiology of the disease is still not fully understood because it has not been possible to transmit the infection experimentally to susceptible cattle by placing them in cohabitation with carrier animals. Despite the fact that the amount of virus borne by carriers is always small, some epidemiologic studies have suggested that carriers are capable of initiating new outbreaks. Although this possibility has not been confirmed, seroconversion has been demonstrated in uninfected animals exposed to carriers. An important point to bear in mind is that antibodies found in carriers can exert selective pressure because of their immunity and in this way contribute to the evolution of new antigenic variants of the virus (Brooksby, 1982).

According to Salt (1993), who has updated the knowledge available on the subject of carriers, circulating antibodies restrict virus replication in the oropharynx. Although the FMD virus can survive for short periods in other organs, its preferred site is the oropharynx, where it can maintain itself and give off excretions for approximately two and a half years in sheep and up to nine months in goats. The virus titer, determined from tissue culture, is low and gradually declines over time. Moreover, the virus in carriers is less cytopathic in cell cultures and less virulent for bovine cattle. However, it can infect swine and regain its virulence after passage in these animals. Hence, its attenuation is reversible.

Systematic vaccination in enzootic areas reduces the incidence of carriers. In a comparative study of two enzootic areas, one in which there had been repeated vaccination initiatives and one with no vaccination program, the carrier rates were 0.49% and 3.34%, respectively (Anderson *et al.*, 1974).

The movement of animals is one of the most common ways to spread FMD. In South America, it is customary to designate marginal agricultural land for the raising of livestock, which are then sold at auction and taken to feedlots for fattening. In some of these marginal areas, vaccination is performed only occasionally and

coverage is poor both because it is difficult to round up the cattle and because of the cost of vaccination. In such areas, the disease tends to be endemic. Transporting the animals from the places where they are raised to the feedlots poses a high risk for transmission of the disease in light of the increased number of carriers, potential sources of infection, and number of susceptible animals being exposed. In a study conducted in Brazil, it was shown that 42% of the cattle from a livestock-raising area in the Mato Grosso lowlands being transported to the midwestern region of the country had antibodies to the VIA antigen.[1] According to the neutralization tests, only 32% of the animals could be considered protected against the three main virus types (Mathias *et al.*, 1981). This mechanism of transmission is common in Brazil and other countries of South America as well.

Wild animals play a role in the epizootiology of FMD only in very special circumstances. One of the occasions on which these tangentially infected hosts played an important role in spreading the disease was when steppe antelope (*Saiga tatarica*) contracted the infection in Kazakhstan in 1967. The population of these animals was estimated at 1 million head, and when they migrated, they spread the infection to cattle in distant regions. The buffalo (*Syncerus caffer*) can serve as a reservoir for the virus in Africa, but transmission of the agent to cattle is very rare (Hedger, 1981).

Man is infected by contact with sick animals or infectious matter through wounds or abrasions in the skin and, according to some authors, through the ingestion of milk. No cases have been found to be the result of ingesting meat or its byproducts. It has been possible to isolate the FMD virus from patients with lesions up to 14 days after onset of the disease and also from the nasal passages of healthy individuals up to 48 hours after exposure. In preliminary experiments conducted in Africa, the FMD virus was recovered from the nasal passages of various persons who had worked with cattle in open corrals. The virus proved to be infectious when it was injected parenterally in susceptible cattle (Hyslop, 1970). At the Pirbright Viral Research Institute in England, swine with FMD being kept in an isolation pen were introduced in a closed corral with susceptible cattle and attempts were made to transmit the virus via the nasal route through sneezing, coughing, and breathing. In one of the experiments, a calf developed fever and lesions and the virus was recovered from a sample taken using a probang, and with another calf it was isolated from blood and the pharynx 15 days after exposure, but no lesions were observed; two other calves remained infection-free. The virus did not survive in the nasal passages of workers at the Institute; in most cases, it had disappeared within 24 hours, and at 48 hours it was no longer present in any of the subjects (Sellers *et al.*, 1971). Transmission of the infection by humans through mechanical transfer of the virus on their clothing, shoes, and soiled hands is very important because the body and clothing can remain contaminated with the virus for several days (Sellers *et al.*, 1971). In several cases, sick patients have been thought to be the source of outbreaks in animals. Although this possibility exists, it is not considered epidemiologically significant and there is no conclusive evidence to support it.

[1] VIA (*virus-infection-associated*) antigen: antigen associated with the virus infection which stimulates antibodies to VIA in infected animals for a period of six months or longer, and in repeatedly vaccinated animals, for a period of several weeks to about two months.

Role of Animals in the Epidemiology of the Disease: FMD is an animal infection; man is an accidental host and rarely becomes infected or develops clinical disease. Human-to-human transmission has never been confirmed.

Diagnosis: Animal inoculation can be used to distinguish between FMD and vesicular stomatitis, swine vesicular disease, and swine exanthema.[2] Horses inoculated intralingually are resistant to the FMD virus and mildly susceptible to the swine exanthema virus. On the other hand, cattle are susceptible to FMD and vesicular stomatitis and resistant to swine exanthema. Swine vesicular disease is only found in that species. Animal inoculation is costly and has been replaced by the crossed complement fixation test or the enzyme-linked immunosorbent assay (ELISA). Both techniques make it possible to differentiate FMD from vesicular stomatitis, and they also identify the type and subtype of the FMD virus. The most suitable material for testing purposes is epithelium from recent lingual vesicles, which is used as antigen in the complement fixation test together with subtype-specific sera produced in guinea pigs. The test is quantitative. The result can be confirmed with cross-serum neutralization tests using suckling mice or tissue cultures. The indirect ELISA test has been the technique used most often to detect and identify the FMD virus types. It is the most sensitive test, and it is not affected by anticomplementarity factors (Crowther and Abu Elzein, 1979; Gomes *et al.*, 1989). The ELISA test can also be used to quantify FMD antibodies in bovine sera.

In man, clinical suspicion of FMD should always be confirmed in the laboratory. The virus can be isolated by intraperitoneal inoculation in suckling mice or tissue cultures. Both the complement fixation and the ELISA tests are reliable.

Control: In disease-free areas, the most important prevention measures are (a) prohibiting the introduction of susceptible animal species, products of animal origin, and any potentially contaminated products, such as plants, coming from countries in which FMD is still active; (b) epidemiologic surveillance through port inspection and quarantine services, and using a reporting system with laboratories competent to perform rapid diagnosis in order to confirm outbreaks; and (c) allocating the necessary human and economic resources to deal with any emergency. The countries in the disease-free area of the Americas maintain bilateral or multilateral agreements to protect against the transborder introduction of FMD. Should an outbreak occur, the establishments involved must be closed down and the sick and exposed animals slaughtered.

In infected areas, control programs consist primarily of compulsory systematic vaccination of cattle until the incidence of foci falls to a level that is compatible with a policy of eradication. In Europe, the ecologic and epidemiologic conditions, coupled with the livestock husbandry practices designed to protect against outbreaks, have allowed for a policy of one single annual vaccination coupled with the sacrifice of animals in accordance with established animal health regulations. The countries of the European Union discontinued vaccination starting in 1992, after the area was declared free of FMD, and only permit emergency vaccination in response to outbreaks.

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[2] Swine exanthema, caused by a virus serotype A of the genus *Calicivirus*, family Caliciviridae, has been restricted to the Pacific coast of North America. Only two outbreaks have been recognized outside that area: one in Hawaii, US, and the other in Ireland (Odend'hal, 1983). In 1956 the disease was officially declared eradicated. The virus was subsequently isolated from marine mammals, and antibodies have been found in several species of wild land animals (Karstad, 1981).

Vaccines of proven quality should be used, and coverage of nearly 100% of the bovine population is necessary. The oil-adjuvant vaccine is currently recommended because it has been shown to be far superior to the aluminum hydroxide-adsorbed vaccine, producing both higher serum antibody titers and longer-lasting protection. Calves under 2 years old should be revaccinated every six months; once they reach 2 years of age, if they were previously vaccinated and revaccinated, one annual revaccination should be sufficient (Bahnemann and Mesquita, 1987). Calves born of vaccinated mothers do not respond to the liquid aluminum hydroxide-adsorbed vaccine at day 30 or 90 postpartum, whereas those inoculated with the oil-adjuvant vaccine acquired antibodies at day 21, and by day 30 they responded in the same manner as adult cattle. Colostrum-deprived heifers vaccinated between 3 and 30 days after birth demonstrated adequate antibody titers. In endemic areas, it is very important to protect calves from a very early age in order to ensure satisfactory herd immunity (Sadir *et al.*, 1988). The vaccination of swine is of doubtful value from the cost-benefit standpoint, and, as long as the cattle are protected, the risk for these animals is almost nil.

In Argentina, all calves are vaccinated as soon as they can stand up, and then they are revaccinated every six months until they are 2 years old, after which the policy is annual revaccination. Sheep are vaccinated once a year.

Advances in knowledge about the molecular structure and chemical composition of the FMD virus, coupled with the availability of recombinant DNA technology, have made it possible to develop vaccines based on protein subunits. A vaccine produced by genetic engineering contains only the VP3 capsid protein of the FMD virion, which is the principal immunogenic component of the virus. It has also been possible to obtain a synthetic peptide of 20 amino acids corresponding to a part of the virion surface protein. In a conjugate with carrier protein, the peptide induced neutralizing antibodies in guinea pigs as well as antibodies and protection in rabbits (Bittle *et al.*, 1982).

All control programs should include mechanisms for the proper treatment of focal and perifocal areas, as well as means for controlling the movement of animals and the disinfection of vehicles, materials, and equipment. In a control or eradication program, it is of the utmost importance to oversee the movement of animals and their products.

Prevention of the disease in man consists mainly of controlling the disease in domestic animals. For individual prevention, persons in contact with sick animals or FMD-contaminated materials should be careful to cover any wounds or abrasions on the skin, and milk should be pasteurized or boiled.

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HERPES SIMPLEX (TYPE 1)

ICD-10 B00.1 Herpesviral vesicular dermatitis

Synonyms: *Herpesvirus hominis*, human herpesvirus (types 1 and 2).

Etiology: The herpes simplex virus (HSV) belongs to the subfamily Alphaherpesvirinae, family Herpesviridae. The viruses in this family have a double-stranded DNA genome, located at the center of an icosahedrally symmetric nucleocapsid. The virion measures 180 to 200 nm in diameter and has a lipid-protein envelope. There are two types of herpes simplex: types 1 and 2. They share a common antigen which causes serologic cross-reactions, and they can be differentiated by the serum neutralization and immunofluorescence tests. Epidemiologically, they differ in terms of the route of transmission: HSV1 is transmitted orally, and HSV2 venereally. When radioimmunoassay (RIA) is used to compare the two HSV types with four different herpesviruses in monkeys, including *Herpesvirus simiae*, the result shows that there are antigenic determinants shared by all six viruses. Competitive RIA has also been used to determine the relative degree of cross-reactivity: HSV1 and HSV2 are the most closely related to one another, and *Herpesvirus simiae* is more closely related to HSV1 (Hilliard *et al.*, 1989). It has also been possible to determine their close relationship using DNA hybridization.

In addition to the epidemiological and clinical criteria, several other characteristics differentiate HSV1 from HSV2, including the size of the pustules on the chorioallantoic membrane and sensitivity to heparin and temperatures over 40ºC. HSV1 forms small pustules and is sensitive to heparin and temperatures over 40ºC. An important technique for differentiation is endonuclease restriction analysis.

All the alphaherpesviruses share the characteristic of latency.

Geographic Distribution: Worldwide.

Occurrence in Man: It is estimated that 70% to 90% of the adult population has antibodies to the herpes simplex virus. Seroprevalence is higher in the lower income brackets.

Occurrence in Animals: With one possible exception, infection in animals is caused by HSV1. Two outbreaks were reported in owl monkeys (*Aotus trivirgatus*) shipped from South America to the US. One of the groups had been gathered for shipment in Barranquilla, Colombia, and the other in Iquitos, Peru. Another epizootic outbreak occurred in a colony of 84 splenectomized white-handed gibbons (*Hylobates lar*). The disease affected six of the gibbons: three of them had excoriated areas at the commissure of the lips, and the other three had small vesicles which rapidly became ulcerated and eventually necrotic. Four of the six animals died of encephalitis, with symptoms of ataxia, convulsions, paralysis of the tongue and swallowing muscles, and a progressively descending paralysis that ended in death. Herpes simplex virus was isolated from three of the animals. HSV neutralizing antibodies were found in 16 of the 84 gibbons in the colony (Smith *et al.*, 1969). The virus has also been isolated from naturally infected skunks and lemurs (Emmons, 1983), as well as tree shrews (*Tupaia glis*) from Thailand that had been shipped to the US (McClure *et al.*, 1972). In a group of six chimpanzees—two common chimpanzees (*Pan troglodytes*) and four bonobos, or pygmy chimpanzees (*P. paniscus*)—

one animal of each species had typical herpes lesions on the external genitalia: the 6-year-old male *P. troglodytes* had pustular vesicles on the penis, and the female *P. paniscus* had lesions on the internal labial fold, with ulceration and the formation of pustular vesicles. The first animal also developed gingival and lingual vesicles. The authors (McClure *et al.*, 1980) attributed the infection to HSV2. The primary origin of the infection could not be determined, but presumably it was transmitted through human contact.

The Disease in Man: The incubation period is 2 to 12 days. The primary infection is usually acquired during early infancy and tends to be asymptomatic. It is estimated that clinical symptoms develop in only about 10% of primary infections. When they do appear, the disease is manifested as an acute herpetic gingivostomatitis with a systemic reaction that varies in seriousness. The vesicles develop in the pharynx and mouth; they open up quickly, and more vesicles can appear on the tongue, the soft palate, the lips, and the cheeks. When the eyes are the portal of entry, the disease takes the form of conjunctivitis and blepharitis. Pharyngitis with vesicular lesions is the common form in adolescents. Keratoconjunctivitis can also occur, and, rarely, meningoencephalitis. A generalized fatal infection (congenital herpes simplex) has been observed in newborns (Benenson, 1990), which has been attributed to the immaturity of the immune system.

HSV infection is characterized by its latency. After the primary infection and the development of antibodies, the virus or its genome remains throughout life in a circumscribed anatomical area consisting of a neuronic ganglion of sensitive nerves together with other elements. The latent infection is often located in the trigeminal, sacral, and vagal ganglia (Hirsch, 1991), and it can reactivate, giving rise to repeated attacks, usually in the form of herpes labialis ("fever blisters") without any systemic reaction. Reactivation usually coincides with an intercurrent illness, immunosuppression, physiological changes, and other debilitating factors. Antibodies do not interfere with reactivation.

The treatment for an ophthalmic infection is application of a vidarabine-based ointment. When the central nervous system is involved, acyclovir is given intravenously.

The Disease in Animals: The infection in the two groups of owl monkeys mentioned earlier was characterized by a generalized and highly fatal disease that began with conjunctivitis, coryza, and lethargy; only four to seven days elapsed between the appearance of symptoms and death. Autopsy revealed necrotic plaques and ulcers on the tongue (although not in all the animals), necrotic foci in the liver, enlargement of the adrenal glands with a speckled cortical region, and petechiae on the lymph nodes.

The clinical picture in the gibbons was characterized by cutaneous lesions and encephalitis (see Occurrence in Animals).

Source of Infection and Mode of Transmission: Man is the natural reservoir of the virus. The most important mode of person-to-person transmission is direct contact with the saliva of a carrier. The virus can be isolated from the saliva of asymptomatic adults.

The infection was probably transmitted to the owl monkeys and other animals by contact with human carriers.

In terms of relationship to the host, the infection caused by HSV is benign in its normal host, man, and produces a highly fatal disease in an accidental host such as the owl monkey or the gibbon. An analogous pattern exists with the infection caused by *H. simiae*, which is asymptomatic or produces a mild illness in its natural reservoir, the rhesus monkey, but is highly fatal in the accidental host, man.

Diagnosis: The virus can be isolated from saliva or vesicular material in tissue culture. It has a cytopathic effect, forming multinucleate giant cells and intranuclear inclusions. In addition, pathological material can be diagnosed using the direct immunofluorescence test or electron microscopy to visualize virus particles (Berría, 1991). If the level of specific antibodies is elevated, the serum neutralization test may be useful. The presence of IgM antibodies suggests a primary infection. Polymerase chain reaction also permits diagnosis of HSV infection.

Control: It is important for persons with herpetic lesions to stay away from newborns and immunodeficient individuals. So far, there is no effective vaccine. There are no practical measures that can be taken to prevent transmission of the infection from man to monkeys.

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HERPESVIRUS SIMIAE

ICD-10 B00.4 Herpetic encephalitis

Synonyms: B virus infection, simian herpesvirus B infection.

Etiology: *Herpesvirus simiae*, also known as *Herpesvirus* B. For further details on the properties of the subfamily Alphaherpesvirinae, see the chapter on Herpes Simplex.

Geographic Distribution: The infection occurs naturally among primates of the genus *Macaca* in Asia. In India, it has been observed that incidence of the disease rises during and after the monsoon season. The SA-8 virus, which bears a close antigenic relationship to *H. simiae*, has been isolated from African green monkeys (*Cercopithecus aethiops*) and baboons (*Papio* spp.). *H. simiae* does not occur naturally in American jungles. Primates belonging to other genera can acquire the infection through contact when they are put together with infected macaques in centers for research or the production of biologicals.

Occurrence in Man: The human disease is rare but highly fatal. Since the virus was isolated for the first time in 1934, more than 25 cases have been identified. The disease occurred in persons who handled monkeys or their tissues at research or vaccine production centers. The highest incidence was recorded in 1957, the result of increased use of rhesus macaques for the production of poliomyelitis vaccine. The rhesus macaques have since been largely replaced by African green monkeys. After 1973, there were no cases until 1987, when three consecutive cases occurred in March among monkey handlers at the Naval Aerospace Medical Research Laboratory at the Pensacola Naval Air Station in Pensacola, Florida (USA); a fourth case occurred in the wife of one of the three monkey handlers (Holmes *et al.*, 1990). In 1989, there were two human cases, one of them fatal, at a research institute in the state of Michigan (CDC, 1989). Also, there was a case in 1991 at a primate center in Texas. Two-thirds of the human cases have occurred in the US, and the remaining third in Canada and Great Britain (Weigler, 1992).

Occurrence in Animals: *H. simiae* infection occurs naturally in Asian macaques. In newly captured rhesus macaques (*M. mulatta*), the rate of positive reactors to the serum neutralization test is 10% to 20%, but after captivity in closed groups, the level can be as high as 90% or 100% within two months. Other *Macaca* species—the stump-tailed macaque (*M. arctoides*), the Taiwan macaque (*M. cyclopis*), the Japanese macaque (*M. fuscata*), the bonnet macaque (*M. radiata*), and especially the long-tailed macaque (*M. fascicularis*)—are highly susceptible and easily become infected.

The prevalence of *H. simiae* among *M. mulatta* varies depending on the age of the monkey. In one study, the rate of animals with antibodies increased from 11.2% at 1 year of age to 33% when they were 3 years or older. In terms of place of origin, overall occurrence was 4.2% among rhesus macaques captured in India, 16.6% among the same species in China, and 35% among *M. irus* from the Philippines and Thailand (Rawls, 1979). Epizootiologic data are often difficult to interpret because of the different serologic methods used by laboratories (Hutt *et al.*, 1981). Natural infection is not found among nonhuman primates in Africa or the Americas. The SA-8 virus, which is closely related to *H. simiae*, is found in baboons (*Papio* spp.).

The Disease in Man: *H. simiae*, when it occurs in man, is a highly fatal disease. Only 15% of the patients have survived, and all had neurologic sequelae (Rawls, 1979). Man is probably not very susceptible to the virus, judging from the large number of monkeys that are handled and the number of bites they inflict on the people who handle them. However, the infection merits special interest and surveillance because of the high fatality rates seen in individuals with clinical manifestations.

Although the length of the incubation period is not known for certain, it is estimated to range between five days and five weeks from the time of exposure. If the infection is produced by a bite or scratch, there may be vesiculation at the wound site, followed by lymphangitis and lymphadenitis. In one of four cases described by Holmes *et al.* (1990), there was no herpetiform eruption. The generalized disease is characterized by fever, cephalalgia, nausea, abdominal pain, and diarrhea. There may also be vesicular pharyngitis, urinary retention, and pneumonia (Rawls, 1979). Neurologic symptoms start with muscular pain or insensitivity, vertigo, diaphragmatic spasms, and difficulty in swallowing. Later on, flaccid paralysis develops in the lower extremities, which spreads to the upper extremities and thorax, ultimately resulting in respiratory collapse. Manifestations of encephalitis or encephalomyelitis may last from 3 to 21 days. The histopathology is similar to that of generalized *H. hominis* infection in children, with encephalitic lesions, myelitis, and necrotic foci in the liver, spleen, lymph nodes, and adrenal glands.

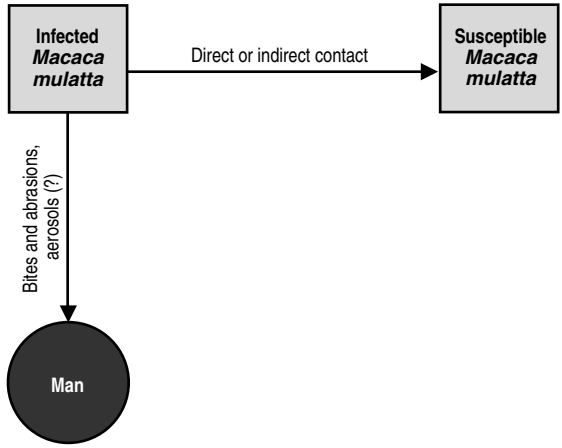
The recommended treatment is intravenous administration of the antiviral agent acyclovir, which is effective when it is introduced early in the course of the disease. Good results have been obtained with this drug on at least four occasions. Another antiviral drug that is recommended is ganciclovir (Weigler, 1992).

The Disease in Animals: In monkeys, the infection produces a benign disease that often goes unnoticed or is completely asymptomatic. In a study of 14,400 rhesus macaques, only 332 had lesions on the tongue and lips (Keeble, 1960). The disease is similar to that produced by *H. hominis* (herpes simplex) in man. The primary infection occurs in young animals. Lesions of the mouth, especially the tongue, are the most common, consisting of a vesicle that bursts and leaves an ulcer which becomes covered with a fibrinous necrotic scab. The entire process takes 7 to 14 days. It does not leave any scars or affect the animal's general state of health. The lesions may go unnoticed unless the animal is anesthetized and its mouth is carefully examined. The herpetiform eruption may also be located on the mucocutaneous border of the lips or, sometimes, on the conjunctiva or the skin. Sometimes there is conjunctivitis and a mucopurulent nasal secretion. Cases of disseminated infection are rare. The primary infection is followed by a state of latency similar to that seen in human herpes simplex infections. The agent has been isolated from the trigeminal ganglia. Reactivation of the virus usually occurs in connection with stress factors such as inclement weather, transportation, and the collection of monkeys in groups for purposes of reproduction.

The disease appears to be more severe in the long-tailed macaque (*M. fascicularis*) than in the rhesus macaque. Many infected monkeys become lifelong carriers and shed the virus intermittently in their saliva. The virus has also been isolated in primary cultures of kidney tissue from animals without macroscopic lesions.

Unlike the Asian monkeys, American species such as capuchins (*Cebus* spp.) and marmosets develop a fatal neurologic disease when they are experimentally

Figure 15. *Herpesvirus simiae.* Transmission cycle.



infected. Histologically, the lesions consist of degeneration and necrosis of epithelial cells, which develop inclusion bodies in the nuclei. Necrosis of the neurons and gliosis can be observed in the central nervous system, as well as a small perivascular lymphocytic infiltration.

Source of Infection and Mode of Transmission (Figure 15): The rhesus macaque (*M. mulatta*) and the long-tailed macaque (*M. fascicularis*) are the main natural reservoir. Other monkeys of the *Macaca* genus may constitute a source of infection for man. There was also a human case caused by the bite of an African green monkey that was living with rhesus macaques. The infection is transmitted within a monkey colony by direct contact, contamination of food and water with saliva, bites, scratches, and perhaps aerosols.

Man contracts the infection from the bite of a monkey or the contamination of a skin abrasion with monkey saliva, and possibly also from aerosols entering through the conjunctiva, nose, or pharynx. Monkeys shed the virus in saliva and secretions from the conjunctiva and genitalia. It is not understood why human cases have not occurred in Asia, where man is often in direct contact with monkeys of the genus *Macaca*. However, it is possible that there have been cases that were not recognized because of lack of adequate diagnostic tools (Weigler, 1992). An accidental laboratory infection occurred when a flask containing a monkey kidney tissue culture was broken. Only 1 case of human-to-human transmission is known: the wife of a patient with *H. simiae*, who later died, applied a zinc oxide cream on her husband's herpetic lesions and also on an open contact dermatitis lesion of her own. Later she began to apply a hydrocortisone ointment on the same lesions. When her dermatitis failed to heal, the dermatologist who was treating her took a biopsy, from which the virus was isolated. The wife was hospitalized and given intravenous acyclovir; her wound healed, and progress of the disease was halted. Although she did not have conjunctivitis, cultures from the conjunctiva were positive for the virus for 18 days. Since the woman had had no contact with monkeys, it is believed that she may have intro-

duced the infection through her eyes when she put on her contact lenses (CDC, 1987; Holmes *et al.*, 1990). In a group of 159 individuals (21 exposed to monkeys and 138 exposed to 1 or more of the 3 research laboratory patients) none developed the illness (Holmes *et al.*, 1990).

Role of Animals in the Epidemiology of the Disease: Man is an accidental host. Human-to-human transmission is exceptional. The human infection always depends on the involvement of an animal source, and macaques are the hosts and reservoirs of the virus.

Diagnosis: The possibility of *H. simiae* infection should be considered in any individual who presents herpetic symptoms and has been in contact with monkeys or monkey tissue. Previously, most human cases were confirmed postmortem by isolation of the virus from the brain or medulla oblongata. When the duration of the disease allows for the development of antibodies, diagnosis can be made by means of the serum neutralization test.

Early diagnosis is of the utmost importance because it may be too late for effective treatment by the time encephalitic symptoms appear.

The molecular methods that have been developed for the direct detection of viral nucleic acid, either through hybridization in situ or polymerase chain reaction, can be highly useful in the diagnosis of human or animal infection (Weigler, 1992; Scinicariello *et al.*, 1993).

H. simiae can be propagated in various cell cultures in which it has a cytopathic effect, but this should only be attempted in high-security (Biosafety Level 4) laboratories. The culture material may consist of biopsy specimens from the site of a bite or other wound inflicted by a monkey or a scratch or scrape caused by the wire of a cage, or from a swab of human or animal tears or animal saliva or genital secretions.

Modern serologic methods make use of the competitive ELISA test to differentiate *H. simiae* and HSV-1 from herpes simplex type 1. A dot immunobinding assay has also been applied to *H. simiae* and *H. simplex* using antigens inactivated with a psoralen derivative and long-wave ultraviolet light. Prior adsorption of the serum with *H. simplex* antigen eliminates the cross-reaction that is frequently found in the human population without affecting the sensitivity of the test. The advantage of this method is that it does not require a high-security laboratory (Heberling and Kalter, 1987).

In monkeys, complement-fixing and neutralizing antibodies appear after primary infection. The titers decline over time. Both serology and virus isolation can be used to obtain a diagnosis.

A correct serologic diagnosis is very important in establishing a colony of nonhuman primates is free of *H. simiae*. Because of the antigenic similarity between *H. simiae*, *H. hominis*, and SA-8, differentiation is difficult. In differential diagnosis it is important to bear in mind that nonhuman primates can often be infected with human strains. Several trials have shown that it is not enough to submit the simian sera to a neutralization test with *H. hominis* because a considerable proportion—as high as 50%—can be negative for this antigen and positive for *H. simiae* (Kalter *et al.*, 1978; Hutt *et al.*, 1981). For serologic diagnosis in monkeys, the same methods as those used for humans can be used. Latent infection is difficult to diagnose.

Control: All recently imported monkeys should be quarantined for six to eight weeks, and any animal with herpetiform lesions should be eliminated. The animals

should not be kept in large groups, and cohabitation of macaques with other species should be avoided. It is recommended that not more than two monkeys be housed in the same cage. If animals are found to be virus carriers, the best control method is to eliminate those that react to the serum neutralization test, and to repeat the test periodically.

Personnel taking care of the monkeys should be provided with protective clothing, and any wound or bite should be treated quickly and appropriately. Strict security measures should be observed in any laboratory where monkey tissue is handled. Studies of rabbits, which are highly susceptible to the experimental infection, have shown that acyclovir might be useful as postexposure prophylaxis; when treatment was started in rabbits within 24 hours after infection, they did not develop disease, and in those treated within 5 days postinfection a significant reduction in fatality was observed (Boulter *et al.*, 1980).

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ILHEUS FEVER

ICD-10 A93.8 Other specified arthropod-borne viral fevers

Etiology: RNA genome virus belonging to the genus *Flavivirus* (group B arboviruses), family Flaviviridae.

Geographic Distribution: The virus has been isolated in Argentina, Brazil, Colombia, Guatemala, Honduras, Panama, and Trinidad and Tobago.

Occurrence: The virus has been isolated from five human patients with mild fever, one patient with encephalitis, and two asymptomatic individuals. In endemic areas, the rate of seropositive reactors can be high. In a serologic survey conducted at a penal colony in the Araracuara forest region in southeastern Colombia, 76 (21%) of 368 serum samples were positive in the neutralization and hemagglutination inhibition tests (Prías-Landínez *et al.*, 1968). Studies done in Brazil, Panama, and Trinidad and Tobago have also demonstrated that clinically inapparent infections are frequent.

The Disease in Man: It is thought that human infection with Ilheus virus is clinically inapparent in most cases and occasionally produces a mild, undifferentiated febrile disease. A natural case with encephalitis occurred in Trinidad and Tobago. When nine patients with inoperable neoplasms were inoculated with the virus to induce oncolysis, three of them developed symptoms of encephalitis, which had a benign course.

The Disease in Animals: The virus has been isolated from several species of birds and sentinel monkeys (*Cebus* spp.). The disease tends to be asymptomatic, although viremia is present.

Source of Infection and Mode of Transmission: Numerous isolations have been obtained from mosquitoes of the genera *Psorophora* (the most frequent) and *Aedes*, which appear to be the main vectors of the virus. The agent has also been isolated from other mosquito genera. It was demonstrated experimentally that bites from *Aedes aegypti*, *A. serratus*, and *P. ferox* mosquitoes could transmit the virus to suckling mice. Birds are the most likely reservoir. In Panama and Trinidad and Tobago, the virus has been isolated from several species of birds. Antibodies have been found in mammals, but the virus has yet to be isolated from them. The studies done to date have not been sufficient to determine the reservoir with certainty.

Man acquires the infection accidentally from the bite of an infected mosquito.

Diagnosis: The virus can be isolated from patient sera by inoculation in mice.

Control: Given the low incidence of the disease, special control measures do not appear to be necessary at this time.

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INFLUENZA

ICD-10 J10.1 Influenza with other respiratory manifestations, influenza virus identified

Synonyms: Grippe [pleural effusion, pharyngitis, acute upper respiratory infection caused by an identified influenza virus].

Etiology: RNA genome virus of the family Orthomyxoviridae. Three types are recognized: A, B, and C. The surface antigens are of particular immunologic and epidemiologic interest. These antigens, which reside in protein subunits on the viral envelope, are hemagglutinin (H) and neuraminidase (N). Fourteen hemagglutinin antigens (H1 to H14) and 9 neuraminidase antigens (N1 to N9) are recognized (WHO, 1980). In the type A virus, these surface antigens occur in a number of different combinations, and each combination constitutes a different subtype of the virus. According to the accepted nomenclature, the influenza strains are identified as follows: 1) virus type (A, B, or C); 2) host of origin when it is other than human (equine, porcine, avian, etc.); 3) geographic origin; 4) strain number; 5) year of isolation; and 6) antigenic description of subtype A strains in parentheses. For example, a duck A strain isolated in Ukraine in 1963 would be designated A/duck/Ukraine/1/63 (H3N8). In the case of strains isolated from man, the host of origin is omitted.

The virion is pleomorphic, ranging in shape from spherical to filamentous, and measures approximately 100 nm in diameter. It has a bilayered lipid envelope covered

with glycoprotein spikes: when the spike is rod-shaped, it is hemagglutinin, and when it is mushroom-shaped, it is neuraminidase. Lining the envelope is the matrix (M), which consists of two proteins (M1 and M2). The purpose of both the envelope and the matrix is to protect the genome inside. The nucleoprotein (NP) has helicoidal symmetry. The M1 protein determines type specificity, distinguishing between influenza A and B viruses. The combination of neuraminidase and the hemagglutinin determines the A virus subtypes. Antibodies to hemagglutinin confer immunity against reinfection by any strain that has the same hemagglutinin (Fenner *et al.*, 1993).

The genome has eight segments of single-stranded RNA, three of which code for the H and N antigens. This property of the virus sets the stage for the genetic recombination that occurs in the different subtypes. There are more than 100 possible combinations of H and N, which gives an idea of the enormous potential for antigenic variation in the type A virus (Shortridge, 1982).

The influenza A viruses infect a large variety of animals as well as man. Phylogenetic studies have revealed species-specific lines of viral genes and have also shown that the prevalence of transmission between animal species depends on the particular animal species involved. Waterfowl are thought to be the source and origin of the influenza viruses that affect other species (Webster *et al.*, 1992). Although the full range of subtypes (combinations of 14 H and 9 N) can be found in birds, mammals harbor only a limited number of them. There is less certainty about influenza types B and C in animals. Some authors doubt that these types, B in particular, can be found in animals at all. According to a 1981 report, 15 strains of the type C virus were isolated from slaughtered swine in the People's Republic of China, and it has been demonstrated experimentally that the pig, in addition to being susceptible, can transmit the virus from one pig to another (Guo *et al.*, 1983). Antibodies to this virus have also been detected in horses, pigs, and dogs (Kawano *et al.*, 1978; Manuguerra and Hannoun, 1992). Working in the north of France, the latter authors collected 134 sera from dogs during the winter of 1988–1989 and detected antibodies to the type C virus in 32% of the animals examined using the hemagglutination inhibition and ELISA tests. They had treated the sera with *Vibrio cholerae* neuraminidase (a receptor-destroying enzyme) in order to remove nonspecific inhibitors. They also demonstrated the specificity of their results by absorbing the antibodies with *Staphylococcus aureus* A protein. In Japan, dogs were infected experimentally with the strain C/Ann Arbor/1/50, and all the dogs became ill, exhibiting the following signs: profuse nasal discharge, tumefaction of the eyelids, and conjunctivitis with pronounced lacrimation. In most of the cases, the symptoms persisted for 10 days (Homma, 1986). With regard to type B, there is a report of isolation of the virus from horses. Antibodies have been detected in horses, pigs, and dogs. In a seroprevalence survey conducted in Japan using the hemagglutination inhibition test, 16 (3.2%) of 504 horses examined were positive for the B virus, as was 1 (0.1%) of 1,030 swine (Kawano *et al.*, 1978).

The changes that occur in the epidemiology and epizootiology of influenza type A are caused by variations in the principal H and N antigens (Kaplan, 1982). All type A viruses undergo variations over time, which may be minor or can signify the emergence of a new subtype. The study of these antigenic changes and the possible role of animals in providing part or all of the genetic material for new human subtypes of influenza is the focus of much research in this field, which seeks to understand the emergence of human pandemics caused by new subtypes (Laver *et al.*, 1984).

Antigenic variations have also been found within type B, but they are not as marked or as common as in type A. The antigenic characteristics of type C are stable.

Geographic Distribution: Worldwide.

Occurrence in Man: Influenza usually occurs as an annual epidemic and is characterized by high morbidity and low mortality. The largest epidemics and pandemics of the last century (in 1918, 1957, and 1968) were all caused by the type A virus. Type B influenza usually causes less extensive epidemics and occurs at longer intervals than type A. A type A epidemic can coincide with an outbreak of type B. In 1985–1986, the US experienced the worst epidemic of type B influenza since 1968–1969. In Central and South America, there have been few reports of this type of influenza: the virus was isolated from children in Panama, and some viral activity was identified in Chile. In Europe, the A (H3N2) and B viruses were in circulation at the same time. Type B influenza predominated in the former USSR and was the only virus isolated in the former German Democratic Republic. It was also the type most frequently isolated in the Federal Republic of Germany (WHO, 1987). The type C infection occurs in limited outbreaks or as sporadic cases, and a large proportion of the infections are clinically inapparent.

The largest and most severe pandemic of the last century occurred in 1918–1919, when approximately 21 million persons died throughout the world. This pandemic was caused by the H1N1 subtype. The previous pandemic, which occurred in 1889, was caused by the H3N2 subtype. Apparently, a major antigenic shift took place in the interim.

During epidemics, the attack rate ranges from less than 15% to 40%. The second pandemic of the last century, which occurred in 1957–1958, was caused by the "Asian flu" virus (H2N2 subtype). It produced an estimated 70 million new cases in the US within a two-month period, and 5 million people were bedridden at some time during that period. In the former USSR, approximately 30% of the total population was affected by the same epidemic.

In institutions such as schools, the attack rate often reaches 70%. Although the case fatality rate is usually low, there is an increase in mortality vis-à-vis the rate expected in a nonepidemic period. For example, in the US there were 62,000 excess deaths during the 1957–1958 pandemic.

The third pandemic, which took place in 1968–1969, was caused by an H3N2 subtype (prototype A/Hong Kong/68 (H3N2)) and was more moderate than the previous ones. In the US, there were an estimated 27,900 excess deaths. Another pandemic occurred in 1977, again caused by the H1N1 subtype. Up until then, the new subtype had always replaced the previous one, but in this pandemic the H1N1 and H3N2 subtypes were both in circulation in some countries because the H3N2 subtype still persisted from the previous pandemic. The pandemics have occurred at highly irregular intervals (from 9 to 39 years) and have been due to major changes in the genes that code the H and N antigens. Also of interest was the reappearance of a subtype like H1N1 after so many years. A possible explanation is that the subtype had spent the intervening time in an animal reservoir (Knez, 1991). During the intervals between pandemics, there are epidemics every year. In cities, these epidemics have a sudden onset, reach their peak in two to three weeks, and last for a total of five to six weeks. They begin with schoolchildren and soon thereafter spread to the adult population. These episodes are followed by reports of an increased num-

ber of hospitalizations for pneumonia. In addition, there is greater absenteeism from schools and jobs (Betts and Douglas, 1990). During the nonepidemic months there are only sporadic cases. The epidemic season in the Southern Hemisphere is from May to September, and in the Northern Hemisphere it goes from December to April—in other words, it occurs during the cold months. In tropical regions, however, the cases do not usually follow a seasonal pattern. During the 1993–1994 flu season, there were 3,963 isolations of the influenza virus in the US, of which 3,959 (99.9%) corresponded to type A and only 4 to type B. In other countries, such as China and Slovakia, there were outbreaks of type B, and in still others there were only sporadic cases. Type A (H3N2) was responsible for most of the viral activity during 1993–1994 in Asia, the US, and Europe, but type A (H1N1) was also isolated on a few occasions in the US, the Russian Federation, Hong Kong, Hungary, and the Netherlands (CDC, 1994). It is also of interest to point out that type A (H3N2) underwent an antigenic variation during 1993–1994: in Asia, the US, and Europe it was more similar to the strain A/Shangdong/9/93 than to the strain A/Beijing/32/92, which it had resembled more closely in the past.

Occurrence in Animals: Type A influenza occurs especially in swine, equines, and numerous wild and domestic avian species.

SWINE: The number of influenza subtypes found in mammals is limited. Two virus A subtypes have been recognized in swine: H1N1 and H3N2. The former is known as classic swine influenza (H1N1) and is one of three subdivisions, based on antigenic and genetic criteria of the H1N1 subtype, along with its avian and human forms (Webster *et al.*, 1992). A new variant has been described in Quebec, Canada (Dea *et al.*, 1992). Swine influenza has been known since 1918, when it appeared in the midwestern US. In the last three or four months of that year, millions of pigs became ill and thousands died. The fact that this epizootic coincided with the devastating pandemic of 1918–1919 (identified serologically as H1N1), coupled with the similarity of the symptoms observed in swine and humans, gave rise to the hypothesis that the pigs might have contracted the infection from man. On the other hand, some investigators have claimed that the opposite scenario is more likely—i.e., that the human infection originated in pigs (Kaplan, 1982). Retrospective serologic studies of older persons have suggested that in 1918–1919 a virus similar to the agent of swine influenza was circulating in the human population. Since 1918–1919, outbreaks of disease among pigs caused by subtype H1N1 have occurred almost annually in the US, and it is possible that the classic strain of the swine influenza virus circulates year-round in that country. In Europe, swine influenza occurred in the 1950s in former Czechoslovakia, Germany, and the UK. It then apparently disappeared and reappeared in 1976 in Belgium and northern Italy, and in 1979 in the south of France. Since 1968, there have been reports of the disease in Africa, South America, Asia, and Canada. All the strains except the one observed in Italy, which is similar to the American strain, bear a closer genetic and antigenic resemblance to strains isolated from ducks (Fenner *et al.*, 1993).

In the US, the infection is widespread throughout the country. Antibodies are detected in 25% to 33% of pigs slaughtered in abattoirs at 6 to 7 months of age, while in those 2 years old and over the rate increases to 45% (Easterday and Hinshaw, 1992). Research indicates that there may be low levels of prevalence in several countries of the world and that the infection is probably enzootic in main-

land China, Hong Kong, and Singapore. A moderate antigenic drift was observed in this swine influenza virus between 1930 and 1977 (Schild, 1981). It has been demonstrated that it is possible for the infection to be transmitted from man to swine. During the 1968–1969 human pandemic caused by the H3N2 subtype, a strain of this subtype was isolated in Taiwan from 139 pigs examined in December 1969, and, similarly, 11 strains were isolated from 276 animals in January 1970. Serologic and virologic studies have also demonstrated the presence of this human subtype in swine in the US, Hong Kong (China), and many other countries. These strains were very similar to the human prototype strain A/Hong Kong/68 (H3N2). Some of the studies have revealed a high prevalence of antigenic variants of the H3N2 virus that are of low pathogenicity for swine. Also, it is of interest that the virus was isolated from swine in Hong Kong in 1976, several years after it had disappeared from the human species. Isolation of the H3N2 virus in swine after it had ceased to circulate in the human population would indicate that it had become established among swine in Asia, suggesting that this species might serve as a reservoir for subsequent transmission to man (Shortridge *et al.*, 1977). In other places where infection caused by the H3N2 human virus occurred in swine—for example, Hawaii (Wallace, 1979a) and Spain (Pérez Breña *et al.*, 1980)—it was not possible to demonstrate that this A subtype had persisted in the porcine population. In the human population, the H3N2 virus underwent antigenic variations with respect to the prototype strain A/Hong Kong/68, whereas in swine the human strains of H3N2 that continued to circulate were closer to the antigenic configuration of the earlier strains than to the human strains that emerged later. Oligonucleotide mapping confirmed that A/swine/Hong Kong/3/76 resembled the early strains of A/Hong Kong/68 more closely than it did the H3N2 virus that circulated in the human population during 1976. Nevertheless, one of the strains isolated from swine (A/swine/Hong Kong/4/76) had an oligonucleotide map similar to that of a contemporary human strain. It was concluded that A/swine/Hong Kong/3/76 was an agent similar to the human virus of 1968, which underwent genetic mutations without a pronounced change in its antigenicity while it was circulating in the porcine population (Nakajima *et al.*, 1982).

Genetic recombination of animal and human viruses during mixed infections is regarded as one of the mechanisms that may give rise to pandemic strains. In Japan, Sugimura (1980) isolated a recombinant (H1N2) virus from swine in which the hemagglutinin was the same as that of the H1N1 strain in swine but the neuraminidase was similar to that of the H3N2 strain isolated from man.

In 1979, during an epizootic outbreak of swine influenza in Belgium, it was possible to isolate an H1N1 subtype that was antigenically related to the strains of H1N1 isolated from wild ducks, which would indicate that an avian virus can be transmitted to swine (Pensaert *et al.*, 1981). In 1984, there were 22 outbreaks in Belgium, 8 of them caused by H3N2. In these outbreaks, the infection was associated with clinical symptoms, which are not usually seen with this subtype. The virus was similar to the human strain A/Port Chalmers/1/73 (H3N2) (Haesebrouck *et al.*, 1985). A study on the seroprevalence of swine influenza in several regions of Chile using the hemagglutination inhibition test showed that of the 303 samples examined, 32.2% were positive for H3N2 and 2.3% for H1N1 (Sanchez and Vicente, 1984). In Japan, a study based on 3,701 samples taken from swine at a slaughterhouse in Hokkaido over the period 1980–1983 revealed antibodies for H3N2 in 14.7% of the

animals in 1980 and 31.4% in 1983, suggesting that they were infected with the human virus when they were sucklings (Hirano *et al.*, 1985).

Not only can swine acquire the infection from humans, but their virus can be transferred to man and dogs as well. In 1976, the classic swine virus (H1N1) was isolated from recruits at the Fort Dix military base in New Jersey, US, and one of them died. In 1978, the same swine virus was isolated from a pig and a man on a ranch (Hinshaw *et al.*, 1978). Two human cases of influenza were detected in south Texas, US. Both patients had been in contact with pigs, and an H1N1 virus with characteristics of a swine strain was isolated (Dacso *et al.*, 1984). In Wisconsin in 1988, a 32-year-old pregnant woman was hospitalized with pneumonia and died eight days later. Four days before she became sick, the patient had visited a fair at which the pigs were suffering from an influenza-like illness, and an influenza-related virus was isolated from the woman. Of 25 individuals who exhibited pigs at the fair, 19 (76%) had antibodies to the A/Wisconsin/3523/88 (H1N1) virus. A member of the hospital staff who attended the patient also became ill and had a positive serologic reaction (Wells *et al.*, 1991).

A human case caused by the swine strain of H1N1 has never given rise to an epidemic. In a seroprevalence study conducted among slaughterhouse workers, antibodies were detected in 20% of the persons examined (Webster *et al.*, 1992). The virus subtype H1N1 with swine strain characteristics can also be transferred to turkeys. When the genes of 11 strains of the H1N1 subtype isolated over the course of 10 years were evaluated using the dot-blot test, 7 of the 11 had the characteristics of swine influenza genes (Wright *et al.*, 1992).

Most outbreaks in the US occur in autumn and extend through winter. The seasonal nature of the disease is attributed to the stress produced by fluctuations in ambient temperature and changes in diet. In a given area, the disease appears simultaneously on many farms and affects almost all herds. These multicentric outbreaks are not usually related to the movement of pigs from one farm to another, which would indicate that the infection persists in the herd from one season to the next. The virus's mechanism for survival during interepizootic periods is unknown. It has been demonstrated that experimentally infected animals are able to transmit the virus to their contacts for up to three months postinoculation. On the other hand, it has been found that classic swine influenza (H1N1) circulates throughout the year, which contributes to its persistence.

EQUINES: Equine influenza is caused by two different subtypes of type A. In 1956, the subtype A/equine/Prague/1/56 (H7N7), or equine virus 1, was isolated in the former Czechoslovakia and later isolated in other parts of the world. The H antigen of equine virus 1 is antigenically related to the fowl plague virus (H7N7) and can protect birds against lethal doses of the latter virus. The second equine subtype, A/equine/Miami/1/63 (H3N8), also known as equine virus 2, was isolated for the first time in the US during an epizootic that spread throughout the country and crossed the border into Canada. During that same year, it appeared in Uruguay and later in Brazil. Two years after the epizootic began in the US, the subtype appeared in Europe and caused major epizootics in France and Great Britain; it then spread to Switzerland, and later, Japan.

The behavior of these viruses varies depending on the immune state and density of the equine population, as well as other factors. When one of the subtypes affects

a population that has had no prior experience with it, it produces an explosive outbreak with attack rates of 60% to 90%. In populations that have suffered previous infections, illness is only observed in young animals and those that have come from disease-free areas. Since it was first isolated in 1963, equine virus 2 has undergone significant antigenic variation relative to the prototype strain. In the epizootic of 1978–1979, horses vaccinated with A/equine/Miami/63 antigen were not protected against the active equine virus (van Oirschot *et al.*, 1981).

For a while, both subtypes continued to cause outbreaks of equine influenza in the world, without A/equi 2 (H3N8) displacing the previous subtype as had been expected. Despite the coexistence of the two subtypes among equines and the opportunity for genetic recombination, it was not possible to verify that any such recombination had occurred. However, competitive RNA-RNA hybridization and nucleotide sequence analysis showed that in fact there had been a switch in the viral genes that code the internal proteins (Webster *et al.*, 1992). The H7N7 subtype has disappeared almost entirely in the US and Europe, but it continues to circulate at low levels in Central Asia. In China, an H3N8 subtype appeared, and its genetic characteristics indicate that it probably came from birds and would have been recently introduced (Webster *et al.*, 1992). In Great Britain, the Netherlands, and the US, it was demonstrated serologically that the human populations of these countries were affected by the A/equi 2 virus, or one that was antigenically similar, between 1889 and 1895. This subtype is also antigenically related to A/Hong Kong/1/68 (H3N2). Human volunteers experimentally infected with A/equine/Miami/1/63 developed signs of disease. It was possible to isolate the virus for six days postinfection, and in 4 of 15 individuals it could be isolated up to day 10. Horses exposed to the "human" Hong Kong virus developed a mild febrile illness, and the virus could be isolated for up to 5 days postinfection. However, it was not possible to determine whether these cross-infections occur in nature (Beveridge, 1977).

BIRDS: Birds, especially waterfowl, have the largest variety of influenza A virus surface antigens, ranging from H1 to H14 and N1 to N9. Birds are currently regarded as the main reservoir and source of the influenza virus for mammals and man. The great majority of subtypes are not pathogenic for domestic or wild birds. In wild ducks, the influenza virus replicates in the intestine and is shed in the feces, causing the surrounding water to become contaminated, which indicates that these birds have a very efficient means of transmitting the virus (Webster *et al.*, 1978). The virus can also be disseminated when these birds migrate from Canada to the southern US or from Siberia to the south of China. The predominant subtypes change from one year to the next. Isolations have been obtained in Australia, southern China, western Europe, and Israel. Phylogenetic studies indicate that the viruses carried by waterfowl from Canada and the US are genetically distinct from those in Asia, Australia, or Europe, possibly because of the different migratory routes (Webster *et al.*, 1992). Influenza viruses have been isolated from domestic fowl (chickens, ducks, turkeys) and such free-living birds as the common tern (*Sterna hirundo*), the wedge-tailed shearwater (*Puffinus pacificus*), wild ducks, and other species. The etiologic agent of fowl plague is an influenza A virus (subtype H7N7). Influenza outbreaks in birds are often focal in nature. In 1983–1984, a severe influenza epidemic broke out in Pennsylvania, US, as a result of which 11 million birds died or were sacrificed in three states. In addition, in Virginia, 125,593 birds

died in 10 establishments. This epidemic came as a surprise, because there had been only three cases of avian influence in the US since 1929 (Anon., 1984). The virus was identified as subtype H5N2 (OIE, 1983). The antigenic composition of the avian viruses is not necessarily related to their virulence; some completely avirulent strains have been isolated which are very closely related antigenically to the agents of fowl plague (Schild, 1981; WHO, 1981).

Outbreaks of severe disease caused by highly virulent influenza viruses are quite rare. Since 1975, there have been two such outbreaks in Australia, one in the US, and one in England. Prior to that date, there was one in Ireland in 1929.

The prototype strain of fowl plague is A/FPV/Dutch/27 (H7N7). Another strain that has been highly virulent is A/chicken/Pennsylvania/1370/83 (H5N2), which caused the death of large numbers of chickens in several states of the US. In 1994, the International Office of Epizootics (OIE) reported an outbreak of fowl plague in the Netherlands in which 138 emus, 41 rheas, 11 cassowaries, and 3 cranes were affected, and all the birds were ordered to be sacrificed (communication, International Office of Epizootics to the Pan American Health Organization, 20 April 1994). Pathology experts do not agree on the definition of "fowl plague." The first foci of this disease were caused by the H7N1 and H7N7 subtypes and were associated with high case fatality rates in chickens, turkeys, and other species. Afterwards, there was an outbreak among chickens in Scotland caused by the H5N1 subtype, with many deaths, and one among swallows caused by H5N3. Although these events led to the assumption that subtypes with H7 or H5 were highly pathogenic, later it was demonstrated that there are viruses with these same hemagglutinins that are avirulent. Some authors prefer the term "highly pathogenic avian influenza viruses" (Easterday and Hinshaw, 1991).

Because birds, especially migratory waterfowl, are thought to play a role in recombination of the influenza virus, given their wide range of subtype genes, studies have been devoted to both domestic and wild birds, and many strains have been isolated from numerous species around the world.

A characteristic feature of influenza in birds is that the virus replicates both in the respiratory system and in the intestine. It is shed in the feces, thereby contaminating the environment. Waterfowl, especially domestic and wild ducks, have been the focus of special attention. The virus can be isolated from the cloaca of these birds and from the ponds where they swim. Domestic ducks can have clinical manifestations of influenza, but such signs have not been observed in wild ducks. In a four-year study of domestic birds in southern China and Hong Kong, the viruses isolated represented 46 different H-N subtype combinations, and the majority of them (43) were obtained from ducks. The diversity of viruses in the duck population of this region may be explained by the large number of ducks that are raised for human consumption, with ongoing transmission by the fecal-oral route to susceptible young ducks in small ponds. The region is of great interest because it is a corridor for the routes of migratory birds from different areas which can introduce new antigenic combinations, and also because it would appear that a number of pandemic viruses have originated there (Shortridge, 1982).

Viruses similar or identical to the classic swine influenza (H1N1) have been isolated from wild mallard ducks (*Anas platyrhynchos*) in Canada, Hong Kong (China), the US, and later Germany. Their biological behavior differs depending on the viruses' origin: those isolated from wild ducks replicate in the birds' trachea and

intestine, whereas those isolated from swine replicate only in the respiratory tract of these birds. With a virus isolated from wild ducks in Germany it was possible to infect suckling pigs both via the nasal route and through cohabitation, and then to re-isolate the virus from them. Some of the piglets developed mild clinical symptoms, but without serologic conversion (Ottis and Bachman, 1980). Both serologic and epidemiologic evidence of infection of turkeys with an agent related to the classic swine influenza virus was found on a property where swine and fowl were kept (Mohan *et al.*, 1981).

OTHER SPECIES: In the former USSR, an influenza A virus was isolated from minke whales (*Balaenoptera acutorostrata*) in the Pacific Ocean which was antigenically similar to the avian subtype of H1N1. Also, antibodies to a human serotype were detected in the northern fur seal (*Callorhinus ursinus*). On the Cape Cod peninsula in the US there was a die-off of harbor seals (*Phoca vitulina*) in the winter of 1979–1980, during which a virus similar to the agent of fowl plague (H7N7) was isolated from the lungs and brain of the animals. It is estimated that about 20% of the seals died, and the principal lesion found was pulmonary consolidation. In 1983, there was another outbreak in seals, but this time the case fatality rate was only 4% and the subtype was H4N5. From the biological viewpoint, the virus behaved more like a mammalian strain than an avian one. In transmission experiments, the virus replicated to a very limited extent in chickens and turkey chicks without causing any disease, and it could be isolated only from the respiratory tract. On the other hand, it was easily replicated in ferrets, cats, and suckling pigs, though still without causing any clinical signs (Lang *et al.*, 1981; WHO, 1981). Personnel who had contact with the seals developed conjunctivitis, and the virus was isolated from one of them (Webster *et al.*, 1981). In the south of Sweden, an influenza outbreak in 1984 affected 33 mink farms, causing almost 100% morbidity and the death of 3,000 animals. The main symptoms of the disease were anorexia, sneezing, coughing, and increased nasal and ocular secretions. Autopsy revealed acute interstitial pneumonia. The subtype isolated was H10N4. Until then, H10 in combination with various N surface proteins had only been isolated from birds, which led to the conclusion that the virus was of avian origin (Klingeborn *et al.*, 1985).

The human A/Hong Kong/68 (H3N2) virus has been isolated from dogs in the former USSR and Taiwan. Antibodies to H3N2 and H1N1 have been found in dogs in Italy and several other countries (Buonavoglia and Sala, 1983).

The Disease in Man: The incubation period is one to three days. The disease has a sudden onset, with fever, chills, cephalalgia, myalgia, fatigue, and sometimes prostration. Other frequent symptoms are conjunctival inflammation, intense lacrimation, nonproductive coughing, sneezing, runny nose, sore throat, and painful swallowing. Approximately 20% of the patients have rales, which do not necessarily indicate pulmonary involvement. The disease has a rapid course, with recovery in about seven days. Convalescence is usually rapid, but the cough may persist for some time. In older adults, convalescence is more prolonged. The most common complications are usually secondary bacterial infections in the form of bronchitis and/or bronchopneumonia. These complications are more frequent in persons over 50 years of age. The attack rate is higher among children than in the older age groups. During the periodic epidemics, pneumonic complications do not exceed 1% of the cases, but in some of the pandemics the rate of complications has been much higher. The influenza types

A and B have similar symptoms, while the type C virus causes a much milder illness, which is usually afebrile with more pronounced coryza. Care for uncomplicated influenza usually consists of treating the symptoms. Patients should get bed rest, drink plenty of liquids, and take remedies for the fever and cough.

Amantadine reduces the duration of the disease by half (Betts and Douglas, 1990), but it has some undesirable side effects (nausea, insomnia, and difficulty concentrating), which are reversible; rimantadine is also effective. An emerging problem is the appearance of virus strains that are resistant to the antiviral drugs.

In the case of pulmonary complications with superposed bacterial infections, the patient must be treated with antibiotics. Support measures include attention to the fluid-electrolyte balance and assisted ventilation (Betts and Douglas, 1990).

The Disease in Animals: The symptoms in animals are usually similar to those of human influenza.

In swine, the disease is characterized by sudden onset, loss of appetite, coughing, nasal and ocular secretions, dyspnea, fever, prostration, and rapid recuperation. The respiratory tract lesions develop quickly and clear up rapidly, except when there are complications. The infection can be asymptomatic in animals that have antibodies to the active subtype. When there are no complications, the case fatality rate is between 1% and 3%. In Quebec, Canada, there was an influenza outbreak that affected seven herds, with a respiratory syndrome characterized by fever, dyspnea, and abdominal respiration. Generalized lymphadenopathy was observed at autopsy, along with hepatic congestion, and pulmonary consolidation. The histopathologic lesions were those of proliferative pneumonia, with necrotizing cells in the alveoli. An influenza type A virus was isolated. Cross-reactions with the human subtypes H1N1, H2N2, and H3N2 were not observed in the hemagglutination inhibition test. Gnotobiotic suckling pigs inoculated with this virus developed the same type of lesions (Dea *et al.*, 1992).

Equine influenza has an incubation period of two to three days. It is characterized by high fever, acute nasal catarrh with a serous discharge, dry cough, myalgia, tracheobronchitis, dyspnea, and depression. The illness lasts from 2 to 10 days, and convalescence takes one to three weeks. The disease tends to be more serious in young colts, which can develop an often fatal viral pneumonia. Interstitial myocarditis caused by the equine 2 virus is often seen either during the illness or after it has followed its course. Case fatality in adult horses is almost nil. The equine 2 virus (H3N8) usually produces a more serious disease than equine 1 (H7N7).

In the seals, the disease was characterized by pneumonia and high case fatality, estimated at 20% of the affected population, but it is not known if other agents intervened in this pathology.

In birds, the influenza virus infection can be inapparent or range from a mild illness to severe disease, as in the case of fowl plague. The 1983–1984 epizootic of avian influenza in the US, which was caused by the H5N2 subtype (see Occurrence in Animals), shows that the fowl plague virus (H7N7) is not the only subtype that can cause extensive mortality in domestic birds. The usual symptoms are lack of appetite, decreased egg production, loss of egg pigment (especially in turkeys), and eggs that are deformed and sometimes fail to develop a shell. Common symptoms are coughing, sneezing, lacrimation, sinusitis, facial edema, cyanosis, nervous disorders, and diarrhea. In chicks, the case fatality rate can be high. The severity of dis-

ease caused by a given influenza virus may vary depending on the avian species in question. Easterday and Hinshaw (1991), citing Murphy, give the example of an H3N8 outbreak among ducks and turkeys in Ireland, in which the ducks showed no signs of disease whereas the turkeys had obvious clinical symptoms.

The infection in wild birds can be subclinical. On the other hand, a 1961 outbreak among common terns (*Sterna hirundo*) in South Africa had a high case fatality rate.

Source of Infection and Mode of Transmission: Human-to-human transmission occurs through direct contact, via Flügge droplets that penetrate the upper respiratory tract. The virus can also be transmitted by means of objects recently contaminated with the secretions of an infected person. Closed environments and crowds favor transmission. The infection confers immunity to the specific subtype. The resistance acquired is usually lower, narrowly specific, and less long-lasting in children than in adults. With increased age and successive exposure to antigenically related viruses, the immunologic base is broadened. A community that has experienced a major outbreak almost always has a low incidence of the same influenza subtype for three or four years.

One of the most notable characteristics of the influenza virus, which has a major impact on the epidemiology of the human disease, is the way in which its antigenic composition changes, thereby producing new variants and subtypes. Two types of variations have been identified: first, the gradual minor antigenic *drift* that a virus undergoes without essential changes in the subtype from the time it first appears, and second, the antigenic *shift* that involves the replacement of one or both of the surface antigens (H and N). The most marked variations are seen in the type A virus, and the most extensive epidemics and pandemics come about following the emergence of a new subtype. The H1N1 virus was prevalent from 1933, when it was first identified, until 1956. In 1957, a completely new subtype emerged (H2N2) and replaced the former one, causing the pandemic of "Asian flu." This subtype remained active through 1967. The following year another subtype emerged, A/Hong Kong/68 (H3N2), which also caused a pandemic. Then, in 1977, the H1N1 subtype reappeared after a 20-year hiatus. These sudden changes have enabled the subtype A virus to spread rapidly, since the human population has not developed any antibodies to the new subtypes. The epidemic associated with reappearance of H1N1 affected children and adolescents in particular, since they had not had any previous experience with this subtype. In 1977, a minor variant of the Hong Kong (H3N2) virus was also active, and both subtypes could be isolated in the same community. In 1981, a minor variant of H3N2 (A/Bangkok/79) and a variant of H1N1 (A/Brazil/78) continued to give rise to outbreaks. That was the first time that two subtypes were active simultaneously (Stuart-Harris, 1981). The minor variations, or drifts, can be accounted for by passage of the virus through partially immune populations. The challenge is to explain the sudden changes, or shifts, that lead to the total replacement of one or both of the surface antigens and the appearance of a new subtype. Two hypotheses have been advanced. According to one of them, the new antigenic subtypes develop as the result of mutation caused by the pressure of acquired immunity in the population. The other hypothesis is that the new pandemic strains arise from the recombination of preexisting human and animal strains. This latter explanation is gaining increased support as a growing body of research demonstrates that subtypes isolated from different hosts recombine easily when they

are cultured together in chick embryo or animal hosts (swine and turkeys) under simulated natural conditions. The accumulated evidence points increasingly to waterfowl as the likely primitive hosts of the A virus and the principal laboratory for genetic recombination leading to the formation of new subtypes. It should be kept in mind that the numerous A virus subtypes that have been isolated from aquatic birds, especially wild ducks, and that all the antigens of the mammalian strains, are present among the avian subtypes. It is also thought that mammals, especially swine, may intervene in the recombination process. The mutation hypothesis, on the other hand, lost most of its appeal after research demonstrated that the hemagglutinin antigen (H) in the A/Hong Kong/68 (H3N2) strain was different from that found in the strains that were active immediately prior to the 1968 pandemic. It is difficult to believe that such a radical change could have occurred in a single mutation. Advocates of the recombination hypothesis are inclined to believe that the new virus is a hybrid of a human and an animal strain in which the neuraminidase (N) was contributed by an earlier human Asiatic strain and the hemagglutinin (H) by an animal strain. It should be remembered that each subtype is composed of a combination of one of the 9 neuraminidase antigens and one of the 14 hemagglutinin antigens. The idea that animals might contribute to the influenza A gene pool is also supported by the fact that the human type B virus, which does not have any counterparts in lower animals, does not undergo sudden changes in its surface antigens (Stuart-Harris, 1981). One of the main objections to the hypothesis of recombination of animal and human viruses has been that the transmission of human viruses to animals is uncommon and transmission from animals to man is even more rare (Kilbourne, 1978). This objection does not stand up, however, since it has been demonstrated that the human Hong Kong (H3N2) strain spread to swine, cattle, dogs, and birds in various parts of the world after the pandemic of 1968. On the other hand, it is true that transmission from animals to man is quite infrequent and, when it does happen, there are few if any secondary cases. The species-specific barrier is not rigid, and, as it was pointed out earlier, an avian strain is known to have caused an epidemic outbreak in marine animals (among seals in the US and whales in the Pacific Ocean). A number of questions remain unanswered. Under the auspices of the World Health Organization, intensive research is being conducted on this subject, which is clearly of importance in the epidemiology and prevention of influenza.

In addition to the fact that influenza A viruses in lower animals and birds may play an important role in the origin of human pandemic subtypes, there have been cases in which animal viruses have been transmitted to man, and it is well to review these briefly. Since 1974, sporadic cases of influenza have been reported in Minnesota and Wisconsin, US, among persons who were in contact with pigs, and the viruses were identified as classic swine influenza (H1N1). In all these episodes, secondary human cases were infrequent (Easterday, 1978). Human infections caused by a virus similar to the agent of swine influenza also occur in persons who have had no known contact with pigs or turkeys. In 1982, a virus bearing a close antigenic relationship to A/New Jersey/8/76 (H1N1) (see below) was isolated from an immunocompromised young girl with acute lymphoblastic leukemia, who died of fulminant pneumonia. Although 5 of the 47 workers at the hospital where she stayed had elevated titers for the virus, this finding could have been an anamnestic or heterotypical response to some other H1N1 subtype. At any rate, human-to-human transmission of the swine influenza virus appears to be lim-

ited, and this agent is unlikely to provoke an epidemic outbreak in man (Patriarca *et al.*, 1984).

An influenza outbreak at the Fort Dix military base in New Jersey, US, caused alarm when a virus with characteristics similar to those of the A/New Jersey/8/76 (H1N1) swine flu virus was isolated from several recruits. Concern arose from the fact that the pandemic of 1918, which caused massive deaths, had been attributed to a similar subtype, and many authors had suggested that it was associated with pigs. However, human-to-human transmission of the strain isolated at Fort Dix was rather limited. An epidemiologic survey showed that about 500 of the 12,000 persons on the base had been infected with the swine influenza strain. This is a low rate if it is kept in mind that the recruits, because of their age, could not have acquired antibodies to the epidemic subtype of H1N1. The virus's period of activity was also limited: it lasted less than five weeks, while the A/Victoria/3/75 (H3N2), a variant of the Hong Kong strain that was circulating at the same time, continued to be active. It was not possible to determine the initial source of infection of the swine virus, which was the source of fewer than 10% of the influenza cases reported on the base. This episode was important because for the first time it was verified that the swine virus can be transmitted from human to human without direct exposure to infected pigs. In the US, antibodies to the swine influenza virus or a similar agent have been found in persons over 50 years of age, suggesting that antigenically similar viruses prevailed in the human population up until 1930. There are also indications that more recently there may have been occasional infections caused by the swine virus among persons in frequent contact with pigs. During the episode in Wisconsin, a woman developed influenza and died after visiting a livestock fair. Antibodies to the H1N1 subtype were found in 76% of the exhibitors, but the infection did not spread to the rest of the community. Undoubtedly there is some constraint against interspecies transmission. It will be recalled that, except for migratory waterfowl, the animal species in question harbor only a limited number of subtypes. Webster *et al.* (1992) investigated various hypotheses and found that the most attractive explanation for the phenomenon was the specificity of the H surface antigen receptor in each animal species. Moreover, competitive inhibitors of the H receptor, which may limit the number of species affected, have been found in the serum of many species. There is also evidence that the neuraminidase component is involved in this constraint, but the mechanism is not understood.

The episode involving transmission of a virus similar to the agent of fowl plague (H7N7) from seals to man (see Occurrence in Animals) also shows that, in certain circumstances, the influenza agent can cross the species barrier. Another example of transfer from one animal species to another was the transmission of type A influenza (H1N1) from swine in Brittany, France, in 1981 and 1982–1983 to turkeys (Aymard *et al.*, 1985).

Epidemiologists point out that almost all the pandemic strains have originated in China. The distribution of wild and domestic ducks is subject to the availability of surface waters such as lakes and ponds. China is the country with the most domestic ducks, and it lies on the migration route of arctic ducks. Wild mallard ducks (*A. platyrhyncos*) disseminate their large collection of influenza subtypes as they migrate southward, contaminating the lakes in the southern part of the country with their excreta. Domestic ducks then acquire the infection in the water, and strains potentially infectious to humans emerge. Also, pigs are very common in China, and

it is recognized that these animals play an important role in transmission to other animal species. So far, there is only circumstantial evidence that the pandemic viruses originate in the south of China (Webster *et al.*, 1992).

Influenza is also spread among animals by means of aerosols and by direct or indirect contact. Although the epizootics are usually seasonal, it is believed that, as in the case of human influenza, the viruses are active throughout the year and give rise to sporadic cases that tend to go undiagnosed. Although a brief carrier state has been demonstrated experimentally in swine, more studies on animal species are needed. Among birds, the virus can be transmitted via aerosols or the fecal-oral route.

Role of Animals in the Epidemiology of the Disease: Although it has not been confirmed that viruses from lower mammals and birds play a role in the genesis of human strains, most authors are inclined to accept this hypothesis.

Influenza fits the definition of zoonosis proposed by the World Health Organization, but there are few known cases of "animal" viruses transmitted to man by lower mammals and birds. Reverse transmission, from man to animals, can occur as well.

Diagnosis: During an epidemic, diagnosis is almost always based on the clinical picture. Cases that occur in interepidemic periods are seldom diagnosed. Laboratory confirmation consists of isolating the virus. To obtain an isolation, chick embryos and cell cultures are inoculated with washings or swabs taken from the nose and throat during the first days of the illness. Various serologic techniques are used to identify and classify the virus. Serologic diagnosis is based on confirmation of a fourfold or greater increase in antibody titer in a comparison of acute- and convalescent-phase sera. The hemagglutination inhibition, complement fixation, and serum neutralization tests can be used.

Control: Preventive measures include the vaccination of individuals at high risk, such as older persons and patients with chronic pulmonary, cardiac, nephritic, and metabolic disease. The degree of protection conferred by inactivated vaccines depends on their potency and their antigenic makeup—i.e., whether or not the antigenic components correspond to the viruses involved in the current epidemic. Because of the constant antigenic shifts taking place in the active strains, vaccine development laboratories are forced to keep modifying their composition. For this reason, WHO convenes experts every year to consult on the composition of the vaccine. The recommendations are based on data from different sources: epidemiologic studies, serologic surveys, and analysis of the antigenic characteristics of thousands of isolated viruses. The three antigenic subtypes recently in circulation have been A (H1N1) and A (H3N2), along with type B. In 1992–1993, the A/Beijing/32/92 (H3N2) strain was recommended, but for the 1993–1994 influenza season, it was decided to change to A/Shangdong/9/93 (H3N2), which was closer to the strains being isolated at that time. The other two components were A/Singapore/6/86 (H1N1) and B/Panama/45/90. Studies of those who received the trivalent vaccine yielded the following positive results with the hemagglutination inhibition test: 55%–70% in children, 65%–90% in adults, and 50%–80% in older persons (titers $\geq$ 40 for H3N2). Antibodies (titers $\geq$ 40) to the A (H1N1) subtype were detected in 70% to 90% of the children tested, 95% to 97% of the adults, and 60% to 85% of the older persons (WHO, 1994). Although not all the vaccinees are protected, those

who develop the disease have a much milder illness. Attenuated live virus vaccines are being studied for wide-scale use in the face of a pandemic in some part of the world, which would allow sufficient time for advance preparation and administration of the vaccine before the arrival of the epidemic wave.

Large gatherings should be discouraged during an epidemic.

Cases of influenza should be reported to the national authorities, which in turn should submit them to the World Health Organization.

For horses, there is an inactivated bivalent vaccine available that protects against both A/equine 1 and A/equine 2. The animals should be vaccinated with two doses, spaced 6 to 12 weeks apart, followed by a booster every year thereafter.

Vaccines against swine influenza have been used with success in the former Czechoslovakia.

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JAPANESE ENCEPHALITIS

ICD-10 A83.0

Synonym: Japanese encephalitis type B.

Etiology: RNA genome virus belonging to the genus *Flavivirus* (former arbovirus group B), Flaviviridae (formerly Togaviridae) family.[1] The virus forms part of the complex that includes the St. Louis encephalitis, Murray Valley encephalitis, Rocio, and West Nile viruses.

The virus is spherical, with an envelope, and it measures 40 nm in diameter.

Geographic Distribution: The infection is widespread throughout large parts of Asia: China, the Philippines, India, Indonesia, Japan and Okinawa (its principal island), Malaysia, Myanmar, the maritime provinces of the Russian Far East, the southeast Asian region of the former USSR, the Republic of Korea, the Lao People's Democratic Republic, Singapore, Sri Lanka, Thailand, Taiwan, and Viet Nam. It is also found in parts of Australia, with cases described on islands in the Torres Strait and on the Cape York Peninsula, in the state of Queensland (Hanna *et al*., 1996; Van Den Hurk *et al.*, 2001).

Occurrence in Man: Japanese encephalitis (JE) in man occurs endemically in tropical areas; clinical cases appear sporadically throughout the year and the rainy season brings epidemic outbreaks. In countries with a temperate climate, the disease is epidemic and seasonal, appearing in late summer and early autumn. In Japan, it has

[1] All the flaviviruses belonging to former arbovirus group B have been transferred from the Togaviridae family to the Flaviviridae family.

recurred annually, with incidence ranging from small outbreaks to more than 8,000 cases a year. During the serious epidemic of 1958, there were 5,700 clinical cases with 1,322 deaths in the Republic of Korea, 1,800 cases with 519 deaths in Japan, and 142 cases with 50 deaths in Taiwan. In Japan, the incidence of human cases has declined to the point that there are now fewer than 100 a year. In the Republic of Korea, despite 80% vaccination coverage in schoolchildren, a 1982 epidemic in the southwestern part of the country produced 1,179 serologically confirmed cases. In China, more than 10,000 cases occur each year, with a case fatality rate of 10% despite the vaccination of 70 million children annually. India has 3,000 to 4,000 cases a year. In Thailand, there were 2,143 cases in 1980; in Nepal, 843 in 1982; and in Myanmar, fewer than 100 a year (WHO, 1984). Since then, the largest epidemics have been in India, Nepal, and Thailand, whereas Japan and Korea have seen a considerable reduction in cases. In two districts of the state of Uttar Pradesh, India, an outbreak of 1,148 cases (396 deaths) took place between September and November 1985 (WHO, 1986), and in one of the districts (Gorakhpur) the situation went from epidemic to endemic. The incidence rose steadily in that district between 1982 and 1988: in 1982, there were 118 cases, with a case fatality rate of 23.7%, and by 1988, the number had climbed to 772 and the case fatality rate had risen to 32.2% (Kar *et al.*, 1992).

According to data from China (Huang, 1982), the age group most affected is children 3 to 6 years of age. Morbidity declines later in life because of immunity acquired from apparent and inapparent infections. Most human infections are clinically inapparent. According to seroepidemiologic surveys, it would appear that for every clinical case there are from 500 to 1,000 inapparent infections. In some epidemics, however, the ratio of clinical to inapparent cases in adults is only 1:25.

Occurrence in Animals: During the periods immediately preceding epidemics, the infection in swine reaches very high levels. Infection in the pig—which is the most common domestic animal in some regions of Asia, such as Japan and Taiwan—is an important source of virus amplification, as well as an economic problem because of the neonatal mortality that it causes. In southern Thailand, 70% of pigs are infected (Burke *et al.*, 1985). High antibody titers have also been observed in equines, bovines, and various species of wild and domestic birds. In China, ducks have been found to have reactor rates of over 20%. In Japan, an examination of 1,339 sera from cattle in different areas of the country revealed reactor rates of 59.7% in the central part of the country and 56.8% in the south, whereas in the north the rate was only 2.1% (Sakai *et al.*, 1985).

The Disease in Man: The infection is usually subclinical. There are indications that an as yet undetermined proportion of the infections can produce a mild systemic illness without neurological symptoms. The most well-known clinical form is encephalitis, with a case fatality rate ranging between 20% and 50%. The incubation period lasts 4 to 14 days, or longer. The disease usually has a sudden onset with high fever, intense cephalalgia, vomiting, and cerebral and meningeal manifestations such as stiffness of the neck, convulsions (in children), confusion, disorientation, delirium, paresis, and paralysis. Convalescence is prolonged, and psychological and motor sequelae are frequent. In fatal cases, death comes within the first 10 days of the disease. It is believed that the variability in the clinical picture is due to differences in the pathogenicity of the various strains of the JE virus (Huang, 1982).

Treatment consists of dealing with the symptoms. The administration of recombinant alpha A interferon has given good results (Chu and Joo, 1992).

The Disease in Animals: In several Asian countries, the infection causes major losses because of the high rate of abortions and neonatal mortality that it causes in swine. In Japan, during the epidemic of 1947–1949, some regions reported abortion or neonatal mortality in 50% to 70% of the porcine population. The fetuses are often found to be mummified and hydrocephalic. The litters usually have varying numbers of stillbirths, mummified fetuses, newborns with neurological symptoms, and normal births, while infected adult pigs may have a clinically inapparent infection or a brief febrile illness. Experimental inoculation of the virus in boars has shown that it can be shed in semen. The virus has also been isolated from orchitic testicles.

Most infected boars return to normal, but some with severe infection can become permanently infertile (Chu and Joo, 1992). It is also possible for the infection to be transmitted venereally. Two serologically negative young sows that were artificially inseminated with infected semen exhibited mild fever, showed seroconversion in the hemagglutination inhibition test, and became sterile (Habu, 1991). Symptoms of encephalitis have been observed in 3-month-old suckling pigs.

In equines, the infection is usually inapparent, but some clinical cases occur every year. For the period as a whole from 1948 to 1967, morbidity in the endemic areas of Asia was estimated at 44.8 per 100,000 equines. In the large epidemic of 1948, the rate in Japan rose to 337.1 per 100,000. Study of some of the outbreaks shows that the case fatality rate can reach as high as 25%. Clinical manifestations include pyrexia, depression, photophobia, muscle tremors, impaired coordination, and ataxia. In Japan, the disease has practically disappeared in equines thanks in part to the reduced number of farm horses and also to the use of pesticides to control the mosquito population (Sakai *et al.*, 1985). When the disease does occur in equines, the most prominent signs are abortion and neonatal death.

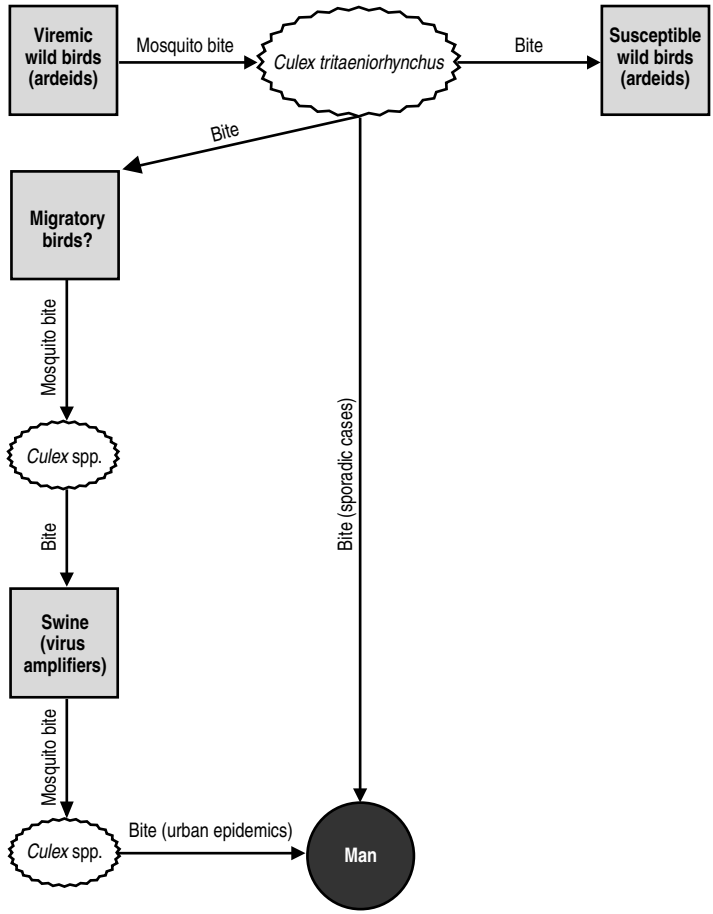
Morbidity is low in cattle, goats, and sheep.

Source of Infection and Mode of Transmission (Figure 16): In China, Japan, and several other countries, *Culex tritaeniorhynchus* is the vector most responsible for transmitting the virus both among wild birds and among pigs and cattle. The same vector transmits the infection to man. This mosquito reproduces in rice paddies and places where water naturally collects. It has a predilection for the blood of domestic animals, birds, and, to a lesser extent, man. It is active at twilight and does not go indoors. The lower morbidity in children under 3 years of age is due to the fact that they are usually kept indoors after sunset (Huang, 1982). The virus has been isolated frequently from this mosquito. In some regions of Asia, other culicine mosquitoes play a major role as vectors. Other important vectors are *C. vishnui*, *C. gelidus*, and *C. fuscocephala*. Although the virus has been isolated from at least 5 species of the *Aedes* mosquito, its epidemiologic role is still uncertain (Rosen, 1986).

The presence of antibodies against the JE virus has been demonstrated in various species of wild and domestic birds. Among the wild fauna, ardeid birds appear to play an important role as hosts of the virus, and the agent has been isolated from the black-crowned night heron *Nycticorax nycticorax* and two species of *Egretta*.

Swine play a major role as amplifiers of the virus for several reasons: they exist in large numbers in the affected countries; they are prolific and short-lived, therefore continuously providing susceptible generations; and they attract the vector. Since

Figure 16. Japanese encephalitis. Transmission cycle.



the viremia in pigs lasts two to four days, they can easily infect the mosquitoes. Equines and bovines are of little epidemiological significance because their viremia is low and they have a relatively long lifespan. In India, where the swine population is small, it is unlikely that they play a significant role as amplifiers of the virus, and therefore the epidemiology of Japanese encephalitis in that country requires further research.

The infection is probably spread between rural and urban areas by migrating viremic birds.

Epidemiologic studies carried out in Japan suggest that there is a direct relationship between the rate of serologic reactors in swine and the occurrence of epidemics in humans. In one of the areas studied, tests in 1963 yielded antibodies in only 5% of the pigs examined, and only three human cases were found in a population of 1.8 million. However, by the next year (1964), all the pigs tested were seropositive and

the area saw one of the major epidemics of the decade. The infection rate in mosquitoes (*C. tritaeniorhynchus*) was higher near the places where swine were being raised. At the same time, there was a positive correlation between vector density and the occurrence of epidemics (Maeda *et al.*, 1978).

Between the time that swine become infected (at a sufficiently high level to infect mosquitoes) and the occurrence of human infection, there is a lag of 18 days: 4 days for the viremia to run its course in the pigs plus 14 days for the virus to incubate in the vectors.

In tropical countries, the continuous activity of the vectors accounts for the year-round presence of JE and for its endemicity. In temperate regions, on the other hand, the seasonal activity of the vectors makes for epidemic outbreaks. The mechanism by which the virus survives the winter in temperate climates is still not fully understood. It has been established that in the *C. tritaeniorhynchus* mosquito the virus is transmitted sexually from the male to the female. A study of bats conducted during 1963–1965 in the principal regions of Japan showed that the populations of these mammals are infected throughout the year, and they may therefore provide an overwintering mechanism for the virus. The behavior of the virus in simulated hibernation was observed by infecting lizards experimentally through *C. pipiens pallens*. When they emerged from hibernation, the lizards had viremia for a few weeks. The hemagglutination inhibition test used on lizards (*Eumeces latiscutatus*) captured in the countryside gave a reactor rate of 14.3%, but the virus could not be isolated. In order to confirm the role of lizards in the virus' overwintering mechanism in temperate climates, it will be necessary to demonstrate that this mechanism occurs in nature (Doi *et al.*, 1983).

The agent's mechanism for maintaining itself in tropical countries is continuous transmission between mosquitoes, pigs, and birds (Monath and Trent, 1981). In the 1980s, several scientists were able to demonstrate vertical transmission in the mosquito vectors of the JE virus (Rosen *et al.*, 1986).

Role of Animals in the Epidemiology of the Disease: Man is an accidental host. Ardeid birds and the mosquito vectors constitute the basic cycle of virus transmission. Swine are important amplifiers of the virus. Vertical transmission in mosquitoes may be an additional mechanism by which the virus maintains itself in nature.

Diagnosis: The etiologic agent can be isolated from the brain of humans, dead animals, and porcine fetuses. Isolation of the virus from blood and cerebrospinal fluid is more unusual. The JE virus can be isolated by intracerebral inoculation in 1- to 5-day-old mice, pig or hamster kidney tissue cultures, or in mosquitoes. In all cases the virus causes a cytopathic effect. The *A. albopictus* mosquito cell line clone C6/36 has given the best rest results (Chu and Joo, 1992). In human patients, diagnosis is based primarily on serologic conversion in acute- and convalescent-phase samples using the hemagglutination inhibition (HI), neutralization, complement fixation (CF), and ELISA tests. HI antibodies appear early in the disease, whereas the rise in complement-fixing antibodies comes in the third or fourth week, and some patients never react to the CF test. The detection of IgM antibodies specific for the JE virus in the HI test obviates the need to investigate cross-reactions with the St. Louis, West Nile, or Murray Valley viruses (Gatus and Rose, 1983). A particle agglutination assay has also been shown to detect anti-JE virus IgM in human sera (Yamamoto *et al.*, 2002). In serologic studies of swine, it is necessary to make

allowance for antibodies from prior vaccination. A latex agglutination test to detect serum antibodies to JE virus in swine has been developed (Xinglin *et al*., 2002).

The use of solid-phase antibody-capture radioimmunoassay has also been reported with human patients (Burke and Nisalak, 1982).

Control: Control is based on vaccination. Several types of vaccines are used to protect humans. One is an inactivated vaccine derived from tissue culture (usually BHK) or the brain of newly weaned mice. The vaccine is inactivated with formalin and purified by precipitation in protamine sulfate followed by ultracentrifugation. Two doses of this vaccine (developed in Japan and evaluated in the US) produced a neutralizing titer of ≥ 8 in 77% of the volunteers. When a third dose was given 6 to 12 months later, all the subjects had titers of ≥ 16 (Poland *et al.*, 1990). Vero-cell derived inactivated JE vaccines are also being developed (Sugawara *et al.*, 2002; Monath, 2002). A modified live virus vaccine, perfected in China and Japan, has given satisfactory results. The use of live vaccines eliminates the need for multiple inoculations. In China, a virulent strain was attenuated through 11 passages in adult mice and subsequently by 100 passages in primary hamster kidney tissue culture at 36–37ºC. The vaccine was developed using a clone of a strain that had lost its neurovirulence through intracerebral passage in mice and rhesus monkeys. The vaccine was administered to 47 children 5 to 6 years of age, who were observed for two weeks. None of the vaccinees had a temperature higher than 37.4ºC or any systemic reaction. At one of the dilutions, seroconversion took place in 100% (n=12) of the subjects. It was concluded that this attenuated vaccine was immunogenic and safe for children (Xing *et al.*, 1988). Currently, a live attenuated vaccine is widely used in China (Monath, 2002).

The vaccination of swine is extremely important for both public health and economic reasons. It prevents viremia in these animals, and hence eliminates their role as amplifiers of the virus, and it also prevents abortions and neonatal mortality. An inactivated vaccine and more recent modified live virus vaccines are all in current use and give satisfactory results. However, it is difficult to maintain vaccination coverage in the swine of a given region because the population is renewed so rapidly (Umenai *et al.*, 1985).

The protection of equines is based on the same measures. There is a tendency to abandon the inactivated vaccine in favor of an attenuated live vaccine. It is recommended that the vaccine be administered twice to mares and young studs two to three weeks before the mosquito season begins (Chu and Joo, 1992).

The reduction of human and animal morbidity in China and Japan is attributable in part to mass vaccination campaigns for humans and swine and in part to the local application of insecticides.

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KYASANUR FOREST DISEASE

ICD-10 A98.2

Etiology: RNA genome virus of the genus *Flavivirus*, family Flaviviridae,[1] belonging to the complex of tick-borne viruses that includes the agents of Russian and Central European spring-summer encephalitis and ovine encephalomyelitis. It is named for the Kyasanur Forest in India, where the first cases were diagnosed.

[1] Formerly a group B arbovirus in the family Togaviridae.

Geographic Distribution: The virus has been isolated only in the state of Karnataka, India. Although the results of some serologic surveys would suggest that there have been other foci of virus activity in the country since 1970, the disease continues to be restricted to that state (Bhat, 1983).

Occurrence in Man and Animals: The disease was first recognized in 1957 during an epidemic in the Kyasanur Forest that also caused mortality in two species of monkeys: the grey langur (*Presbytis entellus*) and the bonnet macaque (*Macaca radiata*) of southern India. During this outbreak, there were 466 human cases, followed by 181 more the year after. Not all the cases were confirmed in the laboratory, and it is possible that some of them had a different etiology. In the study of the outbreak in 1959, the disease was confirmed by isolation of the virus or serologic tests in only 13 out of 28 patients with a presumptive diagnosis.

In the Karnataka endemic area, human cases are seen every year, but their number is highly variable, ranging from 5 cases in 1961 to 1,155 cases (with 150 deaths) in 1983 (Chin, 2000). A statistically significant correlation has been established between the intensity of infection in the main vector, *Haemaphysalis spinigera*, and the number of human cases in the different years (Banerjee and Bhat, 1977).

Both humans and nonhuman primates can have a clinically inapparent infection. Most human cases occur during the dry season. The persons at highest risk of infection are those who live in the small villages located in the endemic areas and go into the forest area to graze their cattle or perform other kinds of work, although 87 cases have also been reported in laboratory personnel (Pavri, 1989). Epidemics are usually preceded by epizootics in monkeys, which serve as a warning sign. In addition to the high mortality seen in monkeys in 1957 and the years thereafter, a total of 1,046 monkeys (860 *P. entellus* and 186 *M. radiata*) died during the period 1964–1973, and the virus was successfully isolated from 118 *P. entellus* and 13 *M. radiata* (Sreenivasan *et al.*, 1986).

The Disease in Man: The incubation period can range from three to eight days. The disease has a sudden onset, with fever, cephalalgia, myalgia, anorexia, and insomnia. On the third or fourth day, the patient tends to experience diarrhea and vomiting. Prostration can be severe. Papulovesicular lesions on the palate are a consistent finding, and the cervical and axillary lymph nodes are usually palpable. Hemorrhagic manifestations are seen especially in agricultural workers who are poor, malnourished, and affected by other diseases as well (Pavri, 1989). Leukopenia is common; coughing and abdominal pain are less frequent symptoms. Although a tendency toward hemorrhaging was noted in the first outbreaks, this has not been a characteristic of outbreaks studied since then. Bradycardia and hypotension are prominent signs. The fever lasts for 6 to 11 days. After an afebrile period of 9 to 21 days, a significant proportion of the patients undergo a second phase of pyrexia that lasts for 2 to 12 days, usually with neurologic symptoms such as stiffness of the neck, mental confusion, tremors, and abnormal reflexes. Gastrointestinal and bronchial problems are common. Convalescence is prolonged. The case fatality rate is approximately 5% to 10%. Patient care consists of treating the symptoms.

The Disease in Monkeys: Monkeys of the species *M. radiata*, when inoculated intravenously with the virus, developed diarrhea, bradycardia, and hypotension, and the disease was fatal in those animals that exhibited the last two signs. Phagocytosis

of erythrocytes and nuclear material was observed in peripheral blood. It is assumed that the nuclear material came from leukocytes that had been destroyed (Webb and Burston, 1966).

During the 1957 epidemic, hemorrhaging and nonspecific degenerative changes in the parenchymatous viscera were observed in 14 of 22 monkeys that were found dead (Iyer *et al.*, 1960).

Source of Infection and Mode of Transmission: Kyasanur Forest disease emerged in the wake of increases in the human and domestic animal populations which altered the ecosystem in places where the virus had previously circulated only between wild animals and its vectors. Man is infected by the bite of *H. spinigera* nymphs. Epidemic outbreaks occur primarily during the dry season when farm workers are more likely to go into the forest and ticks are more active. Human cases come to a stop, as does mortality in monkeys, once the monsoon season begins, during which few larvae and nymphs are found. This fact helps to account for the seasonal nature of the disease.

The natural cycle of transmission is still not well understood. There is little doubt that the main vector is the tick *H. spinigera*, from which the virus has been isolated on numerous occasions. It has also been demonstrated that the infection can be transmitted by the bite of this tick. The *H. spinigera* larvae and nymphs parasitize various small mammals of the forest, as well as birds and monkeys. The adult tick feeds on cattle. The *H. spinigera* larvae and nymphs attach themselves to humans, and the nymphs transmit the virus (Varma, 1989). The virus has also been isolated from *H. turturis*, in the nymphs of which the agent can survive throughout the year, and from six other species of *Haemaphysalis*, several species of *Ixodes*, and the tick *Ornithoros chiropterphila*, family Argasidae, which parasitizes insectivorous bats (Harwood and James, 1979).

The human infection is associated with the bite of *H. spinigera* nymphs. The adult tick prefers large wild or domestic animals. The introduction of cattle in the jungle has facilitated the spread and increased density of *H. spinigera,* along with broader circulation of the virus. Cattle have brought the tick closer to human settlements (Harwood and James, 1979). In a year-long study, 1,260 ticks were found on 493 of 4,668 agricultural workers examined, and 85% of the ticks were *H. spinigera*. At the same time, deforestation changed the uniform conditions of the environment and the biota, with the result that evergreen forest vegetation has been replaced by deciduous vegetation. This change has favored the proliferation of *H. spinigera* over other ticks (Banerjee and Bhat, 1977).

The virus has been isolated in a large number of *Presbytis* and *Macaca* monkeys, many of which develop the disease and die. Others survive the infection, as demonstrated by serologic testing of healthy specimens. As with jungle yellow fever, mortality in monkeys should be a warning that the virus is active and that an epidemic may be imminent. However, it is not believed that monkeys are the reservoir of the virus in nature. In this regard, studies are focusing on small forest mammals that become infected but do not die. The virus has been isolated from several species of rodents in natural foci, and the presence of neutralizing antibodies in these animals has been confirmed. Several circumstances point to the house musk shrew *Suncus murinus*, the white-tailed wood rat *Rattus blanfordi*, porcupines, and squirrels as natural reservoirs: their population density, the high levels of viremia demonstrated

experimentally in these species, and the fact that natural infections have been confirmed by isolation of the virus. However, the possibility of other rodents playing a role in the virus cycle cannot be ruled out. Birds and bats are hosts of minor importance. Monkeys, especially *P. entellus* and *M. radiata*, are amplifiers of the virus (World Health Organization, 1985).

Role of Animals in the Epidemiology of the Disease: Small forest mammals serve as the reservoir of the virus. Deforestation and the introduction of cattle have caused an upsurge in the population of the tick vectors. Monkeys play an important role in amplification of the virus. Man and cattle are accidental hosts.

Diagnosis: Viremia is prolonged, lasting up to 10 days or more. The virus is easily isolated from patient sera inoculated in mice. Serologic diagnosis can be obtained with the complement fixation, hemagglutination inhibition, and neutralization tests, as well as the enzyme-linked immunosorbent assay (ELISA) using acute- and convalescent-phase sera. Serologic diagnosis is more difficult if the patient has been previously exposed to another flavivirus.

Control: The measures usually taken for individual human protection against ticks, such as protective clothing and the use of repellents, are difficult to apply in the endemic area. A formalin-inactivated chick embryo fibroblast tissue culture vaccine produced 72.5% seroconversion in laboratory personnel, but it only demonstrated 59% seroconversion in a field trial in the endemic area. The presence of antibodies to other flaviviruses, especially the West Nile virus, seems to interfere with the vaccine's efficacy. Seroconversion was 1.8% among controls (Dandawate *et al.*, 1980).

In mice, a single inoculation of a live vaccine based on an attenuated strain of Langat[2] virus confers 70% to 100% protection against large doses of Kyasanur Forest virus for at least 18 months. This attenuated strain was administered to human volunteers without secondary effects, and it did not cause any adverse reactions in patients with terminal carcinoma (Thind, 1981).

An experimental vaccine has been used to prevent the disease in endemic areas (Chin, 2000).

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LASSA FEVER

ICD-10 A96.2

Etiology: Double-segmented single-strand RNA genome virus belonging to the genus *Arenavirus*, family Arenaviridae. The virion is pleomorphic, measuring 80 to 150 nm in diameter, and has a lipid envelope, so that it is sensitive to lipid solvents and detergents (see the chapter on Argentine Hemorrhagic Fever for further details on the characteristics of the family Arenaviridae). The virus is antigenically related to the agent that causes lymphocytic choriomeningitis. A very similar virus was iso-

lated in Mozambique from a variety or subspecies of the multimammate rat (*Mastomys natalensis*), which was designated Mozambique virus, and in Zimbabwe antibodies to this virus were found in man, but it is not known if it is pathogenic. Another virus that is also antigenically related to the Lassa virus was isolated from a *Praomys* rodent in the Central African Republic (Odend'hal, 1983).

Geographic Distribution: The infection is endemic in Guinea, Liberia, Sierra Leone, and areas of Nigeria; cases have also been seen in the Central African Republic. Serologic evidence of infection has also been found in the Democratic Republic of Congo, Mali, and Senegal (Chin, 2000). In addition, the disease has been recognized or specific antibodies have been found in Benin, Burkina Faso, Cameroon, Ghana, Ivory Coast, and Sudan (WHO, 1985).

Occurrence in Man: Lassa fever (LF) was recognized for the first time in 1969, in a missionary nurse in Lassa, Nigeria. Two other nurses contracted the disease while taking care of the index patient at a hospital in Jos, Nigeria. Two of the three nurses died, and the third one had a severe and prolonged illness. Between 1969 and 1975, there were six more outbreaks in three West African countries: Nigeria (1970, 1974, and 1975), Liberia (1972), and Sierra Leone (1970–1972 and 1973–1975). It is believed that the low prevalence of antibodies and the low antibody titers found in the human and rodent populations may be caused by previous infection with another arenavirus (Saluzzo *et al.*, 1988). Except for the one in Sierra Leone in 1970–1972, all of the aforementioned outbreaks were nosocomial, since they spread within the hospitals after an index patient had been admitted. Secondary and even tertiary cases have occurred among hospitalized patients, hospital staff, and some family members. In contrast to the nosocomial outbreaks, in Sierra Leone most of the human cases originated within the affected rural communities, and it is now believed that this is the pattern throughout all of West Africa (see below). The fatality rate for hospital cases has ranged from 20% to 66% in the various outbreaks, with an average of 36% (Casals, 1976; Monath, 1975a). The current fatality rate for hospitalized cases is 15%–20%, and only about 1% for infected individuals in general (CDC, 2002).

Cases occur throughout the year in rural areas. Apart from the highly fatal nosocomial outbreaks, the majority of cases of disease are benign, and there are also clinically inapparent infections. For example, there was serologic evidence of recent infection without disease in the population from the villages where the index cases had originated. Understanding about Lassa fever changed considerably when investigation revealed that in the uninterrupted series of 63 cases that occurred in the Sierra Leonean village over the two years prior to a nosocomial outbreak, fewer than 10% had been acquired in the hospital or from contact with another recognized case and that case fatality was lower than 5% (Fraser *et al.*, 1974). On the basis of these findings, it was concluded that the infection was endemic in the region and that only a few of the cases had been nosocomial in origin. Further studies showed not only that the infection was common but also that it was an important cause of death from infectious disease (Monath, 1987). An estimated 100,000 to 300,000 infections occur annually in West Africa, with 5,000 deaths (CDC, 2002). Seroepidemiologic studies suggest that Lassa virus is distributed multifocally in West Africa. Out of 458 human serum specimens collected from 48 different localities in northern Nigeria in 1965–1966, neutralizing antibodies were found in 10 samples from inhabitants of 5 regions. In a series of 281 sera collected from nomadic herders in Nigeria over a

period of 5 years, 23 were positive. In Sierra Leone, 11% of the inhabitants of one locality examined had complement-fixing antibodies, and in another locality the proportion was 3.5% (Monath, 1975a).

The prevalence of antibodies to the Lassa virus in Sierra Leone ranged from 8% to 52% in a survey of 15 villages (McCormick *et al.*, 1987 and 1987a). In Guinea, seroprevalence was studied in various regions of the country using the enzyme-linked immunosorbent assay (ELISA), and the highest levels (25%–55%) were found among the inhabitants of secondary tropical forest areas. The prevalence was lower (4%–7%) among the people living in the mountain regions (Lukashevich *et al.*, 1993). In western Sudan, antibodies were found in 12%–13% of a series of human sera analyzed using the indirect immunofluorescence test, without any indication of human disease (WHO, 1985).

Two cases of LF, one of them fatal, occurred among staff at a research institute in the US. Imported cases have also been seen in other countries, including Israel and Japan, without any reports of secondary cases.

Occurrence in Animals: Because of the relationship that exists between Lassa virus and the other arenaviruses, it was thought from the outset that the reservoir of the virus might be a rodent or rodents. In 1972, during the LF outbreak in Sierra Leone, a group of 641 small vertebrates were captured, representing 15 species of rodents and 10 species of other vertebrates. The agent of the disease could only be isolated from the multimammate rat (*Mastomys natalensis*): 17% of the 82 specimens processed were found to be infected. A high prevalence of infected *Mastomys* spp. was observed in the homes of LF patients. In a later survey conducted in Sierra Leone, it was found that distribution of the infection in *Mastomys* living in and around homes in an endemic area tended to be focal. In the households with cases of the disease, 39% of these rodents had viremia, whereas in the control homes viremia was found in only 3.7% of the animals. In a group of rodents caught in the homes of a village near a diamond mine, 79% were *M. natalensis* (Keenlyside *et al.*, 1983).

The Disease in Man: The incubation period is usually about seven days, but it can be as long as three weeks. Lassa virus infection can be asymptomatic, cause a mild illness, or produce a severe or even fatal disease. The onset is gradual, with fever, asthenia, muscular pain, and cephalalgia, and it can affect many organ systems. The intestinal tract is frequently affected in the form of vomiting, diarrhea, and abdominal pain. Also common are edema of the face and neck, conjunctivitis, pharyngitis, tonsillitis, cough, stertor, and thoracic pain. Ulcerative pharyngitis occurs in 80% of the cases. In many patients, the blood panel shows albuminuria, low serum albumin, and elevated urea nitrogen. Cervical adenopathy and a tendency to hemorrhage are common. When the disease takes a severe course, the high fever persists, the toxic state increases, the patient becomes apathetic, and there is vomiting, diarrhea, capillary hemorrhaging, central nervous system involvement, respiratory insufficiency, oliguria, shock, and often circulatory collapse. Death is usually due to cardiac arrest. The fatality rate among hospitalized patients, who usually suffer from the severe form of the disease, ranges between 30% and 50%. It has been estimated that for every hospitalized patient there are between 10 and 20 infections in the population. Thus, the proportion of infected individuals who die is 1% to 2% (Johnson *et al.*, 1982).

In Lassa fever, unlike Argentine or Machupo hemorrhagic fever, viremia can last 10 to 16 days, and the severity of the disease is directly related to the level of viremia

(Johnson *et al.*, 1982) and the concentration of circulating hepatic enzymes (aspartate transaminase) (WHO, 1985).

The disease is often milder in children than in adults. Following an outbreak in a Sierra Leonean village, a serologic survey of 20 households revealed antibodies to the virus in 20.4% of the children 0 to 14 years old, even though no cases of the disease had been reported (Sharp, 1982).

Those patients who recover have a long convalescence; the most frequent sequelae are partial deafness and alopecia.

Since 1978, ribavirin has been used with beneficial results in treating the disease. This antiviral is given intravenously for the first four days (60 mg/kg/day), and orally thereafter (30 mg/kg/day) (WHO, 1985). The secondary effects of the drug include mild anemia, which is reversible. It is recommended that the intravenous infusion be administered slowly in order to avoid other undesired effects (Fisher-Hoch *et al.*, 1992).

The Disease in Animals: So far, natural infection caused by Lassa virus has been found in *M. natalensis* rodents captured during the Sierra Leone epidemic and, more recently, in northern Nigeria during an interepidemic period. Experiments conducted in Zimbabwe with a race of *M. natalensis* showed that the animals acquired a persistent infection with viremia and viruria when they were inoculated during the first four days of life. Persistent infection is common in rodents infected with arenaviruses (see Lymphocytic Choriomeningitis). Carrier females give birth to the same number of offspring as do normal mothers of the species and, within two weeks, they are all infected; this situation differs from that of the female rodent *Calomys callosus* that carries Machupo virus, in which fetal mortality is almost 100% (Johnson, 1981).

No clinical signs of the disease have been observed in *M. natalensis*. A comparative study of carriers and noncarriers of the virus in *M. natalensis* captured at a home in a Sierra Leonean village revealed that the infected animals were smaller and weighed less than the noncarriers, and that they had more frequent inflammatory lesions (e.g., follicular hyperplasia of the spleen, myocarditis, myositis) than the uninfected animals (Demartini *et al.*, 1975).

Source of Infection and Mode of Transmission: The facts indicate that the reservoir of the virus is *M. natalensis*, a domestic and peridomestic rodent widely distributed in sub-Saharan Africa. This species is the most common household rodent in a number of villages of West Africa, and their infection rate is high where there have been human cases (see Occurrence in Animals). Experiments have shown that the virus is transmitted horizontally among these animals, and perhaps also vertically. Transmission in household colonies is continuous because susceptible rodents are contaminated by the excreta of those that carry the infection. Lassa virus is transmitted from rodents to man through aerosols or direct contact with their excreta (Chin, 2000).

Person-to-person transmission of Lassa virus has been demonstrated by the fact that hospital outbreaks have occurred after patients who acquired the disease at home or elsewhere in the local community were admitted. Secondary cases can result from contact with infected blood pharyngeal secretions and urine, as well as through sexual contact. There have also been cases in which the infection was contracted via skin lesions. Indeed, infection with Lassa virus poses a great risk for hos-

pital and laboratory personnel. In one outbreak, for example, 14 nurses and a physician contracted the disease while taking care of patients. During the 1970 epidemic in Jos, Nigeria, a nurse with a pulmonary illness was the source of infection for 16 other cases.

The fact that a large number of LF cases have appeared as nosocomial infections contracted from hospitalized patients raises the possibility that secondary cases could occur when a patient who became infected in Africa is hospitalized in another part of the world.

Diagnosis: Lassa fever should be included in the differential diagnosis of febrile patients who have visited or worked in LF endemic areas of Africa; early diagnosis is extremely important in order to prevent secondary cases. Specific diagnosis is obtained by isolating the virus or through serologic tests. The virus has been isolated from blood samples and pharyngeal washings or swabs taken from patients within 14 days after the appearance of the disease. Viruria is less common, but it has also been observed up to 32 days after onset of the disease. The virus is easily isolated in Vero cells using patient sera obtained between the third and fourteenth day of the disease. Antibodies do not interfere with virologic diagnosis. The virus has a cytopathic effect, which begins to be observed four days after seeding. The diagnosis can be accelerated by daily examination of the culture using direct immunofluorescence. Direct immunofluorescence with monoclonal antibodies is useful for examining tissue smears fixed in acetone.

Serologic diagnosis consists of verifying the development of neutralizing antibodies in blood samples obtained at the beginning of the illness and during convalescence. With the indirect immunofluorescence technique, it is possible to detect antibodies between 7 and 10 days after the appearance of the disease. IgM antibody capture and antigen detection by ELISA or polymerase chain reaction (PCR), as well as IgG seroconversion by ELISA or immunofluorescence assay, also permits diagnosis (Chin, 2000). Given the extreme biohazard posed by laboratory specimens, it is preferable that diagnostic tests be performed only in facilities with the highest biosafety level installations.

Control: The control measures consist of placing suspected patients in separate units, but not isolating them as rigorously as was formerly recommended (Holmes *et al.*, 1990), and providing masks, gloves, and protective clothing for the service and nursing staff who take care of patients. Special precautions should be taken with the excretions and secretions of patients, and contact with their blood or other body fluids should be avoided. Those contacts who are most exposed can be given ribavirin on a preventive basis, 4 doses of 600 mg/day administered orally for 10 days. For children 6 to 9 years old, the recommendation is 4 daily doses of 400 mg, also given by the oral route (Holmes *et al.*, 1990). These guidelines were used with the contacts of a US citizen who died of Lassa fever after returning from his mother's funeral in Nigeria. The diagnostic material should only be handled in a laboratory that takes maximum security measures for its personnel.

Rodent control measures are warranted to reduce risk of infection to persons living in endemic areas. Efforts include eliminating entry portals and nesting areas in and around home or work environments, as well as reducing and protecting against exposure to rodent excreta.

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LOUPING ILL

ICD-10 A84.8 Other tick-borne viral encephalitis

Synonyms: Infectious ovine encephalomyelitis.

Etiology: Louping ill (LI) virus, an RNA genome virus of the genus *Flavivirus* (former arbovirus group B) in the family Flaviviridae (formerly Togaviridae).[1] It belongs to the complex of tick-borne viruses (Russian spring-summer encephalitis complex).

Geographic Distribution: Scotland, Wales, northern England, and Ireland. The distribution is uneven. There had been doubts that the LI virus existed outside Great Britain and Ireland. Different authors have included Bulgaria, the Iberian Peninsula, and Turkey in its geographic distribution, but in each case the identity of the virus has been doubtful. Gao *et al.* (1993) compared a prototype LI strain from Scotland with a virus from Norway that causes encephalomyelitis in sheep. Monoclonal antibodies prepared for the glycoprotein on the virion envelope failed to distinguish one agent from the other. Homology of nucleotide sequences was greater than 95%, and that of amino acid sequences, greater than 98%. The authors suspected that viruses in continental Europe that cause encephalitis or encephalomyelitis in sheep might in fact be the LI virus. Since all tick-borne members of the genus *Flavivirus* are highly related antigenically, only the new monoclonal antibody techniques and molecular epidemiology will be capable of identifying them.

[1] All the flaviviruses belonging to former arbovirus group B have been transferred from the Togaviridae family to the Flaviviridae family.

Occurrence in Man and Animals: LI is rare in man. Only 37 cases are known, 26 of them acquired in the laboratory and 11 in nature (Smith and Varma, 1981; Davidson *et al.*, 1991). Serologic surveys indicate that sheepherders are less exposed to the infection than laboratory or slaughterhouse workers. In a serologic study of 7 laboratory workers, 5 were found to be reactors, and in another study of 12 such workers, 7 were positive. Of 134 slaughterhouse workers in 2 facilities in Scotland, 15 were reactors. In northern Scotland, 8 of 150 persons who worked with sheep were found to have positive serologic reactions. Among those examined with suspected central nervous system infection, very few had antibodies for the LI virus (Davidson *et al.*, 1991).

The infection is enzootic in several regions of Great Britain. Sheep are the animals most affected, but the disease also occurs naturally in goats, cattle, equines, red deer (*Cervus elaphus*), elk (*Alces alces*) and other cervids, small mammals such as the field mouse *Apodemus sylvaticus* and the shrew *Sorex araneus*, and certain birds, such as the red grouse *Lagopus lagopus scoticus*. The disease has also been described in suckling pigs (Bannatyne *et al.*, 1980). The regional incidence in sheep is about 5%, but it could be higher in some flocks. The greatest losses occur when sheep from infection-free areas are introduced into enzootic areas. In enzootic areas, the morbidity rate is from 1% to 4% in adult sheep; in lambs, on the other hand, it can be as high as 60% (Blood and Radostits, 1989). Lambs born of ewes that are immune remain resistant for three months to a year.

The Disease in Man: The incubation period lasts from 2 to 8 days. The disease is biphasic. The first phase, which lasts 2 to 12 days, is characterized by fever, retroocular pain, cephalalgia, and malaise. After an asymptomatic interval of approximately five days, the second phase, characterized by neurological symptoms, begins. In this phase, the disease may take the form of meningoencephalitis, or it can resemble paralytic poliomyelitis. The symptoms are highly variable. Convalescence may be prolonged, but mortality is nil (Smith and Varma, 1981). In laboratory and slaughterhouse workers, the disease may be limited to the first phase and mistaken for influenza.

The Disease in Animals: The incubation period lasts from 6 to 18 days. In sheep, the disease manifests as biphasic pyrexia. Many animals recover from the first phase, which is febrile and viremic, and afterwards they remain immune. In others, however, the virus goes on to invade the central nervous system and causes encephalomyelitis. The most prominent symptoms in the second phase are fever, impaired motor coordination, tremors, salivation, apathy, and the characteristic hopping gait, in which the animal moves both its hind legs forward at the same time and then the front ones. After one or two days in this state, the affected animal falls to the ground and remains prostrate, and suffers violent movements of the extremities. Only 50% of the animals with encephalomyelitic symptoms recover. The disease occurs primarily in spring and autumn, when the vector *Ixodes ricinus* is most abundant.

In the enzootic areas, sporadic cases also occur in cattle, with symptoms similar to those in sheep.

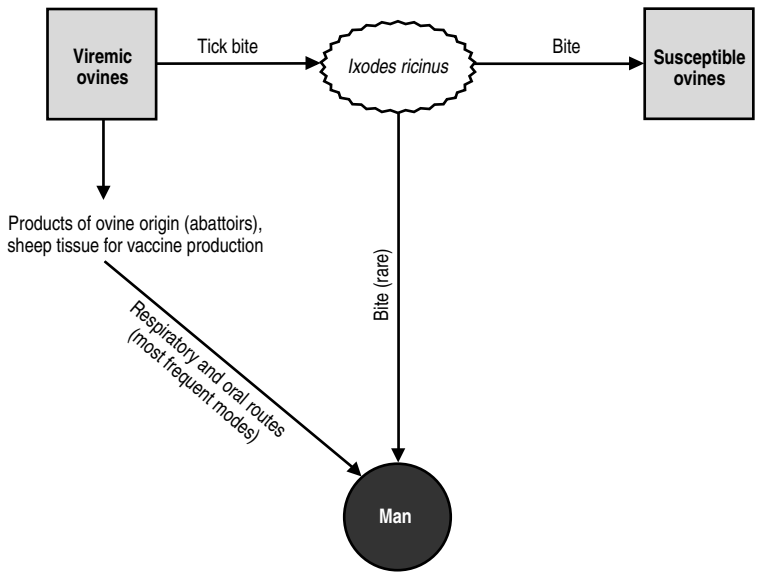
The LI virus also causes disease and death in the red grouse (*Lagopus l. scoticus)*. In areas heavily infested with *I. ricinus*, a very high proportion of these galliform birds have antibodies for LI. Many of their chicks are infected in the first 2 months

of life, and only a small number of the infected ones survive. By the month of July, in areas with little tick infestation the average brood numbers 5.5 hatchlings, whereas in highly tick-infested areas the average is only 0.6 (Reid *et al.*, 1978).

Source of Infection and Mode of Transmission (Figure 17): The disease occurs in Great Britain and Ireland in highland pastures. The main vector of the virus is the tick *I. ricinus*, which requires relatively high humidity in order to survive. The epizootics in sheep tend to occur in springtime, early summer, and autumn, when the vector *I. ricinus* is active. It remains to be understood why some of the animals recover after the first febrile phase while others go on to the second phase and develop symptoms of encephalomyelitis. Explanations that have been offered are a concomitant infection and such factors as transportation of the animal, cold weather, and poor nutrition, which may favor invasion of the central nervous system by the virus.

Sheep seem to be the main reservoir, and the sheep-tick-sheep cycle is capable of perpetuating circulation of the virus in nature. There are many species of small mammals in which antibodies have been found or from which the virus has been isolated. In some of these species, the level of viremia is too low to infect the vector, while in others this aspect has not been investigated. However, these animals play an important role as a source of food for the *I. ricinus* larvae and nymphs. When the population density of some of the small mammals increases, that of the ticks increases as well (Smith and Varma, 1981). This pattern leads to the increased infestation of sheep and hence favors the occurrence of epizootic outbreaks in ovines. Although the red grouse (*Lagopus l. scoticus*) has a sufficiently high level of viremia to infect the ticks, it can only be a temporary amplifier of the virus because its pop-

Figure 17. Louping ill. Transmission cycle.



ulation diminishes rapidly in the active LI foci. The high level of mortality in this bird indicates that it is not a primary host and that its contact with the virus is relatively recent, presumably dating from the introduction of sheep-raising in Scotland in the nineteenth century, which increases the tick population and circulation of the virus in a number of animal species (Reid *et al.*, 1978).

The larvae or nymphs become infected with the virus when they feed on viremic sheep. The virus overwinters in the tick, which transmits it to sheep in the following spring (Martin, 1981). In this vector, it has been established that transmission is transstadial but not transovarial: a larva that becomes infected when feeding on a viremic animal maintains the virus through the nymph and adult stages. The lifespan of the tick is 3 years, and during that time it only spends three weeks on a host. The larvae and nymphs feed on small animals, but the adult tick prefers large animals (Davidson *et al.*, 1991).

The fact that human clinical and subclinical infections are rare in rural areas and more frequent among laboratory and slaughterhouse workers would indicate that inhalation, handling the viscera of infected animals, and needle-prick accidents may be more important in transmission to man than the bite of a tick. The episode in which young pigs contracted the infection and disease from feeding on raw meat from lambs that presumably were infected (Bunnatyne, 1980) would demonstrate that contact or ingestion may be a route of transmission. It was possible to demonstrate experimentally that infected goats as well as infected sheep can shed the virus in their milk: 5 of the 13 suckling kids in the experiment became infected, but none of the 6 lambs did. There are no known human cases acquired from milk. The reason why humans are so rarely infected in nature may be that the vector seldom attaches itself to them.

DIAGNOSIS: In human cases, the virus can be isolated from blood during the first phase of the disease by inoculation in mice, embryonated eggs, and sheep kidney cell cultures. The virus can be isolated from brain tissue and the medulla oblongata of animals with encephalomyelitic symptoms or from those that have died or been sacrificed. The isolation task poses a risk for laboratory workers and proper precautions should be taken; the alternative would be to resort to serologic tests. Diagnosis can be obtained through neutralization, complement fixation, and hemagglutination inhibition, as well as histopathology. Since the LI virus is the only flavivirus found in Great Britain, commercial tick-borne encephalitis antigen can be used for the ELISA test, which is currently recommended. Serologic diagnosis is based on seroconversion. If high titers are detected, the presence of IgM antibodies should be sought (Davidson *et al.*, 1991).

Control: In man, no prophylactic measures are called for other than laboratory safety procedures.

For the immunization of sheep, oil-adjuvant inactivated cell culture vaccine is available. It is recommended that gravid ewes in the late stage of gestation be vaccinated in order to provide passive protection for the newborn lambs. Another useful preventive measure is treatment of the entire flock with tickicides.

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LYMPHOCYTIC CHORIOMENINGITIS

ICD-10 A87.2

Synonym: Armstrong's disease.

Etiology: Single-strand RNA genome virus, genus *Arenavirus*, family Arenaviridae. The virions are round, oval, or pleomorphic and measure approximately 110–130 nm in diameter. The virion interior contains granules resembling grains of sand, which are characteristic of the family and give it its name, while the

surface has hollow golf-club-shaped projections. All the arenaviruses produce persistent infection in rodents, which are their reservoir. The principal reservoir host of the lymphocytic choriomeningitis (LCM) virus is the house mouse (*Mus musculus*).

Geographic Distribution: Unlike the other arenaviruses, which have limited geographic distribution, the LCM virus has been found in the Americas, Europe, and Asia (Morita, 1997). Distribution of the LCM virus is focal because each rodent colony is separate and usually does not mix with others. As a result, the distribution of human cases is also focal. There have been cases of human LCM in Argentina, Brazil, El Salvador, Japan, US, and several European countries. In some of the cases, however, there is doubt as to whether or not the infection was correctly identified. The agent has not been reported in Africa or Australia.

Occurrence in Man: The disease is sporadic and not very common, but occasional outbreaks occur. The distribution of human infection associated with the house mouse corresponds to the presence of the virus in animal colonies. Sporadic cases can occur over a period of several years within the same city block or population. In the former Federal Republic of Germany, clinical cases associated with mice were reported only in the north and northwest, where the rate of serologic reactors in the rural population reached levels as high as 10% in some surveys. By contrast, in the southern part of that country, where there had been no clinical cases, the reactor rate was only 0.18% to 1.6%. The annual incidence of clinical cases is very low. In the former West Germany, there were estimated to be about 1,000 infections a year due to the LCM virus (Ackermann, 1982). In the US, in an 18-month study of 1,600 cases of central nervous system illnesses among military personnel, only 8% were found to have been caused by the LCM virus, and there were only about 7 cases a year (Casals, 1982).

Along with the growth in popularity of hamsters as pets, cases associated with these animals have begun to be seen. In West Germany, 47 such cases were reported between November 1968 and May 1971, distributed throughout the country, and in the US, there were 181 cases in 12 states (57 cases each in New York and California) between December 1973 and April 1974. All the hamsters associated with the US outbreak came from the same commercial breeder, although the animals were acquired from different retail suppliers.

In Argentina, an indirect immunofluorescence study of 7,227 persons was conducted in 41 localities in the endemic area of another arenavirus—namely, Junín virus, the agent of Argentine hemorrhagic fever. The study revealed an average positive LCM reactor rate of 2.4%, while a reactor rate of 6.1% had been observed in two districts (Ambrosio *et al.*, 1994).

In a serologic survey of 1,149 individuals from a low-income inner city area of Baltimore, US, the enzyme-linked immunosorbent assay (ELISA) test established a 4.7% prevalence for the LCM virus. The people who took part in the survey said that they had large numbers of mice in their homes (Childs *et al.*, 1991).

Cases of the disease have also occurred in laboratory personnel who worked on cell cultures that had inadvertently become contaminated with the LCM virus, which is not usually cytopathic, or had had contact with infected animal colonies. Transplantable tumors contaminated with the LCM virus are yet another risk for laboratory workers. In the 1970s, hamster tumor grafts appeared to have been infected (Jahrling and Peters, 1992). During 1973–1975, there were three outbreaks in the

US, for a total of 65 cases, among US laboratory workers who had handled hamsters that had tumor grafts containing the LCM virus (Gregg, 1975). An epidemiological investigation conducted at two institutes traced the outbreaks to hamster tumoral tissue lines that had been acquired from the same supplier. An outbreak of LCM among laboratory personnel working with nude mice was also reported at a US cancer research institute. An overall seroprevalence of 10% was found among 82 employees tested, most of whom had been involved in animal care or had directly handled or touched animals and their tissues (Dykewicz *et al*., 1992).

The disease in humans usually occurs during the cold months. Some researchers attribute this seasonal trend to the density of the mouse population, while others think it has to do with the mice seeking shelter from the cold inside homes and granaries (Johnson, 1990).

Occurrence in Animals: Many animal species are susceptible to the LCM virus, and several species have been found to be naturally infected. However, there is no doubt that the host and natural reservoir is the house mouse (*Mus musculus*). In the former Federal Republic of Germany, where various species of mice were studied, a high incidence of LCM was found in both the house mouse and the field mouse (*Apodemus sylvaticus*). In the research institutes where human cases had been recorded, the infection was found in approximately 40% of the mouse colonies, and approximately 50% of the rodents were carriers of the virus. Animal-to-animal transmission of the infection occurs only in the house mouse and the golden hamster (*Mesocricetus auratus*), which acquires the infection from mice and propagates it among its kind (Lehmann-Grube, 1982).

The Disease in Man: The course of the infection ranges from clinically inapparent to fatal in a few very rare cases. It is usually a benign disease. In most cases, the symptoms are similar to those of influenza. The incubation period is one to two weeks. The clinical picture, which is similar to that of influenza (fever, headache, myalgia, leukopenia, thrombocytopenia), usually clears up in a few days, but some patients may have a relapse with meningeal symptoms 15 to 21 days after onset of the disease. Meningitis can also develop initially without prior symptoms, but when this happens the incubation period is longer (two to three weeks). The symptoms are a stiff neck, fever, cephalalgia, malaise, and muscle pain. The spinal fluid may contain fewer than 100 up to more than 3,000 cells per ml. Of these, 80% to 95% are lymphocytes—hence the name of the disease. Also, on rare occasions, meningoencephalitis may occur, with alterations in the deep reflexes, paralysis, cutaneous anesthesia, and somnolence. Chronic sequelae and death are infrequent. Some patients may have complications such as orchitis, myopericarditis, arthritis, or alopecia—the last-mentioned during convalescence. These complications and the second febrile period could be due to an immunopathological phenomenon (Johnson, 1990). The infection can interfere with gestation or cause prenatal damage to the fetus (encephalitis, hydrocephaly, chorioretinitis) (Ackermann, 1982).

Treatment is symptomatic.

The Disease in Animals: Naturally infected animals, including the house mouse, do not usually present clinical symptoms.

The course of infection was observed in a colony of naturally infected laboratory mice. Although 50% of the animals were infected, morbidity was less than 20%.

Growth was stunted in many of the juvenile mice, but about 40% of them recovered completely. Those that were infected *in utero* carried the virus throughout their lives. The proportion of mice with persistent infection increased over time, and at 4 years all the animals had high titers for the virus, even when they were disease-free. Unlike previous observations, in which some animals were born without the virus and soon became infected through contact, the only mode of transmission in this colony was congenital. It is believed that in nature the infection is maintained among mice by transovarial transmission and that congenital infection is the rule.

Experimental infection in adult mice produces acute disease after an incubation period of five to six days. The disease may end in either death, on the one hand, or complete recovery on the other, with normal immune response and elimination of the virus. If an animal with the disease is picked up by the tail and twirled, it will have a characteristic convulsive attack, which is often fatal. Acute LCM is associated with generalized immunosuppression, which appears during the second week of infection and lasts for several weeks. The immunosuppression results from the virus interfering with the maturation of T-cells (Thomsen *et al.*, 1982). Mice infected during the perinatal period (the first 5 days of life) give a completely different picture. The growth of these animals is apt to be severely stunted for several weeks, and a number of them may die, but the survivors recover completely, despite the fact that the virus continues to replicate and high titers are found in all their organs for the rest of their lives. This immunological tolerance for the choriomeningitis virus has been the subject of numerous studies, but it is still not fully understood. One possibility is that the infection of helper T-cells may be involved in suppression of the specific immune response to the LCM virus, as observed in persistently infected mice (Ahmed *et al.*, 1987).

Persistent infection is a characteristic not only of the LCM virus but rather of all the arenaviruses for which mouse and hamster species serve as reservoir hosts. These animals have marked suppression of cellular immunity and neutralizing antibodies, although the latter can be detected by the immunofluorescence and complement fixation tests. Mice with persistent tolerant infection (especially those that acquire the infection shortly after birth) usually suffer from glomerulonephritis, which will reduce their normal life expectancy by a few months. The lesion is due to the deposit of virus-antibody complex in the kidneys.

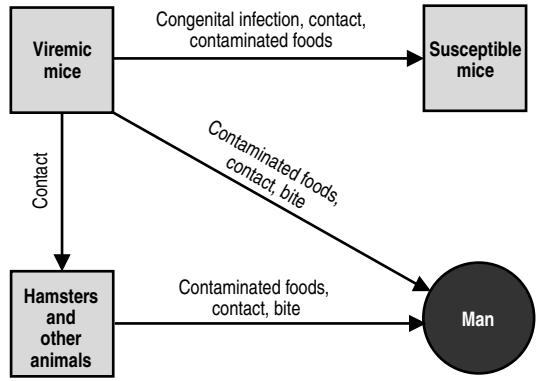
The response of laboratory mice is determined not only by their age but also by the strain of the virus and the route of administration. The hamster can also remain infected for a long time, but not for life; it eventually eliminates the virus (Skinner *et al.*, 1976).

During the period 1980–1990, there were 12 outbreaks of callitrichid hepatitis among marmoset and tamarin colonies in 10 US zoos which were attributed to the LCM virus or a very close relative thereof (Fenner *et al.*, 1993). This disease has also been reported among pygmy marmosets (*Cebuella pygmaea*) and a Goeldi's monkey (*Callimico goeldii*) at a German zoo (Asper *et al*., 2001).

The patterns of both natural and experimental infection lead to the conclusion that horizontal infection is of little epidemiological importance, whereas vertical infection becomes chronic and persistent in mice. As a result of this persistence, they are constantly contaminating the environment through their excreta (Johnson, 1981).

Source of Infection and Mode of Transmission (Figure 18): The primary and probably sole reservoir is the mouse. All other animal species, including man, con-

Figure 18. Lymphocytic choriomeningitis. Transmission cycle.



tract the infection from mice. The infection is persistent in the mouse, whereas in man and other animals its duration is limited. Mice shed the virus through their nasal secretions, urine, semen, feces, and milk. Congenital and neonatal infection is very important in this species. Transmission of the virus is both vertical and horizontal.

The mode of transmission from mouse to man is not well understood. Various observations suggest that more than one portal of entry may be involved. Human cases have been traced to mouse bites (and bites of other rodents) and also to the handling of dead mice. The upper digestive tract is also probably a route by which the virus can gain entry, via food contaminated with mouse feces or urine. Laboratory infections are probably contracted through the respiratory or conjunctival route. The respiratory route has also been implicated, although the agent tends to have little resistance to environmental conditions.

Transmission of the virus via arthropod vectors (ticks, lice, bedbugs, and mosquitoes) has been demonstrated in the laboratory, but it is not known whether this form of transmission takes place in nature. The virus has been isolated from fleas, wild rodents, *Culicoides* flies, several species of *Aedes* mosquitoes, ticks, and cockroaches. The prevailing view of researchers is that, if arthropods do in fact play a role, it is a very limited one.

The mouse can transmit the infection to other animal species, which in turn can infect man. It has been contracted by hamsters and guinea pigs in breeding colonies, probably from mice, and these infections have given rise, in turn, to a number of human cases.

Role of Animals in the Epidemiology of the Disease: LCM is a zoonosis. Cases of person-to-person transmission are the exception. There was one case in which the infection was transmitted during an autopsy. The disease can also be transmitted congenitally (Barton and Hyndman, 2000). The mouse is essential to maintenance of the infection.

Diagnosis: Laboratory confirmation of LCM is based on serologic tests and isolation of the virus. Complement-fixing antibodies appear during the first or second week of

the disease and are gone within six months at the latest. Neutralizing antibodies appear later and persist for years. A high titer in the complement fixation (CF) test is good diagnostic evidence. The serum neutralization test should always be based on a rise in titer during the course of the disease and convalescence. Indirect immunofluorescence, which permits earlier detection of the disease, detects IgM antibodies, indicating recent infection. LCM virus infection can also be diagnosed with ELISA and Western immunoblot (Brezin *et al*., 2000), and through reverse transcription-polymerase chain reaction (Park *et al.*, 1997). The virus is isolated by inoculating mice intracerebrally with blood from febrile patients, or spinal fluid in the case of patients with meningitis. Of course, the mice must come from colonies that are free of the LCM virus. Isolation of the virus in cell cultures is another possible method of diagnosis.

Experimental infection of laboratory animals with the LCM virus, in addition to posing a risk for personnel, raises an inherent problem in the experiment itself which can invalidate its results: many virus strains that have been passed through or harbored in mice have been found to be contaminated with the LCM virus. In an infected colony, serologic diagnosis can be done using either the CF test (the serum-neutralization test will not work) or the immunofluorescence test on liver tissue from mice suspected of being infected. The diagnosis can also be confirmed by experimental intracerebral inoculation of neurotropic LCM strains, which will cause the characteristic disease and death of normal mice but not of those that are carrying the virus. Yet another method is to inoculate guinea pigs with a suspension of organs from the suspect mice.

Control: The main approach is to control the mouse population in dwellings through environmental hygiene and the use of rodenticides. Under no circumstance should mice that have been caught or killed be touched with bare hands.

When the disease is transmitted by other animals—for example, hamsters—the origin of these animals should be traced and their sale to the public should be avoided until the breeding colony is free of the infection.

Colonies of laboratory mice should be tested serologically, and their cages and installations should be secured to keep the animals from escaping and to protect against intrusion of other rodents.

Pregnant women should avoid having pet hamsters or other rodents in the home.

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MACHUPO HEMORRHAGIC FEVER

ICD-10 A96.1

Synonyms: Bolivian hemorrhagic fever, black typhus.

Etiology: Machupo virus, an RNA genome virus belonging to the genus *Arenavirus*, family Arenaviridae, member of the Tacaribe complex (see Argentine Hemorrhagic Fever).

Geographic Distribution: The known endemic foci are located in the provinces of Mamoré, Iténez, and Yacuma in Beni Department, Bolivia.

Occurrence: Machupo hemorrhagic fever (MHF) was recognized clinically in 1959. Outbreaks occurred annually in the provinces of Mamoré and Iténez until 1964. It is estimated that during that five-year period 1,100 persons in a population of 4,000 to 5,000 were sickened by the disease and 260 (24%) of them died. Up until 1962 the disease was limited to small foci in rural areas, but during that year there was an outbreak in the village of El Mojón on the island of Orobayaya and its 600 inhabitants fled in terror. The worst epidemic (650 cases and 122 deaths) occurred between 1963 and 1964 in San Joaquín, capital of Mamoré Province, which at the time had a population of about 2,500 (Comisión de Investigación de la Fiebre Hemorrágica en Bolivia, 1965). Although no cases of person-to-person transmission were observed during these epidemics, in 1963, two cases appeared at a hospital in Panama where two United States researchers had been taken after they contracted the disease in Bolivia. After an extensive outbreak in 1962–1963, the disease disappeared until 1968, when six cases, all of them fatal, were reported in northern Bolivia, near Magdalena in Iténez Province. The following year, nine more cases were recognized in the same area. In 1971, there was an outbreak of special epidemiologic interest in a Cochabamba hospital, outside the endemic area of the disease. This nosocomial outbreak, reminiscent of Lassa fever, consisted of six cases, five of which were fatal. The index case was a nursing student who had visited the town of Fortaleza in Beni Department, where there had been no reports of the infection. She became ill and was admitted to the hospital on her return to Cochabamba. Four secondary cases occurred among her contacts at the hospital, and there was a tertiary case in a pathologist who cut his finger while performing an autopsy on one of the victims.

During the second half of 1971, there were four additional cases in the province of Yacuma, also located in the extreme north of Bolivia. In the months of December 1974 and January 1975 the disease returned with four cases and two deaths in the village of El Recuerdo in Mamoré Province.

In July 1994, an outbreak occurred in the town of Magdalena, in the north-central province of Iténez. A diagnosis of MHF was confirmed in seven family members, six of whom died. The patient with the index case survived. In September 1994, two additional cases were identified. A man living in Magdalena, with no known link to the infected persons, succumbed to MHF, and an agricultural worker from Poponas (El Beni Department) developed a febrile hemorrhagic illness, confirmed as MHF, but recovered (CDC, 1994).

The epidemic outbreaks have been related to large populations of *Calomys* rodents and high rates of infection in these cricetids (up to 35%). Conversely, the absence of human cases has been associated with reduced levels of the rodent population and low rates of infection in the animals (Johnson *et al.*, 1978).

The virus remains active in the *Calomys callosus* reservoir. In May 1977, an ongoing study revealed a high proportion of rodents with splenomegaly in the province of Iténez, near the Brazilian border, and in the province of Cercado de Beni (Pan American Sanitary Bureau, 1982).

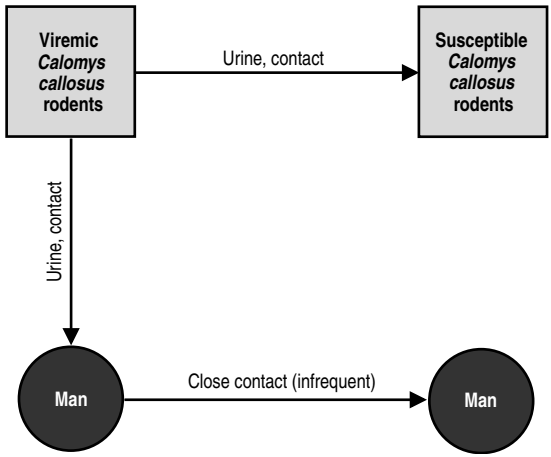
Most cases have occurred in the dry season, between April and September.

The Disease in Man: The incubation period of MHF is one to two weeks, and the onset is insidious. The symptomatology is similar to that of Argentine hemorrhagic fever. All patients have a sustained fever of 38°C to 41°C, which lasts for at least five days. Almost invariably they experience myalgia, conjunctivitis, and cephalalgia. Cutaneous hypersensitivity and gastrointestinal symptoms are also common. A varying percentage of patients (30% or more) experience hemorrhaging on days four through six of the disease. Petechiae of the oral mucosa and hemorrhaging from the gums, nose, stomach, and intestines, and sometimes the uterus, may be seen, but the loss of blood is usually not significant. Hypotension is observed in about 50% of the patients between days 6 and 10; although this condition is transitory in some patients, in others it leads to clinical shock and death. A high proportion of cases (30% to 50%) have central nervous system involvement, with tremors of the tongue and extremities and sometimes convulsions and coma. Leukopenia is a regular sign, and it is especially marked between days five and nine. Hemoconcentration and proteinuria are common. Convalescence is prolonged, and there may be transitory alopecia and transverse furrows in the nails. Some of the pathological findings that have been reported are generalized adenopathy and focal hemorrhages in the gastric and intestinal mucosa, lungs, and brain.

The Disease in Animals: The virus has been isolated only from the cricetid rodent *Calomys callosus*. Infection in this species does not produce acute disease. Experimentally infected newborns have chronic hemolytic anemia with splenomegaly, and their growth is retarded. Females with chronic infection abort. Field studies have shown a positive correlation between the presence of splenomegaly and the virus isolation rate (Johnson, 1981).

Source of Infection and Mode of Transmission (Figure 19): The disease foci are found in the expanses of the Mojos plain, where open pastureland and savannah

Figure 19. Machupo hemorrhagic fever. Transmission cycle.



(at higher locations) alternate with "islands" of semideciduous jungle vegetation. The farming communities are typically found on the periphery of these wooded areas. In the localities where the epidemics occurred, the spiny rat *Proechimys guyannensis* and the cricetid rodent *Calomys callosus* are ubiquitous. The Machupo virus was isolated from 24% of 122 specimens of *C. callosus* examined, but not from *Proechimys* or other rodents. Based on this observation, together with the evidence from experimental trials with *C. callosus*, it has been concluded that this rodent is the reservoir for maintaining the virus in nature. Chronic infection in this host and shedding of the virus through its excretions and secretions ensure persistence of the agent in the cricetid populations. *Calomys* rodents prefer to live in savannah and fallow fields, but food also attracts them to homes, where they proliferate, as was seen during the epidemic in San Joaquín. The *Calomys* population in this town is believed to have risen sharply because of the decline in the number of cats after 1959, when many of them died from DDT used during malaria eradication campaigns. The combination of the absence of their natural enemy and the abundant availability of food in the homes of the townspeople appears to have fostered the migration of *Calomys* rodents from their natural habitat.

According to observations during the San Joaquín epidemic, transmission of the virus was taking place in or around the homes. Success in controlling this epidemic through a campaign to exterminate the *Calomys* confirms the important role played by this rodent in the epidemiology of the disease. During the anti-rodent campaign, Machupo virus was isolated from 13 of 17 captured *Calomys*, and presence of the agent was confirmed in the urine of 5 out of 9 specimens examined.

In the search for a vector, attempts were made to isolate the virus from arthropods, and more than 25,000 specimens, especially rodent ectoparasites, were examined. The results of this study were negative, however, giving further credence to the idea that the source of infection is virus in the urine of infected rodents (Johnson, 1975).

The *C. callosus* breeding unit at the Panama-based Middle America Research

Unit (MARU) of the United States National Institutes of Health made an important contribution to knowledge of the natural history of MHF. The rodent can be infected experimentally via the oral and nasal mucosa and by cohabitation in the same cage. When the virus was inoculated in rodents nine days of age or older, approximately half the infected animals acquired immunologic tolerance and the other half became immunocompetent. In the case of the immunotolerant animals, viremia was confirmed and virus was shed in their urine throughout their life, but they did not develop neutralizing antibodies. By contrast, the immunocompetent animals developed neutralizing antibodies and had no viremia, although the virus could be isolated for a relatively long time from their urine and viscera. In the immunocompetent animals the spleen was of normal size and weight, whereas in the infected animals it was three to six times normal size. The offspring of immunotolerant animals became infected and had viremia throughout life, whereas those born of immunocompetent mothers were passively protected by maternal neutralizing antibodies for about two months, after which they were susceptible. Experimental inoculation of adult *Calomys* produces a clinically inapparent infection. This result is different from the response pattern seen in the domestic mouse infected with lymphocytic choriomeningitis virus. The animals with chronic viremia also had persistent anemia.

Humans are infected in the fields or at home through contact with cricetid rodents or food or water contaminated with their excreta and secretions. Also, the Cochabamba episode showed that close contact with the secretions of a patient facilitated person-to-person transmission and the occurrence of secondary cases. In some human cases it was possible to isolate Machupo virus, or a slight antigenic variant thereof, from a laryngeal swab (but not from urine).

Diagnosis: The Machupo virus can be isolated from the blood of febrile patients and the spleen of those who die from the disease. The material is inoculated intracerebrally in suckling hamsters and mice.

Serologic diagnosis can be achieved with the complement fixation test (group-specific for the Tacaribe viruses), the plaque neutralization on Vero cells (type-specific for Machupo virus), the indirect immunofluorescence test (group-specific), and the enzyme-linked immunosorbent assay. These tests should be performed on paired acute- and convalescent-phase sera. Polymerase chain reaction is also useful in diagnosing the disease (Chin, 2000).

Control: The rodent control campaign in San Joaquín showed that, at least in small cities where *Calomys* rodents have acquired domestic and peridomestic habits, excellent results can be obtained from measures directed against these animal populations. Some 3,000 *C. callosus* were destroyed over a period of 60 days using traps and rodenticide bait. The exercise resulted in an impressive reduction in the incidence of human cases. In light of the fact that these measures are difficult to apply under other ecological conditions, work is under way to develop a vaccine to protect the exposed population in endemic areas.

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MARBURG VIRUS DISEASE

ICD-10 A98.3

Synonyms: African hemorrhagic fever; green monkey disease.

Etiology: Marburg (MBG), a single-strand RNA genome virus belonging to the genus *Filovirus*, family Filoviridae. In addition to the MBG virus, this family includes the Ebola (EBO) (including the Reston strain), to which it is distantly related. The virion is highly pleomorphic and measures 80 nm in diameter by 700 to 1,000 nm in length.

Geographic Distribution and Occurrence: Marburg virus disease was first recognized in 1967 in Marburg and Frankfurt, Germany, and Belgrade, Serbia, and is named for the city where the pathogenic agent was first isolated and identified. The disease appeared in laboratory personnel who had been handling viscera, body fluids, or kidney tissue cultures from African green monkeys (*Cercopithecus aethiops*). There were a total of 25 primary cases, 7 of which were fatal. In addition, five secondary cases developed as a result of contact with blood and tissue of the primary patients; in a sixth case, the infection appeared to have been transmitted by sexual contact. The monkeys that were the source of the outbreak had come from the Lake Kyoga region of Uganda and had been shipped to Europe from Entebbe, Uganda.

In 1975, three human cases were reported in South Africa, and one of the patients died. The first case was an Australian tourist who had been traveling in Zimbabwe for two weeks before falling ill; the other two (one of whom was a nurse) were infected by contact with the first. In 1980, two cases occurred in western Kenya, and one of the patients died before it could be determined if either of them had had any contact with monkeys; another fatal case occurred in Kenya in 1987. In the Democratic Republic of the Congo, one nonfatal case was reported in 1987, and three fatal cases were reported in 1999 (Chin, 2000).

In Liberia, a survey using the indirect immunofluorescence test identified 7 reactors, with titers of 1:16 to 1:128, in the 481 human sera examined (Knobloch *et al.*, 1982), while in the Central African Republic the same technique revealed 2 reactors, each with titers of 1:64 or higher, out of 499 sera (Saluzzo *et al.*, 1982). Seroreactors have also been found in Gabon, the Democratic Republic of the Congo, and the Sudan, but no cases of the disease were detected in any of these countries, possibly because there is no epidemiological surveillance system (WHO, 1984).

The Disease in Man: The incubation period ranges from four to nine days. Primary cases have a case-fatality rate of 29%, which is much lower than with Ebola virus disease. The disease onset is sudden, with fever, cephalalgia, prostration, arthralgia, myalgia, vomiting, diarrhea, and sometimes conjunctivitis, followed by a maculopapular and gastrointestinal hemorrhaging, epistaxis and other hemorrhagic signs, lymphadenopathy, and hepatitis. About half the patients have spontaneous hemorrhaging, and sometimes there is central nervous system involvement, myocarditis, and other complications. Leukopenia is present, and transaminase values are high. Convalescence is prolonged.

The Disease in Animals: No clinical symptomatology was observed in the African green monkeys identified as the source of the human infection in the 1967

outbreaks in Germany and Yugoslavia. Experimental infection produced by the inoculation of different species of monkeys is generally fatal. The only symptoms are a febrile reaction and, in the terminal stage of the disease, lethargy, anorexia, and sometimes petechial eruptions. The pathologic picture is similar to the human disease, and death occurs seven or eight days postinoculation. The virus is not pathogenic for mice; in guinea pigs, however, mortality is 100% after three to five passages of the virus.

Source of Infection and Mode of Transmission: The fact that human cases have originated in Kenya and Zimbabwe suggests that the virus is active in widely separated geographic areas, perhaps in a focal and enzootic form. Neither the reservoir of the virus nor its mode of transmission is known. On the basis of serologic surveys using the complement fixation test, it had been thought that African green monkeys were the main reservoir. Subsequent research, however, showed that the antigen used in the earlier studies, which had been obtained from infected guinea pig organs, was not sufficiently specific. Later, the indirect immunofluorescence test revealed antibodies in 4 out of 136 captive African green monkeys in Kenya (Johnson *et al.*, 1982), but this species is not considered the primary reservoir. More research needs to be done in order to determine the natural reservoir of the infection.

During the 1967 outbreak, the infection in most of the primary cases had been contracted while the individuals were taking blood samples or dissecting African green monkeys; others were preparing kidney cultures or cleaning the test tubes used for tissue culture. Transmission was produced by direct contact with viscera or body fluids. The personnel who had only been exposed to the live animals did not get sick. In five of the six secondary cases, the infection had been contracted through an accidental prick with a hypodermic needle used to take blood samples or inoculate primary patients or by contact with the blood of patients or with viscera and body fluids during autopsy. The sixth secondary case was in a woman who had contracted the infection from her husband by sexual transmission; the man had recovered from the disease and it was possible to isolate the virus from his semen. The disease has never been confirmed in the US despite the large number of green monkeys imported from Africa.

The index case in South Africa suggests the possibility of vectoral transmission, since the patient had not been directly exposed to the animals but rather had been bitten by arthropods while sleeping outdoors in Zimbabwe. Artificially infected monkeys spread the infection by direct contact and indirectly through cohabitation in the same environment in separate cages. Monkeys have been experimentally infected via aerosol transmission. Infected animals can shed the virus through their urine and saliva.

Diagnosis: Specific diagnosis can be made by isolating the virus in tissue culture, especially from the Vero E6 clone. The seeded material can be blood, serum, fluid from effusions or specimens, or tissue obtained from biopsies or autopsies. Both the MBG and the EBO viruses have a cytopathogenic effect on Vero cells. The indirect immunofluorescence test can detect the virus with a specific antiserum 7 to 10 days after being seeded on the tissue culture. When guinea pigs or monkeys are experimentally infected, presence of the virus can be confirmed through electron microscopy and serologic tests based on antigens obtained from tissue culture.

Control: In view of the present lack of knowledge, it is impossible to establish effective control measures. Patients should be isolated. All samples taken for diagnostic purposes, excreta, viscera, natural fluids, and any other materials that may have been in contact with the patient should be regarded as infectious and handled, decontaminated, and/or destroyed using the appropriate procedures. Instruments should be sterilized and rigorously controlled.

To prevent the spread of infection to their partners, males should not engage in sexual intercourse until three months after clinical recovery, or until semen is shown to be free of the virus (CDC, 2000).

The number of health workers assigned to the patient's care should be restricted, and all such individuals should be duly trained and provided with complete protective gear, including gowns, gloves, masks, goggles, caps, and overshoes (Simpson, 1978). Deceased victims should be promptly cremated or buried, preferably in a plastic bag, by persons wearing protective clothing.

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MAYARO FEVER

ICD-10 A92.8 Other specified mosquito-borne viral fevers

Synonym: Uruma fever.

Etiology: Mayaro (MAY) virus, an RNA genome virus belonging to the genus *Alphavirus* (arbovirus group A), family Togaviridae. It is closely related to the agent of Semliki forest fever (see Chikungunya Fever).

Geographic Distribution: MAY virus has been isolated in Bolivia, Brazil, Colombia, French Guiana (Talarmin *et al.*, 1998), Panama, Suriname, and Trinidad and Tobago, and also from a migratory bird in Louisiana, US. According to sero-epidemiologic surveys, it would appear that the virus also circulates in Costa Rica, Guyana, and Peru.

Occurrence: The infection is endemic in several tropical regions of South America. Surveys conducted in Bolivia, Brazil, Guyana, and Trinidad and Tobago using the neutralization test have revealed that between 10% and 50% of the resident population in endemic areas have antibodies to the MAY virus.

In 1955, there was an outbreak of 50 cases in the Brazilian state of Pará. In Bolivia, an epidemic of "jungle fever" occurred during 1954–1955 in Uruma, Santa Cruz Department, among 400 settlers from Okinawa, Japan. Almost half the group became ill, and 10% to 15% of the cases were attributed to Uruma (Mayaro) virus. In 1977–1978, another epidemic took place in Pará, Brazil. In this episode, which occurred in the town of Belterra, nearly 20% of the 4,000 residents were infected, and a large proportion of them became sick. The epidemic began at the start of the rainy season and ended at the beginning of the dry season (LeDuc *et al.*, 1981).

A survey conducted in French Guiana found that 6.3% of 1,962 human serum samples tested positive for anti-MAY virus antibodies; prevalence rates were higher among people living near the tropical rainforest and along the Maroni River (Talarmin *et al.*, 1998).

The Disease in Man: The symptoms are similar to those of other "jungle fevers," without any special characteristics. It is a benign febrile illness of brief duration,

with symptoms of pyrexia, frontal cephalalgia, conjunctival congestion, photophobia, myalgia, and sometimes arthralgia. The fever usually lasts three days, but in some cases it continues a few days longer.

In the 1977–1978 epidemic in Belterra, Brazil, 55 patients with laboratory-confirmed disease were studied clinically. For almost all the patients, arthralgia was a prominent symptom: the wrists, fingers, ankles, and toes were the parts most often affected, and 20% of the patients had edema of the joints. The arthralgia occurred at the beginning of the disease and caused temporary disability. By the fifth day of the illness, two-thirds of the patients developed a macro- or micropapular cutaneous eruption. Leukopenia was constant (Pinheiro *et al.*, 1981).

No deaths attributable to Mayaro fever have been reported.

Source of Infection and Mode of Transmission: Mayaro fever occurs in jungle areas of the American tropics. Because the epidemic in Belterra coincided with an outbreak of yellow fever, it was thought that the same vector might have transmitted both infections. However, in a study of 9,000 insects from 26 different species, MAY virus could only be isolated from the mosquito *Haemagogus janthinomys*. Nine strains of MAY virus and 2 of the yellow fever virus were isolated from 62 pools containing a total of 736 of these mosquitoes captured during the peak of the epidemic. The minimum infection rate in *H. janthinomys* was 1:82 for MAY virus and 1:368 for the agent of yellow fever. There is no doubt that *H. janthinomys* was the main vector of the MAY virus in the Belterra epidemic, and perhaps the only one. Elsewhere, the virus has been isolated from *Culex*, *Mansonia*, *Aedes*, *Psorophora*, and *Sabethes* mosquitoes, and most frequently from *Haemagogus* spp. (Hoch *et al.*, 1981).

During the same epidemic in Belterra, an attempt was made to identify the most probable animal host of the virus using the hemagglutination inhibition test. Out of 1,200 birds examined, 1.3% were positive, and out of 585 mammals, 5.6% had antibodies. The only mammals that reacted were 1 howler monkey and 32 (27%) out of 119 silvery marmosets (*Callithrix argentata*). Both the monkey and the marmosets had antibodies. The virus was isolated from one of the marmosets, and experimental inoculation of these animals produced a viremia which, although brief in duration, was of a sufficiently high level to infect the vector. Although marmosets were probably the amplifying host of the virus in this epidemic, there is evidence indicating that birds, rodents, or both, are the reservoirs in which the virus is maintained during enzootic cycles. In other research, 29% of a group of doves (*Columbigallina* spp.) from the jungle near Belém, Brazil, were found to be positive, and the virus was also isolated from a migratory bird, the orchard oriole (*Icterus spurious*), in Louisiana, US. Among rodents, high reactor rates to MAY virus have been found in rice rats (*Oryzomys*), spiny rats (*Proechimys*), and water rats (*Nectomys*) (Hoch *et al.*, 1981).

Studies of the Belterra epidemic have advanced knowledge about the immediate mechanism responsible for that episode, and primates would appear to have been the reservoir of the virus. However, much remains to be learned about the natural history of MAY virus.

Man is an accidental host who becomes infected upon entering jungle areas, where the virus circulates among wild vertebrates by means of mosquitoes. In addition, a laboratory worker was reported to have contracted the infection via airborne transmission during the preparation of viral antigen (Junt *et al.*, 1999).

Diagnosis: The virus can be isolated easily from the blood of febrile patients at the beginning of the disease. The most effective isolation procedure is intracerebral inoculation of newborn mice.

Serologic diagnosis is based on confirmation of an increase in antibody titer between acute- and convalescent-phase sera in the hemagglutination inhibition or complement fixation tests. The virus can also be identified by the plaque-reduction neutralization test and reverse transcription-polymerase chain reaction, as well as by immunofluorescent antibody testing with specific mouse antibody (Talarmin *et al*., 1998).

Control: Individual preventive measures are the same as for other mosquito-borne diseases—namely, protective clothing, repellents, mosquito netting, and window and door screens to keep out mosquitoes. In practice, these measures are difficult to implement in the tropical regions of the Americas. On the other hand, since the disease is usually benign, no special control measures are justified in tropical America.

Laboratory personnel should take precautions against exposure to the virus via airborne transmission.

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MEASLES

ICD-10 B05

Synonyms: Morbilli, rubeola, hard measles, red measles.

Etiology: *Measles virus,* an RNA genome virus belonging to the genus *Morbillivirus*, family Paramyxoviridae. The same genus includes the antigenically related viruses of distemper (Carré's disease) and bovine plague (rinderpest).

Geographic Distribution: Worldwide.

Occurrence in Man: Prior to the use of vaccines, measles was very common in childhood; more than 90% of all children had the disease before they were 10 years old. The infection was endemic in cities, and epidemics occurred approximately every two years. In areas where effective infant vaccination programs have been implemented, the disease is more common among adolescents and adults. In temperate climates, measles tends to occur most often in late winter and early spring (Benenson, 1990).

In 2000, a total of 817,161 measles cases were reported to WHO. However, WHO estimated that approximately 30–40 million measles cases and 777,000 measles-related deaths occurred worldwide, since substantial underreporting exists, measles is not a notifiable disease in some countries, and weak disease surveillance programs continue to be a problem in many countries. Most (≥90%) of these deaths are estimated to occur in Africa and South-East Asia. The number of measles cases reported by countries in southern Africa have fallen from over 50,000 per year to 100 in 1999, largely due to catch-up vaccination campaigns undertaken. WHO's Eastern Mediterranean region reported 34,971 cases in 2000; over 50% of these cases occurred in countries in the measles elimination stage, most of them in Iran, Libya, and Morocco, which had not yet conducted the initial catch-up vaccination campaign. The number of cases reported in the European Region fell from some 300,000 in 1991 to 36,306 in 2000 (WHO, 2002).

In 2001, there were a total of 537 measles cases reported in the Region of the Americas, a 99% decrease since 1990. The D6 measles virus genotype, which had circulated widely in the Region of the Americas since 1995, caused nationwide outbreaks in Argentina, Bolivia, Brazil, the Dominican Republic, and Haiti during 1997–2001; in 2001, the Dominican Republic and Haiti ended indigenous transmission of this genotype. A measles outbreak introduced by a traveler returning from Europe occurred in Venezuela in August 2001 and was exported to Colombia in 2002 (CDC, 2002).

Occurrence in Animals: Aside from humans, the disease has been observed only in captive nonhuman primates. Measles epizootics have been described in several nonhuman primate species, including the rhesus monkey (*Macaca mulatta*), the crab-eating macaque (*M. fascicularis*), the black-and-white colobus monkey (*Colobus guereza*), the silvered leaf monkey (*Presbytis cristatus*), the cotton-top tamarin (*Saguinus oedipus*), and the common marmoset (*Callithrix jacchus*). Antibodies have also been detected in chimpanzees, orangutans, and gibbons (Montrey *et al.*, 1980). The infection occurs only in captive animals at primate centers, research institutes, and zoos. In some institutions the rate of serologic reactors

to the measles virus can be as high as 100% (Soave, 1981). Serologic surveys conducted among free-living monkeys in their jungle habitat have been negative. In a study of 170 bonnet macaques (*Macaca radiata*) and 195 Hanuman langurs (*Presbytis entellus*) captured in Kamakata, India, no antibodies to the measles virus were found (Bhatt *et al*., 1966). Baboons (*Papio* spp.) in their natural habitat or in limited contact with humans rarely have antibodies (Kalter *et al.*, 1967). Of 87 crab-eating macaques (*M. fascicularis*) shipped to Great Britain from the Philippines in 1985, 65 manifested signs compatible with measles three weeks after their arrival. No further cases were observed. Five of the animals died, and three of the deaths were attributed to measles. According to results from the hemagglutination inhibition test, seven days after the monkeys' arrival, 36 (41.3%) of the 87 already had antibodies to measles. At three weeks after their arrival, all of the 84 surviving animals had high antibody titers for measles (Welshman, 1989).

The Disease in Man: The incubation period, from exposure to the appearance of fever, is 8 to 18 days. The prodromal signs are fever, conjunctivitis, coryza, cough, and Koplik's spots on the buccal mucosa above the first and second upper molars. Inflammation of the pharynx and upper respiratory tract is common. Between three and seven days after onset of the disease, a brownish-red maculopapular eruption appears on the face and later spreads to the rest of the body. The eruption lasts four to seven days and sometimes ends in scaly desquamation. Possible complications are otitis media, pneumonia, and encephalitis. Subacute sclerosing panencephalitis can be a delayed complication appearing even years after the disease, but it is quite rare (1 in every 100,000 cases). Measles is more severe in malnourished children, in whom the case fatality rate can be 5% to 10% (Benenson, 1990).

The Disease in Nonhuman Primates: A large percentage of the infections are subclinical. Since most outbreaks of clinical measles have occurred in recently imported animals, it is thought that the stress of capture, confinement, and transportation is a major factor in clinical manifestation of the infection (Karstad, 1981). The infection in monkeys causes high morbidity, but the fatality rate is low. The symptomatology differs from one outbreak to the next, and the cutaneous eruption and other signs may or may not be present. In the outbreak among silvered leaf monkeys (*P. cristatus*), 24 of the 31 animals had a maculopapular eruption, principally on the ventral surface of the body, which lasted six to nine days and was followed by a two-week period of desquamation. Some of the monkeys also had mucopurulent coryza and conjunctivitis (Montrey *et al.*, 1980). In the outbreak among black-and-white colobus monkeys (*C. guereza*), the predominant signs were rhinitis, conjunctivitis, pneumonia, dry cough, and periorbital and facial edema, without any cutaneous eruption (Hime *et al.*, 1975). Deaths occurred in some of the outbreaks, but it could not be established with certainty that they were due to the measles virus. In the group of 87 crab-eating macaques shipped from the Philippines to Great Britain, 63 of them had bilateral nasal discharge and, occasionally, cough. The maculopapular cutaneous eruption was observed mainly on the ventral thorax and abdomen, and within seven days the eruption began to desquamate. No Koplik spots were found on the crab-eating macaques although they had been described in a previous experimental inoculation (Welshman, 1989).

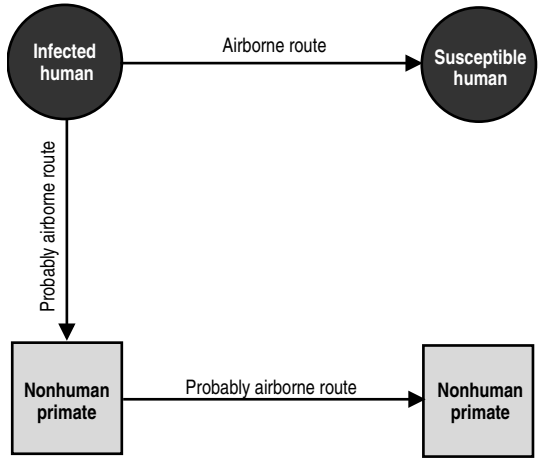
Source of Infection and Mode of Transmission (Figure 20): The only known reservoir is man. The infection is transmitted from person to person mainly via the airborne route, by direct contact with infective nasal or throat secretions, and less often, by contact with objects freshly soiled with such secretions (Chin, 2000). The transmission period begins shortly before the appearance of prodromal symptoms and lasts up to four days after appearance of the eruption, although by the second day of the eruption it is only minimal. The infection is highly contagious, but it does not affect persons who have had the disease, as they have lifelong immunity, or those who have been successfully vaccinated.

Although with nonhuman primates it has not been possible to identify the source of infection in all cases, the evidence indicates that these animals acquire the infection through exposure to humans. In monkeys, it is likely that the infection is propagated the same way as it is in humans (Yamanouchi *et al.*, 1969). Monkeys often become infected shortly after their capture, when they are caged in small groups near human settlements and come in contact with children (Welshman, 1989). Retransmission of the infection from monkeys to humans has not been observed.

Diagnosis: In humans, diagnosis is based on clinical observation and epidemiological data. Specific diagnosis can be made by isolating the virus or by serology. The virus can be isolated in tissue cultures of pharyngeal washes, blood, or urine taken during the prodromal period or the first days of the eruption. Serologic examination to verify seroconversion is done using the complement fixation or hemagglutination inhibition tests. In monkeys, the latter test is mainly used.

Control: Potent attenuated live virus vaccines are now available. With the introduction of immunization in the US in 1963, the annual incidence of approximately 500,000 cases was reduced to 14,000 by 1980 (Katz, 1982). Although these vaccines have been very effective in preventing the disease in developed countries, they have not met with the same success among children in tropical regions. This happens because an infection with wild virus can occur during the brief lapse (depending on

Figure 20. Measles. Transmission cycle.



the child's age) between the loss of maternal antibodies and the time the vaccine takes effect (Black, 1984).

In order to prevent the contagion of nonhuman primates from a human source, and to ensure their availability for measles research, it is recommended that they be kept in strict isolation from the time they are captured until they are incorporated in colonies, always keeping them in individual cages and providing their handlers with masks and protective clothing (Yamanouchi *et al.*, 1969). If the monkeys are intended for measles research, it is possible to vaccinate them, but the susceptibility of different species to the attenuated viruses should be kept in mind. A highly attenuated vaccine from the Edmonston virus strain has been used without any problem on rhesus monkeys, but the same vaccine produces clinical measles and death in marmosets and owl monkeys. For highly susceptible species, it is suggested that an inactivated vaccine be used first, followed a month later by a modified live virus vaccine (Karstad, 1981). The best time to vaccinate is immediately after the monkey has been captured, since the disease has often been seen to develop within a few days after the animal reaches its country of destination. In monkeys, vaccination significantly reduces incidence of the disease (Welshman, 1989).

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MURRAY VALLEY ENCEPHALITIS

ICD-10 A83.8 Other mosquito-borne viral encephalitis

Synonyms: Australian X disease, Australian encephalitis.

Etiology: Murray Valley encephalitis (MVE) virus, an RNA genome virus belonging to the genus *Flavivirus* (formerly arbovirus group B), family Flaviviridae (formerly Togaviridae).[1] The virus forms part of the complex that includes the agents of Japanese, Rocio, and St. Louis encephalitis and West Nile fever.

Geographic Distribution: Australia and New Guinea.

Occurrence in Man: Since 1917–1918, when an unknown human disease (X disease) involving 134 cases of encephalitis was first observed in southern Australia, several epidemics have occurred at irregular intervals in that region of the country, most recently in 1971 and 1974. The virus was isolated in 1951 and given the name Murray Valley encephalitis (MVE) virus, after the place where it was isolated. Although evidence of the infection has been confirmed in all the Australian states and territories and in New Guinea, the epidemics have been limited to the most populous areas of southern Australia. Serologic surveys indicate that for each clinical case of MVE there are 500 to 1,000 inapparent infections. Sporadic cases and small outbreaks have occurred in other regions of Australia, but no epidemics.

Seroepidemiologic surveys conducted in the Northern Territory of Australia point to the existence of endemic foci of the virus. In 11 areas studied, the presence of neutralizing antibodies in the aboriginal population ranged between 7% and 89%; in three of these areas the prevalence of seropositive reactors was 86% to 89%. There are also endemic areas in New Guinea.

Since there have been no outbreaks of the disease since 1974, a study was undertaken to determine the status of immunity in known high-risk areas of New South Wales and Victoria (Hawkes *et al*., 1981). Neutralizing antibodies for MVE virus in 2,873 serum samples were very infrequent in all the districts except Bourke. Results obtained in 1991 were very similar to findings from studies done in 1981 (Hawkes *et al.*, 1993). While the Kunjin (KUN) virus[2] turned out to be enzootic, the MVE

[1] All the flaviviruses belonging to former arbovirus group B have been transferred from the Togaviridae family to the Flaviviridae family.

[2] Kunjin (KUN) virus is another flavivirus from Australia which is antigenicallly related to MVE virus, transmitted by the same vector (*C. annulirostris*), and probably maintained by a cycle involving wild birds-mosquitoes or mammals-mosquitoes (Liehne et al., 1976). A few cases of mild febrile illness have been reported in humans (Doherty, 1981).

virus had apparently been absent since 1974 (Hawkes *et al.*, 1993). In Western Australia, however, a fatal case of encephalitis in an 18-month-old aboriginal child was described by Smith *et al.* (1991). The child had been admitted to the hospital for influenza caused by *Haemophilus influenzae* type b. Postmortem examination revealed a high titer for the MVE virus. Of the mosquitoes captured in the area, 78% were identified as *Culex annulirostris*. The virus was not isolated from these mosquitoes, but serum from a sentinel chicken was serologically positive. This was the second fatal case in Western Australia (Smith *et al.*, 1991).

Occurrence in Animals: High rates of positive reactors have been found in sera from equines, cattle, dogs, foxes, marsupials, and wild and domestic birds.

The Disease in Man: The symptomatology of MVE is similar to that of Japanese encephalitis. The attack rate is highest in children under 10 years of age. The symptoms consist of fever, cephalalgia, myalgia, vomiting, and encephalitic signs. The case fatality rates are high (over 40%) and neurological sequelae are common. The epidemics have occurred in the latter part of summer.

The Disease in Animals: Domestic mammals become infected but do not manifest clinical symptoms. The results of one serologic survey suggested that there might be a link between MVE virus infection and a central nervous system disease of equines. However, failure to isolate the virus prevented the establishment of a cause-and-effect relationship (Gard *et al.*, 1977).

Source of Infection and Mode of Transmission: The natural history of the disease is not yet fully understood. In the endemic areas in northern Australia and New Guinea, the virus probably circulates between aquatic birds and mosquitoes. It has been isolated from *C. annulirostris*, which is considered to be the main vector, and from other mosquito species as well. The virus has been isolated only once from a bird—a heron (*Ardea novaehollandiae*), during the 1974 epidemic. The role of wild and domestic mammals as amplifiers of the virus is also not defined. According to experimental data, many species of birds and animals could play that role (Kay *et al.*, 1981).

In southern Australia (Murray Valley), where the most serious epidemic outbreaks have occurred, sometimes as far as 15 years apart, the origin of these epidemics remains an open question. One hypothesis has been that the virus actually disappears during interepidemic periods and that outbreaks of infection in the northern endemic areas were carried there by young birds. According to this scenario, once the virus was introduced, domestic and aquatic birds played an important role as the source of infection for the arthropod vector. Amplification of the virus through birds and mosquitoes, along with the presence of a dense and susceptible human population, would be the principal factors favoring the occurrence of epidemics.

However, a study of sera samples from feral pigs taken at various sites in New South Wales in the years preceding the 1974 epidemic demonstrated that the MVE virus was active during the interepidemic period. The hemagglutination inhibition test yielded high reactor rates in feral pigs from swampy areas in that region. Neutralization was also applied to some of the positive sera to test for both the MVE and the KUN virus, and in most cases considerably higher titers were found for the former (Gard *et al.*, 1976). In that region, when the rivers flood and more food becomes available, there is a large increase in the populations of swine, aquatic

birds, and mosquitoes. Studies of the habits of *C. annulirostris* have shown that this vector feeds mainly on mammals (Kay *et al.*, 1981). Although the findings from the various studies have been contradictory in some respects, it may be concluded that the vector has been identified. Still unknown, however, are the amplifying hosts of the virus and the factors that give rise to epidemic situations.

Diagnosis: The virus has only been isolated from the central nervous system in fatal human cases, by means of inoculation in mice and chick embryos. For serologic diagnosis, the hemagglutination inhibition, complement fixation, and neutralization tests are used. The latter test is important for distinguishing antibodies for MVE from those produced by other flaviviruses, especially KUN virus.

Control: No vaccines are available. In the event of an epidemic, control measures should be directed against the vector.

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NEWCASTLE CONJUNCTIVITIS[1]

ICD-10 B30.8 Other viral conjunctivitis

Synonyms: Pneumoencephalitis, pseudoplague of fowl, pseudo-fowl pest, paramyxovirus 1.

Etiology: *Newcastle disease virus* (NDV), also known as avian parainfluenza virus 1 (APMV-1), is an RNA genome virus belonging to the genus *Avulavirus*, family Paramyxoviridae. This family also includes eight other avian paramyxoviruses (APMV-2 through APMV-9), along with the parainfluenza viruses and mumps virus. NDV is the prototype species of the genus. In nature, there are several genetically distinct types of the virus which also differ in terms of their virulence and the pathology they produce in birds. According to one criterion—namely, the time it takes for an inoculated chick embryo to die—these viruses have been classified into the following four pathogenic types, or pathotypes: lentogenic (attenuated virulence), mesogenic (intermediate virulence), velogenic (high virulence), and viscerotropic velogenic (also called "Asian" or "exotic").

At first, based on the results of the hemagglutination inhibition test, it was believed that the strains of NDV were antigenically uniform. Subsequently, however, the crossed plaque reduction serum neutralization test demonstrated that there was antigenic variation between the strains studied in different countries, although this finding was not relevant to protection efforts. A study of monoclonal antibodies in 40 virus strains led to the identification of 8 antigenic groups which appeared to share certain biologic and epizootiologic properties (Russell and Alexander, 1983).

Geographic Distribution: The disease in fowl is distributed worldwide.

Occurrence in Man: The disease is infrequent in humans. It has occurred mainly among poultry slaughterhouse workers, laboratory staff, and health personnel applying live virus vaccines. An outbreak with 40 clinical cases was reported at a poultry slaughterhouse in Minnesota, US, that employed 90 workers. At an agricultural school in Israel, there were 17 cases among the kitchen staff, none of whom had been working with the fowl on the farm. It is possible that many sporadic cases of Newcastle conjunctivitis occur which do not receive medical attention because of their benign course, or, if they are seen by a physician, are not subjected to specific laboratory diagnosis. The infection can be subclinical, as was demonstrated by a serologic survey conducted in a poultry slaughterhouse: despite the fact that high titers were found in 64% of the exposed personnel, none of them had experienced clinical symptoms. In other surveys, the prevalence of reactors has been very low, especially among professionals who had no contact with birds.

Occurrence in Animals: The infection caused by NDV is one of the most important diseases of domestic birds, and it also occurs in semidomestic and wild fowl. It can occur in both enzootic and epizootic form, causing major economic losses. In many countries, enzootics occur continually, producing a variable clinical picture

[1] The human disease caused by *Newcastle disease virus* (NDV) is known as "Newcastle conjunctivitis," while the avian disease caused by NDV is known as "Newcastle disease."

depending on the virulence of the active virus. The viscerotropic disease type is probably the form that was first seen in 1926 in Indonesia and then the following year in Newcastle, England, the place for which the illness is named. In parts of Africa, Southeast Asia, and India, there have been reported outbreaks of a highly fatal disease which was probably caused by the same viral pathotype. One of the most important of these was the panzootic caused by the viscerotropic velogenic virus which appeared in the Middle East in 1966–1968, in parts of South America and Europe in 1970, and in Canada and the US in 1970–1971. This form of the disease is characterized by a superacute course, high fatality, and an affinity for the viscera, especially the digestive tract, in which it produces hemorrhages and necrotic areas. The epizootic in the US that started in 1971 lasted for three years and cost US$ 56 million to eradicate. In 1991, there was an episode in the US in the states of California and Nevada, and from April to July of that same year there was also an outbreak in double yellow-headed Amazon parrots (*Amazona ochrocephala oratrix*) in Illinois, Indiana, Michigan, and Texas, which was eradicated before it could spread to domestic birds (Bruning-Fann *et al.*, 1992).

An outbreak caused by the neurotropic form of NDV occurred among European pigeons in 1981, and during 1981–1984 the disease spread through continental Europe and then to Great Britain and the US. The infection in Great Britain affected 23 chicken farms via feed containing contaminated pigeon offal. In the US, 6- to 8-week-old chicks inoculated by the intranasal or cloacal route with the pigeon strain failed to develop a symptomatic infection, whereas day-old chicks inoculated intracerebrally with this strain suffered a fatal neurotropic disease. No signs of disease were observed in three chicks that were in direct contact with pigeons inoculated with the virus; however, they all developed antibodies, and it was possible to isolate the virus from two of them. Since chick embryos inoculated with pigeon strains survived for more than 90 hours, the virus was classified as lentogenic (Pearson *et al.*, 1985).

Another episode of epidemiologic interest occurred between 1990 and 1992: high mortality was observed in waterfowl, first in Canada and later in the US in the area of the Great Lakes, North and South Dakota, Minnesota, and Nebraska. The species most affected were the double-crested cormorant (*Phalacrocorax auritus*) and the American white pelican (*Pelecanus erythrorhynchos*). The sick birds experienced nervous tremors and partial paralysis. Approximately 50% of the young cormorants were infected, and 20% of them died in their nests. In the laboratory, it was possible to isolate a strain of NDV which was identified as neurotropic velogenic and regarded as highly pathogenic for chickens. The disease also affected a farm of 26,000 turkeys in North Dakota, where the same virus type was isolated and the sick birds were sacrificed (Wobeser *et al.*, 1993; USDA, 1992). In Australia, a study was undertaken in free-living birds because there had been indications that a virus of low virulence was in circulation. Swabs were taken from the cloacae of 3,736 birds representing 67 free-living species in Western Australia, and 17 low-virulence strains of NDV were isolated, most of them from wild ducks (Alexander *et al.*, 1986). A 1999 outbreak of Newcastle disease at Mangrove Mountain, New South Wales, Australia, affected several poultry farms and required the sacrifice of nearly 2 million birds as part of efforts to control the disease (*Aust Vet J*, 2000).

In Australia, the situation has been unusual. Following the outbreaks of the infection with clinical manifestations that occurred in 1930 and 1932, several years passed without new outbreaks and a serologic survey conducted in 1964 did not

reveal any reactors. However, a few years later, a strain of the virus was isolated in Queensland, and serologic surveys showed that the infection was widespread in the country. The strains isolated had very low pathogenicity for embryos and chicks, and no symptomatic infections were observed. In 1999, a new outbreak of ND—the first in Australia since 1932—occurred at Mangrove Mountain, New South Wales. Investigation of the oubreaks in the area revealed that they were caused by virulent strains of NDV that evolved through mutation from endemic low-virulence Australian strains (Murray, 1999).

In the Americas, the first outbreak of the viscerotropic velogenic pathotype occurred in Paraguay in 1970. It took a heavy toll on the country's incipient poultry industry, with an estimated loss of 1 million birds. That same year, the pathotype also appeared in Europe and the US. The disease caused by this pathotype is believed to be similar or identical to the form described in Newcastle in 1927, which subsequently disappeared. The outbreak of viscerotropic disease in Europe caused an estimated loss of UK£ 100 million.

The Disease in Man: Man is susceptible to all the pathotypes of the virus, including the lentogenic viruses used in the vaccines. The incubation period is usually one to two days, but may be as long as four days. The clinical picture consists primarily of conjunctivitis with congestion, lacrimation, pain, and swelling of the subconjunctival tissues. The preauricular lymph glands are often affected. The conjunctivitis tends to be unilateral, and systemic reactions are rare. The patient recovers in one week and does not suffer any sequelae. In some cases, a generalized infection lasting three or four days has been observed, with symptomatology similar to that of influenza: slightly elevated temperature, chills, and pharyngitis. This form of the infection has occurred after exposure to aerosols of the virus.

The Disease in Animals: NDV has been isolated from numerous species of birds. The natural disease occurs in domestic fowl, especially chickens, turkeys, and pigeons; ducks and geese are the most resistant. There are several forms of the disease, depending on the pathotype of the active virus and the resistance of the host. The incubation period averages 5 to 6 days, but it can range from 2 to 15 days or longer. The main clinical forms commonly observed are the following:

- Pneumoencephalitic or neurotropic form caused by velogenic strains—characterized by neurological symptoms that appear a few days after onset of the respiratory syndrome. Tremors, torticollis, and opisthotonos are common. The fatality rate can range from 10% to 90% from one poultry farm to another. This form of the disease attacks birds of all ages and does not cause hemorrhagic lesions in the digestive tract.
- Respiratory syndrome caused by some mesogenic strains—affects adult birds and manifests in chicks as respiratory and neurological symptoms. The fatality rate in chicks ranges from 10% to 50%, but in adult birds it is insignificant.
- Inapparent infection caused by lentogenic viruses—occurs in adult birds and provokes mild respiratory symptoms in chicks, with insignificant fatality.

The viscerotropic velogenic form is characterized by a brief incubation period of two to four days, sudden onset, diarrhea, and frequent tracheal discharge. The preponderant lesions are hemorrhaging of the intestinal tract, especially in the proven-

triculus, and sometimes in the gizzard and small intestine. There may also be hemorrhaging in the trachea and edema in the underlying tissues. The tremors and torticollis seen in the neurotropic form are rare, but paralysis can occur. This form is highly fatal, with death occurring one to three days after the onset of symptoms. Other symptoms seen fairly often are edema of the wattles, eyelids, and face—signs that were once considered characteristic of fowl plague.

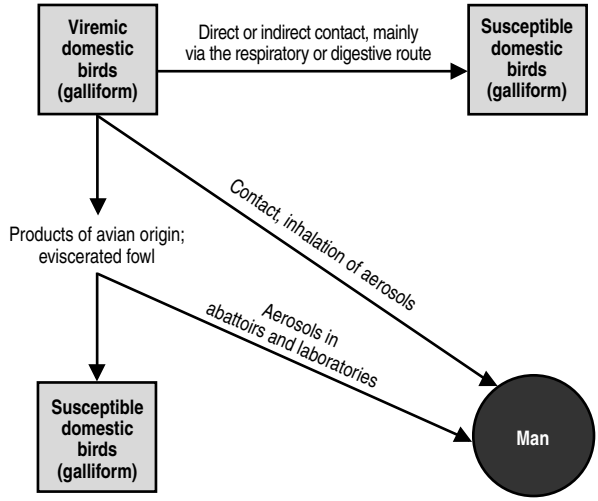
The forms of the disease caused by less virulent viruses produce macroscopic lesions, usually located in the trachea, and sometimes, splenomegaly. There may also be hemorrhaging in the trachea and edema in the underlying tissues.

The disease causes losses not only from death and retarded growth of the birds but also from the sizable reduction in the number of eggs laid. The affected birds stop laying eggs for at least a week. At the start of an outbreak, hens lay eggs with abnormal-looking shells, and this anomaly may be either temporary or permanent.

Source of Infection and Mode of Transmission (Figure 21): Birds are the reservoir of the virus. It has been postulated that the original reservoir was a wild avian species from Southeast Asia because of the explosive and highly fatal nature of the outbreaks that occurred among domestic fowl in Indonesia in 1926. Those episodes would indicate that the virus was poorly adapted to domestic fowl, and that therefore these birds were not a likely reservoir. Since then, the agent's relationship to the host has changed and domestic fowl are now the principal hosts of the virus, or at least for pathotypes that are less virulent than the viscerotropic form.

On a poultry farm, the virus spreads among the birds by direct or indirect contact, usually by the respiratory route and less often by the digestive route. The changes in poultry-raising practices over the last half century have been an essential factor in persistence of the virus. As in any other disease transmitted by aerosols, transmission of the virus depends on population density, and on modern poultry farms there

Figure 21. Newcastle disease virus. Transmission cycle.



is an enormous concentration of birds (Hanson, 1978). The infection is introduced on a farm via infected birds and contaminated objects, as well as the hands and clothing of personnel. Birds vaccinated with mesogenic strains shed the virus in their droppings for 15 to 19 days, and this may be another means by which the infection is introduced. The lentogenic B1 vaccinal strain can only be transmitted from vaccinated to susceptible birds by direct contact.

The permanent carrier state is rare in chickens. It has been shown experimentally that chickens cease to transmit the infection by contact after 34 days. Shedding of the virus appears to be more prolonged in turkeys.

Infected live birds are the most important source of virus transmission within a country and from one country to another. Poultry destined for consumption and slaughterhouse waste are also important sources of infection during transportation within or between countries. The disease is believed to have been introduced in several countries through the importation of frozen eviscerated poultry. It has been demonstrated experimentally that the virus can survive in the lungs and on the skin for 190 days, and in bone marrow for 300 days or longer. Survival of the virus depends on storage temperature. Other vehicles for dissemination of the virus are contaminated truck beds, cages, and crates. It has been established that on several occasions biologicals contaminated with NDV, such as the vaccines against avian pox or laryngotracheitis, have given rise to foci of infection. The virus can also be spread to contiguous farms by wind, the movement of persons, and, in some cases, free-living birds (see Occurrence in Animals). In some instances, the virus has been transmitted from one country to another by the transportation of pheasants and partridges.

The panzootic of the viscerotropic form of the disease that took place in the late 1960s and early 1970s drew the attention of researchers to the role played by birds other than domestic fowl, both free-living and in captivity, including those kept for recreational purposes. In Europe and the US, the viscerotropic velogenic virus has been repeatedly isolated from imported psittacine birds. Another important source of the virus has been illegally introduced fighting cocks. It has been hypothesized that the virus has two types of reservoirs in nature: Nearctic migratory waterfowl, for the agent of the mild respiratory form of the disease, and tropical jungle birds for the agent of the viscerotropic form (Hanson, 1976).

In an area of the US where the viscerotropic form of the disease was epizootic in domestic fowl, a study was conducted to determine the role of wild, semidomestic, and exotic birds in the epizootiology of the disease (Pearson and Cann, 1975). Of 9,446 wild free-living birds that were studied, the virus was isolated from only 3 house sparrows (*Passer domesticus*) and 1 crow (*Corvus brachyrhynchos*), all of which had been in contact with infected chickens; of 4,367 semidomestic birds, it was isolated from 33 (0.76%), mainly ducks, pheasants, and pigeons; of 3,780 exotic birds kept in captivity, the agent was found in 38 (1.01%), mainly psittacines, pittas, and toucans. These results suggest that the disease is primarily linked to confinement.

In the studies on the role of migratory waterfowl, strains of the virus were isolated from ducks and geese, which were classified as lentogenic and heat-stable. This latter characteristic differentiates these strains from the ones that are isolated from chickens. Both the limited contact between migratory and domestic birds and the

fact that the strains were heat-stable, which is characteristic of those found in waterfowl, would suggest that the infection in wild geese and ducks occurs independently in nature (Spalatin and Hanson, 1975).

The main source of the virus in man is poultry and poultry products. Another source of human disease is laboratory virus cultures. Transmission occurs via aerosols in poultry slaughterhouses and laboratories, or from workers rubbing their eyes with hands contaminated from contact with birds or the virus. On poultry farms, the infection can be acquired during the administration of powdered or aerosol vaccines.

Role of Animals in the Epidemiology of the Disease: Newcastle conjunctivitis is a minor zoonosis, given the small number of human cases and benign illness that it produces in man. The avian disease (Newcastle disease) is very important, however, because of the heavy losses that it causes for the poultry industry and because it requires epidemiologic surveillance and repeated vaccination of flocks, both of which have a considerable economic impact.

Diagnosis: Whenever Newcastle conjunctivitis is suspected in a human patient, an attempt should be made to isolate the virus, since a large proportion of infected persons do not respond serologically. Using samples from conjunctival washes and sometimes nasopharyngeal secretions, saliva, or urine, the virus can be isolated by inoculation in chick embryos, susceptible chickens, or cell cultures. Serologic diagnosis is based on the comparison of blood samples obtained during the acute phase of the disease and two or three weeks thereafter, using the neutralization, hemagglutination inhibition, or gel precipitation tests.

The same procedures are used in the case of birds. For the isolation tests, birds that are in the first days of the disease should be selected, and the samples should be taken from tracheal exudate, the spleen, or the lungs for inoculation or culture. In addition to the hemagglutination inhibition and neutralization tests, the enzyme-linked immunosorbent assay (ELISA) may be used with a single serum dilution. The ELISA test has been shown to be a useful alternative to hemagglutination inhibition in terms of both sensitivity and specificity (Hlinak *et al.*, 1992). Serology, however, does not give any information on the type of virus that caused the disease, while isolation and classification of the virus provides an unequivocal diagnosis. Inoculation of 9- to 10-day-old embryonated eggs and culture is the most practical method. Once the virus has been isolated, it is further characterized using such tests for virulence as the average time it takes for the embryo in the egg to die, the intracerebral pathogenicity index in day-old chicks, or the intravenous pathogenicity index in 6-week-old chicks (Alexander, 1991).

Control: The chief control measures in domestic fowl are good hygiene and vaccination. The most widely used vaccines are those that contain the live lentogenic virus, type Hitchner B1 and La Sota. Inactivated vaccines have also been used, and, according to data from Great Britain, they have considerably reduced incidence of the disease. The aluminum hydroxide adjuvant used with killed viruses has been replaced by an oil adjuvant that is much more effective. Although the inactivated vaccines confer immunity for a shorter time, they do not have the secondary effects associated with live vaccines in laying hens. On the other hand, one of the great advantages of the live vaccines is that they allow for the use of mass immunization techniques, inasmuch as individual

vaccination is prohibitively expensive in the modern poultry-raising industry, which maintains large concentrations of birds. With mass immunization, the vaccine can be given by aerosol or in the drinking water, although the latter method is less efficient. On smaller poultry farms, the vaccine can be given to the birds individually by instilling a drop in the conjunctival sac. Although vaccines make it possible to raise poultry under today's conditions of concentration and confinement by preventing the disease, the infection has not been eradicated and remains widespread (Hanson, 1978).

Laboratory workers should take precautions to prevent the formation of aerosols and avoid contaminating their eyes with their hands. Vaccinators can reduce their risk of infection by using masks to protect themselves against ocular or respiratory exposure.

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OMSK HEMORRHAGIC FEVER

ICD-10 A98.1

Etiology: Omsk hemorraghic fever (OHF) virus, an RNA genome virus belonging to the genus *Flavivirus* (arbovirus group B), family Flaviviridae. Antigenically, it belongs to the complex of tick-borne Russian spring-summer encephalitis viruses. Two antigenic varieties have been described.

Geographic Distribution: The virus has only been isolated in western Siberia, in the Russian Federation.

Occurrence: The disease initially occurred among rural workers and children in the steppes of the Omsk region, Russian Federation. Later, it was observed in the Kurgan, Novosibirsk, and Tyumen regions. In 1945, there was an outbreak of 200 cases, and in 1946, another outbreak with 600 cases. Between 1988–1992, additional cases were documented in the Novosibirsk region, the majority of which (83.3%) occurred in September and October (Belov *et al.*, 1995).

The Disease in Man: The incubation period ranges from three to seven days. It is an acute febrile disease with sudden onset, which may or may not have hemorrhagic manifestations. A fever of 39° to 40°C lasts between 5 and 12 days. A significant proportion of patients experience a second febrile phase which is more intense than the first. The most common symptoms are cephalalgia, meningism, vomiting, and exanthem of the palate. In the hemorrhagic cases, the most frequent symptoms are nasal, enteric,

pulmonary, and uterine hemorrhages; congestion of the face and upper parts of the body is also observed, along with conjunctival hyperemia. Bronchopneumonia is common, as is leukopenia. The central nervous system is not usually affected. Alopecia is frequently seen during convalescence. The case fatality rate is between 1% and 2%.

The Disease in Animals: The virus has been isolated from various species of rodents and other small mammals. The muskrat (*Ondatra zibethicus*) is highly susceptible, and many of them die as a result of the infection. In this species, experimental inoculation often produces a hemorrhagic disease with high viremia that can last three weeks or longer. In some species of small mammals, experimental infection causes only a mild transitory illness with asthenia and lethargy, while in other species it does not produce any symptoms at all (Seymour and Yuill, 1981).

Source of Infection and Mode of Transmission: The virus circulates in the forested areas and steppes of western Siberia, where there are many lakes. The main vector is *Dermacentor pictus*, a tick that requires three different hosts for its development; the larvae and nymphs feed on small mammals, and the adults on large wild and domestic animals. The tick also acts as a reservoir, since it can transmit the virus transovarially. The vector parasitizes some 40 species of mammals.

The virus has been isolated frequently from the muskrat (*O. zibethicus*), which was introduced from the Americas. Epizootics in muskrats are associated with high mortality. The muskrat, water vole (*Arvicola terrestris*), root vole (*Microtus oeconomus*), and common shrew (*Sorex araneus*) are all probable amplifiers of the virus. Because of its high-titer viremia, the muskrat plays an important role in transmission of the virus to *D. pictus* and humans. *A. terrestris* has close contact with muskrats during winter because they share the same burrows. Urine is probably the source of infection for rodents. The virus has been isolated from the urine of naturally infected muskrats and water voles (*A. terrestris*) and also experimentally infected *M. oeconomus* and red-cheeked ground squirrels *Citellus erythrogenus*. In addition, it was possible to confirm infection by the oral route in some of these animals (Seymour and Yuill, 1981).

Man can become infected by the bite of a tick or by direct transmission from the muskrat. Most cases occur among workers whose occupation involves handling muskrats (hunters, trappers, and skinners), farmers, and persons who gather wild mushrooms and berries. Laboratory infections are common, probably contracted from aerosols. There are no known cases of human-to-human transmission. The disease in humans occurs primarily between April and October, the time of year when ticks are most active and abundant, although human cases also occur in winter when ticks are inactive.

Diagnosis: The virus can be isolated from the blood of febrile patients. For serologic diagnosis, the neutralization, complement fixation, hemagglutination inhibition, and enzyme-linked immunosorbent assay (ELISA) tests can be used.

Control: An inactivated vaccine of mouse brain origin was developed which afforded protection, but its use was suspended because of adverse reactions.

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OROPOUCHE VIRUS DISEASE

ICD-10 A93.0

Synonym: Oropouche fever.

Etiology: *Oropouche virus* (ORO), an RNA genome virus belonging to the genus *Bunyavirus*, family Bunyaviridae. Serologically, ORO is classified in the Simbu group, one of the 18 serogroups in the genus.

Geographic Distribution and Occurrence in Man: The virus was isolated for the first time in 1955 from a forest worker with fever from the locality Vega de Oropouche in Trinidad, giving the disease its name. A study in which the serum neutralization test was administered to 46 forest workers on the island found antibodies in only 3 of them (Anderson *et al.*, 1961).

Between 1961 and 1978, there were seven epidemics of Oropouche virus disease in the Brazilian state of Pará, all in its most populous area, south of the Amazon river. Epidemics in the state capital, Belém (1961), and the city of Santarém (1975) were estimated to affect 11,000 and 14,000 people, respectively (Pinheiro *et al.*, 1981). It is believed that the seven epidemics together affected at least 165,000. In 1978, a new outbreak began in the hamlet of Quatro Bocas in Pará, spread northward to other rural communities, and ultimately reached epidemic proportions in Belém during 1979–1980 (LeDuc *et al.*, 1981).

Two primary epidemics occurred in the neighboring state of Amazonas, one in the city of Barcelos during May–July 1980 and the other in Manaus from October 1980

to February 1981. The prevalence of hemagglutination-inhibiting antibodies among 496 randomly selected individuals in six Manaus neighborhoods was 4.2% at the beginning of the epidemic and 16.7% at the end. It is estimated that 97,000 of the city's 650,000 inhabitants were affected (Borborema *et al.*, 1982). In December 1987 there was an outbreak in the states of Maranhão and Goiás in the Brazilian Amazon region. The highest incidence was in the 10-to-19 age group. Recurrence of the symptoms was observed in 56% of the cases (Vasconcelos *et al.*, 1989).

So far, epidemics have been limited to the Brazilian Amazon region, but the trend has been for them to occur more frequently and affect an increasingly larger number of people (LeDuc *et al.*, 1981).

The epidemics tend to occur during the rainy season. It is also likely that there are sporadic cases that go unrecognized, as in Trinidad when the virus was first isolated in humans. Serologic surveys conducted during postepidemic periods in nonepidemic areas of the Brazilian Amazon region have established the presence of subclinical infections (Pinheiro *et al.*, 1981).

In addition to northern Brazil and Trinidad, Oropouche virus disease is found in Panama and Peru (Chin, 2000). It is possible that the virus exists in Colombia, where neutralizing antibodies have been found in nonhuman primates in the Magdalena Valley (Berge, 1975).

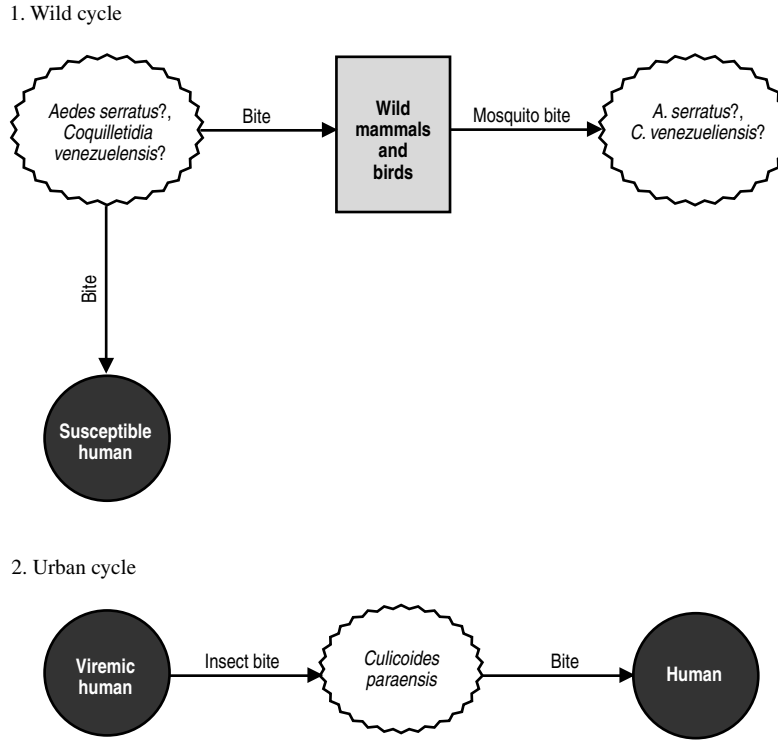
Occurrence in Animals: In Brazil, ORO virus has been isolated only from three-toed sloths (*Bradypus tridactylus*) (Pinheiro *et al.*, 1981). In Trinidad, neutralizing antibodies were found in 9 out of 26 howler monkeys (*Alouatta seniculus insularis*) and 8 out of 26 long-tailed monkeys (*Cebus* spp.) (Anderson *et al.*, 1961). Among a large group of vertebrates captured in the Brazilian Amazon region, most of them birds, hemagglutination-inhibiting antibodies were found in 1% of the rodents, 11.9% of the primates, 4.1% of the sloths, and 2.8% of the birds (Pinheiro *et al.*, 1981).

The Disease in Man: The incubation period ranges from four to eight days. The disease has a sudden onset and its main symptoms are pyrexia (as high as 40°C), intense cephalalgia, chills, myalgia, arthralgia, asthenia, and photophobia. Some patients experience nausea, vomiting, diarrhea, and conjunctival congestion. In fewer than 5% of the cases a maculopapular exanthematic eruption is observed on the trunk and arms, and sometimes the lower extremities. The acute phase lasts two to five days. Nearly 60% of the patients see one or more recurrent crises one or two weeks after the initial symptoms disappear. The cause of these recurrences is unknown. In the 1987 outbreak, it was not possible to isolate the virus from the blood of patients during the recurrent phase (Vasconcelos, 1989). During the epidemic wave of 1980 some patients exhibited symptoms of meningitis (Pinheiro *et al.*, 1982). No deaths attributable to this disease have been confirmed.

The Disease in Animals: The infection is asymptomatic in lower animals. Sloths and primates inoculated subcutaneously with ORO virus developed a viremia that lasted several days (Pinheiro *et al.*, 1981).

Source of Infection and Mode of Transmission (Figure 22): The natural history of ORO virus is not yet fully clarified. Research points to the existence of two different cycles, one wild and the other urban (Pinheiro *et al.*, 1981). The primary

Figure 22. Oropouche fever. Possible circulation of the virus.



reservoir is still not known for certain, nor has the vector of the wild cycle been identified. The virus has been isolated only from three-toed sloths (*B. tridactylus*), but antibodies have been found in primates, rodents, and birds (especially the family Formicariidae). In primates, experimentally infected long-tailed monkeys (*Cebus* spp.), squirrel monkeys (*Saimiri* spp.), and tamarins (*Saguinus* spp.) develop a viremia that can last up to a week. These findings suggest that the reservoir of ORO virus may be sloths, primates, and birds. Not much is known about the vector that transmits the virus in the jungle. The virus was isolated from the jungle mosquito *Coquilletidia venezuelensis* in Trinidad. In Brazil it has been isolated only once, from *Aedes serratus*, despite the fact that more than a million hematophagous jungle mosquitoes (except *Culicoides* spp.) have been studied in that country. As for the urban cycle, the following key epidemiologic facts have been established: a) the disease occurs where there is a high density of the biting midge *Culicoides paraensis*; b) this insect has been shown to be an efficient vector in experimental transmission to hamsters; c) man develops sufficiently high viremia to infect these midges, which in turn can pass the virus on to hamsters (Pinheiro *et al.*, 1982a). In laboratory experiments with the mosquito *Culex quinquefasciatus*, which is also abundant in the urban areas affected by epidemics, this insect proved to be an inefficient vector of ORO virus (Hoch *et al.*, 1987).

Incidence of the disease varies significantly in urban areas. In the Manaus epidemic, reactor rates in the hemagglutination inhibition test ranged from 0 to 40.6% depending on the section of the city. It is believed that this variation in the infection rate is caused by differences in the ecologic conditions in the neighborhoods that either favor or hinder propagation of the vector (Borborema *et al.*, 1982).

Researchers have pointed out that the rate of virus isolations from *C. paraensis*, estimated at 1:12,500, is very low compared with other insect-borne infections. However, the proportionally small number of infected vectors is offset by their great abundance, which would account for the high rate of human infection during epidemics (LeDuc *et al.*, 1981).

The link between the wild and the urban cycles would be humans penetrating the natural foci of infection in the jungle. After acquiring the infection, they return to the urban population in a viremic state and then pass on the infection to *C. paraensis*, thus initiating the urban cycle between the vector and the human population (Pinheiro *et al.*, 1981). Humans would thus be amplifiers of the virus, in addition to being its only host, in the urban setting.

Diagnosis: ORO virus can be isolated from the blood of febrile patients by intracerebral inoculation in suckling mice or adult hamsters. Serologic diagnosis can be obtained by demonstrating seroconversion by using the hemagglutination inhibition test or the enzyme-linked immunosorbent assay (ELISA). The latter is used, especially to detect IgM antibodies, which are indicative of recent infection. RT-nested-PCR can also be used to diagnose Oropouche virus disease (Moreli *et al.,* 2002).

Control: Measures should be targeted at the urban vector to prevent epidemics or curtail them once they begin.

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ORUNGO FEVER

ICD-10 B33.3 Retrovirus infections, not elsewhere classified

Etiology: Orungo virus, a ten-segment RNA genome virus belonging to the genus *Orbivirus*, family Reoviridae. The reovirus virions are spherical, measuring 60 to 80 nm in diameter, and have no envelope.

Geographic Distribution: The virus has been isolated in the Central African Republic, Nigeria, Senegal, and Uganda. There is serologic evidence that the virus is also active in Sierra Leone (Tomori, 1978).

Occurrence in Man and Animals: Approximately 60 human cases have been recorded in Africa. In 1972, there were three outbreaks of the disease in the area of Jos, Nigeria (Fabiyi *et al.*, 1975).

A serologic survey conducted in different ecologic areas of Nigeria using the neutralization test established that the infection was widespread. Of 1,197 human sera examined, 23% were positive, with the highest prevalence in the northern savannah area and the lowest in the rainforest. The prevalence of seropositive subjects increased with age (Tomori and Fabiyi, 1976). The same survey found antibodies in 52% of 44 sheep, 14% of 99 head of cattle, and 24% of the primate specimens examined, representing three species of *Cercopithecus* monkeys.

The Disease in Man: The disease is characterized by a fever that lasts three to seven days, cephalalgia, nausea, vomiting, myalgia, and cutaneous eruption. In addition to these symptoms, diarrhea was observed in one of the outbreaks. A case of progressive paralysis was described in a young girl, who recovered without sequelae. Autopsy of two fatal cases revealed edema and congestion of the spleen, meningeal congestion, and ecchymosis of the cerebellum (Fabiyi *et al.*, 1975).

The Disease in Animals: No clinical symptoms have been described in animals. Experimentally inoculated lambs developed antibodies, but they did not exhibit viremia or any signs of disease (Tomori and Fabiyi, 1977).

Source of Infection and Mode of Transmission: The virus was isolated for the first time in 1962 from a pool of *Anopheles funestus* mosquitoes collected in

Orungo, Uganda. In Nigeria, the agent was isolated from *Aedes dentatus*, and in the Central African Republic, from *Culex perfuscus* and *Anopheles gambiae* (Tomori, 1978). It is thought that the virus is transmitted by *Anopheles* and *Aedes* vectors to humans and domestic animals in urban areas, and among wild nonhuman primates in enzootic rural areas (Tomori and Fabiyi, 1976). Although high reactor rates have been found in sheep, they are not believed to play a role as reservoirs or amplifiers of the virus because they do not present viremia. The virus has not yet been isolated from nonhuman primates, nor have these animals been studied experimentally to determine whether they can develop viremia, and, if so, to what degree; consequently, their role as a reservoir in a probable enzootic cycle is unknown.

Diagnosis: The virus can be isolated from the blood of febrile patients by inoculation in suckling mice. The serologic methods used have been the complement fixation test and the neutralization test on paired acute- and convalescent-phase sera to verify seroconversion.

Control: No control methods have been attempted for combating the disease.

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POWASSAN ENCEPHALITIS

ICD-10 A84.8 Other tick-borne viral encephalitis

Etiology: Powassan (POW) virus, an RNA genome virus belonging to the genus *Flavivirus* (formerly arbovirus group B), family Flaviviridae (formerly Togaviridae),[1] of the tick-borne arbovirus complex (Russian spring-summer encephalitis complex). The virus is named for the locality in Canada where it was first isolated.

[1] All the flaviviruses belonging to former arbovirus group B have been transferred from the family Togaviridae to the family Flaviviridae.

Geographic Distribution: The POW virus has been isolated in Canada (provinces of Ontario and Quebec) and the US (states of California, Colorado, South Dakota, and New York, and the region of New England). Antibodies for the POW virus were reported in Sonora, Mexico. Serologic studies have shown that the virus is present throughout North America. Outside this continent, it is also found in the former USSR (Central Asia and the southern part of the Russian Far East) (Lvov, 1978).

Occurrence in Man: Despite widespread distribution of the virus in nature, human cases are rare, possibly because the tick vector seldom bites man. Between 1958, when the virus was first isolated in Ontario, and 1998, 27 human Powassan encephalitis cases were reported in Canada and the US, three of which were fatal (Gholom *et al*., 1999). Between September 1999 and July 2001, four residents of Maine and Vermont (US) with encephalitis were found to have been infected with the POW virus (CDC, 2001). In a prevalence survey conducted in northern Ontario, Canada, 5% of the population reacted positively in the serum-neutralization test, but less than 1% of the population in enzootic areas had antibodies to the virus (Monath, 1979). Fourteen cases have been recorded in the southern part of the Russian Far East (Leonova *et al.*, 1991).

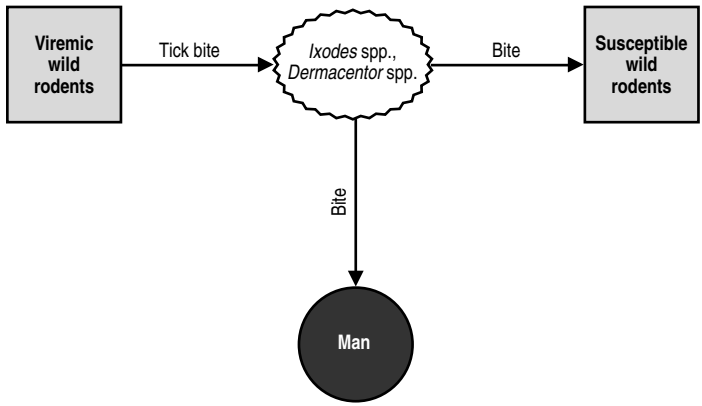
Occurrence in Animals: The POW virus circulates between wild animals and ticks in several enzootic areas. High reactor rates in the serum neutralization test have been found in several animal species. Hemagglutination inhibition was used to test 725 different wild animal species for the St. Louis and Powassan viruses in 22 districts of Ontario, Canada, and gave the following positive reactor rates for both viruses: 50% of the coyotes (*Canis latrans*), 47% of the striped skunks (*Mephitis mephitis*), 26% of the foxes, and 10% of the raccoons (*Procyon lotor*) (Arstob *et al.*, 1986). In Sonoma County, California, US, the POW virus was isolated from a spotted skunk (*Spilogale putorius*). According to the author, that was the first isolation of the virus west of the Rocky Mountains (Johnson, 1987).

In the home of a 13-month-old girl who developed encephalitis following a tick bite, two cats and a dog were serologically positive. In Ontario, Canada, the hemagglutination inhibition test did not produce any positive reactors in a group of 170 cats (Keane *et al.*, 1987). An earlier study, also conducted in Canada, yielded a rate of 1.1% in dogs (Artsob *et al.*, 1984). The virus has been isolated from several species of *Rodentia*, especially squirrels, as well as from weasels and a fox.

The Disease in Man: The few cases observed have been characterized by fever, cephalalgia, prostration, meningitis, spastic paresia, and pleocytosis. An analysis of 14 cases by Leonova *et al.* (1991) in the Russian Far East, concluded that the virus can produce meningoencephalitis, meningitis, an undifferentiated fever, and an inapparent infection. Encephalitis caused by the POW virus is characterized by cerebello-vestibular symptoms, which differentiate it from Russian spring-summer encephalitis.

The Disease in Animals: The infection is probably subclinical. Parenteral inoculation of the virus in woodchucks (*Marmota monax*) and opossum (*Didelphis marsupialis*) produced a high-titer viremia, especially in the former, for 6 to 11 days postinoculation. In foxes, the viremia lasted one to three days. The domestic animals tested (pigs, sheep, and goats) did not develop disease; in young goats, there was a low-titer viremia lasting one day with no clinical symptomatology (Kokernot *et al.*,

Figure 23. Powassan encephalitis. Transmission cycle.



1969). A case of encephalitis and death, possibly caused by POW virus, was reported in a gray fox (*Urocyon cinereoargenteus*).

Source of Infection and Mode of Transmission (Figure 23): Wild animals (marmots, squirrels, mice, rabbits, and mustelids) are the natural reservoirs. The infection is transmitted among them by ticks of the genera *Ixodes* and *Dermacentor.* The ticks *Ixodes cookei* and *I. marxi* have been implicated in Canada, and *I. spinipalpis*, *I. cookei*, and *Dermacentor andersoni*, in the US. In the former USSR, the virus was isolated from *Haemaphysalis longicornis*. It was demonstrated experimentally that *D. andersoni* was able to transmit the virus after feeding on viremic rabbits. Man is occasionally infected by the bite of ixodid ticks.

Diagnosis: The virus has been isolated from the brain of deceased patients using intracerebral inoculation in mice. Serologic diagnosis is done using the complement fixation, hemagglutination inhibition, and serum neutralization tests. These tests will cross-react with antibodies of other flaviviruses, requiring an epidemiologic history of the patient to distinguish them. Tests detecting seroconversion may delay diagnosis, but rapid and specific tests such as polymerase chain reaction and ELISA for IgM antibody are available (Ralph, 1999).

Control: Given the small number of cases observed, control measures are not warranted. Individual prophylaxis consists of avoiding ticks.

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POXES OF MONKEYS

ICD-10 B04 Monkeypox; B08.8 Other specified viral infections characterized by skin and mucous membrane lesions

In 1980, the 33rd World Health Assembly declared human smallpox to be eradicated worldwide. The eradication campaign, based on mass vaccination and epidemiologic surveillance, was launched by the World Health Organization in 1958

and stepped up in 1967. The result has been an unprecedented success: no cases of human smallpox (except two laboratory cases in England in 1978) have occurred since October 1978.

The Global Commission for Certification of Smallpox Eradication, whose work preceded the declaration by the World Health Assembly, formulated several recommendations for the posteradication period, including a call for ongoing surveillance to identify any presumed cases of smallpox, especially cases contracted from nonhuman primates in western and central Africa. The possible existence of an animal reservoir of human smallpox virus has long been a concern of the World Health Organization and researchers in this field, since it would be an insurmountable obstacle to complete eradication. Although the existence of such a reservoir has yet to be verified, there are known animal poxviruses that can be transmitted to humans. These viruses, which have low potential for person-to-person transmission, require continued surveillance and research.

The following section reviews the poxviruses of nonhuman primates that are occasionally transmitted to man. Infection of monkeys in their natural habitat caused by these viruses has been confirmed in the African jungles only.

Prior to 1958, when the monkeypox virus was identified, there had been seven outbreaks of a disease similar to human smallpox among free-living monkeys in Brazil, India, Panama, and Trinidad, and also among monkeys in zoos. Four of these outbreaks were attributed to human smallpox, but the virus was isolated in only one outbreak, and its precise identification could not be established because the strain was lost.

Even though monkeys can be experimentally infected with human smallpox and are capable of transmitting the virus, it has not been demonstrated that the infection exists in these animals in nature. Moreover, countries with large monkey populations have remained free of variola thanks to the eradication measures that have been taken.

1. MONKEYPOX

Etiology: Monkeypox virus belongs to the genus *Orthopoxvirus*, along with the agents of human smallpox (variola), vaccinia, and cowpox, among others. It bears a close antigenic relationship to the variola and vaccinia viruses, and cross-reactions are observed in the neutralization and hemagglutination inhibition tests. Each of the foregoing viruses has type-specific antigens that can be detected using several techniques. Antibodies for these viruses can be differentiated by cross-absorption with heterologous antigens, while specific antibodies can be detected using the immunodiffusion and immunofluorescence techniques. For the latter purpose, radioimmunoassay is a more simplified procedure: after only one adsorption with crude antigenic preparations, it allows direct measurement of the relative concentration of residual antibodies for each virus (Hutchinson *et al.*, 1977). The enzyme-linked immunosorbent assay (ELISA) also can be used (Marennikova *et al.*, 1981). Monkeypox virus produces hemorrhagic lesions on the skin of a rabbit, whereas the variola virus does not infect the animal (Tripathy *et al.*, 1981). In posteradication epidemiologic surveillance it is essential to differentiate between monkeypox and smallpox because the two diseases are clinically identical.

Geographic Distribution: The virus occurs naturally only in western and central Africa in the vicinity of tropical jungles.

Occurrence in Man: Between 1970, when the first human case of monkeypox was discovered in the Democratic Republic of Congo (formerly Zaire), and 1987, a total of 404 cases were investigated in 7 African countries. Of these cases, 95% occurred in the Democratic Republic of Congo (Benenson, 1990). Most of the patients (93% according to one survey) were children, and only a few of them were over 15 years of age. No deaths were recorded in children over the age of 10 or among those who had been vaccinated against smallpox. The overall fatality rate was 11%, but in children 0 to 4 years old it was 15%; previously, the case fatality rate in the same region had been slightly higher with human smallpox. Monkeypox is not transmitted easily from one person to another, and often close contacts do not develop the disease. This observation was confirmed in an investigation of 2,510 contacts of 214 patients conducted in the Democratic Republic of Congo: for 130 primary cases, 22 coprimary and 62 secondary cases were found, and another 14 contacts had antibodies but did not become ill (Jezek *et al.*, 1986). Since the eradication of smallpox, human monkeypox infection has been the most important human disease caused by an orthopoxvirus. Moreover, given its clinical similarity to smallpox, it requires ongoing surveillance.

Occurrence in Monkeys: Since the virus was recognized in 1958, only 10 outbreaks have been reported in captive monkeys at research centers or zoos in the US and Europe, with no cases in personnel who had been in contact with the animals. In a study of 2,242 sera from African and Asian monkeys, no reactors with significant titers were found. From this finding it has been concluded that the infection in nature is not widespread and that it is probably found only in small localized areas (Arita *et al.*, 1972). In serologic studies in western and central Africa, neutralizing antibodies were detected in 7 nonhuman primates and 3 other mammals out of 372 animal specimens collected (Foster *et al.*, 1972). Following the occurrence of a case in a 5-year-old child in Côte d'Ivoire, a serologic study of 115 samples from 10 species of rodents and 6 other mammalian species found neutralizing antibodies in 7 of the rodent species and in 2 groups of birds examined (Breman *et al.*, 1977b). Subsequently, in the area of western Africa where human cases had occurred, examination of sera from 195 primates (previously treated to reduce nonspecific reactions) showed that 8% had high titers and were positive in the hemagglutination inhibition test and 21% were positive in the neutralization test (Breman *et al.*, 1977a). These results indicated that nonhuman primates and other animals such as the African giant squirrel, porcupines, and pangolins had been infected by an orthopoxvirus, but not necessarily monkeypox virus. It should be added that in Asia, where there have been no cases of human smallpox in monkeys, no neutralizing antibodies have been found in nonhuman primates. Few monkeys have been found near villages, and, even though antibodies have been detected in a small number of them, the virus could not be isolated (Arita *et al.*, 1985; Baxby, 1988).

In 1985, the virus was isolated from the Thomas' tree squirrel (*Funisciurus anerythrus*). In another serologic study conducted in the Democratic Republic of Congo, antibodies were detected in 24.7% of 320 squirrels of this species. This finding is a good indication that these animals transmit the virus in areas surrounding the villages. In addition, 6 (16%) of 27 red-legged sun squirrels (*Heliosciurus rufobrachium*) were found to be positive for the virus (Khodakevich *et al.*, 1987).

The Disease in Man: The signs and symptoms are similar to those of human smallpox. The incubation period is 7 to 15 days. During the prodromal period,

which lasts two to three days, the patient experiences extreme fatigue, fever, and muscular and dorsal pain. The eruption appears at approximately the same time on the face and body. The evolution from maculae to papules, vesicles, pustules, and scabs takes about 10 days, and desquamation may last about 3 weeks. The lesions are more numerous on the extremities. The differences in the clinical signs are that lymphadenopathy is more pronounced in human smallpox (variola) than in human monkeypox and that the skin lesions are more numerous (Baxby, 1988).

There is no specific treatment.

The Disease in Monkeys: In captive monkeys, the lesions consist of multiple discrete papules ranging from 1 to 4 mm in diameter. The lesions are most numerous on the palm of the hand, but they can also be found on all parts of the trunk and the tail. The content of the papules is thick and resembles pus. The lesions are often umbilicated. Sometimes circular ulcerative lesions occur on the mouth. Histopathologically, the lesions consist of epidermal proliferation followed by necrosis. Focal areas of acanthosis are also found.

Source of Infection and Mode of Transmission: Human cases caused by the monkeypox virus have occurred only in Africa. Epidemiologic research, especially on prevalence of the disease in children, who do not usually go into the jungle, has led the search for the reservoir to areas surrounding villages near the edge of the forest. In these agricultural areas, which are lands claimed from the jungle, squirrels and terrestrial rodents abound, but there are few monkeys. Squirrels are attracted to these areas by the nuts from the abundant oil palm. In serologic studies, the terrestrial rodents have produced negative results, but high rates of reactors were found in the two species of squirrels (*F. anerythrus* and *H. rufobrachium*). In addition, the virus was isolated from *F. anerythrus*. Of 253 blood samples from 6 genera of monkeys living in the Democratic Republic of Congo, 16 (6.3%) were positive in the radioimmunoassay test. It is still difficult to say whether monkeys play an important role in maintenance of the virus or are merely accidental hosts like man (Khodakevich *et al.*, 1987). Outbreaks of the disease in Asian monkeys at research centers may have resulted from cohabitation with African monkeys. Based on the research conducted so far and the evidence that has been accumulated, there is strong reason to believe that squirrels are the reservoir of the virus, at least in the Congo, which is also the country that has the most cases (95%). The virus's portal of entry is not yet confirmed, but it appears to enter through the mucosa of the upper respiratory tract or through skin abrasions (Weber and Rutala, 2001). People living in the regions described consume both monkey and squirrel meat, and it may be that contact with these animals is the route by which the virus is introduced in the human body. Interhuman transmission from patients to contacts does not play an important role.

Diagnosis: The virus can be isolated from the skin lesions, including the scabs. The isolated strain should be sent to a reference laboratory for correct identification. Verification of an increase in titer between acute- and convalescent-phase sera can aid in diagnosis, but special tests should be used to confirm the presence of specific antibodies for monkeypox virus (see Etiology).

Control: Patients should be isolated, and contact with them should be limited to medical personnel who have been vaccinated against smallpox. Precautions against

transmission via contact and droplets should be taken in patient treatment (Weber and Rutala, 2001). Because of the small number of human cases, other measures are not warranted. The preventive measures in animal colonies are the same as for tanapox (see below).

Prevention of monkeypox in primate research centers consists of employing proper animal handling practices. Asian and African monkey species should not be kept in shared quarters. Special care should be taken in the handling of potentially contaminated gloves and equipment. Skin wounds and abrasions in animal handlers should receive medical attention.

2. TANAPOX

Etiology: Tanapox virus, a DNA virus belonging to the genus *Yatapoxvirus*, family Poxviridae. The virus is antigenically related to Yaba-like disease virus (YLDV) and Yaba monkey tumor virus (YMTV) (see below).

Occurrence in Man: In 1957 and 1962, there were two epidemics that affected several hundred members of a tribe in Kenya located in an isolated area along the Tana River. In a study conducted in the Congo, more than 163 cases of tanapox were observed between 1978 and 1981 (Arita and Gromyko, 1982). In 1966, 23 human cases occurred among personnel who had been working with pox-affected monkeys at three primate centers in the US. A serologic study of the indigenous population in the Tana River valley conducted in 1976 revealed a reactor prevalence of 9.2% in the neutralization test (Axford and Downie, 1979). Other serologic studies have shown that the tanapox virus is endemic in several countries of equatorial Africa. The disease attacks all age groups, but it is most prevalent in adults, and the average age is 23.4 years (Jezek *et al.*, 1985).

Occurrence in Monkeys: Outbreaks caused by this virus have occurred at various primate centers in the US. In a breeding colony at one of these institutes, the infection rate exceeded 30%, and various species of macaques were affected. Nothing is known about the disease's occurrence in the jungle. In one serologic study, 15% of 263 Asian macaques and 76% of 55 African green monkeys (*Cercopithecus aethiops*) reacted positively in the neutralization test. The neutralizing antibody titer in the African green monkeys was high (Hall and McNulty, 1967).

The Disease in Man: During the epidemic in Kenya, the incubation period could not be determined. The illness began with a fever that lasted three or four days in 59% of 258 patients, sometimes accompanied by pronounced cephalalgia and prostration. At first, the lesions were similar to those of smallpox, but they did not turn into pustules. Papules and umbilicated vesicles developed on the arms, face, neck, and trunk, but not on the hands, legs, or feet. A notable characteristic of the disease was that the patients did not have more than one or two lesions. The cutaneous lesions are pruriginous, and some of them ulcerate. The corresponding lymph glands become enlarged. Histopathologic study of the lesions revealed pronounced hyperplasia of the epithelium of the skin, with little damage to the underlying dermis. Destructive alterations of the epithelium such as those seen in lesions caused by the vaccinia or variola viruses were not observed. A disease similar to that described in the Kenya cases was reported in the US among personnel who had been working

with sick monkeys. Tanapox is usually a benign disease, and the ulcers and nodules disappear spontaneously in the course of six weeks (Jezek *et al.*, 1985). The smallpox (vaccinia) vaccine does not protect against tanapox.

The Disease in Monkeys: The disease observed in macaques at the US research centers was characterized by single lesions in some animals and multiple lesions in others (*M. fuscata*). The lesions were located mainly on the face, especially around the lips and nostrils, but they were also found on other parts of the body. They consisted of an enlarged circular area on the skin with umbilication and an adherent scab at the center. They did not develop into vesicles or pustules, and they did not become hemorrhagic. Vaccination with vaccinia virus did not confer resistance to tanapox infection. Morbidity was high, but there were no deaths. The most severe lesions regressed within six to eight weeks.

Source of Infection and Mode of Transmission: The high prevalence of serologic reactors in African green monkeys without any clinical symptomatology would seem to indicate that this species is the natural host of the virus. Also, the epidemics in man have occurred in the jungle areas of Africa. The epidemiology of the disease is still not very clear. After three years of observation in an endemic region of the Congo, Jezek *et al.* (1985) reported that most of the human cases (57%) occurred between November and March and that the lesions formed on parts of the body that were not covered. The seasonal nature of the disease, which coincides with the abundance of mosquitoes and other blood-sucking insects, would indicate that these insects may be biological or mechanical vectors of the virus. It is thought that *Mansonia* spp. mosquitoes were the vectors during the epidemics in Kenya. It is believed that monkeys are the reservoir of the virus and that blood-sucking insects transmit the infection from these animals to man (Jezek *et al.*, 1985). People who handle monkeys in captivity contract the infection through scratches inflicted by the animals (Hall and McNulty, 1967). Presumably, Asian monkeys (*Macaca* spp.) contract the infection by direct or indirect contact with African monkeys at primate centers. Human cases in the laboratory result from contamination of abrasions and scratches on the skin.

Diagnosis: Differential diagnosis is important in the surveillance of poxes. Tanapox should not be mistaken for monkeypox, which is a much more serious disease. Laboratory confirmation can be accomplished by isolating the virus. The isolated strain should be sent to a reference laboratory for correct identification.

Control: Preventive measures against tanapox in primate research centers are the same as those for monkeypox. In the event of an outbreak of tanapox in a monkey colony, the animals can be vaccinated using the virus itself. The vaccinia virus does not protect against tanapox.

3. POXES CAUSED BY OTHER YATAPOXVIRUSES

The genus *Yatapoxvirus* also includes two other viruses, Yaba-like disease virus (YLDV), which causes nodular lesions on the skin of monkeys, and Yaba monkey tumor virus (YMTV). The two viruses are serologically related to one another as well as to tanapox virus. YLDV produced epizootics in 1965 and 1966 at primate centers in the US in California, Oregon, and Texas, which also affected the animal

handlers. In monkeys, this virus causes a brief fever, followed by the development of necrotic maculopapular nodules on the arm, face, neck, and trunk, which usually heal in two to four weeks. YMTV was isolated for the first time in rhesus monkeys in Yaba, Nigeria. In these animals it causes an epidermal histiocytoma consisting of an often suppurative infiltrate of mononuclear macrophages. The human cases have occurred in monkey handlers (Esposito and Nakano, 1991).

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PSEUDOCOWPOX

ICD-10 B08.0 Other orthopoxvirus infections

Synonyms: Milker's nodules, pseudovaccinia, paravaccinia.

Etiology: Pseudocowpox virus is a DNA genome virus belonging to the genus *Parapoxvirus*, family Poxviridae. The members of this genus are ovoid and measure approximately 260 nm by 160 nm. The genus also includes the agents of contagious ecthyma (Orf virus) and bovine papular stomatitis (BPS virus) (see respective chapters in this volume) as well as sealpox (see addendum to this chapter). They differ antigenically from the cowpox and vaccinia viruses, which belong to the genus *Orthopoxvirus*. The parapoxviruses mentioned above are all closely related. Some investigators have thought that the pseudocowpox virus and the agent of bovine papular stomatitis are identical (Nagington *et al.*, 1967); however, electron microscopy shows that their external structures are different. The sera of cattle convalescing from papular stomatitis and pseudocowpox contain complement-dependent antibodies that are cytolytic only for cells infected with the homologous virus (Rosenbusch and Reed, 1983).

Geographic Distribution and Occurrence: Since the time of Jenner, the disease has been recorded sporadically in cattle and humans. Distribution is worldwide, as attested by confirmation of the disease in countries the world over (Tripathy *et al.*,

1981; Hernández-Pérez and Serpas de López, 1981). In many countries, the disease is enzootic in bovines, especially milk cows. The disease's frequency in animals and man is still not well known. A study carried out in a slaughterhouse in Great Britain revealed that 46 of 358 milk cows (13%) were clinically affected. Serologic studies in the US have shown that the infection is widespread and perhaps often clinically inapparent. In countries where milking is done by hand, human disease (milker's nodules) is relatively frequent but seldom diagnosed. In El Salvador, 46 cases were diagnosed on a single dairy farm (Hernández-Pérez and Serpas de López, 1981; Tripathy *et al.*, 1981); in Finland, 44 cases were diagnosed in the Tampere region (Kuokkanen *et al.*, 1976).

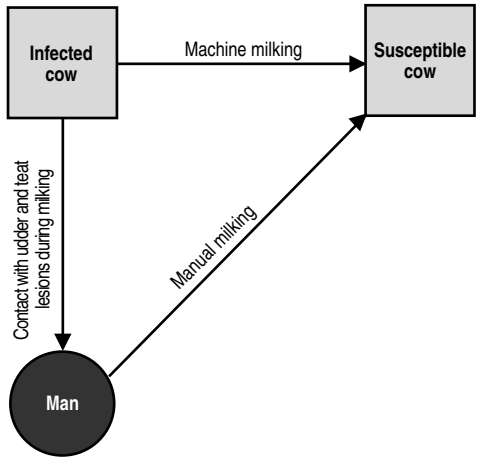
The Disease in Man: The human disease is known as "milker's nodules." It has an incubation period of five to seven days. A benign disease without systemic reaction, it begins with a pruriginous erythematous papule, usually located on the fingers or on a hand but sometimes it is found on other parts of the body. The lesion may take four to six weeks to develop; eventually it becomes a firm nodule 0.5 to 2 cm in diameter, ranging in color from gray to reddish blue or brown. The lesion heals without leaving a scar. In the outbreak of 44 cases in Finland, 10 of them had secondary eruptions with exanthem or lesions similar to multiform erythema (Kuokkanen *et al.*, 1976). This complication has also been observed in Germany (Schwartz *et al.*, 1967).

The Disease in Cows: The disease occurs in milk cows. The lesions are located mainly on the udder and teats. They begin as a small focal area of erythema and develop into a papule with a small central vesicle. The lesion undergoes umbilication and goes into a pustular phase, although the pustules sometimes go unnoticed. They break in two to three days and form dark red scabs. The center of the scab desquamates, leaving a ring- or horseshoe-shaped layer, which is considered pathognomonic (Fenner *et al.*, 1993). The scabs drop off in about two weeks. Individual lesions usually heal within 7 to 10 days, but in some animals they can persist for months. One of the characteristics of pseudocowpox is periodic recurrence of the lesions. Buccal lesions may be seen in nursing calves (Nagington *et al.*, 1967). Milking becomes difficult because the cow's teats are tender.

Source of Infection and Mode of Transmission (Figure 24): Milk cows are the natural hosts of the virus. The infection is spread among cows via the hands of milkers or the cups of mechanical milking machines. It has been possible to isolate the virus from lesions up to six months after their appearance, and this fact may explain the persistence of the agent in a herd (Tripathy *et al.*, 1981). Man contracts the infection while milking, through contact with lesions on the cow's udder or teats or on the mouth of a calf. Skin abrasions facilitate infection. It is also possible for a person with a skin lesion to acquire the infection indirectly through contact with contaminated objects. That would be the case of four patients who received first- and second-degree burns in an accident and two to three weeks later developed multiple nodular lesions confined to the burned areas. The patients had not had contact with livestock, but they had had contact with contaminated objects. The pseudocowpox agent has been isolated in tissue cultures (Schuler *et al.*, 1982).

Diagnosis: The clinical disease may be confused with cowpox, vaccinia virus infection, and mammilitis caused by bovine herpesvirus type 2. The pseudocowpox

Figure 24. Pseudocowpox. Mode of transmission.



virus can be isolated from the lesions in primary bovine kidney tissue cultures, in which it causes a cytopathic effect. On the other hand, it does not replicate on chicken embryo chorioallantoic membrane or on rabbit skin, both of which are good substrates for propagating the vaccinia and cowpox viruses. Electron microscopy is very useful for diagnosing pseudocowpox because the virus has an oval morphology typical of the parapoxviruses. Calves vaccinated against cowpox are not resistant to the pseudocowpox virus.

Control: No vaccines are available. Natural immunity is not long-lasting. Prevention consists mainly of hygienic measures during milking.

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Addendum

SEALPOX

Parapoxvirus infections have been described in various species of seals in different regions of the world. In Canada, an outbreak was described in recently weaned captive gray seals (*Halichoerus grypus*), with transmission to two of their three handlers. The clinical manifestations in the seals were nodular lesions on the flippers, head, and neck, similar to those described in other species of seals with a parapoxvirus infection. The two handlers who contracted the infection had lesions similar to milker's nodules. The lesions, nodules with a red center 5 mm in diameter located on a single figure, appeared in one of the cases 19 days after the person had been in contact with the seals. Starting on day 29 after the lesion was first noted, a clear liquid transudate developed that lasted for several days, following which scabs formed and then fell off a week later. The second patient experienced a similar course but with several recurrences. The virions observed under the electron microscope were similar to those of the milker's nodule parapoxvirus and to the lesions on the seals (Hicks and Worthy, 1987).

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RABIES

ICD-10 A82

Synonyms: Hydrophobia, lyssa.

Etiology: The rabies virus is bullet-shaped and has a single-stranded, nonsegmented RNA genome. It belongs to the genus *Lyssavirus*, family Rhabdoviridae. The virion averages 180 nm in length and measures 75 nm in diameter. Each particle contains a helicoid nucleocapsid with a bilayered lipid envelope. Glycoprotein spikes project from the surface of the envelope. Of the five proteins that have been identified, two are of special interest: the RNA nucleoprotein (N), which is a group-specific antigen, and the glycoprotein (G) contained in the spikes projecting from the surface of the virion, which is responsible for inducing the production of neutralizing antibodies. The "classic" rabies virus (serotype 1) and the morphologically similar viruses that have been isolated in Africa and Europe (see Classification of Rabies and Rabies-related Viruses) have a common group-specific antigen—namely, the internal nucleoprotein antigen. However, more recent studies have shown that these rabies-like viruses lack several antigenic determinants that are found in the nucleocapsid of the rabies agent. Monoclonal antibody tests directed against the glycoproteins have shown that these viruses have even greater differences with respect to the classic rabies virus (Wunner, 1989). The rabies-related viruses can also be differentiated in terms of their superficial and glycoprotein antigens by the neutralization test and the cross-protection assay.

Classic rabies is subdivided into "street virus" and "fixed virus." Street virus refers to the pathogen recently isolated from an animal that has not undergone modification in the laboratory. It is characterized by its capacity to invade the salivary glands and by the highly variable incubation period of the infection, which can be quite prolonged. By contrast, fixed virus refers to strains that have been adapted to laboratory animals by serial intracerebral passages; these viruses do not invade the salivary glands and the infection has an incubation period of only four to six days. The World Health Organization (WHO) Expert Committee on Rabies has pointed out that, under certain conditions, a fixed virus can be pathogenic for man and animals (WHO, 1984). Cases of rabies are known to have occurred in persons who received poorly inactivated rabies vaccine, and one case resulted from inhalation of the virus during the preparation of a concentrated vaccine.

The long-suspected different antigenic makeup of the rabies viruses has been confirmed by cross-protection assays, neutralization tests, kinetic neutralization studies, and counterimmunoelectrophoresis (Díaz and Varela-Díaz, 1980). More recently, monoclonal antibody techniques have demonstrated the broad range of antigenic diversity among the rabies viruses. Analysis of several fixed and street viruses with a monoclonal antibody panel directed against the glycoprotein antigens showed great variations in reactivity (Wiktor *et al.*, 1980). This knowledge along with new techniques have made it possible to confirm that cases of rabies in dogs, cats, and a fox were caused by modified live virus vaccines. A panel of 8 monoclonal antibodies was used to analyze viruses isolated from 14 animals that had been vaccinated with modified and inactivated rabies viruses, and the resulting reactive pattern was identical to that of the vaccine virus (Whetstone *et al.,* 1984). Intensive research is being carried out in several countries to correlate the antigenic differences between

vaccine viruses and the viruses present in the animal population in an attempt to explain why protection failure sometimes occurs in persons vaccinated on a timely basis with the complete indicated course of postexposure prophylaxis. When a panel of 20 monoclonal antibodies was directed against the nucleocapsid in 204 strains of rabies street virus isolated in Africa, Asia, and Europe, it was found that the strains from Iran, Madagascar, and Thailand differed markedly from the others (Sureau *et al.,* 1983).

Use of the monoclonal antibody technique has led to major progress in knowledge about the epidemiology and control of rabies. Essentially, the method consists of placing monoclonal antibodies in contact with the specimen under study, such as an impression smear of infected brain or tissue culture fixed with acetone, and then applying the indirect immunofluorescence technique by staining the slide with fluorescein-conjugated mouse antiglobulin. The presence or absence of fluorescence is determined by microscopy. Usually the panel of monoclonal antibodies is selected on the basis of known reactivity to strains of various origins (Barrat *et al.*, 1989).

This technique has made it possible to demonstrate the existence of antigenic variation in the rabies viruses. The epidemiologic importance of these variations is that they provide better knowledge about the animal species where the virus originated and its geographic distribution.

Analysis of strains from different parts of the world with monoclonal antibodies against the G and N proteins has shown that strains isolated from a given animal species or a particular area have a unique reactivity profile. Thus, for example, in the polar ecosystem, where the principal rabies reservoir is the Arctic fox, the same pattern of reactivity is observed in the reindeer and seals that share its habitat, evidently because the infection is transmitted from the fox to these animals (Rupprecht *et al.*, 1991). Smith (1989) has explored in depth the subject of epitope variation and its usefulness in ecologic studies. Here we limit ourselves to a few illustrative examples. In the US, there are marked divergences in the antigenic patterns of rabies virus strains isolated from different geographic areas in which one or another wild species predominates. Several rabies enzootic areas can be identified, and in each area there is a predominant animal species that maintains the enzootic. The viruses isolated from the different areas had four different patterns of reactivity to the monoclonal antibodies directed against the internal protein N. A single reactivity pattern was found in 37 viruses isolated from red foxes (*Vulpes vulpes*) in the northeastern US and in southern Ontario and Quebec, Canada, while viruses isolated from Arctic foxes (*Alopex lagopus*) in the Canadian Northwest Territories and Alaska, US, had an identical antigenic profile. By the same token, the viruses isolated from areas where skunks predominate along the mid-Atlantic coast and in the southeastern states of the US had another reactivity pattern in common. On the other hand, two reactivity patterns were found in viruses isolated from skunks that maintain rabies enzootics: one pattern was found in California and the north-central states of the US as well as the bordering provinces of Canada, while the other pattern associated with the same species was found in the south-central states of the US (Smith, 1989). There are also differences between the antigenic profile of bats and that of land mammals in the US and indeed between different species of bats.

In a cooperative investigation (Díaz *et al.*, 1994), 288 rabies viruses isolated in 17 countries of Latin America and the Caribbean were studied by using a panel of monoclonal antibodies directed against the antigenic determinants of the nucleoprotein

(N). Eight antigenic variants were detected. Variants 1 and 3 (numbered for the purpose of this study only) were widely distributed agents of human rabies; variant 1 was common in dogs; and variant 3, in vampire bats. Variants 1 and 3 were found in cattle, and so were variants 2 and 5 to a lesser extent. Variant 4 was isolated from insectivorous Mexican free-tailed bats (*Tadarida brasiliensis)*. As for variants 6, 7, and 8, variants 7 and 8 were detected only in a few unique strains isolated from land mammals and an unidentified bat. The rabies virus isolated from eight *T. brasiliensis* bats yielded a reactivity pattern different from that of the vampire bat and also that of *Tadarida* in the US (Smith, 1989). The vampire bat (*Desmodus rotundus*), in turn, has its own reactivity pattern different from that of dogs. This same pattern was also found in the few domestic animals that purportedly contracted rabies from vampire bats.

In the industrial countries of Europe, where canine rabies has been eradicated, the infection is prevalent in red foxes (*V. vulpes*). Rabies in other animals, both wild and domestic, is spread by the fox. Viruses isolated from land mammals all yield the same reactivity pattern. In Central and Eastern Europe, an antigenic variant found in raccoon dogs (*Nyctereutes procyonoides*) is the same as that found in the Arctic fox (Chomel, 1993) but unlike that in the red fox (Smith, 1989).

In Africa, in addition to the reactivity pattern in dogs, which is identical to that of dogs in Latin America, Asia, and some regions of Europe, another variant has been isolated from the greater kudu (*Tragelaphus strepsiceros*); it was isolated first from jackals and possibly spread horizontally to kudus (Smith, 1989).

Moreover, the fixed viruses, which are considered antigenically and biologically similar, also vary in their antigenic determinants. Monoclonal antibodies directed against the antigenic determinants of the glycoprotein (G) have demonstrated that laboratory fixed viruses share only 50% to 85% of the protein G determinants.

Classification of rabies and rabies-related viruses

The genus *Lyssavirus*, family Rhabdoviridae, has been subdivided into the following serotypes:

- **Serotype 1:** The category that includes most of the viruses that cause rabies in man and animals, as well as laboratory fixed viruses. The prototype strain is known as the "challenge virus standard" (CVS).
- **Serotype 2:** Lagos bat virus (LBV), isolated from three species of frugivorous bats in the Central African Republic, Nigeria, and South Africa and from a cat in Zimbabwe.
- **Serotype 3:** Mokola virus (MOK), isolated from African fetid shrews (*Crocidura* spp.), man, and, more recently, cats and a dog (Foggin, 1983) in Cameroon, Nigeria, and Zimbabwe.
- **Serotype 4:** Duvenhage virus (DUV), isolated from man in South Africa and later from bats in South Africa and Zimbabwe.

A virus similar to DUV was isolated from serotine bats (*Eptesicus serotinus*), designated "European bat lyssavirus" (EBL-1), and from *Myotis* bats (EBL-2) in various European countries. Of 550 bats examined in Denmark, 104 were positive. Bats were also found to have *Lyssavirus* in Finland, France, Germany, the Netherlands, Spain, and the former USSR. At first, these viruses were thought to belong to serotype 4 (DUV), but more recent studies have shown that they are different from the African viruses, and serotype 5 has therefore been proposed to accommodate them (Bourhy *et al.*, 1992).

The Kotonkan viruses (KOT), isolated from flies of the genus Culicoides in Nigeria, and Obodhiang virus, isolated from mosquitoes (*Mansonia uniformis*) in the Sudan, are genetically and antigenically the least like the other species of *Lyssavirus* and share very few epitopes with the rabies virus.

At present, it does not appear that any of these rabies-related viruses has much epidemiologic importance, although MOK and DUV viruses have caused some cases of human disease and death. The fact that MOK virus was isolated from cats and a dog in Zimbabwe (Foggin, 1983) should be kept in mind because of the possibility of transmission to man.

The rabies-related viruses may cross-react to some extent with the classic rabies virus in immunofluorescence and complement fixation tests, thus posing some confusion in the diagnosis of rabies. It should be kept in mind that the rabies vaccine does not confer protection against rabies-related viruses.

In comparative pathogenesis studies in hamsters with classic rabies strains, LBV, and MOK, the three viruses have proven to be similar in terms of their tropism and the course of their infection. Experiments have also shown that mice, hamsters, dogs, and monkeys are susceptible to intracerebral inoculation of the African viruses (LBV and MOK) and that the agents can then be isolated from the brain and salivary glands; on the other hand, inoculation of these serotypes by other routes is rarely fatal for the animals. Strains isolated from mosquitoes (OBOD) are pathogenic only for suckling mice when inoculated intracerebrally. Neutralizing antibodies for KOT virus isolated from *Culicoides* are often found in cattle, sheep, and equines, as well as in rodents and insectivores in northern Nigeria.

Geographic Distribution: Rabies occurs on all continents, but not in most of Oceania. A number of countries are currently free of the infection, including Barbados, Jamaica, and several other Caribbean islands, as well as Uruguay, in the Americas; Japan in Asia; and Bulgaria, Ireland, the Netherlands, Portugal, Spain, the United Kingdom, and some of the Scandinavian countries in Europe. Rabies is not uniformly distributed in the infected countries, which may have areas free of the disease, with low or high endemicity, or with epizoodemic outbreaks.

Occurrence: Rabies has both an urban and a wild cycle. Most human cases are reported in cities and are caused by the bites of rabid dogs. In those countries that have managed to control or eradicate canine rabies, even though they still have a wild cycle, the number of human cases has been reduced to very low levels. Such is the situation in the US, where in 1938 there were 47 human cases, but recently the number has been down to between 0 and 3 a year.

Most of the European countries are in a similar situation. In 1991, there were a total of 1,326 cases of human rabies in the world, compared with 1,135 recorded by WHO in 1984. Asia has the largest number of human cases. In the Americas, there were an average of 283 human cases a year during 1980–1989, a figure almost unchanged from 1970–1979 (280 cases a year). Table 5 shows the average annual number of cases between 1980 and 2000 in the Region of the Americas. Several countries, including Canada, Chile, Costa Rica, Panama, Uruguay, and the countries of the non-Latin Caribbean, had no human cases. In 1990–1999, the Andean area was the American subregion with the largest number of human cases (66), followed by Brazil (41) and Mexico (30) (PAHO data, 2000). Most of the cases occurred outside large cities. The incidence of human rabies was highest in males (58.7%) and

TABLE 5. Average annual number of reported cases of human rabies in the Americas, by subregion and by country, 1980–2000.

Subregion/country	1980–1989	1990–1999	2000
Andean Area	79.0	65.9	18
Bolivia	11.1	10.3	3
Colombia	14.3	5.2	7
Ecuador	21.5	21.6	3
Peru	26.4	26.6	4
Venezuela	5.7	2.2	1
Southern Cone	5.0	4.8	1
Argentina	0.8	0.5	0
Chile	0.8	0.1	0
Paraguay	3.4	4.2	1
Uruguay	0	0	0
Brazil	84.8	40.9	26
Central America	32.4	19.7	11
Belize	0.5	0	0
Costa Rica	0	0	0
El Salvador	16.4	8.9	2
Guatemala	8.0	7.0	6
Honduras	5.4	2.8	3
Nicaragua	2.1	1.0	0
Panama	0	0	0
Mexico	62.0	30.6	4
Latin Caribbean	6.2	2.9	1
Cuba	0	0.5	0
Dominican Republic	4.0	1.2	0
Haiti	2.2	1.2	1
North America	1.0	2.7	6
Canada	0	0	1
United States	1.0	2.7	5
Total	270.4	167.5	67

Source: Regional Information System for the Epidemiological Surveillance of Rabies in the Americas, SIRVERA (PAHO).

in children under 10 years old (35.4%). The main source of infection was dogs (76.2%), followed by bats and cats (5.4%) (PAHO data, 2000).

In many developing countries, the epidemiologic surveillance of rabies is inadequate and case reporting is incomplete; however, throughout Latin America a weekly rabies reporting system is in place. The public health importance of rabies does not lie in the number of cases, which the foregoing data show is relatively small, but rather in the fact that nearly 100% of the patients die. No less important is its psychological and emotional impact, including the suffering and anxiety experienced by those bitten faced with the fear of developing the disease. There are also economic losses in terms of person-hours spent on administering treatment against rabies. In 1991, a total of 453,769 individuals were given rabies postexposure treatment in 106 countries, and by 1999 the number had reached 933,260, 33% of whom completed the course of postexposure prophylaxis (PAHO data, 2000).

Natural infection occurs in almost all domestic and wild animals, although different species show varying degrees of susceptibility. In cities, dogs are the main

sources of infection for man, followed by cats. In 1991, 21,248 domestic animals were diagnosed with rabies in 106 countries of the world (WHO data, 1991). Table 6 shows the average annual number of cases of canine rabies in Latin America and the Caribbean between 1990 and 2000.

In 1991, 18,634 wild animals of different species were diagnosed with rabies throughout the world (WHO data, 1991). In the Americas, nearly 90% of the cases were diagnosed in Canada and the US. However, this great preponderance of cases in North America compared with the rest of the hemisphere probably does not reflect the true situation, since little attention has been given to rabies in wildlife; outside Canada and the US surveillance has been deficient.

Wild rabies is an important problem in Europe, where an epizootic in red foxes (*V. vulpes*) broke out in Poland around 1940, spread to a large part of the continent, and is still active. In northern regions, rabies is maintained in Arctic foxes (*A. lagopus*), while their counterpart in South America is the Argentine gray fox (*Pseudalopex griseus*). When brain tissue from 58 gray foxes captured in the southernmost region of Chile (province of Magallanes, Riesco Island, and Tierra del

TABLE 6. Average annual number of reported cases of canine rabies in Latin America and the Latin Caribbean, by subregion and by country, 1990–2000.

Subregion/country	1990–1994	1995–1999	2000
Andean Area	2,649	1,229	255
Bolivia	1,115	254	0
Colombia	162	101	66
Ecuador	708	502	79
Peru	574	247	54
Venezuela	90	125	56
Southern Cone	336	466	57
Argentina	61	10	4
Chile	1	0	0
Paraguay	274	456	53
Uruguay	0	0	0
Brazil	669	1,072	761
Central America	623	379	179
Belize	1	7	…
Costa Rica	0	0	0
El Salvador	92	138	35
Guatemala	144	163	126
Honduras	342	52	18
Nicaragua	44	19	0
Panama	0	0	0
Mexico	4,803	669	244
Latin Caribbean	107	97	94
Cuba	28	34	24
Dominican Republic	28	27	31
Haiti	51	36	39
Total	9,187	3,912	1,590

… Data not available.

Source: Regional Information System for the Epidemiological Surveillance of Rabies in the Americas, SIRVERA (PAHO).

Fuego) was studied in mice by direct immunofluorescence and inoculation techniques, 8.62% of the animals were found to be positive for rabies (Durán and Favi, 1989). In Africa, the Indian subcontinent, and the Middle East, jackals are important hosts of the rabies virus, as are wolves in eastern Europe and throughout much of Asia. Rabies is found in wild carnivores elsewhere in the world as well. When the infection is enzootic, it usually goes unnoticed, but it becomes a problem when the wild cycle takes on epizootic proportions and affects man and domestic animals.

Jackals are the main reservoir of wild rabies in Africa, and the occasional epizootics coincide with canine rabies. Mongooses are vectors of rabies in India, Nigeria, South Africa, Sri Lanka, and Zimbabwe, where they contribute to the occurrence of human infections. In the nineteenth century, the small Indian mongoose (*Herpestes auropunctatus*) was introduced to several Caribbean islands for the purpose of containing the rat population, and today these animals serve as hosts for rabies in Cuba, the Dominican Republic, Grenada, and Puerto Rico, where they are responsible for infections in man and other mammals.

Rabies virus has been isolated from rats and other rodents in different parts of the world, but the potential for transmission to man is thought to be low. Also, there is some doubt about the accuracy of past diagnoses, because most of the cases were examined before modern techniques for this purpose were perfected (Beran, 1981). This subject needs to be explored more fully (Winkler, 1991). Between 1971 and 1984, rabies virus was isolated from 104 rodents and lagomorphs in the US (80% of these isolations performed between 1980 and 1984). The largest number (67) was isolated from marmosets (*Marmota monax*) in connection with a rabies epizootic in raccoons (*Procyon lotor*). Three isolations were obtained from domestic rats (*Rattus* spp.). A rabies virus of very low virulence has been isolated in the laboratory, from field mice in several European countries. Monoclonal antibody techniques demonstrated a close similarity between these isolations and the fixed viruses, so it has been assumed that laboratory contamination occurred at the time several blind passages were made in mice (Rupprecht *et al.*, 1991).

Rabies in bats is a problem unrelated to rabies infection cycles in other mammals. Moreover, the situation is different in vampire and nonhematophagous bats. Rabies in nonhematophagous bats occurs throughout the Americas and has been confirmed in numerous species, including insectivorous, frugivorous, and omnivorous bats. Since the first case was recognized in Florida, US, in 1953, there have been a number of human rabies cases transmitted by the bite of these bats, especially in that country. Rabies in bats has been diagnosed in all the states of the US except Hawaii. Rabies viruses have also been isolated from bats in several European countries, most notably from *Eptesicus serotinus*, as well as a few strains from *Myotis* spp. and *Pipistrellus* spp. In Denmark, 104 of 550 bats tested positive for rabies in a study conducted in 1986. In the Netherlands, 23 of 249 bats (*P. pipistrellus* and *E. serotinus*) were positive in a 1989 study, and 24 persons who had been in contact with them were given prophylactic treatment (Netherlands epidemiologic data, 1990). Bat rabies is extremely rare in Asia. In Africa, there have been no isolations of serotype 1 in bats, but rabies-related viruses have been identified. In South Africa, 530 bats representing 13 species were studied serologically using the enzyme-linked immunosorbent assay (ELISA); none of the serum samples showed antibodies for the rabies glycoprotein (G) and none of the brains revealed antigen against the nucleocapsid (Oelofsen and Smith, 1993). Of 8,645 rabid animals found in the US

in 1992, 647 were bats, most of them insectivorous (Krebs *et al.*, 1993). Human cases of rabies are seldom contracted from bats. As of 1993, there had been 17 human cases in the US and 3 in Canada. In British Columbia and the Atlantic region of Canada, bats are the only reservoir of rabies (Chomel, 1993). In Europe, only two human cases of bat-transmitted serotype 1 rabies have been recorded.

Rabies in hematophagous, or vampire, bats is a limited problem in Latin America and in Trinidad and Tobago. Infection has been confirmed in three hematophagous species, *Desmodus rotundus, Diphylla ecaudata*, and *Diaemus youngi*, but only the first of these species is of epidemiologic importance. The range of vampire bats (*D. rotundus*) extends from Mexico to central Argentina. *Desmodus* is responsible for appreciable losses in the Latin American livestock industry, especially on account of bovine rabies, which has prevented the development of new regions in the American tropics. Table 7 shows the number of cases of bovine rabies in Central and South America in 1990, 1991, and 1999. In some cases, the cattle may have been bitten by rabid dogs. It is difficult to calculate the true extent of losses caused by bovine rabies because in many countries the disease occurs in marginal livestock-raising areas where the shortage of veterinarians and lack of diagnostic laboratories hamper the confirmation and accurate reporting of outbreaks. With mortality estimated at nearly 50,000 head of cattle, indirect losses in terms of meat and milk, coupled with the devaluation of hides as a result of vampire bat bites, bring economic losses due to rabies to more than US$ 44 million a year. Chile and Uruguay are the only countries in South America that have not reported vampire bat-borne rabies, while all the Caribbean islands except Trinidad are free of rabies transmitted in this manner. Since 1929, when

TABLE 7. Number of cases of bovine rabies in Central and South America, 1990, 1991, and 1999.

Country	1990	1991	1999
Argentina	1	…	31
Belize	0	0	6
Bolivia	…	…	41
Brazil	1,871	1,781	2,628
Chile	0	0	0
Colombia	51	45	0
Costa Rica	7	3	2
Cuba	…	…	7
Dominican Republic	…	…	6
Ecuador	26	25	20
El Salvador	10	17	5
Guatemala	23	26	3
Honduras	11	4	6
Mexico	…	…	108
Nicaragua	2	1	3
Panama	15	4	96
Paraguay	48	62	95
Peru	32	20	49
Uruguay	0	0	0
Venezuela	128	198	30
Total	2,225	2,186	3,136

… Data not available.

Source: Pan American Health Organization. *Bull Epi Surv Rabies in the Americas* 31:30, 2000.

human rabies was first attributed to the bite of vampire bats, more than 180 such cases have been reported in Latin America. In 1953, an outbreak in Guyana near a forest stream sickened 9 of 43 diamond miners in the area (Nehaul, 1955), and during 4 months in 1990 there were 29 cases of rabies in two rural communities of the Peruvian Amazon region, which together had a total population of 636 (López *et al.*, 1992).

Urban rabies has been eradicated in Canada, Japan, many European countries, and the US, but wild rabies persists in a number of these places. In Latin America, Argentina, Chile, and Uruguay have been free of canine rabies for several decades, and other countries have had successful campaigns. In 2000, 20 of the 21 capital cities of Latin America were free of canine-borne human rabies, and for the first time the number of human cases in the Region of the Americas was under 100 (PAHO data, 2001). In the US, a total of 8,505 cases of canine rabies were diagnosed in 1945, but by 1992 the figure for all types of animal rabies was down to 182 (2.11% of all cases of animal rabies). The cases of rabies that are still occurring in dogs are due to transmission by wild animals rather than transmission from one dog to another. In Canada, where wild rabies persists but canine rabies is controlled, there have been only three human cases contracted from bats since 1971.

The Disease in Man: The incubation period ranges from 2 to 8 weeks, usually lasting between 20 and 90 days, but it can be as short as 10 days or as long as 8 months and occasionally even years (Bernard and Fishbein, 1990). In a study of 500 cases, between 4% and 10% had incubation periods of six months or longer. The duration can be affected by the dose of virus injected at the time of the bite, the site of the wound, and the severity of the laceration. The incubation period is longer when the bite is farther away from the central nervous system.

The disease begins with a feeling of anxiety, cephalalgia, slightly elevated body temperature, malaise, and indefinite sensory alterations, frequently around the site of the lesion, where the patient may also feel pain and irritation. The excitation phase that follows is characterized by hyperesthesia and extreme sensitivity to light and sound, dilation of the pupils, and increased salivation. As the disease progresses, spasms occur in the deglutitory muscles and liquids are violently rejected by muscular contractions. This swallowing dysfunction is seen in most patients, many of whom experience spasmodic laryngopharyngeal contractions at the mere sight of a liquid and even refuse to swallow their own saliva, a phenomenon known as hydrophobia. There may also be spasms of the respiratory muscles and generalized convulsions. The excitation phase may predominate until the patient dies, or it may be followed by generalized paralysis. In some cases, the excitation phase is very short, and in others the paralytic symptomatology predominates throughout the entire course of the disease. The patients remain conscious, and many are aware of their situation and the disease they are suffering from. The disease lasts from two to six days and sometimes longer, and it almost invariably ends in death. There are only three documented cases of patients who survived after developing clinical symptoms: one in Argentina and two in the US (Bernard and Fishbein, 1990). One of these patients was a technician who had been infected by a laboratory strain of the virus.

The postexposure treatment is effective and should be initiated as soon as possible after exposure to the infection (see Prevention of Human Rabies below).

Patients should be isolated and hospital personnel should be provided with adequate supplies and equipment for treating them.

The Disease in Animals: Two forms of the disease are distinguished in animals according to the predominant neurological symptoms: furious rabies and paralytic, or dumb, rabies.

DOGS: The incubation period lasts from 10 days to 2 months or longer. During the prodromal phase, dogs exhibit behavior changes: they hide in dark corners, act unusually agitated, and circle nervously. Reflex excitability is heightened and the animal is startled by the slightest stimulus. Other symptoms are anorexia, irritation around the area of the bite, stimulation of the genitourinary organs, and a slight rise in body temperature. After one to three days the symptoms of excitation and agitation intensify: the dog becomes dangerously aggressive and is apt to engage in biting behavior, attacking objects, animals, and humans, including its owner, and even itself, inflicting serious injury. Salivation is abundant because the animal's swallowing muscles are paralyzed and it cannot swallow its saliva; in addition, its bark turns into a hoarse, prolonged howl because of partial paralysis of the vocal cords. Rabid dogs have a propensity to leave their home and travel long distances, furiously attacking other dogs and animals. Generalized convulsions develop in the terminal phase of the disease, followed by muscular incoordination and paralysis of the trunk and extremities.

The dumb form of the disease in dogs is characterized by predominance of paralytic symptoms with only a brief excitation phase or none at all. Paralysis begins in the muscles of the head and neck; the animal has difficulty swallowing, and sometimes its owner becomes exposed to the infection by trying to help the dog, thinking it has swallowed a bone. Then comes paralysis of the extremities, generalized paralysis, and death. The course of disease can take from 1 to 11 days.

In western Africa a special form of rabies occurs in dogs, known as *oulou fato*. This form has the general characteristics of dumb rabies without the furious phase. Other characteristics are inclusion bodies that are unlike Negri bodies, a short incubation period, diarrhea, and progressive paralysis. *Oulou fato* is thought to be caused by an attenuated rabies virus (Beran, 1981).

CATS: The incubation period is similar to that in dogs, but in one case it was reported to be as long as two years. Most often the disease is the furious type, with symptoms similar to those seen in dogs. Paralysis develops in the posterior third of the body two to four days after the onset of excitation.

CATTLE: Vampire bat-transmitted rabies has a long incubation period, ranging from 25 to more than 150 days. The predominant symptoms correspond to the paralytic form of the disease, and it is therefore referred to as paretic or paralytic bovine rabies. Affected animals distance themselves from the rest of the herd. The symptoms may include dilated pupils and raised hair or somnolence and depression. Other observations may be abnormal movements of the posterior extremities, lacrimation, and nasal catarrh. Furious manifestations are rare, but there may be muscular tremors, restlessness, priapism, and hypersensitivity in the area of the vampire bat bite, causing the animals to scratch themselves to the point of causing ulceration. As the disease progresses, muscular incoordination is observed, along with tonic-clonic contractions in the muscles of the neck, trunk, and extremities. The animals have difficulty swallowing and cease to ruminate. Finally they fall, cannot rise again, and die. Prominent symptoms are emaciation, foamy yellowish spittle

covering the snout, and severe constipation. The paralytic signs usually develop two or three days after the onset of symptoms. The disease usually lasts from 2 to 5 days, and it can occasionally extend up to 8 or 10 days. Symptomatology alone is not sufficient to distinguish vampire bat-transmitted rabies from the disease transmitted by dogs, particularly if it occurs only sporadically. Epizootiologic data such as the presence of hematophagous bats, the discovery of bat bites, the occurrence of multiple cases, the preponderance of paralytic manifestations, and above all the absence of canine rabies in the region lead to the suspicion of vampire bat-transmitted rabies. With use of the monoclonal antibody technique it is now possible to identify antigenic differences that distinguish vampire bat-transmitted viruses from those transmitted by dogs.

OTHER DOMESTIC ANIMALS: The symptomatology of rabies in equines, sheep, and goats is similar to that in cattle. An excitation period of varying duration and intensity is followed by paralytic phenomena that cause difficulty in swallowing and later incoordination of the extremities. The animal's sense of taste is altered, and many of them eat indigestible objects. In all cases, there are changes in behavior. In swine, the disease begins with a very violent excitation phase, and the symptoms are usually the same as those in dogs. Rabies occurs infrequently in sheep, goats, and swine.

WILD ANIMALS: Rabies occurs naturally in many species of Canidae and other mammals. Experimental and epidemiological data indicate that foxes, coyotes, jackals, and wolves are the most susceptible animals. Skunks, raccoons, bats, and mongooses are susceptible to a lesser degree, and opossums are relatively resistant. Experiments have shown that the dose of virus necessary to infect skunks is 100 times greater than the amount needed to infect foxes. The incubation period varies, but it is rarely less than 10 days or longer than 6 months. The clinical symptoms in experimentally infected foxes, skunks, and raccoons are similar to those seen in dogs. Most wild animals manifest the furious type of rabies, but some have dumb rabies. The disease lasts two to four days in foxes and four to nine days in skunks. In both hematophagous and nonhematophagous bats, the furious type is most common, although sometimes dumb rabies is seen as well.

Pathogenesis: When the rabies virus is inoculated subcutaneously or intramuscularly, as happens in nature with a bite, it spreads along peripheral nerves from the site of inoculation to the central nervous system. In the laboratory, neurectomy of the regional nerves prior to inoculation with a fixed virus prevents the animal from developing the disease. Furthermore, experiments have revealed that the virus remains at the inoculation site for quite a while before it begins to spread. Thus, in most mice inoculated with the street virus in the plantar cushion it was possible to prevent the disease by amputating the inoculated paw up to 18 days after exposure. This finding suggested that during the period prior to neural invasion the virus had been reproducing in myocytes at the inoculation site. A similar result was confirmed in hamsters with advanced-stage infection and was assumed to be an amplification of what had been taking place from the outset. However, the conclusion cannot be made with certainty, nor is it known which part of the peripheral nerve is used by the virus to reach the central nervous system, since here again the virus could be identified in the axons during the advanced stage of the infection (Baer, 1991). The

lapse between inoculation of the virus and neural invasion is possibly the only time when prophylactic vaccinal postexposure "treatment" can be effective.

Once the infection is established in the central nervous system, the virus spreads centrifugally to the salivary glands and other organs and tissues via peripheral nerves just as it had earlier traveled centripetally.

Much higher viral titers have been found in the salivary glands than in the brain, and high titers have also been seen in the lungs. These observations would indicate that the agent can reproduce outside the central nervous system. The virus has been isolated or detected in a number of different organs and tissues, such as the suprarenal glands, brown fat (interscapular gland) of bats, kidneys, bladder, ovaries, testicles, sebaceous glands, germinal cells of hair follicles, cornea, tongue papillae, and intestinal wall. Although distribution of the virus is not uniform and the frequency of infection observed in different organs is variable, it is important to point out that whenever the virus is isolated from the salivary glands it will also be found in the central nervous system.

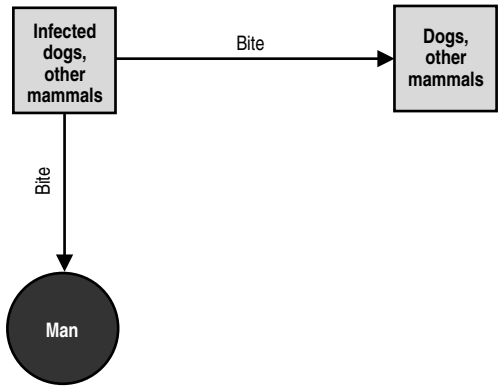
The finding of virus in saliva is of special epidemiologic interest because the bite is the principal means by which the infection is transmitted. In most cases, shedding of the virus in saliva starts with the onset of disease, but in many animal species the agent's appearance in saliva has been confirmed before the development of clinical symptoms. Thus, for example, in dogs it has been possible to detect the virus 1 to 3 days and even as long as 14 days before symptoms appeared. A study of dogs experimentally exposed to a street virus yielded the following results: 4 of 9 animals that contracted rabies after exposure to a virus of Ethiopian origin were found to shed the agent for up to 13 days prior to the appearance of clinical manifestations, while 8 of 16 dogs that became rabid after inoculation with a virus of Mexican origin shed the virus for up to 7 days prior to the appearance of symptoms. It was concluded that the time of appearance of virus in saliva depends not only on the dose but also on the strain of the virus. Given that the virus can be shed for longer than 10 days, and that this is the length of time recommended for observation of biting dogs, it is suggested that this period be extended (Fekadu *et al.*, 1982). In cats, the shedding of virus in saliva has been confirmed to occur between 1 and 3 days before the development of clinical manifestations; in cattle, between 1 and 2 days; in skunks, up to 14 days; and in clinically healthy Arctic foxes and vampire and nonhematophagous bats, for an undetermined period (Beran, 1981).

Although an early transient low-level viremia has been demonstrated on several occasions, hematogenous dissemination of the virus has not been proven, nor has it been possible to show that this type of dissemination plays any role in the pathogenesis of rabies.

Source of Infection and Mode of Transmission: The animal hosts that maintain rabies virus in nature are carnivores and bats. Herbivores and other nonbiting animals, rodents, and lagomorphs do not play any role in the epidemiology of the disease.

URBAN RABIES (Figure 25): The dog is the main vector of urban rabies. Approximately 90% of all human cases of rabies in the world are attributed to rabid dogs. The infection is transmitted from one dog to another and from dog to man and domestic animals via bites. Despite the fatal outcome of the disease, rabies is maintained in urban areas by the presence of a significant proportion of susceptible dogs. The high density of dogs and their high rate of annual reproduction are important

Figure 25. Urban rabies. Transmission cycle.



factors in the canine rabies epizootics in Latin America and other geographic areas. Another important factor in maintenance of the virus is the long incubation period of the disease in some dogs: on several occasions it has been demonstrated that the virus appears in saliva 2, 3, and even as long as 13 days before onset of the disease and that the agent may continue to be shed by this route until the animal dies. However, not all rabid dogs shed the virus through saliva, and hence some bites are not infectious. It is estimated that 60% to 75% of all rabid dogs shed the virus in saliva, and the viremia may range from scarcely a trace to very high titers. Obviously, the risk of the virus being transmitted to man by a bite or through an abrasion is greater when the viral dose being shed is higher. Likewise, the risk of contracting the infection increases when the bite is on the face, neck, or hands and the risk diminishes when it is on the trunk or lower extremities. Many minor bites or scratches fail to introduce enough virus to cause disease, especially if the wound is inflicted through clothing. On the other hand, experiments have shown that the virus can also gain entry through the conjunctiva and other mucosa. It is rare for the infection to be transmitted by means other than bites—i.e., through abrasions or scratches or the licking of open wounds or mucous membranes (Fishbein and Robinson, 1993). In the US, about 40% of the persons who undergo postexposure treatment attribute their exposure to mechanisms other than a bite (Helmick, 1983; Bernard and Fishbein, 1990). Prior to the establishment of postexposure prophylaxis schedules, it was estimated that only 20% of persons bitten by rabid dogs became infected.

According to current estimates, in Latin America and the Caribbean more than 370,000 persons are bitten by dogs every year and 260,000 undergo treatment. A study conducted in an industrial suburb of Buenos Aires, Argentina, found that 3,295 persons (854 per 100,000 population) had attended the rabies center for the treatment of dog bites. The group most at risk was children under 15 years of age, especially males. Because of their shorter stature, one-fourth of them had been bitten on the face or neck. Of those bitten, 43.8% had been attacked by loose dogs near their owners' homes; 47.9% of the wounds were puncture or punctiform, and a significant number of them required medical and/or surgical treatment. Most bites occur during the months when temperatures are highest (Szyfres *et al.*, 1982).

Cats are second to dogs in the number of confirmed rabies cases in urban areas, but they can serve as an important source of human infection and therefore their vaccination coverage should be increased (Diesch *et al.*, 1982). Cats may acquire rabies from infected dogs or wild animals with which they come in contact.

It is appropriate to discuss here "abortive" rabies in dogs and the carrier state. Some mice inoculated with rabies virus in the laboratory become ill and then recover. There is numerous evidence to suggest that rabies is not always fatal. Cases of abortive rabies, although few in number, have been described in several animal species, including man. In an enzootic area of Buenos Aires, Argentina, the cerebroneutralization test was used to examine the brains of 1,015 dogs and 114 cats that had responded negatively to attempts to isolate the virus and to the immunofluorescence test for the diagnosis of rabies. Of all the animals examined, the brain specimens of only two dogs and one cat showed significant titers in the cerebroneutralization test (in the absence of the virus), which is accepted as proof that the animals had recovered from the disease, since in vaccinated animals or those that have died of rabies this test is negative (Díaz *et al.*, 1975). To judge from this study, the incidence of "abortive" rabies is very low. In rabies enzootic areas, serum-neutralizing antibodies have been found not only in dogs but also in wild terrestrial animals and vampire bats. This finding can be interpreted to mean either that the animals were already infected but did not manifest any symptoms, or else that they had recovered from the disease. In an experimental study of 47 dogs inoculated with rabies virus, 39 died and 8 survived. The surviving animals were followed for two years and none of them had neutralizing antibodies in serum or cerebrospinal fluid. When these 8 dogs and 10 controls were then inoculated with a high dose of street virus, none of the 8 survivors died, but the 10 controls succumbed to rabies. The 8 dogs that resisted the challenge all had a high level of serum antibodies, which would indicate an anamnestic response (Fekadu and Shaddock, 1984).

A matter that has long been a subject of controversy is the possible existence of carriers—that is, clinically normal animals that shed the virus in their saliva. For a long time, there was no convincing proof that a rabies carrier state existed. In Ethiopia and India, however, the virus has been isolated over very prolonged periods from the saliva of several asymptomatic dogs. Of 1,083 apparently healthy dogs examined in Ethiopia, 5 were intermittent shedders of the virus in saliva. The carrier state was confirmed later in Ethiopia in a bitch that was infected experimentally by intramuscular inoculation with virus isolated from the saliva of a dog that appeared to be healthy, developed rabies, and then recuperated. The virus was isolated from her saliva at days 42, 169, and 305 post-recovery, and 16 months after her recuperation she died giving birth to 2 stillborn pups. The presence of viable rabies virus was confirmed in her tonsils but not in the brain or other organs (Fekadu *et al.*, 1981; Fekadu *et al.*, 1983). It has been proposed that the carrier state may serve to maintain the rabies virus when there is optimum density of susceptible animals. It is also important to consider the bite of an unprovoked dog as a possible source of infection in a rabies enzootic area (Fekadu, 1991).

Interhuman transmission of rabies is rare. Under this heading are two known cases of rabies transmitted by corneal transplant, one in the US and the other in France. In neither case had rabies been suspected in the donor. The presence of rabies virus in the cornea of animals and man has been confirmed by the impression technique and by direct immunofluorescence (see the discussion below of airborne transmission).

RABIES IN WILDLIFE: In nature, rabies in wildlife is perpetuated in much the same way as with urban rabies: one or two mammalian species in a given ecosystem, typically carnivores and bats, are responsible for maintaining the virus. Around the world there are various wild species that maintain its cycle in their respective ecosystems (see Occurrence). In the US, different animal species maintain more or less independent epizootics in different areas. In the eastern part of the country, from New England to the southern Atlantic seaboard states, foxes (*Vulpes fulva* and *Urocyon cinereoargenteus*) are the main rabies hosts and vectors. Rabies in skunks (*Mephitis mephitis*) has been endemic in the southeastern states since the 1950s, but when these animals were introduced in the mid-Atlantic states for the benefit of recreational hunting, a major epidemic was started that spread to the states of North Carolina, Virginia, Connecticut, and New York. In 1992, there were more cases of rabies in skunks than any other animal species, representing nearly 50% of all animal cases of the disease (Krebs *et al.*, 1993; Chomel, 1993). Raccoons (*Procyon lotor*) are responsible for enzootics in the states of Florida and Georgia. The rabies virus has also been isolated on occasion from apparently healthy Arctic foxes (*Alopex lagopus*), but it is not known whether some or all of these foxes had already contracted the infection and were in the incubation phase (Beran, 1981). Epizootics and enzootics among these animals depend mainly on population dynamics. When the population density is high, rabies takes on epizootic proportions and a large number of animals die. In foxes, for example, it is estimated that up to 60% of the population may die during an epizootic. When the density is low, rabies may occur enzootically or disappear entirely with time. New epizootic outbreaks occur when there is a susceptible new generation. The annual renewal rate for fox populations is very high, reaching levels of up to 70% of the total population. However, the exact population density required to create epizootic conditions for an animal species is unknown. The variable incubation period, which in some animals can be very long, facilitates continuous propagation of the virus.

Rabies virus antibodies have been found in several wild species, such as foxes, raccoons, mongooses, and both insectivorous and hematophagous bats, which suggests that rabies infection does not always lead to disease and death. In less susceptible animals, such as raccoons, the reactor rate may be high in the postepizootic period. Low virus titers have been found in the salivary glands of rabid mongooses, suggesting that they could transmit sublethal doses by bite. Even in highly susceptible species such as foxes, some specimens are found to have a very low virus titer in the salivary glands. In a four-year study conducted in Grenada, 498 of 1,675 mongooses (30%) were found to have neutralizing antibodies against rabies virus (Everad *et al.*, 1981). It is believed that naturally acquired immunity in a population of wild animals is an important factor in determining whether an epizootic outbreak will occur in a given species and area. In other words, a high proportion of animals with antibodies may permit sporadic transmission of the virus but would make it difficult for transmission to reach epizootic proportions (Bigler *et al.*, 1983). Nevertheless, good vaccination coverage is necessary to obtain a degree of immunity sufficient to reduce the incidence of infection or eradicate it completely.

Both in Canada and the US, as well as in many European countries that are free of canine rabies, wild animals are primarily responsible for maintenance of the rabies virus.

The epizootiology of rabies in bats follows the same lines as in other mammals.

It has not been proven that there is a carrier state in bats, as was once believed; bats die when they contract rabies, and the virus has never been isolated from the salivary glands without virus also being found in the brain. It has been confirmed that some bats shed the virus in saliva for 10 days or more before they died. This phenomenon has also been seen in other animal species; for example, the agent has been isolated from the saliva of skunks for at least 18 days, and from that of foxes for 17 days. Thus, it may be assumed that some bats recover from the disease and, as in the case of other wild mammals, neutralizing antibodies are found in vampire bats in areas where there have been outbreaks of bovine rabies. In such an area in Argentina, antibodies were found in the serum of 24 of 99 vampire bats examined even though presence of the virus could not be confirmed in the brain or other tissues, nor were there neutralizing antibodies in the central nervous system, which would indicate that the animals had not been sick with rabies (Lord *et al.*, 1975). It has been suggested that the serum antibodies may have been due to repeated sublethal infections, but experimental evidence is lacking.

Wild rabies is an ongoing danger for man and domestic animals. When wild animals are rabid, they approach towns and may attack humans and domestic animals. It should also be kept in mind that a larger proportion of wild carnivores shed the virus in saliva than do dogs. The main victims are usually cattle, both in Europe and in Canada and the US. In areas where canine rabies has been eradicated, the disease may be reintroduced by wild carnivores if the canine population is not adequately immunized.

The transmission of both wild and urban rabies occurs mainly when an animal that is shedding virus in its saliva bites another susceptible animal or a human. There are cases on record of human rabies acquired by airborne transmission. Two cases occurred in scientists who stayed for a few hours without being bitten in a cave in Texas (Frio Cave), US, inhabited in summertime by millions of Mexican free-tailed bats (*Tadarida brasiliensis*) (Constantine, 1971). In the same cave, airborne transmission of the disease was also demonstrated in coyotes and foxes kept in bat- and arthropod-proof cages. It is believed that aerosols were produced by the saliva and urine of the insectivorous bats. The virus was also collected from the cave air with special devices and inoculated into foxes, which became sick and died of rabies. Another case occurred in a laboratory: the victim was a microbiologist who was preparing a concentrated vaccine. An epizootic outbreak was reported at an experimental station in Las Cruces, New Mexico, US, where different species of wild animals, including foxes, coyotes, and opossums, were kept in individual cages without any possibility of direct contact or transmission by biting (Winkler *et al.*, 1972). Transmission was attributed to airborne dissemination of the virus, which was probably of bat origin and would have been specially suitable for transmission via aerosols. Laboratory animals have been infected experimentally through the digestive tract, and infection through cannibalism has been confirmed in dams of suckling mice inoculated with rabies virus. This mode of transmission is believed to play a role in the propagation of rabies among wild animals. There is no record of human cases of rabies acquired by ingestion, even when the virus has been detected in the milk of rabid cows.

Diagnosis: The preferred test is direct immunofluorescence, which is rapid, highly sensitive, and specific. The efficacy of the test depends on the competence of the tech-

nician and the quality of the reagents, especially the conjugate. The WHO Expert Committee on Rabies recommends that when this test is introduced in the laboratory it should be coupled with diagnosis by inoculation in suckling mice for at least a year (WHO, 1984); if the immunofluorescence test is negative, brain tissue from the suspect animal should be inoculated in mice to confirm the negative result. The immunofluorescence technique has the advantage over other tests that it can be performed when the patient or rabid animal is still alive by using corneal impression smears, scrapings from the lingual mucosae, bulbar tissue of the hair follicles, and frozen sections of skin. However, the sensitivity of the test under these conditions is limited: although a positive result constitutes a confirmed diagnosis, a negative result does not exclude the possibility of infection. Use of these tests on biting animals is very helpful in deciding whether to institute early prophylactic treatment of exposed individuals.

More recently an ELISA technique has been developed, called rapid rabies enzyme immunodiagnosis (RREID), that entails the detection of rabies virus nucleocapsid antigen in brain tissue. This test can be conducted under field conditions with a special kit, since the antigen can be seen with the naked eye. The technique is especially useful for epidemiologic studies, always bearing in mind that RREID can give a negative result when the immunofluorescence test is positive (WHO, 1992).

Intracerebral inoculation of mice to isolate the virus is one of the most widely used methods for diagnosing rabies in many countries. Suckling mice up to 3 days old should be used for this procedure, since they are more sensitive than older animals. For the most reliable result, this test should be combined with immunofluorescence. To obtain a rapid diagnosis, which is important in making a decision about prophylactic treatment for an exposed individual, a larger group of mice can be inoculated with material from the biting animal; then, starting on day 4 postinoculation, one or more animals is sacrificed daily and the brain tissue is then examined by the immunofluorescence test.

In developing countries, microscopic examination for Negri bodies, a simple, rapid, and economical procedure, also continues to be a useful diagnostic tool. Although it is a less sensitive method, experienced personnel can obtain a correct diagnosis in 80% to 90% of the cases, especially in dogs that have died of furious rabies. Detection of Negri bodies with Seller's, May-Grünwald, Mann's, or other staining techniques confirms a diagnosis of rabies, but the absence of Negri bodies does not rule out the possibility of infection.

Examinations should not be limited to nerve tissue; an attempt should also be made to identify the virus in the salivary glands, especially the submaxillary glands.

It is very important that samples arrive at the laboratory properly preserved. A study of gradually deteriorating tissue showed that the first test to give negative results was examination for Negri bodies, followed by inoculation in mice and, finally, the immunofluorescence test.

Serologic tests are typically used to determine the immunogenic capacity of vaccines and the immune response of persons subjected to pre- or postexposure treatment. In addition to the plaque reduction neutralization test in mice and the fluorescent focus inhibition test, other rapid procedures that have been perfected include modified counterimmunoelectrophoresis (Díaz, 1983), immunoadherence hemagglutination (Budzko *et al.*, 1983), and the ELISA technique (Nicholson and Prestage, 1982). All tests that measure neutralizing antibodies are useful in determining the degree of host resistance to the infection.

For the isolation of rabies virus it is recommended that use be made of murine neuroblastoma cells (Na CI300), which are more susceptible than any other cell line. Isolation in these cultures is at least as efficient as inoculation in mice, and the result is available in 2 days, compared with 10 to 15 days with inoculation in mice. Once isolated, the virus can be typed with monoclonal antibodies. Fortunately, equipment for working with cell cultures is gradually becoming available to laboratories in the developing world (WHO, 1992).

Control: The following aspects should be considered: 1) control and eradication of urban rabies; 2) control of rabies in wildlife; 3) measures governing the international transport of animals; and 4) prevention of human rabies through both pre- and postexposure vaccination.

1. Control and Eradication of Urban Rabies: The most rational approach to preventing human rabies is to control and eradicate the infection in domestic animals, especially dogs. One of the greatest challenges is the unchecked growth of metropolitan areas with the steady influx of people migrating from rural areas to the urban outskirts in search of work. These migrants come with their animals, including dogs and cats. A large percentage of the people in these periurban settlements live below the poverty line and have many unmet needs; few of them can afford to vaccinate and care for their animals. As a result, dogs and cats often wander in the streets, rummaging in household waste for food. The canine population in Latin America and the Caribbean is estimated at 40 million, for a ratio of 1 dog to every 8 to 13 persons (Escobar Cifuentes, 1988). A similar situation exists in some of the Asian countries. Chomel (1993) considers that the endemicity of rabies is attributable not only to large numbers of dogs but also to factors such as the particular ecology of an area, the implications of cultural characteristics, and regulations governing the ownership of dogs.

The procedures used in programs for the control and eradication of urban rabies are aimed at rapidly reducing the population of susceptible animals by immunizing domestic dogs and cats, reducing this population through sterilization, and eliminating street dogs. There is some doubt, however, that the indiscriminate culling of street dogs regardless of whether they are strays or have owners will be sufficient to check the growth of this undesirable population. In Guayaquil, Ecuador, a series of three campaigns to eliminate street dogs proved to be not only ineffective but counterproductive; the number of dogs with rabies actually increased (Beran, 1991). Similar outcomes have been seen in urban areas of Asia (Meslin, 1989). A program cannot be based on culling alone. In nonendemic and rabies-free areas, as long as there are foci of disease elsewhere in the country, it is important to keep dogs immunized and to curtail growth of the canine population by sterilizing both males and females, or, if that is not possible, to capture street dogs, vaccinate them, and release them. The latter strategy will be more feasible when vaccines can be delivered orally in bait, pieces of which can be scattered around in places frequented by the dogs. In epizootic areas, the best approach is to capture street dogs and destroy them if they are not claimed by their owners within a specified number of days. In the event of an urban epizootic, mass vaccination should be undertaken as soon as possible with a view to immunizing at least 80% of the entire canine population in the city and adjacent areas. Once the epizootic has been interrupted, vaccination efforts should continue to target both older generation animals not previously vaccinated and those

entering the canine population either through birth or introduction from other areas. Vaccination campaigns can be conducted using house-to-house visits, established health posts, or mobile clinics that go to places where there are concentrations of dogs in different neighborhoods. When resources permit, house-to-house coverage is preferable.

For the immunization of dogs, a large number of safe and highly effective vaccines are available, based on both inactivated and modified live virus (MLV). The inactivated vaccines include those prepared with fixed virus in nerve tissue and those developed in cell cultures. Among the MLV vaccines are those prepared in chicken embryo after only a few passages ("low egg passage," LEP) or after many passages ("high egg passage," HEP) and a vaccine prepared in swine kidney cells (ERA strain). Because a few rabies cases have been associated with the MLV vaccines in dogs and cats, inactivated virus vaccines afford the best guarantee of safety.

The most widely used vaccine in Latin America is the inactivated suckling mouse brain (SMB) vaccine (Fuenzalida-Palacios), followed by several tissue culture vaccines (CEPANZO data, 1980). Comparative studies of different types of animal vaccines have shown that the MLV cell culture vaccine and the Flury LEP chicken embryo vaccine confer immunity for three years after a single injection and that the inactivated SMB vaccine protects all immunized dogs for one year and 80% of them for three years (Sikes, 1975). Thus, the two types of vaccine most widely used in Latin America are of proven efficacy. However, it is still recommended that each lot of any type of vaccine be tested for potency and safety. A vaccine produced in BHK cells and inactivated with ethylenamine (PV-BHK-EL), developed by the PAHO/WHO Pan American Zoonosis Center, protected all dogs challenged with street virus 12 and 25 months after they were vaccinated and 89% of these animals 3 years postvaccination (Larghi *et al.*, 1979). The WHO Committee of Experts on Rabies (1992) recommends that nerve tissue vaccines be replaced by those prepared in cell cultures.

The Committee also recommends that annual mass vaccination campaigns provide primary immunization for all dogs between 3 months and 1 year of age. Revaccination would depend on the duration of immunity conferred by the type of vaccine used. Pups under 3 months old may be given an inactivated vaccine, but they should be revaccinated as soon as possible after they reach that age. Vaccination coverage in Latin America reaches about 70% of the canine population each year; it is generally 100% in rabies-affected areas and not as high in areas unaffected by the disease (PAHO data, 2000). It is hoped that in the near future oral vaccines will be available, which can be used to protect street dogs, thus eliminating that source of infection for man and domestic dogs and cats.

Cats may be vaccinated with an inactivated or an MLV vaccine, except the Flury LEP vaccine, which can be pathogenic for these animals. The recommended vaccination age is the same as for dogs, and revaccination should be done annually until more information is available on the duration of immunity in cats.

Dogs and cats bitten by a rabid animal should be destroyed. An exception may be made when it is certain that the bitten animal was vaccinated with an active vaccine and that it is still within the period of immunity conferred by that vaccine. If the bitten animal is not destroyed, it should be kept confined and under observation for at least three months. Some research has indicated that prompt treatment of dogs exposed to rabies with rabies vaccine in combination with monoclonal antibody can provide protection against developing the disease (Hanlon, 2002b).

2. Control of Rabies in Wildlife: The following should be considered: a) bat-borne rabies, and b) rabies transmitted by terrestrial carnivores.

a) Control of rabies transmitted by hematophagous bats is of special interest for Latin America. The two main approaches to control are vaccination of cattle in exposed areas and reduction of the vampire bat population. Excellent vaccines are currently available, most notably the ERA vaccine, which provides adequate protection for more than three years. Other useful vaccines are the Flury HEP chicken embryo vaccine and the SMB and PV-BHK-EL with an aluminum hydroxide adjuvant.

The epizootiology of bovine rabies is still not well understood, but observations from several countries indicate that the infection is focal in nature. Thus it would be possible to protect cattle against vampire bat-borne rabies by means of focal and perifocal vaccination efforts without having to resort to costly mass campaigns. However, further epizootiologic studies and an adequate surveillance system are still needed.

Another method that has been used to control bat-borne rabies involves the use of anticoagulants such as diphenadione to reduce the vampire bat population in areas affected by bovine rabies. The procedure consists of capturing the vampire bats with nylon nets ("mist nets") set up around corrals or pastures, smearing diphenadione on their backs, and releasing them. When the treated bats return to their roosts, the other members of the colony lick off the preparation in the course of mutual grooming and then die as a result of internal hemorrhages caused by the ingestion of diphenadione. Trials have shown that this procedure is effective in achieving a significant reduction in the number of vampire bats in colonies and in preventing bovine and human rabies caused by these animals. However, there was concern that the bodies of the dead vampire bats might pose a threat for animals of other species. To address this question, the anticoagulant residue on the dead vampire bats was examined by gas chromatography, and only 1.17% of the diphenadione that had been used to treat them was found. Although this study showed that the risk for other species was low, the authors (Burns and Bullard, 1980) recommend caution in the use of anticoagulants because the susceptibility of different species to the compound is unknown. Another substance that is less expensive and just as effective as diphenadione is warfarin suspended in Vaseline. This combination proved to be selective for vampire bats without affecting other species. Warfarin can also be used on the surface of their roosts.

To prevent human cases caused by nonhematophagous bats, the public, especially children, should be instructed to refrain from touching bats that are on the ground or attempting to capture those seen flying during the day. Also, bats should be kept out of buildings by sealing entrances and exits. At the same time, it should be kept in mind that insectivorous bats are beneficial to agriculture and should not be destroyed indiscriminately. The important thing is to protect their victims: dogs, cats, and other domestic animals.

b) The approach to controlling wild rabies in terrestrial carnivores has shifted radically in recent years, from reducing the populations to creating immune populations through vaccination. Several investigators had voiced objection to the culling of populations, claiming that it entails the indiscriminate destruction of both immune and susceptible animals, and that as an area repopulates there is potential for increased numbers of the latter. This argument is valid, particularly in the case of

animal species that are relatively resistant to rabies virus such as raccoons and mongooses (Everard *et al.*, 1972; Everard *et al.*, 1981; Carey *et al.*, 1978). Experiments have shown that foxes can be immunized orally via bait impregnated with a modified live virus vaccine, especially ERA or WIRAB (derived from the former and cultured in BHK). Currently, use is being made of vaccines derived from the Street Alabama Duffering (SAD) strain, such as ERA, SAD-Bern, SAD-B19, and Vnukovo-32. It has been demonstrated in North America and Europe that these vaccines, even though they are pathogenic for adult mice and other species of rodents when applied intracerebrally, intramuscularly, or orally, are innocuous when given orally to wild carnivores. Moreover, the SAG vaccine, a mutant of SAD, is not pathogenic for rodents either in the laboratory or in the wild.

In Switzerland the SAD-Bern vaccine has been used extensively in bait (chicken heads) to vaccinate foxes. After the distribution of 1.3 million pieces of bait, only three cases of vaccine-induced rabies were detected. The SAD-B19 vaccine was distributed in 20 million pieces of bait in Belgium, France, Germany, Italy, and Luxembourg without any reports of deaths in foxes or animals of other species that share the same range. In France and Switzerland, a total of 250,000 pieces of bait containing the SAG vaccine were distributed between 1989 and 1991 without any record of deaths due to the vaccine (WHO, 1992). A study in North America showed that orally administered attenuated SAG-2 vaccine was effective in protecting skunks and raccoons (Hanlon *et al.*, 2002a). A recombinant vaccine (RVG) has been developed that expresses the rabies virus glycoprotein gene, the vector of which is the vaccinia virus. Removal of the thymidine kinase gene greatly diminishes the pathogenicity of the vaccines for mice when administered intracerebrally or intraperitoneally. Oral vaccination of a dozen animal species failed to reveal any residual pathogenicity or dissemination of the recombinant virus outside the area in which it was administered. In Belgium and France, a million pieces of vaccine-impregnated bait were distributed between 1988 and 1990 with no adverse effects observed (WHO, 1992). A recombinant vaccinia-rabies virus was found to be effective in bats (Aguilar-Setien *et al.*, 2002).

In Austria, canine rabies was eliminated in 1950 and wild rabies in 1955, but the latter reappeared in 1966. A campaign to reduce the population of foxes was unsuccessful. In 1986, the immunization of foxes was initiated in one of the provinces, and by 1991 a total of 1,200,000 vaccine-impregnated pieces of bait had been distributed in all the provinces. These vaccination campaigns were repeated in 1992 and 1993. As of the following year, rabies was concentrated in three provinces and the disease had appeared in the province of Salzburg, an area not included in the campaigns (WHO, 1994). Switzerland became free of rabies in foxes following oral vaccination with pieces of bait that were distributed mostly by hand. As a result of the success of this campaign, several cantons no longer require vaccination of dogs and cattle. Italy was also declared free of wild rabies, but some areas have been reinfected along the border with the former Yugoslavia. In Belgium, incidence of the disease was greatly reduced by use of SAD-B19 vaccine-impregnated bait distributed by hand and recombinant RVG vaccine distributed by air. Other European countries have also succeeded in freeing some of their areas of rabies.

3. Measures Governing the International Transport of Animals: Countries that are free of rabies should prohibit the importation of dogs and cats from infected

areas, as is done in Australia, or establish a prolonged quarantine of six months while simultaneously immunizing the animals introduced into the country with an inactivated vaccine. In countries where rabies exists and a prolonged quarantine is not possible, only dogs and cats with a valid official vaccination certificate should be permitted entry, and they should be confined to the owner's home under veterinary supervision for a reduced period of quarantine.

The same measures should be taken with wild animals. As far as possible, the introduction of animals from enzootic areas should be prohibited. Use of inactivated vaccines is recommended because the MLV vaccine could be pathogenic for some wild species.

4. Prevention of Human Rabies (Table 8): a) Pre-exposure prophylaxis should be limited to high-risk groups such as workers in laboratories, antirabies services, and animal rabies control programs; veterinarians; quarantine personnel; mail carriers in endemic areas; and naturalists. Mass vaccination is not recommended, even in epizootic areas, because no vaccine is completely safe. In Latin America, the SMB vaccine is used for pre-exposure immunization. This vaccine for human use, which is prepared with day-old mice and purified by centrifugation at 1,700 ×g for 10 minutes, is highly immunogenic and virtually free of the encephalitogenic factor. It yields high neutralizing titers when administered in three doses. A blood sample should be taken 10 to 12 days after the third dose to demonstrate seroconversion. If the titer is lower than 0.5 IU/ml, a booster dose should be given, followed again by serologic control. All personnel engaged in diagnosis, research, and live vaccine production should be examined serologically every six months. If serologic testing is not available, then an annual booster dose is recommended. If vaccinated individuals who have a satisfactory antibody response are exposed to the infection, they should receive one or more booster doses. In developed countries, the human diploid cell vaccine (HDCV), which is highly immunogenic, is used for pre-exposure prophylaxis, but its cost is prohibitive for developing countries. In adults, the vaccine is administered intramuscularly in the deltoid region; it should not be given in the buttocks because the resulting antibody titer is lower. In children, it can be given in the anterolateral area of the thigh. Vaccines obtained from tissue culture or purified duck embryo may be injected intradermally (WHO, 1992). Serologic conversion occurs in more than 99% of those treated and lasts two years in 100% of persons vaccinated when three doses are administered on days 0, 7, and 28. Intradermal inoculation is less costly and as effective as intramuscular administration when performed by specialized personnel. Undesirable side effects—muscular pain, cephalalgia, and pain at the site of injection—are observed in fewer than 1% of those immunized (Turner *et al.*, 1982; Dreesen *et al.*, 1982).

According to data from the US, over a period of 46 months there were 108 cases of generalized allergic reactions (11 of every 10,000 persons immunized with the HDCV vaccine). The effects ranged from urticaria to anaphylaxis; a few of the affected individuals had to be hospitalized, but none of them died as a result of these reactions. The 108 cases were classified as follows: 9 were immediate hypersensitivity, presumably type I; 87 were late onset (2 to 21 days after one or more doses were administered), presumably type III (deposit of the antigen-antibody complex in tissues, activation of the complement, and inflammation); and 12 were cases of undetermined type (CDC, 1984).

TABLE 8. General and specific treatment of rabies.

	Status of biting animal irrespective of previous vaccination		
Nature of exposure	**At time of exposure**	**During 10-day observation period[a]**	**Treatment recommended**
Contact but no lesion; indirect contact; no contact	Rabid	Healthy	None
Skin licked, scratches or abrasions, minor bites (covered areas of arms, trunk, and legs)	a) Supected as rabid[b]	Healthy	Initiate vaccination; stop treatment if animal remains healthy for five days[a,c]
	b) Wild animal[d] or animal that cannot be placed under observation	Rabid	Initiate vaccination; if diagnosis is positive, administer serum and complete vaccination schedule
Mucosae licked, serious bite (multiple bites or bites on face, head, finger, and neck)	Rabid domestic or wild[b] animal; animal suspected as rabid[d] or animal that cannot be placed under observation		Administer serum and vaccine; stop treatment if anmal remains healthy for five days[a,c]

[a]Observation period applies only to dogs and cats.
[b]In endemic areas, all unprovoked bites should be considered suspect unless proven negative by laboratory examination (brain fluorescent antibody test).
[c]Or if its brain is found negative upon fluorescent antibody examination.
[d]Exposure to rodents and rabbits seldom if ever requires specific antirabies treatment.

b) The prevention of rabies after exposure consists basically of local treatment of the wound and passive and active immunization of the individual.

Local treatment of the wound is extremely important. Proper treatment alone can prevent many cases of rabies by eliminating or inactivating the inoculated virus. The wound should be washed as soon as possible under a strong jet of water and cleaned with soap or detergent and water, followed by application of 40% to 70% alcohol, tincture of iodine, iodized alcohol, or a 0.1% compound of quaternary ammonium. The wound should not be sutured immediately. Tests in laboratory animals have shown that infiltration of the wound with antirabies serum is a very effective means of preventing infection, and therefore infusion of serum in and around the wound is recommended. If any serum is left over, it should be injected intramuscularly in the buttocks.

The long incubation period typical of most cases of human rabies makes it possible to undertake postexposure prophylactic immunization. Vaccination must be initiated as soon as possible to ensure that the patient will be immunized before the rabies virus reaches the central nervous system. An estimated 500,000 to 1,500,000 persons worldwide, possibly even more, undergo antirabies treatment each year.

Abbreviated vaccination schedules are now in use. The choice of schedule depends on the country's economic development situation as well as on the vaccine used. There is no question that cell culture vaccines derived from human diploid or Vero cells are much safer and produce higher neutralizing antibody titers. However, they are prohibitively expensive for developing countries, where they are needed the most (Sureau, 1988; Larghi, 1991; Fishbein and Robinson, 1993). According to data obtained by the World Health Organization, in 1992 a total of 784,026 persons from four continents—Africa, Asia, and the Americas (excluding Canada and the US)—received antirabies treatment. If the countries of Central and Eastern Europe are added to this number, it can easily be said that a million persons undergo treatment each year. Estimates of the cost of treatment with the human diploid cell vaccine range from US$ 240 to US$ 1,000 per person. Thus, poorer countries are obliged to resort to other vaccines. Even so, insofar as possible, efforts should be made to switch to the production of cell culture rabies vaccines to avoid the presence of encephalitogenic substances.

The SMB vaccine continues to be used in Latin America. The abbreviated schedule currently in use consists of seven doses (one dose every 24 hours on days 0 through 6) and three booster doses on days 10, 20, and 60. When serum is used in the event of severe exposure, the classic schedule should be applied: 14 doses 24 hours apart and two booster doses on days 10 and 20 after completion of the 14-day series (Guarnera *et al.*, 1994).

A duck embryo vaccine inactivated with beta-propiolactone is used in other countries. The purified vaccine affords the same immunogenicity and safety as cell culture vaccines (WHO, 1992).

The conventional vaccination schedule for human diploid cell culture vaccines and the purified duck embryo vaccine is intramuscular administration on days 0, 3, 7, 14, and 30. The abbreviated schedule calls for two doses on day 0 (one injected in the right deltoid region and the other in the left deltoid region), followed by one dose each on days 7 and 21. This schedule, known as 2-1-1, is especially useful when the treatment does not entail the administration of serum.

The vaccine used in the People's Republic of China is derived from primary hamster kidney cell cultures, either with an adjuvant or concentrated and lyophilized. The adjuvant vaccine has been used in postexposure treatments, confirming its protective efficacy and its safety (Lin, 1990). In some countries, vaccines derived from adult animal brain are still in use.

The combined administration of serum and vaccine is the most effective method of antirabies prophylaxis. It may be used in all cases, but it is especially indicated when severe exposure is involved. The serum may be heterologous, obtained by hyperimmunization of equines, or homologous antirabies human immunoglobulin. It is administered just once, intramuscularly, at a dose of 40 IU per kg of bodyweight in the case of heterologous serum or, with homologous serum, 20 IU per kg of bodyweight. At the same time, the first dose of vaccine is administered at another body site, and treatment is continued until completion of the vaccination schedule, followed by booster doses on days 10, 20, and 90 after completion of the initial series. The serum should be administered as soon as possible, regardless of how much time has elapsed since exposure, in an effort to neutralize the virus inoculated with the animal bite.

Only inactivated vaccines are indicated for human prophylaxis. The WHO Expert Committee on Rabies recommends that the use of vaccines containing residual live

virus, such as the Fermi type (cultured in nerve tissue and inactivated with phenol at 22ºC), be suspended.

When prophylactic treatment is being prescribed for humans, it should be kept in mind that both the serum and the vaccine can cause complications. Since the heterologous serum can cause an anaphylactic reaction even when it is highly purified, an intradermal or ophthalmic sensitivity test should be done before it is administered. It is estimated that 15% to 25% of those treated with equine serum suffer from anaphylactic reactions along with characteristic "serum sickness." Such accidents are now less frequent with the highly purified sera. Complications with homologous serum are rare, but unfortunately this serum is costly to produce and is not readily available.

None of the vaccines is completely innocuous. The incidence of neuroparalytic complications with nerve tissue vaccines differs from one country to another, ranging from 1.2 to 34 per 10,000 persons vaccinated. The number of postvaccinal accidents in Latin America has dropped significantly as the use of SMB vaccine has become more widespread. Between 1970 and 1980, there were 141 cases of neurologic complications, or an average of 13 accidents a year, out of some 3 million postexposure treatments administered over the 11 years (Acha, 1981). This number has no doubt dropped considerably with the introduction of more modern production standards, but no up-to-date statistics are available. Although the HDCV vaccine is considered the safest, a case of Guillain-Barré syndrome was reported in Norway (Boe and Nyland, 1980) and there was a case of transitory neuroparalytic disease in the US (Bernard *et al.*, 1982). Both cases were temporally associated with postexposure treatment.

For the reasons discussed, every effort should be made to avoid unnecessary treatment. Although in enzootic or epizootic areas the treatment of a person who has been bitten should be started immediately, it is necessary to capture the biting cat or dog and place it under observation for a period of 10 days; if the animal turns out to be healthy, the administration of subsequent doses should be suspended. If the bite was caused by a wild animal, this animal should be euthanized immediately and its brain tissue tested by immunofluorescence. Technological advances in genetic engineering suggest the possibility of developing a vaccine that contains only those rabies virion subunits that induce immunity. Also, it has been possible to biosynthesize the virus glycoprotein (GP) by transferring rabies virus genes to *Escherichia coli* (Yelverton *et al.*, 1983). If a vaccine could be developed on the basis of this fraction, it probably would not have side effects and would be less costly, allowing its use on man and animals. Also, biotechnology has now made it possible to cultivate continuous cell lines in a microcarrier fermenter, which will yield large, low-cost harvests of virus.

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RIFT VALLEY FEVER

ICD-10 A92.4

Synonym: Enzootic hepatitis.

Etiology: Rift Valley fever (RVF) virus, a three-segment RNA genome virus belonging to the genus *Phlebovirus*, family Bunyaviridae, forms part of the complex of mosquito-borne viruses. The virions of the Bunyaviridae family are spherical, measuring 90 to 100 nm in diameter, and have a bilayered lipid envelope with three circular nucleocapsids, each with helical symmetry.

Geographic Distribution: The disease occurs throughout a large part of Africa, including Madagascar, as well as in Saudi Arabia and Yemen.

Occurrence: Since 1931, when the virus was isolated from a sheep on a ranch in Rift Valley, Kenya, several epizootics of the disease have occurred at irregular intervals. The most serious was an episode in South Africa during the summer of 1950–1951, which killed approximately 100,000 sheep and cattle and caused some 20,000 cases of human disease. In the same region of the South African high plateau, limited outbreaks occurred in the animal and human populations in 1953, 1956, and 1969. In 1974–1976, another extensive epizootic affected domestic animals and caused numerous human cases with at least four deaths. This characteristic of enzootic periods followed by epizootics at variable intervals has been observed in other countries as well. Extensive epizootics in domestic ruminants accompanied by human cases have been reported in eight countries in southern and eastern Africa (Shimshony and Barzilai, 1983).

Up until 1977, the disease had been confined to countries south of the Sahara Desert. That year it erupted in an alarming manner in Egypt, causing between 20,000 and 200,000 human cases and some 600 deaths. The following year there were at least 400 additional cases. The fatality rate in the civilian population was estimated at 3%. The prevalence of antibodies ranged between less than 1% and 25% in the different provinces, and an estimated 1 million persons were infected (Brés, 1981).

The disease had a devastating impact on livestock production because of the abortions and morbidity it caused in sheep, cattle, and buffaloes. The disease in animals preceded the human cases by a few months. A serologic survey conducted in the Nile Valley with the hemagglutination inhibition test revealed high reactor rates in sheep (35.7%), cattle (56.6%), buffaloes (19.3%), and camels (31.4%), as well as lower rates in goats and burros (Hoogstraal *et al.*, 1979). The average rates of abortion and stillbirth on government ranches during 1978 were 28% in sheep, 18.8% in cattle, and 12.1% in buffaloes, and fatality rates on the same ranches were 20% in sheep, 17.5% in cattle, and 20.4% in buffaloes (Malik, 1981).

The unexpected and dramatic appearance of RVF in Egypt was cause for concern for various reasons: presence of the disease in an ecological region completely unlike any other that had been affected up to that time, the severity of some of the clinical pictures theretofore unknown, and the high morbidity and fatality rates, unprecedented in the history of the disease.

Cases have also occurred among laboratory personnel and veterinarians who per-

formed autopsies. Such cases have been recorded not only in Africa but also in laboratories in Great Britain, Japan, and the US.

The extensive epizootics usually occur after heavy rains, when the population of mosquito vectors increases. However, the RVF epidemic in Egypt occurred in the Nile Delta, an area with little rainfall that relies on irrigation and has high human and animal population densities—highly favorable conditions for the breeding of mosquitoes. In 1987, RVF appeared in an area that had no history of epizootics or epidemics of the disease—namely, Mauritania, in northeastern Africa, where 337 human cases were reported, 49 of them fatal. The disease broke out in the environs of the city of Rosso on the Senegal River and spread to nomad camps 88 km to the north. The human cases were associated with the disease in animals: it was determined that most of the patients kept animals and that shortly before or at the time they got sick their livestock had experienced abortions. Serologic tests of 173 sheep and goats in southeastern Mauritania revealed that 65% of the animals had IgG antibodies, and, of these, 64 also had IgM antibodies. These findings confirmed that there had been a recent outbreak in the livestock (WHO, 1988). According to estimates by the Pasteur Institute, in Dakar, which conducted epidemiologic studies in Mauritania, there were a total of 1,264 human cases and 224 deaths. This was the first outbreak to occur in western Africa (Walsh, 1988).

After 12 quiet years, in 1993, the disease reappeared in man and animals in the Egyptian governorate of Aswan. Ophthalmologic disease, usually an infrequent delayed symptom of the infection, was reported in 41 human patients. Specific IgM antibodies were detected, in many cases with high titers, in 27 of 35 patients examined. In animals, numerous abortions were observed, antibodies were detected, and the virus was isolated from an aborted buffalo fetus. Based on serologic surveys, it was estimated that there had been 6,000 human infections in Aswan. The infection also spread to the Nile Delta, where abortions occurred in a herd of sheep, and two persons in contact with the animals were found to be serologically positive. Ocular problems were reported in both animals and humans in several governorates. When 500 slaughterhouse workers from various governorates were examined, 24 of them had IgM antibodies (WHO, 1994).

According to surveillance reports, in western Africa, there was active transmission of the virus in sheep during 1989–1991 in the Ivory Coast. In eastern and southern Africa, the infection is endemic in Kenya, Malawi, Tanzania, and Zimbabwe. In 1993, there were outbreaks in Zambia and Zimbabwe. In 1998, there were outbreaks in Kenya, Mauritania, and Somalia.

In 2000, cases of RVF were reported for the first time outside Africa (excluding cases among laboratory personnel working with the virus), in both Saudi Arabia and Yemen. By April 2001, the Ministry of Health of Saudi Arabia documented 882 confirmed cases of RVF, with 124 deaths (Balkhy and Memish, 2003). Yemen identified 1,087 suspected case-patients, including 121 (11%) who died. Of the 490 case-patients that were serologically tested, 136 (26%) had IgM antibody to RVF and 17 (3%) had weakly reactive test results (CDC, 2000).

The Disease in Man: As described in the sub-Saharan countries, the disease is usually mild with few complications. The incubation period is four to six days. Patients experience fever, intense cephalalgia, myalgia, arthralgia, and photophobia and sometimes also vertigo, prostration, nausea, vomiting, and altered vision. The

disease lasts only a few days, but the fever can reappear at around day 6. Recovery is usually complete, except for some patients with lesions on the retina that can last for months or years. In the 1974–1976 epidemic in South Africa, 12 patients had encephalitis and 4 died from a hemorrhagic form of the disease.

During the epidemic in Egypt, a study of the patients led to establishment of the following clinical forms: RVF without complications, which is the most common; hemorrhagic RVF with meningoencephalitis; and RVF with ocular complications (Meegan *et al.*, 1981).

The hemorrhagic syndrome is the main cause of death. The patients have fever for two to four days and then exhibit jaundice, hemorrhages such as hematemesis, melena, hemorrhagic gingivitis, and petechial and purpuric cutaneous lesions. Hepatic necrosis was one of the lesions found at autopsy. The meningoencephalitic syndrome appears in some patients 5 to 15 days after the febrile period, with disorientation, hallucinations, and vertigo. Meningitis and pleocytosis are common. In 80 patients with ocular complications, loss of visual acuity with lesions on the retina, often bilateral, occurred between 5 and 15 days after the febrile period. Nearly half the patients with more severe macular lesions of the retina suffered permanent loss of central vision (Meegan *et al.*, 1981).

When viremic titers are high, they can persist for more than a week, which suggests that man can participate in amplification of the virus during epidemics such as the one in Egypt. With uncomplicated cases, medical intervention is needed only to treat the symptoms. Nevertheless, the World Health Organization has recommended a controlled trial of ribavirin to evaluate its usefulness in preventing complications, as the drug has proved to be effective in treating and preventing infection in monkeys, cats, and mice. Cases with hemorrhagic complications can be treated with high doses of intravenous ribavirin, but, as mentioned above, it would be best to conduct a controlled clinical trial. Immune plasma and interferon may also be useful. It is not necessary to isolate patients, but they should not travel to uninfected areas when they are in the viremic state, and it is important that they take measures to avoid exposure to the vector.

The Disease in Animals: RVF occurs naturally in sheep, goats, cattle, and buffaloes. In some outbreaks the disease is seen only in lambs; in other cases, it also occurs in adult sheep and cattle.

The incubation period is very brief, and in experimental infections the first symptoms can be seen 20 to 72 hours postinoculation. In newborn lambs, the disease follows a rapid course, without any specific symptomatology, and it is highly fatal; their case-fatality rate can be as high as 95%. In pregnant ewes, abortion is common during the illness or convalescence, and of those that abort, nearly 20% die. In nonpregnant adult sheep, vomiting is sometimes the only symptom observed. In cattle, the symptoms may include abortion, a brief fever, loss of appetite, profuse salivation, abdominal pain, and diarrhea. Fatality rates in this species are almost always low. At autopsies of sheep, the most common lesion is focal necrosis in the liver, which in young lambs can affect the entire organ, giving it a greasy appearance and a bright yellow color. As acidophilic cytoplasmic degeneration of the hepatocytes progresses, hyaline bodies are formed and there are alterations in the nuclei. Abortions and death can also occur in dogs and cats.

Source of Infection and Mode of Transmission: The virus has been isolated from nearly 30 species and 6 different genera of mosquitoes as well as from flies

(*Culicoides* and *Simulium* spp). Shimshony and Barzilai (1983) assessed the capacity of 17 of these species to transmit the virus to laboratory and domestic animals, and found that 14 of them could do so. The most important epizootics in South Africa and Zimbabwe occurred in highland plateau regions, which are not considered the natural habitat of the virus, and it is assumed that the agent was introduced from an as yet unidentified enzootic area. The enzootic vectors are probably from the genus *Aedes* (*A. dalzieli*, *A. vexans*, and *A. mcintoshi*). Epizootics and epidemics, on the other hand, usually involve a large number of species of various genera. In the 1993 outbreak in Egypt, the most numerous mosquitoes in the governorate of Aswan were *Aedes caspius*, *Culex perexiguus*, and *Culex pipiens*, whereas in the country's 1977 epidemic, *Culex theileri* and *Aedes caballus* were considered the main vectors. In West Africa, RVF virus has been isolated from *Culex poicilipes*, *Aedes ochraceus*, *Ae. dalzieli*, and *Ae. vexans* (Diallo *et al.*, 2000; Fontenille *et al.*, 1998).

In the laboratory, the virus has been transmitted to mice by numerous species of *Aedes*, *Anopheles*, *Culex*, and *Eretmapodites*. There is also the possibility of transovarial and transstadial transmission by *Cx. pipiens*: observations in nature indicate that these mosquitoes perform the role of both vector and reservoir (Lefevre, 1989). Species of *Aedes* are abundant after heavy rains, but they disappear rapidly in the dry season. The vectors transmit the infection to domestic animals when they bite them. Sheep and cattle, and perhaps also goats, have very high-titer viremia for one to seven days, and they are efficient amplifiers of the infection in conjunction with mosquitoes.

Little is known about the virus's basic cycle of circulation in nature. It has been suggested that rodents may be the natural reservoir, but this suspicion has not been confirmed. Nor has it been possible to determine the role played by wild ruminants in the cycle, and thus the primary host of the virus is still not known. It is probable that the cycle involving domestic animals and mosquitoes bears only a tangential relationship, if any, to an as yet unclarified cycle in the wild.

In Zimbabwe, on the other hand, it has been concluded that RVF is enzootic in those areas that have epizootics in livestock and that the epizootics are due more to intensified activity of the virus in the same area than to introduction of the agent from an unknown enzootic area. One of the factors that may precipitate epizootics and epidemics is heavy rainfall, which increases the density of the vector population. During interepizootic periods there is an increase in the number of susceptible animals (Swanepoel, 1981). It is believed that in eastern Africa, the RVF virus maintains an enzootic cycle in the *dambos*, or pools formed by the rain, where the *Aedes* mosquitoes breed. When the rains are unusually persistent and heavy, the *dambos* fill up with water and develop a special type of vegetal growth that facilitates the hatching of eggs laid by *Aedes* spp., and hence the appearance of large numbers of mosquitoes, which then proceed to feed on livestock. If the mosquitoes are infected, they transmit the virus to the vertebrate animals and thus amplify it. The vertebrates, in turn, serve as a source of infection for other mosquitoes of different species (Davies, 1985).

According to field observations and experimental studies, the main vector in Egypt is thought to be *Cx. pipiens*, a mosquito that is very abundant on the Nile Delta and feeds on both domestic animals and man. Although the rate of virus isolations from the vector isolations has been low, the abundance of the mosquitoes

compensates for the low levels of the virus. The role of other arthropods in circulation of the virus has yet to be determined.

The virus's maintenance mechanism in nature is still unknown. Studies have failed to demonstrate transstadial or transovarial transmission in mosquitoes. However, the virus was isolated from *Aedes lineatopennis* larvae in Kabete, Kenya, and it is therefore possible that the agent survives in the eggs of this mosquito during interepizootic periods (OIE, 1983).

In summary, mosquitoes are the principal mode of virus transmission between animals and man. In addition, man can contract the infection during the slaughtering process through contact with fetuses; during the autopsy of diseased animals; and in the laboratory. Apparently healthy animals may be a source of infection, as demonstrated by isolation of the virus from the spleens of lambs recovering from an experimental infection between days 11 and 21 postinoculation (Yedloutschnig *et al.*, 1981). The virus probably penetrates the skin and mucosae, but there are indications that other routes of entry may exist as well. It has been demonstrated experimentally that aerosols of the virus are highly infectious for mice, and hence the airborne route may be important in the infection of slaughterhouse workers, veterinarians, and laboratory personnel (Brown *et al.*, 1981). Several investigators became ill three days after witnessing the slaughter of a sheep, without having any direct contact with the animal, and it is likely that aerosols from the blood were the source of infection (Hoogstraal *et al.*, 1979). Although the virus was isolated from the milk of an experimentally infected cow, there is no indication that the digestive tract is an entry point. The occurrence of cases in laboratory personnel who handled strains attenuated by multiple passages (as many as 300) in mice showed that man is susceptible not only to the virus in nature but also to modified viruses.

It is not known with certainty how the virus was introduced in Egypt in 1977. One possibility is that it came from the Sudan, which borders the country on the south and was the site of an epizootic in 1976. The infection may have been introduced by viremic camels or humans, or via arthropods carried by the wind from the Intertropical Convergence Zone to the Aswan area, where it was then amplified in domestic animals (Shimshony and Barzilai, 1983).

Diagnosis: In man, diagnosis is confirmed by isolation of the virus in the blood of an acute-phase patient inoculated intraperitoneally in adult mice or hamsters; the virus kills the animals in two or three days. The agent may be identified by neutralization with a reference antiserum. Serologic diagnosis can be accomplished with the serum neutralization, complement fixation, hemagglutination inhibition, gel diffusion, indirect immunofluorescence, and enzyme-linked immunosorbent assay (ELISA) tests, all of which confirm if there has been seroconversion. The ELISA test is especially useful for diagnosis because it identifies the type of IgM antibodies and therefore can show if the infection is recent. IgM antibody levels drop rapidly in cattle, and only 27% of the animals are still positive after 2 months (Morvan *et al.*, 1992). Reverse transcription-polymerase chain reaction has also been shown to be useful in diagnosing RVF in the early phase of the disease in both humans and animals (Drosten *et al.*, 2002; Espach *et al*., 2002; Sall *et al*., 2002).

One of the most rapid methods for confirming diagnosis is the combination of blood or autopsy material seeded on tissue culture medium and application of the immunofluorescence test, which can give a result the day after seeding.

Diagnosis of the disease in animals can be based on histopathologic examination of tissue from the liver, which is the site of the disease's pathognomonic lesions (necrosis and acidophilic intranuclear inclusions). The virus can be isolated from blood and various organs. Differential diagnosis should take into account Wesselsbron disease, which has similar symptoms and epidemiology.

Special precautions should be taken during autopsies and in the handling and shipping of material to the laboratory as well as in processing samples.

Control: The unforeseen nature of the outbreaks makes it difficult to adopt systematic prophylactic measures against RVF in animals; the best way to prevent the disease is to vaccinate the animals. Inactivated vaccines have been used in South Africa for many years. It is assumed that by immunizing domestic animals, which are the main amplifying hosts of the virus, epizootics and epidemics caused by invasion of the virus from a neighboring country can be prevented. In 1978, faced with the risk that the RVF virus might spread from Egypt to Israel, the Israeli animal health authorities conducted a national campaign to vaccinate sheep and cattle. There is also a modified live virus vaccine for animals that can be administered to females prior to breeding them. This vaccine should not be used in pregnant females because it can provoke an abortion, nor should it be used on newborn animals. Moreover, given the possibility that the virus could become virulent, its use is not recommended in RVF-free areas. Because of its low cost and ease of preparation, the modified virus vaccine was very useful in containing epizootics in South Africa and Kenya (Shope *et al.*, 1982). The inactivated vaccines do not confer as long-lasting immunity as the live attenuated vaccine, and they require a series of vaccinations plus annual revaccination. Moreover, immunity develops more slowly, taking from one to two weeks. When a vaccine is being prepared with local virulent strains, it is necessary to use high-security laboratory installations and adequate protection for personnel. Special care should be taken to ensure that no residual live virus remains in the vaccine. In the future, inactivated vaccines will be prepared with a strain that has been attenuated and then inactivated.

A live attenuated vaccine is being used in South Africa with good results. The vaccine is prepared in tissue cultures at a very low cost—US$ 0.05 per dose, versus $0.40 to $0.80 per dose for the inactivated vaccine—and the immunity that it confers can last for the lifetime of the animal. However, the live vaccine is not recommended for newborn animals or for gestating ewes because it can cause abortions and it is also teratogenic.

An important and promising advance is the live vaccine developed by passage of a human strain of the virus in human fibroblast culture in the presence of the mutagenic drug 5-fluoracil (Caplen *et al.*, 1985; Hubbard *et al.*, 1991). The variant has been designated MP-12 and is immunogenic and avirulent. It does not cause abortions or fetal damage in sheep and cattle, and it appears to confer protection in both species. Since the MP-12 genome has at least one attenuating mutation in each of its three segments, it is considered that reversion to virulence is unlikely. Its possible application in humans is being studied, especially for high-risk groups. Another vaccine that is being studied is clone 13, a natural mutant of the RVF virus.

The prevention of infection in man mainly consists of controlling the infection in domestic animals by vaccination, combined with vector control in the areas of outbreaks. Epidemiologic surveillance is important. In the known enzootic regions, it

would be desirable to carry out serologic surveillance with groups of sentinel lambs in places where the disease has occurred in the past.

The countries of the European Mediterranean have watched the advance of the infection in northern Africa with concern. The same concern also exists in more distant geographic areas. Several authors (Lupton *et al.*, 1982; House *et al.*, 1992) consider that the Americas are also at risk. In 1979, an infected person from Kenya migrated to Canada. Fortunately, the person entered the country during the winter, when mosquitoes were not active. This case shows that with rapid air travel there is a potential danger the virus could spread, given that the viremia in man is very high. Other potential risks are the importation of cattle and accidental transportation of the vectors in airplanes (House *et al.*, 1992).

In the event of an epizootic, precautions should be taken in handling diseased or dead animals, and personnel should be provided with protective clothing. A formalin-inactivated vaccine has been developed that can be used to protect individuals at high occupational risk, such as laboratory workers and veterinarians.

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ROCIO ENCEPHALITIS

ICD-10 A83.6 Rocio virus disease

Etiology: RNA genome virus belonging to the genus *Flavivirus* (arbovirus group B), family Flaviviridae (formerly Togaviridae).[1]

Geographic Distribution and Occurrence: Rocio encephalitis is an emerging zoonosis that first appeared in March 1975 on the southern coast of the state of São Paulo, Brazil. Between March 1975 and July 1978, there were 821 human cases with a case fatality rate of 10%. No further cases have been reported since then. The epidemic spread to 20 municipalities in Vale do Ribeira and Baixada Santista. This is a warm and humid low-altitude region covered with residual forests, propitious for the accumulation of stagnant water and the breeding of mosquitoes (Iversson, 1980).

Of 153 wild birds examined by the hemagglutination inhibition test, 34 (22.2%) had antibodies for the Rocio virus. From a total of 1,007 specimens studied, the agent was isolated from the blood of one rufous-collared sparrow (*Zonotrichia capensis*). High reaction rates were also found in rodents and marsupials (de Souza Lopes, 1978a).

The Disease in Man: The incubation period lasts an average of 12 days, and the clinical manifestations are variable. The disease has a sudden onset with fever and cephalalgia, along with vomiting in more than 50% of the patients and abdominal pain in 20% of the cases. The neurological manifestations are stiffness of the neck, mental confusion, and motor and equilibrium disturbances. About 20% of the survivors suffer from significant impairment of mental functions. The histological lesions in the brain are the same as those seen in other acute viral encephalitides, with the special characteristic that the structures most affected are the thalamus, the dentate nucleus, and the hypothalamic nuclei (Rosemberg, 1977).

Source of Infection and Mode of Transmission: In the epidemiological investigation of the outbreak that occurred, it was found that in 75% of the cases the disease affected a single member of the nuclear family, which indicates that interhuman transmission was not important. Nor were there cases among the hospital personnel who took care of patients. These findings, coupled with the antigenic relationship of Rocio virus to other mosquito-borne flaviviruses, suggested that the infection was transmitted by an arthropod (de Souza Lopes *et al.*, 1978b). It is also noteworthy that the epidemic occurred in a primarily agricultural area and that most of the cases were in males who were in close contact with the rural environment, especially farmers and fishermen (Iversson, 1980). The male-female ratio was 2:1, and the highest incidence was among persons 15 to 30 years of age (de Souza Lopes, 1986).

Entomological studies conducted in the residual forest of the area where the epidemic occurred showed that *Aedes scapularis* and *A. serratus* were the mosquitoes most frequently attracted to human bait. Both species are diurnal with moderate nocturnal activity. *A. scapularis* is active both inside and outside the forest and is more likely to come in contact with the human population (Forattini *et al.*, 1981). In an

[1] All the flaviviruses belonging to former arbovirus group B have been transferred from the family Togaviridae to the family Flaviviridae.

attempt to isolate the virus from mosquitoes, 2,230 pools consisting of 38,896 specimens of various species of mosquitoes (including *A. scapularis* and *A. serratus*) were examined; the virus was isolated from only 1 pool of 47 specimens of *Psorophora ferox* (de Souza Lopes *et al.*, 1981). This finding has been the only isolation of the virus from mosquitoes in nature. However, it is doubtful that this mosquito is a competent vector of the virus. In the laboratory, only a few *P. ferox* females, inoculated via the oral route, have been successfully infected. Since the most abundant species in the epidemic area was *A. scapularis*, the competence of this mosquito as a vector was investigated experimentally and it was found to be susceptible to infection by the oral route and highly capable of transmitting the virus when it bit 2-day-old chicks (Mitchell and Forattini, 1984). Although there are strong reasons to assume that *A. scapularis* is the principal vector, its infection in nature has yet to be demonstrated. The Rocio virus has been reproduced experimentally in various species of laboratory-bred mosquitoes, and the infected mosquitoes were able to transmit the infection to birds, producing a high-titer viremia (Mitchell *et al.*, 1981).

The high rate of wild birds with antibodies for the Rocio virus suggests that they are the natural reservoir of the infection. Mammals have been ruled out because of their small numbers in the region.

In summary, the natural history of the disease is still poorly understood, although there is little doubt that the infection is transmitted to man by mosquito bites. Also, it remains unknown how this one epidemic emerged and why the disease disappeared. The highest incidence of the disease was reported in April 1975, with about 55 cases per 100,000 population, and again at approximately the same time of year in 1976, with about 90 cases per 100,000; few cases were reported in 1977 and 1978 (Iversson, 1980). Seroepidemiologic surveys of the area's population showed that the rate of inapparent infection was low, and it can therefore be assumed that the disappearance of the disease was less likely to be related to the absence of a susceptible human population than to the population dynamics of the vectors or the reservoirs (Iversson *et al.*, 1982). As for the origin of the epidemic, the possibility has been suggested that the virus may have been circulating between nonanthropophilic vectors and their primary hosts in the wild and that the virus may have appeared in the human population when anthropophilic vectors happened to acquire the infection (Iversson, 1980).

Diagnosis: The virus was successfully isolated from the brains of patients who died six days after onset of the disease by inoculating the material intracerebrally in 2-day-old mice. The isolations were obtained only from the brain stem, but not from the cerebral cortex or other organs. The virus could not be isolated from the blood of any of the patients (de Souza Lopes, 1986). Serologic diagnosis may be done by hemagglutination inhibition, complement fixation, or serum neutralization, with paired sera to assess seroconversion. A diagnosis may also be obtained with the plaque reduction neutralization and IgM antibody-capture enzyme-linked immunosorbent assay techniques [MAC-ELISA] (Romano-Lieber and Iversson, 2000).

Control: No vaccines are available. In the event of an epidemic, the same guidelines as for other arboviruses should be followed.

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ROTAVIRAL GASTROENTERITIS

ICD-10 A08.0 Rotaviral enteritis

Synonyms: Infantile gastroenteritis; acute gastroenteritis of children, calves, suckling pigs, foals, and lambs; neonatal calf diarrhea; Nebraska calf diarrhea; suckling mouse diarrhea.

Etiology: Rotaviruses of the genus *Rotavirus,* family Reoviridae. The recognized species of the genus are *Rotavirus A* through *E*; *Rotavirus F* and *Rotavirus G* are tentative species. This family also includes the genera *Orbivirus* and *Orthoreovirus*. Rotaviruses differ from the other two genera in their morphologic and serologic characteristics and in their polypeptide composition. The term rotavirus, derived from the Latin *rota*, refers to the fact that the outer capsid of this double-capsid virus looks like a wheel with spokes. The virion measures about 60 nm in diameter and has no envelope. The genome has 11 double-stranded RNA segments.

All rotaviruses have a common group-specific antigen, which is found in the VP6 protein on the inner capsid. This antigenic determinant is found in 99% of the strains isolated throughout the world, regardless of the animal species from which they come. All these strains belong to serogroup A. The strains that do not have this common antigen, formerly classified as atypical, have now been placed in serogroups B through G (Gómez and Grinstein, 1991; Paul and Lyoo, 1993). The strains that do not belong to serogroup A cannot be detected by the enzyme-linked immunosorbent assay (ELISA), which has largely replaced immunoelectron microscopy.

The serogroup A rotaviruses have been divided into two (possibly three) subgroups and 11 serotypes. The determinants of the subgroups are also found in the VP6 protein on the inner capsid. The determinants of the serotypes are in proteins VP7 and VP4 on the outer capsid. The serotype is determined by serum neutralization in tissue culture.

Another classification scheme is by electropherotypes based on the electrophoretic migration pattern of the 11 RNA bands in polyacrylamide gel. This technique is much less complicated than serotyping, both for classification and for diagnosis. The electropherotypes have two basically different RNA patterns: short, in which the RNA bands move more slowly in electrophoresis, and long, in which the RNA bands migrate more rapidly. With a few exceptions, subgroup 1 of human serogroup A includes strains with short RNA patterns, while the animal rotaviruses in subgroup 1 have long RNA patterns. Hence, it is possible that subgroup 1 strains that have long RNA patterns and have recently been isolated from man may be of animal origin (Nakagomi *et al.*, 1990).

Four serotypes of the group A human rotavirus, numbered 1 through 4, and 10 minor serotypes, are found in humans. There is increasing evidence that serotype G9, which has a wide geographic distribution, is a more important cause of disease in humans than previously thought (Steele and Ivanoff, 2003; Kirkwood *et al*., 2002; Cunliff *et al*., 2001). Serotype 3 strains are found not only in man but also in simians, dogs, felines, and equines; serotype 4 strains are found in both man and swine. Serotype 5 is associated with swine and equines; serotype 6, with cattle; serotype 7, cattle and chickens; serotype 8, turkeys; and serotype 9, chickens (Herrmann and Blacklow, 1991). The first report of serotypes 1 and 2 found in animals was presented by Bellinzoni *et al.* (1990a). In two herds in the province of Buenos Aires, Argentina, 25 samples of fecal material from suckling pigs were obtained for study. The ELISA technique was used to characterize the rotaviruses by serotype, with specific monoclonal antibodies for human serotypes 1, 2, 3, and 4. The rotaviruses found in swine were classified antigenically as follows: one specimen belonged to serotype 1, four to serotype 2, and two to serotype 3. Six specimens reacted with the monoclonal sera for serotypes 1 and 2, and six corresponded to other serotypes. Two of the specimens that reacted with the monoclonal sera for serotypes 1 and 2, and that were successfully replicated in tissue culture and then purified by plaque selection, reacted as serotype 1 only in the ELISA. Hybridization assays of human strains and strains from six animal species showed that there was greater genetic homology among RNA segments of strains from one animal species than among those of other species. However, a high degree of homology was found between the feline rotavirus (cat strain 97) and the canine rotavirus (K9), and between the human rotavirus (strain AU-1) and the feline rotavirus (strain FR-1). The fact that strains from different species

share a common genetic constellation suggests that interspecies transmission took place in nature at a recent point in the evolutionary history of the rotaviruses (Nakagomi and Nakagomi, 1991). It may therefore be concluded that there is a species-specific barrier (Flores *et al.*, 1986), but the barrier can be crossed.

Indeed, it has been demonstrated that at least some of the serotypes (see below) are not strictly species specific. Strains isolated from dogs, simians, swine, and equines were in no way different from human strains assigned to tentative human serotype 3 (Hoshino *et al.*, 1983b).

Rotaviruses of human origin that were transmitted to suckling pigs, calves, young lambs, dogs, and newborn rhesus monkeys caused infection only in dogs and caused diarrheal disease in the remaining animals. In experiments, it was possible to transmit bovine rotavirus through a series of five passes to gnotobiotic suckling pigs, and each pass caused diarrhea. It was also possible to infect the suckling pigs with rotavirus of equine and simian origin (Holmes, 1979). Cats experimentally infected with bovine rotavirus shed the agent in their feces for two weeks, and dogs and cats exposed to these cats by cohabitation became infected and also excreted the virus, but they did not develop any illness (Schwers *et al.*, 1982). These findings indicate that the animal species barrier is not strict, but it is not known to what degree the viruses cross over between species in nature. The identification of serotype strains that are shared between man and certain animals also suggests that the virus can cross the animal species barrier.

The existence of the different serotypes, which have been established by various immunobiologic methods, is of interest both epidemiologically and from the point of view of protection. For example, these differences would account for the fact that some children may have a recurrence of the disease long after their first episode of diarrhea (Rodríguez *et al.*, 1978). The number of human serotypes is still a subject of debate, both because of the antigenic affinity of the different strains and also because the techniques that have been used lack the necessary sensitivity or specificity.

Two serotypes have been found in cattle by the cross-neutralization test. When colostrum-deprived calves are inoculated with either of the bovine rotaviruses, they produce neutralizing antibodies only against the homologous type. In naturally infected herds, some calves react to only one of the types, but most of them have neutralizing antibodies for both types, perhaps because of successive infections (Murakami *et al.*, 1983). As in children, the disease tends to recur in calves (Woode and Bridger, 1975). In equines, serotypes 3 and 5 were identified by the plaque-reduction neutralization technique. Serotype 5 was similar or identical to the porcine rotavirus, while serotype 3 was similar or identical to the simian rotavirus, which in turn is antigenically related to strains of human serotype 3 and includes the canine and feline rotaviruses as well as simian (Hoshino *et al.*, 1983a). A diversity of serotypes has also been demonstrated in birds (McNulty *et al.*, 1980). Some avian strains are antigenically related to mammalian group A rotaviruses, and these have been called the avian rotavirus group. However, several authors have questioned this classification. In addition to the strains just mentioned, strains from other serogroups have been found in birds. The relationship of strains in serogroups B, C, and E found in birds to those found in mammals has not been sufficiently studied, but serogroup D is considered to be exclusive to birds (McNulty, 1991).

Geographic Distribution: Worldwide.

Occurrence in Man: Gastroenteritis caused by different agents is the most common disease of children throughout the world and constitutes one of the leading causes of morbidity and mortality in this population. According to recent studies, rotaviruses are the most important cause of gastroenteritis in children. Since 1973, when rotavirus was detected for the first time in stools of children with diarrhea in Australia, morphologically identical viruses have been described in various countries of Africa, the Americas, Asia, and Europe. In a year-long study conducted in children with enteritis at a hospital in Melbourne, Australia, the presence of rotavirus was confirmed in more than 50% of the patients (Davidson *et al.*, 1975). The disease mainly affects children up to 5 years of age, and the highest incidence is among infants 6 months to 1 year old.

The infection also occurs in newborns, but it tends to be mild or asymptomatic. In the area around Baltimore, in the US, a series of sudden deaths claimed five infants ranging in age from 8 days to 5 months over a period of three weeks. The syndrome was attributed to rotavirus, given the fact that it was the only agent identified in the stools of the five children and was also found in the trachea of two of them (Yolken and Murphy, 1982). The disease can also affect school-age children and adults, but it is rarer in those groups.

In the US, the Rotavirus Surveillance System, established in January 1989 with 99 participating laboratories, has made more precise data available. Over a 23-month period (1989–1990), a total of 48,035 fecal samples from children were examined for the purpose of detecting rotaviruses, and 20% were positive. The highest incidence was during the winter months: 36% in February compared with only 6% in October. It is now considered that rotaviruses are the most important agents of pediatric gastroenteritis and the cause of one-third of all hospitalizations of children for diarrheal disease. The rotaviruses are also responsible for 20% of the deaths of children with diarrhea (CDC, 1991).

Data from other countries, especially those in the developing world, are fragmentary. In Goiânia, Brazil, 557 fecal samples from hospitalized children 0 to 5 years old, both with and without gastroenteritis, were examined. Of 291 children with diarrhea, rotavirus was detected in 29.2%, versus 4.1% in the 266 children without diarrhea. Of the specimens examined by electrophoresis, 96.6% were from serotype 11, and they exhibited 13 different electrophoretic patterns. The predominant electrophoretic profile changes every year (Cardoso *et al.*, 1992). In northern Nigeria, stools from 392 children were examined between June 1986 and May 1987, and rotavirus was found in 27% of the samples (Gomwalk *et al.*, 1993). Differences in the incidence of rotaviral diarrhea in industrialized and developing countries are not always apparent. At a hospital in Saitama, Japan, 25.4% of 665 fecal specimens from children hospitalized with diarrhea were positive for human rotavirus group A, whereas in Delhi, India, 44 (15.3%) samples from 288 hospitalized children with diarrhea were positive.

In the developing countries of Africa, Asia, and Latin America, every year there are hundreds of millions of cases of diarrhea and 5 to 10 million deaths associated with this cause. However, even though the rotaviruses are recognized to be an important agent, their relative role in morbidity and mortality from diarrhea is still not fully known (Kapikian *et al.*, 1980). According to some sources, 20% to 40% of

the diarrhea cases in hospitalized children up to 5 years of age in tropical countries are caused by rotaviruses, compared with 40% to 60% in temperate countries. In studies carried out in communities in El Salvador and Guatemala, it was demonstrated that between 7% and 14% of all episodes of diarrhea in children under 3 years of age were caused by rotaviruses, and almost all children had experienced an episode of rotaviral diarrhea during their first three years of life (PAHO, 1982). A study of nonhospitalized diarrheic children carried out in Costa Rica over a period of several years found rotaviruses to be the most common agent, with a rate of 45.3%, while enterotoxigenic *Escherichia coli* ranked second, at 13.4% (Mata *et al.*, 1983).

The peak incidence of the disease occurs in the cold months of winter in temperate climates, and in the cool, dry season in tropical climates.

In a survey conducted in Washington, DC, the immunofluorescence and complement fixation tests showed that 60% of all children had been infected with rotavirus by the end of their first year of life and few escaped the infection by the time they were 4 years old (PAHO, 1982).

Occurrence in Animals: Neonatal diarrhea in domestic animals is important from the economic standpoint, both because of high morbidity and because of the deaths it causes. The large number of bacterial and viral agents that cause diarrhea and the frequency of mixed infections make it difficult to determine the incidence of a single etiologic agent. Bacterial infections often occur concurrently with viral infections and aggravate the clinical picture.

Viral and serologic studies indicate that 90% to 100% of suckling pigs and calves and 38% of lambs acquire rotaviral infection at a very early age. In suckling pigs and calves, infections caused by rotavirus tend to be less severe than those caused by *E. coli* or coronavirus in terms of mortality, although some epizootics have been known to cause fatality rates as high as 90% (WHO, 1980). Subclinical infections are probably frequent, which could be accounted for either by passive immunity conferred by the mother's colostrum or by strains of the virus with low pathogenicity (Woode, 1978).

In the UK, a study of rotaviral diarrhea in dairy herds and beef cattle found a history of enzootic or sporadic gastroenteritis as well as epizootic outbreaks in all the herds. In units where calves were fed milk from pails, the outbreaks were almost always explosive but generally limited to groups of 3- to 14-day-old calves that had been in contact with each other. On the other hand, in pasturing beef cattle, outbreaks occurred among calves 4 to 6 weeks old, and within a week, the majority of calves had diarrhea, and 1- to 3-day-old newborns also acquired the infection (Woode, 1978). In Argentina, 33 dairy establishments were studied, and rotavirus was detected in 57.5% of them. The virus was shed by more than 50% of the calves in 6 of the 33 dairy herds. Rotavirus was also the most widespread agent in 36 beef herds; it was detected on 88.9% of the ranches studied, and in half the herds, more than 50% of the calves were found to be shedding the virus. *Rotavirus* and *Cryptosporidium* were found in 55.6% of the beef herds and 39.4% of the dairy herds, and these two agents plus *Salmonella* were found in 11.1% of the beef herds and 3% of the dairy herds (Bellinzoni *et al.*, 1990).

A serologic survey of various localities in Japan yielded a high rate of reactors with the complement fixation test: more than 70% of the horses, sheep, swine,

calves, rabbits, and rats studied were positive. The highest titers were found in the sera of sheep, rabbits, and calves (Takahashi *et al.*, 1979).

The Disease in Man: The incubation period is usually less than two days, but it can be as long as seven days. In most cases, vomiting precedes the onset of watery diarrhea. The feces contain mucus in about 25% of the cases but rarely blood. Low-level pyrexia occurs in 30% to 50% of the patients, and some clinical studies have found patients with a fever of 39 °C or higher. The disease lasts about one week, and virus is shed in the feces for up to 10 days, reaching its peak level between day 2 and 5 after the onset of diarrhea (Stals *et al.*, 1984). In the most severe cases, dehydration and electrolyte imbalance can lead to a child's death. Infections in newborns and adults are asymptomatic.

A syndrome of hemolytic uremia and disseminated intravascular coagulation has been observed in several infected children. Disease of the respiratory tract and sudden infant death syndrome (SIDS) have been described in nursing babies and young children. In two of five children who died of SIDS, rotavirus was identified in both the trachea and feces, and in the remaining three children it was found in the feces (Yolken and Murphy, 1982).

The rotaviruses infect and replicate in the absorbent epithelial cells of the villi in the small intestine and cause blunting and erosion of the villi, proliferation of crypt cells, and lymphocytic infiltration of the lamina propria. These changes indicate that diarrhea may be related to diminished absorption capacity of the small intestine.

Treatment consists of rehydration and reestablishment of electrolyte balance.

The Disease in Animals: Unlike its pattern in man, the disease in animals occurs mainly in the newborn and the young, although it can occur at any age. In experimentally infected gnotobiotic animals, the incubation period was 18 hours. The symptoms include depression, anorexia, and diarrhea. Vomiting has been observed only in suckling pigs. The disease is usually afebrile if no other microorganisms are involved. Prolonged diarrhea can result in dehydration and death.

Gnotobiotic calves experimentally inoculated with rotavirus had diarrhea for only six to eight hours and recovered. When an invasive strain of *E. coli* was introduced prior to inoculation of the virus, the picture became more serious and often proved fatal. It is likely that the epithelial lesion of the small intestine caused by rotavirus permitted the proliferation of other microorganisms and thus complicated the clinical picture. It may be helpful to give the affected animals water instead of milk for 30 hours after the onset of diarrhea. In addition, the administration of antibiotics is recommended to counteract concurrent bacterial infections, along with oral electrolyte and glucose solutions to combat dehydration (Fenner *et al.*, 1993).

Source of Infection and Mode of Transmission: The epidemiology of the disease is not yet fully understood. The virus is resistant and can survive in feces for months at ambient temperature. As a result, contamination of the environment can be a source of infection for animals, because animals such as suckling pigs and calves can shed between 10^7 and 10^{11} infective doses per gram of fecal material for a period of five to nine days (Woode, 1978). Nosocomial neonatal infection caused by rotavirus is very common and causes epidemics or endemics of diarrhea as well as asymptomatic infections. In nurseries, children 5 to 10 days old have been found to shed rotavirus (Holmes, 1979). Given the high incidence of the disease and the

occurrence of reinfections, it is possible, moreover, that the virus perpetuates itself by this mechanism (Gillespie and Timoney, 1981).

Transmission may be by direct or indirect contact. As in other intestinal infections, there is every indication that the mode of transmission is fecal-oral in both man and animals. Oral administration of the virus has resulted in infection in both animals and human volunteers. There are also indications that outbreaks of gastroenteritis in human populations were caused by rotaviral contamination of tap water (Hopkins *et al.*, 1984). Samples of drinking water from Mexico and Egypt have been found to contain viable rotavirus particles (PAHO, 1982). It is also possible that the virus is transmitted by aerosols, as evidenced by the presence of specific IgA antibodies in pharyngeal secretions from children with diarrhea and viral antigen in secretions from children with pneumonia (Hermann and Blacklow, 1990; Stals *et al.*, 1984; Santosham *et al.*, 1983). When nasopharyngeal secretions from 30 children ranging from 9 months to 12 years of age were examined using the ELISA technique, rotavirus antigen was detected in 2 of them (Fragoso *et al.*, 1986). Also, it was found that rotaviral diarrhea in suckling mice could be prevented by covering their cages with filters, suggesting that airborne transmission is important, at least for these animals.

Rotaviruses are not strictly species specific, and experimental cross-infections with human and animal rotaviruses in several animal species have been confirmed. The finding of serotypes common to man and various animal species might indicate that some serotypes can infect both (see Etiology). A rotavirus isolated from a child in England was found to bear a close serologic relationship to a bovine strain, and a strain isolated from a suckling pig was more closely related to a bovine strain than to the porcine strain (WHO, 1980). Although it is not known to what degree cross-infections between species occur, or how animals participate in the epidemiology of the human disease, it is not believed that they play a significant role.

Diagnosis: In enteritis in children, the most profuse shedding of virus in fecal matter occurs between day 3 and 5 after onset of the disease, and the agent is rarely detected after day 8. The presence of virus can be confirmed in extracts of fecal matter by electron microscopy. More recently, other methods have been developed that do not require such expensive equipment to detect the virus in feces—for example, immunoelectroosmophoresis, a modified complement fixation test, ELISA, erythroimmunoassay, and radioimmunoassay. ELISA is now the preferred test for detecting common/shared rotavirus antigen in the VP6 protein on the inner capsid. This test can rapidly detect the presence of group 1 rotaviruses in the feces of man and animals. With monoclonal sera, the ELISA technique can serotype rotaviruses found in feces. Polyacrylamide gel electrophoresis is another method that is often used, especially in developing countries, both for diagnosis and for determining the electropherotype (Gómez and Grinstein, 1991); this test has been found to be more reliable than ELISA for testing samples from newborns, given that the latter method yields a high rate of false positives in this population (Chen *et al.*, 1999). Latex agglutination is a simple test that can be used in clinical practice (Haikala *et al.*, 1983). This technique, using particles sensitized with antisera to the virus, is as sensitive as electron microscopy, though less specific, and therefore is indicated as a screening test. Also, the difficulties associated with isolating human rotavirus in cell cultures have now been overcome, and this advance has made it possible to cultivate

the viruses in a stable cell line (MA 104) derived from embryonic rhesus monkey kidneys in the presence of trypsin (Sato *et al.*, 1981). Monkey kidney tissue cultures can also be used. The methods for isolating the human viruses are difficult to execute and are time-consuming.

The presence of antibodies can be determined by various techniques, but the results are of little use. The radioimmunoassay, immunofluorescence, and ELISA tests measure IgM, IgG, and IgA. Currently, ELISA is the technique that is most widely used.

Rotaviral diarrhea in animals can be diagnosed by the same methods. For a long time it has been possible to isolate the virus in tissue cultures, and the process is less laborious than culturing human rotavirus.

For the diagnosis of rotaviruses other than those in group A, it is necessary to use electron microscopy with a specific antiserum for each group.

Control: Given that the fecal-oral route is the main mode of transmission, prevention of the disease in children must be based on education and observation of the basic rules of personal hygiene. As with all water- or food-borne diseases, it is important to promote environmental sanitation. Several studies have shown that breast-fed babies have a lower incidence of disease than bottle-fed babies. In hospitals and nurseries, good hygiene practices are essential. The rotaviruses have relatively high resistance to chlorine and other common chemical disinfectants. However, the virus can be destroyed by treating it with 5 mM ethylenediaminetetraacetic acid, ethylene glycol, hydrochloric acid, isopropyl alcohol, glutaraldehyde, hexachlorophene, or povidone-iodine. In the developing world, the real problem underlying mortality from diarrhea of any kind is malnutrition.

Because rotaviral diarrhea in animals occurs mainly during the first days of life before there has been time for young animals to become actively immunized, investigators have focused their attention on passive protection. Ingestion of maternal colostrum is not always sufficient to prevent disease. To be effective, colostrum has to possess a high antibody titer, as was demonstrated in an experiment that vaccinated cows with a modified virus vaccine with incomplete Freund's adjuvant (Saif *et al.*, 1983). There are now several vaccines available on the market for cattle and swine: for cattle, there is an attenuated vaccine that is administered parenterally; for swine, two kinds of vaccines are used, one inactivated and the other live attenuated. The modified live vaccine is given orally to sows three to five weeks before they farrow and once again intramuscularly one week beforehand. The vaccine is also given to suckling pigs 7 to 10 days before weaning. The inactivated vaccine is administered intramuscularly to sows before they farrow and to suckling pigs by the parenteral route (Paul and Lyoo, 1993). These vaccines build up antibody levels in the colostrum and milk of the cow and the sow, and they also prolong the excretion of antibodies. The main protective antibody is IgA secreted from the intestine. It has been proposed to give colostrum supplements in milk during the period of risk.

In humans, the situation is different because the greatest incidence of disease occurs after the age of 5 or 6 months, which allows time for active immunization to take place. Vaccines for human use are still in the stage of development and evaluation. Bovine vaccine RIT 4237 was withdrawn from the market, while bovine WC-3 gave good results in trials conducted in the US and is being evaluated in other

countries. A vaccine developed with a simian rotavirus strain, rhesus MMU 18006 (or RRV-1), has afforded good protection in controlled trials in Sweden, the US, and Venezuela, but it failed in other trials in Finland and the US, probably because it was being tested against a different serotype. Another attempt to develop a vaccine for humans involves a recombinant version of bovine vaccine WC-3 incorporating a human serotype, which is currently undergoing evaluation. There is also a recombinant simian-human vaccine, in which the VP7 antigens from human serotypes 1 and 2 have been incorporated into the simian vaccine rhesus MMU 18006. Trials conducted in Finland and the US showed protection levels of 88% and 67%, respectively, against rotaviral diarrhea serotype 1.

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RUSSIAN AND CENTRAL EUROPEAN SPRING-SUMMER ENCEPHALITIS

ICD-10 A84.0 Far Eastern tick-borne encephalitis [Russian spring-summer encephalitis]; A84.1 Central European tick-borne encephalitis

Synonyms: Tick-borne group B virus encephalitis, Far East spring-summer encephalitis, biphasic meningoencephalitis, biphasic milk fever.

Etiology: Tick-borne encephalitis (TBE) virus, an RNA genome virus belonging to the genus *Flavivirus* (Casals arbovirus group B), family Flaviviridae (formerly Togaviridae).[1] The virus forms part of the complex that includes Powassan virus, Louping ill virus, Kyasanur Forest disease virus, Omsk hemorrhagic fever virus, and Langat virus. TBE virus has three antigenic variants: European, Far Eastern, and Siberian.

Geographic Distribution: The virus has been isolated in the European and Asiatic regions of the former USSR, and in Austria, Bulgaria, the former Czechoslovakia, Denmark, Finland, eastern Germany, Hungary, Norway, Poland, Sweden, Switzerland, the former Yugoslavia, and possibly Greece. The European variant of the virus is present in the European countries, the Far Eastern variant is found in Asia, and both variants have been isolated in the western part of the former USSR. In Yunan, China, two strains related to the eastern TBE virus were isolated from *Ixodes ovatus* (Hou *et al.*, 1991).

Occurrence in Man: The disease, caused by a tick bite, is sporadic and mainly affects adults, whereas the form that comes from drinking goat's milk contaminated with the European variant tends to cause household outbreaks, affecting both adults and children. In the former Czechoslovakia, there was an epidemic of 660 cases in 1951. The annual number of cases ranges from the hundreds to as many as 2,000, with a morbidity rate of up to 20 per 100,000 population (Monath, 1982). According to Varma (1989), approximately 80% of the patients who contracted the Siberian variant of the virus lived between 3 and 8 km from the Taiga forest in Siberia, which they visited on weekends and holidays for relaxation and recreation. Some of them

[1] All the flaviviruses belonging to former arbovirus group B have been transferred from the Togaviridae family to the Flaviviridae family.

were confirmed to have been bitten by the *Ixodes persulcatus* tick, the main vector of the Siberian variant of the virus.

Seroepidemiological surveys have shown that clinically inapparent infections are common in humans. The disease occurs in the summer, when ticks are in abundance.

Occurrence in Animals: The virus has been isolated from small mammals, especially rodents, and from goats and cattle. In a study of 2,922 small land mammals from 12 different species conducted in 6 localities of western Slovakia, 14.6% of the animals were found to have antibodies to the agent of Central European encephalitis. Almost all the positive animals were *Clethrionomys glareolus*, and the predominant tick in the region was *Ixodes ricinus* (Kozuch *et al.*, 1990). In the woods of Berlin, Germany, 5 of 15 serum samples taken from deer had antibodies to TBE virus, and the virus was also isolated from *Ixodes ricinus* (Kahl and Radda, 1988). In two studies conducted in Greece, antibodies to TBE virus were found in 0.97% of 206 dogs and 8.6% of 429 dogs, respectively (Chambouris *et al.*, 1989).

The Disease in Man: The disease caused by the Far Eastern and Siberian variants tends to be more severe than that caused by the European variant. In the Russian Far East, the infection is characterized by sudden onset with intense cephalalgia, rapidly rising pyrexia, vomiting, hyperesthesia, and photophobia. Symptomatology characteristic of encephalomyelitis is common in that region, with temporary or permanent flaccid paralysis, nystagmus, visual disturbances, deafness, vertigo, somnolence, epileptiform convulsions, delirium, and coma. Convalescence is prolonged, and sequelae, consisting mainly of paralysis of the upper extremities and back muscles, are common. Sometimes motor disorders and paralysis can appear months or even years after the acute phase of the disease. There is evidence, but no definite proof, that these delayed syndromes may be due to persistence of the virus in the nervous system (Asher, 1979). The case fatality rate is approximately 20%.

In Europe and parts of Siberia, the disease is more benign and usually follows a biphasic course. The first phase corresponds to the viremic period and is characterized by a mild febrile influenza-like illness that lasts for a week. The patient improves, but after 7 to 10 days there is a relapse with cephalalgia, stiffness of the neck, and vomiting. The disease often follows the course of aseptic meningitis or mild meningoencephalitis. Serious cases with paralysis or death are rarer than with the Far Eastern and Siberian variants of the virus. Convalescence is prolonged, and the case fatality rate is between 1% and 2%.

It has been estimated that infection from the European variant of the virus leads to clinically apparent disease in only 2% of the cases, and that just 0.2% of the infections develop the severe second phase (Kunz, cited in McNeil *et al*., 1985).

The tick-borne infection has an incubation period of 8 to 20 days, whereas the form caused by drinking contaminated milk lasts only 4 to 7 days.

The Disease in Animals: The infection is usually asymptomatic in wild animals and only occasionally causes disease in dogs, lambs, and goats. Experimental inoculation of the virus in adult sheep results in a viremia that may last up to five days, with shedding of the virus from the second to the seventh day. In lambs, it causes viremia, encephalitis, and death in five to six days (Gresíková and Beran, 1981). In the naturally occurring disease in sheep and goats, the symptomatology corresponds to that of meningoencephalitis. Animals infected with the Western variant walk in

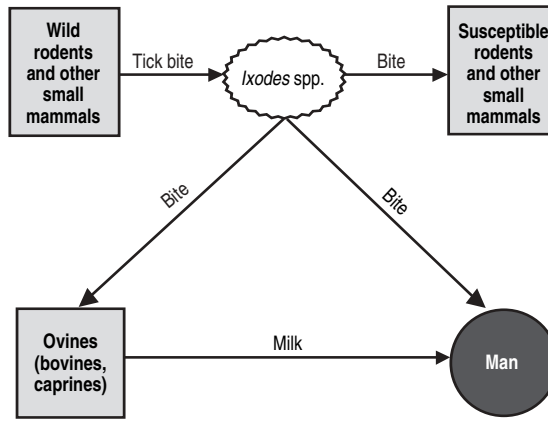
circles, develop spastic paresis in the rear extremities (when it is not of cerebellar origin), and lockjaw with chattering of the teeth (when the 5th pars cranialis is involved), and approximately 12% of them die. The Siberian variant causes an explosive meningoencephalitis with severe spastic tetraparesis, rigidity, lockjaw, chattering of the teeth, and opisthotonos; the case fatality rate is 100% (Poppensiek, 1986).

Source of Infection and Mode of Transmission (Figure 26): The infection is nidal in character and occurs in wooded areas or pastureland inside forests. The virus circulates between ticks and small mammals, especially rodents. The principal vector of the Far Eastern variant is *Ixodes persulcatus*, and that of the European variant, *I. ricinus*, but other tick species, such as *Haemophysalis concinna*, *H. japonica douglasi*, and several species of *Dermacentor*, can also act as vectors. It has been established that the main vectors (*I. persulcatus* and *I. ricinus*) are capable of both transstadial and transovarial transmission, the latter occurring in approximately 6% of the infected vectors.

The complete life cycle of *I. persulcatus* takes two to four years. The young ticks feed on small mammals and wild birds, while the adult ticks feed on large mammals, both wild and domestic. The geographic range of *I. ricinus* starts at the Ural Mountains and extends to the Atlantic Ocean (Varma, 1989). Small mammals serve as amplifiers of the virus in spring and summer. At least 10 species of wild rodents have high, long-lasting viremic titers (Gresíková and Beran, 1981). The tick maintains the infection from the larval stage through adulthood.

It has been demonstrated in the laboratory that several species of small mammals and wild birds, when they are inoculated peripherally or by tick bite, produce prolonged viremia, and the infection is clinically inapparent in most cases. In some animals, such as the hedgehog, dormouse, and bat, the virus persists in the blood for a long time during hibernation.

Figure 26. Russian and central European spring-summer encephalitis. Transmission cycle.



Humans and domestic animals such as goats and sheep contract the infection through a tick bite when they enter the natural foci of the virus. Humans can also acquire the infection by ingesting milk or cheese from an infected goat or sheep. Goats and sheep become infected by ticks when they graze in enzootic areas, and they shed the virus through their milk. It was possible to demonstrate experimentally in cattle and sheep that the bite of an infected tick produces viremia and the shedding of virus in their milk, but no human cases are known to have been acquired from drinking cow's milk. Birds can serve as vehicles for carrying the ticks to new localities.

The disease in humans is seasonal, corresponding to the period of tick activity, which in the Russian Far East lasts from spring to early summer, whereas in Europe it extends until autumn.

Role of Animals in the Epidemiology of the Disease: In addition to being vectors, ticks are also reservoirs of the virus due to both transstadial and transovarial transmission. However, it is still not known whether this capacity is lost over time, in which case the involvement of vertebrates would be necessary (Gresíková and Beran, 1981). Wild rodents serve as amplifiers of the virus, and the virus can persist in the blood of these animals during hibernation. Infected goats and sheep that shed the virus through their milk are a source of infection for humans.

Humans are accidental hosts, becoming infected via tick bites or the ingestion of milk or cheese. In the former Soviet Union, incidence of the disease increased with the penetration of natural foci by humans as development advances into forested areas of Siberia and the Russian Far East.

Diagnosis: The virus can be isolated during the first phase of the disease by inoculating the patient's blood intercerebrally in suckling mice and hamsters, or by seeding it on cell cultures. Serologic diagnosis consists of demonstrating seroconversion (at least a four-fold increase in titer) using complement fixation, hemagglutination inhibition, serum neutralization, and the ELISA test (Roggendorf *et al.*, 1981; Hofmann *et al.*, 1983).

Control: In eastern Europe and the former Soviet Union, an inactivated vaccine is used to protect high-risk groups (forest workers, military personnel, farmers). Some 20 million doses of an inactivated vaccine have been administered in Austria and other European countries. This vaccine, developed by passage through a primary chick embryo cell culture, produces a seroconversion rate of 99%. In Austria, several hundred cases occurred before the mass vaccination campaign got under way, but afterwards the disease virtually disappeared (Kunz, cited in Brandt, 1990; Kunz *et al.*, 1980). A highly purified inactivated vaccine, obtained from a virus particle, conferred protection in mice and produced neutralizing antibodies against both the eastern and the western forms of the virus. A live attenuated vaccine for animals is in the experimental stage.

To avoid epidemic outbreaks, it is important that milk be pasteurized or boiled. For individual protection, the use of protective clothing and repellents in endemic areas is recommended.

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SINDBIS FEVER

ICD-10 A92.8 Other specified mosquito-borne viral fevers

Synonyms: Karelian fever; Ockelbo disease.

Etiology: Sindbis (SIN) virus, an RNA genome virus belonging to the genus *Alphavirus* (arbovirus group A), family Togaviridae. It is antigenically related to the agent of western equine encephalitis. Studies have explored the nucleotide sequence of the Sindbis virus genome and the related Ockelbo virus from northern Europe. Using the plaque-reduction neutralization test and monoclonal antibodies in the enzyme-linked immunosorbent assay (ELISA), numerous strains of the virus from different geographic areas were examined (Lundstrom *et al.*, 1993). The investigators concluded that the Ockelbo virus in Sweden and the agent of Karelian fever in Russia are subtypes of the Sindbis prototype (from Egypt). Although there is some antigenic variation between the viruses isolated in Africa, Australia, and Europe, they are all subtypes of the Sindbis virus.

Geographic Distribution: SIN virus has been isolated in a number of countries in Africa (Cameroon, Central African Republic, Egypt, Mozambique, Nigeria, Senegal, South Africa, and Uganda), Asia (India, Israel, Malaysia, and the Philippines, and the island of Borneo), and Europe (former Czechoslovakia, Karelia in Russia, and Sweden), and also in Australia.

Occurrence: The infection is manifested clinically only in humans; at least 30 clinical cases are known. Seroepidemiologic surveys conducted in Egypt (in the Nile Delta region) and in the Sudan indicate that the rate of inapparent infections is high among the population living in endemic areas. The human cases occur in summer, when the mosquito vectors are abundant. Antibodies have been found in wild birds and in cattle, sheep, and equines.

The Disease in Man: Human cases were recognized for the first time in Uganda in 1961. The symptomatology consisted of fever, cephalalgia, and articular pain; mild jaundice was observed in two of the five patients. In South Africa, where manifestations of the disease have been more severe, a maculopapular eruption has been observed on the trunk and limbs, with a tendency to form vesicles, especially on the feet and palms of the hands. Some patients experience periocular pain, nausea and vomiting, asthenia, and lymphadenopathy. The acute disease disappears quickly, but arthralgia can persist for some time. In approximately 20% of the patients, arthralgia can last for several years, accompanied by the persistence of specific antibodies (Niklasson, 1988). In Australia a case was described with hemorrhagic manifestations and several recurrences, which lasted four months (Guard *et al.*, 1982).

The SIN virus is one of the alphaviruses that causes arthritis, the others being Chikungunya, Mayaro, O'nyong-nyong, and Ross River (epidemic polyarthritis) (Tesh, 1982), and Barmah Forest virus.

The Disease in Animals: The infection is subclinical in domestic animals, and viremia has never been confirmed. Infection in wild birds, which are the natural reservoir of the virus, is probably asymptomatic. A high-titer viremia has been produced in experimentally inoculated chicks, and some of them have even died.

Source of Infection and Mode of Transmission: The SIN virus has been isolated from several species of wild birds, and in some countries, antibodies have been found in these bird populations. The facts suggest that the basic cycle of infection takes place between birds and ornithophilous mosquitoes. The most probable vectors, and those from which the virus has been isolated repeatedly, are *Culex univittatus* in Africa and *C. annulirostris* in Australia. The virus has also been isolated from other mosquitoes, especially culicines such as *C. pseudovishnui* in Borneo. Humans and domestic animals are only accidental hosts.

Diagnosis: The virus is isolated with some difficulty from viremic patients during the first three days of the disease by means of inoculation in suckling mice. Another diagnostic method is to confirm serologic conversion in patients using the hemagglutination inhibition test.

Control: Measures consist of individual protection against mosquito bites.

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SPONGIFORM ENCEPHALOPATHIES OF ANIMALS AND MAN

ICD-10 A81 Slow virus infections of the central nervous system

From the standpoint of comparative pathology, etiology, and epidemiology, the study of transmissible subacute spongiform encephalopathies is of great interest. This group of human and animal diseases is characterized by the absence of inflammatory lesions, similar histopathology of the central nervous system, similar etiologic agents (still not fully characterized), and an unusually long incubation period. The first of these diseases to be recognized, and also the one that has been the most studied and which serves as a model and prototype for the others in the group, is lumbar prurigo of sheep and goats, better known as "scrapie." The study of scrapie has provided the basis for greater understanding of three other similar diseases in man: kuru, Creutzfeldt-Jakob disease (CJD), and Gerstmann-Sträussler-Scheinker syndrome (GSS), as well as transmissible mink encephalopathy and chronic wasting disease of deer. Another animal disease was added to this group in 1986—namely, bovine spongiform encephalopathy (BSE), which is more important economically than the others.

Both natural and experimental disease in animals can serve as human disease models. It has been suggested, however, that the closely related agents of all these diseases may in fact be strains of a single agent that has been modified through adaptation to different hosts (Gajdusek, 1977). This thesis is based on the observation that passage of the agent of scrapie through nonhuman primates changes its host spectrum such that the virus no longer produces disease in the original hosts—namely, sheep and goats. These diseases also share in common a long incubation period, as well as a protracted clinical course that inevitably ends in death.

All the spongiform encephalitides of man and animals exhibit similar cerebral lesions, which are characterized by noninflammatory astrocytosis. The most distinctive lesion is found inside the neuropil, where vacuoles of varying sizes give the organ a spongiform appearance (Tuler, 1991).

Both scrapie and the spongiform encephalitides in man, in addition to being transmissible, have a genetic determinant. A test in this regard is the differing susceptibility of the various breeds of sheep (Brown et al., 1991).

Another shared characteristic which is of diagnostic value is the presence of scrapie-associated fibrils (SAF), which can be seen under the electron microscope by treating the affected brain tissue with detergents and using a negative stain.

Synonyms: Subacute spongiform encephalopathies, infectious amyloidosis, unconventional slow virus degenerative encephalopathies, prion diseases.

Etiology: The etiologic agent has not been isolated or characterized, but some of its properties have been determined indirectly: (a) it is filterable using bacteriologic filters; (b) it can be transmitted by inoculation in laboratory and domestic animals; and (c) it is resistant to high temperatures, ultraviolet rays, and many chemical agents. In order to neutralize its infective capacity, it is necessary to destroy the cell membrane, to which it firmly attaches itself. Several hypotheses have been advanced with regard to the nature of the agent:

1) It is an unconventional virus, estimated to measure 25 nm in diameter, according to some investigators, and 30 to 50 nm, according to others. To date, no structure resembling a virion has been seen under the electron microscope. Several characteristics of this group are different from those of other known viruses—in particular, they do not produce specific antibodies, they do not cause inflammation in nerve tissue, and they are unusually resistant to physical agents.

2) It is a "virine"—a term coined to indicate that the protein necessary to protect the genome is encoded by the host, since the agent may be too small to do so. This explanation would also account for the lack of immune response, since there would not be any antigens alien to the host (Kimberlin, 1992).

3) It is a viroid—a very small single-strand RNA virus without a capsid which is pathogenic for certain plants (this hypothesis has now been ruled out).

4) It is a prion—a term coined by Prusiner (1982). This is the hypothesis that has attracted the most adherents. In the 1990s, a large body of information has been gathered on the biological, physical, and genetic properties of the proteinaceous particle, or prion protein (PrP), which is encoded by the host rather than by the agent. This protein, also referred to as PrPc (c = cell), is protease-sensitive and is the normal product encoded by a host gene. Upon infection, a scrapie-specific protein, referred to as PrPsc (sc = scrapie), is produced (Prusiner, 1992; Oesch *et al.*, 1991). This protein, which is protease-resistant, would be the infective particle of scrapie, or at least its major component. PrPsc builds up in the brain of animals with scrapie. The agent's mechanism for replicating itself is not yet understood.

The infective agent of the spongiform encephalopathies undergoes variation and mutation, which would indicate the presence of a genome. No scrapie-specific nucleic acid has been found to date, despite an intensive search by many investigators (Prusiner, 1992). Those who subscribe to the prion hypothesis have yet to demonstrate how the variation and mutation of the scrapie agent can take place in a normal protein that has been modified posttranslationally[1] (Kimberlin, 1992).

DISEASES OF ANIMALS

1. Scrapie

Synonyms: Lumbar prurigo, enzootic ovine paraplegia, rida (Iceland).

Geographic Distribution and Prevalence: The disease has been diagnosed in Canada, Cyprus, France, Germany, Iceland, India, Ireland, Italy, Norway, Sweden, the UK, the US, and Yemen. With the importation of British sheep, it was also introduced in Australia, Kenya, and South Africa, but prompt diagnosis and sacrifice of the affected animals made it possible to eradicate the infection (Eklund and Hadlow, 1981). The disease was also diagnosed in a sheep in Rio Grande do Sul, Brazil (Fernándes *et al.*, 1978). The full global distribution of the disease has not yet been defined, but outbreaks have also been reported in Austria, Belgium, Colombia, for-

[1] In genetics, translation is the formation of a polypeptide chain in a specific amino acid sequence through the coding of messenger RNA.

mer Czechoslovakia, Lebanon, Netherlands, Somalia, Switzerland, and United Arab Emirates. In Spain, the infection is limited to Aragón (Detwiler, 1992). The disease occurs in sheep, goats, and mouflons (*Ovis musimon*).

In both the UK and the US, Suffolk sheep are the most affected, possibly because this breed has a genetic predisposition to the particular strain of the agent (a biotype introduced from the UK), or because control measures have prevented the infection from spreading to other breeds. In certain Suffolk lines, up to 50% of the sheep can be affected. In the US, scrapie has been reported in all but 11 states. A total of 460 flocks have been affected, with a case fatality rate of 5%. Of the infected flocks, 340 were Suffolk sheep and the rest corresponded to 9 other breeds, of which Cheviot and Hampshire were the most affected. Scrapie, which had once been considered a minor disease, took on greater importance with the emergence of bovine spongiform encephalopathy (BSE) in the UK (see below) (Gloyd, 1990). Death from scrapie occurs in sheep when they are 30 to 50 months old (Eklund and Hadlow, 1981). In affected countries besides Iceland, the UK, and the US, most flocks are scrapie-free or incidence of the disease is insignificant, but in some establishments it is a major economic problem because it causes death in 10% to 15% of the affected animals (Stamp, 1980). It is very difficult to know the exact prevalence of the infection because there are no serologic tests for the purpose. Iceland has an active surveillance program, aimed at eradicating the infection from its ovine flocks. Since 1978, 10,000 to 15,000 brain samples have been examined histologically each year. Symmetric neuron vacuolization was observed in 10% of the clinically normal animals from highly infected flocks, and it was possible to identify 15 infected flocks before the appearance of clinical cases (Detwiler, 1992).

In a survey conducted in the UK for the purpose of determining the prevalence of scrapie in ovine milking flocks, it was found that 17% of the animals had the disease. The average prevalence was 0.31 in 1987 and 0.5 in 1988 (Morgan and Nichols, 1991).

The Disease in Sheep and Goats: Scrapie is primarily a disease of sheep, but it can sometimes affect goats that share the same pastures. The incubation period for the natural infection is very long, estimated at one to four years. The length of the period is dictated genetically by a gene that appears identical to the gene that encodes PrP. It has been demonstrated experimentally in mice that this gene has a significant effect on the length of scrapie incubation in mice (Aiken and Marsh, 1990). The onset of the disease is insidious. The affected individuals are more excitable, and they exhibit a slight tremor in the head and neck, which accounts for the name in French, *maladie tremblante.* The most evident symptom, and often the first to appear, is prurigo, which starts in the lumbar area (hence "lumbar prurigo") and can extend to other parts of the body. The intense itching prompts the animal to rub itself against wire fences and other objects and to gnaw at its flanks and extremities. The consequent loss of wool can extend to other areas of the body. In the advanced stages, the animal becomes emaciated. Impaired motor control and coordination are common. The disease can last from several weeks to several months, and it usually ends in death.

No macroscopic lesions have been observed at autopsy other than skin abrasions from intense rubbing. Histopathology reveals spongiform encephalopathy, astrocyte hypertrophy, and neuron degeneration and vacuolization. The most pronounced lesions are seen in the cerebellar cortex, medulla oblongata, pons cerebelli, mesen-

cephalon, diencephalon, and corpus striatum, whereas the cerebral cortex is rarely affected (Eklund and Hadlow, 1981).

Source of Infection and Mode of Transmission: Sheep clearly have a genetic predisposition to the disease, which to some extent dictates their susceptibility. Experimental genetic selection has produced lines of high and low susceptibility to the scrapie agent and has also demonstrated that response to the infection is controlled by a single gene, with the allele that confers susceptibility being dominant (Kimberlin, 1981). Experiments have also shown that the properties of the scrapie agent are not consistent: there are differences in virulence and pathogenicity between different strains and subpopulations, and these differences may well determine the course of the disease and even its potential to favor certain breeds or genetic lines.

Of special interest is the confirmation that the scrapie agent reproduces slowly over a long incubation period in lymphoreticular tissue before invading the central nervous system. Studies have also shown that the agent is first detectable in the intestinal tract, before it progresses to the regional lymph nodes, spleen, and central nervous system (Hadlow *et al.*, 1982), which would indicate that the sheep may be infected orally. It has been possible to infect sheep experimentally by the oral route, by scarification, and through the conjunctiva. The agent is found in many tissues and in large numbers in the fetal membranes. Hence it is very likely that sheep can contract the infection in contaminated pastures, since the agent, or at least part of its population, is highly resistant to environmental factors. In Iceland, when infected farms were depopulated and kept without animals for one to three years, sheep introduced from disease-free farms acquired the infection in subsequent years, which indicates that the agent can survive for a long time in the environment (Kimberlin, 1981). In order to at least partially understand the mechanism of transmission from the mother to her young, a study was undertaken of maternal transmission by embryo transfer. Donor ewes were infected experimentally with scrapie and artificially inseminated six months later with semen from a disease-free ram; the embryos were then removed five or six days after insemination and, without being washed, were transferred by laparoscopy to recipient ewes which had been selected for their very low genetic susceptibility to scrapie. Six of the 26 lambs born to the recipient mothers developed scrapie (Foster *et al.*, 1992).

Animals have contracted the disease from cohabiting with infected sheep or living in an infected environment. Breeding pens in livestock-raising establishments pose a high risk for uninfected ewes because they can easily come in contact with placentas and fetal fluids from infected animals. Transmission of the etiologic agent can be from the mother to her offspring or to other sheep or goats that are in her proximity. Another important factor is the length of time the newborn lambs or kids remain with the infected mother. Studies have shown that the longer they stay with her, the more exposed they are to the infection.

According to data from the UK, most clinical cases occur in sheep between 2 and 4 years of age.

So far, there are no known human cases contracted from sheep or goats (Detwiler, 1992). Creutzfeldt-Jakob disease, one of the human spongiform encephalopathies, occurs in Australasia, where scrapie does not exist, in the same way as it does in the US or Europe. In Iceland, where prevalence of the ovine disease is very high and the consumption of ovine products is popular, the incidence of Creutzfeldt-Jakob disease is below the world average (Sigurdarson, 1991). It has also been suggested,

though not confirmed, that man can acquire Creutzfeldt-Jakob disease from eating scrapie-infected sheep tissue.

Diagnosis: Diagnosis is based primarily on histopathology of tissue from the central nervous system and, if necessary, inoculation in animals. The infection can be reproduced in mice (with a minimum incubation period of 100 days) or hamsters (with an incubation period of 50 days). So far, it has not been possible to detect antibodies to the agent, and consequently, there are no serologic tests that can be used for diagnosis (Stamp, 1980; Marsh, 1983).

Control: Countries free of the infection should prohibit the importation of animals from countries with scrapie. Australia succeeded in eliminating scrapie through early diagnosis and the sacrifice of imported animals, their offspring, and their contacts. In endemic areas, it is possible to reduce the infection and its spread by sacrificing the animals on affected farms. Eradication is difficult to achieve because of the agent's resistance to environmental factors.

2. Transmissible Mink Encephalopathy

This is a rare disease that occurs in mink-raising facilities where these animals are fed sheep organs and tissues. There have been outbreaks of the disease in Canada, Finland, eastern Germany, Russia, and the US. The last outbreak occurred in 1985 in Wisconsin, US, and appears to have started with the feeding of beef to mink. This would imply that the infection had been present in bovine cattle (Marsh and Hadlow, 1992), which has not yet been confirmed in that country. Some of the outbreaks have caused high mortality rates in adult animals. Mink can be infected experimentally via the oral route, but the incubation period is much longer than for natural infection (from 7 to 12 months). It has also been shown that the infection can be transmitted experimentally when one mink bites another, especially while they are being fed (Kimberlin, 1981).

This disease is of interest because it shows that infection by the agent of scrapie or a similar agent can occur in carnivores and that the species barrier is not inviolate. What probably happens is that, once this barrier has been crossed, a subpopulation of the agent gets selected which is capable of replicating itself in the new host. The natural infection is foodborne only; there are no known cases of animal-to-animal transmission.

As with scrapie, the onset of the disease is insidious. The first changes in behavior are excitability, hyperesthesia, and increased aggression. After a few days or a week, the rear legs start to show signs of unsteadiness. As the disease progresses, the unsteadiness in the rear legs becomes more pronounced and the forelegs are also affected. In the final stages, the animal engages in compulsive self-mutilation. The disease is always fatal (Marsh and Hadlow, 1992).

The agent of mink encephalopathy can be transmitted to hamsters, nonhuman primates, and many other animal species (Marsh and Hadlow, 1992).

3. Chronic Wasting Disease of Deer

In 1967, a syndrome was recognized in nondomestic ruminants of the family Cervidae (*Odocoileus hemonius hemonius* and *Cervus elaphus nelsoni*) with pathology similar to that of scrapie. The cases were diagnosed at four wild animal research

camps in Colorado and Wyoming, US. Between 1970 and 1981, 90% of the 60 deer at one of the camps (Fort Collins) for two or more years developed the wasting syndrome and died or were euthanized. Morbidity and mortality were similar at the other camps, where there were fewer deer. The disease has also been observed in some of the free-living cervids in the proximity of the camps with captive animals. However, domestic cattle that were in physical contact with the affected cervids did not contract the infection. The clinical signs observed in adult deer included behavioral changes and progressive weight loss, followed by death within two weeks to eight months. The histopathological lesions of the central nervous system tissue were identical to those seen in scrapie. Experimental infection has been transmitted intracerebrally to ferrets, squirrel monkeys (*Saimiri sciureus*), mink (*Mustela vison*), other deer, and a domestic goat. Natural infection has also been recognized in the wapiti *Cervus canadiensis* (Marsh, 1983). Deer-to-deer transmission is probably both vertical and horizontal. The infection has been transmitted to other wild animal species living in the proximity of affected deer.

This disease is not to be confused with the epizootic that affected five species of antelope (family Bovidae) in zoos in England, which was traced to the same source as cases of bovine spongiform encephalopathy—i.e., scrapie-contaminated protein feed supplements (Williams and Young, 1992).

4. Bovine Spongiform Encephalopathy

Synonym: Mad cow disease.

Geographic Distribution and Occurrence: Bovine spongiform encephalopathy (BSE) was first diagnosed in England in November 1986, at the beginning of a devastating epizootic. Epidemiologic studies indicated that the cases in this epizootic all stemmed from a common source and that a few cases had appeared as early as April 1985. Starting in June 1988, the reporting of BSE cases was made compulsory in the UK. In 1989, after a year of compulsory notification, more than 7,000 cases had been reported; at the end of 1990, the number was already up to 20,000; and by 1994, the figure had reached 92,000 (WHO, 1994).

As of 21 November 2001, a total of 181,368 cases had been reported in the United Kingdom (178,194 in Great Britain, 1,890 in Northern Ireland, 437 on the Isle of Man, 149 on Jersey, and 698 on Guernsey) (OIE, 2002a). Cases have also been reported in Austria (1), Belgium (65), the Czech Republic (2), Denmark (8), Germany (138), Finland (1), France (515), Greece (1), Ireland (875), Italy (54), Japan (3), Liechtenstein (2), Luxembourg (1), the Netherlands (30), Portugal (628), Slovakia (5), Slovenia (1), Spain (106), and Switzerland (413) (OIE, 2002b). Imported cases were reported in Canada (1), the Falkland Islands (1), and Oman (2) (OIE, 2001c). The importing from Great Britain of contaminated meat and bone meal for food supplementation has contributed to the disease's geographic expansion.

The Disease in Cattle: The neurological symptoms include changes in mental state and behavior, expressed by apprehension and excitability, fixed gaze, and humpback. In 93% of the cases, there are postural anomalies and locomotor dysfunction with subsequent ataxia, tremors, and falling.

In 95% of the cases, there are changes in sensitivity, with hyperesthesia to touch and sound. An important difference between the neurological symptoms of BSE and

those of scrapie is the absence of prurigo; otherwise the two are very similar. Weight loss and reduced milk production may also be seen. The disease is progressive and ultimately fatal; its course ranges from less than two weeks to a full year, and the average duration is one to two months (Kimberlin, 1992). The incubation period may range from two-and-half years to eight years or more.

In the UK, the disease has mainly affected dairy cattle, in which the attack rate is 10 times higher than in beef cattle.

Source of Infection and Mode of Transmission: The epizootic of 1986 was typical of those that originate from a common source: all the affected animals were index cases and there were no secondary cases from transmission. The only factor common to the various establishments affected was the feed. The cerebral lesions were similar to those found in scrapie, the disease in sheep, which dates back several centuries in the UK and is very widespread. Everything pointed to scrapie as the main source of infection, and it was soon determined that supplements made of meat and bone meal, which were being fed to dairy cattle in particular, were made largely from the viscera of infected dead or sacrificed sheep (Wilesmith *et al.*, 1988). It is thought that exposure to the agent first occurred in 1981–1982 and that most of the animals became infected when they were calves. However, the question remained why BSE had appeared so suddenly, since protein supplements from bovine or ovine sources had been used for much longer. One factor may well be a change in the treatment of meat and bone meal which was introduced at approximately the same time—specifically, reductions in the use of solvents to extract fat. This procedure, which used to be performed for eight hours at 70ºC, probably reduced infectious capacity and made the product more sensitive to the second passage, which was to treat the meat and bone meal with very hot steam to eliminate the rest of the solvent. This explanation coincides with the fact that in Scotland and northern England, where treatment with solvents continued, incidence of the disease has been much lower (Wilesmith, 1991; Kimberlin, 1992).

Another factor that may have played an important role in the epizootic is the recycling of the agent through the incorporation of beef brain in feed supplements for cattle. This practice may have caused the selection of a strain specifically adapted to this species—a mutant that would now differ from the original scrapie strains in terms of its shorter incubation period.

A large proportion of the bovine population in the UK was at risk of contracting the infection between 1981–1982 and 1988, when the use of supplements made with products of ruminant origin was banned.

The enzootic has now declined. The year 1991 saw the highest incidence of the disease in 4- or 5- year-old animals. The youngest case that year was a 22-month-old calf, born before the ban against the use of ruminant-derived protein in feed. The falling trend in new cases in young animals continued in 1992, with a lower incidence in cattle under 3 years of age, and in 1993, with the lower incidence in those under 4 years of age (WHO, 1994). British epidemiologists expected the epizootic to be over by the end of the decade if control measures continued to be applied.

An encouraging aspect is that, so far, it has only been possible to transmit the infectious agent by intracerebral or oral inoculation of mice using a homogenized brain and spinal cord preparation from affected cattle. Experimental oral exposure to milk and tissue from the udder, spleen, placenta, and mesenteric and supramam-

mary lymph nodes has failed to produce the disease, as has intracerebral and intraperitoneal inoculation of sperm or spleen, muscle, placenta, bone marrow, and other tissues. By comparison, lymphoreticular tissue, and sometimes other tissues as well, has been shown to transmit scrapie in sheep (WHO, 1994).

As with transmission of scrapie to mink, cattle, and other animal species, the infectious agent can cross the species barrier (see Encephalopathies in Other Animal Species below), and this is a matter of concern for public health authorities. The BSE enzootic in the UK prompted the establishment of surveillance for the disease. To date, there are no confirmed human cases resulting from contact with animals or from ingestion of their products. The incidence of Creutzfeldt-Jakob disease has not increased relative to the period prior to the BSE epizootic. Between May 1990 and April 1993, 250 suspected cases were reported to the surveillance service, of which 117 were classified as confirmed or probable. Measures have been taken to ensure that certain ovine tissue and viscera are kept from entering the human food chain in order to prevent any possibility of transmission to man (WHO, 1992).

Diagnosis: No serologic or other immunologic tests are available as yet. Laboratory confirmation is based on histopathology. The most important lesion is neuroparenchymatous vacuolization in the brain, as in the other spongiform encephalopathies. For a first-time diagnosis of the disease in a given country or region, it is necessary to take transversal sections representative of the most significant regions of the encephalon. Once the existence of the disease has been confirmed, the procedure can be simplified. A single section of the medulla oblongata taken from the obex is adequate for identification in 90% of the cases (Kimberlin, 1992).

Prevention: Scrapie-free countries should not import sheep, or ruminant-derived protein feed supplements that might be contaminated, from infected countries. Although every case of BSE is a primary case and there are no known cases of cattle-to-cattle transmission, it is best not to import these animals from countries with the disease. In April 1991, the Parliamentary Secretary of the UK Ministry of Agriculture went before Parliament, in response to a question that had been raised, and announced a possible case of maternal (vertical) transmission of the infection. The disease had appeared in a 26-month-old calf which was born three months after the ban on ruminant-derived protein supplements (*Veterinary Record*, 1991). A research study under way seeks to determine whether or not there is vertical transmission, and if so, the incidence thereof (WHO, 1994). The possibility of eradicating the infection will depend to a large extent on the results of this undertaking. Several European countries, Argentina, Uruguay, and the US have carried out epidemiologic studies with a view to formulating a risk assessment as well as surveillance programs.

The quarantine of imported animals is of no practical use, given the long incubation of the disease.

5. Spongiform Encephalopathies in Other Animal Species in the UK

CATS: In the UK, 21 cases of spongiform encephalopathy had been recognized in cats as of 1991. It is believed that the disease is new in these countries and that the infection comes from a commercial cat food that contains protein of bovine origin. The cat food industry responded by voluntarily eliminating these ingredients. It is

believed that cases of this disease may continue to appear in cats for another four or five years, after which it will disappear.

The clinical symptoms observed in five cats were those of a progressive neurological disease with locomotor impairment, behavioral changes, and sensory alterations (Wyatt *et al.*, 1991). The signs observed were ataxia, especially in the hind legs, increased aggressiveness or shyness, hyperesthesia, profuse salivation, nodding of the head, and muscle contractions. The symptomatology is very similar to that of BSE and also to the disease produced when cats are inoculated with cerebral matter from persons affected with Creutzfeldt-Jakob disease. Histopathology revealed pathognomonic lesions common to all the spongiform encephalopathies, such as vacuolization of the gray matter and neuronal perikaryon.

Cats are the second carnivore, after mink, that have proven to be susceptible to the infection.

WILD BOVINES: During the BSE epizootic, there were also a few sporadic cases of spongiform encephalopathy among exotic bovines in zoos. These animals had been fed rations containing meat and bone meal of ruminant origin before it was banned. The disease has been reproduced in mice using brain matter from a nyala and a greater kudu. The disease had a shorter duration than in domestic cattle and appeared at a younger age. A second case occurred in a kudu (*Tragelaphus strepsiceros*) that had not been fed the protein supplement. Since the mother had also had the disease, it was concluded that the animal had been infected vertically (Kimberlin, 1992).

HUMAN DISEASES

1. Kuru

ICD-10 A81.8 Other slow virus infections of the central nervous system

Geographic Distribution and Occurrence: Kuru is limited to Papua New Guinea: 80% of all the known cases have occurred among the people of the Fore linguistic group living on the island's eastern plateau. Between 1957 (when the disease was first recognized) and 1975, more than 2,500 deaths were attributed to kuru. Incidence began to fall when the traditional ritual of honoring dead relatives by consuming their cadavers was prohibited, and the disease has virtually disappeared (Gajdusek, 1977). Kuru affected all age groups and, in adults, was more common among women than men. It disappeared first in children and adolescents.

The Disease in Man: The onset of kuru is insidious. The disease is characterized by cerebellar ataxia and tremors, which develop into complete motor incapacity and death within less than a year. Speech difficulties are frequent and progressive. Fever and convulsions are not observed. *Kuru* is a Fore word meaning "tremor," which is the most noticeable clinical sign and affects the head, trunk, and legs. The results of electroencephalogram, electromyogram, and cerebrospinal fluid examination are all normal (Lehrich and Tyler, 1991).

The incubation period is very long, lasting a minimum of 4 years up to a maximum of 30 (Benenson, 1981).

The histopathological lesions of kuru are similar to those of the other diseases in the group—namely, spongiform alterations in the gray matter, neuron loss, and astrocytosis (Eklund and Hadlow, 1981).

Source of Infection and Mode of Transmission: The source of infection was cadaver tissue, especially from the central nervous system, which was consumed during rituals of mourning. This mode of transmission is confirmed by the fact that the disease began to decline once cannibalism ceased, and it has practically disappeared. The much higher incidence in women and children is explained by the fact that the women officiated during the ritual and gave brain parts to children which contained large amounts of the infectious agent (as much as 1 million infective doses per gram). The men and initiated male youths rarely participated in the mortuary rites, much less in the preparation and cooking of the meat from the bodies of the dead. The portal of entry may have been the skin, conjunctiva, or oral mucosa (Gajdusek, 1977).

The epidemiology of kuru is similar to that of transmissible mink encephalopathy, in that the infection is transmitted by the ingestion of, or contact with, infected tissue.

Kuru may have originated from a case of Creutzfeldt-Jakob disease (which occurs throughout the world), from which a chain of transmission was produced through the particular cultural habits of the Fore group in Papua New Guinea.

Diagnosis: Diagnosis is based on the typical clinical symptomatology in the affected population and on the histopathology of tissue from the central nervous system.

The agent is transmissible to a large number of primate species and also to mice.

2. Creutzfeldt-Jakob Disease

ICD-10 A81.0

Synonym: Subacute spongiform encephalopathy.

Geographic Distribution and Occurrence: A rare disease of worldwide distribution, Creutzfeldt-Jakob disease (CJD) is always fatal. The average annual mortality rates range between 0.5 and 1 case per million a year (Chin, 2000). In the US, incidence is estimated at 200 cases a year. In the UK, a total of 250 suspected cases were reported between May 1990 and April 1993, of which 117 were classified as confirmed or probable. In Chile, 46 cases were diagnosed between 1978 and 1983 (Brown and Gajdusek, 1991); in Argentina, 14 cases between 1945 and 1980, and 14 between 1981 and 1989 (Taratuto *et al.*, 1989). In France, 178 cases were confirmed during the period 1978–1982, and in Italy, there were 87 during 1972–1985 (Brown and Gajdusek, 1991), while in Switzerland the reported incidence is 0.9 cases per million a year (Desgrandchamps *et al.*, 1994). In Israel, a study conducted among inhabitants of various origins revealed a much higher incidence (31.3 per million) among Jews of Libyan origin than among those from elsewhere. In the US, a similar pattern of incidence has been observed among the different Jewish communities (Kahana *et al.*, 1974).

CJD is usually a randomly occurring disease with a much higher incidence in cities than in rural areas. National surveys conducted in France failed to reveal any clustering of cases; however, clusters of cases have been found in small rural areas in Chile, Hungary, and the US, which are difficult to evaluate statistically. Clusters of cases in two rural areas of Slovakia and the cases mentioned above among Jews of Libyan origin were more consistent because they had a strong familial component

(Brown, 1991). A genetic study of these clusters revealed an identical mutation in codon 200 of the PrP gene on chromosome 20 (Goldfarb *et al.*, 1990). It remains to be determined whether this mutation initiates the disease or whether it is merely a predisposing factor that makes the individual more susceptible to acquiring the infection from some source in the environment (Brown, 1991).

A new variant of Creutzfeldt-Jakob disease (vCJD), possibly linked to bovine spongiform encephalopathy, was reported in 1996 (Will *et al.*, 1996). Ten cases, all in young adults or adolescents, presented early ataxia and behavioral disorders. The disease's course was prolonged (up to two years) and the EEG changes characteristic of CJD were absent. There was extensive kuru-type amyloid plaque formation and vacuolation. The spongiform changes were highly evident in the basal ganglia and the thalamus with high-density prion protein accumulation in the immunocytochemical analysis, particularly in the cerebellum (Hope, 1998).

The new variant of CJD is clearly a potential zoonosis, with the accumulation of actual proof that vCJD was acquired from bovines infected with BSE. It has been shown that vCJD has biochemical properties similar to those of BSE transmitted to mice, domestic cats, and macaques, and that are different from other types of CJD (Collinge, 1996).

The Disease in Man: The disease usually occurs in persons between 50 and 75 years of age. The length of incubation is unknown in most cases. However, in one patient the origin has been attributed to a corneal transplant 18 months earlier, and in another, to the application of contaminated intracerebral electrodes 27 to 30 months earlier. The onset of the disease is insidious, without fever. It is characterized by rapidly progressing dementia; myoclonic spasms appear early in the disease; and frequently there are also extrapyramidal signs, cerebellar ataxia, visual problems, and behavioral disturbances. Soon after onset of the disease the electroencephalogram appears abnormal. The duration of CJD is usually two to five months, but it can last as long as two years, and it is invariably fatal (Benenson, 1990). The histopathology of the central nervous system is similar to that of the other diseases in the group. In about 15% of the cases, there are amyloid plaques in the brain. The findings from routine analysis of the cerebrospinal fluid are normal (Benenson, 1990).

Source of Infection and Mode of Transmission: In most cases, the mode of transmission is not known with certainty. The exceptions are iatrogenic cases. One such case came from a cornea transplanted from a person who had died from CJD, while others have been traced to the application of contaminated intracerebral electrodes and to the use of inadequately sterilized surgical instruments. A case has also been attributed to administration of human pituitary-derived gonadotropin over a period of 8 months, which produced symptoms 13 years later (Cochius *et al.*, 1990). There are indications that another biological product derived from human pituitary, namely human growth hormone, may also give rise to the infection. A study tested 76 lots of this product by inoculating it in three squirrel monkeys and in chimpanzees. After five-and-a-half years, one of the squirrel monkeys developed progressive neurological disease which, upon histological examination, was confirmed to be CJD; the other two monkeys, however, failed to contract the disease (Gibbs *et al.*, 1993). A dozen patients who received grafts made from a certain commercial brand of cadaveric dura mater contracted CJD. All recipients of such grafts are at

risk for at least 8 years (CDC, 1993). In total, there are more than 30 victims of iatrogenic CJD.

It has been suggested that the ingestion of brain and other tissue from scrapie-infected sheep and goats may give rise to human cases of CJD, in much the same manner as mink have acquired the infection from these animals by the oral route. Of interest in this connection is the high incidence of the disease among Jews from Libya and other parts of North Africa whose traditional diet includes the brains and eyes of sheep and goats (Gajdusek, 1977). However, the available literature on the subject has no data to offer on the occurrence of scrapie in the small ruminants of Libya or other North African countries. Against this hypothesis, it may be pointed out that the incidence of CJD is similar in the UK, where scrapie is enzootic, to the levels in Australia, where scrapie does not occur. It is more likely that man is the reservoir of the CJD agent, since, although it is possible for the agent(s) to cross over between species, as shown in the case of mink and cattle, cats, and exotic bovines in zoos, experimental adaptation to a new species is a slow process that requires several passages. Consequently, man is probably more easily infected by an agent adapted to humans than one adapted to animals (Marsh, 1983). However, cases of CJD are highly scattered, there is little contact between them, and secondary cases are unknown.

The possibility does exist, however, for man to acquire CJD from the ingestion of scrapie-infected organs or tissues, as shown in the experiment with squirrel monkeys (*Saimiri sciureus*), in which infection resulted from feeding them infected brain, kidney, and spleen tissue (Gibbs *et al.*, 1980). So far, it has not been shown that humans can become infected by contact or by the ingestion of lamb or beef. Studies have been done on the relationship between incidence of the disease and eating habits, such as the consumption of brains, and also in groups exposed to contact with the animals and their viscera (slaughterhouse workers, butchers, veterinarians, ranch and farm workers), but no differences have been found with these occupations compared with others.

Diagnosis: Diagnosis is based on the clinical signs and on the histopathology of tissue from the central nervous system.

3. Gerstmann-Sträussler-Scheinker Syndrome

ICD-10 A81.8 Other slow virus infections of the central nervous system

Gerstmann-Sträussler-Scheinker syndrome (GSS) may be a dementia or a slowly evolving cerebellar ataxia, or both. The course of the disease can last three to five years, and its first symptoms are seen in persons between 35 and 55 years old, a much younger age group than the one normally afflicted with Creutzfeldt-Jakob (50–75 years). Spinocerebellar symptoms and ataxia appear early in the disease; later on the manifestations are dementia, pyramidal signs, and muscular atrophy. Spongiform alterations, astrocytosis, and numerous multicentric amyloid plaques are seen at autopsy. GSS occurs worldwide, but its incidence is very low (0.4 per 1 million population). The epidemiologic pattern is that of a familial disease caused by a mutation in codon 102 of the PrP gene, unlike the mutation in the familial cases of CJD (Brown *et al.*, 1991). Two families with GSS have been found to have a mutation in codon 117, and one family with the disease does not have any mutation.

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ST. LOUIS ENCEPHALITIS

ICD-10 A83.3

Synonym: Type C lethargic encephalitis.

Etiology: St. Louis encephalitis (SLE) virus, an RNA genome virus belonging to the genus *Flavivirus* (former arbovirus group B), Flaviviridae (formerly Togaviridae) family.[1] The virus forms part of the complex that includes the agents of Japanese and Murray Valley encephalitis and West Nile fever.

Studies show that the location from which a strain of the virus is isolated will affect its capacity to produce viremia in birds (Bowen *et al.*, 1980), virulence in 3-week-old mice, and neurovirulence in rhesus monkeys (Monath *et al.*, 1980). The nucleotide mapping technique has demonstrated considerable genetic variation between the different strains of the virus, and it has been proposed to refer to these geographic variants as topotypes (Trent *et al.*, 1981).

Geographic Distribution: The agent has been found from Argentina to Canada, but the disease is unknown outside the Americas.

Occurrence in Man: In the western US, the disease occurs endemically and sporadically, but epidemics are unusual. On the other hand, east of the Mississippi River

[1] All the flaviviruses belonging to former arbovirus group B have been transferred from the Togaviridae family to the Flaviviridae family.

there are occasional epidemics. There have also been epidemics in Canada and Mexico (Monath, 1979). Elsewhere in the Americas, only a few isolated cases of human disease are reported. Sporadic cases have occurred in Argentina, French Guiana, Jamaica, Trinidad, and possibly Curaçao (Spence, 1980). At most, 25 clinical cases have occurred outside Canada, Mexico, and the US since 1953, and the majority of these have been without neurological symptoms (Monath, 1979).

St. Louis encephalitis (SLE) ranks first or second (depending on the year) among the arboviral encephalitides in the US. The great majority of cases (about 75%) occur in the eastern part of the country. Since 1933, outbreaks of varying magnitude have occurred at irregular intervals over a broad area of the US, some of them with as many as 500 clinical cases and others with more than 1,000 (CDC, 1993). The last nationwide epidemic took place in 1975–1976 and affected 35 states. The 2,194 cases reported in this epidemic were preceded by a small rise in incidence in 1974. The number fell to 132 in 1977 and 26 in 1978. A large outbreak occurred in Florida from August 1990 through January 1991, resulting in 226 clinical cases and 11 deaths (Day, 2001). Another important outbreak took place in northeastern Louisiana in 2001. Seventy cases had a presentation of encephalitis and were serologically confirmed; there were three deaths (Jones *et al*., 2002).

In the city of Hermosillo, Mexico, there was an epidemic outbreak in 1974, with an incidence of 19 cases per 100,000 population, 51 hospitalized patients, and a case fatality rate of 20%. The first outbreak in Ontario, Canada, occurred in 1975 and produced 22 cases.

As with other arboviruses, the number of inapparent SLE virus infections is much greater than that of clinical cases. A serologic survey following a 1962 epidemic in Florida, US, revealed that the rate of inapparent infections in the population of Clearwater was 4,291 per 100,000, compared with a clinical case rate of 109.6 per 100,000. In 1964, after an epidemic in Houston, Texas, the rate of inapparent infections in a random sampling of the population in that city was 8%, and in the primary epidemic area, which corresponded to the poorest socioeconomic sector, the rate was 34%. The ratio of clinical cases to inapparent infections is 1:800 in children under 9 years old and 1:85 in the population over age 60 (Monath, 1982).

Inapparent human infections are also common in Central America, the Caribbean, and South America, as indicated by serologic studies (Monath, 1979). In Argentina, hemagglutination inhibition studies showed that the prevalence of reactors in humans ranged from 3% to 50%, while in equines the rate was 33% to 66%. There were only three laboratory-confirmed cases and one presumptive diagnosis. These figures coincide with reports from other countries in Central and South America, where seroprevalence is also high and clinical cases of St. Louis encephalitis in man are rare (Sabattini *et al.*, 1985).

St. Louis encephalitis occurs in the latter part of summer and early autumn.

Occurrence in Animals: The virus has been isolated from a large number of wild avian and mammalian species in both the US and other parts of the Americas. Serologic surveys have established presence of the infection in many domestic animal species as well, including equines. Clinical cases associated with the SLE virus have occurred in horses (Walton, 1992).

The Disease in Man: Manifestations of the clinical disease range from an undifferentiated flu-like febrile illness to severe encephalitis. Three syndromes may be

distinguished: febrile illness, aseptic meningitis, and encephalitis. The febrile syndrome is usually benign, with fever and cephalalgia for several days, followed by full recovery. The aseptic meningitis is characterized by sudden onset, fever, stiffness of the neck, and positive Kernig's and Brudzinski's signs (but without neurological dysfunction), and pleocytosis is common. The encephalitic form of the disease also has a sudden onset with fever, along with one or more signs of inflammation of the brain, such as personality changes, confusion, delirium, lethargy, paresis, and convulsions (Brinker and Monath, 1980). The encephalitic syndrome is more frequent in older persons: the rate in patients under 20 years of age is 56%, and it rises to 87% in the population over 60. Convalescence in these cases takes several weeks. In a 1991 outbreak in Arkansas that produced 28 cases and 5 deaths, half the patients were over 60 and almost half of them suffered from hypertension (Bleed *et al.*, 1992). It would appear that hypertension and vascular disease predispose a patient to encephalitis (Marfin *et al.*, 1993).

The incubation period is estimated at 4 to 21 days.

In 2,261 confirmed cases in the US between 1955 and 1968, the case fatality rate was 5% to 10%. Most of the deaths occurred in persons over 50 years old, among whom the case fatality rate can be 30% or higher (Luby *et al.*, 1969). During the 1962 epidemic in Tampa Bay, Florida, the highest fatality rate (36.3%) was recorded in patients over 65 years of age in Pinellas County, where there is a high concentration of retirees. The general fatality rate in this county was 22.2%, compared with 9.8% in the three other counties of the region in question (Bond *et al.*, 1965).

In Central and South America there have been no signs of central nervous system involvement in the few cases reported.

As with other viral encephalitides, the treatment consists of dealing with the symptoms.

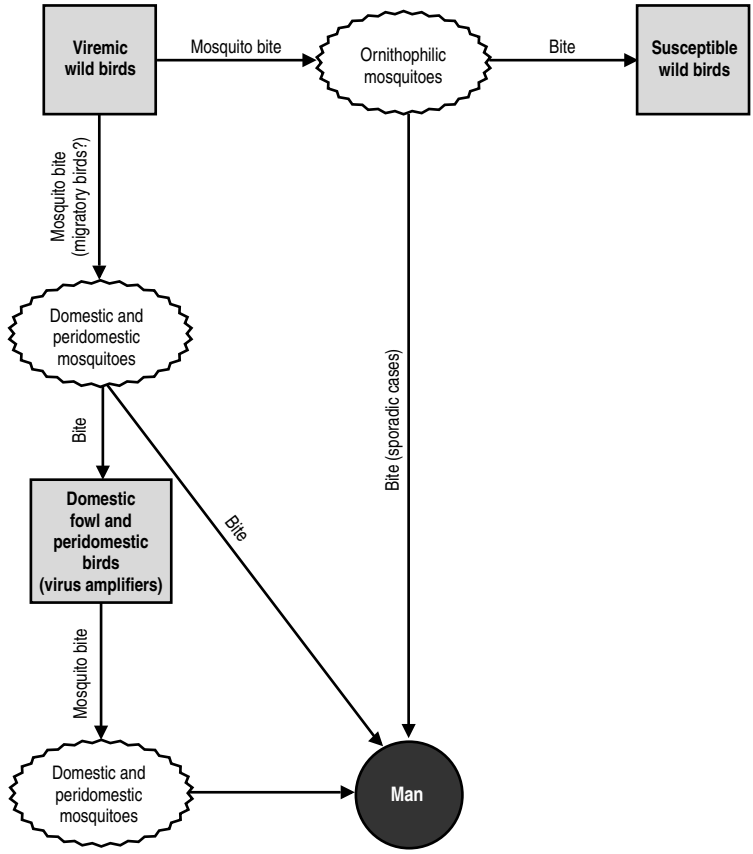
The Disease in Animals: The infection is subclinical in animals. Experimental peripheral inoculation of the virus produces viremia without clinical symptoms in domestic and wild birds and in various species of insectivorous bats.

When the disease occurs in man, antibodies for the SLE virus are usually also found in horses and some other mammals. Unlike eastern, western, or Venezuelan equine encephalitis, St. Louis encephalitis almost never occurs as a clinical disease in equines. However, viremia is sometimes produced when equines are inoculated experimentally.

Source of Infection and Mode of Transmission (Figure 27): The basic infection cycle takes place between wild birds and ornithophilic mosquitoes. *Culex salinarius*, from which the SLE virus has been isolated, may be the vector in the wild enzootic cycle. In the US, there are two different epidemiologic situations, dictated by the habits of the primary vector and other ecologic conditions. West of the Rocky Mountains the disease is rural and sporadic because the vector, *C. tarsalis*, is sparse in this region, while at the same time the widely scattered human population has a high rate of subclinical infection which protects against reinfection. There are high concentrations of vectors and birds in areas using flood irrigation, but there are few human cases, for the reasons given.

In the south-central and north-central US, on the other hand, the disease is found in urban and suburban areas, mainly because the vector mosquitoes, *C. quinquefasciatus* and *C. pipiens*, are domestic and peridomestic. These vectors proliferate in

Figure 27. St. Louis encephalitis. Probable cycle of the virus.



collected water contaminated with organic waste in poorer urban and suburban areas where environmental sanitation is deficient. The same conditions favor the proliferation of sparrows, pigeons, and other birds, which find abundant food in household waste. Domestic fowl and peridomestic birds serve as amplifiers of the virus, and this fact, combined with the high density of the human population, creates the necessary conditions for epidemics. During a 1964 epidemic in Houston, Texas, the virus was isolated from geese, domestic pigeons, and several other avian species. At the same time, antibodies were found in 20% of the birds examined, especially sparrows (*Passer domesticus*), as well as in almost all the flocks of chickens that were tested. After an outbreak in Pine Bluff, Arkansas, US, which produced 25 human cases, the serum neutralization test was used to examine 363 birds representing 33 different species, and reactor rates of 25% were found in 11 species. The most abundant species were house sparrows (*Passer domesticus*) and robins (*Turdus migrato-*

rius), which also had the highest prevalence rates (McLean *et al.*, 1993). It is not known how the virus penetrates urban areas, but it may be introduced by migrating wild birds.

In the epidemic in Hermosillo, Mexico, the vector was *C. tarsalis*. The incidence was higher in children than in adults, possibly because the older age groups had been previously exposed to the virus and were immune.

In the 1962 epidemic in Florida, US, the vector was *C. nigripalpus*, a mosquito of tropical and subtropical regions that breeds in a large variety of habitats and feeds on human and avian blood. The SLE virus was isolated from the same mosquito species in Jamaica.

In Central and South America, the virus has been isolated from numerous mosquito species. However, the relative importance of the different species as vectors (their vectoral competence) remains to be assessed. *C. pipiens quinquefasciatus*, which is an efficient vector of the SLE virus east of the Mississippi River in the US, is found in the Caribbean region and South America. The virus has been isolated from this mosquito species in the province of Santa Fe, Argentina, while an Argentine mosquito of the same species bred in a US laboratory and infected orally with the Argentine virus had the same capacity to become infected and transmit the infection to chicks as did the *C. pipiens quinquefasciatus* mosquito originating in the US. The Argentine strain of the virus did not show any difference relative to the US strains in terms of its capacity to infect these mosquitoes or be transmitted by them (Mitchell *et al.*, 1980).

Various hypotheses have been advanced to account for the fact that SLE epidemics do not occur in the Caribbean region or Central or South America, but none of them is totally satisfactory. Several virus strains isolated in Central and South America have been classified as highly virulent (Monath *et al.*, 1980). Moreover, the species *C. pipiens quinquefasciatus* is a very efficient vector and has the propensity to attack man (Mitchell *et al.*, 1980). Therefore, neither low virulence of the agent nor inefficiency of the vector could account for the absence of epidemics. Several investigators have suggested that the human populations in the Caribbean and Central and South America acquire immunity early in life and that this immunity builds up with age. The prevalence of antibodies in these populations is high, and it may be that immunity in the older age groups, in whom the infection tends to manifest itself clinically, could be a factor that helps to prevent epidemics (Mitchell *et al.*, 1980). In Argentina, when the hemagglutination inhibition test was used to survey wild birds, only 3% reacted positively. The virus has also been isolated from wild rodents in Argentina and in Brazil as well (Sabattini, 1985; de Souza Lopes *et al.*, 1979), suggesting that the life cycle may be perpetuated between wild rodents and such mosquitoes as *Mansonia*, *Sabethes*, *Wyeomyia,* and *Culex* spp. in these countries. Sabattini (1985) observed that in Argentina the strains isolated from *Calomys* sp. and the house mouse (*Mus musculus*) were not very virulent for mice or rhesus monkeys, produced a low-titer viremia in sparrows, and were even less infective for mosquitoes. Such characteristics would also help to explain the relative absence of human cases. However, it has also been demonstrated experimentally that some mammals, such as rodents (Sciuridae and Cricetidae), can develop viremia with a sufficiently high titer to infect mosquitoes (McLean *et al.*, 1985).

The virus has been isolated from hibernating adult female *C. pipiens* mosquitoes, which indicates that the virus can overwinter inside the vector in temperate climates

(Bailey *et al.*, 1978). Low-level transovarial transmission in *C. pipiens* has been demonstrated in the laboratory (Francy *et al.*, 1981). It has also been shown that *C. quinquefasciatus*, an important vector in the central US, can transmit the virus venereally (Shroyer, 1990).

In addition, transovarial transmission has been demonstrated experimentally in *C. tarsalis*, *C. pipiens*, and *C. quinquefasciatus*. However, in several thousand specimens of *C. tarsalis* and *C. quinquefasciatus* collected in the field in California, US, the virus could not be isolated from the larvae or pupae raised to the adult stage in the laboratory (Hardy *et al.*, 1984). Experimental transovarial transmission was repeated with mosquitoes in Florida, US. In addition, vertical transmission was demonstrated in eight species, including *C. salinarius* and *Aedes taeniorhynchus*. Relatively high rates of transovarial and venereal transmission have been observed in *A. taeniorhynchus*. The abundance of this mosquito in Florida and the relatively high rate of vertical transmission suggest that this species could play a role in maintenance of the SLE virus during winter (Nayac *et al.*, 1986).

Role of Animals in the Epidemiology of the Disease: Man is an accidental host of the virus and does not participate in its maintenance cycle in nature. The facts indicate that wild birds are the basic reservoir, as well as perhaps the mosquito vectors themselves, and that domestic fowl and peridomestic birds are amplifiers of the virus, which circulates from one host to another via mosquitoes. Wild and domestic mammals do not appear to play a role in circulating the virus, given their short-term low-level viremia and the low virulence of the virus strains that have been isolated (Monath *et al.*, 1980). It was demonstrated in Panama that sloths inoculated with the SLE virus developed long-lasting high-titer viremia, but the role of these animals in natural conditions has yet to be determined. Bats are thought to play a role in maintenance of the virus during winter in temperate climates within the enzootic foci, as well as in its spread to epizootic foci, and this possibility should be the subject of further research (Herbold *et al.*, 1983).

Diagnosis: St. Louis encephalitis is clinically similar to other febrile illnesses and to encephalitis and aseptic meningitis caused by other agents, and hence laboratory confirmation is essential. Laboratory diagnosis is based primarily on serology. The etiologic agent has only been isolated from viremic patients on a few occasions; most isolations are made from the brain of patients who died shortly after falling ill.

The diagnostic criterion is serologic conversion of the patient based on a comparison of titers in sera from the acute and convalescent phases. The tests most commonly used are complement fixation, serum neutralization (which is the most specific), and hemagglutination inhibition. Antibodies can be detected by the hemagglutination inhibition and serum neutralization tests during the first week of the disease, whereas complement-fixing antibodies appear in the second or third week; the enzyme-linked immunosorbent assay is another method that detects IgM antibodies to SLE virus in acute-phase serum (Chin, 2000). In the Latin American and Caribbean countries, where there are several flavivirus infections, it is necessary for the tests to include all the other viruses in the group that are known to be present in the area. There is also a capture enzyme immunoassay for detecting viral antigen in mosquitoes (Tsai *et al.*, 1987), as well as a rapid dot immunoassay for the detection of antibodies in sentinel chickens (Oprandy *et al.*, 1988).

Control: The only preventive measure available is control of the vector. In the US, epidemiologic surveillance and vector control programs have given satisfactory results against *C. tarsalis* in California, *C. nigripalpus* in Florida, and *C. quinquefasciatus* in Texas using various methods, especially seroconversion among sentinel chickens in Florida and isolation of the virus from mosquito vectors in Texas. No effective vaccine is available.

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SWINE VESICULAR DISEASE

ICD-10 B08.8 Other specified viral infections characterized by skin and mucous membrane lesions

Etiology: Swine vesicular disease virus (SVD) is a single-strand RNA genome virus belonging to the genus *Enterovirus*, family Picornaviridae. RNA hybridization tests have demonstrated that it is closely related to the human coxsackievirus B5.[1] The virion measures 28 nm, is ether-resistant, and remains stable over a broad spectrum of pH.

The extraordinary resistance of SVD virus to environmental factors is very important from the epidemiological point of view. The agent can persist four to six weeks in slaughterhouse effluents at temperatures of 18°C to 22°C. It also resists desiccation in the presence of organic matter and fermentation and smoking in the processing of pork products. The virus can survive 400 days in dried sausages and up to 780 days in processed sausage casings (Loxam and Hedger, 1983).

Geographic Distribution and Occurrence: SVD has been the subject of considerable interest because of its clinical similarity to foot-and-mouth disease in swine and because it is widespread in a number of Asian and European countries. The disease was recognized for the first time in 1966 in Lombardy, Italy, where outbreaks in swine were observed on two farms. A second episode was recorded five years later in Hong Kong. From the latter half of 1972 onward, a series of outbreaks have occurred in Austria, Belgium, France, Germany, Great Britain, Greece, Hong Kong, Italy, Japan, Malta, the Netherlands, Poland, Portugal, Romania, Spain, Switzerland, Taiwan, and Ukraine. During the winter of 1972–1973, an outbreak of disease occurred among staff working with the SVD virus at the Institute for Animal Health (formerly the Animal Virus Research Institute), in Pirbright, England. Immunodiffusion tests on serum from a patient convalescing from aseptic meningitis provided direct evidence that the SVD virus had been the causal agent. To date there is no knowledge of human cases contracted in the field. In the Netherlands, the Central Veterinary Institute reported that in 1975 the infection had appeared in three herds. Three outbreaks were reported in 1992, and drastic measures were taken, including sacrifice of the herds, and by the end of that year the infection was deemed to be eradicated. In Belgium, the last outbreak of the disease was in 1979; in 1992, the epidemiologic surveillance system detected the infection in imported swine. Foci appeared in three countries between 1980 and 1982: Great Britain (60 cases in 1980, 12 in 1981, and 14 in 1982); Italy (29 cases in 1980, 5 in 1981, and 8 in 1982); and Germany (1 case in each year) (Loxam and Hedger, 1983; Knowles, 2003). With the exception of Italy, countries of the European Union have been declared free of the disease. There have been yearly outbreaks in Italy since 1972 and it is considered to be endemic in the south of that country (OIE, 2003; Escribano-Romero *et al.,* 2000). The last reported outbreak in Asia occurred in Taiwan in 1999, and Africa, the Americas, and Australia have remained free of the disease (OIE, 2003).

[1] Human coxsackievirus B is a biological subgroup of the genus, which comprises six serotypes of human enteroviruses.

The Disease in Man: In laboratory personnel, the disease resembles the illness caused by Coxsackie B5 virus. There have been no cases with vesicular eruption. In view of the fact that Coxsackie B5 antiserum neutralizes the SVD virus and antiserum of the latter has the same effect on the Coxsackie B5 virus, it was necessary to discover which of the two viruses was causing the disease. By means of immunodiffusion it was determined that the two viruses share common antigens and also have specific antigens. When serum from the convalescent patient with aseptic meningitis was tested by immunodiffusion, the presence of antibodies to SVD-specific antigen was demonstrated. Subsequently, the two viruses were differentiated using the serum neutralization test. Inoculation of swine with the human Coxsackie virus did not produce SVD.

The Disease in Animals: SVD is limited to swine. The clinical symptomatology of SVD has not been observed in any other domestic animal species that has been in contact with diseased swine. The incubation period in swine is three to seven days. In some herds, the infection spreads rapidly and produces very high morbidity, while in others, it spreads slowly and morbidity is low. When an outbreak starts in a herd, animals can be found with antibodies to SVD virus but without clinical symptoms. The subclinical infection is attributed to the animals' exposure to small doses of the agent.

The clinical picture is highly variable but at the same time quite similar to that of other vesicular diseases in swine, including foot-and-mouth disease. The most severe symptoms are seen in suckling pigs, but in all cases recovery is rapid and the case fatality rate is insignificant (Loxam and Hedger, 1983). The first clinical manifestation is fever, which can reach 41°C and disappears in two or three days. Vesicular lesions are seen mainly on the lateral part of the coronary band, and after they rupture, they leave an eroded area with granulated tissue and loose epithelium at the edges. Before the lesions appear on the main hoofs, one or more of the dewclaws may be affected, but vesicles are rarely seen in the interdigital cleft of the feet. A prominent symptom of SVD is lameness, which is noted especially when the animal has to walk on hard ground. The limping ceases once the vesicles rupture. It is common for the hoof to separate from adjacent tissue, always beginning along the coronary band, but it is rare for the entire hoof to fall off, as can happen in foot-and-mouth disease. Between 5% and 10% of the animals develop vesicles on the snout, the mouth, and sometimes the teats. Symptoms of nervous system involvement, such as ataxia, convulsions, and circling, have also been seen during outbreaks in Europe.

Source of Infection and Mode of Transmission: Swine are the only natural hosts of the virus. No other domestic species becomes infected under natural conditions. Replication of the virus has been observed in sheep living in close and prolonged cohabitation with diseased swine, and the agent has been isolated from the pharynx, but it is doubtful that this species can contract the infection under natural conditions or play any role in transmission of the virus.

Studies have shown that most primary foci originate from the ingestion of, or contact with, raw waste and feed containing infected pork products and that secondary foci arise from the movement of animals, contact with infected livestock at auctions, and transport of the animals in contaminated vehicles. The SVD virus has various portals of entry. Experiments have shown that abraded skin is the tissue most susceptible to infection and that a smaller amount of virus is needed to infect an animal

by this route than by the mouth, nose, or conjunctiva. The dermal route is probably the most frequent pathway at the start of a focus. In such a scenario, one or two swine might become infected through exposure to relatively small amounts of virus in raw waste or contaminated objects. Probably at that point, the infection is introduced by the most susceptible route, namely through a lesion on the skin, especially on the coronary band of the foot (Mann and Hutchings, 1980). Large quantities of the virus are shed in the secretions and excretions of infected swine. The period of maximum infectivity is during the initial two weeks of the infection, and other swine can easily become infected by contact. The cycle would end quickly in the absence of susceptible animals were it not for the fact that virus survives for long periods outside the host, persisting in pork and pork by-products and resisting the change in pH that accompanies rigor mortis (see the section on etiology) (Mann, 1981). The disease is spread from one establishment to another, or from one country to another, mainly via raw waste and as a result of the movement of animals. Pork products that have not been heat-treated can harbor the virus for several months. Given the agent's resistance to environmental factors, it can survive in livestock quarters and open fields for a very long time (Fenner *et al.*, 1993).

The risk for man is apparently insignificant, since the few known human cases have been traced to handling of the virus or contact with diseased animals in the course of scientific research. So far, there is no knowledge of veterinarians working in SVD control who have developed antibodies or shown any signs of the disease.

It has been speculated that the SVD virus, because of its similarity to human Coxsackie B5 virus, may have originated as a mutation of the latter in an infection transmitted from man to swine.

Diagnosis: It is important to differentiate SVD from other vesicular diseases, such as foot-and-mouth disease, vesicular stomatitis, and vesicular exanthema of swine. Differential diagnosis must be done with laboratory tests. The virus can be isolated in tissue culture or by inoculation in laboratory animals. In monolayer cultures of primary swine kidney tissue or a continuous line of 1B-RS-2 swine kidney cells, a cytopathic effect is obtained in one to three days. However, this effect is not observed with BHK-21 cells or calf kidney tissue, as it is with the foot-and-mouth disease and vesicular stomatitis viruses. The SVD virus can also be isolated in suckling mice. Rapid diagnosis can be made with the complement fixation test using epithelium from vesicles as antigen and guinea pig hyperimmune serum with purified virus in an oil adjuvant. The microneutralization test is useful for identifying SVD-specific antibody (OIE, 2000). The serologic tests recommended for diagnosis and seroepidemiologic studies are counterimmunoelectrophoresis, the enzyme-linked immunosorbent assay (ELISA), and double gel immunodiffusion. The serum neutralization test is used mainly to corroborate the results of the aforementioned tests.

Control: The presence of swine vesicular disease has not been confirmed in Africa, the Americas, much of Asia, or Australia, and in these places it should be treated as an exotic disease in order to prevent its introduction. In the event of its accidental introduction, all diseased and exposed animals should be destroyed immediately. Any outbreaks of SVD in pigs should be assumed to be foot-and-mouth disease until laboratory tests can prove otherwise (OIE, 2000). Even though the virus can survive for a long time in soil, most countries of Asia and Europe have

managed to eradicate the infection by applying a strict policy of sacrificing infected herds coupled with border surveillance to prevent reinfection.

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VACCINIA VIRUS INFECTION

ICD-10 B08.0 Other orthopoxvirus infections

Synonyms: Vaccinia, *Poxvirus officinalis*.

Etiology: Vaccinia virus is a DNA genome virus belonging to the genus *Orthopoxvirus*, family Poxviridae. The genus includes, among others, the agents of smallpox, cowpox, monkeypox, whitepox, and mousepox. The history and origin of laboratory strains of the vaccinia virus are not well known. The properties and characteristics of most of the strains seem to indicate that this virus is derived from cowpox virus.

Geographic Distribution and Occurrence: Live vaccinia virus was used universally for over 100 years in the control of smallpox. The last naturally occurring case of smallpox was in 1977 in Somalia, and worldwide eradication of the disease was certified in 1980. As a result of the threat of bioterrorism, the United States Government began voluntary, large-scale smallpox vaccination in early 2003, targeting military personnel who might be exposed to biological weapons disseminating the variola virus and health workers who might come in contact with smallpox cases.

Studies carried out in the US in the 1950s and 1960s indicate that while rare, severe adverse effects of smallpox vaccination are a cause for concern in vaccinees and their contacts, particularly in individuals with atopic dermatitis (eczema) and other acute, chronic, or exfoliative skin conditions; those who are immunocompromised (persons with HIV/AIDS, solid organ or stem cell transplant, generalized malignancy, leukemia, and lymphoma); pregnant and nursing women; and children under 1 year of age. Compared with the health situation at the height of the smallpox eradication era, there are more people today with contraindications to smallpox vaccine, particularly in hospital settings.

Nosocomial spread of the vaccinia virus was reported 12 times from 1907 through 1975 in Brazil, France, Germany, Scotland, Sweden, and the US, resulting in 85 secondary cases. The outcome of nosocomial transmission may be fatal in up to 11% of cases. Family outbreaks usually have occurred as a result of the spread of vaccinia from a recently vaccinated child to an unvaccinated sibling or other family member. In reports of eight family outbreaks in Canada, England, and the US

between 1931 and 1981, 5 family members had received vaccine, 27 family members were infected, and 3 died from the disease (Sepkowitz, 2003).

In a 10-state survey carried out in the US in 1968, it was estimated that per 1 million first-time vaccinees, 935.3 developed serious but not life-threatening reactions; 52.3 developed life-threatening reactions; and 1.5 deaths occurred (Cono *et al.,* 2003). In another study of adverse reactions to smallpox vaccination in the US, it was reported that between 1959 and 1968, there were 36 deaths resulting from postvaccinial encephalopathy (52% death rate) and 19 deaths from progressive vaccinia (28% death rate) in first-time vaccinees, and 12 deaths resulting from eczema vaccinatum transmitted by contact with a vaccinee (Lane *et al*., 1970, cited in Cono *et al*., 2003).

Occupational spread of vaccinia has primarily affected those milking cows; outbreaks of the disease in dairies have been described in various Latin American countries. Lacking evidence of recent vaccination, it has been very difficult to determine the frequency with which outbreaks occurred because data for the agents of vaccinia, cowpox, and even milker's nodules (pseudocowpox) have not been well differentiated. The confusion was due mainly to the similarity in the clinical symptomatology of the infection caused by the vaccinia and cowpox viruses in both man and cows.

The Disease in Man: Vaccinia infection resulting from smallpox vaccination can be transmitted from a vaccinee's unhealed vaccination site to other persons by close contact and can lead to the same adverse effects as in the vaccinee. Normal reactions include fever, headache, fatigue, myalgia, chills, local skin reactions, nonspecific rashes, erythema multiforme, lymphadenopathy, and pain at the vaccination site. A normal vaccination appears as a papule in three to four days, progresses to a vesicle with surrounding erythema by the fifth or sixth day, and becomes a well-formed pustule by the eighth or ninth day. By the twelfth day, the pustule crusts over forming a brown scab. After two to three weeks, the scab detaches and a scar remains (CDC, 2003).

Potentially serious adverse reactions include inadvertent inoculation, generalized vaccinia, eczema vaccinatum, progressive vaccinia, postvaccinial encephalopathy, and fetal vaccinia (Cono *et al.,* 2003). Inadvertent inoculation results from accidental implantation of the virus in the eye, mouth, or other parts of the body of the vaccinee or a contact. Generalized vaccinia is characterized by a systemic spread of virus from the vaccination site, which usually occurs six to nine days after first-time vaccination. This condition is benign. Eczema vaccinatum occurs among persons with a history of atopic dermatitis (eczema), and is a localized or generalized papular, vesicular, or pustular rash, with a tendency to occur in areas of previous atopic dermatitis lesions. Rash is often accompanied by fever and lymphadenopathy. It tends to be more severe among first-time vaccinees or unvaccinated contacts. If unrecognized and untreated, the patient will manifest severe systemic symptoms resembling septic shock, and death ensues (Cono *et al.*, 2003; CDC, 2003). Progressive vaccinia is a rare, severe, and often fatal complication among persons with immunodeficiencies, characterized by painless progressive necrosis at the vaccination site. Vaccinia virus can metastasize to other sites in the body (e.g., skin, bones, and other viscera) through viremia (Cono *et al.,* 2003). Fetal vaccinia, resulting from vaccinial transmission from mother to fetus, is a rare, but serious, complication of smallpox vaccination during pregnancy or shortly before conception. It is

manifested by skin lesions and organ involvement, and often results in fetal or neonatal death (Cono *et al*., 2003). Central nervous system disease, which includes postvaccinial encephalopathy and postvaccinial encephalomyelitis, occurs after smallpox vaccination. Postvaccinial encephalopathy is most common among infants under 12 months of age. Clinical symptoms of central nervous system disease indicate cerebral or cerebellar dysfunction with headache, fever, vomiting, altered mental status, lethargy, seizures, and coma (CDC, 2003).

When vaccinia infection occurred among milkers who had not been vaccinated against smallpox, the incubation period was two to seven days. The lesion or lesions appeared mainly on the fingers and hands, although sometimes they were found on other parts of the body. The lesion started as a papule, which turned into a vesicle and then a pustule, with characteristic umbilication. The patient experienced itching and sometimes pain. After a few days, the lesion dried and was covered by a scab, which fell off after 10 to 14 days. In general, the lesions were not very numerous, but if the patient happened to be suffering from eczema as well, they could involve large areas of skin. Fever and malaise were observed in some cases, obliging the patient to stop working for a day or more.

The Disease in Cattle: The lesions in cattle, located on the teats and the skin of the udder, were similar in appearance to those in man. The milking process produced ulcerations on the skin and delayed healing. The most common complication was mastitis.

Source of Infection and Mode of Transmission: Beginning about four days after vaccination, the vaccination site contains high titers of vaccinia virus, which is easily transferred to the hands and to fomites, especially since itching is a common part of the local reaction (CDC, 2003). Studies of nosocomial spread of eczema vaccinatum suggest that health care workers carried the virus on their hands or clothing, or that patients presenting eczema vaccinatum were not immediately isolated. Another route of transmission was demonstrated by an outbreak in Italy, where 23 secondary cases of vulva-urethral vaccinia occurred over a five-week period; each of the patients had been catheterized with a contaminated urinary catheter. In family outbreaks, sharing close quarters was a significant factor in vaccinia infection (Sepkowitz, 2003).

Cattle acquired the infection from humans who had been recently vaccinated against smallpox. By scratching the vaccination lesion and then milking a cow, the milker inoculated the virus into the animal with his or her fingers and nails. The infection was passed from one cow to another during the milking process, and other milkers could contract the disease from cows with lesions.

Diagnosis: An adverse reaction to smallpox vaccination must be distinguished from other diseases. Patient history regarding recent vaccination or contact with vaccinees is an important part of this process. Vaccinia virus can be isolated, and then identified, in various primary cell cultures and in continuous tissue culture lines, as well as in the chorioallantoic membrane of embryonated eggs. In addition to cattle, guinea pigs and hamsters are very susceptible to vaccinia virus. (Smallpox virus cannot be serially propagated in cattle or rabbits; besides man, only monkeys are susceptible to it.) The appearance and histology of the focal lesions on chorioallantoic membrane and rabbit skin help to distinguish infections caused by vaccinia

virus from those produced by smallpox (see also Cowpox). The development of polymerase chain reaction diagnostic techniques promises a more accurate means of identifying vaccinia.

Control: Health personnel providing direct patient care should keep their vaccination sites covered with gauze or a similar absorbent material to provide a barrier for containment of vaccinia virus to minimize the risk of transmission. Hand washing is important to prevent accidental inoculation. In non-patient care settings in which transmission of vaccinia is a concern due to close personal contact with children or other persons, the vaccination site should be covered with gauze or a similar absorbent material and covered with clothing (CDC, 2003).

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VENEZUELAN EQUINE ENCEPHALITIS

ICD-10 A92.2 Venezuelan equine fever

Synonyms: Venezuelan equine encephalomyelitis, Venezuelan encephalitis.

Etiology: Venezuelan equine encephalitis (VEE) virus, an RNA genome virus belonging to the genus *Alphavirus* (former arbovirus group A), family Togaviridae. The recognition of the existence of different antigenic variants is of great epidemiologic importance. A classification of the viruses in this complex was developed by applying the kinetic hemagglutination inhibition test to a large number of strains

from different regions (Young and Johnson, 1969). The complex has six subtypes (I to VI); subtype I, in turn, has six antigenic variants. Jahrling and Eddy (1977) confirmed the findings of Young and Johnson using single-column hydroxyapatite chromatography.

Antigenic variation has been determined by examining monoclonal antibodies directed against the E1 and E2 glycoproteins on the outer envelope. This technique has made it possible to differentiate 11 epizootic (or epidemic) and enzootic (or endemic) strains of the virus (Rico-Hesse *et al.*, 1988), a distinction that is important from the epidemiologic standpoint. Variants AB and C of subtype I (I-AB and I-C) are highly virulent for equines and are responsible for epizootics/epidemics. The variants D, E , and F of subtype I (I-D, I-E, I-F) and subtypes II (Everglades), III (Mucambo), IV (Pixuna), V (Cabassou), and VI (strains AG 80-663, Argentina) are the enzootic strains that are not pathogenic for equines.

Geographic Distribution: The VEE virus is native to the Americas; its presence has not been confirmed outside the hemisphere. Epizootics/epidemics have occurred from Texas, US, to south of Ica, Peru (see Occurrence in Man and Animals). In the tropical and subtropical regions of the Americas, there are a number of known natural foci of VEE in which the enzootic antigenic variants of the virus circulate between lower vertebrates and mosquitoes. Among the recognized enzootic foci are those located in Belém, Brazil (Mucambo and Pixuna viruses); Magangué, Colombia; south Florida, US; Veracruz, Mexico; Almirante, Panama; Paramaribo, Suriname; and Bush Bush, Trinidad and Tobago. In addition, there are foci in Argentina, Belize, Guatemala, Honduras, and Peru. It has also been confirmed that the virus circulates in the Peruvian Amazon, as well as in the western US (Tonate virus, Bijou Bridge strain), and there are probably other natural foci in various tropical and subtropical regions of the Americas that have not yet been recognized. For example, numerous isolations of VEE complex viruses from *Culex delpontei* in the Argentine provinces of Chaco and Corrientes suggest the existence of enzootic foci in that country (Sirivanakarn and Jakob, 1981). There is also evidence of enzootic foci in the south of Brazil (I-F virus) (Calisher *et al.*, 1982) and the Venezuelan Guajira (I-D virus) (Walder *et al.*, 1984).

Occurrence in Man and Animals: Since the isolation of VEE virus in 1938, there have been many outbreaks and epizootics/epidemics in the Americas. VEE epizootics/epidemics have affected the following countries (from south to north): Peru, Ecuador, Colombia, Venezuela, Trinidad and Tobago, Costa Rica, Nicaragua, Honduras, El Salvador, Guatemala, Mexico, and the US. From 1935 until 1961, the outbreaks were mainly limited to Colombia and Venezuela, but there were also some in Peru and Trinidad and Tobago. However, there were outbreaks every year from 1962 until 1972 that affected Central America, Mexico, and the US.

The largest epizootic/epidemic wave began in 1969. Caused by the I-AB subtype, it advanced across an area stretching from Ecuador through all of Central America to Guatemala, then spread to Mexico, and ultimately extended north into Texas, US, in June 1971. In just two years, this epizootic/epidemic had covered a distance of 4,000 km and caused tens of thousands of human cases as well as considerable morbidity and mortality in equines.

VEE epidemics tend to be explosive. An example is the one in 1962 in the Colombian Guajira which occurred between the months of October and December

and managed to cause 3,000 human cases with 20 deaths in Colombia, and 6,762 cases with 43 deaths in Venezuela. Equally explosive was the great epizootic/epidemic of 1969, apparently originating in Ecuador, which caused some 31,000 human cases with 310 deaths. The epidemics are usually characterized by a high attack rate, which can exceed 10% of the human population in the affected region. After 1972, there was no epidemic or epizootic activity until 1977, when small outbreaks in equines, possibly due to the VEE virus, occurred in Guyana, northern Peru, and La Guajira peninsula, in Venezuela (Monath, 1979).

Epidemiologic surveillance has declined in Latin America, and few countries have reported sporadic cases or outbreaks of encephalitis in equines. However, a document of the Pan American Health Organization (1993), which summarizes the information available for 1989–1993, infers that there have been outbreaks of neurological disease in equines compatible with the equine encephalitides in Mexico, Central America, Colombia, and Venezuela. Studies conducted in El Salvador, Guatemala, and Honduras revealed that transmission of the VEE virus, including strains similar to the I-AB epizootic subtype, had occurred. Serum neutralization tests performed on 2,000 equine serum samples showed a high reactor rate, with elevated titers, in unvaccinated animals. Animals with signs of encephalitis have been observed in several areas of Colombia. The hemagglutination inhibition test yielded high VEE titers in these symptomatic equines as well as some of their contacts. An outbreak of encephalitis cases and fatalities was reported in the state of Trujillo, Venezuela, which appears to have started in December 1992. The VEE virus was isolated from five equine serum samples, and serologic studies in febrile human patients and the general population revealed antibodies as well. This outbreak prompted a national alert. In July 1993, an outbreak occurred in a circumscribed area in the state of Chiapas, Mexico, which led the government to take drastic measures to limit the focus, including quarantine of the area, mass vaccination, and aerial spraying of insecticides. In this outbreak, 136 horses were clinically affected and 61 of them died. No new cases occurred after September 1993 (Kahler, 1993).

The 1995 outbreak of VEE in Venezuela and Colombia was the result of several interdependent factors: 1) insufficient equine vaccination, 2) lack of sustained epidemiologic surveillance, 3) limited knowledge of the ecology of equine encephalitis, and 4) a higher level of viral activity in areas in which the disease had been seen since 1993, in a susceptible equine population. In Venezuela, the outbreak affected the departments of Carabobo, Cojedes, Falcon, Guarico, Lara, Yaracuy, and Zulia. A total of 11,390 suspected human cases, 185 confirmed cases, and 16 deaths were reported. A total of 504 clinical cases in equines were identified, with 475 deaths. The outbreak in Colombia occurred in the towns of Riohacha, Manure, Miacao, and Uribia in the Department of La Guajira. A total of 14,156 suspected cases were reported, with 1,258 hospitalized cases and 26 deaths (PAHO, 1995).

In the town of General Belgrano, Argentina, there was an outbreak in April 1989. Blood samples were taken from 22 human patients, most of them schoolchildren between the ages of 5 and 15, to study various viruses from both the Togaviridae and Flaviviridae families. The reactors were positive to two viruses from the VEE complex: subtype VI strain AG80-663 (an enzootic virus) and subtype I-AB (an epizootic virus). In the serum neutralization test, 51.6% of the patients reacted positively to the enzootic virus type and 26.8% to the epizootic type (strain TC-83). Since in that test there was no cross-reaction between the two subtypes, the authors

concluded that both viruses were present in the area under study. Six of the patients showed seroconversion to subtype VI, which indicated that this virus had produced infection in the patients but did not permit the researchers to conclude that it was the etiologic agent of their disease, since it had not been possible to isolate and type the virus (Contigiani *et al.*, 1993).

The epizootics in equines start before the human epidemics, and the latter usually end when the cases in animals cease. The economic impact is serious: in the affected areas, mortality in equines tends to run between 20% and 40%, with case fatality ranging between 38% and 83%. It has been estimated that between 38,000 and 50,000 equines died in the epizootic/epidemic that began in 1969; Ecuador alone lost approximately 20,000 horses, representing a cost of US$ 1.2 million. In addition, mortality in equines affects the rural economy, since many farmers use these animals in agricultural work and for transportation of their produce to market.

The Disease in Man: The incubation period lasts from two to five days. The symptomatology can range from an undifferentiated fever similar to that seen in the flu to serious encephalitis. In most cases, it is characterized by the sudden onset of fever, accompanied by malaise, chills, myalgia, cephalalgia, and often nausea, vomiting, and diarrhea. Pronounced leukopenia is usually observed in samples taken soon after the fever begins. The course of the disease can last one to four days or longer, and the period of convalescence depends on the duration of the fever. When the fever is brief, the patients recover rapidly and completely, but when the illness is prolonged, they experience marked asthenia and convalescence takes several weeks. The case fatality rate is low, estimated at 0.2% to 1% of clinical cases.

Children develop symptoms of encephalitis more frequently than adults. In one outbreak in Colombia, encephalitis occurred in 4% of the infections in children and 0.4% of those in adults. The range of peripheral neurological signs—i.e., flaccid or spastic paralysis and altered reflexes—are no different from the neurological symptoms in other arboviral encephalitides. Meningeal inflammation is rarely seen. According to postepidemic serological studies, the rate of subclinical infections is high. The attack rate tends to run between 11% and 20% of the general population and may be even higher. From 4% to 14% of the clinical cases exhibit encephalitic symptoms. In an epidemic in the Venezuelan Guajira, birth defects, including anencephaly, were observed in the fetuses of gestating women who had developed the illness during pregnancy (Sanmartín, 1972).

The enzootic subtypes and variants of the virus sometimes cause sporadic cases of undifferentiated fever and meningitis.

The Disease in Animals: The epizootic VEE virus (variants AB and C of subtype I) has been isolated from 21 species of domestic and wild vertebrates, and serologic surveys have shown that many other species contract the infection in nature. However, it is only in equines (horses, mules, and donkeys) that the disease is clinically apparent and of economic importance. The incubation period lasts from one to three days. The symptomatology in equines varies depending on the seriousness of the disease: in some animals, it takes the form of a benign febrile illness, with pyrexia for one or two days, anorexia, and depression. These symptoms are accompanied by mild leukopenia and either low-titer viremia or none at all. Neutralizing antibodies appear within four to six days. The animals recover without sequelae. Other animals also exhibit the characteristic encephalomyelitic course of the dis-

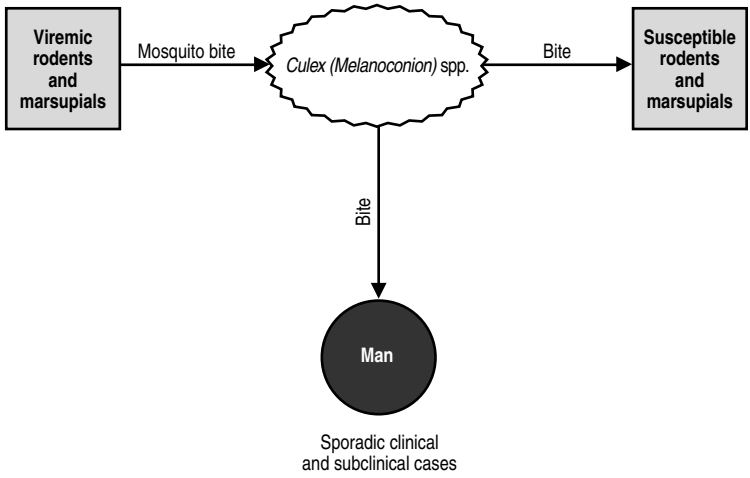
ease. There is sudden onset with high fever, deep depression, pronounced anorexia and weight loss, chattering of the teeth, and diarrhea or constipation. The viremic titer is high, and leukopenia is common. The encephalitic symptoms are similar to those of western equine encephalitis (WEE) and eastern equine encephalitis (EEE). Some of the animals fall into a deep stupor, stand with their legs splayed to keep their balance, lean their head against an object for support, are reluctant to move, and often fall and are unable to get up. Other animals become excitable, hypersensitive to touch and sound, and aggressive; they may walk in circles, stumble, and experience increasingly frequent convulsions. The fatality rate in equines with encephalitic symptoms is very high, sometimes as high as 80% of the cases. During epizootics, cattle and pigs can also become infected (though not diseased), with sufficiently high viremia to infect mosquitoes. In addition, dogs can exhibit symptoms and even die as a result of the disease; the viremic titer is usually low, but high enough to infect the vectors (Sanmartín, 1972).

The enzootic subtypes do not affect solipeds.

Source of Infection and Mode of Transmission (Figures 28 and 29): The natural foci of the enzootic infection are found in American tropical rainforests and perennially swampy regions. The cycle of infection takes place between rodents (including species of the genera *Sigmodon*, *Proechimys*, *Peromyscus*, and *Oryzomys*) and marsupials, on the one hand, and, on the other, mosquito species of the genus *Culex* (*Melanoconion*), especially *C. aikenii*, *C. opisthopus*, and *C. portesi*, which serve as vectors that transmit the infection from viremic animals to susceptible ones. The infection in rodents is asymptomatic, but the viremia is sufficiently high to infect the vectors. Birds act as reservoirs in the cycle of the Tonate (III-B) variant. There are seasonal variations in the activity of the virus, which is more pronounced in the rainy season. However, its activity is continuous, and in the dry season, low-level transmission occurs between rodents and mosquitoes, particularly in species that develop more slowly (*C. portesi* and *C. cedecei*), making it possible to maintain the cycle. Humans become infected by the enzootic viruses when they enter the latter's natural foci. The cases are sporadic, and the enzootic viruses (variants D, E, and F of subtype I and subtypes II, III, IV, V, and VI) have never caused large epidemics or epizootics. However, sometimes these viruses have irrupted into areas adjacent to their enzootic foci and produced small outbreaks in the susceptible human population. Such a scenario could explain the outbreak on the Argentine island of General Belgrano, where serologic conversion for subtype VI in several patients suggests that this wild virus was the etiologic agent (Contigiani *et al.*, 1993).

Surveys conducted on Indian reservations in south Florida, US, suggest that communities in endemic areas have high rates of seropositivity and immunity to these viruses. The principal explanation for the nonepidemic behavior of these strains of the virus is their low degree of pathogenicity for equines. Experimental inoculation of horses with nonepidemic enzootic viruses produced fever, mild leukopenia, moderate antibody titers, and a low-titer viremia that was insufficient to infect the mosquito vectors. By contrast, horses inoculated with epizootic strains exhibited signs of the disease, high antibody titers, and high-titer viremia. A high viremic titer in a single equine infected with an epidemic strain (variants AB and C of subtype I) would be enough to infect several thousand mosquitoes in a day. These titers sometimes last for four or five days in an infected equine. For this reason, equines are

Figure 28. Venezuelan equine encephalitis. Enzootic wildlife cycle (variants D, E, and F of virus subtype I and subtypes II, III, IV, V, and VI).



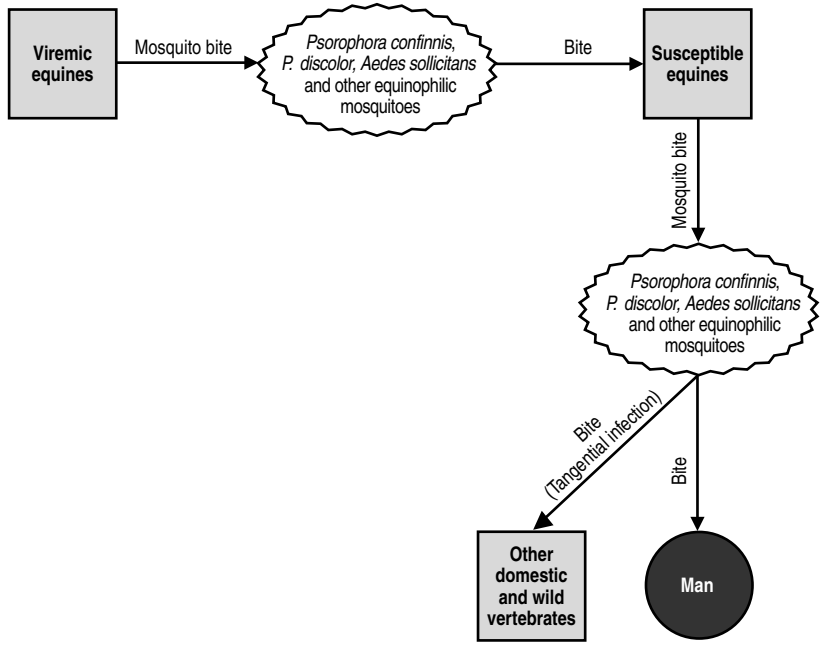
considered amplifiers of the virus and essential to the propagation of epizootics and epidemics. Epidemiologic studies have indicated that the epizootics and epidemics cease when there are no longer any susceptible equines to serve as amplifying hosts (Walton *et al.*, 1992).

The epidemic virus has been isolated numerous times from mosquitoes—in fact, from a total of 34 species belonging to 8 different genera. One or more mosquito species can predominate as transmitter(s) of the infection in a given area. High rates of infection have been found in some species, which would account for the explosive nature of VEE. According to both laboratory and field tests, a number of mosquito species, including *Psorophora confinnis*, *Aedes aegypti*, *A. sollicitans*, *Mansonia tittilans*, *M. indubitans*, *C. tarsalis*, and *A. taeniorhynchus*, are efficient vectors (Monath and Trent, 1981). It is important to understand the relationship between the mosquito and the host, particularly the mosquito's habits of feeding on the equine epizootic host (Sanmartín *et al.*, 1973).

In summary, the epizootic viruses depend on equines as the primary hosts and on being circulated via equinophilous mosquitoes, which transmit the infection from a viremic equine to a susceptible equine, human, or other vertebrate.

The origin of the epidemic virus and its mechanism for maintaining itself during interepizootic periods are unknown. It has not been possible to demonstrate transovarial transmission in the mosquito vectors. One possibility would be low-level transmission of the virus from one equine to another, by which the virus would propagate slowly until there was a large susceptible equine population and conditions were right for an epizootic. Unlike the epizootics of EEE and WEE, which begin and end abruptly within the space of a few months, the VEE epizootics can go on for

Figure 29. Venezuelan equine encephalitis. Epidemic/epizootic cycle (AB and C variants of virus subtype I).



several years—as, for example, in the last epidemic/epizootic. Over the period 1953–1961, Venezuela had sporadic outbreaks of between 7 and 60 equine cases of VEE every year. This pattern would seem to indicate that the virus can be perpetuated during interepizootic periods by passage from one equine to another via a vector. Consideration has also been given to the possibility that the epidemic virus develops in a wild VEE focus as a mutation of the enzootic virus, but this has not been proven. Highly sensitive techniques of absorption chromatography permit the detection of minuscule amounts of epidemic virions in the strains isolated from enzootic foci. To this end, guinea pigs, which are extremely sensitive to the epizootic virus, are being used as sentinels (Monath, 1979). The findings would seem to indicate that there is no relationship between the enzootic viruses found in the natural foci of the Americas and the epizootic viruses that cause the epizoodemics. There are areas of the hemisphere with wild enzootic foci in which VEE outbreaks have never been observed in equines. The two cycles would seem to be independent of one another, and the cycle of epizootic viruses is apparently maintained during the dry season by low-level transmission between equines and surviving epizootic vectors, or else between the animal hosts and drought-resistant mosquito species that feed on them. However, there may be other mechanisms that account for the origin and maintenance of the epidemic virus during interepizootic periods, and it is hoped that research under way will clarify this much-debated topic.

Unlike the circulation pattern of wild viruses in enzootics, epizootics occur more frequently in arid or semiarid regions or in those that have moderate but seasonal rainfall. Epizootics/epidemics always start with an outbreak in equines, followed some weeks later by the epidemic in humans. Transmission to man is via mosquitoes, but cases are also known in which the infection has been contracted through the bite of a fly or in the laboratory by inhalation of the virus.

Role of Animals in the Epidemiology of the Disease: In the wild cycle caused by enzootic viruses, the main reservoirs are rodents, and for some of the variants, such as subtype III-B, birds. The virus circulates between these animals and the mosquito vectors (*Culex* spp.), and it rarely appears outside its natural focus. The human cases with clinical symptomatology occur sporadically or in small outbreaks as a result of man having entered the natural niches. The epizootic virus cycle is maintained between equines and various species of equinophilous mosquitoes. The role of equines as amplifiers of the epizootic virus is essential. Infection in other vertebrates, including man, plays a secondary role in the life cycle of the virus.

Diagnosis: In man, specific diagnosis is based on isolation of the virus and serologic tests. The virus is easily isolated from the blood and nasopharyngeal swabs of human patients. In the early days of the disease, the isolation can be done by inoculation of guinea pigs, newly weaned mice, embryonated eggs, and cell cultures. The isolated viruses can be identified by various serologic tests. For the identification of subtypes, which is of epidemiologic importance, the techniques described in the Etiology section can be used. Serologic diagnosis makes use of the complement fixation, hemagglutination inhibition, and neutralization tests, as well as antibody-capture enzyme-linked immunosorbent assay; the diagnosis is based on establishing the difference between acute-phase and convalescent-phase titers. Neutralizing and hemagglutination-inhibiting antibodies appear during the first week of the disease, and complement-fixing antibodies during the second week.

Diagnosis in equines is based on the same procedures, but it is necessary to keep in mind that the viremia may already have disappeared in symptomatic animals. The same difficulty may be encountered in attempting to isolate the virus from the brain of animals that died after a relatively prolonged illness. For this reason, it is a good idea to take blood samples from asymptomatic animals that are in contact with sick or febrile ones without symptoms of encephalitis.

A good indication of the presence of VEE is the explosive nature of the epidemic, which causes disease and death in large numbers of solipeds as well as febrile cases in man (Sanmartín, 1972).

Control: In areas at risk for epizootics/epidemics, the most practical and effective measure on the national level is the systematic vaccination of equines. With this measure, it is possible to eliminate the mosquitoes' main source of the virus from the epizootic/epidemic cycle and thus prevent epizootics (with economic losses) and subsequent epidemics (with high human morbidity).

An attenuated live vaccine (TC-83) is available which has given very satisfactory results in the immunization of equines. The vaccine is prepared from an epizootic strain of VEE that was isolated in Trinidad in 1943 from the brain of a burro. It is attenuated using laboratory procedures, especially passages in guinea pig fetal heart cells; the 83rd passage is the one used in the product. This vaccine was originally

developed for the immunization of humans, and it has been administered to more than 6,000 persons, 90% of whom developed antibodies at the end of two weeks and maintained them for a prolonged period. A high proportion of individuals (about 25%) had severe systemic reactions, with fever, myalgia, and leukopenia. The live vaccine also provoked an abortion and hydrops fetalis in a woman who had been vaccinated shortly before becoming pregnant (Casamassima *et al.*, 1987).

As of 1985, the TC-83 vaccine had been administered to more than 15 million equines. In immunizations conducted during the course of the epizootics, it was observed that equine deaths ceased 8 to 10 days after the initiation of vaccination. Since death rarely occurs in equines before the fifth or sixth day of infection, it is believed that the vaccine confers immunity in three to four days. In all cases in which the vaccine was administered correctly, the seroconversation rate was nearly 100% and the antibodies persisted for a minimum of two years. Except for a passing fever, systemic reactions were rare.

There have been a few reports of immunization failure, some of them because the vaccine was exposed to tropical heat and others because of the interference of preexisting antibodies for WEE or EEE as a result either of earlier vaccination against these diseases or of natural infections with the viruses in question. The preexisting antibodies for WEE and EEE interfere with replication of the virus contained in the TC-83 vaccine and hence with the immune response. The TC-83 vaccine should not be used in areas free of the disease. The vaccine produces a low-level viremia that is usually insufficient to infect mosquitoes. However, in Louisiana, US, a VEE virus with biological characteristics similar to those of the TC-83 strain was isolated from one of 928 pools of *P. confinnis* mosquitoes captured 12 days after the vaccination of equines in the area. Although it is remotely possible that this finding reflects the establishment of a horse-mosquito-horse cycle, such a scenario is highly unlikely, given the rarity of mosquito infection with a vaccine strain. Nevertheless, caution is recommended, especially since it has not been entirely ruled out that TC-83 could revert to a more virulent state. In the laboratory, it was possible to boost the virulence of the strain through passage of the vaccine virus in suckling mouse brain, and therefore allowance must be made for the chance that such a phenomenon could occur in nature if a mosquito-rodent-mosquito cycle were to get established under suitable ecological conditions. Progressive boosting of the virus in a cycle of this kind could presumably give rise to an epizootic. Fortunately, no such reversion has been observed as yet in nature.

In light of these limitations of the attenuated vaccine, and also because of the severe systemic reactions that it often causes in man, an inactivated vaccine was developed using the same TC-83 strain (Cole *et al.*, 1974). The formalin-inactivated vaccine, prepared from the attenuated strain cultured in embryonic chick cells, gave very encouraging results in activity trials with mice. Also, a trivalent vaccine (EEE, WEE, and VEE) gave satisfactory results when it was evaluated in equines (Barber *et al.*, 1978). The inactivated vaccine offers the advantages that the risk is eliminated and previous exposure to EEE or WEE vaccines does not interfere with the immune response, but the duration of immunity is shorter and annual revaccination is required. In the face of a full-blown epizootic/epidemic, the modified live virus vaccine, which has proved to be highly valuable in such circumstances, should be used. An example of its efficacy was the mass vaccination of equines in Texas in 1971, which halted the advance of the epizootic/epidemic to other regions of the US.

In Latin America, special attention should be called to the problems associated with inactivated vaccines developed in chick embryo cells from virulent strains of VEE, given the high risk that they entail. This type of vaccine is very difficult to inactivate and often contains residual live virus that cannot be detected by ordinary laboratory methods. The residual virus can replicate in the vaccinated equine and give rise to outbreaks of VEE. Indeed, it is suspected that outbreaks have been caused by these "inactivated" vaccines and that such a scenario may account for the infection's leap from Ecuador to Central America in the great epizootic/epidemic of 1969. Some of the outbreaks in Argentina in the 1950s are also considered to be vaccinal in origin (Sabattini *et al.*, 1985). Yet another concern is that the handling of virulent VEE strains poses a risk for personnel in industrial laboratories.

The formalin-inactivated vaccine prepared from the attenuated TC-83 strain was evaluated in a trial of 28 human volunteers. Only a few minor local and systemic reactions were observed. The vaccine was administered subcutaneously in two doses, 28 days apart, and a third dose 6 months later. In volunteers with no prior history of vaccination against the equine encephalitides, the vaccine induced high neutralizing titers that lasted at least 14 months (Edelman *et al.*, 1979).

A monoclonal antibody antipeptide has been isolated that makes it possible to differentiate the VEE virus strains that occur in nature (except subtype VI) from the vaccine strain TC-83. This technique makes it possible to determine whether or not an outbreak is of vaccinal origin (Roehrig *et al.*, 1991).

In addition to vaccination, another highly useful method of controlling the epizootics/epidemics is to prohibit the transportation of equines in order to prevent the infection from spreading. In an emergency, the vectors may be controlled by the aerial application of ultra-low-volume insecticides such as malathion. The best time to apply insecticides is during the peak period of adult mosquito emergence, before they have had a chance to feed on horses and before the virus completes its period of extrinsic incubation in the vectors. Such an operation is costly, and timing of the application is not easy. It is very important to establish and maintain constant epidemiologic surveillance in regions where there have been outbreaks of VEE. Horses are excellent sentinels for this purpose; based on the information they provide, prevention activities can start up with the vaccination of equines and reduction of the mosquito population. Another measure of risk is the level of infection in the mosquito vectors.

Personal prevention measures include the use of protective clothing, repellents, and screens in windows and doors.

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VENEZUELAN HEMORRHAGIC FEVER

ICD-10 A96.8 Other hemorrhagic fevers caused by arenaviruses

Etiology: Guanarito virus is a new member of the Tacaribe complex, genus *Arenavirus*, family Arenaviridae (for more details on this family, see the chapter on Argentine Hemorrhagic Fever).

Geographic Distribution and Occurrence: In September 1989, an outbreak of hemorrhagic disease occurred in the municipality of Guanarito, Portuguesa State, in the central plains (Los Llanos) of Venezuela. The disease was thought to be dengue until the Guanarito virus, with characteristics of an arenavirus, was isolated.

A total of 104 suspected cases were recorded between May 1990 and March 1991, and 26 of those patients died. They were all rural inhabitants of the municipality of Guanarito in the state of Portuguesa and adjacent areas of the state of Barinas. In 1992, sera from 195 persons in the endemic area were examined, and 2.6% of them had antibodies to Guanarito virus. These preliminary observations suggest that the prevalence of infection is relatively low, whereas the proportion of persons who become gravely ill is relatively high (Tesh *et al*., 1993). Epidemiological information suggests that Venezuelan hemorrhagic fever (VHF) behaves cyclically, with high-incidence epidemics occurring every four to five years (Salas *et al*., 1998). The period of peak incidence is from November to January, the months of high agricultural activity in the endemic region (de Manzione *et al*., 1998). Few cases are reported during the interepidemic periods (Salas *et al*., 1998).

When the Guanarito virus was isolated and found to have characteristics of an arenavirus, researchers thought the reservoir might be a rodent, as in the case of the other arenaviruses. When 11 wild rodents were captured for the purpose of a small

epidemiologic study, Guanarito virus was isolated from the hispid cotton rat *Sigmodon hispidus*, and antibodies to this agent were found in rice rats of the genus *Oryzomys* (Salas *et al*., 1991). Tesh *et al.* conducted a broader investigation in 1992 (see Source of Infection and Mode of Transmission).

The Disease in Man: Fifteen patients from Guanarito, ranging in age from 6 to 54 years old, were the subject of clinical, virologic, and serologic studies (Salas *et al*., 1991). The most salient symptoms were fever, prostration, cephalalgia, arthralgia, cough, pharyngitis, nausea, vomiting, diarrhea, epistaxis, bleeding gums, menorrhagia, and melena. Other symptoms were conjunctivitis, cervical adenopathy, facial edema, pulmonary crepitation, and petechiae. Most of the patients had thrombocytopenia and leukopenia. Nine of the 15 patients died. Autopsy revealed lesions similar to those of other South American hemorrhagic fevers caused by arenaviruses: pulmonary edema with intraparenchymatous and subpleural hemorrhages, hepatic congestion with focal hemorrhages, cardiomegaly, splenomegaly, and blood in the gastrointestinal tract, bladder, and uterus.

Guanarito virus was isolated from the serum and spleen of all the deceased patients and from two of those who survived.

In a study of 57 family contacts of the patients, the indirect immunofluorescence test revealed antibodies to Guanarito virus in 10.5% of them. Some of these contacts reported having had a mild febrile disease, which could indicate the existence of less severe forms of the infection.

Source of Infection and Mode of Transmission: In 1992, field investigations were expanded with a view to determining the reservoir of the infection (Tesh *et al*., 1993). Traps were used to capture 234 rodents of 9 different species in 4 areas of the municipality of Guanarito where human cases had occurred. The virus was isolated from the spleens of 31 rodents of two species—specifically, 19 of 40 specimens of the cotton rat *S. alstoni*, and 12 of 106 specimens of the cane mouse *Zygodontomys brevicauda*. Nine of the 12 *Z. brevicauda* from which the virus was isolated also had serum antibodies to the same agent. On the other hand, none of the *S. alstoni*, from which the virus was isolated in the spleen, were serologic reactors. These findings suggest that *S. alstoni* is a host that develops a persistent infection without immunity, whereas *Z. brevicauda* responds to the infection by forming antibodies. The authors (Tesh *et al*., 1993) concluded that *S. alstoni* is probably the main reservoir of Guanarito virus. Other research has pointed to *Z. brevicauda* as the natural reservoir of the virus, as viremia in this species can be chronic, with persistent shedding of infectious virus in oropharyngeal secretions and urine (Fulhorst *et al*., 1999).

As with other arenaviruses, man probably acquires the infection by contact with infected rodents and their excreta.

Diagnosis: The virus and its antiserum cross-react with other members of the complex in the complement fixation and indirect immunofluorescence tests, but the serum neutralization test is specific and serves to differentiate Guanarito fever from the other hemorrhagic fevers caused by arenaviruses. Definitive diagnosis is achieved by isolating and identifying the virus. The virus grows well in Vero cells or mosquito cells (C6/36). The virus is lethal for suckling mice but not for the adults.

Control: As with all the hemorrhagic diseases caused by arenaviruses, tests for virologic diagnosis should be performed in high-security laboratories.

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VESICULAR STOMATITIS

ICD-10 A93.8 Other specified arthropod-borne viral fevers

Synonym: Sore mouth of cattle and horses, vesicular stomatitis virus disease, vesicular stomatitis fever, Indiana fever.

Etiology: Several single-stranded RNA genome viruses belonging to the genus *Vesiculovirus*, family Rhabdoviridae. The virions of the Rhabdoviridae family are bullet-shaped and measure approximately 70 nm in diameter by 170 nm in length. The nucleocapsid is protected by a bilayered lipid envelope. Another member of this family is the rabies virus, which belongs to the genus *Lyssavirus*.

Vesicular stomatitis (VS) in domestic animals occurs only in the Americas. The disease is caused by four viruses: Cocal virus (COCV) (formerly Indiana subtype 2), vesicular stomatitis Alagoas virus (VSAV) (formerly Indiana subtype 3), vesicular stomatitis Indiana virus (VSIV), and vesicular stomatitis New Jersey virus (VSNJV). Other recognized vesiculoviruses are Piry, Chandipura, and Isfahan. Piry virus is endemic in some areas of Brazil, Chandipura is endemic in India and Nigeria, and Isfahan, in certain areas of Iran. The first two are antigenically related. Experience with natural and laboratory infections caused by Piry and Chandipura viruses indicates that they can produce disease in man and therefore should be

regarded as zoonotic agents. Two additional vesiculoviruses, Carajas and Maraba, were isolated from phlebotomine sandflies in Brazil in 1984. Maraba is antigenically related to COCV, VSAV, and VSIV. A single glycoprotein, protein G, projects from the viral envelope and is the main antigenic determinant, since it produces the neutralizing antibodies (Gearhart *et al.*, 1987). Protein G is also the main factor in the virulence of the agent and in the neutralizing antibodies that confer protection against the disease.

Geographic Distribution: VS is limited to the Western Hemisphere. There are enzootic areas of VSNJV and VSIV in Central America, Colombia, Ecuador, Mexico, Peru, the US, and Venezuela. COCV was isolated in the Bush Bush forest, Trinidad and Tobago, and in Belém, Brazil, from mites found on a rice rat (*Oryzomys* sp.), none of them related to any clinical case of VS, although antibodies were found among equines in Trinidad and Tobago. In Argentina, the clinical disease was diagnosed in horses in 1939, but it was not until 1963, when an outbreak occurred among horses in the province of Salta and later in the province of Buenos Aires, that the infection was confirmed by isolation of the virus. The virus, which apparently affected equines only, was identified as COCV—i.e., the same agent found in Trinidad and Tobago. In Brazil, the disease was confirmed for the first time in 1964, during an outbreak in the state of Alagoas. The outbreak affected mainly mules and horses, although cases were also observed in cattle and humans. The agent was identified as a new virus, VSAV. So far, VSAV has been recognized in Brazil in the states of Alagoas, Minas Gerais, Pernambuco, São Paulo, and Sergipe. In Colombia, the same agent has also been isolated from phlebotomine sandflies (*Lutzomyia* spp.). Transovarial transmission was demonstrated in experimentally infected *L. longipalpis* (Tesh *et al.*, 1987). COCV has been recognized in the states of São Paulo and Rio Grande do Sul. In the latter state, an outbreak affected horses at 15 establishments during the summer of 1978–1979, and the diagnosis was confirmed serologically at that time (Prado *et al.*, 1979).

VS displays two distinct patterns of occurrence in the US. In the southeastern states of Alabama, Georgia, North Carolina, and South Carolina, clinical cases in livestock occurred yearly from the early 1900s until the mid-1970s, when viral activity in that region became focal and limited to isolated wildlife populations. In the southwestern states of Arizona, Colorado, New Mexico, and Utah, outbreaks occur sporadically (approximately every 10 years), with the last cycle of activity lasting from 1995 to 1998. The viral lineages of viruses occurring in the southeast region are different from those seen in the southwest, which for the past 70 years have been more closely related to viruses in endemic areas of Mexico than to viruses that had caused previous outbreaks in the southwest (Rodríguez, 2002).

Occurrence in Man: The precise frequency of the clinical disease is not yet known. The disease often goes unnoticed because of its benign course, its similarity to influenza, and the difficulty of isolating the virus in man. Most human cases have been diagnosed in laboratory workers. Of 74 persons exposed to virulent material or responsible for handling infected laboratory animals, 54 had antibodies to VSIV and 31 (57.4%) of them had clinical symptoms (Johnson *et al.*, 1966). Clinical cases have also been observed under field conditions, although most of these may not have been identified by the correct procedures. Serologic surveys indicate that the prevalence of infection may be high among some populations in enzootic areas (for exam-

ple, in a rural locality in Panama more than 90% of the adult population were affected). As in other endemic situations, the rate of reactors increases with age. In four selected rural communities in Panama, the rates of positive reactions to VSNJV and VSIV in the serum neutralization test were 21% and 9%, respectively, in the 0- to 5-year age group and 80% and 63% among 16- to 20-year-olds (Tesh *et al.*, 1969). Seroprevalence is especially high in the tropics, where the disease in animals is enzootic. The average prevalence of serologic reactors in Central American countries was found to be 48% (Johnson *et al.*, 1969). On the other hand, during the 1982–1983 epizootic in Colorado, US, a study carried out among veterinarians and veterinary students showed a prevalence of 22% among 48 individuals who had been sickened by VSNJV versus 5.8% among 52 persons who had not been exposed (Reif *et al.*, 1987). In two small towns in the area of Santander del Norte, Colombia, where VSAV was isolated from phlebotomine sandflies, the seroprevalence rates were 63% and 83%, respectively. Since these rural inhabitants had limited access to medical care and diagnostic laboratories, the disease had gone undiagnosed or had been mistaken for some other febrile condition (Tesh *et al.*, 1987).

Occurrence in Animals: The infection occurs in cattle, equines, swine, sheep, wild animals, and, more rarely, in goats. In a study conducted in Panama, antibodies to VSIV were found in arboreal and semiarboreal species, and to VSNJV, in bats, carnivores, and some rodents (Srihongse, 1969).

VS is endemic in forested plains in tropical and subtropical areas of the Americas, where the virus persists in one or several wild hosts yet to be identified, and where the disease reappears in domestic animals almost every year. On the other hand, in the temperate zones of the hemisphere, VS appears in epidemics at irregular intervals, and there is no evidence that the virus persists during interepidemic periods (Hanson, 1981).

In enzootic areas, the disease spreads slowly and the number of animals with clinical symptoms is relatively small. Serologic surveys in cattle have shown the presence of antibodies at all ages, with higher reactor rates in older animals. Several Central American countries have had explosive outbreaks, especially in swine, which have caused heavy losses.

Epizootics occur at irregular intervals both north and south of the tropical endemic area. In the US, these episodes have occurred about every 10 years in the upper Mississippi Valley and in the Appalachian and Rocky Mountains. The infection tends to spread irregularly rather than contiguously, and adjacent farms may often be unaffected. As a rule, VS spreads more slowly than foot-and-mouth disease, and it usually affects fewer animals, with an attack rate ranging from 10% to 100%.

The epizootic in the US caused by VSNJV began in Arizona in May 1982 and ended up affecting 14 states, reaching as far as Oregon, Washington, and Wyoming in the north. This epizootic is thought to have originated in Central America, traveled up through Mexico, and crossed into the US through Arizona. The phenomenon affected 829 livestock establishments (American Veterinary Medical Association, 1983). At the end of 1982, the disease reentered the state of California, having been absent since 1945. Reintroduction of the infection was attributed to infected cattle that had been purchased in Idaho (Hansen *et al.*, 1985).

Central America and Mexico constitute a VS enzootic area. In South America, the

countries most affected by VS in 1992 were Colombia and Peru. In Argentina, the disease was reported among equines in 1939, and in 1963 an outbreak caused by COCV again occurred in these animals. In Pará, Brazil, COCV was isolated in 1962, and VSAV was isolated in 1964. In 1984, more than 100 foci appeared in the state of Minas Gerais and in the northeast of Brazil, with cattle, equines, swine, goats, and sheep affected by VSAV (Astudillo *et al.*, 1986).

The rate of inapparent infection is always greater than that of apparent infection. Epidemiologic studies conducted at 16 livestock establishments during epizootics in the US revealed that, while the rate of sick animals was 7% among cattle and 42% among horses, the incidence of serologic reactors was 74% and 67%, respectively (Reif *et al.*, 1983).

There have also been outbreaks of the disease in endemic areas such as Central America and northern South America. In some countries, the relative importance of VS among the vesicular diseases can be significant, as shown by Colombian data: of 477 samples received for diagnosis in 1972, 283 were positive for foot-and-mouth disease and 145 for VS (109 for VSNJV and 36 for VSIV) (Cadena and Estupiñán, 1975).

The disease is seasonal: it occurs in summer in temperate climates and immediately after the rainy season in tropical climates.

The Disease in Man: The incubation period is one to two days. The symptomatology resembles that of an acute flu-like illness, with pyrexia lasting one or two days, cephalalgia, retroocular pain, and myalgia. Other signs that may be seen are vesicles in the mouth or pharynx or on the hands, and nausea, vomiting, and diarrhea. Although it is usually a mild and brief illness, and patients return to normal within a few days, some cases may require hospitalization. A case of severe encephalitis occurred in a 3-year-old Panamanian child who was hospitalized for 40 days and discharged with grave sequelae. A similar case occurred in a child in India, in which the Chandipura vesiculovirus produced severe and ultimately fatal encephalopathy (Quiroz *et al.*, 1988).

The Disease in Animals: According to an epidemiologic study conducted during an outbreak of VS due to VSNJV in California, US, the average incubation period was 8.9 days, counting from the date on which susceptible cattle were introduced into a dairy herd (Thurmond *et al.*, 1987). The symptomatology is similar to that of foot-and-mouth disease, for which it can easily be mistaken. The disease is characterized by a brief febrile period and the appearance of papules and vesicles in the mouth, on the udder, in interdigital spaces, and on the coronary band. Profuse salivation is often the most prominent symptom. In cattle, the papules do not always become vesiculated. Under experimental conditions, only 30% of the animals developed evident vesicles. The site of the lesions can vary from one outbreak to another; sometimes the oral site is predominant, while in other instances the mammary site is seen more often. Pedal lesions are not present in every outbreak, and they tend to be more frequent in swine and equines. The animals usually recover within a week. The disease caused by VSNJV tends to be more serious than that produced by VSIV (Mason, 1978). The most common complications are secondary bacterial infections, myiasis, and mastitis. Case fatality is low. The disease can cause appreciable economic losses, especially when it affects dairy cows and swine. In dairy cows, there is a reduction in milk production. It is not uncommon to see vesicular lesions on the udders and teats of cows, and mastitis can be a sequela of secondary infection.

Source of Infection and Mode of Transmission: The ecology of the agents of VS is still not well understood, and there are many gaps in knowledge about the basic cycle of infection. There are numerous unanswered questions about where and how the viruses maintain themselves in nature, how they are transmitted from one animal to another, and how it is introduced into herds that are free of the infection. It is possible that VSNJV and VSIV have different cycles.

The infection caused by VSIV in enzootic areas is common in wild arboreal or semiarboreal animals. The agent has been isolated from phlebotomine sandflies and *Aedes* mosquitoes, and it was confirmed that the phlebotomine sandfly *Lutzomyia trapidoi* can transmit the infection transovarially to its progeny and, in the laboratory, they can infect mice by biting them. Also, serologic conversion has been observed in sentinel monkeys placed in individual cages in the Panama jungle, which is an endemic area for VSIV. These findings, along with the fact that the disease occurs during the season when arthropods are abundant, suggest that there might be a cycle between wild animals and arthropods. However, this hypothesis has been challenged for several reasons. For one, the viremia observed in various animals experimentally exposed to the virus has been insufficient to infect biting arthropods, and also, the rate of infection in arthropods is low. Moreover, transmission by arthropods could not account for oral lesions, among other phenomena, since vesiculation in the oral cavity is produced only by experimental inoculation. Another factor that would argue against this explanation is the irregular distribution of the disease during outbreaks, when it sometimes skips over contiguous farms. Finally, there have been epizootics during which the virus could not be isolated from arthropods. Other hypotheses that have been suggested are that the virus is in the soil or grass that the animals graze on and that they become infected through inoculation of the skin or oral mucosa, or else that the reservoir of the virus is a plant or insect and vertebrates are only accidental hosts. It has also been suggested that the mode of transmission may be different in enzootic situations, in which arthropods play an important role, and epizootics, in which several mechanisms may be involved at the same time.

During the 1982 epizootic in the US, VSNJV was isolated from various dipterans—*Culicoides variipennis* (the biting midge) (which in that country is a vector for the bluetongue disease virus), Simuliidae, Chloropidae, Anthomyiidae, *Musca domestica*, and *M. autumnalis*—but it is still not known whether these insects can play the role of biological vector or contribute to dissemination of the virus by mechanical means (Walton *et al.*, 1983). A study conducted on Ossabaw Island off the coast of Georgia, US, where VSNJV circulates every year, showed that the infection is transmitted in microhabitats. As confirmed by the seroconversion of both domestic and wild sentinel swine, the cycle begins in late spring. According to epidemiologic criteria, the phlebotomine sandfly *Lutzomyia shannoni* would be both the vector and the reservoir of the virus: the insect feeds on mammals, including wild pigs; its range of activity is limited, and its distribution on the island appears to correspond to the distribution of the virus. The agent was isolated from 6 of 610 pools of *L. shannoni*, and the incidence of seroconversion in wild pigs was 50% from April to August 1988 (Corn *et al.*, 1990). It was also possible to demonstrate experimentally that the virus replicates itself in these dipterans and that they can transmit the infection by biting suckling mice or adult hamsters. It has also been demonstrated that the virus is transmitted transovarially, but in only a small percentage of the cases studied (Comer *et al.*, 1990). As the Ossabaw Island study sug-

gests that phlebotomine sandflies are both vectors and reservoirs of VSNJV, this possibility cannot be ruled out for VSIV as well. The Carajas and Maraba viruses have also been isolated from phlebotomine sandflies.

The endemic tropical areas have a large number of wild animal species that react to serologic tests, which may implicate them in the ecology of the agents of VS. However, so far it is not known whether they are reservoirs for survival of the agent in nature or simply accidental hosts. An ecological study carried out in Antioquia, Colombia, revealed a very high rate (30% to 40%) of wild animals with antibodies to VSNJV and VSIV, both at low montane elevations and on the coastal plain. In the dense montane forest conditions, where there are few domestic animals, the presence of high reactor rates in wild animals would suggest that the VS viruses have a wild cycle apart from their circulation in equines, cattle, and swine (Zuluaga and Yuill, 1979).

Although the ecology and epidemiology of VS remain unclear, there is enough evidence to state that during the milking process the infection can be transmitted directly from a cow with infected teats to one that is healthy. Infection may also be transmitted by ingestion when there are preexisting abrasions or wounds on the epithelium. In this connection, it has been noted that equines with lesions rub their lips against various objects, including the edges of the feed trough, and that cows with lesions on their teats contaminate milking machines. The latter route has been demonstrated experimentally: when swine were fed embryonated acarids together with the virus, vesicles appeared on the snout where there had been breaks in the skin. Presence of the virus in saliva, coupled with the frequency of preexisting lesions on the animals' skin and oral mucosa, suggests that direct contact could play an important role, at least in transmission of the disease caused by VSNJV, although some authors downplay the importance of this possibility. One study found that contact transmission occurred only when vesicular lesions were apparent, and that it occurred quickly, with pigs infected by contact shedding the virus as soon as one day postexposure (Stallknecht *et al.*, 2001). During the 1982 epizootic in New Jersey, US, it was demonstrated that outbreaks of the disease in four states coincided with the arrival of infected bovine herds from outside the state. Another salient finding has been the observation that animals recovering from the disease developed new lesions after being transported to other areas, suggesting that there are latent infections that become apparent as a result of stress. Nonsystemic transmission of a VS virus with *Simulium* sandflies—without the host developing viremia—has been demonstrated and may explain the transmission mechanism in systems in which it has not been possible to identify the veterbrate hosts (Lord and Tabachnick, 2002).

None of the hypotheses regarding persistence and transmission of the virus is satisfactory. The scenarios of transmission by vectors, plants, and direct contact all have gaps and raise unanswered questions (Mason, 1978). The findings from the US epizootic of 1982 tie in with the possibility that transmission occurs from direct contact and that the virus persists in the animal in an inapparent form. Further study is needed to clarify the ecology and epidemiology of VS.

Man contracts the infection through contact with domestic animals, either by inhaling aerosols via the nasopharyngeal route, or by contact with abrasions on the skin. The direct sources of infection may be saliva, exudate or epithelium from open vesicles, or the virus itself when it is handled in laboratories. The virus is not shed in the animal's milk, and there is no knowledge of infection via the digestive tract.

Diagnosis: The diagnosis of VS in man is based mainly on serologic testing (complement fixation and serum neutralization). Two blood samples should be obtained, one at the beginning of the disease and the other two weeks later, to verify the increase in antibody titer. Viremia in man is of very short duration, and it is difficult to isolate the virus from blood. When there are vesicles, an attempt should be made to isolate the agent.

In domestic animals, rapid laboratory diagnosis is very important in order to distinguish VS from foot-and-mouth disease. It is not foot-and-mouth disease when horses are affected at a given establishment in addition to ruminants and swine, because equines are resistant to foot-and-mouth disease. The most useful test is complement fixation with vesicular epithelium as antigen. An indirect method has been developed based on the enzyme-linked immunosorbent assay (ELISA), which is comparable to the serum neutralization test in terms of sensitivity and specificity but is more laborious. When polyclonal and monoclonal sera are used in an indirect ELISA sandwich, VSIV can be typed and subtyped (Alonso *et al.*, 1991). At the Pan American Foot-and-Mouth Disease Center, the indirect ELISA test is used to distinguish the three types of foot-and-mouth disease from VS. VSIV is identified using polyvalent serum, and VSNJV with monovalent serum. This procedure has been more satisfactory than complement fixation using epithelial samples from infected animals (Gomes *et al.*, 1989). The virus can be isolated easily from vesicular epithelium or fluid in embryonated eggs or Vero cell cultures and also by intracerebral inoculation of suckling mice.

Control: To prevent the disease in man, safety procedures should be followed in laboratories, especially with regard to avoiding the production of aerosols. Persons who handle sick animals in the field—veterinarians, dairy workers, and others—should be provided with protective clothing and gloves. Lesions should be properly treated.

Because of the gaps in current epidemiologic knowledge about the disease, it is not possible to set up programs to control the infection in animals, but prohibiting the transport of sick and exposed animals can help to reduce spread of the disease. Natural immunity is short-lasting. Not only do cattle that recover from one virus type remain susceptible to the other type, but some herds have been known to become reinfected with the same virus type as many as three times in the course of a single year. Swine appear to be more resistant to reinfection.

Vaccines are in the experimental stage. Some of them have proven useful during epizootic waves and under enzootic conditions. Inactivated live virus vaccines have been studied using various adjuvants (Arbaláez *et al.*, 1982). An inactivated commercial vaccine developed with VSNJV was widely used in the state of Colorado, US, during the 1982–1983 epizootic, but the results of the evaluation were not satisfactory. In an experimental trial with a dairy herd, this formalin-inactivated vaccine was administered intramuscularly in 2 doses 30 days apart. A high neutralizing antibody titer was obtained after the second dose, but by day 175 postinoculation the titer had dropped to a low level. Although neutralizing antibodies are known to protect against infection, in this case it is possible that they do so for only a short time (Gearhart *et al.*, 1987), which means that revaccination would have to be undertaken annually or even more often. Since epizootics occur every few years in the US, it is doubtful that vaccination would be cost-effective.

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VIRAL HEPATITIS OF MAN AND NONHUMAN PRIMATES

ICD-10 B15 Acute hepatitis A; B16 Acute hepatitis B; B17 Other acute viral hepatitis; B18 Chronic viral hepatitis; B19 Unspecified viral hepatitis

Currently, five different primary agents of hepatitis are distinguished. The viruses are designated by the letters A, B, C, D, and E. Although the viral hepatitides are a major public health problem, here they are discussed solely from the zoonotic standpoint—i.e., their capacity to be transmitted between man and other primates.[1]

Synonyms: Viral hepatitis A: epidemic hepatitis, epidemic jaundice, infectious hepatitis; viral hepatitis B: serum hepatitis, Australia antigen hepatitis; viral hepatitis C: parenterally transmitted non-A non-B hepatitis, post-transfusion non-A non-B hepatitis, non-B transfusion-associated hepatitis; viral hepatitis D: delta agent; viral hepatitis E: enterically transmitted non-A non-B hepatitis.

Etiology: The hepatitis A virus (HAV) has been characterized and classified as an RNA genome virus. It is a picornavirus, very similar to members of the genus *Enterovirus*, family Picornaviridae (Gust *et al.*, 1983). Hepatitis B virus (HBV) is a DNA genome virus belonging to the new family Hepadnaviridae, along with similar viruses found in marmosets, California ground squirrels, and Pekin ducks (Melnick, 1986). Hepatitis C virus (HCV), which previously belonged to the non-A non-B hepatitides group, has the characteristics of a single-stranded RNA genome flavivirus, measures 30 to 50 nm in diameter, and has a lipid envelope. The agents of hepatitides B and C are transmitted by the parenteral route.

Hepatitis D virus (HDV), or the delta hepatitis agent, requires coinfection with HBV to complete its replication cycle. HDV requires HBsAg provided by HBV to synthesize its own envelope protein, which is used to encapsulate the HDV genome. The core protein (delta antigen) is found toward the interior of the particle and, together with the single-stranded RNA genome, forms the nucleocapsid. The RNA of HDV does not show hybridization with the DNA of HBV. This agent can be found in acute coinfection with HBV or in a superinfection in HBV carriers.

Hepatitis E virus (HEV) also belongs to the non-A non-B hepatitides group, but it is transmitted enterically. The virus has not yet been fully characterized, but the following facts are known: it is a single-stranded RNA genome virus and is spherical, measuring 32 to 34 nm in diameter; it has no envelope; and it is highly labile (Bradley, 1990).

Geographic Distribution: The hepatitis A, B, C, and D viruses are distributed worldwide. Epidemics have been caused by the HEV virus in Algeria, China, India, Libya, Myanmar, Nepal, Pakistan, Somalia, and the former USSR. The attack rate is higher in young adults than in other age groups. Most of the epidemics started from a water source, but there have also been outbreaks and sporadic cases whose origin could not be determined.

[1] For further information, see Oubiña and Fay (1991) and Benenson (1990).

Occurrence of Zoonotic Cases: Since the first outbreak, which occurred in 1958–1960 on an Air Force base in the US, there have been more than 200 human cases in that country of hepatitis infection associated with nonhuman primates. Secondary cases have been observed in only two separate outbreaks (Deinhardt, 1976). It is likely that all these cases were caused by HAV and that chimpanzees were the main species involved, although other species of nonhuman primates have been considered.

Several surveys have been undertaken to determine the prevalence of HAV and HBV in nonhuman primates. In captive chimpanzees the prevalence of HBV antibodies (anti-HB) increases with age and can be 80% or higher in animals over 10 years old. Up to 25% of chimpanzees captured in the jungle have been found to have HBV antibodies when they were examined a few weeks or months after arrival at their destination. It was found that 10 of 26 chimpanzees being kept by a distributor in Africa were already positive for HB_sAg[2]. These findings suggest that the infection might have resulted from human transmission shortly after the animals were captured, but the possibility that HBV occurs naturally in these primates should not be ruled out (Deinhardt, 1976). At a primate center in the US, tests on sera taken from seven nonhuman primate species and from the center's human personnel found that 2.4% of 82 serum samples from chimpanzees and 1.6% of 62 human serum samples were HB_sAg positive, and 29.9% of the chimpanzees, 36.2% of the baboons (*Papio cynocephalus*), 5% of the squirrel monkeys (*Saimiri sciureus*), and 11.3% of the humans had antibodies to HB_sAg (Eichberg and Kalter, 1980). Five of nine chimpanzees at the London Zoo were found to be carriers of HBV and the remaining four had antibodies to the virus. Three of the carriers were born at the zoo to a carrier mother or father, suggesting that perinatal transmission may have occurred as it does in humans (Zuckerman *et al.*, 1978). The prevalence of HAV antibodies at the primate center mentioned earlier was even higher, and the number of reactive species was greater. In Panama, of 145 recently captured owl monkeys (*Aotus trivirgatus*), only 2 were found to have antibodies soon after their capture, but almost all of them reacted serologically after being kept 100 days in the colony of a scientific institute there (Lemon *et al.*, 1982). In South Africa, sera from 13 captive nonhuman primate species were examined, and HAV antibodies were detected in 7 of the species. Four baboons (*Papio ursinus*) examined serologically four weeks after they were captured had IgG antibodies, indicating that the infection may have originated before their capture. The fact that HAV antibodies have been found in recently captured nonhuman primates in widely separated geographic areas, from Malaysia to South Africa, suggests that the jungle may harbor foci of HAV or some other similar virus (Deinhardt and Deinhardt, 1984). To see if monkeys can really become infected in nature before contact with man, cynomolgus monkeys (crab-eating macaques) (*Macaca fascicularis*) living in remote areas of Malaysia far from human habitation were captured and examined serologically within the first 3 days after their capture.[3] There were two groups, one of 54 monkeys taken from the depths of the primary jungle, and a second group of 52 monkeys from an area imme-

[2] HB surface antigen (HB_sAg) can be detected in human serum several weeks before symptoms appear and from days to months afterward and persists in chronic infections.

[3] In experimentally infected chimpanzees, antibodies have been detected as recently as 16 days after exposure (Cohen *et al.*, 1989).

diately adjacent to a palm oil plantation. Examination by radioimmunoassay revealed HAV antibodies in 18 of the 54 animals in the first group and in 6 of the 52 in the second group. These results indicate that there may be a wild cycle of HAV (Burke and Heisey, 1984). Calculating the age of the animals on the basis of their weight, the authors estimated that at 3 to 4 years of age monkeys living in the jungle have a seroprevalence rate of 50%. Other investigators (Smith *et al.*, 1980; *Lancet*, 1981) have also established the existence of HA in naturally infected monkeys.

A strain of the virus isolated in Panama from a recently captured owl monkey (*A. trivirgatus*) and from other monkeys is antigenically indistinguishable from the human HAV reference strain MS-1, but it propagates more rapidly both in monkeys and in monkey tissue cultures. Moreover, the two viruses proved to be similar in cross-neutralization studies and preliminary assays with monoclonal antibodies (Lemon and Binn, 1983). At the same time, however, genomic heterogeneity has been demonstrated between human HAV strains and those found in monkeys (Lemon *et al.*, 1987; Brown *et al.*, 1989).

The Disease in Man: When the human disease is associated with nonhuman primates, the infection is usually mild and short-lived, and it is clinically indistinguishable from HA acquired usually as a result of contact with infected persons or of ingestion of contaminated water or food. The incubation period is 3 to 6 weeks—much shorter than that of HB (serum hepatitis), in which the average is 60 to 90 days. The zoonotic disease has a sudden onset, with fever, nausea, and anorexia. The patient may or may not exhibit jaundice. In some individuals the disease is identified only by hepatic function tests. No deaths have been recorded.

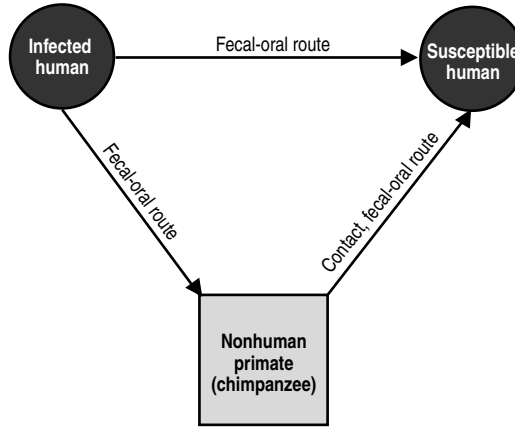
The Disease in Animals: As far as it is known, the only animals that can be infected naturally are nonhuman primates. The infection tends to be clinically inapparent. Those cases with clinical symptoms of liver involvement are thought to be caused by intercurrent disease.

In an outbreak of five human cases in Pennsylvania in the US, the serum of the chimpanzee that caused it had 85 IU (normal: 0 to 15 IU) of glutamic-oxaloacetic transaminase and 2 mg/dL of bilirubin (normal: 0.1 to 0.5 mg/dL).

Once it was known that the infection can be transmitted naturally from nonhuman primates to humans, and that the infection in animals is biochemically and histologically similar to the form that occurs in man, efforts were stepped up to use these animals as models. As a result, significant advances have been made in knowledge about the viral hepatitides in man. Currently, the animals being used most often in studies are marmosets, and the species *Sanguinus mystax* appears to be the most susceptible. The infection in marmosets can be transmitted regularly in series by both parenteral and oral routes. Some specimens of experimentally infected *S. mystax* develop clinical disease and have even died from acute hepatic insufficiency, but they usually recover. These animals have not been observed to develop either chronic hepatitis or cirrhosis of the liver (Deinhardt, 1976).

Source of Infection and Mode of Transmission (Figure 30): Probably all human infections acquired from close contact with nonhuman primates are caused by HAV. Of 173 human patients who had been in contact with a single nonhuman primate species, 151 contracted the disease from chimpanzees and the remaining 22 from other simians. Almost all the cases originated from contact with young animals

Figure 30. Hepatitis A transmitted by nonhuman primates. Probable transmission cycle.



that had been recently imported, the time when they require the most assiduous human care. No human infection was caused by animals that had been in captivity for more than 6 months. The cases occurred among workers at research institutes, primate centers, and zoos; persons engaged in importing nonhuman primates; and, sometimes, members of families that had acquired monkeys and were keeping them in their homes.

The route of infection is fecal-oral. Since chimpanzees customarily handle their feces and even ingest them, humans have ample opportunity to become infected by contact with the hands, mouth, and skin of these animals. Nonhuman primates acquire the disease from their own kind when they live in the jungle and from other simians and man when they are in captivity. When infected animals are introduced into a colony, the infection spreads to the others. The infection can travel both from human to animal and from animal to human, as well as from animal to animal. The most important source of infection for man is man, who is the principal reservoir in human communities. In Africa it is common practice to capture young chimpanzees and keep them in the home, where they are in close contact with people. Also, many chimpanzees approach human dwellings in search of food from cultivated fields, and thus they may also become infected by contaminated waste. Also, collectors inoculate some of these animals with human serum to protect them against human diseases, and this might explain how they acquire HBV infection.

A study conducted in a colony of *A. trivirgatus* in Panama (Lemon *et al.*, 1982) showed that HAV was present in the feces of most infected monkeys before antibodies appeared. The viruses could not be distinguished antigenically from the agent of human HA. Evidently, genetic differences, but not antigenic differences, between the viruses in monkeys and humans do not constitute a barrier to interspecies infection with human HAV.

The preponderance of chimpanzees in human HAV infection associated with nonhuman primates may be explained by the fact that these apes, especially the young ones, have more contact with man. Still, it has been demonstrated on several occasions that the infection can be transmitted to man by other nonhuman primates.

Despite the high seroprevalence of HBV in nonhuman primates, there are no documented cases of its transmission to man. Chimpanzees at the London Zoo were found to have high serologic titers presumably caused by HBV, but no human cases were recorded. This may be explained by the lack of prolonged contact between the keepers and the chimpanzees, a condition that appears necessary for nonparenteral transmission of HBV to man (Kessler *et al.*, 1982). It should be remembered that HBV is usually transmitted by transfusions, contaminated needles, and exposure to infected blood. Vertical (mother-to-child) transmission of HBV is important in humans, but it has not been proven to occur in nonhuman primates. HB_sAg has never been detected in simians, which suggests that natural HBV infection may not occur in these species. Unlike HAV, HBV is not transmitted by the fecal-oral route.

Role of Animals in the Epidemiology of the Disease: The participation of nonhuman primates in the epidemiology of human hepatitis is minimal. Man is the main reservoir of the viruses, and nonhuman primates are seldom implicated in human infection.

The real importance of demonstrating the presence of natural infection in these animals and its transmission to man is that these animals have been shown to be suitable models for studying the human disease. Their use for this purpose has led to major advances in knowledge about the hepatitides.

Diagnosis: Human hepatitis cases contracted from nonhuman primates have been classified as HA and differentiated from HB on the basis of their shorter incubation period and the invariably negative results of tests for the HB ("Australia") surface antigen. This conclusion contradicts some of the earlier findings. Specific diagnosis of HA can be made by verifying the presence of virus particles or specific antigens (HAAg) in feces or by demonstrating a rise in titer and detecting anti-HAV IgM antibodies. The latter approach is the method of choice (Deinhardt and Gust, 1983). The enzyme-linked immunosorbent assay (ELISA) is currently the preferred test and makes it possible to detect antibodies as viral antigens. Specific IgM antibodies can be detected during the 4 to 6 months following onset of the illness. Different associations of serologic markers for HBV have been established to indicate the degree of infectivity of blood or the degree of acquired immunity (Deinhardt and Gust, 1983). An ELISA test has been developed for a non-A non-B hepatitis antigen, and it was possible to infect a chimpanzee with a patient's serum containing this antigen (Duermeyer *et al.*, 1983).

Control: To prevent the transmission of HA from nonhuman primates to man, the following measures are recommended: a) careful personal hygiene and use of protective clothing when primates or their excreta are handled; b) administration of prophylactic doses of immunoglobulin to persons who are in constant or frequent contact with young, recently imported simians, especially chimpanzees; and c) limitation of the number of persons assigned to look after recently imported nonhuman primates.

A commercial laboratory has developed an HA vaccine in collaboration with The

Johns Hopkins Hospital in the US and Hadassa Hospital in Israel. The vaccine was shown to be very effective in a double-blind study of 1,000 children conducted in New York, US (Hoffman, 1991).

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WESSELSBRON DISEASE

ICD-10 A93.8 Other specified arthropod-borne viral fevers

Synonym: Wesselsbron fever.

Etiology: Wesselsbron (WSL) virus, an RNA genome virus belonging to the genus *Flavivirus*, family Flaviviridae[1]; it forms part of the complex of mosquito-borne viruses. Like the other flaviviruses, the virion is round and enveloped, and measures 40 to 50 nm in diameter.

Geographic Distribution: WSL virus has been isolated from both animals and mosquitoes in Cameroon, the Central African Republic, Nigeria, Senegal, South Africa, Uganda, and Zimbabwe, and only from mosquitoes in Thailand. Serologic surveys have shown that the infection occurs throughout a wide area of sub-Saharan Africa. According to the surveys, the virus may also exist in Angola, Botswana, Madagascar, Mozambique, and possibly Ethiopia.

Occurrence in Man and Animals: The virus has a large number of hosts among mammals and possibly also among birds. In low-lying areas of Natal, South Africa, the prevalence of neutralizing antibodies in cattle, sheep, and goats reaches 50%, and several serious epizootic outbreaks have occurred among sheep in southern Africa. Subclinical infection is also common in the human population in enzootic

[1] Formerly arbovirus group B, family Togaviridae.

areas. Studies using the serum neutralization test revealed 36 positive reactors in a group of 83 individuals examined in northern Kenya, 17 from among 54 persons tested in Angola, and 48 out of 141 in Uganda (Henderson *et al.*, 1970). In Uganda, the prevalence varied from one region to another, from zero in the mountainous areas to high in the Nile basin. The infection has been associated with clinical manifestations on at least nine occasions among laboratory or field personnel who had been working with the virus or had handled contaminated material. Despite the virus's wide diffusion and the large number of persons infected, few cases of clinical disease have been recorded, and even fewer cases have been attributed to mosquito bites.

The Disease in Man: The incubation period is two to four days. The symptoms include fever, cephalalgia, arthralgia, myalgia, and sometimes cutaneous hyperesthesia and a mild skin eruption. The fever lasts about two or three days, but muscular pain can persist much longer. However, this clinical picture occurs in only a small proportion of infected individuals. The high prevalence of reactors to the serum neutralization test in endemic areas indicates that the infection is often subclinical or else produces mild clinical symptoms, such as a slight fever, that are attributed to other causes. Patient care consists of treating the symptoms.

The Disease in Animals: The distribution, epizootiology, and clinical symptomatology of Wesselsbron disease are similar to those of Rift Valley fever. The sheep is the most susceptible animal species. In experimental infections, the incubation period has been one to four days. Sheep of any age are susceptible to natural or experimental infection, and neonatal mortality can be high. Pregnant ewes frequently abort, and their fatality rate is high because of the resulting complications. Nonpregnant ewes, on the other hand, have only a febrile reaction without other clinical manifestations. However, during an outbreak in South Africa in 1957, symptoms of the disease included jaundice, nasal discharge, diarrhea, and swelling in parts of the head, with a high fatality rate. It could not be determined whether there was any other concurrent disease during this outbreak. However, it is believed that the WSL virus, which is hepatotropic, might be a triggering factor for "enzootic jaundice," which in that region is associated with chronic copper poisoning. This explanation would account for the high mortality and atypical symptomatology and pathology.

In adult sheep and goats, experimental inoculation of WSL virus produced only a moderate to severe febrile reaction without other clinical signs or death. Histopathologic studies have revealed lesions in the liver in the form of small necrotic foci (Coetzer and Theodoridis, 1982). Viremia developed two days postinoculation and lasted for only one day in an experimental trial with West African dwarf goats in which the animals were inoculated with a Nigerian strain of the virus. The case fatality rate was 100% (Baba *et al.*, 1989).

Cattle, equines, and swine respond to experimental inoculation with a febrile reaction but no other symptoms. However, it is suspected that WSL virus infection can provoke abortions in cattle. In Zimbabwe, where WSL virus is the predominant flavivirus and about 50% of the cattle have antibodies against it, abortions or pathological alterations in the fetus have only occasionally been attributed to this agent. Cattle inoculated experimentally have a febrile reaction and viremia. When one heifer gave birth to a weak calf that died shortly thereafter, the calf already had anti-

bodies to WSL, suggesting an intrauterine infection (Blackburn and Swanepoel, 1980).

In March 1996, there was an outbreak of Wesselsbron virus disease in the northern Free State Province, South Africa, which resulted in the death of lambs on a farm near Bultfontein (Jupp and Kemp, 1998).

Source of Infection and Mode of Transmission: WSL virus infection occurs mainly in low-lying humid areas, where mosquitoes are abundant. The disease is seasonal, occurring from late summer through autumn. The virus has been isolated repeatedly from *Aedes circumluteolus* and *A. caballus*, species that have been shown to transmit the infection in the laboratory. *A. lineatopennis* may also be an important vector. The infection is transmitted from animal to animal and from animals to humans by mosquito bite. In humans, the clinical disease occurs mainly in personnel handling the virus or contaminated material in the laboratory or the field, who acquire the infection by contact or via aerosols.

It is still not fully understood how the virus survives in nature. Sheep and cattle have high-titer viremia for three or four days and can therefore serve as a source of infection for mosquitoes. The virus has been isolated from *Desmodillus*, a wild gerbil in which viremia lasts for one week. Antibodies to the virus have been found in several species of wild birds, and viremia has been demonstrated in birds that have been experimentally infected.

Diagnosis: Laboratory methods, either isolation of the virus or serology, are necessary in order to confirm the diagnosis. For isolation, blood or serum from the febrile patient is inoculated intracerebrally in suckling mice. On one occasion, the virus was isolated from a pharyngeal wash. The virus can also be isolated from the blood (or serum), liver, and brain of an aborted ovine fetus or from the spleen or liver of a dead lamb by inoculating the material in suckling mice or on lamb kidney cell culture. Serologic diagnosis consists of demonstrating seroconversion using the hemagglutination inhibition, neutralization, complement fixation test, or enzyme-linked immunosorbent assay (Williams *et al*., 1997).

Control: An attenuated live virus vaccine is available for the immunization of sheep and is used simultaneously with Rift Valley fever vaccine. Since the vaccine can cause abortion in pregnant ewes, it should be administered three weeks prior to breeding. Lambs born of immune mothers acquire passive immunity through the colostrum. It is recommended that they be vaccinated after 6 months of age.

In laboratories, care should be taken not to expose personnel to the virus or contaminated material. Gloves and protective clothing are required, and measures must be taken to prevent the production of aerosols. The same precautions should be taken during autopsies and field work.

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WESTERN EQUINE ENCEPHALITIS

ICD-10 A83.1

Synonyms: Western equine encephalomyelitis, western encephalitis.

Etiology: Western equine encephalitis (WEE) virus, an RNA genome virus belonging to the genus *Alphavirus* (formerly arbovirus group A), family Togaviridae; it is a member of the complex of the mosquito-borne arboviruses.

WEE virus is part of an antigenic complex that includes 14 other closely related viruses. Several of these viruses are subtypes of WEE virus, and others are subtypes of Sindbis virus; Highlands J (HJ) virus and Aura virus are different from the other members of this antigenic complex (Calisher *et al.*, 1988). The pathogens of inter-

est in this complex are the classic WEE virus and the HJ virus. A comparative study in adult mice of the relative virulence of different components of the WEE complex found that the epizootic strains of WEE virus are neuroinvasive and neurovirulent, while five viruses, including HJ, Fort Morgan, and Aura, are not. The HJ virus proved to be intermediate in virulence between the epizootic and the enzootic strains (Bianchi *et al.*, 1993).

Geographic Distribution: The virus has been isolated in Argentina, Brazil, Canada, Guyana, Mexico, the US, and Uruguay.

Occurrence in Man: In the US, a total of 941 human cases of western equine encephalitis (WEE) were recorded between 1955 and 1978. The annual incidence in that country is highly variable: in 1975, there were 133 cases and 4 deaths, while in 1976, only 1 case was recorded, and in 1982, there were none at all (CDC, 1981 and 1982). The WEE virus ranks third overall among the arboviral encephalitides in the US, after St. Louis and California encephalitis. West of the Mississippi River, there have been both human and equine cases. The largest epidemic occurred in 1941 in the north-central states of the US and the neighboring provinces of Canada, affecting more than 3,000 persons and several hundred thousand equines. Clinical cases of WEE have also been seen in Brazil.

As with other arbovirus diseases, inapparent infections are much more frequent than clinical infections. It has been estimated that there are 1,150 subclinical infections for every case of encephalitis in the population over 15 years of age, and in children under 5 years of age, the ratio is estimated at 1:58. Serologic surveys using the hemagglutination inhibition and neutralization tests have shown that the prevalence of reactors varies and can reach very high levels in hyperendemic areas.

Occurrence in Animals: In the western US, there are epizootics or sporadic cases of the disease in equines every year. In 1937, approximately 174,000 equines, and in 1938 another 184,000, were affected by either western or eastern equine encephalitis. Between 1966 and 1970, there were 7,638 cases of encephalitis in equines, and 1,773 of these died. The WEE virus was responsible for a large number of these cases. Although no human cases were reported in 1992, 9 cases were reported in equines. Serologic surveys using the neutralization test have yielded very high reactor rates in hyperendemic areas. Another virus in the same complex, HJ, is active in the eastern US but rarely causes disease in equines and would appear not to have caused any human cases. It is now accepted that cases of equine encephalitis occurring on the Atlantic coast, except for those caused by the EEE virus, are probably attributable to the HJ virus (Karabatsos *et al.*, 1988). The WEE virus has also been isolated from equines in Argentina, Brazil, and Uruguay. In Argentina, an epizootic affecting 300 horses occurred in late 1982 and early 1983, and the disease was confirmed in provinces where it had not occurred previously (Centro Panamericano de Zoonosis, 1983). That country has had epizootics caused by WEE at varying intervals since the beginning of the 1900s. In the summer of 1972–1973, there was an epizootic that extended over much of the temperate regions in Argentina and Uruguay. After this epizootic, between 1983 and 1985, there were 5 cases presumably caused by the WEE virus among 16 diseased equines from the 13 reported foci. The prevalence of antibodies in sentinel horses was 13% in the province of Santa Fe, where the 1982 epizootic began, and 4% in the province of

Córdoba. The antibodies disappeared in 40% of the equines within a year (Aviles *et al.*, 1993). There were no human cases in Argentina.

The Disease in Man: The disease occurs in the summer months, and the attack rates are highest in young adults and children under 1 year of age. The incubation period lasts from 5 to 10 days. In adults, the onset is abrupt, with fever, cephalalgia, stiffness of the neck, and lethargy, and mental confusion is common. In children, fever, headache, and malaise come a few days before the neurologic symptoms; convulsions are common, as are vomiting, stiffness of the neck, and headache. Flaccid and spastic paralyses, and abnormal reflexes are seen more frequently in children than adults. The febrile state lasts from 7 to 10 days. Adult patients usually recover fully. Permanent sequelae are rare in adults but frequent in children, who may undergo personality changes and suffer from mental retardation, spastic paralysis, and recurrent convulsions. The case fatality rate ranges from 3% to 14%.

Treatment is symptomatic: combating the fever, treating the convulsions (phenytoin), and providing intensive care.

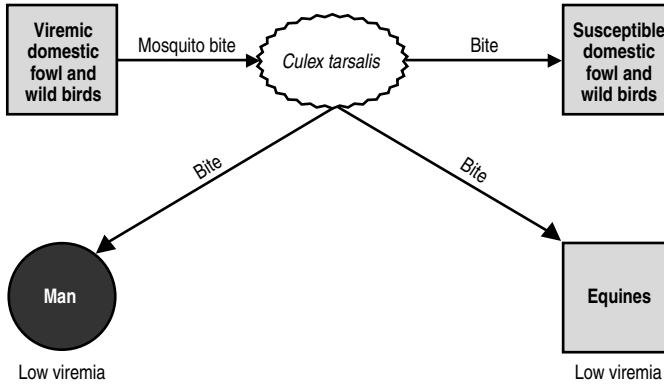
The Disease in Animals: The WEE virus has multiple hosts, but it is manifested clinically only in equines. The disease tends to appear sporadically at the beginning of summer, following which it can reach epizootic proportions, and it ends with the arrival of cold weather, when the mosquitoes disappear. The incubation period lasts from one to three weeks. Fever is the only clinical manifestation before the neurological symptoms develop; by the time the latter appear, the viremia and fever have run their course. As in man, only some equines develop the clinical illness. The principal signs of the neurological phase of the disease are restlessness, unsteady gait, lack of coordination, and somnolence. The animal butts against obstacles, walks around in circles, and becomes totally disoriented. During the lethargic phase, it is common for the animal to stand immobile with its head resting on a fence or some other object. In the final paralytic phase, the animal is unable to get up when it falls, its lower lip is flaccid, and it has difficulty swallowing. Death may come one or two days after the appearance of neurological symptoms. In those animals that recover, neurologic sequelae are common, especially abnormal reflexes. The fatality rate in equines with encephalomyelitic symptomatology ranges between 20% and 30% and can be as high as 50%.

There is no specific treatment. Supportive care is important, including the administration of anti-inflammatory medication, control of convulsions, and close monitoring of sick animals.

Source of Infection and Mode of Transmission (Figure 31): The natural reservoirs of the WEE virus are domestic fowl and wild birds. The virus has been isolated from many species of birds, especially passerines, and including sparrows. In the endemic areas of the western US, antibodies have been found in at least 15 different avian species. Once they are infected, the birds develop viremia with a sufficiently high titer to infect the mosquito vectors. The virus has been isolated from experimentally infected wild birds up to 10 months after inoculation.

The main vector in the western US is *Culex tarsalis*, which is also responsible in the same area for transmission of the St. Louis encephalitis virus. *Aedes dorsalis* also transmits the virus in some regions where it predominates. The basic cycle of infection is maintained by transmission of the virus from a viremic bird to a susceptible

Figure 31. Western equine encephalitis. Transmission cycle.



bird by a vector. Viral activity peaks in early and mid-summer. Wild birds, especially chicks (because of their susceptibility), are the enzootic and amplifying links in the circulation of the virus. The vector *C. tarsalis* occurs widely in irrigated croplands and flooded pastures, as well as along lakeshores. In spring and early summer, the vector is eminently ornithophilous, but in mid-summer it starts to feed more and more on mammals (Monath and Trent, 1981). It has also been demonstrated that different populations of *C. tarsalis* vary significantly in terms of their competence as vectors of the virus (Hardy *et al.*, 1979).

C. tarsalis infects humans and horses when it feeds on their blood, but the clinical disease may not present itself. Nevertheless, both humans and horses are accidental hosts in which the virus produces a low-titer viremia, and for this reason they are not involved in the basic cycle. Thus, the role of the equine in the epidemiology of this disease is very different than it is in Venezuelan equine encephalitis, in which it serves as an important amplifier of the virus. Use of the word "equine" in the name of western equine encephalitis, as well as eastern equine encephalitis, comes only from the fact that the virus was isolated for the first time in this species; it does not mean that equines are a reservoir of the etiologic agent.

The virus's mechanism for overwintering is not yet fully understood, but there are indications that reptiles may play a role. In Utah, US, the virus was isolated from the blood of 37 in a collection of 84 snakes of three different genera (*Thamnophis*, *Coluber*, and *Pituophis*) which had been captured and examined in early spring. The viremia in these animals is cyclical, appearing and disappearing along with changes in the ambient temperature. Viremia disappears during hibernation, but it reappears when the ambient temperature begins to rise, and it reaches levels high enough to infect a large percentage of *C. tarsalis*. Viremia has also been found in the offspring of infected snakes. In Canada, the virus has been isolated from snakes of the genus *Thamnophis* and also from frogs (*Rana pipiens*); neutralizing antibodies were found in 50 of 179 frogs examined. Even so, there is still considerable doubt that infection in reptiles and amphibians is the mechanism by which the virus maintains itself in winter. Three strains of the virus were isolated from adult *Aedes dorsalis* mosqui-

toes collected in the larval stage from a brackish swamp on the California coast. This finding is regarded as proof that the virus is transmitted vertically (transovarially) in this and possibly other related species. Such a mechanism would enable the virus to be maintained during cold weather when there is no horizontal transmission (Fulhorst *et al.*, 1994).

In western Canada, epizootics in equines have occurred in areas where *C. tarsalis* is scarce, and it is suspected that, in this case, the vector may be *Culiseta inornata*, a mosquito adapted to cold climates (Monath, 1979).

In the eastern US, the main vector is *Culiseta melanura*, which transmits the infection between wild birds but rarely to equines. The virus strains that have been isolated from birds, mosquitoes, or sentinel mice in the states of this region and along the Gulf of Mexico all correspond to a single prototype (HJ) and can be distinguished antigenically from the strains of the virus in the western US and Canada. Although these strains found in the eastern states are closely related to the WEE virus, they are considered to belong to a different virus in the same complex. The absence of human cases of the disease and its rarity in equines in the eastern US may perhaps be explained by the habitat of this mosquito (freshwater swamps), its strongly ornithophilic habits, and the low virulence of the HJ strains in mammals (Hayes and Wallis, 1977).

In Argentina, in the provinces of Chaco and Corrientes, the WEE virus has been isolated several times from *Culex ocossa* (Sirivanakarn and Jakob, 1981), which might be the vector of a WEE virus subtype in natural foci. More recently, it was established that *Aedes albifasciatus*, which has been found infected in nature, has the properties of an efficient vector. Mosquitoes of this species caught in the province of Córdoba, Argentina, proved to be highly susceptible to infection by the oral route when they fed on viremic chicks. In assays performed 9 to 16 days after they had fed on the blood of the viremic chicks, they were able to transmit the virus to susceptible chicks upon biting them. The distribution and feeding habits of *A. albifasciatus* are compatible with an epizootic and epidemic vector (Aviles *et al.*, 1992). Subsequent to an epizootic in Argentina, systematic research was undertaken with a view to clarifying the ecology of the disease, which has been the subject of little study in Latin America.

Diagnosis: Either isolation of the virus or serology can be used to obtain a specific diagnosis. It is difficult to isolate the virus from sick humans or equines, since by the time it is recognized clinically the viremic period is usually over. Most of the successful isolations have been from the brain tissue of people or animals who have died from the infection. In the case of equines, a useful sample can be obtained by sacrificing an animal that is already in grave condition, or a collection of samples can be gathered from febrile animals that do not appear to be sick and are grazing together with animals that already have full-blown encephalitis (Walton, 1992). Serologic diagnosis is the demonstration of a four-fold or greater increase in antibody titer in sera obtained during the acute and convalescent phases using the complement fixation, hemagglutination inhibition, serum neutralization, and immunofluorescence test, and the antigen-capture or IgM-capture enzyme-linked immunosorbent assay (Calisher *et al.*, 1986).

Most of the time it is difficult to obtain more than one serum sample from equines. If the serum neutralization test (which by itself detects 80% of infections) is used

together with the complement fixation test (which detects 56.3%) and the hemagglutination inhibition test (which detects 43.8%), a presumptive diagnosis can be obtained with a single sample in more than 90% of the cases (Calisher *et al.*, 1983).

Control: Preventive measures focus on controlling the vector. Satisfactory results have been achieved in areas where programs have been set up for the control of *C. tarsalis*. For individual prevention, the use of protective clothing, repellents, mosquito netting, and metal window screens in dwellings is recommended.

For the protection of equines, a formalin-inactivated chick embryo vaccine is available. The vaccine can be monovalent (against the WEE virus only), bivalent, or trivalent, including protection against the viruses of eastern and Venezuelan equine encephalitides as well (see the respective chapters). The vaccine is administered annually in the spring in two intradermal doses 7 to 10 days apart. Immunity is established about two weeks after the first dose.

An epizootic outbreak in equines, which tends to precede human cases by a week or more, should alert public health authorities to institute control measures. An epidemiological surveillance program should take into account the density of the vector population, its rate of infection, seroconversion in sentinel birds, and the infection rate in birds born that year. In Argentina, the epidemiological conditions were such that sentinel birds failed to provide any useful information, since *A. albifasciatus*, the vector of the WEE virus, is not ornithophilous. On the other hand, equine sentinels did yield useful results.

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WEST NILE FEVER

ICD-10 A92.3

Etiology: West Nile (WN) virus, a single-stranded RNA virus belonging to the genus *Flavivirus*, family Flaviviridae (formerly Togaviridae)[1]; it forms part of the complex that includes the St. Louis, Murray Valley, Japanese, and Rocio encephalitis viruses. In Madagascar, an antigenic study using monoclonal antibodies from 53 strains of West Nile virus revealed that there were five antigenic groups of the virus in that country: four groups closely related to the strain Eg 101 found in Egypt and unlike the strains found in South Africa and India, and one group closely related to the strain found in India. Antigenic variation is observed in each transmission cycle, a phenomenon attributed to the fact that, in Madagascar, the virus is exchanged among migratory birds (Morvan *et al.*, 1990).

Recent outbreaks of WN fever have been accompanied by an apparent evolution of a new virus variant, which can be divided into two lineages. Only members of lineage 1 WN viruses have been associated with clinical human encephalitis. Lineage 2 WN viruses are maintained in enzootic foci in Africa and have not been associated with clinical human encephalitis. Among lineage 1 WN viruses, those causing the recent human and equine outbreaks throughout Europe and Asia have been closely related to a WN virus first isolated in Romania in 1996 (ROM96) and subsequently in Kenya in 1998. The WN virus responsible for the outbreak in the US is genetically distinguishable from the ROM96-like viruses. The closest relative of NY99 virus was that circulating in Israel from 1997 to 2000 (Isr98). The genotype of the NY99 WN virus in the US has remained stable with few genomic changes (Petersen and Roehrig, 2001).

Geographic Distribution: The virus has been isolated from humans, other mammals, birds, and arthropods in Africa (Central African Republic, Democratic Republic of Congo, Egypt, Madagascar, Mozambique, Nigeria, South Africa, and Uganda), Asia (India, Israel, Pakistan, the former USSR, and the island of Borneo), and Europe (Cyprus and France). Moreover, serologic evidence suggests that the infection is present throughout practically the entire African continent and also in Albania, Malaysia, the Philippines, Thailand, and Turkey.

[1] All the flaviviruses belonging to former arbovirus group B have been transferred from the family Togaviridae to the family Flaviviridae.

The outbreak of WN virus in the Western Hemisphere in the summer of 1999 marked the first introduction of an Old World flavivirus into the New World in recent history (Nash *et al.*, 2001). Surveillance showed the spread of viral activity in the eastern and southern US, extending to 12 states in 2000, from the Canadian border to North Carolina, a distance of some 900 km (Marfin *et al.*, 2001). The close genetic relationship between the WN virus isolates from New York and Israel suggests that the virus was imported into North America from the Middle East. The means of its introduction (via infected bird, mosquito, human, or other vertebrate host) will likely remain unknown.

Occurrence: West Nile fever is both endemic and epidemic. In hyperendemic areas, the infection is acquired at a young age and most of the adult population is immune. In regions where the virus is less active, occasional epidemics occur among persons of all ages (Tesh, 1982). The disease is endemic in the Nile delta in Egypt, where it primarily affects children. In Israel, it occurs in epidemic form and clinical disease is observed in a large number of individuals. In South Africa, the disease is sporadic, with some small epidemic outbreaks occurring regularly during the summer. The most extensive West Nile fever epidemic in South Africa occurred in 1974, concurrently with Sindbis fever, in the Karroo region and the northern part of Cape of Good Hope Province. A serologic survey conducted after the epidemic showed that 55% of the population in the area had been infected by the WN virus and 16% by Sindbis virus (McIntosh *et al.*, 1976). Serologic studies using the serum agglutination test have shown high reactor rates in human populations. Of 1,168 human serum samples obtained in an endemic region of the Nile delta, 61% had neutralizing antibodies against the disease (Taylor *et al.*, 1956). In the Karachi Region in Pakistan, following the occurrence of several cases of encephalitis, a seroepidemiological study of 237 individuals conducted between July and October 1983 and in 1985 using the hemagglutination inhibition and serum neutralization tests revealed a prevalence rate of 50% to 55%, with variations within that range depending on the year and the serologic test used. Of 156 paired sera obtained in 1985, 13% converted to positive and 8% turned negative. The virus had been isolated from *Culex tritaeniorhynchus*. Conversion from positive to negative might indicate that during the period of study there may have been asymptomatic infections in the area (Sugamata *et al.*, 1988). The virus has been isolated from several species of birds, equines, camels, and a bat. High reactor rates to the neutralization test have been seen in horses (183 of 375 animals examined in Egypt), nonhuman primates, cattle, and dogs.

The Disease in Man: Infection in humans can be subclinical or produce symptoms ranging in severity from a passing fever to serious encephalitis. The disease tends to be mild in children and more severe in the elderly. The incubation period lasts from three to six days. The onset of the disease is sudden, with fever, cephalalgia, lymphadenopathy, and a maculopapular cutaneous eruption mainly on the trunk; myocarditis, meningitis, and encephalitis occur less frequently. Fatality rates are insignificant. The level of viremia in humans is low, and lasts approximately six days. The disease occurs during the summer, when mosquitoes are abundant.

The Disease in Animals: Among domestic animals, clinical manifestations have been observed only in horses, but even in this species most infections are asympto-

matic. The characteristic picture is that of meningoencephalitis. A West Nile fever outbreak among equines in Camargue, France, in 1962–1964, produced 10% morbidity with a case fatality rate of 25%.

Little is known about the course of the infection in birds. In crows (*Corvus corone sardonius*) experimentally infected through mosquito bites, the mortality rate was high. Many of these birds have neutralizing antibodies in nature, indicating that a large number of them survive infection. It is probable that the virus can cause disease in other species of birds, as evidenced by the fact that the etiologic agent was isolated from a domestic pigeon captured in Egypt which had clinical symptoms (Taylor *et al.*, 1956).

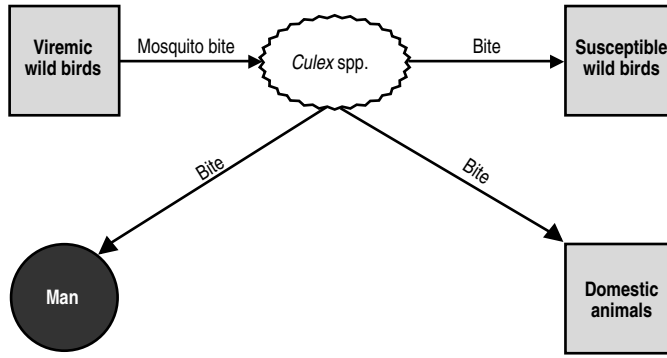
Source of Infection and Mode of Transmission (Figure 32): The WN virus infects a large number of vertebrate hosts, including humans, domestic animals, and several species of fowl. Only birds meet the necessary criteria to serve as a reservoir: they have a high-titer and prolonged viremia that would enable them to serve as a source of infection for the arthropod vector. Moreover, areas within the range of the virus have many birds that reproduce at a sufficient rate to provide enough susceptible young to maintain the infection cycle. The virus has been isolated from pigeons (*Columba livia*), a species of crow (*Corvus corone sardonius*) in Egypt, the long-billed crombec (*Sylvietta rufescens*) in South Africa, and the turtle dove (*Streptopelia turtur*) in Israel. It has also been possible to isolate the virus from wild birds in Borneo, Cyprus, and Nigeria, and its presence has been confirmed by neutralizing antibodies in a number of countries.

Ornithophilic mosquitoes of the genus *Culex* serve as the vector. They become infected when the female feeds on the blood of a viremic bird, and they pass the infection along when they bite a susceptible avian or mammalian host. The virus has been isolated from several species of *Culex.* It is clear that in Egypt, Israel, and South Africa, *Cx. univittatus* plays a key role in transmitting the infection and maintaining the virus in circulation in nature, but the main vector has not yet been definitively identified in other areas. In India and Pakistan, the *Cx. vishnui* complex appears to be important. In Camargue, France, this role is attributed to *Cx. molestus*. A few isolations have been obtained from *Aedes anopheles* and from argasid and ixodid ticks.

It is not yet fully understood how the virus overwinters. One hypothesis holds that the mechanism consists of delayed transmission by mosquitoes that remain active during the cold months. There have been reports of female *Cx. univittatus* found feeding on occasional warm days in winter, and the virus has also been isolated from sentinel pigeons during that time of year. Vertical transmission has been demonstrated in the laboratory in *Aedes albopictus*, *Ae. aegypti*, and *Cx. tritaeniorhyncus* (Baqar *et al.*, 1993) and in argasid ticks (Abassy *et al.*, 1993); experimentally infected *Argas arboreus* ticks have transmitted the virus both horizontally and vertically (Abassy *et al.*, 1993). However, it remains to be confirmed whether transmission occurs naturally in mosquitoes and ticks.

A striking feature of the initial human epidemic in New York City in 1999 was the high number of avian deaths, particularly in American crows (*Corvus brachyrhynchus*) and other corvids. Subsequent work demonstrated fatality rates of almost 100% among American crows experimentally infected with the NY99 WN virus strain (Eidson *et al.*, 2001). A study in 1955 showed high fatality rates among

Figure 32. West Nile fever. Transmission cycle.



Egyptian hooded crows (*Corvus corone*) and house sparrows (*Passer domesticus*) experimentally infected with the prototype Egypt 101 WN virus strain.

In the United States in both 1999 and 2000, infections in humans peaked in August and in horses in September, suggesting either different mosquito species transmitting the virus to humans and horses, or temporal differences in exposure to the same species. In 2000, 14 mosquito species in five states had evidence of WN virus infection (by culture or nucleic acid amplification). *Cx. pipiens* and *Cx. restuans*, the common ornithophilic maintenance vectors of St. Louis encephalitis virus in the northeastern US, were by far the most frequently identified species with WN virus. One important observation in the New York City area was the high virus infection rates and abundance of *Cx. salinarius* mosquitoes on Staten Island in 2000, which temporally coincided with the human outbreak. This species indiscriminately feeds on both birds and mammals and readily bites humans.

Role of Animals in the Epidemiology of the Disease: West Nile fever is a zoonosis transmitted from birds to humans and other animals by mosquitoes of the genus *Culex*. Humans, equines, sheep, and cattle are only accidental hosts of the virus, and they are not involved in the agent's basic cycle. Viremia in equines, sheep, and cattle is low-level, or may even be absent in cattle, and it is incapable of infecting the vector. On the other hand, wild birds have high-titer viremia and can serve as a reservoir. It has been demonstrated experimentally that several species of mosquitoes and argasid ticks are capable of serving as both reservoirs and vectors.

Diagnosis: Laboratory confirmation consists of either isolation of the virus by inoculating blood from acute-phase patients in mice or serologic conversion, primarily by means of the serum neutralization test. In addition, a polymerase chain reaction assay has been developed for rapid detection of the virus (Porter *et al.*, 1993).

Control: A mixed vaccine to prevent human infection with the WN virus and other group B arboviruses is in the experimental stage.

At present, control of the vector is difficult, since the mosquito species that transmit the infection to humans are not yet fully known in the different countries.

Although *Culex* mosquitoes are ornithophilic, they are not always anthropophilic. In some countries where the virus is present, there is probably a vector that serves as a link between the wild cycle and the infection in humans. Should that be found to be the case, controlling the population of that "liaison" vector would be the most logical action to take.

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YELLOW FEVER

ICD-10 A95.0 Sylvatic yellow fever; A95.1 Urban yellow fever

Synonym: Black vomit.

Etiology: Yellow fever virus (YFV), a single-stranded RNA genome virus, genus *Flavivirus* (formerly arbovirus group B),[1] family Flaviviridae, belonging to the complex of mosquito-borne viruses. There is an antigenic difference between the African and American strains. The virion is enveloped, like all the flaviviruses, and measures some 40 nm in diameter. This virus shares antigens with the West Nile, Wesselsbron, and dengue viruses, among others.

Geographic Distribution: Yellow fever (YF) has never become established outside Africa and the Americas. At one time, urban YF, transmitted among humans by *Aedes aegypti*, was a scourge in the Americas from the eastern US all the way to Argentina. Currently, the infection in the Americas is limited to an exclusively jungle cycle, while in Africa, it occurs in both urban and jungle areas. The infection is enzootic in jungles and circulates between mosquitoes and monkeys (and probably other mammals). In Latin America, the areas of greatest activity of the jungle virus are the basins of the Amazon, Magdalena, and Orinoco rivers and the Brazilian regions of Ilhéus (in the northeast) and Mato Grosso. In Africa, the enzootic area extends from Bissau, Guinea-Bissau, in the north to Benguela, Angola, in the south.

Jungle YF in the Americas is constantly on the move within its enzootic areas or ecological niches. Under favorable conditions, the infection extends from permanent foci to adjacent areas via nonhuman primates and mosquitoes. Beginning in 1950, an epizootic wave spread from the Isthmus of Panama to the Guatemala-Mexico border, which is the northern limit of the nonhuman primate hosts of the virus. Cases have also occurred as far south as northern Argentina. While *Aedes aegypti*-borne urban YF has been absent from the Americas since 1942 (except for a few cases reported in Trinidad in 1954), almost every year human cases of jungle YF are reported in different countries of South America.

The only Latin American countries in which jungle YF has not been observed since the existence of this epidemiologic variety was confirmed are Chile, El Salvador, and Uruguay.

[1] All the flaviviruses belonging to former arbovirus group B have been transferred from the family Togaviridae to the family Flaviviridae.

Occurrence in Man and Animals: The World Health Organization estimates that some 200,000 cases of YF occur each year, including 30,000 deaths, over 90% of which occur in Africa (Mutebi and Barrett, 2002). Between 1965 and 1983, a total of 2,252 cases were reported in the Americas. The incidence peaked in 1966 with 304 cases. In 1981–1982, Bolivia, Brazil, Colombia, Ecuador, and Peru reported a total of 368 cases and 183 deaths (a case fatality rate of 49.7%). Except for an epidemic in 1981 in Rincón del Tigre, Santa Cruz, Bolivia, all the cases during that two-year period occurred in known endemic areas. In 1987, a total of 235 cases and 211 deaths were reported in South America. More than 70% of the cases occurred in Peru for the second consecutive year, and the rest were in Bolivia, Brazil, and Colombia. Of the 179 cases in Peru, 170 were fatal. The patients, who came from the highland plateau, were forestry or agricultural workers whose jobs had taken them into endemic areas of the jungle (WHO, 1989). The number of cases of YF reported to the World Health Organization from South America was 237 (with 191 deaths) in 1989, 88 (with 69 deaths) in 1990, 151 (with 90 deaths) in 1991, 119 (with 81 deaths) in 1992, and 175 (with 79 deaths) in 1993 (WHO, 1995).

Jungle YF is mainly an occupational disease of males (farmers, hunters, and workers in forests and on rubber plantations and public roads) whose work takes them into the jungle or nearby areas. In the 1972–1973 epidemic in the state of Goiás, Brazil, which involved 71 confirmed cases and 44 deaths, the ratio of infected males to females was 9:1 (Pinheiro *et al.*, 1978). Serologic surveys conducted among populations living in jungle regions show a high rate of reactors to the group B arboviruses, which include the agent of YF. Hence, the population living in an enzootic area is usually less affected than workers coming from disease-free areas, and it is likely that programs for the settlement of jungle areas in Latin America will expose new human populations to the infection. The age bracket most affected is 20- to 39-year-olds. Most cases occur during the rainy season, when there is a high density of the *Haemagogus* mosquito, the main vector of jungle YF in the Americas. More recently, outbreaks occurred in the Amazon region of Brazil in 1998 and 1999, with 23 cases and 8 deaths, and 24 cases and 8 deaths, respectively (Vasconcelos *et al*., 2001b). During the first half of 2000, Brazil reported 77 cases of jungle YF, of which 39 died (Vasconcelos *et al.*, 2001a).

Urban YF has disappeared from the Americas, but the danger of an epidemic of this type will remain as long as its vector, *A. aegypti*, has not been eradicated from the hemisphere. The habitat of this mosquito is both domestic and peridomestic. The campaign to eliminate *A. aegypti* began in 1947, and by 1960, it had been successfully eradicated from 80% of the infested area, covering nearly 12 million km^2. Unfortunately, implementation of the campaign met with some setbacks, and many countries became reinfested (see the chapter on Dengue, section on control). The risk of an *A. aegypti*-borne infection is always latent, and epidemics of dengue, which is also transmitted by *A. aegypti*, occur in most countries of the Americas. Studies have revealed high densities of the mosquito in a number of areas, an indication that epidemics of urban YF could occur if the virus is transported from its jungle habitat to an urban setting.

In the Americas, the urban YF cycle consists of transmission of the virus from *A. aegypti* to man and back to *A. aegypti*. Four factors are considered to determine the risk of extension of the jungle cycle to cities: 1) the titer and duration of viremia in man; 2) the population density of *A. aegypti* and its competence as a vector; 3) the

frequency of the vector's exposure to viremic patients in urban areas; and 4) the level of immunity of the urban population (Woodall, 1981). It is theorized that by the time patients are taken to a city hospital it is likely that either the viremic phase has already passed or the level of viremia has fallen too low to infect the vector and give rise to an urban cycle. Another factor believed to help prevent the urban spread of YF is the generally high prevalence of antibodies to other flaviviruses, especially the agent of dengue. In reality, however, the conditions that ultimately determine the urbanization of jungle YF are still not known (Groot, 1980). Until these mechanisms are understood, precautionary measures are advised.

Yellow fever can reappear after long periods of inactivity. For example, in 1978–1979, the disease reappeared in Colombia and in Trinidad and Tobago after an absence of 19 years, and in 1981, it showed up in Bolivia after 30 years of epidemic quietude. Following the 1978–1979 Trinidad and Tobago outbreak, which occurred in the country's jungle areas and produced 10 cases with 5 deaths, it was decided to conduct an extensive vaccination campaign, as a result of which 96.4% of the population on the island over 1 year of age was immunized (CDC, 1980; PAHO, 1983b).

In Africa, 33 countries are at risk of YF virus infection (WHO, 1993) and the continent has seen extensive YF epidemics in the last 30 years. In 1960–1962, there were some 100,000 cases in southwestern Ethiopia; an epidemic occurred in Senegal in 1965; and in 1969, there were epidemics in five other countries. The epidemiology of the disease varies from one region to another. The number of cases of YF reported to the World Health Organization from Africa was 3,270 (with 618 deaths) in 1989, 4,248 (with 341 deaths) in 1990, 2,561 (with 661 deaths) in 1991, 176 (with 21 deaths) in 1992, and 218 (with 38 deaths) in 1993. Nigeria accounted for 10,207 of the total reported cases and 1,518 deaths (WHO, 1995). Two types of situations tend to occur in Africa: 1) with urban YF, the virus is transmitted among urban residents by the vectors *A. aegypti* and *Aedes simpsoni*; and 2) with jungle YF, *Aedes africanus*, a mosquito that lives in the rainforest canopy, transmits the infection from monkey to monkey. For its part, *A. simpsoni*, which breeds in vegetation around houses, provides the link between the jungle and the urban cycle, and, with or without the assistance of *A. aegypti*, transmits the infection from human to human (Varma, 1989). The increase in the number of YF cases seen over the past 15 years, particularly in West Africa, where most cases occur, is due in part to a breakdown in YF vaccination and mosquito control programs (Mutebi and Barrett, 2002).

The frequency of the disease in monkeys is difficult to determine. Virus activity in Latin American rainforests often produces high mortality in howler monkeys (*Alouatta* spp.). Serologic surveys conducted in certain enzootic areas of Africa have revealed high reactor rates in various species of nonhuman primates.

The Disease in Man: Serologic surveys in Latin America using the serum neutralization test have yielded reactor rates as high as 90% of the population in enzootic areas. The incubation period of the disease is three to six days after the bite of an infected mosquito, and viremia occurs during the first four days of the disease. Four forms of YF may be identified based on the gravity of the clinical picture, ranging from very mild infection to severe fatal disease (WHO, 1985).

In the first and mildest of the clinical forms, the patients experience fever for a few hours and passing cephalalgia. These cases present an indefinite clinical picture, which is difficult to distinguish from other common febrile conditions.

The second form, which is still clinically mild, is characterized by more intense fever and cephalalgia, and often nausea, epistaxis, and Faget's sign (the pulse is rapid at first and then tends to slow down as the patient's temperature rises); in addition, there is mild albuminuria, sometimes epigastric and dorsal pain, general malaise, vertigo, vomiting, and photophobia.

The third clinical form is moderately severe: the disease has a sudden onset with high fever, cephalalgia, dorsalgia, chills, prostration, nausea, and vomiting. The fever is often biphasic: the first phase, characterized by fever lasting three to four days, is followed by a brief period during which the fever temporarily subsides; it then returns with the onset of the second phase, which is accompanied by hepatic and renal insufficiency and the tendency to develop hemorrhages (for example, "black vomit," melena, or uterine hemorrhage). As the disease progresses, the pulse rate becomes slow relative to the degree of fever present, and the patient becomes hypotensive. Epistaxis and oral and gastrointestinal hemorrhages occur, along with hematemesis ("black vomit") and melena. In addition to the hemorrhages, which are probably caused by the liver's inability to synthesize sufficient quantities of coagulating factors, hepatic involvement is manifested by varying degrees of jaundice (hence the name of the disease). Nevertheless, jaundice is not a constant sign of YF. Renal decompensation is marked by albuminuria and, sometimes, severe renal insufficiency with oliguria and concomitant azotemia.

The fourth clinical form is malignant. In fulminant cases, the patient dies between the sixth and eighth day of the disease. Death comes after one or two days of coma, or else suddenly after an episode of hematemesis, or "black vomiting," with hypothermia. Fulminant cases can occur without hepatic or renal signs (WHO, 1985). If the illness lasts beyond 10 days, the patients tend to recover. In autochthonous populations within endemic areas, the case fatality rate is lower than 5%.

Anatomical pathologic findings are not particularly characteristic of YF. Jaundice, sometimes only slight, may be observed, as well as hemorrhagic lesions in various organs. Histopathology reveals the most characteristic changes. Hepatic lesions include mottled necrosis in the mid-zone, acidophilic degeneration, and adipose metamorphosis. Round bodies produced by acidophilic or eosinophilic degeneration of the infected hepatocytes, known as Councilman's bodies, are typical but not pathognomonic of YF.

Treatment should emphasize careful monitoring of hepatic function, as it is crucial to initiate therapy at the first signs of decompensation. The most significant sign of hepatic dysfunction is prolonged prothrombin time (double the normal value). It is also recommended to maintain adequate nutrition and to prevent hypoglycemia by intravenous administration of a 10%–20% glucose solution. Patients should be carefully observed and treated immediately if hypotension should develop. Prothrombin time should be kept between 25 and 30 seconds by the administration of plasma. If hemorrhaging is present, blood volume should be maintained with fresh plasma (Monath, 1987; PAHO, 1987). Oliguric patients should be monitored for prerenal azotemia and acute tubular necrosis. With prerenal insufficiency, the volume of circulating blood should be optimized. The presence of acute tubular necrosis requires peritoneal dialysis or hemodialysis. The administration of cimetidine is recommended to prevent gastric hemorrhaging. Cephalalgia and fever may be treated with paracetamol.

The Disease in Animals: Jungle YF is a zoonotic infection that circulates between nonhuman primates and mosquitoes in the rainforests of Africa and the Americas.

Knowledge about the symptoms and pathology of the disease in nonhuman primates is based on experimental exposure. The various primate species exhibit different degrees of susceptibility. Thus, for example, African monkeys become infected but few of them die as a result of experimental inoculation, whereas several species of American and Asian monkeys succumb within a few days after developing the illness. The difference is thought to be due to long-term adaptation of the virus in the African monkeys. The infection is of much more recent origin in the Americas and appears to have been introduced by *A. aegypti* from Africa. Experimental studies indicate that six genera of neotropical monkeys are susceptible to the YF virus: owl or night monkeys (*Aotus* spp.), howler monkeys (*Alouatta* spp.), capuchin or white monkeys (*Cebus* spp.), spider monkeys (*Ateles* spp.), marmosets (*Callithrix* spp.), and squirrel monkeys (*Saimiri* spp.). The infection is almost always fatal in howler and spider monkeys. These monkeys play different roles in the jungle cycle of YF. Macaques (*Macaca* spp.), which come from Asia, are susceptible, but they cannot be natural hosts because YF does not exist in Asia.

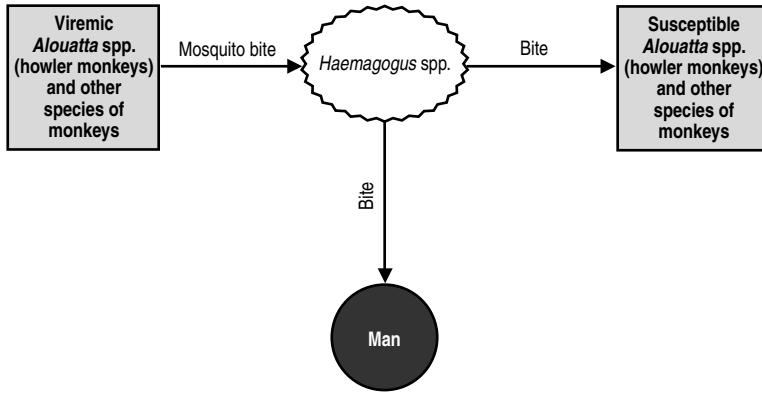
The symptomatology and pathology of YF is similar in monkeys and man, and the liver is the most affected organ. Infection of Kupffer's cells can be observed at 24 hours postinoculation, and acidophilic degeneration precedes hepatocellular degeneration. Tubular renal necrosis occurs in the final 24 to 36 hours.

Source of Infection and Mode of Transmission (Figure 33): There are two epidemiologic varieties of YF: urban and jungle. It is very likely that urban YF originated from the jungle cycle. The only known host of the urban variety is man, and transmission is via the biological vector *A. aegypti.* The mosquito acquires the infection by biting a human host in the viremic phase, and it is able to transmit the infection to another human after 10 to 12 days of extrinsic incubation.[2] Jungle YF, on the other hand, is a zoonotic disease; its main hosts are monkeys, and man is only an accidental host. The virus circulates in tropical rainforests and is transmitted from one host to another by the bite of infected mosquitoes. The urban and jungle cycles are independent and self-sufficient, but under favorable conditions the infection can be transferred from one cycle to the other.

The disease in Latin America differs in terms of various epidemiological and ecological aspects from the disease in Africa. In Latin America, the primary vectors of the virus are *Haemagogus* mosquitoes, especially *Haemagogus janthinomys* and *Haemagogus spegazzini*, which inhabit the rainforest canopy. Several species of this genus are diurnal and descend to ground level in cleared areas of the jungle. Tree felling, especially, favors contact between these mosquitoes and man. The range of *H. spegazzini* extends from northern Honduras to southern Ecuador. Naturally infected

[2] For most arthropod-borne diseases, there are considered to be two periods of incubation: extrinsic and intrinsic. The extrinsic incubation period occurs in the biological vector, and during this time the etiologic agent propagates or transforms itself so that it is capable of infecting and transmitting the infection to the host. The intrinsic incubation period is the time interval between the agent's penetration of the host organism and the appearance of symptoms of the disease.

Figure 33. Jungle yellow fever in the Americas. Transmission cycle.



Aedes leucocelaenus and *Sabethes chloropterus* mosquitoes have also been found, but they are thought to play only a secondary role. *S. chloropterus* is drought resistant and can provide the biological mechanism for the virus's survival during the dry season.

Knowledge about the animal reservoir of the virus is still incomplete. It is believed that the YF virus moves in waves through infected mosquitoes that transmit the infection to susceptible monkeys from other regions of the jungle. The howler monkey has a primary role in the epizootiology of the virus in the jungle cycle. These monkeys are highly susceptible to the virus and die in large numbers during epizootics. The absence of their characteristic howling sound in the jungle is a warning that the virus may be active. A single infected monkey can be the source of infection for many mosquitoes in a tree. The infection can be transmitted from one troop of monkeys to another when their territories are contiguous, and it can also be carried over long distances via infected mosquitoes transported on air currents. However, because of the great susceptibility of howler monkeys and their high fatality rate, it is likely that partially resistant monkeys, such as capuchins (*Cebus* spp.), play an important role as reservoirs. Apparently, the other species of susceptible monkeys are less important because of their ranges and habits. Man contracts the infection accidentally from the bite of infected *Haemagogus* mosquitoes when he enters an area where the monkey-mosquito-monkey cycle is present.

In some regions where sporadic cases occur in the human population even though the monkey population alone is insufficient to maintain the jungle cycle, there are indications that some small arboreal mammals, including marsupials, the kinkajou (*Potos flavus*), and the olingo (*Bassaricyon gabbii*), may intervene in the epizootiology (Strano *et al.*, 1975). A high rate of serologic reactors has been found among marsupials, suggesting that they may participate in circulation of the virus, but their actual role has yet to be determined (Woodall, 1981).

In eastern and central Africa, the main vector in the jungle cycle is *A. africanus*, a mosquito that inhabits the forest canopy and spreads the virus in the monkey population. Infected monkeys carry the virus to cultivated fields bordering the forest,

such as banana plantations, and the disease is transmitted from nonhuman primate to man by *A. simpsoni*, a mosquito that lives in vegetation around houses. The epidemic that occurred in southwestern Ethiopia in 1960–1962, which produced some 100,000 cases and 30,000 deaths in a population of a million inhabitants, was preceded by an epizootic in the jungle that developed between monkeys and *A. africanus*. Subsequently, baboons (*Papio* spp.) carried the infection to banana plantations and infected *A. simpsoni*, which in turn transmitted the infection to man and initiated a possible secondary mosquito-man-mosquito cycle. Moreover, when *A. aegypti* is present in a locality, it can give rise to a cycle involving man-*A. aegypti*-man. In other regions of Africa, it has been found that *A. simpsoni* tends not to be anthropophilic, and it is suspected that *A. africanus* may transmit the virus directly from monkey to man.

The epidemics that have occurred in Africa in recent years have stimulated research on the survival mechanisms of the virus during interepidemic periods. During these periods, numerous strains of the virus have been isolated from *A. africanus*, *Aedes opok*, *Aedes furcifer-taylori*, and *A. luteocephalus*; transovarial transmission has been confirmed in *A. aegypti* and *A. furcifer-taylori*; and the virus has been isolated from the eggs and adult form of the cattle tick *Amblyomma variegatum*. Although these findings may account for survival of the virus during the dry season, their real significance is not yet known. Transovarial transmission is infrequent, and when it does occur, it tapers off by the fourth ovarian cycle, hence the need for virus amplification in vertebrates such as monkeys and man. Experimental transovarial transmission has also been achieved with the South American jungle vector *Haemagogus* spp., but the phenomenon has not been found in nature, despite extensive studies conducted in Trinidad and Tobago following the 1978–1979 outbreak (WHO, 1985).

The main YF hosts in Africa are green monkeys (*Cercopithecus* spp.), the patas monkey (*Erythrocebus patas*), baboons (*Papio* spp.), colobus monkeys (*Colobus* spp.), and bushbabies (*Galago* spp.) (Seymour and Yuill, 1981).

Role of Animals in the Epidemiology of the Disease: Jungle YF is an infection of wild animals, chiefly nonhuman primates. To date, there is no evidence that *Haemagogus* mosquitoes serve as the reservoir in the Americas. Man is an accidental host. When conditions are favorable, the jungle cycle can give rise to an urban cycle, in which man is the main host and *A. aegypti* is the vector. In Africa, the monkey is a transitory amplifier of the virus and the mosquito is the reservoir that maintains the infection throughout its life and transmits the virus transovarially (WHO, 1985). In urban YF, the vector *A. aegypti* is also the primary reservoir.

Diagnosis: Laboratory confirmation is obtained by isolation of the virus or serologic testing. Virus isolation is the most rapid and reliable procedure. This method uses blood samples taken from the patient during the first three or four days of the illness. The virus can be isolated in tissue culture, mice, or rhesus monkeys. An enzyme-linked immunosorbent assay (ELISA) has been perfected to detect the virus in serum samples; IgM antibodies to the YF virus are used. The procedure has been evaluated in viremic monkeys with satisfactory results (Monath and Nystrom, 1984). Serologic examination can be done using the hemagglutination inhibition, neutralization, complement fixation, indirect immunofluorescence, or ELISA test. The latter test gives results comparable to the neutralization test and more sensitive

and specific than the hemagglutination inhibition and complement fixation tests (Deubel *et al.*, 1983). Antibodies appear in the hemagglutination inhibition and neutralization tests about five days after onset of the disease and reach maximum titers three to four weeks later. Diagnosis is based on confirmation of a significant increase in titer when acute- and convalescent-phase sera are compared. Cloning and determination of the genome sequence of the 17D virus (vaccine strain) make it possible to detect the viral genome in clinical samples by nucleic acid hybridization (Rice *et al.*, 1985).

With deceased patients, diagnosis may be based on histopathologic examination, which is important for epidemiologic surveillance, or the immunohistochemical method, which can detect YF viral antigen with immune sera from rabbits and hamsters, or hyperimmune ascitic fluid from mice (De Brito *et al.*, 1992). This method has enabled investigators to detect YF viral antigen not only in the liver but also in the kidneys and heart.

Laboratory diagnosis is important both for epidemiologic surveillance and for the treatment of patients.

Control: In South America, the principal measure for controlling jungle YF is vaccination of persons who go into or live in enzootic areas. The 17D chicken embryo vaccine is preferred. This attenuated live virus vaccine, which should be lyophilized, confers the longest protection. Revaccination every 10 years is recommended. For the 33 African countries that have areas at risk, the World Health Organization recommended in 1989 that the vaccine should be included in their routine vaccination programs for children. As of March 1993, almost 2 million children had been immunized against YF, representing 11% of the children in the endemic area (WHO, 1993). The vaccine should not be administered to children under 6 months of age. In each of the French-speaking countries of Africa, the entire population was immunized and revaccinated every 4 years between 1940 and 1960. As a result of these efforts, incidence of the disease dropped to zero (WHO, 1986). The 17D vaccine can be given at the same time as measles vaccine. Immunization was also successful during construction of the trans-Amazon highway in Brazil (Brés, 1986). The subject of *A. aegypti* control in the Americas is covered in the chapter on dengue.

Since 1966, more than 250 million persons have been immunized with the 17D vaccine and there have been only 3 cases of postvaccination encephalitis. Two of the patients recovered and one of them died. The latter was an apparently healthy female child 39 months of age who had been vaccinated at the same time as her parents. A strain of the virus (P-16065) isolated from the child's brain appeared identical to the vaccine strain when it was examined with monoclonal antibodies. However, a difference could be seen when the vaccine strain and the strain isolated from the child were examined with monoclonal antibodies from the field strain; strain P-16065 from the child could be recognized, but vaccine strain 17D-204 could not. Apparently an envelope protein had mutated by at least one epitope. The mutant strain proved to be neuroinvasive and virulent for mice inoculated intranasally (Jennings *et al.*, 1994). The authors propose that tests for vaccine quality include, in addition to tests for neurovirulence in monkeys, tests in mice inoculated intranasally and that monoclonal antibodies be used for the field virus to detect any reversion of the virus to its virulent state. In February 2001, an apparently healthy man who

received YF vaccine in Australia died after developing vaccine-derived YF (Chan *et al*., 2001). In June 2001, seven cases of YF vaccine-associated viscerotropic disease (formerly known as multiple organ system failure) were reported among recipients of 17D-derived YF vaccine in the US (Cetron *et al.*, 2002); later that year, the US Centers for Disease Control and Prevention issued updated recommendations for yellow fever vaccination (CDC, 2002).

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ZOONOSES AND COMMUNICABLE DISEASES COMMON TO MAN AND ANIMALS

Third Edition

Volume III

Parasitoses

Scientific and Technical Publication No. 580

PAN AMERICAN HEALTH ORGANIZATION
Pan American Sanitary Bureau, Regional Office of the
WORLD HEALTH ORGANIZATION
525 Twenty-third Street, N.W.
Washington, D.C. 20037 U.S.A.

2003

Also published in Spanish (2003) with the title:
Zoonosis y enfermedades transmisibles comunes al hombre y a los animales: parasitosis
ISBN 92 75 31991 X (3 volume set)
ISBN 92 75 31992 8 (Vol. 3)

PAHO HQ Library Cataloguing-in-Publication
Pan American Health Organization
Zoonoses and communicable diseases common to man and animals: parasitoses
3rd ed. Washington, D.C.: PAHO, © 2003.
3 vol.—(Scientific and Technical Publication No. 580)

ISBN 92 75 11991 0—3 volume set
ISBN 92 75 11993 7—Vol. 3
I. Title II. (Series)
1. ZOONOSES
2. PARASITIC DISEASES
3. DISEASE RESERVOIRS
4. COMMUNICABLE DISEASE CONTROL
5. FOOD CONTAMINATION
6. PUBLIC HEALTH VETERINARY
NLM WC950.P187 2003 v.3 En

This volume was updated by Omar O. Barriga, Professor of Parasitology in the Faculty of Medicine of the University of Chile, and consultant for PAHO's Veterinary Public Health Unit from 1997 to 2001.

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PROLOGUE

In recent years, zoonoses and communicable diseases common to man and animals have gained increasing attention worldwide. Human diseases that have their origins in infected animals, such as AIDS or Creutzfeldt-Jakob, have highlighted the need for a better understanding of animal diseases in terms of their epidemiology, mechanism of transmission to man, diagnosis, prevention, and control. Social and demographic changes have also contributed to the importance of gaining and disseminating knowledge about zoonoses. For instance, as people encroach further and further on ecological areas with which they had little contact and whose fauna may not be well known, their exposure to animals—and the infections they transmit—has increased. New knowledge is also being developed in the area of urban ecology. The ease and speed of modern travel also facilitates the spread of diseases once confined to specific geographic areas, as recently occurred with severe acute respiratory syndrome (SARS). Animal migration and trade pose a similar threat, as was shown by the outbreaks in the United States of West Nile fever, and most recently, monkeypox—two diseases not previously known in the Western Hemisphere. Each of these examples highlights the need for improved knowledge and surveillance of and response to zoonoses.

The negative effects of zoonoses are far reaching. High incidence rates continue to cause significant morbidity and mortality in both humans and animals. Their economic impact is seen in lost labor productivity due to illness; reduced travel and tourism to affected areas; reduced livestock and food production; death and destruction of affected animals; and restrictions on and reductions in international trade. Zoonoses can be a serious drain on a country's economy, which in turn can have wide repercussions for a society's health.

To help solve these problems, the Pan American Health Organization (PAHO)—an international public health organization that has devoted itself to improving the health and living conditions of the people of the Americas for over one hundred years—established the Veterinary Public Health Unit. The Unit's overall objective is to collaborate with PAHO's Member Governments in the development, implementation, and evaluation of policies and programs that lead to food safety and protection and to the prevention, control, or eradication of zoonoses, among them foot-and-mouth disease.

To this end, PAHO's Veterinary Public Health Unit has two specialized regional centers: the Pan American Foot-and-Mouth Disease Center (PANAFTOSA), created in 1951 in Rio de Janeiro, Brazil, and the Pan American Institute for Food Protection and Zoonoses (INPPAZ), established on November 15, 1991, in Buenos Aires, Argentina. INPPAZ's precursor was the Pan American Zoonoses Center (CEPANZO), which was created through an agreement with the Government of Argentina to help the countries of the Americas combat zoonoses, and which operated from 1956 until 1990.

Since its creation in 1902, PAHO has participated in various technical cooperation activities with the countries, among them those related to the surveillance, prevention, and control of zoonoses and communicable diseases common to man and animals, which cause high morbidity, disability, and mortality in vulnerable human populations. PAHO has also collaborated in the strengthening of preventive medi-

cine and public health through the promotion of veterinary health education in learning, research, and health care centers. An example of this work is the preparation of several publications, among which the two previous Spanish and English editions of *Zoonoses and Communicable Diseases Common to Man and Animals* stand out.

Scientific knowledge has progressed since the last edition was published in 1986. Also, the countries of the Americas have modified their livestock production strategies in recent years, which has affected the transmission of zoonotic infections and their distribution. The publication of this third edition is an attempt to address these changes. The third edition is presented in three volumes: the first contains bacterioses and mycoses; the second, chlamydioses, rickettsioses, and viroses; and the third, parasitoses.

We believe that this new edition will continue to be useful for professors and students of public health, medicine, veterinary medicine, and rural development; workers in public health and animal health institutions; and veterinarians, researchers, and others interested in the subject. We also hope that this publication is a useful tool in the elaboration of national zoonosis control or eradication policies and programs, as well as in risk evaluation and in the design of epidemiological surveillance systems for the prevention and timely control of emerging and reemerging zoonoses. In summary, we are confident that this book will contribute to the application of the knowledge and resources of the veterinary sciences for the protection and improvement of public health.

MIRTA ROSES PERIAGO
DIRECTOR

PREFACE TO THE FIRST EDITION

This book considers two groups of communicable diseases: those transmitted from vertebrate animals to man, which are—strictly speaking—zoonoses; and those common to man and animals. In the first group, animals play an essential role in maintaining the infection in nature, and man is only an accidental host. In the second group, both animals and man generally contract the infection from the same sources, such as soil, water, invertebrate animals, and plants; as a rule, however, animals do not play an essential role in the life cycle of the etiologic agent, but may contribute in varying degrees to the distribution and actual transmission of infections.

No attempt has been made to include all infections and diseases comprised in these two groups. A selection has been made of some 150 that are of principal interest, for various reasons, in the field of public health. The number of listed zoonoses is increasing as new biomedical knowledge is acquired. Moreover, as human activity extends into unexplored territories containing natural foci of infection, new zoonotic diseases are continually being recognized. In addition, improved health services and better differential diagnostic methods have distinguished zoonoses previously confused with other, more common diseases. A number of diseases described in this book have only recently been recognized, examples of which include the Argentine and Bolivian hemorrhagic fevers, angiostrongyliasis, rotaviral enteritis, Lassa fever, Marburg disease, and babesiosis.

The principal objective in writing this book was to provide the medical professions a source of information on the zoonoses and communicable diseases common to man and animals. Toward that end, both medical and veterinary aspects, which have traditionally been dealt with separately in different texts, have been combined in a single, comprehensive volume. As a result, physicians, veterinarians, epidemiologists, and biologists can all gain an overview of these diseases from one source.

This book, like most scientific works, is the product of many books, texts, monographs, and journal articles. Many sources of literature in medicine, veterinary medicine, virology, bacteriology, mycology, and parasitology were consulted, as were a large number of reports from different biomedical disciplines, in order to provide up-to-date and concise information on each disease. It is expected that any errors or omissions that may have been committed can, with the collaboration of the readers, be corrected in a future edition.

Where possible, explanations were attempted with special emphasis on the Americas, particularly Latin America. An effort was made, one which was not always successful, to collect available information on diseases in this Region. Data on the incidence of many zoonoses are fragmentary and frequently not reliable. It is hoped that the establishment of control programs in various countries will lead to improved epidemiologic surveillance and disease reporting.

More space has been devoted to those zoonoses having greatest impact on public health and on the economy of the countries of the Americas, but information is also included on those regionally less important or exotic diseases.

The movement of persons and animals over great distances adds to the risk of introducing exotic diseases that may become established on the American continent given the appropriate ecologic factors for existence of the etiologic agents. Today,

public health and animal health administrators, physicians, and veterinarians must be familiar with the geographic distribution and pathologic manifestations of the various infectious agents so that they can recognize and prevent the introduction of exotic diseases.

We, the authors, would like to give special recognition to Dr. Joe R. Held, Assistant Surgeon-General of the United States Public Health Service and Director of the Division of Research Services of the U.S. National Institutes of Health, who gave impetus to the English translation and reviewed the bacterioses sections.

We would also like to express our utmost appreciation to the experts who reviewed various portions of this book and offered their suggestions for improving the text. These include: Dr. Jeffrey F. Williams, Professor in the Department of Microbiology and Public Health, Michigan State University, who reviewed the chapters dealing with parasitic zoonoses; Dr. James Bond, PAHO/WHO Regional Adviser in Viral Diseases, who read the viroses; Dr. Antonio Pío, formerly PAHO/WHO Regional Adviser in Tuberculosis and presently with WHO in Geneva, and Dr. James H. Rust, PAHO/WHO Regional Adviser in Enteric Diseases, both of whom reviewed the bacterioses; and Dr. F. J. López Antuñano, PAHO/WHO Regional Adviser in Parasitic Diseases, who read the metazooses.

We would like to thank Dr. James Cocozza, PAHO/WHO Veterinary Adviser, for his review of the translation and Dr. Judith Navarro, Editor in the Office of Publications of PAHO, for her valuable collaboration in the editorial revision and composition of the book.

PEDRO N. ACHA
BORIS SZYFRES

PREFACE TO THE SECOND EDITION

The fine reception accorded the Spanish, English, and French versions of this book has motivated us to revise it in order that it still may serve the purpose for which it was written: to provide an up-to-date source of information to the medical profession and allied fields. This book has undoubtedly filled a void, judging by its wide use in schools of public health, medicine, and veterinary medicine, as well as by bureaus of public and animal health.

The present edition has been considerably enlarged. In the seven years since the first edition was published, our knowledge of zoonoses has increased broadly and rapidly, and new zoonotic diseases have emerged. Consequently, most of the discussions have been largely rewritten, and 28 new diseases have been added to the original 148. Some of these new diseases are emerging zoonoses; others are pathologic entities that have been known for a long time, but for which the epidemiologic connection between man and animal has been unclear until recently.

The use this book has had outside the Western Hemisphere has caused us to abandon the previous emphasis on the Americas in favor of a wider scope and geomedical view. Moreover, wars and other conflicts have given rise to the migration of populations from one country or continent to another. A patient with a disease heretofore known only in Asia may now turn up in Amsterdam, London, or New York. The physician must be aware of these diseases in order to diagnose and treat them. "Exotic" animal diseases have been introduced from Africa to Europe, the Caribbean, and South America, causing great damage. The veterinary physician must learn to recognize them to be able to prevent and eradicate them before they become entrenched. It must be remembered that parasites, viruses, bacteria, and other agents of zoonotic infection can take up residence in any territory where they find suitable ecologic conditions. Ignorance, economic or personal interests, and human customs and needs also favor the spread of these diseases.

Research in recent years has demonstrated that some diseases previously considered to be exclusively human have their counterparts in wild animals, which in certain circumstances serve as sources of human infection. On the other hand, these animals may also play a positive role by providing models for research, such as in the case of natural leprosy in nine-banded armadillos or in nonhuman primates in Africa. Of no less interest is the discovery of *Rickettsia prowazekii* in eastern flying squirrels and in their ectoparasites in the United States, and the transmission of the infection to man in a country where epidemic typhus has not been seen since 1922. A possible wild cycle of dengue fever is also discussed in the book. Is Creutzfeldt-Jakob disease a zoonosis? No one can say with certainty, but some researchers believe it may have originated as such. In any case, interest is aroused by the surprising similarity of this disease and of kuru to animal subacute spongiform encephalopathies, especially scrapie, the first known and best studied of this group. Discussion of human and animal slow viruses and encephalopathies is included in the spirit of openness to possibilities and the desire to bring the experience of one field of medicine to another. In view of worldwide concern over acquired immunodeficiency syndrome (AIDS), a brief section on retroviruses has also been added, in which the relationship between the human disease and feline and simian AIDS is

noted. Another topic deeply interesting to researchers is the mystery of the radical antigenic changes of type A influenza virus, a cause of explosive pandemics that affect millions of persons around the world. Evidence is mounting that these changes result from recombination with a virus of animal origin (see Influenza). That this should occur is not surprising, given the constant interaction between man and animals. As a rule, zoonoses are transmitted from animal to man, but the reverse may also occur, as is pointed out in the chapters on hepatitis, herpes simplex, and measles. The victims in these cases are nonhuman primates, which may in turn retransmit the infection to man under certain circumstances.

Among emerging zoonoses we cite Lyme disease, which was defined as a clinical entity in 1977; the etiologic agent was found to be a spirochete (isolated in 1982), for which the name *Borrelia burgdorferi* was recently proposed. Emerging viral zoonoses of note in Latin America are Rocio encephalitis and Oropouche fever; the latter has caused multiple epidemics with thousands of victims in northeast Brazil. Outstanding among new viral disease problems in Africa are the emergence of Ebola disease and the spread of Rift Valley fever virus, which has caused tens of thousands of human cases along with great havoc in the cattle industry of Egypt and has evoked alarm around the world. Similarly, the protozoan *Cryptosporidium* is emerging as one of the numerous agents of diarrheal diseases among man and animals, and probably has a worldwide distribution.

As the English edition was being prepared, reports came to light of two animal diseases not previously confirmed in humans. Three cases of human pseudorabies virus infection were recognized between 1983 and 1986 in two men and one woman who had all had close contact with cats and other domestic animals. In 1986, serologic testing confirmed infection by *Ehrlichia canis* in a 51-year-old man who had been suspected of having Rocky Mountain spotted fever. This is the first known occurrence of *E. canis* infection in a human. These two diseases bear watching as possible emerging zoonoses.

The space given to each zoonosis is in proportion to its importance. Some diseases that deserve their own monographs were given more detailed treatment, but no attempt was made to cover the topic exhaustively.

We, the authors, would like to give special recognition to Dr. Donald C. Blenden, Professor in the Department of Medicine and Infectious Diseases, School of Medicine, and Head of the Department of Veterinary Microbiology, College of Veterinary Medicine, University of Missouri; and to Dr. Manuel J. Torres, Professor of Epidemiology and Public Health, Department of Veterinary Microbiology, College of Veterinary Medicine, University of Missouri, for their thorough review of and valuable contributions to the English translation of this book.

We would also like to recognize the support received from the Pan American Health Organization (PAHO/WHO), the Pan American Health and Education Foundation (PAHEF), and the Pan American Zoonoses Center in Buenos Aires, Argentina, which enabled us to update this book.

We are most grateful to Dr. F. L. Bryan for his generous permission to adapt his monograph “Diseases Transmitted by Foods” as an Appendix to this book.

Mr. Carlos Larranaga, Chief of the Audiovisual Unit at the Pan American Zoonosis Center, deserves our special thanks for the book’s artwork, as do Ms. Iris Elliot and Mr. William A. Stapp for providing the translation into English. We would

like to express our most sincere gratitude and recognition to Ms. Donna J. Reynolds, editor in the PAHO Editorial Service, for her valuable collaboration in the scientific editorial revision of the book.

PEDRO N. ACHA
BORIS SZYFRES

INTRODUCTION

This new edition of *Zoonoses and Communicable Diseases Common to Man and Animals* is published in three volumes: I. Bacterioses and mycoses; II. Chlamydioses and rickettsioses, and viroses; and III. Parasitoses. Each of the five parts corresponds to the location of the etiologic agents in the biological classification; for practical purposes, chlamydias and rickettsias are grouped together.

In each part, the diseases are listed in alphabetical order to facilitate reader searches. There is also an alphabetical index, which includes synonyms of the diseases and the etiologic agents' names.

In this edition, the numbers and names of the diseases according to the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), are listed below the disease title. However, some zoonoses are not included in ICD-10 and are difficult to classify within the current scheme.

In addition, for each disease or infection, elements such as synonyms; etiology; geographical distribution; occurrence in man and animals; the disease in man and animals; source of infection and mode of transmission; role of animals in the epidemiology; diagnosis; and control are addressed. Patient treatment (for man or other species) is beyond the scope of this work; however, recommended medicines are indicated for many diseases, especially where they are applicable to prophylaxis. Special attention is paid to the epidemiological and ecological aspects so that the reader can begin to understand the determining factors of the infection or disease. Some topics include simple illustrations of the etiologic agent's mode of transmission, showing the animals that maintain the cycle of infection in nature. Similarly, other graphics and tables are included to provide additional information on the geographical distribution or prevalence of certain zoonoses.

The data on the occurrence of the infection in man and animals, along with data on the geographical distribution, may help the reader judge the relative impact that each disease has on public health and the livestock economy in the different regions of the world, given that the importance of different zoonoses varies greatly. For example, foot-and-mouth disease is extremely important from an economic standpoint, but of little importance in terms of public health, if animal protein losses are not considered. In contrast, Argentine and Machupo hemorrhagic fevers are important human diseases, but their economic impact is minimal, if treatment costs and loss of man-hours are not taken into account. Many other diseases, such as brucellosis, leptospirosis, salmonellosis, and equine encephalitis, are important from both a public health and an economic standpoint.

Finally, each disease entry includes an alphabetical bibliography, which includes both the works cited and other relevant works that the reader may consult for more information about the disease.

3. Acanthocephaliases and Nematodiases

ACANTHOCEPHALIASIS

ICD-10 B83.8 Other specified helminthiases

Synonym: Macracanthorhynchosis.

Etiology: The agents of this disease are the acanthocephalans, or thorn-headed helminths *Macracanthorhynchus hirudinaceus* (synonyms *Gigantorhynchus hirudinaceus*, *G. gigas, Echinorhynchus gigas*), *Moniliformis moniliformis*, *Acanthocephalus rauschi*, *A. bufonis* (*A. sinensis*), *Corynosoma strumosum,* and *Bolbosoma* sp. The first two are rare in man and the others are uncommon.

The definitive hosts of *M. hirudinaceus* are swine, wild boars, and, occasionally, bovines, rodents, dogs, monkeys, or man, in whose small intestine the parasite lives. The parasites are milky white or slightly pink, cylindrical, and somewhat flattened; females measure 35 cm or more in length by 4–10 mm in width, and males are about 10 cm long by 3–5 mm wide. On the surface, they resemble a wrinkled ascarid, but are easily distinguished from it because acanthocephalans have a retractile oral proboscis with five or six rows of curved spines. The eggs are ovoid and about 70–110 μm long; they are already embryonated when expelled with the feces of the definitive host. To continue their development, the eggs must be ingested by a beetle, usually a dung beetle of the family Scarabaeidae. Once inside these intermediate hosts, the eggs hatch in the midgut and the freed larvae penetrate the body cavity of the insect, where they continue their development and encyst. When a swine or another definitive host (peccary, squirrel, muskrat, or man) ingests a parasitized coleopteran, the larva sheds its cystic envelope and, after two to three months, reaches maturity and begins oviposition. A female can produce more than 250,000 eggs per day for approximately 10 months. The eggs are very resistant to environmental factors and can survive in the soil for several years.

Definitive hosts of *M. moniliformis* are several species of rats and other small rodents. Intermediate hosts are beetles and cockroaches. The vertebrate hosts of *Corynosoma strumosum* are the arctic fox (*Alopex lagopus*), dog, sea otter (*Enhydra lutris*), and several species of cetaceans and pinnipeds. The intermediate host is probably an amphipod crustacean (*Pontoporeia affinis*). Many species of fish serve as paratenic hosts. The intermediate hosts of *Acanthocephalus* are crustaceans. *Bolbosoma* is a parasite of cetaceans whose juvenile state has been found in fish.

Geographic Distribution and Occurrence: *M. hirudinaceus* is found in swine throughout much of the world; western Europe seems to be free of the infection. In some areas, the infection is common in swine and can reach high rates: in Belarus, 17% to 32% of the herds were found to be infected, and prevalence rates ranged from 0.9% to 5%, and occasionally up to 23% (Soulsby, 1982). Prevalence rates in China varied from 3% to 7.4% in one province, and from 50% to 60% in another (Leng *et al.,* 1983). Human infection was said to be common during the last century in the region of the Volga in the former Soviet Union, owing to the consumption of raw *Melolontha* beetles; however, other studies have not confirmed human cases (Leng *et al.,* 1983), with the exception of one case of a 5-year-old child recorded in 1958 (Faust *et al.,* 1974). Radomyos *et al*. (1989) reported on the ninth known human case in Thailand; isolated cases have also been described in Brazil, Bulgaria, the former Czechoslovakia, and Madagascar. Since 1970, human infection has necessitated emergency surgery on children in three provinces in northern China and one in southern China. A study of hospital records demonstrated that in Liaoning province, more than 200 surgical interventions were required for intestinal perforations, and that 115 cases of abdominal colic caused by macracanthorhynchosis were treated in another hospital (Leng *et al.,* 1983).

Isolated cases of human infection by *M. moniliformis* have been described in Israel, Italy, Indonesia (island of Java), and Sudan. In 1989, the first autochthonous case in the US was reported, in a 15-month-old child (Neafie and Marty, 1993). In Nigeria, a case of *M. moniliformis* was reported in a man (Ikeh *et al*., 1992), and the infection was found to affect 39% of rats (*Rattus rattus*) (Mafiana *et al*., 1997). A case of human infection by *Acanthocephalus bufonis* was described in Indonesia, one by *Corynosoma strumosum* in Alaska, US, and one by *A. rauschi,* also in Alaska (Schmidt, 1971). Prociv *et al*. (1990) reported two cases of unidentified acanthocephalans in two children from Australia.

The Disease in Man: The pathologic effect and symptomatology of the human infection have not been well studied. The case histories recorded in China, which are the most numerous, refer to extreme cases with acute abdominal colic and perforation of the intestine. The two most recent cases in children required resection of a part of the jejunum, which had multiple perforations (Leng *et al.,* 1983). In an experimental autoinfection by *M. moniliformis,* a researcher experienced acute gastrointestinal pain, diarrhea, somnolence, and general debility. The patient reported on by Ikeh *et al*. (1992) complained of weakness, occasional dizziness, and an intermittent burning sensation in the area of the navel. Other cases have been asymptomatic.

The Disease in Animals: *M. hirudinaceus* attaches with its proboscis to the wall of the swine's jejunum, duodenum, and ileum. The parasite produces an inflammatory reaction that can progress to necrosis and the formation of small, sometimes caseous nodules. Clinical manifestations depend on the intensity of infection, the degree of penetration of the parasite into the intestinal wall, and, especially, the presence of a secondary bacterial infection. The most severe cases are due to perforation of the intestine, leading to peritonitis and death. Generally, clinical symptoms are not apparent. In mink, which are accidental hosts, *C. strumosum* has caused bloody diarrhea and anemia.

Source of Infection and Mode of Transmission: The development of the parasite requires an intermediate host. Although swine and wild boars are the reservoirs

and main hosts of *M. hirudinaceus*, the species specificity of the parasite is not strict and it can infect more than 12 different species of vertebrates, including man (De Giusti, 1971). Swine are infected by ingesting scarabaeid coleopterans, which serve as intermediate hosts. In China, besides these scarabaeids, members of the family Carambycidae were found infected with the larvae of the last immature stage of the acanthocephalus (cystacanth) (Leng *et al.,* 1983). Man becomes infected in a manner similar to swine, by accidental or deliberate ingestion of coleopterans. Most infections occur in children from rural areas, who catch beetles for play, and sometimes eat them lightly toasted but insufficiently cooked to kill the larvae. In southern China, some peasants believe that coleopterans are effective against nocturia and administer them to children for that reason.

Diagnosis: Diagnosis can be made by confirming the presence in the feces of thick-shelled eggs containing the first larval stage (acanthor). The eggs are easier to see after centrifugal concentration. The adult parasite can be examined after the patient is treated with piperazine citrate and expels it. In many cases, diagnosis is made after emergency surgery.

Control: Human infection can be prevented by avoiding the ingestion of coleopterans. To control the parasitosis in swine, the animals should be kept under hygienic conditions and provided with abundant food to discourage rooting and ingestion of coleopterans.

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ANGIOSTRONGYLIASIS

ICD-10 B81.3 Intestinal angiostrongyliasis;
B83.2 Angiostrongyliasis (*Parastrongylus cantonensis)*

Synonyms: Angiostrongylosis, eosinophilic meningitis, eosinophilic meningoencephalitis (*A. cantonensis*), abdominal angiostrongylosis (*A. costaricensis*).

Etiology: The agents of this disease are the metastrongylid nematodes *Angiostrongylus* (*Morerastrongylus*) *costaricensis*, *A. cantonensis,* and *A. malaysiensis*. Some authors prefer to place them in the genus *Parastrongylus*. The first of these nematodes was recognized as a parasite of man in Taiwan in 1944; the second was described in Costa Rica in 1971, although the human disease had been known since 1952; the third was identified in Japan in 1990 and was subsequently diagnosed in aborigines in Malaysia. The first species is responsible for abdominal angiostrongyliasis; the second for eosinophilic meningitis or meningoencephalitis; and the third, *A. malaysiensis*, has not been associated with any pathological picture. The definitive hosts of all three species are rodents; man is an accidental host. All three require mollusks as intermediate hosts.

A. costaricensis is a filiform nematode measuring 14–35 mm long by 0.3 mm in diameter which lives in the mesenteric arteries (and their arterioles) of the cecum of the cotton rat (*Sigmodon hispidus*). Some 12 other rat species have been found to be infected; coatis (*Nasua arica*), monkeys (*Saguinus mystax*), and dogs can be experimentally infected. The female lays eggs in those arteries; the eggs are then carried by the bloodstream and form emboli in the arterioles and capillaries of the intestinal wall. The eggs mature and form a first-stage larva which hatches, penetrates the intestinal wall to the lumen, and is carried with the fecal matter to the exterior, where it begins to appear around the twenty-fourth day of the prepatent period of the infection. In order to continue their development, the first-stage larvae have to actively penetrate the foot of a slug of the family Veronicellidae (particularly *Vaginulus plebeius*) or be ingested by it. In Brazil, four species of Veronicellidae slug were found to be infected: *Phyllocaulis variegatus, Bradybaena similaris, Belocaulus angustipes,* and *Phyllocaulis soleiformis* (Rambo *et al*., 1997). In the slug, the larvae mature and change successively into second- and third-stage larvae in approximately 18 days. The third-stage larva, which is infective for the definitive host, is eliminated with the slug's mucous or slime, and contaminates the soil and plants around it (Mojon, 1994). When the definitive host ingests the infective larva in the free state or inside the mollusk, the larva migrates to the ileocecal region, penetrates the intestinal wall, and invades the lymphatic vessels. In this location the larvae undergo two molts before migrating to their final habitat: the mesenteric arteries of the cecal region. The parasite can complete the life cycle in man, an accidental host, reaching sexual maturity and producing eggs, but the eggs usually degenerate, causing a granulomatous reaction in the intestinal wall of the host.

A. cantonensis is a small, thin nematode, 17–25 mm long and 0.3 mm in diameter, that lives in the pulmonary arteries of rodents of the genera *Rattus* and *Bandicota*. The intermediate hosts are various species of land, amphibian, or aquatic gastropods, e.g., *Vaginulus, Laevicaulus, Achatina,* and *Bradybaena*. Five species of *Oncomelania* snails have been experimentally infected. The development cycle is

similar to that of *A. costaricensis.* The definitive hosts can become infected by ingesting the infective third-stage larvae, either with infected mollusks or with plants or water contaminated with the larvae that abandon the mollusk. In addition, infection can occur as a result of consuming transfer hosts (paratenic hosts), such as crustaceans, fish, amphibians, and reptiles, which in turn have eaten infected mollusks or free larvae. When a definitive host ingests an infected mollusk or infective larvae, the larvae penetrate the intestine and are carried by the bloodstream to the brain, where they undergo two additional changes to become juvenile parasites 2 mm long. From the cerebral parenchyma, they migrate to the surface of the organ, where they remain for a time in the subarachnoid space and later migrate to the pulmonary arteries, where they reach sexual maturity and begin oviposition. The eggs hatch in the pulmonary arterioles or their branches, releasing the first-stage larva, which penetrates the pulmonary alveoli and migrates through the airways to the pharynx; there it is swallowed and is eliminated with the feces starting six weeks after infection. In man, who is an accidental host, the larvae and young adults of *A. cantonensis* generally die in the brain, meninges, or medulla oblongata. The nematode can occasionally be found in the eyes and, more rarely, the lungs. Snails or slugs, which are the intermediate hosts, become infected when they ingest the feces of infected rodents. The third-stage infective larva forms in the mollusk in 17 or 18 days and can remain there for some time or be expelled and contaminate the environment. A large number of paratenic or transport hosts, such as crustaceans, fish, amphibians, or reptiles, may become infected with these larvae and, in turn, infect rats or human beings.

A. malaysiensis is a nematode resembling *A. cantonensis;* it was isolated from *Rattus norvegicus* in Japan in 1990. This nematode showed biologic and isoenzymatic differences when compared to *A. cantonensis* (Sawabe and Makiya, 1995). Subsequently, the infection was diagnosed in 23% of 108 aborigines in Malaysia by enzyme-linked immunosorbent assay (ELISA) with monoclonal antibodies (Ambu *et al*., 1997). The adult parasite has been found in rats, and its larva infects the snail *Biomphalaria glabrata*, although not as easily as it infects *A. cantonensis*.

Geographic Distribution and Occurrence: Abdominal angiostrongyliasis caused by *A. costaricensis* is primarily a disease of the Americas. It has been identified in children in Costa Rica since 1952, and more than 130 human cases had been diagnosed when Morera and Cespedes described the parasite in 1971. Morera (1991) indicated that about 300 cases a year were diagnosed in Costa Rica alone. In 1992, two cases were discovered in children on the French island of Guadeloupe in the Caribbean (Juminer *et al*., 1993). Neafie and Marty (1993) described the first human case in the US. The first known epidemic occurred in 1994–1995 in Guatemala and affected 22 persons (Kramer *et al*., 1998). The human disease has also been confirmed in Brazil, El Salvador, and Honduras. Based on epidemiological studies, Graeff-Teixeira *et al*. (1997) found that the human prevalence in two endemic areas of southern Brazil was 30% and 66%, respectively. Suspected clinical cases have occurred in Nicaragua and Venezuela. With respect to the animal definitive hosts, 15% of *Rattus norvegicus* and 6% of *R. rattus* on the island of Guadeloupe were found to be infected (Juminer *et al*., 1993). In Panama, the adult parasite was found in five species of rodents belonging to three different families. Parasites were also found in several specimens of *Sigmodon hispidus* in the US state

of Texas, *Oryzomys caliginosus* in Colombia, and slugs (*Vaginulus* spp.) in Guayaquil, Ecuador. It is highly probable that the parasitosis is much more widespread than is currently recognized. Morera (1991) mentions that a case was reported in Africa.

Human cases of angiostrongyliasis by *A. cantonensis* have occurred in Australia, Cambodia, the Philippines, Indonesia, Japan, Thailand, Taiwan, Viet Nam, and several Pacific islands. In 1992, 27 cases had been reported in Japan, the majority in the prefecture of Okinawa. The geographic distribution of *A. cantonensis* was once believed to be limited to Africa, Asia, Australia, and the Pacific islands. However, its presence has been confirmed in Cuba, where infected rats (*R. norvegicus*) and mollusks have been found (Aguiar *et al.,* 1981). Likewise, five human cases with meningoencephalitis have been attributed to *A. cantonensis* (Pascual *et al.,* 1981). It is believed that the parasite was introduced to the island some years ago by rats from a ship from Asia. A review published in a local journal in Japan in 1992 describes how *A. cantonensis* spread, after the Second World War, from South and Southeast Asia to the islands of the western Pacific and from there, east and south through Micronesia and Australia to Polynesia. Since 1950, cases have been identified in Indonesia (island of Sumatra), Philippines, Taiwan, and even Tahiti. Later, in the 1960s, there were cases in Cambodia, Thailand, Viet Nam, and even in the US state of Hawaii. It subsequently appeared in Australia, mainland China, India, and Japan (Okinawa). In the 1970s and 1980s, the parasite was found in rats in Cuba, Egypt, Puerto Rico, and the city of New Orleans, US; it has been found in man in the Côte d'Ivoire, Cuba, and the French island of Reunion. There seems to be an autochthonous focus in the city of New Orleans, Louisiana, US, since infections were found in a primate in a zoo and in rats (García and Bruckner, 1997). In a study carried out on rat species (*R. norvegicus*, *R. rattus,* and *R. exulans*) on the Hawaiian Islands, US, and the Society Islands, French Polynesia, the parasite was found in more than 40% of the specimens captured. In Egypt, 32.7% of 55 specimens of *R. norvegicus* harbored the parasite. In the province of Havana, Cuba, 12 of 20 captured *R. norvegicus* were infected (Aguiar *et al.,* 1981). The confirmed cases of eosinophilic meningitis caused by *A. cantonensis* number in the hundreds, and thousands have been diagnosed clinically.

A. malaysiensis has been found in rats in Japan (Sawabe and Makiya, 1995) and in aborigines in Malaysia (Ambu *et al*., 1997).

The Disease in Man: The clinical manifestations of abdominal angiostrongyliasis caused by *A. costaricensis* are moderate but prolonged fever, abdominal pain on the right side, and, frequently, anorexia, diarrhea, and vomiting. Leukocytosis is characteristic (20,000 to 50,000 per mm^3), with marked eosinophilia (11% to 82%). Palpation sometimes reveals tumoral masses or abscesses. Rectal exploration is painful and a tumor can occasionally be palpated. Lesions are located primarily in the ileocecal region, the ascending colon, appendix, and regional ganglia. Granulomatous inflammation of the intestinal wall can cause partial or complete obstruction. Out of 116 children with intestinal eosinophilic granulomas studied from 1966 to 1975 in the National Children's Hospital in Costa Rica, 90 had surgery (appendectomy, ileocolonic resection, and hemicolectomy). Appendicitis was the preoperative diagnosis in 34 cases. All but two of the children survived and recovered. The highest prevalence (53%) was found in children 6 to 13 years old, and

twice as many boys as girls were affected (Loría-Cortés and Lobo-Sanahuja, 1980). Ectopic localizations may occur, such as those found in the livers of Costa Rican patients with visceral larva migrans-like syndrome (Morera *et al.,* 1982).

In Taiwan, the disease occurs mainly in children, but in other endemic areas it occurs in adults. A study of 82 children found that the incubation period was 13 days, shorter than the average of 16.5 days in adults; meningoencephalitis was the predominant clinical form in 30% of the children, as opposed to the 5% observed in adults in Thailand, and the most common symptom was fever (91.5% of patients), followed by vomiting and headache. Cranial nerves VI and VII showed alterations in 19.5% and 11% of the cases, respectively, and papilledema was found in 25% of the children but in just 12% of the adults (Hwang and Chen, 1991). The symptomatology of meningitis and eosinophilic meningoencephalitis was studied in 1968 and 1969 in 125 patients from southern Taiwan. Most patients had a mild or moderate symptomatology, and only a few suffered serious manifestations; four of the patients died and another three had permanent sequelae. Young specimens of *A. cantonensis* were found in the cerebrospinal fluid of eight patients, and the parasite was found during autopsy in another. In 78% of the patients, the disease had a sudden onset, with intense headache, vomiting, and moderate intermittent fever. More than 50% of the patients experienced coughing, anorexia, malaise, constipation, and somnolence, and less than half had stiffness in the neck. Pleocytosis in the cerebrospinal fluid was particularly pronounced in the second and third weeks of the disease. The percentage of eosinophils was generally high and was directly related to the number of leukocytes in the cerebrospinal fluid. Leukocytosis and eosinophilia in the blood were also high. Legrand and Angibaud (1998) found that the most common signs were moderate meningeal irritation, paresthesia, and abnormalities in cranial nerves II, III, IV, and VII. While there are no effective anthelminthic and the headaches and weakness can last a few weeks, as a general rule the patient recovers without sequelae.

Angiostrongyliasis caused by *A. cantonensis* is generally expressed as eosinophilic meningitis, but there have also been isolated outbreaks in which the spinal cord, spinal nerves, and brain were extensively affected. The reason for the different clinical pictures is not known, but the severe cases may be due to the higher number of parasites present (intensity of infection). Eosinophilic meningitis usually occurs after the ingestion of paratenic hosts or contaminated vegetables containing few larvae; the most serious forms of the disease are due to direct consumption of highly infected intermediate hosts (Kliks *et al.,* 1982). In American Samoa, an outbreak of radiculomyeloencephalitis was described in 16 fishermen who had consumed raw or undercooked *Achatina fulica* (giant African snail), an intermediate host of *A. cantonensis,* considered a delicacy by many Asians. The incubation period was 1 to 6 days, and the disease lasted 10 weeks. In addition to eosinophilia in the spinal fluid and the blood, the disease was characterized by acute abdominal pain, generalized pruritus, and later by pain, weakness, and paresthesia in the legs, and dysfunction of the bladder (urinary retention or incontinence) and the intestine. Half of the patients suffered transitory hypertension or lethargy; three entered a coma and one died. Of the 12 hospitalized patients, 10 had to use wheelchairs (Kliks *et al.,* 1982). Serologic surveys carried out in Australia, in human populations living in localities where the infection occurs in rats and those living in other places where it does not, indicate that many human infections are asymptomatic.

The Disease in Animals: In rodents, *A. costaricensis* lesions are located primarily in the cecum, with focal or diffuse edema of the subserosa, a reduction of mesenteric fat, and swelling of the regional ganglia. In highly parasitized animals, eggs and larvae may be found in various viscera of the body. No significant difference in weight between parasitized and nonparasitized animals has been confirmed.

Rats infected by *A. cantonensis* may have coughing, sneezing, dyspnea, and fibrosis in the lungs. However, the physical appearance of the animals does not reflect the degree of pathologic changes.

For both parasites, the prevalence of the infection is greater in adult than in young rodents, which suggests that rodents do not develop resistance to the infection.

Source of Infection and Mode of Transmission: Several species of rodents serve as definitive hosts of *A. costaricensis*. In a study carried out in Panama (Tesh *et al*., 1973), the highest prevalence of the infection was found in the cotton rat (*S. hispidus*), which was also the most abundant rodent in the six localities studied. The cotton rat inhabits areas close to dwellings in both tropical and temperate zones, feeding on both plants and small vertebrate and invertebrate animals, including slugs. All these facts suggest that this rat is a prime reservoir and that it plays an important role in the epidemiology of the parasitosis. Rodents are infected by ingesting food or water contaminated with the infective larvae in the mollusk secretions (slime) or by eating the infected mollusks. Man may acquire the infection in the same way, for example, by eating poorly-washed vegetables containing small slugs or their secretions. A study in Guatemala showed that the consumption of mint leaves, alone or as a seasoning in traditional uncooked dishes, correlated directly with the presence of the infection in man (Kramer, 1998). It is believed that children can become infected while playing in areas where slugs are abundant by transferring mollusk secretions found on vegetation to their mouths. An increase in cases in children occurs in Costa Rica during the rainy season, when slugs are plentiful. Humidity is an important factor in the survival of both the first- and third-stage larvae, since they are susceptible to desiccation.

A. cantonensis has been found in a dozen species of the genus *Rattus* and in *Bandicota indica* and *Melomys littoralis.* These rodents, natural definitive hosts, are infected by consuming mollusks or paratenic hosts that harbor third-stage larvae. The infection rates of mollusks as intermediate hosts are usually high; both the prevalence and the number of larvae an individual mollusk can harbor vary according to the species. Man, who is an accidental host, is infected by consuming raw mollusks or paratenic hosts such as crustaceans or fish.

The ecology of angiostrongyliasis is closely related to the plant community in which the mollusks and rodents live. The frequency of the human parasitosis depends on the abundance of these hosts and the degree to which they are infected, and, also, in the case of *A. cantonensis,* frequency is connected with eating habits (consumption of raw mollusks, crustaceans, and fish).

Diagnosis: Diagnosis of the human infection caused by *A. costaricensis* can be made by examining biopsied or surgical specimens and confirming the presence of the parasites or their eggs. Graeff-Teixeira *et al*. (1991) established histopathological patterns for diagnosis. Also, an enzyme-linked immunosorbent assay (ELISA) was developed that demonstrated a sensitivity of 86% and a specificity of 83% when used with sera adsorbed with *Ascaris suum* antigens (Graeff-Teixeira *et al*., 1997).

In endemic areas, meningitis or meningoencephalitis caused by *A. cantonensis* is suspected in the presence of the characteristic signs of eosinophilia in the blood and eosinophilic pleocytosis of the cerebrospinal fluid. In places such as Thailand, where infection of the central nervous system caused by *Gnathostoma spinigerum* has a high prevalence, the two diseases must be differentiated. Punyagupta *et al*. (1990) indicate that gnathostomiasis causes sharp pain in the nerve roots, signs of cerebral and spinal disease, and yellowish or bloody cerebrospinal fluid. Although most reports indicate that only in a few cases can the parasite be found in patients' cerebrospinal fluid or eyes, Hwang and Chen (1991) reported having recovered it by lumbar puncture in 41.5% of 84 pediatric cases. Serologic tests are useful for confirming the presumptive diagnosis (Legrand and Angibaud, 1998). Two varieties of ELISA have shown a specificity of 100%, but sensitivity of just 50% to 60% (Eamsobhana *et al*., 1997).

Control: While human angiostrongyliasis is not very prevalent, except in a few areas of high endemicity, prophylaxis is important because there is no known therapeutic treatment for the infection. Theoretically, angiostrongyliasis could be controlled by reducing rodent and mollusk populations, though practical application seems doubtful. Preventive measures for individuals consist of thoroughly washing vegetables, and hands after garden or field work; not eating raw or undercooked mollusks and crustaceans; and not drinking water that may be unhygienic. Experiments have shown that incubation of infective *A. costaricensis* larvae for 12 hours at 5°C in 1.5% sodium hypochlorite kills all the larvae. Incubation in saturated sodium chloride or in commercial vinegar reduced the number of larvae but failed to prevent the infection in mice (Zanini and Graeff-Teixeira, 1995).

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ANISAKIASIS

ICD-10 B81.0

Synonyms: Anisakiosis, anisakidosis, herring worm disease, cod worm disease.

Etiology: The agent of this parasitosis is the larval stage of nematodes of the genera *Anisakis, Pseudoterranova* (synonyms *Porrocaecum, Terranova, Phocanema*), or *Contracaecum*. These parasites belong to the order Ascaridida, family

Anisakidae, which some authors call "marine ascarids." The species mentioned most often in the literature as parasites of man are *Anisakis simplex* and *Pseudoterranova decipiens*. Before identification techniques were refined, the Japanese literature referred to the third-stage larva of *P. decipiens,* frequently found in man, as type A or type 1 Anisakidae larva.

The adult stage *Anisakis* and *Pseudoterranova* parasites lodge in the stomach or small intestine of piscivorous marine mammals such as dolphins, porpoises, whales, and seals; *Contracaecum* lodges in the digestive tract of fish, where it lays eggs which are expelled, unembryonated, in the feces of the definitive host. While floating in the water, the eggs form a second-stage larva and are ingested by a variety of small crustaceans that act as intermediate hosts, inside which the third-stage larva forms. Many fish ingest these parasitized crustaceans and act as transfer (paratenic) hosts; there the third-stage larvae accumulate and encyst, waiting for definitive hosts. These fish may be ingested by larger fish or by man, in which case the worm just transfers from one to the other, or by definitive hosts, in which case the worm matures, mates, and begins oviposition (Mehlhorn and Walldorf, 1988).

Man is an aberrant host in whom the larva ingested with raw fish or squid does not reach maturity. There are two exceptions in which juvenile *P. decipiens* were recovered from human hosts.

Geographic Distribution and Occurrence: Parasites of the genus *Anisakis* are found in most oceans and seas, but some species have a more restricted distribution. Human infection occurs in countries where marine fish are eaten raw, lightly salted, or smoked. From 1955, when human infection was described for the first time, to 1968, 160 cases occurred in the Netherlands. Since 1969, when freezing fish for 24 hours before marketing became mandatory, only a few cases have occurred. The country with the highest prevalence of human anisakiasis is Japan, where 487 cases occurred up to 1976. In both Japan and the Netherlands, the prevalence was found to be higher in men than in women. In Japan, the highest rate of infection is in the 20- to 50-year-old age group. In the Republic of South Korea, 107 cases were diagnosed between June 1989 and June 1992 in a parasitological laboratory in Seoul. Most of the cases were due to *A. simplex,* and the rest were due to *P. decipiens*. In France, about 80 cases had been described up to 1995, and isolated cases have been reported in Belgium, Denmark, England, and Germany. When 244 patients were examined in a hospital in Indonesia, 11% were found to have antibodies against *Anisakis* spp. (Uga *et al*., 1996). Of 1,008 apparently healthy people examined for anisakiasis in Spain by enzyme-linked immunosorbent assay (ELISA), 47 showed titers 1.5 to 2 times higher than the controls, and 14 showed titers more than 2 times higher than the controls (García-Palacios *et al*., 1996). Oliveira *et al*. (1999) identified seven clinical cases in three months in a Madrid hospital. In the Western Hemisphere, up to 1997, 23 cases had been recorded in North America, 16 of which occurred in the US (11 in the state of California and 5 in the state of Alaska) (Kliks, 1983), and 3 in Chile. Most of the cases in the US were due to *P. decipiens*, and the others were caused by *Anisakis* spp. The number of cases in the US increased during the 1990s; in 1991, four cases were described in the state of Hawaii, bringing the total number of cases for the Hawaiian Islands to seven.

Many species of fish have been found to be naturally infected. The prevalence of infection in fish can be very high. A study of Baltic herring found that up to 95% of

the fish were infected at certain times of the year, with an average of 14 larvae each. In Peru, larvae of *Anisakis* spp. have been found in three species of marine fish caught close to the port of Callao: 48.6% of 222 specimens of jacks (*Trachurus murphyi*); 1.5% of 381 croakers (*Sciaena deliciosa*); 1.6% of 180 "cocos" (*Polyclemus peruanus*); and none of 250 "cojinobas" (*Seriolella violacea*). The highest rates of infection were found between December and March. In Chile, 27% of 311 jacks (*Trachurus murphyi*) harbored larvae of *Anisakis* spp.; likewise, infection by other Anisakidae has been confirmed in *Merluccius gayi* (hake), *Cilus montti* (corvina), and *Thyrsites atun* (sierra), all fish that are consumed regularly (Torres *et al*., 1978). *P. decipiens* larvae have been found in cod caught in the Atlantic Ocean near the South Pole.

The Disease in Man: Anisakiasis can occur clinically in several forms (Ishikura *et al*., 1993). The larvae may remain in the cavity of the stomach or intestine without penetrating the tissues, causing an infection that is often asymptomatic. In general, asymptomatic or mild cases are caused by *Pseudoterranova* spp. These infections are discovered when live larvae are expelled by means of coughing, vomiting, or defecating. In laboratory examinations of two cases recently infected by *Pseudoterranova* spp., only mild and transitory eosinophilia was found. In the invasive forms, the larvae penetrate the gastric or intestinal submucosa, causing edema, erosion, ulcers, and bleeding. In Japan, 56 *A. simplex* larvae were recovered from a woman (Kagei *et al*., 1992). In the anatomicopathological examination of cases of invasive anisakiasis, ulcerations and hemorrhagic foci are found in the mucosa, and localized or diffuse tumors are found in the intestinal or stomach wall. An intense eosinophilic infiltration is observed in the histopathological sections, with edema, histiocytes, lymphocytes, neutrophils, plasmocytes, and sometimes, giant cells suggestive of an allergic reaction. Allergy symptoms have also been found in many patients suffering from anisakiasis caused by *A. simplex*, many with symptoms of acute urticaria (Mendizabal-Basagoiti, 1999), anaphylaxis, and, occasionally, gastric symptoms which are often attributed to fish or shellfish allergies (Moreno-Ancillo *et al*., 1997). The considerable edema in the large gastric curvature observed by endoscopy and leukocytosis also suggest an allergic origin for the gastric pathology (Kakizoe *et al*., 1995).

In gastric anisakiasis, the symptoms appear 12 to 24 hours after the consumption of raw fish, and consist of sudden epigastric pain, often with nausea and vomiting. Eosinophilia is present in about half of the patients, but not leukocytosis. The gastric form of the disease is seldom diagnosed correctly; it can become chronic, lasting more than a year. In Japanese patients, in whom gastric anisakiasis is more prevalent than intestinal anisakiasis, occult blood has been found in the gastric juice, as well as hypoacidity or anacidity. The clinical picture of gastric anisakiasis is similar to and has been confused with that of peptic ulcer, gastric tumor, acute gastritis, cholecystitis, and other gastrointestinal pathologies.

Intestinal anisakiasis has an incubation period of about seven days and manifests as severe pain in the lower abdomen, nausea, vomiting, fever, diarrhea, and occult blood in the feces. There is leukocytosis, but seldom eosinophilia (Smith and Wootten, 1978). Intestinal anisakiasis can be confused with appendicitis and peritonitis. Sometimes the parasites perforate the intestinal wall and lodge in the mesenteric veins and various organs. In these invasive forms, the larvae are found in

eosinophilic granulomas, phlegmons, or abscesses. The clinical picture of mesenteric anisakiasis varies with the organ affected. There have been two reported cases of pulmonary infection with high fever, dyspnea, and pleural effusion after eating raw fish (Matsuoka *et al*., 1994).

In a clinicopathologic study of 92 cases in Japan, anisakiasis was localized in the stomach of 65% of patients and in the intestine (large or small) of 30%. In the Netherlands, intestinal anisakiasis was more prevalent than gastric anisakiasis. Most cases in the US were due to a transitory, noninvasive anisakiasis caused by larvae of *Pseudoterranova* spp. located in the lumen of the digestive tract. The main symptoms consisted of mild epigastric pain and nausea beginning when the infected fish was ingested and lasting up to 20 hours; in about 2 weeks, the parasite was expelled by coughing or vomiting or was found in the mouth (Kliks, 1983).

The Disease in Animals: The larvae of anisakids can cause pathologic changes in many species of marine fish. The parasitosis can affect various organs, and the number of larvae may reach several hundred per fish. The most commonly affected organ is the liver, and atrophy is the most frequent change. A cod parasitized by *Contracaecum* spp. weighs less than a normal fish, and if the number of larvae is large, the fat content of its liver may be significantly reduced. In young fish, *Contracaecum* can cause death when they invade the cardiac region. In addition to the liver, anisakid larvae can encapsulate in other organs, causing perforations of the stomach wall, visceral adhesions, and muscle damage. In spite of these observations by several researchers, the pathologic effects on fish are not clear (Smith and Wootten, 1978).

In marine mammals, the parasites are deeply embedded in tumors of the gastric mucosa. It can thus be assumed that parasitic invasion affects the health of these animals. Lesions are usually observed when the parasite burden is large, and especially when large numbers of nematodes are inserted in one spot of the gastric mucosa or submucosa. More than 500 parasites have been recovered from a sea lion. The parasites that are free in the lumen of the digestive tract do not cause any apparent pathology.

In 1993, the infection of cats' intestines with anisakid larvae was reported in Korea.

Source of Infection and Mode of Transmission: The main source of infection for man is marine fish, many species of which are highly parasitized. Human cases are caused by consuming raw, lightly salted, or smoked fish, whether or not it has been refrigerated. In the Netherlands, the occurrence of the disease is due to the habit of consuming raw or lightly salted herring ("green herring"). Although the habit persists, the incidence of human anisakiasis has been drastically reduced by the requirement that fish be frozen before it is sent to market. The highest incidence of the disease has been recorded in Japan, where various fish dishes are eaten raw or pickled in vinegar. In the US, at least two cases were caused by eating ceviche (a dish consisting of pieces of raw fish seasoned in lemon juice for 24 hours), and others by eating Japanese raw fish dishes. The conditions necessary for transmission to humans exist on the Pacific coast of Latin American countries. In Peru and Chile, anisakid larvae have been found in the stomach wall, intestinal wall, and mesentery, and on the surface of the gonads of several species of commercial marine fish. In addition, in Peru and other countries along the Pacific coast, ceviche is a very pop-

ular dish. According to Japanese parasitologists, anisakid larvae found in cephalopods such as cuttlefish and octopus are third-stage larvae and so would be infective for man (and for the natural definitive hosts) when the cephalopods are consumed raw or undercooked. Marine fish can become infected second intermediate hosts by eating invertebrates; they can also become paratenic hosts by ingesting the infective third-stage larvae of other fish.

Diagnosis: Direct diagnosis by examination of the parasite is the preferred method, but in 50% to 70% of gastric cases, the parasite can be visualized and recovered by endoscopy (Deardorff *et al*., 1991). In colonic anisakiasis, it is difficult to see the parasite by endoscopy, but the lesions and X-rays are very useful for diagnosis. In fact, the parasites were visible on X-ray in four out of six cases (Matsumoto *et al*., 1992). The presence of ascites, dilation of the small intestine, and edema of the Kerckring's folds found using sonography in patients with acute abdomen who have eaten fish or shellfish recently are indications of intestinal anisakiasis (Ido *et al*., 1998). Serologic tests, particularly the enzyme-linked immunosorbent assay (ELISA) and Western blot, are very useful for clinical evaluation; but cross-reactions with *Ascaris* have been reported (Petithory *et al*., 1991).

Control: Human infection can be prevented by not eating raw fish. Most species of anisakids that are dangerous for humans die when exposed to temperatures of –20°C for 24 hours or 60°C for one minute. Since these are the temperatures to which the larva must be exposed, and since there are a few species that are more resistant, it is recommended that the fish be cooked at 70°C or frozen to –20°C for 72 hours in order to have a margin of safety. The freezer unit of a good home refrigerator can generally achieve temperatures of –20°C. The requirement that fish be subjected to low temperatures before being sent to market has drastically decreased the infection in the Netherlands. Salting is also effective when concentrated salt solutions that reach all parts of the fish are used. Prohibiting the sale of fish that has not undergone these processes is the most effective measure for controlling anisakiasis in the community. It is also important to eviscerate fish immediately after they are caught to prevent the *Anisakis* larvae from passing from the intestine to the muscle. Apparently, salmon farming prevents their infection with anisakids; Deardorff and Kent (1989) found that all the wild salmon they caught in the state of Washington, US, were infected with *A. simplex,* but none of those bred in commercial pens had the parasite.

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ASCARIASIS

ICD-10 B77

Synonyms: Ascaridiasis, ascaridiosis.

Etiology: The agents of human ascariasis are the nematode of humans, *Ascaris lumbricoides*, and occasionally, the nematode of swine, *A. suum*. The two species are closely related and show only slight morphologic and physiologic differences (Barriga, 1982). Both species can occasionally infect the heterologous host and reach a certain degree of development inside it. The literature mentions that *A. lumbricoides* infects chimpanzees, gorillas, rhesus monkeys, and swine. Experimentally, it has been possible to infect suckling pigs with *A. lumbricoides,* and the nematodes have reached maturity and produced eggs. In addition to swine,

A. suum infects goats, bovines, sheep, and humans, but it rarely reaches maturity in the latter; in general, the nematode does not go beyond the larval stages in the lung and only rarely advances to the intestinal phase.

Ascarides are large nematodes: the female is 20–35 cm long and 3–6 mm in diameter; the males are smaller and have a curved distal portion. The life cycles of both seem to be similar. The eggs of *A. suum,* which are eliminated with the feces, contain just a single cell. Under ideal conditions of humidity, temperature, shade, and availability of oxygen, a third-stage infective larva develops within the egg in 15 to 20 days; under adverse conditions, this process can take much longer. Once a new host ingests the eggs with food or drinking water, the infective larvae emerge from the egg in the intestine and invade the mucosa of the cecum and colon in a few hours, remain there approximately 12 hours, and migrate to the liver via the portal circulation (Murrell *et al*., 1997). The larvae are then carried in the bloodstream from the liver to the heart, and from there to the lungs. After a period of time, they break out of the pulmonary capillaries, enter the alveoli, and migrate through the bronchial tubes and trachea to the pharynx, from whence they are swallowed and carried to the intestine. In the intestine, they complete their maturation and develop into male and female adults. In man, the prepatent period of *A. lumbricoides*—from the onset of infection until the eggs appear in the feces—is 60 to 75 days; in swine, the prepatent period of *A. suum* is 50 to 60 days.

Geographic Distribution and Occurrence: Ascariasis is one of the most widespread parasitoses, and both *A. lumbricoides* and *A. suum* are found worldwide. It has been estimated that between 644 million and more than 1 billion persons are infected, 42 million of whom are in Central and South America. The estimated worldwide mortality due to ascariasis is 20,000 per year due to intestinal complications; annual morbidity is a million cases, mainly due to pulmonary disorders and malnutrition (Walsh and Warren, 1979). The parasitosis is most prevalent in rural areas, where contamination of the soil and contact between hands or food and larvae are more common, and in hot, humid areas, which favor maturation of the eggs. The highest rate of infection is found in children, probably because of their less hygienic habits, but also because an immune resistance is acquired along with the infection. Prevalence rates vary considerably according to differences in environmental sanitation, health education of the population, personal and food hygiene, type of soil and climate, and other factors.

A. suum is found wherever swine are raised. Studies carried out in slaughterhouses have shown that the prevalence rate is high, ranging from 20% to 70% or more. The highest rate is found in piglets 2 to 5 months old; it declines with age thereafter. Since swine have the same contact with the soil at any age, the difference is believed to represent some level of acquired immunity against the infection. It is not known to what extent *A. suum* is involved in human infection, but it is probably not very important. Suckling pigs have been infected experimentally with embryonated eggs of *A. lumbricoides,* resulting in a patent infection, with adult, egg-laying parasites. Cases caused by accidental ingestion of *A. suum* eggs have been seen in a laboratory worker and some students, and one case occurred in a child who ingested swine feces. Intestinal infection was verified in 7 of 17 volunteers after each one was administered 25 eggs of *A. suum* containing infective larvae. These facts indicate that human intestinal ascariasis by *A. suum* can occur, but is probably seldom recognized.

A World Health Organization (WHO) Expert Committee on the Control of Ascariasis said, "When infective eggs are ingested the larvae of *A. suum* unquestionably develop in the intestine, and migrate to the lungs in man as they do in many other mammals. It is a reasonable assumption that a significant proportion of respiratory illnesses observed in people having contact with pigs is caused by *A. suum* as well as by *A. lumbricoides*" (WHO, 1967). In developing countries where humans and swine are in close contact and personal and environmental hygiene are deficient, it could be anticipated that the larval phase of *A. suum* might participate together with *A. lumbricoides* in the pulmonary alterations caused by the parasite's migration, and that a small fraction of human intestinal ascariases might be due to the porcine parasite.

The Disease in Man and Animals: The course of the disease and the symptomatology are similar in both humans and swine. Children and suckling pigs are most affected. In the early age group, not only is the rate of infection higher, but parasite burden is larger. Two phases of the disease are distinguished: the initial phase, produced by migrating larvae, and the latter phase, caused by adult parasites.

Invasion of the liver of swine and turkeys by the ascarid larvae produces traumatic microfoci which become inflamed and heal with connective tissue. These microlesions are more serious and show allergic components in reinfections, but rarely result in clinical signs (Barriga, 1997). In man, there is generally no hepatic component in the migration, although it has been shown that the excreta and secretions of *A. lumbricoides* cause liver damage in hamsters (Mazumder *et al*., 1992). The pulmonary phase is characterized by respiratory symptoms attributable to the damage produced by the larvae during pulmonary migration. In intense and repeated larval invasions, the symptomatology consists of fever, irregular and asthmatic breathing, and spasmodic coughing. Aberrant larvae located in the brain, eyes, and kidneys are rare, but can give rise to serious symptoms. Recently, studies conducted principally in Japan have confirmed several human cases of visceral larva migrans in patients with serologic reactivity against *A. suum*. These cases have been attributed to infections with the swine ascarides (Inatomi *et al*., 1999). The same situation has occurred in France (Petithory *et al*., 1994). Ascariasis caused by *A. lumbricoides* was once prevalent in Japan, but its incidence has been reduced to less than 0.01%. That notwithstanding, between 1994 and 1995, 14 human cases with high peripheral eosinophilia, elevated titers against *Ascaris,* and absence of *Ascaris* eggs in the feces were found. Most of the patients were asymptomatic, but laboratory tests showed liver dysfunction in seven and pulmonary infiltration in five. All lived in an area with many pig farms. Based on this evidence, the investigators believe that it was an epidemic of ascariasis by *A. suum* (Maruyama *et al*., 1997). Japanese investigators also described an eosinophilic gastroenteritis caused by *A. suum* in man, similar to the one caused by *Ancylostoma caninum* and described by the Australians (Takeyama *et al*., 1997).

In the intestinal phase with adult ascarides, the symptomatology also depends on the number of parasites. Mild infections are generally asymptomatic; but when the parasite burden is larger, there may be vague abdominal discomfort, colic, diarrhea, and vomiting. The most serious complications in children include intestinal obstruction by a large mass of parasites, obstruction of the pancreatic choledoch or duct, and complications resulting from the aberrant migration of adult parasites to various organs. Large numbers of ascarides in the intestines can cause diarrhea and stunted

development in swine. Food conversion is affected and susceptibility to viral respiratory infections is increased in infected swine, but there are no other clinical manifestations (Barriga, 1997).

No information is available on the frequency and seriousness of the disease caused by the larval phase of *A. suum* in humans. Four students who ingested a large number of *A. suum* eggs with their food manifested, after 10 to 14 days, pulmonary infiltration, eosinophilia, asthmatiform symptoms, and an increase in circulating IgE, indicating the allergic nature of the disease. The adult larvae of *A. suum* remain in the human intestine a relatively short time—approximately 10 months—judging from the experimental infections induced in volunteers.

Source of Infection and Mode of Transmission: Humans are the reservoir of *A. lumbricoides,* as swine are for *A. suum.* The sources of infection include soil (geohelminthiasis), edible plants, or drinking water contaminated with fecal matter containing eggs of *Ascaris.* Transmission to man can occur directly from the soil or indirectly, by means of dust, water, vegetables, or objects to which the parasite's eggs have adhered. The infection is almost always acquired by ingestion, but there are unconfirmed reports that, in some areas, it may occur by inhalation of eggs. The main factor in maintaining human ascariasis is fecal contamination of the soil around dwellings, particularly in family gardens, and contamination of sources of water for drinking or irrigation. Clay soils are particularly suited to the survival of *Ascaris* eggs because they retain moisture. To have some idea of the degree of soil contamination possible, it should be borne in mind that a single female *Ascaris lumbricoides* can produce 200,000 or more eggs per day, and a female *A. suum* can produce 1 to 2 million. It is not uncommon to find 100 eggs per gram in a child's feces and 2,000 eggs per gram in swine feces. The higher rates of infection in preschool children are explained by their more frequent contact with soil and their lack of personal hygiene. The epidemiology of swine ascariasis is similar to that of human ascariasis, although the swine are in permanent and close contact with the soil.

Role of Animals in the Epidemiology of the Disease: The role played by swine in the epidemiology of human ascariasis is not well defined. It has been confirmed experimentally that cross-infections can occur between swine and humans or between humans and swine. However, the frequency of heterologous infections is unknown, given the difficulty of distinguishing between the two agents. In man, *A. suum* rarely achieves oviposition because it stays a relatively short time in the intestine. However, there is no doubt that intestinal infections by *A. suum* occur in humans, as illustrated by the case of a child in Great Britain who ingested dirt from a garden that had been fertilized with swine excreta. When the parasite was expelled, study showed it to be *A. suum* (Crewe and Smith, 1971). Later, a case of intestinal obstruction by multiple specimens of *A. suum* was described in a 9-year-old girl in Zimbabwe (Davies and Goldsmid, 1978).

An investigation into the role of swine in the epidemiology of *A. lumbricoides* ascariasis was carried out in a village in southwestern Nigeria where the inhabitants lived in close contact with swine. The study identified the intestinal infection caused by *A. lumbricoides* in both swine and the human population. However, an effort to experimentally infect pigs with eggs of *A. lumbricoides* was unsuccessful (Kofie and Dipeolu, 1983). Other studies have indicated that repeated exposure to small doses, as occurs in nature, is more effective than infection with a large number of eggs.

Occasionally, *A. lumbricoides* has been found in the intestine of nonhuman primates, and its larvae have been found in the lungs of several other species of animals. *A. suum* can infect cattle, sheep, and goats and can reach sexual maturity in these animals. However, in some described cases, doubt exists about the identity of the parasite. While *A. lumbricoides* and *A. suum* are distinguished by studying the denticles on the lips, which are different in the two species, it is now known that the shape of the denticles of the swine parasite changes over time.

Diagnosis: In the hepatic or pulmonary migration phase of the larvae, it is difficult or impossible to confirm the diagnosis by means of laboratory tests. Sometimes larvae can be found in the bronchial secretions of both humans and suckling pigs. Hepatic and pulmonary migrations produce antibodies that can be detected using various immunological tests. However, while cross-reactivity is rare with other superfamilies of nematodes, *Anisakis simplex, A. suum, A. lumbricoides,* and *Toxocara canis* share common somatic and excretory antigens (Kennedy *et al*., 1988).

In the intestinal phase, the characteristic eggs are found in the feces.

Control: Human ascariasis is a public health problem, especially in areas with a low economic level, deficient environmental sanitation, and low standards of personal hygiene. In several industrialized countries, the prevalence rate of the parasitosis has been significantly reduced as a result of an improved standard of living, without the adoption of specific control measures. The principal measures that should be included in a control program consist of massive and periodic treatment of the human population to prevent environmental contamination, sanitary excreta disposal, provision of potable water, and health education for the purpose of instilling personal hygiene habits in the population. In some countries (Korea, Israel, and Japan), human ascariasis has been practically eradicated.

It is important to remember that ascaris eggs are extremely resistant to environmental factors. In experiments with *A. lumbricoides*, contamination of the soil with eggs has persisted for up to five years. Treatment of solid sewer waste in stabilization ponds is insufficient to kill the eggs of ascarides; Ayres *et al*. (1993) reported that up to 12% of *A. lumbricoides* eggs recovered from a pond were viable after 2.5 years of operation. Treatment of sewer waste with ammonium hydroxide at 30°C, or at 40°C without the alkali, destroys them, but a temperature of 22°C, with or without ammonium, has no lethal effect (Ghiglietti *et al*., 1995). While it has not been employed, biological control of ascarides seems to be a possibility. Apart from the insects that eat the eggs, at least the fungus *Verticillium chlamydosporium* invades the eggs and kills the *A. lumbricoides* larvae (Lysek and Sterba, 1991).

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BAYLISASCARIASIS

Etiology: The agents of this infection are larvae of *Baylisascaris procyonis*, an ascarid found in the small intestine of raccoons. Natural patent infections have been found in two dogs, and rats, squirrels, and opossums have developed some specimens of adult ascarids in experimental infections. Other species of *Baylisascaris* are found in skunks, badgers, sables, and bears; no human infections by these other

species have been reported, although the larvae migrate in mice and experimental infections have been produced in mice and chickens with *B. transfuga*.

B. procyonis is a typical ascarid; the female measures about 23 cm and the male, about 12 cm. The females lay eggs in the small intestine; these are expelled with the feces and, in three to four weeks, develop into infective larvae. These eggs may be eaten by the raccoons themselves or by intermediate hosts such as rodents, rabbits, or birds. Larvae that seem to belong to *B. procyonis* have been found in 19 species of mammals—mainly rodents and lagomorphs—and in 13 species of birds. These appear to be intermediate rather than paratenic hosts (see below). Young raccoons can become infected by ingesting infective eggs, but adult raccoons become infected only by ingesting the parasites in intermediate hosts. In young raccoons, the larvae develop first in the intestinal mucosa and then in the lumen; the eggs start to appear in the feces 50 to 76 days after infection. In adult raccoons, the larvae develop in the intestinal lumen and the eggs start to appear 32 to 38 days after infection. There is no extra-intestinal migration; transmission through the uterus or milk has not been studied.

Geographic Distribution and Occurrence: The infection is presumed to occur in areas where raccoons live. The prevalence of the infection in these animals can be very high, particularly in the northern and northeastern parts of the US; the infection in young animals has been 92% and 94%, respectively, in these areas. Seventy-two percent of 1,425 raccoons studied in the state of Indiana, 82% of 310 raccoons in the state of Illinois, and 70% of 33 raccoons in the state of Texas were found to be infected (Kerr *et al*., 1997). Prevalence of the infection is low in the western US and very low to nonexistent in the southeast.

The first human infection was reported in 1984 (Huff *et al*., 1984). Up until 1989, there were just two confirmed and two suspected cases of cerebral baylisascariasis and two cases of ocular baylisascariasis. Between 1989 and 2000, there were reports of one case of subacute diffuse unilateral neuroretinitis (Goldberg *et al*., 1993), one case of meningoencephalitis in a 13-month-old child (Cunningham *et al*., 1994), and one cardiac case in a 10-year-old child (Boschetti *et al*., 1995).

The Disease in Man: Man is an intermediate rather than paratenic host. The human infection seems to be identical to that found in laboratory animals, in which it has been shown that the *B. procyonis* larvae continue to migrate, and that they molt and grow from 300 to 1,900 μm until they develop into eosinophilic granulomas.

B. procyonis causes visceral, ocular, and cerebrospinal syndromes in man. The severity of the disease depends on the number, location, and activity of the larvae. A mild infection with a small number of larvae, which mostly encapsulate in the connective and muscular tissue, will probably not produce clinical manifestations. A more intense infection can cause the typical signs of visceral larva migrans: fever, leukocytosis, eosinophilia, hepatomegaly, and pneumonitis. Due to the size and motility of the larvae, any infection that causes symptoms of visceral larva migrans can probably also cause nervous symptoms. The symptoms appear two to four weeks after infection, and include lethargy, lack of muscular coordination, torticollis, ataxia, and nystagmus, which progress to stupor, coma, and death. Ocular cases occur when the larvae invade the eye; the symptoms include unilateral vision loss, photophobia, and retinitis. Tunnels have been observed in the retina at seven days postinfection in experiments in monkeys.

The Disease in Animals: Infected raccoons are asymptomatic. In endemic areas, adult animals harbor 12 to 14 parasites and young animals harbor 48 to 62. Severe infections in young animals produce intestinal obstruction. There have been cases of symptomatic systemic or fatal infection caused by *Baylisascaris* larvae in puppies (Rudmann *et al*., 1996), a gibbon in a zoo (Ball *et al*., 1998), and a newborn lamb (Anderson, 1999), and other cases have been reported in monkeys, rodents, lagomorphs, and birds.

Source of Infection and Mode of Transmission: The source of infection is infected raccoons, which can eliminate millions of eggs a day. The eggs can survive in the soil for months or years. Man is thought to become infected accidentally by ingesting food or water, or through hands contaminated with the feces of infected raccoons.

Diagnosis: The human infection is suspected when symptoms of visceral larva migrans are accompanied by signs of alteration of the central nervous system, high peripheral eosinophilia, eosinophilia of the cerebrospinal fluid, and a history of exposure to raccoons. There are immunological tests for baylisascariasis, in particular, enzyme immunoassay and immunoelectrotransfer (Cunningham *et al*., 1994). *Baylisascaris* is antigenically closer to *Ascaris* than to *Toxocara*. The four human cases reported since 1994 were positive for *Baylisascaris* and negative for *Toxocara*, but one was positive for *Ascaris*. In raccoons, diagnosis of the infection is made by a finding of eggs in the feces or parasites in the feces or vomit. The eggs are similar to those of *T. canis*, but smaller. *Baylisascaris* eggs measure 62–70 µm by 52–58 µm, while *T. canis* eggs measure 85–90 by 73–77 µm.

Control: According to the available information, human baylisascariasis is very rare, but its control is important because people tend to keep raccoons as pets and the disease has no treatment. Pet raccoons should be examined for the parasite's eggs. If the examinations are positive, they should be treated with a medication effective against ascarids. Also, it should be borne in mind that the eggs can appear in the feces up to two and a half months after infection. In areas where raccoons are present, chimneys and other openings through which these animals can enter a dwelling should be sealed. If nests are found, the feces should be burned. Like those of the other ascarids, *Baylisascaris* eggs are highly resistant to external environmental factors and disinfectants. If an area needs to be decontaminated, it is best to treat it with fire. Dryness and sunlight will kill the eggs, but it is not known how long this takes.

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CAPILLARIASIS

ICD-10 B81.1 Intestinal capillariasis; B83.8 Other specified intestinal helminthiases

Synonym: Capillariosis.

Etiology: The agents of intestinal, hepatic, and pulmonary capillariasis are the nematodes *Capillaria philippinensis, C. hepatica,* and *C. aerophila,* respectively. The three species have different development cycles.

C. philippinensis is a filiform nematode. The female measures 2.5–5 mm long, and the male 1.5–4 mm. Its anterior extremity lodges in the mucosa of the small intestine in humans, particularly in the jejunum. The females can produce either larvae or eggs. The eggs are barrel-shaped and have opercula at both ends, very similar to those of *Trichuris*; they are eliminated with the feces, and when they enter fresh or contaminated bodies of water, they embryonate in 10 to 14 days and are ingested by a fish, in whose intestine they form infective larvae in approximately three weeks. If a larva is eaten by an appropriate host (man or a bird), it continues to develop, reaches the adult stage in about two weeks, and begins to lay larvae. These larvae do not leave the host's intestine. They develop to maturity and lay eggs, which will begin the external infection cycle anew. However, some females continue laying eggs, which mature in the host intestine without leaving it. In most cases, there is an overlap of oviparous and larviparous females, and as a result there is a combination of eggs, larvae, and adults in the host's feces (Neva and Brown, 1994). Although man is the only known host, it is thought that piscivorous birds are the natural hosts and that man is merely an accidental host who becomes infected by eating infected fish, which are the intermediate hosts (Cross and Basaca-Sevilla, 1991). In addition, experimental infections have been produced, using fish larvae, in monkeys and gerbils.

C. hepatica is also a filiform nematode, but it is longer than *C. philippinensis*; the females measure 5–8 cm long, and the males about half that. This is a common parasite of rodents and, occasionally, many other mammals. It lodges in the hepatic

parenchyma, where it lays eggs, which remain trapped in the organ but do not develop to the infective stage. In order for *C. hepatica* to continue its development, the infected rodent must be eaten by a carnivore, which digests and releases the eggs enclosed in the hepatic tissue and eliminates them with the feces into the external environment, where they disseminate. To become infective, the eggs require a one- to two-month incubation period under favorable conditions of temperature, shade, aeration, and moisture. When the infective eggs are again eaten by a rodent, the larvae are released in the intestine, enter the intestinal wall, and are carried through the bloodstream to the liver, where they mature in approximately a month. *C. hepatica* is a helminth that is transmitted via the soil; therefore, hepatic capillariasis is a geohelminthiasis. In moist soils, the eggs can remain viable for many months.

C. aerophila is a filiform parasite some 2–3 cm long. Its anterior extremity lodges in the mucosa of the trachea and bronchi of foxes, dogs, coyotes, and more rarely, other wild animals or cats. Human infection is rare. The eggs enter through the airways, are carried by the cilia and by coughing to the pharynx, are swallowed, and are eliminated with the feces. They develop an infective larva in five to seven weeks. When an appropriate host, such as a fox or dog, ingests the eggs, the larvae are released into the intestine and migrate through the bloodstream to the lungs in 7 to 10 days. Around 40 days after infection they reach maturity and begin oviposition.

Geographic Distribution and Occurrence: Intestinal capillariasis caused by *C. philippinensis* was first recognized in 1963 on Luzon Island in the Philippines. During the next five years, more than 1,500 cases were reported, with a 6% fatality rate. However, the prevalence of the infection seems relatively low, as eggs of the parasite were found in the feces of less than 3% of the 4,000 inhabitants of the endemic area examined during the epidemic outbreak in 1967 (Banzón, 1982). Aside from the Philippines, the most affected country seems to be Thailand, where 17 reported cases were reviewed (Peng *et al.*, 1993). From 1989 to 2000, 41 cases were reported throughout the world: 3 in Egypt, 1 in the United Arab Emirates, 2 in Spain, 1 in Greece, 1 in India, 1 in Indonesia, 3 in the Republic of Korea, 20 in Thailand, and 9 in Taiwan. One of the cases diagnosed in Spain involved a citizen of Colombia (Dronda *et al.*, 1993).

C. hepatica is found on all continents among synanthropic and wild rodents, with a prevalence rate that ranges from 0.7% to more than 85%. In Marseilles, France, the parasite was found in 44% of 82 rats (Davoust *et al.*, 1997), and in Thailand, in 8% of 76 rats (Namue and Wongsawad, 1997). Besides rodents, the parasite has occasionally been found in other species of domestic and wild mammals. Infection in man is very rare; up until 1985, 11 cases of hepatic infection had been confirmed in Europe (9 in the former Czechoslovakia and 2 in Italy) and 14 others in the rest of the world (among them, 1 in Brazil, 5 in the US, 1 in Mexico, and 3 in South Africa). From 1989 to 2000, 10 other cases were reported: 1 in Germany, 1 in Japan, 3 in Mexico, 1 in the Republic of Korea, 3 in Switzerland, and 1 in Yugoslavia. In 1997, the worldwide prevalence was estimated at some 30 cases (Davoust *et al.,* 1997).

C. aerophila has been identified in animals in North America, Europe, the former Soviet Union, Australia, Chile, and Uruguay. In most animals, the prevalence is under 5% and often below 1%. Prevalences as high as 38% have been reported. Up until 1977, there were only nine known cases of human infection: one in Iran, one in Morocco, and seven in the former Soviet Union (Aftandelians *et al.,* 1977).

The Disease in Man: Intestinal capillariasis caused by *C. philippinensis* is a serious and fatal disease if not treated in time. Most patients are 20–45 years of age, with males predominating. The disease begins with insignificant symptoms such as borborygmus and vague abdominal pains. Intermittent diarrhea, which becomes persistent as the disease progresses, begins in two or three weeks, along with marked weight loss and cachexia. Gastrointestinal function is seriously affected; in addition, malabsorption and the loss of large quantities of protein, fat, and minerals have been confirmed. Death occurs as a result of heart failure or an intercurrent infection a few weeks or months after the onset of symptoms (Cross, 1992).

Clinical cases of hepatic capillariasis are due to a massive invasion of the liver by *C. hepatica*, which reaches maturity and begins to produce eggs in that organ. The disease is serious and frequently fatal. A prominent sign is hepatomegaly; other very common symptoms are high morning fever, nausea, vomiting, diarrhea or constipation, abdominal distension, edema of the extremities, splenomegaly, and sometimes pneumonia. A large part of the symptomatology is due to secondary infections in weakened patients, most of them children. In a case in an adult from Nigeria, the most prominent pathological feature was severe hepatic fibrosis and functional disorders related thereto (Attah *et al*., 1983). Laboratory examinations find hyperleukocytosis with eosinophilia and hypochromic anemia, with abnormal values in liver function tests. Autopsy reveals the presence of grayish-white nodules on the surface of the liver. Histologically, the principal lesions consist of necrotic foci and granulomas. The adult parasites and eggs are found in the necrotic masses. Subclinical human infections undoubtedly occur, as attested to by solitary hepatic granulomas found in nine individuals autopsied during a study in the former Czechoslovakia. In seven of the nine cases, only one parasite larva was found in the lesions (Slais, 1973).

Pulmonary capillariasis caused by *C. aerophila* causes asthmatiform symptoms with coughing, mucoid or sometimes blood-tinged expectoration, fever, dyspnea, and moderate eosinophilia. Biopsy reveals granulomatous lesions with cellular reaction to a foreign body (Aftandelians *et al.*, 1977).

The Disease in Animals: *C. philippinensis* has not been found in land animals, but fish-eating birds are believed to be the natural hosts, though it is not known whether it causes symptoms in them. Experimental infection in primates of the genus *Macaca* or in wild rats is asymptomatic. In gerbils, on the other hand, the infection is manifested by a symptomatology similar to that in man (Banzón, 1982).

C. hepatica infections in rodents cause damage proportional to the parasite burden: mild infections may be subclinical; intense infections can cause hepatitis, splenomegaly, ascites, and eosinophilia; and massive infections can eventually cause hepatic necrosis. Although hepatic capillariasis does not have a high mortality rate, it could contribute to the control of rodent populations (McCallum, 1993). The infection was also found in one dog (Brander *et al.*, 1990).

C. aerophila infections are most severe in foxes, particularly in young animals. Intense infections can cause rhinitis, tracheitis, and bronchitis, which may end in bronchopneumonia caused by a secondary bacterial infection. Massive infections are often fatal.

Source of Infection and Mode of Transmission: Man is the only known definitive host of *C. philippinensis*. There are epidemiological reasons to suspect that the definitive natural hosts are piscivorous birds and that the intermediate hosts are fish in clean

or contaminated waters. The main source of infection for humans seems to be infected fish, and the manner of infection is the ingestion of undercooked fish. Contamination of bodies of water with the excreta of humans or the birds that serve as hosts ensures perpetuation of the cycle. Given that the infection can be transmitted experimentally from one gerbil to another, with the parasite at different intestinal stages of development, direct person-to-person transmission may also occur (Banzón, 1982).

The main reservoir of *C. hepatica* is rodents. The infection is transmitted by ingestion of embryonated eggs that have been released from the liver of rodents and disseminated through the external environment by carnivores. In the peridomestic environment, the disseminating agents can be cats and dogs that hunt rodents. The eggs can also be released by cannibalism among rodents or by death and decomposition of their cadavers. For man, the source of direct infection is the soil, and the source of indirect infection is contaminated hands, food, or water. There are more than 30 described cases of spurious infections due to the ingestion of raw liver of rodents or other mammals, such as squirrels, monkeys, and wild boars, infected with unembryonated eggs. In such cases, the eggs of the parasite pass through the human digestive tract and are eliminated with the feces without causing true infection.

The source of *C. aerophila* infection for man and animals is the soil, where the eggs deposited with the feces of animals continue their incubation and the larvae reach the infective stage. Larvae can remain viable inside the eggs for a year or more. Children probably acquire the infection by ingesting dirt or water and food contaminated with eggs.

Diagnosis: A diagnosis of intestinal capillariasis caused by *C. philippinensis* is suspected in endemic zones when prolonged diarrhea with borborygmus and abdominal pain is observed in individuals who eat raw fish. Coprologic examination confirms the diagnosis, though a series of them may be necessary.

A specific diagnosis of hepatic capillariasis is suspected from the presence of fever, hepatomegaly, and eosinophilia in a patient in an endemic area. Confirmation can be obtained only from liver biopsy and identification of the parasite or its eggs. The discovery of *C. hepatica* eggs in human feces does not signify infection, but rather the passage of eggs through the intestine after ingestion of the liver of an infected animal.

Diagnosis of pulmonary capillariasis can be obtained by confirmation of the presence of eosinophils or the typical eggs in the sputum, or by biopsy of pulmonary tissue in which larvae or aspirated eggs can be found.

Control: In endemic areas, intestinal capillariasis can be prevented by refraining from eating raw or undercooked fish. Patients should be treated with thiabendazole, both for therapeutic reasons and to decrease the dissemination of parasite eggs. Hygienic elimination of human excreta is very important.

Hepatic capillariasis is a geohelminthiasis in which the eggs develop to the infective stage in the soil; they then penetrate the host orally through contaminated food or water or, in the case of man, via contaminated hands that are brought to the mouth or handle food. Consequently, individual prevention consists of carefully washing suspected foods and avoiding eating them raw; boiling both water and suspected foods; and washing hands carefully before eating. Since the infection is common in young children, who often eat dirt, and in homes in which rats abound, supervision of children's hygiene and rodent control can be important.

To prevent pulmonary capillariasis in animals and personnel on fox breeding farms, the animals must be kept in clean, well-ventilated, and sunny facilities to promote the destruction of the eggs. Young animals, which are the most susceptible and have the largest parasite burden, must be separated from adults. Any infection must be treated as soon as possible to prevent contamination of the environment with the eggs. Individuals can avoid infection by following strict hygiene rules to prevent infections with geohelminths.

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CUTANEOUS LARVA MIGRANS

ICD-10 B76.9 Hookworm disease, unspecified

Synonyms: Creeping verminous dermatitis, serpiginous eruption, larva currens (infection caused by the larvae of *Strongyloides* spp.).

Etiology: Cutaneous larva migrans is a clinical description more than an etiologic diagnosis. The principal etiologic agent is the infective larva of *Ancylostoma braziliense*, an ancylostomid of dogs, cats, and other carnivores. Experimental infections have been produced in human subjects with other animal ancylostomids, such as *A. caninum* of dogs, *Uncinaria stenocephala* of dogs and cats, and *Bunostomum phlebotomum* of cattle. Since cases of cutaneous larva migrans have been seen occasionally in areas where these latter parasites are prevalent, it is assumed that they can also infect man in nature. However, the larvae of *A. braziliense* produce much more hyaluronidase (the substance that makes it possible to break down intercellular cement and invade tissue) than do those of the other ancylostomids (Hotez *et al*., 1992), which may explain the greater incidence of this species. Cutaneous infection caused by the larvae of *Strongyloides stercoralis*, which progresses more rapidly than that caused by the larvae of ancylostomids, is currently called "larva currens," but it is also known as cutaneous larva migrans. In addition, some authors extend the validity of this term to gnathostomiasis (Díaz-Camacho *et al*., 1998). Also, a case of invasion of human skin by *Pelodera strongyloides*, a free-living soil nematode related to *S. stercoralis* (the third known case in the world), was reported as cutaneous larva migrans (Jones *et al*., 1991). The name "cutaneous larva migrans" has even been applied to the larvae of some arthropods that can colonize human skin, such as *Gasterophylus* and *Hypoderma* (Cypess, 1982). In individuals who have suffered previous infections, the human ancylostomids *A. duodenale* and *Necator americanus* can cause a picture of cutaneous allergy similar to that of cutaneous larva migrans. Here consideration is given only to the canine ancylostomes, with particular focus on *A. braziliense*.

Man is an aberrant host, in which the infective larvae cannot complete their development cycle and become adults. *A. braziliense* is a small species of *Ancylostoma*; the female measures about 1 cm long by 0.37 mm wide. Its life cycle is similar to that of the other ancylostomes (see the chapter on Zoonotic Ancylostomiasis).

Geographic Distribution and Occurrence: *A. braziliense* occurs in tropical and subtropical areas; *A. caninum* and *B. phlebotomum*, in temperate climates; and *U. stenocephala*, in colder parts of temperate regions (Barriga, 1997). Human cutaneous larva migrans occurs more frequently in tropical and subtropical areas. The disease has been reported in Argentina, Australia, southern Brazil, the Caribbean islands, France, Germany, India, Israel, Mexico (especially along the Gulf Coast), the Philippines, South Africa, Spain, southeastern US, and Uruguay, among other places. The prevalence of human infection is unknown. The fact that cases appear only sporadically in the literature suggests that it is a relatively infrequent condition. Nevertheless, a hospital in Paris, France, recorded 269 cases in a two-year period (Caumes *et al*., 1995), and a hospital in Munich, Germany, registered 98 cases in four years (Jelinek *et al*., 1994), most of them in travelers who had acquired the infection outside the country.

Infections caused by *A. braziliense* and other ancylostomes in dogs and cats can reach high prevalence rates: Malgor *et al*. (1996) found *A. braziliense* in 49% and *A. caninum* in 96% of 80 dogs autopsied in Uruguay, while Saleh *et al*. (1988) found *Ancylostoma* sp. in 68% of dogs examined in the Netherlands Antilles.

The Disease in Man: The infective larva produces a pruriginous papule upon penetrating the skin. In the days that follow, the larva travels around in the germinal layer and produces sinuous tunnels, advancing a few millimeters to several centimeters a day and forming vesicles along the tunnels on the outer surface of the skin. The migration of the larvae and the corresponding tissue reaction cause intense pruritus, especially at night, and may keep the patient awake. Secondary bacterial infections are common because the pruritus induces the patient to scratch. The lesion, which can be single or multiple, is most often located on the lower extremities (73% of the cases) and less frequently on the trunk and upper extremities (7% of the cases), but it can occur on any part of the skin exposed to contaminated soil. Lesions on the palm of the hand or the sole of the foot are particularly painful. The larvae usually remain alive and travel in the skin for two to eight weeks, at the end of which the disease is cured spontaneously. However, there have been patients in whom the infection persisted for as long as 18 to 55 months (Richey *et al*., 1996). In a few cases, the levels of IgE and peripheral eosinophilia are elevated (Jelinek *et al*., 1994). In one-third of the cases, the larvae manage to invade the lungs. Some patients suffer a transitory pneumonitis with eosinophilia (Loeffler syndrome), and in such cases larvae may be found in the sputum. *Ancylostoma* larvae have also been found in the cornea. This finding confirms the hypothesis that the larvae of animal ancylostomids can sometimes produce visceral infections in man. When the cause of larva currens is *S. stercoralis*, the lesion is less clearly defined than in cutaneous larva migrans and is characterized by intense erythema as well as by its rapid progression and quick disappearance. Oral albendazole and ivermectin have given excellent therapeutic results.

The Disease in Animals: The disease caused by ancylostomes in carnivores is mainly intestinal and is manifested by diarrhea, anemia, and malabsorption. Invasion of the skin by the larvae of *B. phlebotomum* in cattle or *U. stenocephala* in dogs can cause an allergic dermatitis, especially in repeated infections, which is generally short lived. The lesions are limited to the interdigital spaces, and the most prominent signs are erythema, pruritus, and papules that disappear about five days after the initial infection. Occasionally, the reactions are quite severe, prompting self-mutilation.

Source of Infection and Mode of Transmission: The source of infection is infective ancylostomid larvae found in the soil. The larvae develop from eggs that are shed in the feces of infected dogs or cats and land in a favorable environment—i.e., with warm temperatures and high humidity and sheltered from direct sunlight. Moist and sandy soils are the most propitious for development of the larvae. In countries with a temperate climate, the human infections occur in summer, whereas in tropical climates, they occur during the rainy season. Man is infected by contact with contaminated soil. The groups most exposed to the infection are children who play in the sand; workers who have close contact with the soil, such as gardeners, farmers, construction workers, and miners; and people who spend time at the beach. A study of contamination of children's sandboxes showed that *Toxocara* species

were much more prevalent than *Ancylostoma*, perhaps because *Toxocara* eggs are more resistant to environmental conditions (Barriga, 1997).

Diagnosis: Clinical diagnosis is based on the nature and symptomatology of the lesions—i.e., serpiginous inflammations and intense pruritus. Although clinical detection can be challenging, in a series of 269 patients presenting at a tropical disease unit, cutaneous larva migrans was the most frequent diagnosis (25%), compared with pyoderma (18%), pruritic arthropod-reactive dermatitis (10%), myiasis (9%), tungiasis (6%), and urticaria (5%) (Caumes *et al*., 1995). Diagnosis can be confirmed by biopsy of the affected skin to confirm the presence of larvae, but this method is only about 25% efficient. It is also difficult to identify the parasite in histological section, and because of this difficulty, it has not been possible to determine the percentage of cases due to *A. braziliense* compared with other species. Differential diagnosis should take into account the other parasites mentioned at the beginning of this chapter.

Control: The principal control measures are regular treatment of dogs and cats and the elimination of stray animals to reduce contamination of the soil. Dogs and cats should not be allowed on beaches or in places where children play in the sand. Whenever possible, areas susceptible to contamination should be kept dry, clean, and free of vegetation. The larvae of *Ancylostoma* live for almost a month in moist and grassy soils, but only one or two days on terrain that is bare, dry, and in direct sunlight (Barriga, 1997). Since the infective larvae develop in about four to five days at optimum temperatures, the removal of canine feces twice a week also reduces contamination.

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DIOCTOPHYMOSIS

ICD-10 B83.8 Other specified helminthiases

Synonym: Dioctophymiasis.

Etiology: *Dioctophyma* (*Dioctophyme*) *renale* is a large, blood-red nematode that in the adult stage lodges in the kidneys of minks, occasionally other mustelids, and at times, wild and domestic canids. In dogs, the adult female of the parasite can reach up to 1 m long and 5–12 mm wide and is therefore known as the "giant kidney worm." The male is much smaller. The size of the parasite depends on the host species; for example, in minks it is not more than a few centimeters long.

The definitive host eliminates the eggs of the parasite via the urine. The eggs develop in water and, depending on the temperature, form a first-stage larva in 15 to 102 days. The larval eggs must be ingested by the free-living aquatic oligochaete annelid *Lumbriculus variegatus*, in whose intestine they hatch quickly and then invade the coelomatic cavity. There, the larva undergoes two molts and becomes an infective, third-stage larva in 70 to 120 days or more. Several fish, such as *Ictalurus nebulosus* and *Esox lucius* in North America or *Idus* spp. in Europe, or frogs such as *Rana pipiens*, *R. clamitans*, and *R. septentrionalis*, can ingest the infected worm. In that case, the infective larva encysts in the mesentery or liver without continuing its development to the adult stage. These animals are paratenic or transport hosts. If a mink or other suitable host ingests an infected worm or paratenic host, the larva is released by digestion of the tissues, penetrates the mammal's stomach wall, molts in the submucosa, migrates to the liver, passes into the peritoneal cavity, and reaches the kidney. The juvenile nematodes, which are already several centimeters long, penetrate the renal pelvis, mature, and begin laying eggs five or six months after infection. In dogs, some specimens remain in the peritoneal cavity, near the kidney, but never really invade it (Barriga, 1982).

Geographic Distribution and Occurrence: With the possible exception of Africa and Oceania, the parasite is distributed worldwide and has been found in many species of carnivores. The most commonly reported form is canine dioctophymosis. In the Americas, the animal parasitosis has been described in Argentina, Brazil, Canada, Paraguay, Uruguay, and the US, and in other countries as well. Prevalences of between 18% and 48% have been found in minks, 2% in otters, and 1.5% in weasels. Although prevalences of 37% in dogs and 35% in jackals have occasionally been reported, in most cases the infection rate in dogs is under 1%. *D. renale* is, in fact, rarely discovered in veterinary practice; 60% of *D. renale* in dogs

are not located in the liver and are therefore not patent and can go unnoticed. Until 1969, only 204 cases of canine dioctophymosis had been reported in the world literature. It is very infrequently reported in bovines, equines, and swine. These numbers, the fact that the parasite is almost always found in the kidney of minks, from which it can eliminate its eggs to the outside, and the fact that the parasite is found less than half the time in the kidney of dogs, indicate that mustelids, particularly minks, are the definitive natural hosts of the parasite. The infection is very rare in man. Until 1982, the literature described just 13 well-documented cases of infections in the human kidney (Barriga, 1982). There are also three human cases in which larvae of *D. renale* were found in ectopic locations (Gutiérrez *et al.,* 1989).

The Disease in Man and Animals: In humans and dogs, the nematode usually locates in just one kidney, most often the right one, and in most cases, only one parasite is found. As it grows, *Dioctophyma* destroys the renal parenchyma and, in extreme cases, leaves only the capsule of the organ. The most prominent symptoms include renal colic and hematuria or pyuria. In some cases, the parasite migrates to the ureter or urethra and blocks the flow of urine. In dogs, cases in which the parasite remains in the peritoneum are usually asymptomatic, though this localization can occasionally cause peritonitis. The healthy organ compensates for the loss of renal function and generally hypertrophies.

Source of Infection and Mode of Transmission: Minks seem to be the main reservoirs. The definitive wild hosts are infected when they ingest the infected intermediate hosts (worms) or the paratenic hosts (frogs or fish). Humans and, very probably, dogs are accidental hosts that almost always harbor only one parasite. Both are probably infected by eating undercooked fish or frogs. The rarity of human infection is explained by the fact that the larvae are located in the mesentery or liver of fish or frogs, organs that man generally does not consume.

Diagnosis: When the parasite infecting a human or dog is a female that is in contact with the urinary tract, the parasitosis can be diagnosed by observing its eggs in urinary sediment. Renal infections caused by a male parasite or located in the peritoneum can be diagnosed only by laparotomy or at autopsy.

Control: The infection can be prevented, both in humans and dogs, by avoiding the consumption of raw or undercooked frogs and fish.

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DRACUNCULIASIS

ICD-10 B72

Synonyms: Dracontiasis, dracunculosis, guinea-worm disease.

Etiology: The agent of this infection is *Dracunculus medinensis*, one of the longest nematodes known, despite its variable size. The female measures 50–120 cm long and 1–2 mm wide, while the male is much smaller, measuring 12–29 mm long and 0.4 mm wide. The male is rarely seen in patients because it dies soon after copulation. In its adult stage, *D. medinensis* parasitizes man and a variety of domestic and wild animals, including monkeys, carnivores, cattle, and equines. The species *D. insignis*, found in North America, has a life cycle similar to that of *D. medinensis*, but it infects carnivores and rodents, especially those with semiaquatic habits such as raccoons, dogs, skunks, weasels, nutrias, and muskrats. The females of the two species are indistinguishable, but *D. insignis* has not been observed in human infections.

The first-stage larvae of *D. medinensis* are expelled through the skin by the gravid females. In order to continue its development, the larva must be ingested within one to three weeks by an intermediate host, which is a copepod microcrustacean of the genus *Cyclops.* About 15 different species of *Cyclops* are known to serve as intermediate hosts. Once the larva is ingested by an appropriate species of copepod, it will continue its development in the coelomic cavity of the intermediate host for three to six weeks, until it becomes an infective third-stage larva. When the copepod, acting as intermediate host, is ingested in turn by a definitive host, the larva is released in the intestine of the latter, traverses the intestinal wall, and, probably migrating through the lymphatic system, finds a site in deep subcutaneous or retroperitoneal conjunctive tissue, where it becomes embedded. The worms mature in about three to four months. They then copulate, after which the male dies and the female penetrates deeply into the tissue, remaining there for months until her uterus is filled with first-stage larvae. Ten to 14 months after the initial infection, the parasite migrates to the surface of the body, especially the legs, feet, ankles, knees, and wrists, and occasionally other parts, and positions its anterior end in close contact with the inner surface of the skin. There, it produces an irritation which at first forms a hard papule on the skin. The papule soon turns into a vesicle, and eventually, an ulcer. When this part of the skin is immersed in water, the parasite starts to have uterine contractions that rupture the vesicle (if it has not yet ulcerated), and releases about 500,000 first-stage larvae into the external environment. Subsequent contacts with water repeat the phenomenon, but the number of larvae released is smaller. In general, the females live for 12 to 18 months, although many of them die and are expelled spontaneously. Sometimes additional live larvae are extracted from patients.

Geographic Distribution and Occurrence: Dracunculiasis is restricted to tropical and subtropical regions of Africa and Asia, probably because the *D. medinensis* larva develops best at 25°C to 30°C and cannot grow at temperatures lower than 19°C (Muller, 1979). The infection is endemic in several regions of western and eastern Africa, as well as western India and Pakistan. In Africa, it is found within a triangle formed by Côte d'Ivoire, the border between Ethiopia and Kenya, and Mali. The countries most affected are Benin, Ghana, Nigeria, and Togo. In the past, there have been minor endemic foci in parts of Asia, such as Iran, Yemen, Saudi Arabia,

and possibly Iraq, but these foci seem to have disappeared. In 1947, Stoll estimated that there were 43 million infections worldwide, but this figure would appear to be quite exaggerated. The World Health Organization (WHO) calculated the worldwide prevalence in 1976 at about 10 million. However, in 1978, only 26,980 cases were reported. This disease is obviously underregistered. A study carried out in Togo in 1977 found that less than 4% of the cases observed had been reported to the public health authorities (WHO, 1982). In Ghana and Nigeria, the countries with the highest prevalences of dracunculiasis, incidence of the infection in 1991 was down 33% relative to 1990 and 57% relative to 1989 (CDC, 1992). Although in 1992 there were still 3 million people infected and some 100 million at risk for the infection in India, Pakistan, and 17 African countries, these figures represented a dramatic improvement over the situation that existed a decade earlier (Hopkins and Ruiz-Tiben, 1992). In 2000, only 75,223 cases were reported to WHO, all of them from sub-Saharan Africa (WHO, 2003a).

In some endemic foci, a high proportion of the population is infected. In southern Togo, for example, in 1989 the prevalence of infection was estimated at 80% and the incidence at 50% (Petit *et al*., 1989). A study of 1,200 individuals in Nigerian villages revealed that 982 (82%) were infected (Okoye *et al*., 1995). In some villages of Ghana and southern India, 50% of the people have been found to be infected. The age group most affected was 20- to 40-year-olds, and reinfection was common (Johnson and Joshi, 1982).

In the Western Hemisphere, there have been foci in some parts of the Antilles, Brazil (Bahia), French Guiana, and Guyana, all of which have disappeared spontaneously. It is believed that the infection was brought from Africa along with the slave trade. In addition, there have been imported cases of dracunculiasis outside the known endemic areas. For example, since 1995 there have been two cases in the US, both of them imported from Sudan (CDC, 1998). In the eastern US, some sporadic cases of human dracunculiasis were attributed to *D. insignis* (WHO, 1979).

Dracunculus medinensis occurs naturally in monkeys, wild and domestic carnivores, cattle, and equines. In northern Argentina, four cases of *Dracunculus* infection were reported, but the species were not identified (Hoyos *et al*., 1995).

The Disease in Man: The prepatent period, from initial infection until emergence of the parasite in the skin, lasts about a year and does not produce any symptoms in the host. Indeed, the first sign of the infection is usually the papule or vesicle that appears prior to larviposition by the parasite, approximately a year after the initial infection. It may be that allergic symptomatology is absent during this period because the parasite covers itself with host proteins that hide it from the immune system (Bloch *et al*., 1999). Symptoms appear when the parasite initiates its final migration to the skin surface. Shortly before or at the same time the vesicle is formed, some of the following allergic manifestations begin to develop: urticaria, pruritus, dyspnea, vomiting, mild fever, and sometimes fainting. Once the vesicle is formed and before the parasite emerges, the patient feels a strong burning sensation, which he may try to alleviate by immersing the affected part in cold water. The symptoms disappear when the vesicle ruptures and the parasite emerges. The vesicle and subsequent ulcer usually appear on the skin of the feet, ankles, legs, knees, wrists, and, less often, the upper part of the body. The ulcer forms a scar about a month after the patient is rid of the parasite.

The most serious complications stem from secondary bacterial infections that gain entry through the open lesion and can propagate along the length of the tunnel excavated by the parasite. These infections often occur as a result of failed attempts to extract the parasite. If it ruptures in the process, larvae may remain trapped in the subcutaneous tissue and give rise to cellulitis and abscesses. Chronic ulcers, arthritis, and tendon contractions are other common sequelae. Although the parasite triggers antibody reactions, it does not appear to induce protective immunity (Bloch and Simonsen, 1998).

Even when there are no complications, many patients remain incapacitated for several weeks or months. According to a study conducted in the district of Ibadan, Nigeria, patients remained disabled for an average of 100 days. The degree of incapacity was related to the number of parasites and their localization: sites in the ankle and foot were the most serious (Kale, 1977). A study of 1,200 persons in Nigerian villages showed that 982 (82%) were infected. Of these, 206 (21%) were totally incapacitated; 193 (20%) were seriously incapacitated; 431 (44%), moderately incapacitated; and 152 (16%) were unaffected (Okoye *et al*., 1995).

The Disease in Animals: The course and clinical manifestations of dracunculiasis in animals are very similar to those seen in man. In dogs, there have been clinical cases of purulent fistulated skin nodules caused by *D. insignis* (Beyer *et al*., 1999).

Source of Infection and Mode of Transmission: The disease is found in rural areas and is directly linked to the lack of potable water in poor tropical and subtropical regions, an arid climate, or prolonged dry seasons. Transmission is more intense during the dry season, when lagoons, ponds, and other water bodies are at low levels and the density of infected copepods increases. In desert climates, however, transmission of the infection is more frequent during the rainy season. The main sources of infection for man are shallow lagoons, ponds, wells dug in dry river beds, cisterns, and wells that are accessed via steps and that people enter to obtain water. The infective element is the copepod harboring third-stage larva, which can only live in still water. Frogs and tadpoles are paratenic hosts for *D. insignis* (Eberhard and Brandt, 1995). It is not known if there are paratenic hosts for *D. medinensis.*

Infected humans contaminate the water with larvae escaping from their cutaneous parasitic ulcers, and the larvae, in turn, infect other humans when they drink water containing infected copepods. The infection is distinctly seasonal in nature because of two factors: a) climatic changes that affect the various sources of water, and b) the development cycle of the parasite itself (Muller, 1979). The transmission period peaks at different times depending on the particular endemic area and on ecological conditions. In the Sahel region of Africa, where annual precipitation is less than 75 cm^3, infection occurs during the rainy season and for a few months thereafter, until the lagoons dry up. On the other hand, in the desert foci of southern Iran, where rainwater is collected in large protected cisterns that are rarely empty, the incidence is higher during the dry season, when the density of copepods is greater. In each endemic area, one or two species of *Cyclops*—usually the largest and most carnivorous—serve as intermediate hosts. In an endemic region of Nigeria, it has been estimated that each inhabitant ingests some 75 infected copepods a year.

Man is undoubtedly the main definitive host and reservoir of the parasite. The role

of animals in the epidemiology of human dracunculiasis is not yet clear and has been the subject of debate. Domestic animals, especially dogs, can be an additional reservoir of secondary importance in areas with high rates of human infection. Even though there are indications that these animals alone can maintain the infection in nature, the proportion of these hosts that may be infected by *D. medinensis* relative to other species of *Dracunculus* is still unknown. Indeed, *D. medinensis* occurs in some places where the human infection has not been recorded, such as Malaysia and Tanzania. In Kazakhstan, for example, after an endemic focus of human dracunculiasis was eradicated, a study found that 11.7% of 213 dogs examined were parasitized. However, the animal infection does not appear to have interfered with numerous successful campaigns to eradicate the human infection.

Diagnosis: Diagnosis presents no difficulties once the cephalic end of the parasite has emerged. If necessary, the infection can be confirmed by pouring a little cold water on the ulcer and then examining a drop of the exudate for the presence of first-stage larvae. Radiologic examination reveals dead and calcified parasites. Several immunologic tests have been used for diagnosing this parasite. The enzyme-linked immunosorbent assay (ELISA) used with the antigen of first-stage larvae to detect IgG4 antibodies was 83% sensitive and 97% specific. Moreover, it was possible to increase sensitivity to 97% by refining the antigen and measuring various types of antibody at the same time (Bloch and Simonsen, 1998). An attempt was made to diagnose the disease on the basis of parasite antigen in the bloodstream, but none could be found (Bloch *et al*., 1998).

Control: In 1980, the US Centers for Disease Control initiated a global campaign to eradicate dracunculiasis, and WHO considers that it can be eradicated successfully (WHO, 2003b). The most important preventive measure is to provide populations with a regular supply of potable water. In Nigeria, the provision of piped water to a city of 30,000 inhabitants reduced incidence from 60% to 0% in the course of two years. When economic conditions in an area are inadequate to provide potable water, prevention consists of educating the population and identifying subterranean water sources. Individuals can boil or filter surface water, treat their drinking water to kill the intermediate hosts, and take precautions to avoid contaminating water sources.

Public health education is of the utmost importance in the control of dracunculiasis because patients in hyperendemic areas do not look upon the parasite as an agent of infection; they see it as a normal condition of the human body, and hence they do not associate it with the ingestion of contaminated water (Bierlich, 1995). Moreover, two-thirds of the population consider that boiling or filtering water is inconvenient and impractical (Ilegbodu *et al*., 1991). Digging wells to extract subterranean water with hand pumps appears to be a very effective solution. When this approach was tried in Ghana's Upper Region, it protected between 88% and 96% of the population there (Hunter, 1997). Treatment of drinking water with temephos to kill the crustaceans that are intermediate hosts is simple and effective. Also, providing the population with nylon mesh strainers to filter out copepods has yielded excellent results (Kaul *et al*., 1992). A study conducted in Pakistan showed that the filters were adequate to remove the copepods even after 12 to 15 months of use (Imtiaz *et al*., 1990). Filters with 200-micron holes capture the large copepods, which are the ones that harbor *Dracunculus* larvae. Finally, in Tashkent and Samarkand,

Uzbekistan, the disease was eradicated more than half a century ago by the simple strategy of closing all the stepped wells and replacing them with curbed wells, so that people could no longer go inside and contaminate the water.

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ESOPHAGOSTOMIASIS AND TERNIDENSIASIS

ICD-10 B81.8 Other specified intestinal helminthiases

Synonyms: Helminthoma, helminthic abscesses, nodular worm infection.

Etiology: The agents of these diseases are strongylid nematodes of the species *Oesophagostomum bifurcum, O. stephanostomum, O. aculeatum (O. apiostomum),* and *Ternidens deminutus.* They live in the intestine of nonhuman primates and sometimes humans, causing the formation of nodules in the intestinal wall. The taxonomy of the esophagostomes in primates is still not fully understood. Levine (1980) has suggested that *O. bifurcum* is at least partially homologous with *O. stephanostomum, O. apiostomum,* and other species. Apparently most recent authors agree with this view, because *O. bifurcum* is the only human esophagostome mentioned in the literature since 1989.

The life cycles of the species of *Oesophagostomum* that occur in primates have not been fully elucidated, but it is assumed that they follow patterns similar to those of other species of the genus, which are common parasites of domestic animals. Adult females measure 8–13 mm long and live in the large intestine. The eggs are shed with feces, mature, and release a first-stage larva. In five to seven days at ambient temperature, the first-stage larva develops into a third-stage larva, which is encysted within the cuticle of the second-stage larva and is infective. Primates acquire the infection by ingesting third-stage larvae. In the stomach and small intestine of the host, the larva frees itself from its cuticular sheath, penetrates the intestinal mucosa, and transforms into the next stage. Growth of the fourth-stage larva in the mucosa, especially of the large intestine, produces nodules 1–3 mm in diameter, known as a "nodular worms." When the larva emerges from the intestinal lumen, it leaves an ulcer several millimeters in diameter, and the nodule fills with pus (Barriga, 1997). The larva continues to mature until it reaches the adult stage and mates. At 30 to 40 days after the initial infection, the female begins to lay eggs. However, most of the parasites found in man are immature or nongravid.

The females of *T. deminutus* measure 12–16 mm long and 0.6 mm wide. The parasite localizes mainly in the large intestine, but sometimes it has been found in the

small intestine. Its life cycle is still not fully understood. From the time its eggs are shed in feces until it transforms into a third-stage larva in soil, its evolution is similar to that of the esophagostomes, but what happens to the parasite from that point on is not known. Attempts to infect human volunteers and baboons with third-stage larvae have failed. Consequently, some authors suspect that *T. deminutus* may require an intermediate host for its subsequent development, which would be unusual for this taxonomic group. The eggs of *Oesophagostomum* spp. and *T. deminutus* are indistinguishable from those of the ancylostomids.

Geographic Distribution and Occurrence: The esophagostomes that infect man are natural parasites of monkeys and apes. Human infection is accidental and relatively infrequent: as of 1989, about 70 cases had been reported, almost all of them in Africa (Ross *et al.,* 1989). There have also been cases of human esophagostomiasis attributed to various species in Brazil, Indonesia, and Nigeria, where it is said that 4% of a prison population was infected. The first human case in Malaysia was reported in 1992 (Karim and Yang, 1992). In West Africa, *O. bifurcum* is common in northern Ghana and Togo, where human prevalence can be as high as 59% in small isolated villages and the infection usually occurs in association with ancylostomids. The human infection begins to appear in children 3 to 5 years old, and prevalence stabilizes at the age of 10 (Krepel *et al.*, 1992). *Oesophagostomum* infection is common in nonhuman primates. Among imported monkeys in the US, the infection rate of *O. bifurcum* has been as high as 53%, and that of *O. apiostomum*, 70% (Flynn, 1973).

T. deminutus is found in nature among monkeys and apes of Africa, India, and Indonesia. It is infrequent in laboratory primates, but prevalence has been as high as 76% among monkeys in South Africa (Flynn, 1973). The human infection has been observed in the southern half of Africa in Malawi, Mauritius, Mozambique, Democratic Republic of Congo, Tanzania, South Africa, Uganda, Zambia, and Zimbabwe, as well as in Comoros (Goldsmid, 1982). In Zimbabwe, infection rates have been as high as 87%. A coprologic survey of 5,545 patients in a Zimbabwe hospital found that *T. deminutus* was the second most frequent parasite (3.75% versus 5.75% for ancylostomids), but the intensity of infection was almost always low.

The Disease in Man and Animals: Pages *et al.* (1988) reviewed 28 cases of intestinal pseudotumors caused by esophagostomes. The lesions consist of nodules in the intestinal wall, primarily the large intestine, each of which contains a larva surrounded by purulent or necrotic matter. These nodules can produce abscesses, fistulas, and tumors in the intestinal wall. Mild human infections caused by *Oesophagostomum* spp. go unnoticed. In clinical cases, the symptoms range from vague abdominal pain to intestinal obstruction associated with tumors. The disease can be mistaken for ameboma, carcinoma of the colon, appendicitis, or ileocecal tuberculosis. A subcutaneous nodule caused by one of these species has been reported in a human patient (Ross et al., 1989).

Heavily parasitized monkeys develop dysenteric diarrhea. Several authors think that *Oesophagostomum* spp. are important pathogenic agents in nonhuman primates that can sometimes cause fatal disease. However, the available descriptions are insufficient to determine whether the parasitosis was in fact the main cause of death.

The larvae of *T. deminutus* form nodules and even ulcers in the intestine. Despite the fact that the adult larvae ingest blood, the infections do not cause significant

symptoms; many of them are asymptomatic, and the rest pass with only mild diarrhea and vague abdominal pain.

Source of Infection and Mode of Transmission: Nonhuman primates are the main reservoir of the infection. In esophagostomiasis, the source of infection is the soil, where the infective larvae are found. The infection is produced by the ingestion of larvae in food or water or from contaminated hands, and it occurs almost exclusively during the rainy season (Krepel *et al.*, 1995). Man is an accidental host in whom the parasite seldom reaches maturity and oviposition. The epidemiology of *T. deminutus* infection has not yet been clarified. Some investigators admit the possibility that, in addition to the cycle between monkeys and humans, there may be a person-to-person cycle as well, and they also suspect the intervention of an intermediate host (Goldsmid, 1982).

Diagnosis: Human esophagostomiasis is difficult to diagnose because the symptoms are not specific and, in most cases, the parasites do not reach maturity and do not lay eggs. In such cases, diagnosis is confirmed by histologic examination of biopsies or surgical material. When eggs are observed, they should be differentiated from other species. *T. deminutus* infection is diagnosed by examining eggs in feces. The eggs of ancylostomids, *T. deminutus, Oesophagostomum, Strongyloides,* and *Trichostrongylus* are very similar, and it is therefore necessary to culture them and study the third-stage larvae in order to differentiate the species. Goldsmid (1982) has published useful criteria for identifying the eggs and third-stage larvae of these species. It has been calculated that each female *O. bifurcum* lays an average of 33.7 eggs per gram of feces (Krepel and Polderman, 1992), but this figure is relatively unimportant because most of the damage produced by the esophagostomes results from the activity of larvae and not the adult parasites. Several immunologic tests have been tried for detecting esophagostomiasis, but most of them are not sufficiently specific. Nevertheless, up to 95% specificity has been attained with an enzyme-linked immunosorbent assay (ELISA) designed to detect IgG4 antibody (Polderman *et al.*, 1993). In addition, there are differences in rDNA between *O. bifurcum* and *Necator americanus,* which suggests that the two species could be differentiated using polymerase chain reaction (Romstad *et al.*, 1997).

Control: Esophagostomiasis, and probably ternidensiasis, are geohelminthiases in which the eggs reach the infective stage in soil and penetrate the host via the oral route through contaminated food, water, or hands. Therefore, protective measures for individuals consist of carefully washing or boiling suspicious foods, boiling water, and washing hands carefully before eating. The infections are not sufficiently frequent to justify community prevention campaigns.

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GNATHOSTOMIASIS

ICD-10 B83.1

Synonyms: Gnathostomosis, larva migrans caused by *Gnathostoma*, wandering swelling.

Etiology: The agents of this infection are larvae of *Gnathostoma spinigerum*, *G. hispidum*, *G. doloresi,* and *G. nipponicum. G. spinigerum* is a spiruriod nematode parasite of dogs and domestic and wild felines. It has been known since 1890 that it can infect man. *G. hispidum* is a parasite of swine and wild boars, and has been known as a parasite of humans since 1924. Only in 1989 was it recognized that *G. doloresi*, a parasite of swine and wild boars, also infects man (Nawa *et al*., 1989). Around the same time, it was found that *G. nipponicum*, a parasite of weasels, can also occasionally infect man. The larvae of the various species are differentiated by the number of hooks on the head bulb (see below) and the structure of the intestinal canal section (Akahane *et al*., 1998). For example, the infective larvae of *G. nipponicum* have three rows of hooks with an average of 34.5, 36.7, and 39.7 hooks in the first, second, and third rows, respectively.

G. spinigerum is a reddish worm that lives in the stomach wall of its definitive hosts. The cuticle forms a globose ring (the head bulb) behind the lips (characteristic of the genus), and it has eight transversal rows of small spines. The female parasite measures 2.5–5 cm, and the male, about half that. The eggs are eliminated with

the feces of the definitive host; they hatch in water after one to three weeks of incubation and release a first-stage larva. This larva actively penetrates a copepod of the genus *Cyclops*, invades its hemocele and, in about 10 days, changes into a second-stage larva with a spiny head bulb. When an appropriate freshwater fish ingests the infected copepod, the larva continues its development; it passes from the fish's intestine to the musculature where, after a month, it transforms into a mature third-stage larva and encysts. This infective larva measures about 4 mm, has four rows of spines on the head bulb, and more than 200 rows on the body, and is coiled in a spiral inside a fibrous cyst about 1 mm in diameter. When one of these hosts eats another, infected, host, the larva transfers from the first to the second without developing, so the second host acts as a transport or paratenic host. Cats, dogs, and all other natural definitive hosts are infected by consuming fish or paratenic hosts that contain the infective larvae. In the stomach of the definitive hosts, the larvae are released from their cysts, penetrate the stomach wall, migrate to the liver, and from there, go to other organs and tissues (muscular and connective). Then, from the peritoneal cavity they again penetrate the stomach and lodge in the mucosa. After about six months, they mature into adults and begin oviposition.

Studies with *G. nipponicum* indicate that the larva which invades the copepod would be an early third-stage larva, which develops into the mature third-stage larva when it is ingested by a fish (Ando *et al*., 1992). Experimental infection has shown that about 36 species of freshwater fish, amphibians, reptiles, crustaceans, birds, and rodents can serve as second intermediate hosts. In Thailand, certain freshwater fish, ducks, and chickens are particularly important as sources of infection for man. Many animal species, such as snakes, birds, and some mammals, can serve as transport hosts.

G. doloresi and *G. hispidum* parasitize the stomach mucosa of pigs and wild boars. The development cycle of *G. doloresi* also requires two intermediate hosts: the first are copepods and the second are salamanders and serpents. *G. hispidum* requires only one intermediate host: the larvae released by the eggs are ingested by *Cyclops* copepods and the infective larvae develop in their coelom in one or two weeks. Fish, frogs, and reptiles can serve as paratenic hosts. When the salamanders or snakes, in the case of *G. doloresi*, or the copepods, in the case of *G. hispidum*, are ingested by a pig, the larva develops into the adult stage in a manner similar to *G. spinigerum.*

G. nipponicum is a parasite of the esophageal mucosa of the weasel *Mustela sibirica itatsi*. This species also requires two intermediate hosts: the first are copepods and the second are fish and small snakes. Fish, salamanders, frogs, mice, and rats have been infected experimentally with immature larvae obtained from copepods, but small snakes, birds, or weasels have not. In other words, the infested species should be considered second intermediate hosts. However, it was possible to infect frogs, snakes, birds, and rats with mature larvae obtained from fish. Since the larvae do not develop into adults in these hosts, but remain in the larval state, they should be considered paratenic hosts. Weasels infected with mature larvae obtained from fish began to produce eggs 69 to 90 days after infection (Ando *et al*., 1992).

Geographic Distribution and Occurrence: The most common gnathostomiasis is caused by *G. spinigerum*, which is endemic in the countries of Asia, especially China, Japan, and Thailand (Rusnak and Lucey, 1993). It is common in Thailand,

which made it possible to carry out treatment studies with 98 patients in a Bangkok hospital in 1998. Gnathostomiasis caused by *G. spinigerum* seems to be an emerging disease in Latin America: the first two human cases there were recognized in Mexico in 1970, but 300 additional cases were identified between 1992 and 1995 in Culiacán, in northern Mexico (Díaz Camacho *et al*., 1998), and between 1993 and 1997, there were 98 cases in Acapulco, in southern Mexico (Rojas-Molina *et al*., 1999). Cases of human infection also have been described in Argentina and Ecuador (Ollague *et al*., 1988). The highest concentration of human cases has been in Thailand and Japan, where hundreds of patients are reported every year. The human infection is infrequent or rare in China, India, Indochina, Indonesia, and Malaysia. Sporadic cases have also been registered in Australia, Israel, and the state of California, US. *G. spinigerum* in animals is much more widely distributed than in humans. In an endemic area in southern Japan, 35% of cats and 4% of dogs had *G. spinigerum* parasites, and 60% to 100% of freshwater fish (*Ophiocephalus argus*) contained larvae. In the markets of Thailand, larvae were found in 37% of fish, 80% of eels, and 90% of frogs.

G. hispidum has been found in humans in China, Korea, and Taiwan. Urban cases of gnathostomiasis in Japan are the result of *G. hispidum*, introduced by fish imported from China, Korea, or Taiwan. The infection is relatively common in pigs in Asia, Australia, and Europe. A study of 3,478 pigs carried out in China in 1991 found the infection in 15% of them. Of 38 species of animals that serve as intermediate or paratenic hosts, 23 are shared with *G. spinigerum*. *G. nipponicum* occurs in China, Japan, and Korea, due to imported fish. *G. doloresi* has been found in man only in southern Japan. The first case was reported in 1989, and 25 cases had been reported by 1997: 23 cutaneous, 1 pulmonary, and 1 colonic (Nawa *et al*., 1997).

The Disease in Man: Man is an aberrant host in which the parasite only exceptionally reaches sexual maturity: the larva continuously migrates and does not become established in the human stomach. In most cases, a single larva is responsible for the clinical picture. The most common symptoms are localized, intermittent, and sometimes migratory swelling of the skin, often accompanied by pain, pruritis, and erythema. It can also affect the internal organs (Rusnak and Lucey, 1993). The first symptoms appear one or two days after the ingestion of raw fish or the meat of paratenic hosts, such as chickens and ducks. The symptoms include nausea, salivation, urticaria, pruritis, and stomach discomfort; mild leukocytosis and very marked eosinophilia are common. Later, the symptoms are due to the migration of the larva into the liver and other organs. The movements of the larva inside the abdominal or thoracic organs can cause acute pain of limited duration. The symptoms resemble cholecystitis, appendicitis, cystitis, or other diseases, depending on the organ affected by the larvae (internal or visceral gnathostomiasis). Approximately one month after the infective food is eaten, the larva locates in the subcutaneous tissue, usually of the abdomen, extremities, head, and chest. This is the beginning of the chronic phase, in which the organic symptoms abate or disappear and eosinophilia gradually decreases. The most prominent symptom is an intermittent subcutaneous edema that changes location each time the larva moves. The edema is pruriginous but not painful, and initially lasts a week or more; its duration then becomes progressively shorter. In older infections, the edemas recur at longer intervals. The larva

can survive in the human body for a long time; and one case lasting 16 years has been recorded.

In its erratic migration, the larva can affect a variety of different organs and tissues. When it penetrates the skin, it can cause a clinical picture similar to that of cutaneous larva migrans (see the chapter on that disease). The most serious localizations, fortunately rare, are in the brain and eyes. In 300 cases of *G. spinigerum* in Mexico, the lesions occurred mostly on the face, neck, arms, and legs. There was just one ocular case, and 75% of the patients developed peripheral eosinophilia. Skin biopsies obtained from 35 patients showed larvae in just 12 of them. The infection in 93 individuals was identified by enzyme-linked immunosorbent assay (ELISA) with extracts of *G. doloresi* (Díaz Camacho *et al*., 1998).

In a case of *G. doloresi* studied in Japan, the patient had epigastric pain three days after eating fish (*Oncorhynchus masou masou*) and developed a scaly rash on the trunk three days later. The rash spread and he sought medical attention 18 days after eating the fish. Biopsies were negative, but two days later blisters appeared on the lower abdomen, and a nematode was obtained from one of them. The next day he had swelling of the jaw that lasted for a week. All the lesions began to shrink on the 25th day and had disappeared by day 30 (Akahane *et al*., 1998).

Punyagupta *et al*. (1990) believe that *G. spinigerum* is one of the main causes of meningitis and eosinophilic meningoencephalitis in Thailand and that it can be clinically distinguished from the similar disease caused by *Angiostrongylus cantonensis*, even though it is very difficult to recover the parasite for purposes of a definitive diagnosis. Intraocular gnathostomiasis is rare and should be differentiated from that caused by filariae or *Angiostrongylus*; up until 1994, just 12 cases had been found (Biswas *et al*., 1994).

The Disease in Animals: *G. spinigerum* larvae can cause necrotic tunnels during their migration—before reaching the stomach—in the liver, pancreas, and other abdominal tissues of the natural definitive hosts (cats and dogs). In the adult stage, the parasite lodges in the stomach wall, where it produces intense inflammation, with the formation of cavities full of serosanguineous fluid that become fibrous cysts. These cavities develop fistules that are connected to the lumen of the stomach to discharge the parasite's eggs. When the fistules open onto the peritoneum, they can cause severe peritonitis (Barriga, 1997). *G. hispidum* and *G. doloresi* can cause similar damage to the abdominal organs and stomach ulcers in pigs. The disease is infrequent but, when it occurs, it manifests with anorexia and weight loss. *G. nipponicum* produces nodules in the esophagi of weasels that can interfere with swallowing.

Source of Infection and Mode of Transmission: The reservoirs of the parasite are cats, dogs, pigs, weasels, and several species of wild mammals that can act as paratenic hosts. The definitive hosts and humans become infected by consuming infected fish or paratenic hosts. The habit of eating fish or fowl raw or only seasoned with vinegar is the essential factor in the occurrence of the human disease and its endemicity in Japan and Thailand. The parasitosis in animals is much more widespread than the human infection, since it occurs even in places where people do not eat raw fish or fowl. In Japan, very high rates of infection were found in two species of fish, *Ophiocephalus argus* and *O. tadianus*; each fish can contain hundreds of larvae. In Thailand, besides several species of *Ophiocephalus*, sources of infection

include catfish (*Clarias batrachus*), eels, frogs, freshwater snakes, chickens, and ducks (Daengsvang, 1982).

Diagnosis: In endemic areas, migratory and recurrent subcutaneous edemas accompanied by leukocytosis and high eosinophilia can be considered pathognomic. Since the parasites do not develop to the adult stage in man, eggs are not found in the feces. Specific diagnosis in man can be made by identifying the larva in surgically obtained specimens. The immunobiological tests include an intradermal reaction of questionable specificity. ELISA with *G. doloresi* antigens is widely used to identify infection by any species of *Gnathostoma*, despite the fact that it cross-reacts in patients with *Toxocara canis*, *Anisakis* sp., *Paragonimus westermani,* and *Fasciola* sp. The antigens obtained from infective larvae of *G. spinigerum* are more specific for the species (Anantaphruti, 1989). In patients with cerebral gnathostomiasis by *G. spinigerum*, attempts have been made to confirm the infection by looking for antigens, immune complexes, or antibodies in the cerebrospinal fluid; of 11 patients, just one had antigens and another had immune complexes, but nine had antibodies (Tuntipopipat *et al*., 1989).

In dogs and cats, diagnosis can be made by detecting eggs in the feces, but it must be borne in mind that the eggs are sometimes few in number or are eliminated irregularly.

Control: In enzootic areas, the best way to prevent disease is by abstaining from eating raw or undercooked fish and fowl. According to García and Bruckner (1997), cooking or immersing raw meat in strong vinegar for five hours kills the larvae, but lemon juice or chilling at 4ºC for a month does not kill them.

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GONGYLONEMIASIS

ICD-10 B83.8 Other specified helminthiases

Synonym: Gongylonematosis.

Etiology: The agent of this disease is *Gongylonema pulchrum*, a spiruroid nematode of the family Thelaziidae, whose main hosts are ruminants, swine, and wild boars. It is also found in horses, carnivores, monkeys, rodents, and other animals (Cappucci *et al*., 1982). Moreover, it has been found in macaques in Japan and squirrels (*Sciurus niger*) in the state of Florida, US (Coyner *et al*., 1996).

The adult parasite lives in the esophageal mucosa and submucosa of the definitive hosts, but can also be found in the rumen and oral cavity. It is filiform and its size varies according to the host. In ruminants, the male can reach approximately 62 mm in length and 0.15–0.3 mm in diameter, and the females, up to 145 mm by 0.2–0.5 mm. The parasite is smaller in humans and swine.

The females of *G. pulchrum* lay embryonated eggs in the esophagus or rumen of the definitive host. The eggs are eliminated to the exterior with the feces, and must be ingested by an intermediate host for the life cycle to continue. These hosts are several species of coprophilic beetles of the genera *Aphodius*, *Blaps*, *Ontophagus,* and others. Experimental infection of the cockroach *Blatella germanica* was also possible. The egg hatches in the insect's intestine, and the larva penetrates its hemocele where, in about a month, it develops into the third (infective) stage and encysts. Ruminants acquire the parasitosis upon ingesting the small beetles with grass or other infested food, and swine become infected by coprophagia. The migration route

of the larva in the definitive host is not well known, but experimental infections in guinea pigs provide evidence that the larva frees itself from the coleopteran in the stomach and migrates through the stomach wall to the esophagus, where it matures in about two months and reinitiates the cycle with oviposition.

Geographic Distribution and Occurrence: Human infection by *G. pulchrum* is rare: just 46 cases were recorded between 1864 and 1982, 2 more were reported by 1994, and an additional 2 by the year 2000. Of these, one was in the US (Eberhard and Busillo, 1999) and the other was in Germany, but originated in Hungary (Jelinek and Loscher, 1994). The human infection has been diagnosed in China, Bulgaria, Germany (in a Greek immigrant), Hungary, Italy, Morocco, New Zealand, the former Soviet Union, Sri Lanka, Turkey, the US, and the former Yugoslavia.

G. pulchrum is widely distributed geographically in animals. It has been found in Asia, the US, Europe, and the Russian Federation. The prevalence of the infection in domestic ruminants varies with the area. In surveys carried out in the US, the parasite was found in 5.9% of 1,518 pigs, with a range of 0% to 21% depending on geographic origin; in 10% of 29 bovines in the state of Georgia; and in 5% of 20 bovines in the state of Florida. In slaughterhouses in Ukraine, the parasite was found in 32% to 94% of adult cattle, 39% to 95% of sheep, and 0% to 37% of swine. In a slaughterhouse in Teheran, Iran, *G. pulchrum* was found in the esophagi of 49.7% of the cattle examined.

The Disease in Man: The lesions caused by the parasite are mainly irritative, due to its movement through the mucosa and submucosa; parasites have been found actively moving in the submucosa of lips, gums, hard palate, soft palate, and tonsils. Pharyngitis and stomatitis have sometimes been confirmed. Two cases described in China included bloody sialorrhea and eroded and bleeding patches on the esophageal mucosa.

The Disease in Animals: In ruminants, *G. pulchrum* is found mainly in the mucosa and submucosa of the esophagus, but the mature parasite can move in different directions and invade the pharynx, oral cavity, and rumen. In swine, it is found in the stratified squamous epithelium of the tongue mucosa. According to observations in Iran, there were no lesions that would indicate that the infection produced a pathologic condition. Histologic examination of swine tongues in the US revealed a mild and chronic inflammatory process. On the other hand, in the former Soviet Union, lesions, sometimes important, of the esophagi of infected bovines have been found, with hyperemia, edema, and deformations of the organ. Likewise, the infection is blamed for occlusions of the esophagus due to a reflex reaction caused by irritation of the nerve receptors.

Source of Infection and Mode of Transmission: Ruminants and other animals become infected by ingesting coleopterans containing third-stage larvae. Man is an accidental host who does not play any role in the maintenance of the parasite in nature and probably is infected by the same mechanism. Salads and raw vegetables are thought to be the vehicles by means of which man ingests the small beetles. It has also been suggested that the species of *Aphodius,* because of its size (4–6 mm) and capacity for flight, could be accidentally inhaled and then swallowed.

The maintenance of the parasite in nature is assured by its broad diffusion and prevalence among herbivores, swine, and other animals (definitive hosts), and the large number of susceptible species of beetles (intermediate hosts). In Ukraine, 60% to 90% of

the beetles were found to be infected. The highest rates corresponded to several species of *Aphodius* and *Geotrupes*; the number of larvae ranged between 1 and 193.

Diagnosis: Most of the human cases were diagnosed because the patient felt something moving in the submucosa of the oral cavity or observed the parasite emerging from the mouth. Specific diagnosis is done by extracting the parasite and identifying it under the microscope.

Diagnosis in live animals is rarely achieved. The eggs are not always found by fecal examination, even when flotation or sedimentation methods are used. The parasites can be detected by postmortem examination of the esophagus (ruminants) or the tongue (swine).

Control: Because of the rarity and mildness of human infection, special control measures are not justified. Individual protection can be obtained by observing the rules of personal, food, and environmental hygiene. With a few exceptions, helminthologists agree that *G. pulchrum* does not cause major damage to animals. Moreover, it would not be feasible to adopt measures aimed at protecting animals at pasture from ingestion of beetles.

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LAGOCHILASCARIASIS

ICD-10 B83.9 Helminthiasis, unspecified

Etiology: The vector of this disease is *Lagochilascaris minor*, a small ascarid. The female measures 6–20 mm long by 0.20–0.80 mm wide; the male is smaller. It has been identified in man, but parasites that seem to belong to the same species have been found in wild carnivores and in the agouti. Eggs, larvae, and adults of the ascarid are continually found in the abscesses produced by the parasite in man, suggesting ongoing reproduction in the lesion (Moraes *et al.,* 1983). While the parasite's natural life cycle is not known, laboratory mice have been infected with larvae from eggs obtained from human beings; infections have been produced with adult parasites in cats infected by those mice. In mice, the larvae encysted in the muscu-

lar and subcutaneous tissue. In cats, the larvae were released in the stomach and migrated through the esophagus, pharynx, trachea, otorhinopharynx, and cervical lymph nodes, to mature into adults in any of these organs 9 to 20 days after infection (Campos *et al*., 1992).

Geographic Distribution and Occurrence: The disease occurs in Latin America and the Caribbean. It is very rare: only 19 human cases were known up to 1982 (7 in Brazil, 1 in Costa Rica, 5 in Suriname, 5 in Trinidad and Tobago, and 1 in Venezuela) (Volcan *et al.,* 1982; Moraes *et al.,* 1983). Between 1982 and 2000, 7 more cases were described (1 in Bolivia, 5 in Brazil, and 1 in Mexico).

The Disease in Man: The disease begins with a tumor in the neck, mastoid apophysis, tonsils, maxillae, or paranasal sinuses. Eventually, it opens to the surface of the skin, releasing pus, in which adult parasites, larvae, and eggs are intermittently found. Fistulas form, and may open in the nasopharynx, in which case purulent material and parasites are eliminated through the nose and mouth. The process is chronic and may last for years. The case of a girl in Mexico began with a hard, lobulate tumor in the neck, measuring 3 cm by 5 cm, with a purulent central pustule that contained parasites and that had been developing for six months. Neither repeated treatment with thiabenzadole nor surgical removal improved the picture (Vargas-Ocampo and Alvarado-Alemán, 1997). Three Brazilian patients had fistulous abscesses in the area of the neck and ear, and a mastoid process containing parasites; two of them had central nervous system involvement. Treatment with anthelmintics and surgical removal of the abscesses produced temporary improvement, but there were relapses in two of the cases (Veloso *et al*., 1992). Treatment with ivermectin, a veterinary anthelmintic, was successful in the other case (Bento *et al*., 1993).

The Disease in Animals: Just two cases have been described, both in Brazil, of fistulated abscesses in cats (Amato and Pimentel-Neto, 1990). The parasite has also been discovered in the trachea of a bush dog (*Speothos venaticus*) (Volcan and Medrano, 1991).

Source of Infection and Mode of Transmission: The natural reservoir is unknown. The rarity of the human infection would indicate that man is an accidental host and is unable by himself to maintain the parasite in nature. It is not known how humans become infected. In a review of the genus *Lagochilascaris*, the possibility was suggested that man is infected by ingesting embryonated eggs (possibly eliminated by another animal species), and that the third-stage larva ascends to the trachea, but rather than being swallowed, as occurs with the larva of *Ascaris lumbricoides*, it would become established in the retropharyngeal region. The findings of Campos *et al*. (1992) provide some support for this theory.

Diagnosis: Specific diagnosis is made by identifying the parasite found in lesions. The eggs are also characteristic and resemble those of *Toxocara cati* or *A. lumbricoides.* In a case described in Venezuela, eggs of *L. minor* were found in the feces of the patient (an occurrence that had not been observed before) and were at first confused with *A. lumbricoides* (Volcan *et al.,* 1982).

Control: Lack of knowledge about the transmission cycle of this parasite to man prevents determination of effective control measures.

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MAMMOMONOGAMIASIS

ICD-10 B83.3 Syngamiasis

Synonym: Syngamosis.

Etiology: The agents of this disease are the nematodes *Mammomonogamus (Syngamus) laryngeus* and *M. nasicola* of the family Syngamidae. The former is a parasite of the laryngotracheal region, and the latter is a parasite of the nasal fossae of bovines, bubalines, and occasionally sheep, goats, and deer. Some helminthologists consider *M. nasicola* and *M. laryngeus* to be homologous.

The nematodes are red; the female measures about 10 mm by 0.5 mm and the male measures 3 mm by 0.3 mm. Since they remain in permanent union and the female has the vulva near the anterior end, they look like the letter Y. The development cycle of syngamids in mammals is not well known; it is believed to be similar to that of the fowl parasite *Syngamus trachea.* The eggs deposited by the parasite in the tracheal mucus are swallowed and eliminated with the feces. In the external environment, the infective larvae (third stage) can develop within or outside of the egg. Herbivores are infected by ingesting the infective larva, inside or outside of the egg, when they consume contaminated fodder or water. The infection can also probably be produced by ingestion of paratenic hosts, such as earthworms, snails, and several types of arthropods, as happens with avian *S. trachea*. In a herbivore's digestive tract, the larvae are released from their protective membranes, cross the intestinal wall to the mesenteric veins, and migrate to their final localization (tracheolaryngeal

or nasal), where the two sexes couple and remain in permanent union. The cycle is reinitiated with oviposition.

Geographic Distribution and Occurrence: *M. laryngeus* is found in ruminants in tropical America and in the Philippines, India, Malaysia, and Viet Nam. *M. nasicola* occurs in Africa, Brazil, the Caribbean, and the eastern region of the former Soviet Union.

In a slaughterhouse in the state of São Paulo, Brazil, 27 (45%) of 60 slaughtered cows were found to be infected (Santos and Fukuda, 1977), as were 18 (37.5%) of 48 young bulls in the state of Rio de Janeiro (Freire and Biachin, 1979). In Honduras, only 2.8% of 70 bovines examined were parasitized (Secretariat of Natural Resources of Honduras, 1980). In the Philippines, 23% of 597 bovines were parasitized with *M. laryngeus* (Van Aken *et al*., 1996).

Human infection is rare. Only 79 cases had been reported up to 1988 (Cunnac *et al*., 1988)—51 of them in inhabitants of or visitors to Martinique (Mornex *et al.,* 1980)—and about 100 up to 1995 (5 of them in North America) (Nosanchuk *et al*., 1995). Nine more cases were reported between 1988 and 2000. With the exception of three cases in Asia—one each in the Philippines, Thailand (Pipitgool *et al*., 1992), and Korea (Kim *et al*., 1998)—all the cases occurred in the Caribbean and Brazil.

The Disease in Man and Animals: In man, the symptomatology consists of tracheolaryngeal irritation with persistent cough but without fever. Some patients experience hemoptysis. A case was reported (Birrel, 1977) in an Australian woman who lived in Guyana for 10 months; she had respiratory symptoms consisting of a chronic cough and hemoptysis, and experienced loss of weight. In April 1977, she was admitted to Brisbane Hospital, Queensland, Australia, where bronchoscopy revealed larvae of a parasite that was identified as *M. laryngeus.* Extraction of the parasite resulted in disappearance of the symptoms. A similar case was described in the US (Gardiner and Schantz, 1983).

The animal infection is rarely symptomatic, and large numbers of *M. laryngeus* are required to produce an afebrile laryngitis or tracheitis. No symptoms have been observed in nasal infections caused by *M. nasicola*.

Source of Infection and Mode of Transmission: The reservoirs of *M. laryngeus* and *M. nasicola* are ruminants. Man is infected only accidentally. The sources of infection for man are probably raw plant foods and water contaminated with eggs or free larvae of the parasite. The sources of infection for ruminants are soil, pasture, and water. It is thought that the exogenous development of these parasites is similar to that of *Syngamus trachea* of fowl. In this parasite, the paratenic hosts are very important, since the third stage infective larva encysts in the coelom and can survive a year or more.

Diagnosis: The eggs of the parasite can be observed in feces and, more rarely, in sputum. Coughing fits may expel these parasites, which are easy to identify. Animal mammomonogamiasis is most often found on autopsy. Diagnosis in humans is usually effected by bronchoscopy and detection of the parasite.

Control: Prevention consists of observing the rules of food hygiene: wash raw food very well, boil suspicious drinking water, and wash hands well before eating.

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MICRONEMIASIS

ICD-10 B83.8 Other specified helminthiases

Etiology: *Micronema deletrix*, a very small, free-living nematode with a rhabditiform esophagus. The female measures barely 250–445 µm in length. It was originally described as *Halicephalobus gingivalis* by Stefanski in 1954. Anderson *et al*. (1998) reviewed the taxonomy of *M. deletrix* and concluded that both parasites were the same; consequently, *M. deletrix* is a synonym for *H. gingivalis*, although the latter name has priority. Other authors, such as Teifke *et al*. (1998), call it *H. deletrix*. We will use the name *Micronema deletrix* because it is the most widely known by health professionals.

The parasite lives as a saprophyte in soil rich in decomposing organic matter. All developmental stages of the nematode are found in that natural environment: eggs, larvae, and the female and male adult forms (Shadduck *et al.,* 1979). *M. deletrix* is a facultative parasite of man and equines. Eggs, larvae, and mature females, but not males, have been found in animal tissue; therefore, it has been deduced that the par-

asitic females are parthenogenic, like *Strongyloides stercoralis*. It has been suggested that it may be erroneous to attribute all the cases of infection to *M. deletrix* without having more information on the different species of the genus *Micronema* (Gardiner *et al.,* 1981). At least one case of granulomatous verminous mastitis in a mare, which could have been confused with micronemiasis, was due to another free-living nematode of the genus *Cephalobus* (Greiner *et al*., 1991).

Geographic Distribution and Occurrence: The distribution of the nematode in its natural habitat has been studied very little; presumably it is distributed worldwide. Only three human cases are known, and all of them were fatal: one in Canada (Hoogstraten and Young, 1975) and two in the US (Shadduck *et al.,* 1979; Gardiner *et al.,* 1981). No cases were described between 1988 and 2000.

Cases of micronemiasis in equines have been diagnosed in North America, Europe, and in Egypt. Its occurrence is rare: only 7 cases were reported up to 1985, and 12 more were reported between 1988 and 2000 (2 in Germany, 1 in Canada, 8 in the US, and 1 in Great Britain). However, the infection may occur more frequently in equines and go undiagnosed. For example, a study carried out in Egypt found *M. deletrix* in 2 of 28 dead equines that had shown symptoms of encephalitis (Ferris *et al.,* 1972).

The Disease in Man and Animals: The three known human cases died after manifesting symptoms of meningoencephalitis. In two patients, the lesions and nematodes were limited to the brain; in the third, micronemes were also found in the liver and heart.

The disease in equines can take several forms, depending on the localization of the parasites. Chorioretinitis, gingivitis, rhinitis, sinusitis, encephalomyelitis, pneumonitis, nephritis, osteoarthritis, and osteomyelitis have been described. A nasal tumor was described in one horse, and in another, granulomas in the maxillae and the respective sinuses. In this last case, up to 87,500 parasites per gram of granulomatous mass were extracted. In two cases, other organs were affected in addition to the brain (Alstad *et al.,* 1979). In the forms that affect the central nervous system, the symptomatology is similar to that of viral encephalitides, with lethargy, ataxia, incoordination, lateral or sternal decubitus, and kicking; these often end in death.

In both humans and equines, the lesions consist of numerous foci of granulomatosis or encephalomalacia when they occur in the brain, especially in areas adjacent to the larger blood vessels. The nematodes are found in the walls of the vessels and the perivascular spaces, and are abundant in the lesions (Shadduck *et al.,* 1979).

Source of Infection and Mode of Transmission: The source of infection is soil rich in humus and decomposing organic matter, which is the natural habitat of *M. deletrix.* Neither the mode of transmission nor the route of penetration of the nematode into the animal body is known. In the case of a Canadian child, the nematode probably entered through the multiple lacerations the child received in an accident that became contaminated with equine feces. In another case, it is suspected that the nematode penetrated through decubitus ulcers. In equines, the cases of gingivitis may have been acquired by ingestion of the parasite; the nasal and pneumonic forms may have been acquired by inhalation, and the rest of the systemic cases may have been acquired by penetration of the parasite through pre-existing wounds.

Diagnosis: Diagnosis can be made by biopsy and histopathologic examination of the affected tissues and identification of the nematode. In all of the human cases and several of the equine cases, diagnosis was made postmortem.

Control: Because of the rareness of the disease, special control measures are not justified.

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STRONGYLOIDIASIS

ICD-10 B78

Synonym: Strongyloidosis.

Etiology: The agents of this disease are the nematodes *Strongyloides stercoralis* and *S. fuelleborni.* Although man can be infected experimentally with the swine parasite *S. ransomi*, this latter infection does not appear to occur in humans spontaneously in nature. A prominent characteristic of these nematodes is that free-living generations alternate with parasitic ones.

The adult female of *S. stercoralis* is filariform, measures about 2.2 mm in length and 50 microns in diameter, and lives in the mucosa of the duodenum and jejunum of man, other primates, and dogs. Cats have been infected experimentally. Reproduction is parthenogenetic; males are never observed during the parasitic phase of the nematode's life cycle. Oviposition takes place in the epithelium or even

in the submucosa. The eggs are transformed into first-stage larvae with a rhabditiform esophagus and migrate to the intestinal lumen. These larvae are shed with feces and may follow either of two courses of development: a direct (homogonic) cycle, or an indirect (heterogonic) cycle. In the direct cycle, the larva undergoes two successive molts and is transformed into a third-stage larva with a filariform esophagus, which is the infective element for the host. In the indirect cycle, the rhabditiform larvae undergo four successive molts, and within two to five days they turn into free-living adult males and females. Like all free-living adult nematodes, these adults have a rhabditiform esophagus. The males and females mate, and the fertilized females lay eggs in the soil. The eggs develop in a few hours and turn into first-stage free-living rhabditiform larvae. The larvae undergo a second stage, and finally they develop into third-stage filariform larvae, which are infective for the host. Hence the indirect (heterogonic) cycle introduces a generation of free-living worms between the generations of parasitic worms. There is evidence that the free-living parasites give rise to only one generation of free-living larvae and that the next generation is always parasitic. The parthenogenetic female apparently produces three types of eggs: haploid, which generate free-living males; diploid, which generate free-living females; and triploid, which generate female parasites. Although all eggs develop to the point of becoming first-stage larvae, only those that can tolerate the prevailing environmental conditions continue to evolve. Adverse conditions (acid or wet soils, temperatures under 20°C or over 37°C, shortage of food) inhibit development of the larvae that will turn into free-living worms, but they favor the formation of infective larvae. Favorable conditions, on the other hand, inhibit development of the infective larvae but stimulate development of the free-living cycle (Barriga, 1997).

The filariform larvae produced by either cycle penetrate the skin of the host with the assistance of enzymes and travel via the bloodstream and lymphatic system to the heart and the lungs, where they settle within 24 hours after the initial infection. Once there, they rupture the capillaries and pulmonary alveoli, crawl through the respiratory tract to the pharynx, are swallowed, and reach the intestine, where they are transformed into parthenogenetic females. The larvae of this generation appear in the feces of man between two and four weeks after the initial infection, and in dogs, after 8 to 16 days.

In dogs, three other routes of infection have been observed: oral, transmammary, and uterine. In all three instances, the larvae settle in the intestine, where they mature into adults, and do not migrate to the lungs. The only difference occurs when the ingested larvae gain entry via blood vessels in the oral mucosa instead of being swallowed. In this case, they follow the same migration pattern as in transcutaneous penetration.

In man, there are two forms of superinfection (acquisition of a new infection on top of a previous one): hyperinfection and autoinfection. In hyperinfection, the rhabditiform larvae turn into infective filariform larvae in the upper part of the intestine; penetrate the mucosa in the lower part of the ileum or the colon; migrate to the lungs, trachea, and esophagus; and, finally, are carried by the bloodstream back to the intestine, where they mature. In autoinfection, some of the filariform larvae shed with the feces remain in the perianal or perineal region long enough to repenetrate the skin of the same host. In both cases, the ultimate effect is that, unlike any other nematodes of man, *S. stercoralis* is capable of reproducing itself in the host without having to abandon it, and thus causes prolonged, very intense infections. It is not

known if these forms of superinfection occur in dogs, but persistent strongyloidiases have been observed that could have been the result of self-infection. Nearly one-third of experimentally exposed dogs are unable to eliminate the infection spontaneously, which is somewhat similar to the situation in man. Persistence of the chronic infection in man is illustrated by the fact that 30% of the US veterans who were prisoners of war in Southeast Asia were still infected 35 years later (Grove and Northern, 1982).

Although the canine nematode *S. stercoralis* is similar to the *S. stercoralis* that infects man in terms of both morphology and physiology, animals vary in their susceptibility to different biotypes and geographic strains. Trials by several researchers have shown that dogs were susceptible to human strains of *S. stercoralis* coming from one region of the world but not from another (Grove and Northern, 1982). However, studies elsewhere have made it possible to document molecular differences between the human and canine strains of *S. stercoralis*, and hence it is possible that the two strains are really different species or subspecies.

S. fuelleborni inhabits the intestine of man and nonhuman primates in Africa and Asia. Its development cycle is similar to that of *S. stercoralis*, except that the eggs hatch in the external environment rather than in the intestine. Hence eggs, rather than larvae, appear in fresh feces. Other animal species of *Strongyloides* can also infect man, but they remain as larval forms in the skin and cause symptoms similar to those of cutaneous larva migrans (WHO, 1979).

Geographic Distribution and Occurrence: *S. stercoralis* occurs worldwide, but it is more common in tropical and subtropical climates than in temperate regions. Not much is known about the prevalence of the infection. In 1947, it was estimated that nearly 34 million people throughout the world were parasitized, distributed as follows: 21 million in Asia, 8.6 million in Africa, 4 million in tropical regions of the Americas, 400,000 in North America, and 100,000 in the Pacific islands. A subsequent estimate in 2000 increased the number of human infections throughout the world to 200 million (Marquardt *et al*., 2000). The infection has been observed in Mexico, all the countries of Central America, and parts of South America. Between 1965 and 1985, the following rates were cited: Argentina, 7.6%; Colombia, 16%; French Guiana, 23.6%; Panama, 20%; and Uruguay, 4.3%. In Iquitos, Peru, the rate was 60%; in Brazil, prevalence ranged from 4% to 58% depending on the area of the country; and in Chile, there have been only occasional cases in man or dogs. In Brazil, in an indigenous group of the Amazon region, the prevalence was 5.6% in 126 individuals in 1992 and subsequently dropped to 0% in 174 subjects from the same locality in 1995. Other studies in Brazil showed a prevalence of less than 1% in 264 food handlers in the state of Minas Gerais; 10.8% in 37,621 parasitologic examinations performed at a São Paulo hospital in 1993; 10.4% in 222 individuals from São Paulo in 1995 and 11.3% in 432 persons from the same locality in 1997; 5.8% in 485 persons from Pernambuco; and 15.2% in 99 AIDS patients in Rio de Janeiro. In Argentina during 1989–1999, the prevalence rate was 2% in 207 children from Corrientes and 83.3% in 36 children hospitalized in Salta. In Peru, the rate was 16% in 110 children and 2.4% in 1,511 hospitalized patients. During that same period, the infection was found in 20% of 241 Sudanese refugees and in 33% of 275 children in southern Sudan; 4% of 70 children in Kenya; 6.4% of 800 children in Guinea; 2.2% of 137 children in the Lao People's Democratic Republic; 10.1% of

2,008 inhabitants and 25.1% of 2,462 people from two communities in Nigeria; and 0.4% of 216,275 coprologic examinations performed by state laboratories in the US. The infection rate can reach as high as 85% in poor socioeconomic groups living in warm, humid regions of the tropics and in institutions such as hospitals for the mentally ill, where there are frequent opportunities for fecal contamination. On the other hand, in hot, semiarid areas the infection rate rarely exceeds 3%.

Strongyloidiasis in dogs appears to be distributed worldwide, but its prevalence is moderate. It was found in 6.3% of dogs and 4.8% of cats in Malaysia; in 2% and 1.5% of dogs in Canada and the US, respectively; and in only 2 of 646 dogs examined in Australia.

S. fuelleborni is a common parasite of nonhuman primates in Africa and Asia. It is frequently found in these animals both in the wild and in colonies. At a primate center in California, US, the parasite was detected in 50% of the imported monkeys and 75% of those born in captivity (Flynn, 1973). In man, it is more prevalent than *S. stercoralis* in the humid jungle regions of Central Africa—for example, Cameroon, Ethiopia, and the Central African Republic. Human *S. fuelleborni* infection is also prevalent in the African savannah. For example, Hira and Patel (1977) found that 9.9% of the strongyloidiasis cases in Zambia were caused by *S. fuelleborni*. In a study conducted in a small town in the Democratic Republic of Congo, the prevalence was 34% in 76 children examined and 48% in 185 individuals from the general population (Brown and Girardeau, 1977). In a jungle area of southern Cameroon, *S. fuelleborni* was found 31% of 154 Pygmies examined, while the rate for *S. stercoralis* was only 1%. In another area, the infection rates were 7% and 2%, respectively, for the two species.

The Disease in Man: In a high proportion of human patients, *S. stercoralis* infection can be of very long duration. The evidence suggests that, even though host immunity inhibits the development and pathogenicity of larvae, it does not terminate the infection. These hypobiotic larvae can remain in the patient's tissues for years as an asymptomatic and overlooked infection, until a breakdown of immunity enables them to resume their development and become pathogenic once again. Mild infections are usually well tolerated in immunocompetent individuals and produce no symptoms at all, or at most only vague and variable intestinal complaints. However, in persons with large parasite burdens or lowered immunity, the clinical picture can be cutaneous, pulmonary, or digestive, depending on the localization of the parasite, and the seriousness of the infection can range from mild to fatal (Liu and Weller, 1993).

The cutaneous symptoms that develop when the larva penetrates the skin may be the only manifestation of the infection apart from peripheral eosinophilia. The first sign is a small erythematous papule at the invasion site, which may be associated with intense pruritus, urticaria, and petechiae in patients who have been sensitized by previous exposure. After that, a linear, serpiginous, urticarial inflammation appears, known as *larva currens*, which is virtually pathognomonic of the infection; a similar lesion can be caused by the larvae of nonhuman ancylostomids such as *Ancylostoma braziliense* and *A. caninum* (Chabasse *et al*., 1995). Some patients experience periodic urticaria, maculopapular exanthema, and pruritus, coinciding with attacks of diarrhea and the reappearance of larvae in feces. Skin lesions can be caused by other species of *Strongyloides* in addition to *S. stercoralis.* Based on

experimental infections in a volunteer, it is suspected that cases of dermatitis with serpiginous eruptions among hunters in swampy areas of Louisiana, US, were caused by *S. procyonis*, a parasite of raccoons, or *S. myopotami*, of otters.

During the larvae's pulmonary migration phase, symptoms may range from an irritating cough to full-blown pneumonitis or bronchopneumonia, sometimes with eosinophilic pleural effusion (Emad, 1999). A review of patients with severe pulmonary manifestations revealed that most of them had had some risk factor for strongyloidiasis, such as corticosteroid use, age over 65 years, chronic pulmonary disease, use of antihistamines, or some chronic debilitating disease. Almost all the patients were experiencing cough, dyspnea, panting, and hemoptysis; in addition, 90% had pulmonary infiltrates, 75% had peripheral eosinophilia, 60% were suffering from secondary infections, 45% had adult respiratory distress syndrome, 15% had bacterial lung abscesses, and 30% of the patients died (Woodring *et al*., 1996). In most cases, the bronchopulmonary manifestations are discrete and disappear within a few days. The serious pulmonary symptoms are usually associated with autoinfection.

Intestinal symptoms are predominant in the clinical picture. The intestine of parasitized individuals shows villous atrophy and cryptal hyperplasia (Coutinho *et al*., 1996). Depending on the severity of the lesions caused by the parasites in the intestinal mucosa, the symptoms may correspond to an edematous catarrhal enteritis with thickening of the intestinal wall or an ulcerative enteritis. Among the other symptoms, epigastric pain, diarrhea, dyspepsia, nausea, and vomiting are common. Both abdominal pain and diarrhea occur intermittently. Leukocytosis and peripheral eosinophilia are common. Although 50% or more of infected individuals do not present symptoms, it should be kept in mind that asymptomatics can suddenly develop serious clinical disease if their immune resistance is lowered. This aggravation of a preexisting infection may come from a rapid rise in the parasite burden due to an endogenous hyperinfection triggered by the renewed development of hypobiotic larvae following the breakdown of immunity. A disruption of this kind in the equilibrium of the host-parasite relationship can occur in individuals weakened by concurrent illnesses, malnutrition, treatment with immunosuppressive drugs, or immunodeficiency diseases.

Several fatal cases of strongyloidiases have occurred in patients treated with corticosteroid or cytotoxic drugs. Most of these patients did not have symptoms of the infection and were not shedding larvae until the treatment was initiated. The clinical picture consists of ulcerative enteritis with abdominal pain, intense diarrhea, vomiting, malabsorption, dehydration, hypoproteinemia, and hypokalemia, and it can sometimes lead to death. In immunocompromised individuals such as patients with AIDS, strongyloidiasis becomes a disseminated infection, often with hyperinfection, which can affect any organ and be very serious. In most of these cases, the predominant symptoms are respiratory and pulmonary (Celedón *et al*., 1994) and may include asthma, cavitation, opacities, consolidation, and infiltrates. Often, secondary bacterial infections can develop, such as bacteremia, peritonitis, meningitis, endocarditis, and abscesses at various sites. It is believed that the filariform larvae spread bacteria from the intestine to different parts of the body (Ramos *et al*., 1984). There have also been reports of purulent meningitis (Foucan *et al*., 1997) and nephrotic syndrome (Wong *et al*., 1998) caused by the parasitosis. In addition, cases have been described of strongyloidiasis transmitted through an organ transplant

obtained from a donor with a hypobiotic infection. The parasite does not seem to affect the organ recipient as long as he or she is receiving cyclosporin but can appear when the drug is suspended, perhaps because cyclosporin also has an inhibitory effect on the nematode (Palau and Pankey, 1997).

The pathogenicity of *S. fuelleborni* has been studied very little. Because simultaneous parasitoses occur so frequently in the tropics, it is difficult to link a particular symptom to a specific parasite. The most common complaints associated with this agent are abdominal pain and occasional diarrhea, as was observed in patients in Zambia and also in an experimentally infected volunteer (Hira and Patel, 1977). In general, infections caused by *S. fuelleborni* are not sufficiently intense to cause illness, and no superinfections have been reported.

The Disease in Animals: In dogs, the age of the host is an important factor. Clinical manifestations of *S. stercoralis* infection are seen only in young animals. Dogs and cats that have gotten rid of the parasite, either spontaneously or with treatment, are resistant to reinfection for more than six months. Unlike the human infection, which generally lasts for a long time if left untreated, the parasitosis in animals is of limited duration. The infection can be subclinical or symptomatic. In symptomatic cases, the first signs to appear in puppies are loss of appetite, purulent conjunctivitis, cough, and sometimes bronchopneumonia. The larval penetration phase can produce violent pruritus, erythema, and alopecia. The intestinal phase begins a week to 10 days later, with diarrhea, abdominal pain, and vomiting. Serious cases may include dehydration, emaciation, bloody diarrhea, and anemia, and they can even lead to death. In experimental infections, it has been observed that strongyloidiasis can become chronic in some adult dogs, but in veterinary practice the disease is limited to puppies.

In nonhuman primates infected with *S. fuelleborni*, the predominant symptom is diarrhea, which can vary from mild and benign to intense and hemorrhagic. In massive infections, the disease can be severe in weakened or very young animals.

Source of Infection and Mode of Transmission: Man is the principal reservoir of *S. stercoralis*. For both man and animals, the main source of infection is feces that contaminate the soil. The parasite usually enters by the cutaneous—rarely the oral—route, when the host comes in contact with third-stage or filariform larvae. Warm, moist soil is propitious for exogenic development of the heterogonic (indirect) cycle, which produces the free-living nematodes, because it allows for rapid multiplication of the infective larvae. For this reason, the infection is more common in tropical than in subtropical regions.

The role of dogs and cats in the epidemiology of strongyloidiasis has not yet been fully clarified. The susceptibility of dogs to certain biotypes or geographic strains would suggest that, at least in some parts of the world, these animals may contribute to human infection by contaminating the soil. However, the literature has recorded only one case (Georgi and Sprinkle, 1974) in which the source of human infection was attributed to canine feces. It is difficult to determine the frequency of human-animal cross-infections because there are no characteristics that distinguish the adults or larvae of *S. stercoralis* in man from those that occur in animals, but there are molecular differences, as mentioned earlier, that would suggest the human and canine parasites are different species or subspecies.

The reservoirs of *S. fuelleborni* are African and Asian simians. The source of

infection is primate feces (nonhuman and human). Originally, the infection was zoonotic (from nonhuman to human primates), but there is growing evidence that *S. fuelleborni* in various parts of Africa is transmitted from human to human. Studies carried out in Zambia have confirmed that the parasitosis occurs among populations in periurban and urban areas, settings in which nonhuman primates are not usually found, and also in very young children (34% of 76 infants under 200 days old) (Hira and Patel, 1980; Brown and Girardeau, 1977). In such cases, it is undoubtedly man who maintains the cycle in nature. Likewise, the high prevalence of infection in some communities, such as the Pygmies, would suggest that the parasite has a tendency to adapt to the human species.

Other animal species of *Strongyloides* rarely succeed in completing their life cycle in man. In a volunteer experimentally infected with infective *S. procyonis* larvae from raccoons, very few specimens reached maturity and oviposition. Most animal species of *Strongyloides* are capable of invading human skin and causing transitory dermatitis.

Role of Animals in the Epidemiology of the Disease: Strongyloidiasis caused by *S. stercoralis* is a common disease and apparently intercommunicable between man and dogs. It has been thought that, in some areas, the infection can be transmitted from one species to another by means of contaminated soil, but the evidence of transmission from dog to man and vice versa is scant and circumstantial.

Strongyloidiasis caused by *S. fuelleborni* is an infection of both zoonotic and interhuman transmission. Dermatitis in man caused by other species of *Stongyloides* is zoonotic.

Diagnosis: Laboratory confirmation of the infection consists of finding rhabditiform *S. stercoralis* larvae or *S. fuelleborni* eggs in host feces. With strongyloidiasis, there are various means of improving the results of the coprologic examination. De Kaminsky (1993) studied 427 fecal samples to compare direct smear, the modified Baermann technique, and agar-plate culture: the smear revealed 9 infections; the Baermann technique, 42; and the culture, 70. However, the smear is the most economical; the Baermann technique was 4 times more expensive, and the culture, 15 times more costly. The larvae or eggs can be shed intermittently, and the tests should be repeated on three different days. Duodenal aspiration varies in its effectiveness, and this method is best used as a complement to the coprologic examination. Larvae can occasionally be observed in sputum. An enzyme-linked immunosorbent assay (ELISA) has been introduced which has presented some problems of cross-reactivity with other nematodes. However, adsorption of problem sera with *Onchocerca gutturosa* extract and the use of selected antigens has made it possible to achieve 94% to 97% specificity and 100% sensitivity (Lindo *et al*., 1994). The conventional ELISA test is only 13% sensitive in immunodeficient patients, but it improves to 100% with the use of biotinylated conjugates or avidin-peroxidase (Abdul-Fattah *et al*., 1995). Also, indirect immunofluorescence reaction has been reported to produce 92% to 94% sensitivity and 94% to 97% specificity (Costa-Cruz *et al*., 1997).

Control: The most important community control measure is reduction of the source of infection through the sanitary disposal of human feces. It is important to treat all infected persons, even if they are asymptomatic, in order to reduce the possibility of contaminating the environment. As with ancylostomiasis, wearing shoes

provides good protection in endemic areas because it prevents larvae from penetrating the skin of the foot. Since strongyloidiasis can be acquired by the oral route, good personal hygiene habits, such as washing one's hands before eating, are also important.

Prior to the initiation of any immunosuppressive treatment, it is recommended that the patient be tested for *S. stercoralis.* In the event that the results are positive, this infection should be treated first to prevent the possibility of hyperinfection.

Although the importance of domestic pets in transmission of the infection to man has not been determined, it is recommended to take basic precautions, such as treating infected dogs or cats.

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THELAZIASIS

ICD-10 B83.8 Other specified helminthiases

Synonyms: Conjunctival spirurosis, thelaziosis, eyeworm.

Etiology: The agents of this disease are *Thelazia callipaeda*, *T. californiensis,* and *T. rhodesii*. These parasites are nematodes of the superfamily Thelazioidea whose adult stage lodges in the conjunctival sac and conjunctiva of domestic and wild mammals and, occasionally, of man. The other species of the genus *Thelazia* have not been found in humans; the correct identification is doubtful in the only human case attributed to *T. rhodesii*.

T. callipaeda is a parasite of dogs and other canids. The female measures 7 mm to 17 mm and the male measures 7 mm to 11.5 mm. The female lays embryonated eggs in the conjunctival sac, and the first-stage larvae are released and deposited on the conjunctiva. To continue their development, *Thelazia* spp. require a fly as an intermediate host. The flies, by sucking conjunctival secretions, ingest the larvae (or the eggs containing them). These larvae develop inside the insect for several weeks, until they become infective third-stage larvae. The infective larvae migrate to the proboscis of the fly and infect new conjunctiva when the arthropods resume sucking conjunctival secretions. In 2 to 6 weeks, the third-stage larva matures into an adult and begins to produce eggs. The intermediate host of *T. callipaeda* is not well known. In the Russian Far East, larvae of the parasite have been found in the fly *Phortina variegata,* and it is believed that this species could be the vector. The intermediate host of *T. californiensis* is the fly *Fannia thelaziae*, a member of the *F.*

benjamini complex (Weinmann, 1982). The intermediate hosts of *T. rhodesii* are various species of *Musca* (*M. autumnalis*, *M. convexifrons*, *M. larvipara*), *Morellia simplex,* and *Stomoxys calcitrans.*

Geographic Distribution and Occurrence: *T. callipaeda* is found in dogs and wild canids in the Far East. Up until 1985, more than 20 human cases had been reported in China, Korea, Japan, India, Thailand, and the eastern region of the former Soviet Union. Up until 2000, 9 more cases were reported: 1 in China; 4 in Korea, bringing that country to a total of 24 cases (Hong *et al*., 1995); 1 of an undetermined species in India; 1 in Indonesia; 1 in Thailand; and 1 in Taiwan.

T. californiensis occurs in the western US, where it parasitizes the black-tailed jackrabbit (*Lepus californicus*), deer, coyotes, foxes, raccoons, bears, dogs, and less frequently, cats and sheep. Up until 1985, approximately 10 human cases had been reported, and 3 more had been reported by 2000. All the cases occurred in California, US, or in neighboring states.

T. rhodesii parasitizes bovines, goats, sheep, bubalines, and deer in North Africa, Europe, and the Middle East. One human case was described in Spain, but the identification of the etiologic agent has been questioned (Weinmann, 1982).

The Disease in Man and Animals: In man, *Thelazia* sp. lodge in the conjunctival sac, where they cause irritation, lacrimation, conjunctivitis, and sometimes, corneal scarring and opacity (Cheung *et al*., 1998; Doezie *et al*., 1996). Some infections manifested only as a bothersome sensation of a foreign body in the affected eye.

In animals, the parasite is found under the nictitating membrane. The symptomatology is similar to that of human thelaziasis. Conjunctivitis is often aggravated by pruritis, which causes the animal to rub against various objects. Corneal lesions are more common in animals than in humans, but it has not been well established whether they are due to the parasites or to other, concurrent causes. The intensity of symptoms is quite variable and may depend on the species of *Thelazia* affecting the animal; *T. rhodesii* is considered to be the most pathogenic, but it may not be infective for humans.

Source of Infection and Mode of Transmission: The reservoirs are several species of domestic and wild mammals. In a village in Thailand, where one human case caused by *T. callipaeda* occurred, five of seven dogs examined were infected. The infection is transmitted from one animal to another or from animal to man by various species of flies. Some species of *Thelazia* are very particular about their intermediate hosts and the first-stage larva develops only in certain species. This particularity largely determines the geographic distribution of both *T. californiensis* and *T. callipaeda.* The predilection of the different vectors for feeding on particular animal species is important in the epidemiology and is a factor that limits the number of human cases. Transmission is seasonal and occurs when vector flies are abundant.

Diagnosis: After a local anesthetic is administered, the parasites are seen as white threads in the conjunctiva or conjunctival sac, and are extracted with ophthalmic forceps and identified.

Control: Special prevention measures are not justified because human infection is so rare.

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TRICHINOSIS

ICD-10 B75 Trichinellosis

Synonyms: Trichiniasis, trichinelliasis.

Etiology: The agents of this disease are nematodes of the genus *Trichinella*, particularly *T. spiralis.* This species is a small nematode of the intestine of predatory mammals and the muscles of mammals preyed upon by other animals. In the intestine, the adults measure 1–3 mm; in the muscles, the larvae measure less than 1 mm. *T. spiralis* was described by Owen in 1835 and was thought to be a single species until, in 1972, Soviet researchers determined that there were several species. The taxonomic category, species, subspecies, strains, or varieties of the new entities were debated for a long time. After the detailed review by Pozio *et al*. (1992), most authors seem to have accepted their categorization as comparatively new species. Differentiation of those species by polymerase chain reaction restriction fragment length polymorphism (Wu *et al*., 1999) supports this opinion. Bessonov (1998) holds the opposite opinion, but his writings are less widely read, being in Russian. Apart from three phenotypes of *T. spiralis* of uncertain taxonomic category, the generally accepted species (Barriga, 1997) are *T. spiralis*, *T. nativa*, *T. nelsoni*, *T. pseudospiralis*, and *T. britovi*. Most of our knowledge about the parasite, the infection, and the disease results from studies of the classic species, *T. spiralis.*

T. spiralis is adapted to temperate zones where swine are raised; it is found in domestic, peridomestic, and wild epidemiological cycles. It is highly infective to mice, rats, guinea pigs, rabbits, and swine, and moderately infective to hamsters. It does not infect birds. The species is highly pathogenic to mice and rats and moderately pathogenic to humans. In the muscle, the larva does not survive more than 10 or 20 days at –15°C.

T. nativa is adapted to the northern circumpolar regions, above the 40th parallel,

where it circulates among wild carnivores, such as bears and foxes, and their prey. The species is highly infective to mice and slightly infective to rats, hamsters, guinea pigs, rabbits, and swine. It does not infect birds. The larva survives in the muscle for more than 12 months at temperatures of –15°C.

T. nelsoni is adapted to the tropical and semitropical areas of Africa, Asia, and Europe, and areas near the Mediterranean Sea; it circulates among carnivores such as foxes, panthers, leopards, lions, hyenas, and wild boar. The species is slightly infective to mice, rats, hamsters, and swine, moderately pathogenic to mice, slightly pathogenic to rats, and less pathogenic than *T. spiralis* to humans. It does not infect birds. The larva survives in the muscle for 6 or more months at –12°C or –17°C and is resistant to high temperatures.

T. pseudospiralis is distributed in North America, India, and the former Soviet Union; it is thought to circulate among predators of birds and their prey. The species is highly infective to hamsters, slightly infective to rats, and less pathogenic than *T. spiralis* to monkeys and, presumably, to humans. Unlike the other species, it does not encyst, and it infects birds. The larva in the muscle dies in three days at –12°C or –17°C.

T. britovi is adapted to the temperate and subarctic regions of Eurasia; it circulates among wild carnivores, mainly foxes, but also wolves and mustelids, and their prey, the wild boar. The species is slightly infective to mice, rats, and swine, less pathogenic than *T. spiralis* to humans, and less resistant to freezing than *T. nativa*.

When a carnivore or omnivore ingests meat with infective first-stage *Trichinella* larvae, the larvae are released in the small intestine, penetrate the mucosa, go through four rapid molts, return to the lumen, and mature into adults in just two days. The adult parasites mate, the female invades the intestinal mucosa again, and begins to release live larvae on the fifth day of infection, with the highest number being released on the ninth day. The period of larviposition and the number of larvae produced are limited by the immune response of the host. In a primary infection, larviposition lasts 10 to 20 days in mice and rats, and about 6 weeks in man; each female produces between 200 and 1,700 larvae. The larvae are disseminated through the organism by the circulatory system and, in a few hours, penetrate the striated muscle fibers, where they coil up and grow for the next 10 days. The parasite prefers the most active muscle groups, especially the jaw, lingual, ocular, back, and lumbar muscles, and the pillars of the diaphragm. The larva quickly takes control of the muscle cell's function and converts it to a nurse cell which satisfies the metabolic needs of the parasite. The larvae that penetrate tissues other than the striated muscles do not continue to develop. The larva becomes infective for the next host approximately 16 days after invading the muscle. At around day 10, a collagen cyst formed by the host starts to surround the larva. The cyst is completely formed in about three months, is shaped like a lemon measuring approximately 1 mm, and, in most cases, contains a single larva. The cysts generally begin to calcify at around six months, but the parasites can live inside them for up to three years or more. Ingestion of those infected muscles by another host reinitiates the cycle. It is worthy of note that the same host acts first as the definitive host and then as the intermediate host.

Geographic Distribution: *T. spiralis* is widely distributed in the temperate countries. Steele (1982) undertook a detailed review of its distribution up until approxi-

mately 1980. Its presence has not been confirmed in Australia or in several tropical or semitropical countries in Africa, Latin America, and Asia. However, it should be borne in mind that research has been limited for the most part to the domestic cycle in swine, rats, and man. Thus, the possibility exists that the infection may occur in wild or synanthropic animals without human cases having been reported. For information on the geographic distribution of the other species, see Etiology. In several countries there is more than one species. For example, *T. spiralis* and *T. britovi* have been found in China and Spain; *T. spiralis* and *T. nelsoni* in France; and *T. spiralis*, *T. britovi*, and *T. nativa* in Estonia. *T. spiralis* is found in domestic or peridomestic environments, and the other species in wild environments (Pozio *et al*., 1998).

Occurrence in Man: There is a great difference between the real prevalence of trichinosis and that diagnosed or reported. During the time when approximately 2% of the US population was infected, there were less than two hundred known clinical cases. This may be due to the fact that trichinosis is easy to confuse with influenza, which results in many erroneous diagnoses.

In the Americas, the disease has occurred in Argentina, Canada, Chile, Mexico, the US, Uruguay, and Venezuela. In some other countries or territories, isolated cases have been recorded, but it is not clear whether they were autochthonous or imported cases. Few outbreaks of trichinosis have been recorded in Canada. In 1974, 1975, and 1976, there were 49, 3, and 31 clinical cases, respectively. Examination of the diaphragms of persons who died from other causes revealed percentages of infection ranging from 1.5% in Toronto to 4%–6% in British Columbia. Infection among indigenous peoples is frequent in northern Canada, but clinical cases are sporadic or affect only small groups. In that region the source of infection is wild mammals, both terrestrial and marine, and the etiologic agent is probably *T. nativa.* While the parasite is virtually nonexistent in swine, and human cases originating in swine have not occurred for nearly 20 years, cases still occur because of the consumption of wild boar. The 1993 outbreak in Ontario affected 24 people (Greenbloom *et al*., 1997). In the US, 1,428 cases were recorded in the 10 years from 1972 to 1981, for an annual average of 143 cases, 7 deaths, and a fatality rate of 0.49%. Distribution of the disease was unequal: of the 188 cases that occurred in 1981, 81.3% originated in five northeastern states and Alaska. The rate per million inhabitants was 0.8 for the whole country, 36.7 for Rhode Island, and 33.9 for Alaska (CDC, 1982).

The reduction in the incidence and intensity of the disease is noteworthy: in the period 1947–1956, an average of 358 cases were recorded each year, with 84 deaths and a fatality rate of 2.3%; between 1984 and 1988, just 44 cases per year were recorded on average. The reduction is due essentially to the decline of the infection in swine, but the importance of the infection from game animals has increased: Dworkin *et al*. (1996) reported on an epidemic of 15 cases in Idaho caused by cougar meat infected with *T. nativa*. While the rates are low, the infection still exists in swine in the US and can affect humans who eat the raw pork: 90 refugees from Southeast Asia were infected in Iowa in 1990 by eating raw sausages prepared with store-bought pork (McAuley *et al*., 1992). The real prevalence of the infection has also declined, as confirmed by autopsies. Between 1936 and 1941, an estimated 12% of the population was infected, while in 1970 the adjusted rate of infection was 2.2%. In 1940, 7.3% of inhabitants had live trichinae in their diaphragms—suggesting relatively recent infection—while in 1970, the rate was 0.7%. In Mexico, stud-

ies carried out between 1939 and 1953 discovered trichinae in 4% to 15% of autopsies; a study in 1972–1973 found the larvae in 4.2% of cadavers. In 1975, just three cases were diagnosed in the country. However, in Zacatecas, there were 17 outbreaks with a total of 108 cases between 1978 and 1983 (Fragoso *et al*., 1984).

Outbreaks of trichinosis occur periodically in Argentina and Chile, which are the only South American countries where the disease is important from the public health standpoint. In 1976, the rate per 100,000 population was 0.1 for Argentina and 0.5 for Chile. In 1982, in Santiago, Chile, a 2.8% rate of infection was found in the cadavers of people who died in accidents or by other violent means. The percentage is similar to that reported in studies carried out in 1966–1967 and 1972; however, in 1982, all the larvae were calcified and the prevalence shifted to older age groups, which could be interpreted as a decrease in new infections. The epidemic reported in Argentina in 1991 affected 18 people in southern Buenos Aires (Venturiello *et al*., 1993), and the epidemic reported in Chile in 1992 affected 36 people in the southern part of that country (Zamorano *et al*., 1994).

The morbidity rate has also declined in Europe. For example, in Poland, where previously more than 500 cases occurred per year, the incidence has diminished notably and no major outbreaks were reported in the last years of the twentieth century. In the former Soviet Union, the endemic area with the highest prevalence is found in Belarus, where 90% of all cases have occurred. The sporadic cases recorded in the northern and central Asian regions of the former Soviet Union resulted from the consumption of wild animal meat. An outbreak in Italy in 1975, which affected 89 people who ate horse meat imported from eastern Europe, was attributed to *T. nelsoni.* A similar outbreak occurred in France (Bellani *et al*., 1978). Later, an outbreak of trichinosis was discovered in Paris, France, with more than 250 human cases caused by the consumption of raw or undercooked horse meat imported from the US (Ancelle and Dupouy-Camet, 1985). In 1993, there was another outbreak in France, affecting 554 people, attributed to the consumption of horse meat (Dupouy-Camet *et al*., 1994). Infection caused by horse meat is surprising because strictly herbivorous animals such as horses would not have the opportunity to become infected. It has been hypothesized that these animals may have inadvertently eaten infected rodents with their fodder, or that the horses became infected by eating necrophagous insects in their pasture. Trichina larvae have been proven to survive five to eight days in the intestines of these insects and, since they multiply in the host's intestine, a few larvae ingested in this manner could cause a significant infection in a horse (Barriga, 1997).

In Asia, human trichinosis was not considered important until the 1960s and 1970s. In Thailand, the first outbreak occurred in 1962 in the northern part of the country, and from then until 1973, 975 cases and 58 deaths were recorded. The first outbreak in Japan occurred in 1974, and a total of three outbreaks had been reported by 1991: the first affected 15 people in 1974; the second affected 12 people in 1980; and the third affected 60 people in 1981. All the infections were due to consumption of bear meat (Yamaguchi, 1991). A domestic cycle does not seem to exist in that country. In Lebanon, an epidemic probably affected more than 1,000 people in 1982, and another affected 44 people in 1995 (Haim *et al*., 1997). Two epidemics reported in China occurred in an endemic area in the center of the country: one affected 54 people in the 1980s and the other affected 291 in the period 1995–1996 (Cui *et al*., 1997). In China, larvae have been found in swine, dog, sheep, and bear meat.

The situation in Africa is peculiar. In countries of northern Africa bordering on the

Mediterranean, some outbreaks of human trichinosis were known in Algeria and in Egypt among Copts and tourists, but it was believed that the disease did not exist south of the Sahara. The first outbreak in Kenya, due to *T. nelsoni*, was diagnosed in 1959. The investigation demonstrated that the human infection originated as a result of consumption of meat from a bush pig (*Potamochoerus porcus*). Later research discovered that the infection is widely distributed in the wild fauna of Africa, including warthogs (*Phacochoerus aethiopicus*), hyenas, jackals, and some felids.

The infection is frequent in the Arctic regions and is mainly due to the consumption of bear meat. Cases linked to walrus meat were first described in Greenland and then in the northern part of Alaska. The species that circulates at these latitudes is *T. nativa*, which is characterized by greater resistance to freezing temperatures.

Human cases are unknown in Australia. The Hawaiian Islands are the only endemic area in the Pacific; a survey conducted in 1964 found the parasite in 7.4% of cadavers autopsied. In New Zealand, the first human case was diagnosed in 1964, and the first human infection attributed to *T. pseudospiralis* was identified in 1994; the species of the parasite was confirmed by molecular biology techniques (Andrews *et al*., 1995). In 1994–1995, an epidemic in Thailand caused by raw meat from an infected wild pig affected 59 people and caused one death (Jongwutiwes *et al*., 1998).

In general, human trichinosis is still widespread in many parts of the world, but morbidity rates are low and declining.

Occurrence in Animals: *T. spiralis* has a wide range of hosts among domestic and wild animals. The infection has been confirmed in 150 species of mammals, from primates to marsupials, including cetaceans and pinnipeds. Of special interest among domestic animals are swine, whose meat and by-products are the main source of infection for man. The infection rate in swine depends on how they are managed and, in particular, how they are fed. There is a marked difference in the rates of infection in grain-fed swine and those fed raw waste from either the home or from slaughterhouses. In the US, in 1950, the prevalence of trichinosis in swine fed waste was 11%, while it was only 0.63% in those fed grain. When mandatory cooking of waste intended for swine food was established in order to prevent viral infections, the prevalence decreased rapidly to 2.2% between 1954 and 1959, to 0.5% in the 1970s, and to even lower rates later on, when less than 1% of swine in the US were fed waste. The source of the infection is not clear, especially because, on several occasions, the role of rats was discounted. In a serologic examination of 4,078 swine on 156 farms in the region of New England and the state of New Jersey, US, 15 positive swine were found on 10 farms, for an individual prevalence of 0.37% and a herd prevalence of 6.4%. The most important risk factors were access of swine to live wildlife and wildlife carcasses on the farm. However, since there was no association between the infection and the consumption of scraps of human food, the recycling of infected pork is no longer an important factor in that area (Gamble *et al*., 1999).

In many European countries, the parasitosis is no longer found in swine; the highest frequency is 0.1%, usually on small farms. In 1976 in Germany, only one infected pig was found out of 32 million examined by trichinoscopy (observation of larvae by pressing a muscle sample between two slides and viewing it under a microscope). In the Netherlands, not a single infected pig was discovered by

trichinoscopic examination between 1926 and 1962. However, use of the digestion method (digestion of muscle samples and observation of larvae in the sediment) demonstrated that some pigs had very low intensity infections, with 0.025 larvae per gram of meat (Ruitenberg *et al.*, 1983).

In Brazil, Colombia, Ecuador, Paraguay, and Venezuela, the parasite has not been found by trichinoscopic examination. In Argentina and Chile, trichinoscopy records indicate a general frequency of 0.14% and 0.33%, respectively. Of course, the prevalence is much higher in selected samples, such as pigs that roam around garbage dumps or pigs from small farms that are fed kitchen waste, and it is these animals that frequently give rise to epidemic outbreaks in South America.

Dogs and cats have ample opportunity to become infected both in the domestic cycle, with raw meat provided by their owners, and in the wild cycle, through the hunting of omnivorous rodents. For this reason, the prevalence in these animals is generally higher than in pigs. Studies of street dogs in Santiago, Chile (Letonja and Ernst, 1974) found rates ranging from 1.2% to 4%, while 72% of 36 dogs captured in 1955 in the municipal slaughterhouse were infected. In a later study in Valdivia Province, in southern Chile, 30 urban dogs and 30 rural dogs were examined, and 6.6% and 16.6%, respectively, were found to be infected (Oberg *et al*., 1979). In Mexico City, 3.3% of 150 dogs examined had trichinellosis, while in Maracay, Venezuela, all 600 animals examined were free of infection. Infection rates of 45% to 60% have been found in dogs in Alaska, Greenland, and Siberia. The parasite was discovered in 7 of 12 cats examined in San Luis, Argentina; in 2% of 50 cats in Santiago, Chile; and in 25% of 300 cats studied in Mexico. By contrast, in Maracay, Venezuela, none of the 120 cats examined gave a positive result. In the US, Europe, and the former Soviet Union, the infection in dogs and cats is relatively frequent, with prevalence rates higher than those in pigs.

Rats also participate in the synanthropic or peridomestic cycle. In the US, rural rats are not infected, but a high rate of infection has been found among rats living in garbage dumps (5.3% of 1,268). In the former Soviet Union, 1.6% of 8,037 rats were found to be infected. High rates of infection have been found in Lebanon (36% in a survey in 1952) and in British Columbia, Canada (25% in 1951). Studies in Costa Rica, Ecuador, Panama, Puerto Rico, and Venezuela, and more recently in Santos and São Paulo, Brazil (Paim and Cortes, 1979), yielded negative results. Almost all of these studies employed trichinoscopy, which is not very sensitive for detection of the parasite, so very low levels of infection cannot be discounted. Numerous surveys have been done in Chile, where an important role in the epizootiology is attributed to rats. Of rats captured in garbage dumps in Santiago and Antofagasta, 8% and 28.6%, respectively, were found to be infected. Surveys conducted in 1951 and 1967 in the municipal slaughterhouse of Santiago revealed infection rates in *Rattus norvegicus* of 10% and 25%, respectively. A high rate of infection (86%) was also found in rats captured in 1983 in several sectors of the city of Concepción. In the epidemiologic investigation of an outbreak that affected 60 persons, 12.3% of swine and 30.7% of *R. norvegicus* were found to be infected.

The main reservoirs of trichina in nature, however, seem to be the wild carnivores. The fox (*Vulpes vulpes*) is important in Europe because of its abundance and high infection rates. Trichinosis is also frequent among Old World badgers (*Meles meles*), wolves (*Canis lupus*), lynxes (*Felis lynx*) and wild boar (*Sus scrofa*). In the state of Alaska and other areas of the Arctic and Subarctic, high rates of infection have been

found in the polar bear (*Thalarctos maritimus*), with an average of 45% parasitized, as well as in other ursids, Arctic and red foxes, and several species of mustelids. Among marine mammals, the infection has been confirmed in walruses (*Odobenus rosmarus*), with a prevalence of 0.6% to 9%, and low rates have been found in other pinnipeds and cetaceans. In the US, the parasite was discovered in 5% of minks and 6.4% of foxes in Iowa. Low-intensity infection was found in wild rodents (*Microtus pennsylvanicus*, *Sigmodon hispidus*, and others) in Virginia (Holliman and Meade, 1980). There is enough evidence to assume that the wild cycle of trichinosis is self-sustainable. However, on at least one occasion, it seems that a coyote became infected through infected swine (Minchella *et al*., 1989).

In sub-Saharan Africa, only the wild cycle is known. The parasite is widely distributed among wild carnivores. The infection has been confirmed in hyenas, jackals, leopards, lions, servals (*Felis serval*), and wild pigs. Hyenas (*Crocuta crocuta* and *Hyaena hyaena*) seem to be the main reservoirs; 10 of 23 *C. crocuta* tested were positive.

Except in Argentina and Chile, studies have not been done on the wild fauna of Latin America. In central Chile, 2,063 wild animals were examined, of which 301 were carnivores (usually very parasitized) and 1,762 were rodents (generally not very parasitized), and the infection was not found in any of them. Out of 20 animals examined in Argentina, a fox (*Pseudalopex gracilis*), an armadillo (*Chaetophractus villosus*), and a rodent (*Graomis griseoflavus)* were found to be infected.

The Disease in Man: Only a small proportion of infections—those that are intense—are manifested clinically. It is thought that man needs 10 to 100 parasites per gram of muscle in order to show symptoms. Many sporadic cases pass unnoticed or are confused with other diseases.

In classic trichinosis caused by *T. spiralis*, the incubation period lasts about 10 days, but can vary greatly—from 1 to 43 days—and seems to be directly related to the number of larvae ingested. Three phases of the disease are described: intestinal, larval migration, and convalescence. The intestinal phase is uncommon and occurs in about 15% of patients; it is expressed as a nonspecific gastroenteritis, with anorexia, nausea, vomiting, abdominal pain, and diarrhea.

Seven to 11 days after ingestion of the infective food, the signs of the larval migration phase begin, with fever, myalgias (which may be pronounced and in diverse locations), edema of the upper eyelids (a very common and prominent sign), cephalalgia, sweating, and chills. In a small proportion of patients with severe disease there may be urticaria or scarlatiniform eruptions, and respiratory and neurologic symptoms. The vast majority of patients have leukocytosis and eosinophilia. In 95.9% of 47 Chilean patients, eosinophilia with values above 6% was found. The disease lasts about 10 days in moderate infections, but may persist a month or more in massive infections. In the convalescent phase, muscular pains can sometimes persist for several months. In cases of infection caused by *T. spiralis* in Italy, Pozio *et al*. (1993) found eosinophilia in 100% of the patients, specific IgG antibodies in 100%, high levels of creatine phosphokinase in 90%, fever in 60%, myalgia in 50%, diarrhea in 40%, and antibodies against the newborn larva in 30%. In epidemic outbreaks, mortality is usually under 1%.

In a study of 150 patients suffering from trichinosis due to *T. nelsoni* in an outbreak in Italy, myalgia was found in 88%, myositis in 62%, muscular weakness in

60%, and arthralgia in 20%. The degree of myositis was directly related to the degree of hypereosinophilia, and the muscle damage observed microscopically was often related to eosinophilic infiltration of the muscle. The arthralgia was closely related to the myalgias/myositis. There was no relationship between the clinical manifestations and the IgG or IgE antibodies. There was no vascularitis or involvement of the nervous system or heart. *T. nelsoni* seems to mainly affect the muscular system, with a favorable prognosis (Ferraccioli *et al*., 1988).

In *T. britovi* infections, Italian authors have observed that the patients present milder gastrointestinal symptoms, lower levels of creatine phosphokinase, and less persistence of specific IgG antibodies in comparison with patients suffering from classic *T. spiralis* (Pozio *et al*., 1993).

In an outbreak caused by *T. pseudospiralis* in Thailand, the most striking clinical manifestations were muscular swelling, myalgia, and asthenia of more than four months' duration (Jongwutiwes *et al*., 1998).

The Disease in Animals: Trichinosis does not cause clinical manifestations in animals at the level of infection found in nature. However, massive experimental infections cause illness or death in rats, dogs, cats, and swine; the infected animals exhibit peripheral eosinophilia, fever, anorexia, emaciation, and muscle pain.

Source of Infection and Mode of Transmission: Trichinosis in nature is an infection of wild animals. The parasite circulates between predatory carnivores and omnivorous or necrophagous animals. The former become infected by hunting and consuming the latter, and the latter become infected by eating the carcasses of the former. From the epidemiological standpoint, the parasite's resistance to putrefaction is important; live, often infective, larvae have been found in badly decayed flesh for up to four months, which facilitates the infection of carrion eaters. A domestic, peridomestic, or synanthropic cycle derives from this wild cycle when synanthropic animals such as rats, dogs, cats, and swine become infected by eating infected wild animals and carry the infection to the domestic environment. In an extensive study, Gamble *et al*. (1999) found that the risk factors for the infection in swine are access to live wildlife or wildlife carcasses on the farm. The consumption of garbage did not constitute a risk for infection. In places where modern technology is applied to swine breeding, such as Japan and Switzerland, the wild cycle can exist without extending to the domestic environment (Gotstein *et al*., 1997; Yamaguchi, 1991). There is some evidence that the infection can also extend from the domestic to the wild environment: Minchella *et al*. (1989) found a coyote infected with swine trichinae.

It is assumed that, once in the domestic environment, the parasite circulates among pigs, dogs, cats, and rats. The parasite is transmitted from pig to pig mainly by the ingestion of food scraps containing raw pork. The incidence of trichinosis in swine fed raw waste from kitchens, restaurants, or slaughterhouses is 20 times higher than that in grain-fed swine. Another source of infection for swine may be dead infected animals, including rats, but also dogs, cats, or wild animals, which are sometimes found in garbage dumps. One theory is that the consumption of infected rats explains the swine infections which, in turn, cause outbreaks of the infection in man. While it is true that an association between high rates of infection in rats and swine has sometimes been found, there is also solid research that casts doubt on this association (Campbell, 1983). It has also been shown that the pig can acquire the

infection from another pig by coprophagia, since some trichina larvae are eliminated in the feces of swine that ingest infected meat for up to five days after ingestion, and they can infect another swine that eats them. Infection of swine by chewing the tails of other (infected) swine has also been described. These last two transmission mechanisms are of little practical importance.

Dogs and cats probably become infected when they eat scraps of infected raw pork provided by their owners or by hunting infected rats or ingesting infected dead domestic, peridomestic, or wild animals. Sled dogs in the Arctic are infected by eating wild animal meat fed to them by man or by consuming carrion they find in their habitat. This explains the extremely high rates (50% or more) found among dogs in that region. In turn, dog and cat carcasses transmit the infection to other carrion eaters, rats, and swine.

Rats become infected by eating infected domestic or wild animals and by cannibalism. The role of the rat in the epidemiology of trichinosis, considered central for a long time, has not been objectively proven. In the opinion of most modern investigators, its epidemiological role seems to be secondary.

Man is an accidental host in whom the parasite finds a dead end, except in unusual circumstances, such as in eastern Africa, where some tribes abandon the dead or dying to the hyenas. The human infection occurs mainly as a result of consuming raw or undercooked pork or pork by-products, but also as a result of eating wild game. It is estimated that the meat of a single parasitized pig weighing 100 kg can be a potential source of infection for 360 persons. Since pork is frequently added to beef in the manufacture of sausage, the potential risk is even greater. In Argentina and Chile, outbreaks most commonly occur in rural areas, with the source of infection being a pig killed by its owner and thus not subjected to veterinary inspection. The sources of infection are almost always pigs fed waste from kitchens, restaurants, or local slaughterhouses and, in small towns, animals kept at garbage dumps. However, even pigs inspected in slaughterhouses can give rise to infections, albeit probably mild infections, since trichinoscopy cannot detect low-level parasitoses (fewer than 1–3 larvae per gram of muscle). The US is one of the few developed countries in which trichinosis is still a public health problem, although on a much smaller scale than it used to be. Of 947 human cases for which the source of infection could be ascertained, 79.1% were attributable to pork products, 6% were due to ground beef (probably contaminated with pork), and 13.9% were linked to wild animal meat, especially bear. In Alaska, half the cases were due to bear meat and the other half to walrus meat. In Japan, all the cases were due to the consumption of wild animals. In contrast to the epidemiological pattern in Latin America, where the infection often results from slaughter of animals and preparation of sausages at home, 81% of the tainted pork products in the US were acquired in supermarkets, butcher shops, or similar outlets. Products acquired directly from farms caused only 13.8% of the cases recorded between 1975 and 1981 (Schantz, 1983). This is due to the fact that inspection for *Trichinella* is mandatory in slaughterhouses in most of the Latin American countries where the parasite occurs, but not in the US.

In man, as in animals, the frequency of the infection and its intensity increase with age, as a result of longer opportunity for infection and reinfection. In the US, between 1966 and 1970, the average intensity for people who died under the age of 45 was 2.4 trichinae per gram of diaphragm material, while the same study found that for older persons, it was 12.2 per gram (Zimmermann and Zinter, 1971).

Religion and ethnic origin have a great influence on the prevalence of the infection. The prevalence of trichinosis is very low among Muslims, Jews, and Seventh Day Adventists, whose religious beliefs prohibit the consumption of pork. In the Middle East, the disease occurs in Lebanon, where the Christian population is large, but is very rare in the predominantly Muslim countries. On the other hand, prevalence rates in the US are higher in some ethnic groups, such as Italians, Germans, and Poles, because of their preference for pork products processed at a temperature insufficient to destroy the larvae. In the former Soviet Union, the habit of consuming raw salt pork (which contains muscle fibers) explains why this product is one of the main sources of infection.

Food preservation technology and the peculiarities of the different variants of *Trichinella* also influence the occurrence and prevalence of trichinellosis. The reduction in the incidence and intensity of human infection observed in the US in the last decades of the twentieth century is due in large part to the generalized practice of freezing pork products, both commercially and at home. Freezing is an effective means of killing the *T. spiralis* larvae found in pork or pork products. Regulations in Canada and the US establish that pork products less than 15 cm thick must be frozen at –15°C for 20 days or –30°C for six days. These temperatures are sufficient to kill the *T. spiralis* larvae, but not the *T. nativa* larvae, which are found in terrestrial and marine mammals of the Arctic region. For example, viable larvae have been found in bear meat frozen at an ambient temperature of –32°C for several weeks, and in walrus meat kept in a home freezer at –12°C for a month.

Most outbreaks in Argentina and Chile occur in winter or early spring when home slaughter of pigs is more frequent. Neighbors usually participate in sausage-making and eat the recently made products at community meals.

In some parts of the world, such as the Arctic and Subarctic and eastern Africa, the meat of wild animals constitutes the main source of human infection. In Africa, three outbreaks are known to have been caused by consumption of bush pig (*Potamochoerus porcus*) meat. Although the immediate source of human infection was the meat of wild swine, the main reservoirs seem to be wild canids, especially hyenas. Outbreaks in the Arctic region generally affect only a few persons. Nevertheless, an epidemic was recorded in Greenland in 1947 that caused 300 cases and 33 deaths. The origin of that epidemic was not discovered, but in a later outbreak, the source of infection was found to be walrus meat. Two more outbreaks were subsequently described in Alaska due to the consumption of walrus meat (Margolis *et al.*, 1979). The relative rarity of clinical cases at those latitudes is explained by the low intensity of the parasitosis in wild animals. Outside the Arctic region, cases of human trichinosis whose source of infection was bear meat have occurred. Between 1967 and 1981, 5% of the human cases in the US resulted from the ingestion of such meat (Schantz, 1983). In several European countries, infection due to bear or wild boar meat is playing an increasing role in the epidemiology of the disease, and outbreaks of this nature have been described in the former Czechoslovakia and the former Soviet Union (Ruitenberg *et al.*, 1983). There were also 58 cases of trichinosis in China due to consumption of bear meat (Wang and Luo, 1981) and 87 in Japan (Yamaguchi, 1991).

Role of Animals in the Epidemiology of the Disease: Trichinosis is an infection

of wild and domestic animals that is accidentally transmitted to man by the ingestion of raw or undercooked meat or meat products. It is a food-originated zoonosis.

Diagnosis: The clinical diagnosis of trichinosis is difficult due to its nonspecific symptomatology and its similarity to common infectious diseases such as influenza. Individual or sporadic cases are often confused with other diseases, but the diagnosis can be supported by the epidemiological circumstances (such as the recent consumption of pork or bear meat and the concurrent occurrence of other, similar cases) and with confirmation of peripheral eosinophilia, increased enzymes that indicate muscle damage, and increased erythrosedimentation. Specific diagnosis can be made by muscle biopsy and observation of the larvae. This technique is rarely used in man because it is painful and of limited utility. It is justified only for ruling out collagen diseases with which trichinosis may be confused.

Very precise immunobiologic and molecular biology tests are available (Ko, 1997). The preferred tests for diagnosis of the human infection, because of their sensitivity and specificity, are indirect immunofluorescence, enzyme-linked immunosorbent assay (ELISA), immunoelectrotransfer, and polymerase chain reaction. Some authors still recommend the use of undefined mixtures as antigens (Sandoval *et al*., 1995), but there is strong evidence that the antigen used is crucial to the sensitivity and specificity of the tests and how early they will detect the disease (Homan *et al.*, 1992). Consequently, modern authors prefer to use well-defined antigens. Ben *et al*. (1997) compared indirect immunofluorescence with the enzymatic immunohistochemical technique and found a high correlation between them; the latter showed sensitivity of 100% and specificity of 93%. ELISA is considered to be sensitive and versatile because it detects different classes of immunoglobulins. In a study during an outbreak caused by bear meat in which 58 persons were affected (92% confirmed by muscle biopsy), ELISA detected IgG specific antibodies in 100% of the cases in the first month of the disease and IgM antibodies in 86% of the cases. In a high percentage of cases, these antibodies persisted up to 11 months after the study. It was also possible to detect IgA antibodies, which were presumed to have been of intestinal origin, in 62% of the patients in the first month of the disease; their detection is important, since patients can be treated with anthelmintics at that stage. The indirect immunofluorescence test was somewhat less sensitive (95%), but became negative faster (van Knapen *et al.*, 1982). A problem with immunobiologic reactions is that they take about three weeks to appear and last months or years. This hinders early diagnosis and the ability to distinguish current infections from long-standing ones. To resolve these problems, ELISA techniques have been designed to detect the parasite antigens, rather than the antibodies, in the patient's blood. In experimentally infected rats, the antigen is found starting on the fourth day of infection and, in a third of human patients, at the end of the third week of infection (Dzbenski *et al*., 1994). In these patients, the sensitivity was 100% and the specificity was 96.8%; there were cross reactions with capillariasis, gnathostomiasis, opisthorchiasis, and strongyloidiasis (Mahannop *et al*., 1995). As with other diseases, two blood samples should be taken two weeks apart to observe the change in the antibody titers, which can indicate an active infection.

To diagnose the infection in animals, direct methods are used, such as trichinoscopy and artificial digestion; immunobiologic methods such as indirect immunofluorescence, ELISA, and Western blot; and molecular biology techniques

such as PCR and random amplified polymorphic DNA analysis (RAPD). Unlike the human infection, in which early diagnosis is needed, only a sensitive diagnosis is needed in swine because the larvae do not become infective until after the 16th day of infection. Trichinoscopy is used in the veterinary inspection of pork in slaughterhouses and meat-packing facilities in many countries. It is a rapid process, but it is not very sensitive and does not reveal light infections. In Sweden in 1961 and in Germany in 1967, epidemic outbreaks involving several hundred cases occurred following consumption of pork and pork products that had passed trichinoscopic examination. Some experts estimate that trichinoscopy can detect the infection only when there are three or more larvae per gram of muscle; according to others, the figure is 10 or more larvae per gram. The artificial digestion method is much more efficient and cheaper, but it is slow and does not lend itself to the rhythm of hog processing in large slaughterhouses and industrial packing plants. Its sensitivity is primarily attributed to the use of a sample that is 50 to 100 times larger than that used in trichinoscopy. A practical modification of this method has been proposed, which consists of mixing samples of the diaphragmatic pillars of 20 to 25 hogs from the same source. If trichinae are found in the composite sample, a 50–100 g sample of diaphragm muscle tissue from each individual pig is examined. Venturiello *et al*. (1998) compared trichinoscopy, artificial digestion, indirect immunofluorescence, and ELISA in 116 swine and found that the direct parasitology techniques were much less sensitive than the indirect techniques, and that ELISA was less sensitive than immunofluorescence when the intensity of the infection was low. ELISA has been automated for use in slaughterhouses, with substantial savings of resources and time. One of the drawbacks of this test was the high proportion of false positives (about 15%). This drawback has been surmounted by the use of purified antigens (Gamble and Graham, 1984). RAPD has shown a sensitivity of 100% and a specificity of 88% to 100% for detection of a single larva of the parasite (Pozio *et al*., 1999).

Control: The purpose of a control program should be to reduce and eventually eradicate the infection in swine, whose meat is the main source of human infection. The requirement that kitchen or slaughterhouse waste intended for pigs be heat-treated (100°C), introduced as part of the campaign to eradicate vesicular exanthema in swine and hog cholera, has proven beneficial in controlling trichinosis in the US. However, compliance with this regulation is very difficult to ensure, and, therefore, the results are not always satisfactory.

The trichinosis problem in some Latin American countries centers on the small rural farms raising a few pigs fed with household or restaurant scraps. These farms are very difficult to supervise, and pigs are slaughtered by the farmers without veterinary inspection. Continuous education of the population could at least partially remedy the situation. Another source of human infection is swine kept in town or village garbage dumps. In these cases, municipal and health authorities should prohibit this practice.

Trichinoscopy, which is practiced in slaughterhouses in Argentina, Chile, and other countries, has been shown to be effective in protecting the population. Although its sensitivity and cost leave much to be desired, when correctly executed, it protects the consumer against massive infections. The digestion method is much more efficient and cheaper in large slaughterhouses, but is costly for small plants in

developing countries. Hopes are founded on implementing automated immunologic or molecular biology tests.

At the individual level, humans can avoid the infection by abstaining from eating pork or pork products of dubious origin, without veterinary inspection. Pork or pork products that have not been inspected can be submitted to several processes to destroy the trichinae. Cooking at 57°C is more than sufficient to inactivate the parasites. This temperature turns the raw pork, which is pink and semi-translucent, whitish and opaque. Special care should be taken with rib roasts, pork chops, and pork sausages, which are not always sufficiently cooked, particularly close to the bone. The use of microwave ovens is not recommended because they heat unevenly and they may leave live parasites in portions of the meat. Trichinae are also destroyed by freezing the meat at –15°C for 20 days or at –30°C for 6 days, as long as the piece is not thicker than 15 cm. Smoking, salting, or drying of pork are not sure methods of killing larvae. The meat of wild animals should be cooked; this is the only sure method of destroying the larvae in the Arctic.

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TRICHOSTRONGYLIASIS

ICD-10 B81.2

Synonyms: Trichostrongylosis, trichostrongylidosis.

Etiology: The agents are several species of the genus *Trichostrongylus* (nematode) that inhabit the small intestine and stomach of sheep, goats, and bovines, and sometimes infect other domestic and wild animals or man. The following have been identified in humans: *T. axei*, *T. colubriformis*, *T. orientalis*, *T. skrjabini*, *T. vitrinus*, *T. probolurus*, *T. capricola*, *T. brevis*, *T. affinis,* and *T. calcaratus.* The species are difficult to differentiate, and human case histories often indicate only the genus and not the species. Other trichostrongylids have occasionally been found in humans. Among these are three cases caused by *Haemonchus contortus* in Australia, one in Brazil, and one in Iran; two cases caused by *Ostertagia ostertagi* in Iran and one in Azerbaijan; and one case caused by *O. circumcincta,* also in Azerbaijan.

Trichostrongylids are short parasites, measuring 1 cm or less in length, and are as slender as an eyelash, and therefore, difficult to see. The mouth is a simple orifice and the males have a well-developed copulatory sac. The development cycle is direct. The eggs of the parasite are eliminated with the feces of the host, and, under favorable conditions of temperature, humidity, shade, and aeration, they release the

first-stage larva in one or two days. This is a free-living worm that makes its home in the soil and feeds on organic waste or small organisms; it quickly molts into a second-stage larva, which is also free-living; then it molts into a third-stage larva, which is infective to the host. The infective larva can develop in just a week; when ingested by a host, it matures into the adult stage in close contact with the intestinal or gastric mucosa, mates, and begins to produce eggs during the fourth week of infection.

Geographic Distribution and Occurrence: Trichostrongylids are very common parasites of domestic ruminants and their distribution is worldwide. Human trichostrongyliasis occurs sporadically. In general, the prevalence is very low, but where people live in close contact with ruminants and food hygiene conditions are inadequate—as in nomadic communities—high rates of infection can occur. Human prevalence rates found in Iran were 7.5% in the northern part of the country and 69% to 85% in Isfahan. In southern Sudan, 2.5% of 275 children were found to be infected (Magambo *et al*., 1998). In 1993, a 1% rate of infection with *Trichostrongylus* sp. was found in 99 Thai workers in Israel. In southern Ethiopia, 19 communities were studied, and 0.3% of those examined were found to be infected (Birrie *et al*., 1994). In a total of 52,552 stool samples examined in a hospital in Seoul, Republic of Korea, 0.1% were found to contain *T. orientalis* eggs (Lee *et al*., 1994). In Australia, 5 cases were found out of 46,000 coprologic examinations (Boreham *et al*., 1995).

Endemic areas are dispersed; in particular, they cover southern Asia from the Mediterranean to the Pacific, and the Asian areas of the former Soviet Union, where nomadic tribes are still found. In some localities in Iraq, up to 25% of the population has been found to be infected. The infection is very common in some areas of Korea and Japan, as well as in parts of Africa, such as the Democratic Republic of the Congo and Zimbabwe.

Human infection has also been described in Germany, Australia, and Hungary. In the Americas, the infection has been confirmed in Brazil, Chile, Peru, the US, and Uruguay. In Brazil, 75 cases of infection by *Trichostrongylus* spp. were found in 46,951 persons examined. In Chile, 45 cases were diagnosed between 1938 and 1967, and 17 cases were found among 3,712 persons examined in the province of Valdivia between 1966 and 1971.

The Disease in Man: The parasites lodge in the duodenum and jejunum. Infections are usually asymptomatic or mild and are discovered in coprologic examinations carried out to diagnose other parasitoses. In acute infections, with several hundred parasites, there may be transitory eosinophilia and digestive disorders, such as diarrhea, abdominal pain, and weight loss; sometimes, slight anemia is observed. The infection can last several years if left untreated. The clinical picture in man has not been studied very much and is difficult to define, since other species of parasites are generally found in an individual infected with trichostrongylids.

The Disease in Animals: The different species of *Trichostrongylus*, together with gastrointestinal parasites of other genera, constitute the etiologic complex of parasitic or verminous gastroenteritis of ruminants, an important disease in terms of its economic impact, because it causes major losses in meat, milk, and wool production, and occasionally causes death (Barriga, 1997).

In ruminants, trichostrongylids cause accelerated reproduction of the cells of the intestinal epithelium, which alters the structure of the epithelium and permits the filtration of plasma proteins to the lumen (Hoste *et al*., 1995). This does not seem to occur in man, probably because of the small number of parasites he harbors. In animals, peripheral eosinophilia is also uncommon.

Source of Infection and Mode of Transmission: The reservoirs of trichostrongylids are domestic and wild ruminants. However, *T. orientalis* is a parasite of man and only occasionally of sheep. This species occurs in Asia and is transmitted between humans, especially in areas where human fecal matter is used as fertilizer in agriculture. *T. orientalis* is the predominant species in human infections. *T. brevis* is another human species that has been described in Japan. The species of animal origin produce rather sporadic cases in man, although areas of high prevalence are known. The number of species of *Trichostrongylus* that infect man varies in different areas. In Isfahan, Iran, seven different species have been found in the rural inhabitants of the region.

The source of infection is the soil where infected ruminants deposit the eggs when they defecate. Man and animals are infected orally by consuming contaminated food or water. Man acquires the infection mainly by consuming raw vegetables. The rains that wash the feces of infected ruminants out of the soil and carry them to bodies of water can contaminate sources of drinking water. A lack of food hygiene, and close contact with ruminants, which is common among rural populations at a low socioeconomic level in endemic areas, facilitate transmission. The use of manure as fertilizer or fuel can also facilitate transmission.

Diagnosis: The infection can go unnoticed because patients are asymptomatic; sometimes they present only peripheral eosinophilia or mild gastrointestinal disturbances (Boreham *et al*., 1995). Diagnosis often occurs accidentally while looking for another parasite. Parasitological confirmation is established by identifying the eggs in the feces. The eggs of *Trichostrongylus* are quite similar to those of six or seven other genera, including ancylostomids found in man. Therefore, it may be necessary to cultivate the eggs to produce third-stage larvae and study their morphology in order to determine the genus. In the case of human ancylostomids, the eggs are much smaller than those of *Trichostrongylus* (56–75 μm by 36–45 μm versus 73–95 μm by 40–50 μm).

Parasitic gastroenteritis in ruminants can be diagnosed by finding and counting the eggs in the feces, but autopsy is more effective for determining the number and species of infective parasites.

Control: Preventive measures for the human infection consist of improved food, environmental, and personal hygiene. In endemic areas, it is prudent to avoid eating vegetables or other raw foods that could be contaminated with the larvae of the parasite and to boil suspicious drinking water.

In animals, control measures are directed toward keeping both pasture contamination and animal infections at low levels. To achieve this objective, the animals must be kept well nourished. Anthelmintics should be administered at the appropriate times of the year to prevent the accumulation of parasites in animals and pastures.

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TRICHURIASIS OF ANIMAL ORIGIN

ICD-10 B79 Trichuriasis

Synonyms: Trichocephaliasis, trichocephalosis.

Etiology: The agent of trichuriasis is *Trichuris vulpis* of canids and, secondarily, *T. suis* of swine. *Trichuris trichiura* is a species that parasitizes man and that has been found in chimpanzees, monkeys, and lemurs. However, there is no proof that its transmission is zoonotic, except in unusual circumstances. Despite the fact that the name *Trichuris* means "tail as thin as a hair," the thin portion of the parasite's body is actually the head. For this reason, various authors prefer the term *Trichocephalus*, which is morphologically correct. While it should be noted that the name *Trichuris* has priority, some authors incorrectly use *Trichocephalus* as the taxonomic denomination.

T. vulpis lives in the cecum and in neighboring portions of the large intestine of domestic and wild canids. It measures 4.5 cm to 7.5 cm long, and the posterior two fifths are much thicker than the anterior portion. This is typical of the genus and is the reason the English literature refers to it as whipworm. The male has a very long spicule, 8 mm to 11 mm, with a sheath that is also very long. The females produce eggs which, as in all species of *Trichuris*, resemble lemons: they are oval, thick-shelled, and have two polar plugs; they measure 72–90 μm by 32–40 μm.

T. suis lives in the cecum and in neighboring portions of the large intestine of domestic pigs and wild boars. It measures 30 cm to 50 cm in length; the male's spicules measure 2–2.3 mm and the female's eggs measure 50–56 µm by 21–25 µm.

T. trichiura lives in the cecum and in neighboring portions of the large intestine of humans and some lower primates. The worms, spicules, and eggs are the same size as those of *T. suis* (Barriga, 1997). These parasites must belong to different species because *T. suis* has six chromosomes and *T. trichiura* has just four, and its ability to infect heterologous hosts is deficient. That notwithstanding, the authors who compared the two species insist that they cannot be differentiated on morphological bases (Barriga, 1982).

The development cycle is similar in all species of *Trichuris*: the female lays eggs that are eliminated to the exterior with the feces. Under favorable conditions of humidity, temperature, shade, and aeration, in two weeks or more the zygote develops inside the egg into the infective first-stage larva. When the host ingests those eggs, the larvae are released in the small intestine, lodge in the crypts for about 10 to 14 days, return to the lumen, and move to the large intestine, where they mature and begin oviposition in about three months. The prepatent period of *T. vulpis* is 70 to 90 days in dogs; that of *T. suis* is 41 to 45 days in swine; and that of *T. trichiura* is 1 to 3 months in humans. *T. vulpis* lives approximately 16 months in dogs, and *T. suis*, approximately 4 to 5 months in swine.

Geographic Distribution and Occurrence: The two zoonotic species and *T. trichiura* occur all over the world and, in general, their distribution is similar to that of the ascarids transmitted through the soil, such as *Toxascaris leonina* (dogs and cats), *Ascaris suum* (swine), and *A. lumbricoides* (man). This is because *Trichuris* spp. and *Ascaris* spp. need very similar environmental conditions in order for their infective larvae to develop, and the mechanisms of transmission to the host are almost identical. Both are highly prevalent in warm, humid climates, less prevalent in moderate humidity or temperatures, and scarce or nonexistent in arid and hot or very cold climates.

T. vulpis is very common in dogs. The prevalence of the infection in dogs brought to veterinary clinics is generally between 10% and 20%, and in stray dogs, approximately 40%. For example, in the state of New Jersey, US, 38% of 2,737 dogs examined were infected; in New York, the prevalence was 31%, and in Detroit, 52%. The first case of human infection caused by *T. vulpis* was reported in 1956; Barriga (1982) compiled 40 more reports, 34 of which were from Viet Nam, by 1980. By 2000, 8 more cases were reported: 1 in an autopsy in the US (Kenney and Yermakov, 1980), 5 in a survey in India (Singh *et al*., 1993), and 2 clinical cases involving children in India (Mirdha *et al*., 1998). It is interesting that three cases prior to 1980 were found on fecal examination of 1,710 patients in the state of New York; the 34 cases in Viet Nam were found in 276 individuals examined, and the 5 cases reported by Singh *et al*. (1993) were found in 83 individuals studied. In these examples, the prevalences were 0.2%, 12.3%, and 6%, respectively. However, it must be taken into consideration that most diagnoses of *T. vulpis* in humans were made by measuring eggs in the feces, which might not be completely reliable. Moreover, only a particularly discerning technician would note that the eggs he or she is observing are larger than usual, so many cases of human infection caused by *T. vulpis* may go undetected.

In general, *T. suis* is common in swine, with prevalences of 2% to 5% in adult animals and 15% to 40% in suckling pigs. In 1938 and 1940, unsuccessful attempts were made to infect humans experimentally with swine parasites. In the 1970s, two human volunteers were infected, and later an accidental infection in a laboratory worker was studied. The three subjects passed a few eggs of low fertility in 11 to 84 days (Barriga, 1982). While these studies documented the possibility of human infection with swine parasites, their practical importance is not known. Moreover, experiments involving the infection of swine with *T. trichiura* failed to produce patent infections.

The Disease in Man and Animals: Trichuriasis is very similar in humans and canines. The infection is much more common than the disease and much more prevalent in young individuals. In infections with a large number of parasites, there may be abdominal pain and distension as well as diarrhea, which is sometimes bloody. In very heavy infections in children (hundreds or thousands of parasites), there can be strong tenesmus and rectal prolapse. Massive parasitoses occur mainly in tropical regions, in children 2 to 5 years old who are usually malnourished and often infected by other intestinal parasites and microorganisms. Geophagy and anemia are common signs among these children. Most cases of human infection with zoonotic *Trichuris* have been asymptomatic or the patients have complained only of vague intestinal disturbances and moderate diarrhea.

Source of Infection and Mode of Transmission: The reservoirs of zoonotic species of *Trichuris* are dogs and other wild canids and, possibly, the swine. The sources of infection are soil or water contaminated with eggs of the parasite. The mode of transmission is, as in other geohelminthiases, the ingestion of eggs in the food or water, or hands contaminated with infective eggs. As indicated earlier, *Trichuris* eggs have the same climatic requirements as *Ascaris* eggs and, therefore, occur in the same regions. However, *Trichuris* eggs are considerably more sensitive to climatic conditions. With constant temperatures of 22°C, the infective larva forms in 54 days; with temperatures fluctuating between 6°C and 24°C, the process takes 210 days. It is also less resistant to drought, heat, and chemical disinfectants. Even in a moist environment, few eggs survive more than two weeks. Soil contamination studies carried out in Switzerland showed that 16% of samples of dog feces had *Toxocara canis* eggs, but fewer than 1% had *T. vulpis* eggs (Tost *et al*., 1998). In Nigeria, it was found that 10% to 20% of soil samples from playgrounds were contaminated with *Ascaris lumbricoides* eggs, 8% with *T. canis,* and 4% with *T. vulpis* (Umeche, 1989).

Therefore, infection by *Trichuris* occurs more often when there is a constant source of environmental contamination, such as infected small children who defecate on the ground. The role of dogs or swine does not seem to be important in human trichuriasis.

Diagnosis: Diagnosis is based on confirmation of the presence in the feces of the typical eggs. The eggs of *T. vulpis* (72–90 µm by 32–40 µm) can be distinguished from those of *T. suis* (50–56 µm by 21–25 µm) or *T. trichiura* by their size, although the reliability of this characteristic is not known. The eggs of *T. suis* are indistinguishable from those of *T. trichiura*. The females of these species can be distinguished by the size of the eggs inside them. *T. vulpis* males can be distinguished from *T. suis* or *T. trichiura* males by the size of the spicules.

Control: As with all geohelminthiases, prevention of human trichuriasis requires improvement of environmental hygiene through the adequate disposal of excreta to avoid contamination of the soil, personal hygiene, the washing of raw food and of hands, and the boiling or filtering of suspicious water. For obvious reasons, the adequate disposal of excreta is difficult in the case of zoonotic diseases and, while the infected animals can be treated to prevent them from contaminating the environment, zoonotic trichuriasis is so rare that mass methods of control are not justified except under highly unusual circumstances.

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VISCERAL LARVA MIGRANS AND TOXOCARIASIS

ICD-10 B83.0 Visceral larva migrans

Synonym: Larval granulomatosis.

Etiology: Visceral larva migrans refers to the presence of parasite larvae that travel in the systemic tissues of man but not in the skin. The use of the qualifier "visceral" should be discontinued because it corresponds to only one of the four clinical forms of the disease. There are several helminths whose larvae can cause this condition: for example, species of *Baylisascaris*, *Gnathostoma*, *Gongynolema*, *Lagochilascaris*, *Dirofilaria*, and *Angiostrongylus.* However, the term visceral larva migrans is usually reserved for extraintestinal visceral infections caused by nematodes of the genus *Toxocara*, especially *Toxocara canis*, and to a lesser extent, *T. cati* (*T. mystax*), which will be covered in this chapter.

T. canis is an ascarid which, in its adult stage, lives in the small intestine of dogs and several wild canids. The female measures 9–18 cm long and the male, 4–10 cm. One of the characteristics of the genus is that the males have a caudal terminal appendage, which is digitiform. The eggs contain a zygote and they are shed in the host feces. These eggs are very resistant to environmental conditions, and they can remain viable for several years in moist, shaded soils when temperatures are cool. Under favorable environmental conditions of humidity, temperature, shade, and aeration, a third-stage infective larva forms inside the egg in about 10 days at 24°C and 90% relative humidity, or in about 15 days at 19°C (Araujo, 1972; Maung, 1978). When a puppy under 4 or 5 weeks old ingests eggs containing infective larvae, the parasites emerge in the intestine, pass through the intestinal wall, and enter the bloodstream, which carries them to the liver and then to the lungs. There they rupture capillaries and pulmonary alveoli and migrate through bronchioles, bronchi, and the trachea to the pharynx, where they are swallowed. Once again the parasite reaches the intestine, and this time it develops into the adult stage. The first eggs begin to appear in feces between four to five weeks after the initial infection. The average lifespan of *T. canis* in the intestine is about four months, and most of the parasites are expelled six months after the onset of infection (Schantz and Glickman, 1983).

In puppies older than 5 weeks, the ingested larvae initiate the migration described above, but increasingly larger proportions go into hypobiosis in different systemic tissues, and they do not reach the airway or the intestine. In those 3 months of age and older, almost none of the parasites reach the intestine; some settle in the liver, others in the hepatic parenchyma, and the rest bypass the lungs and lodge in muscle, the kidneys, etc. (Barriga, 1997). This migration that bypasses the lungs is referred to as somatic migration. Since the larvae lapse into hypobiosis within a few days, they become very resistant to anthelmintics (Carrillo and Barriga, 1987). In gravid females, the parasites remain resistant until the final third of pregnancy. In addition to the age factor, the ultimate destination of the larvae (whether by tracheal or somatic migration) is determined by the infective dose. Dubey (1978) demonstrated experimentally that puppies infected orally with 10,000 eggs did not exhibit patent parasitosis—with the elimination of eggs in their feces—but did do so when they received 1,000 eggs. Patent infection was observed in 3 of 6 adult dogs that were infected with 100 eggs. It may be speculated that a large parasite burden stimulates immunologic mechanisms that prevent maturation of the parasite (Barriga, 1998). When bitches harboring hypobiotic larvae reach the final third of their pregnancy (starting at approximately day 42), the larvae reactivate and resume their migration, many of them traveling to the liver of the fetuses and, after the birth of the pups, migrating to the trachea and appearing in their feces when the animals are about 21 days old.

Almost all puppies born of infected mothers are infected, which indicates that transplacental infection is a highly important mode of transmission for the parasite. Other reactivated larvae pass into the intestine of the mother and mature. Starting at day 25 postpartum, the adult parasites lay eggs for three and a half months. One-third to half of all bitches shed eggs after they deliver a litter. Finally, some of the larvae in their bloodstream also pass to their pups through their milk for up to five weeks (Barriga, 1991).

When man and other noncanid hosts, such as rodents, swine, and lambs, ingest

infective eggs, the larvae are released into the intestine, where they initiate somatic migration and remain in the tissues as hypobiotic larvae. These species can act as paratenic, or transport, hosts.

T. cati is a somewhat smaller ascarid than *T. canis.* Its natural hosts are cats and wild felids. Although the life cycle of *T. cati* is similar to that of *T. canis*, there are a few important differences: the cat develops patent infection with eggs ingested at any age; it does not experience prenatal infection; and transmammary infection appears to be common. Eberhard and Alfano (1998) reported the presence of adult or subadult *T. cati* in the intestine of four children who did not have symptoms or antibodies corresponding to the infection. The authors consider it more likely that the children became infected from ingesting subadult parasites passed on by cats than that they ingested infective eggs. The role of *T. cati* in the production of human larva migrans is still being debated (see below).

Geographic Distribution and Occurrence: *T. canis* and *T. cati* are found in dogs and cats throughout the world. Data collected by Barriga (1988) from around the world indicate that the infection is present in 99.4% of all newborn pups, about 40% of dogs of both sexes under 6 months of age, and 20% of males and 5% of females over 6 months old. In studies of apparently healthy humans using the enzyme-linked immunosorbent assay (ELISA), 6.7% of 1,150 sera in the US, 4.7% of 358 sera in Canada, and 3.6% of 1,321 sera in Great Britain had antibodies to the parasite. In 1981 alone, 675 cases of ocular toxocariasis were diagnosed in the US. The clinical disease has been diagnosed in 48 different countries, and more than 1,900 human cases were reviewed by Ehrhard and Kernbaum (1979). Of 780 well-documented cases, 56% were in children under 4 years old. Most of the clinical cases have been reported in industrialized countries because they have better diagnostic facilities, but the data collected by Barriga (1988) indicate that the infection is actually more prevalent in the developing countries.

Intestinal infection with adult parasites is very rare in man. Two cases have been attributed to *T. canis* and a somewhat larger number due to *T. cati* have been described, but the accuracy of these diagnoses has been questioned in several reports.

The Disease in Man: Toxocariasis is caused by the presence of *T. canis* or *T. cati* larvae in various human tissues. These larvae produce small tunnels of traumatic, inflammatory, and necrotic lesions in the course of their migration, followed by a granulomatous reaction with an abundance of eosinophils, and sometimes abscesses, once the larvae settle in a particular site. Toxocariasis is basically an allergic disorder. Originally two forms were described (visceral and ocular), but later four clinical forms were recognized: visceral (perhaps better referred to as systemic), ocular, neurological, and covert.

The visceral, or systemic, form occurs when most of the larvae are lodged in the liver or lungs, the first organs they travel through in the course of their migration. Clinical manifestations depend on the number of larvae and their anatomic localization. Usually, the infections are mild and asymptomatic, with the exception of persistent eosinophilia. In symptomatic cases, the seriousness of the clinical picture varies, but cases with mild symptomatology are predominant. The most notable sign is chronic eosinophilia. Eosinophils can represent more than 50% of the total leukocyte count. Hepatomegaly and pneumonitis with hypergammaglobulinemia are

common during the early stages of the disease. In the cases reviewed by Ehrhard and Kernbaum (1979), 56% of the patients were under 3 years old and 18% were adults. The most frequent manifestations in children were hepatomegaly (79%), respiratory signs (72%), and fever (69%); in adults, the most common signs were fever (71%), asthenia (63%), and digestive symptoms (60%). Reinfections often affect the liver and lungs at the same time, weakening the patient considerably. Older children and adolescents frequently have fever, coughing spells, nausea, vomiting, and dyspnea during the first week, and the symptoms may recur for several months. The disease can be more severe in younger children, with asthmatic attacks, high fever, anorexia, arthralgia, myalgia, nausea, vomiting, hepatomegaly, lymphadenopathy, and sometimes urticaria and angioneurotic edema. Four of eight patients with systemic toxoplasmosis studied by Rugiero *et al*. (1995) had cardiac symptoms, three had pulmonary symptoms, and two were affected in various organs, while all of them had eosinophilia (35% to 90%) and seven had leukocytosis (14.5 to 160 million per mL). All were positive in the ELISA test, with titers ranging from 64 to 1,000. The cardiac cases responded only moderately to treatment; the patients suffered frequent decompensation, and one of them died. Eosinophilia has been known to last for up to 20 years, which suggests how long the larvae can survive.

The ocular form occurs in older children and sometimes adults. It is seldom preceded by or concurrent with the visceral form. The presence of larvae in the eye can cause progressive loss of vision and sudden blindness. Strabismus is common. The infection is unilateral and generally without systemic symptoms or eosinophilia. The single granulomatous lesion is located near the optic disc and the macula retinae. Endophthalmias caused by *Toxocara* larvae have often been mistaken for retinoblastomas, resulting in enucleation of the affected eyeball. Apart from the fact that the migrating larvae induce a granulomatous response in the host, the mechanism by which they cause damage is still not understood. It has been found that in visceral and optical cases the symptoms correlate with the presence of antigen-antibody complexes and with levels of IgE, suggesting that the pathogenic mechanism includes type I and III hypersensitivities (Obwaller *et al*., 1998). Eosinophils have also been mentioned as possible agents of pulmonary damage.

The neurological form occurs when the larvae settle in the central nervous system. There, they can give rise to meningoencephalitis (Barra *et al*., 1996) or other neurological manifestations. This form appears to be more common than was once believed: when irritability and minor behavioral disorders are excluded, one-fourth of 233 patients reviewed by Ehrhard and Kernbaum (1979) exhibited neurological symptoms, consisting mainly of convulsions and motor deficiencies, and 15 cases of encephalitis or meningitis were reported, some of them fatal. Several authors have found a correlation between this infection and epileptic symptoms, although others have not been able to verify such a connection.

The covert form is considered more common than any of the other forms. It is described as a disorder found in patients with positive serology for *Toxocara* and a few systemic or localized symptoms, mainly abdominal pain, which do not correspond to the syndrome of the visceral, ocular, or neurological form of the disease. One-fourth of these patients did not have peripheral eosinophilia, and in some cases, the symptoms lasted for months or even years (Nathwani *et al*., 1992).

Regardless of the form of the disease, fatal cases of visceral larva migrans are rare.

The Disease in Animals: Adult dogs and cats with larva migrans do not appear to suffer. Both species can maintain a large number of larvae in their tissues. Otherwise, uterine and lacteal transmission of *T. canis* and lacteal transmission of *T. cati* would not be possible. However, veterinarians in small animal practice do not see clinical signs attributable to the larvae of these nematodes. Intestinal infection with adult parasites can cause symptoms in puppies and kittens a few weeks old, especially digestive disorders, diarrhea, vomiting, flatulence, and loss of vitality. Puppies infected prenatally with a large number of parasites can die at the age of 2 or 3 weeks. Sudden death is often due to obstruction and rupture of the small intestine and consequent peritonitis. Prenatally infected puppies sometimes exhibit signs of pneumonia immediately after birth because their lungs have been invaded by a large number of larvae passed on by the mother. Intestinal infections with few parasites tend to be asymptomatic, as is often the case in adult animals as well. Dogs and cats that survive the critical period of infection recover fully and expel the parasites from their intestine during the first six months of life.

Source of Infection and Mode of Transmission: The reservoir of larva migrans for man is infected dogs. The source of infection is soil contaminated with infective eggs, and the mechanism of transmission is the ingestion of these eggs in contaminated food or water, or via contaminated hands.

For a long time, there was speculation about whether the feline *T. cati* is equally dangerous for man. Using the Western blot technique, Petihory *et al*. (1994) found that twice as many patients responded to *T. canis* antigen as they did to *T. cati*, and other authors have published similar results. In Iceland, however, the virtual elimination of dogs (but not cats) nearly eradicated the visceral form of larva migrans, suggesting that the parasite of cats plays an insignificant role as an etiologic agent.

A mild *T. canis* infection produces 10,000 eggs per gram of feces, and a dog sheds an average of 136 grams of feces daily; hence every mildly infected dog contaminates the environment with nearly 1.4 million *T. canis* eggs in a single day (Barriga, 1988). The eggs of *T. canis* are highly resistant to physical and chemical factors in the environment. Since the eggs can survive for years in a place that is cool, humid, and shady, once the environment is contaminated it remains so for a long time. On the other hand, since the eggs take 10 days to become infective, direct contact with dogs is less significant than contact with soil contaminated with their feces. The dog itself becomes a risk when it picks up infective eggs in the environment (Overgaauw, 1997). A review of reports from around the world as of 1986 regarding contamination of the soil with *T. canis* eggs revealed that usually 2% to 25% of the samples were contaminated, and in some places, the percentages were much higher (Barriga 1988). In Japan, Shimizu (1993) found that 68% of 144 puppies were infected and that 87.5% of the soil samples from parks and children's playgrounds were contaminated. Cases of human infection usually occur individually, but small outbreaks of up to seven people have been described (Bratt and Tikasingh, 1992).

Dogs are infected by transplacental and transmammary transmission, by ingestion of paratenic hosts, or by ingestion of infective eggs. The transplacental route is the most important: five experiments with a total of 669 newborn puppies found that 99.4% were born with the infection (Barriga, 1988). Cats can be infected by transmammary transmission, by ingestion of paratenic hosts, or by ingestion of infective eggs.

Since children have more contact with the soil and tend to be more lax about personal hygiene, they are more exposed and have the highest rates of prevalence. Moreover, geophagy is not uncommon in children and plays an important role in transmission of the infection. Adults can acquire the infection if they do not follow the basic rules of personal hygiene: dirty hands are almost always the vehicle for the parasite's eggs.

Diagnosis: Human larval toxocariasis is suspected mainly when there is leukocytosis, persistent eosinophilia, hypergammaglobulinemia, and hepatomegaly. Other factors to be considered in the diagnosis are age under 4 years and a history of geophagy or exposure to soil contaminated with canine feces. In the case of ocular toxocariasis, the diagnosis is confirmed by ophthalmoscopic examination, and by histopathologic examination of the eyeball if it has been enucleated. Histopathology is also used with biopsies of the liver. Identification of the larvae in tissue is a painstaking procedure that requires serial sections from the pathologic specimen. Even with an organ as small as the eyeball, it is sometimes necessary to study more than 100 sections before finding any larvae. In several extraocular cases, definitive diagnosis was obtained by laparotomy and resection of a visible granuloma on the surface of the liver. Differential diagnosis between ocular larva migrans and retinoblastoma is especially important. In the case of ocular larva migrans, examination of the aqueous humor usually reveals numerous eosinophils.

The difficulty of basing the diagnosis on clinical signs and the uncertainty of the diagnosis has stimulated the development of immunobiologic tests. In particular, ELISA has been used with larval excretory-secretory antigen and sera adsorbed with extracts of *Ascaris lumbricoides* to eliminate cross-reacting antibodies. It is estimated that this test is 78% sensitive and 92% specific in the visceral form and 73% sensitive and 95% specific in the ocular form (Schantz and Glickman, 1983). A modified ELISA test to show *T. canis* antigen in circulating blood was positive in 68% of 28 acute patients, 10% of 10 patients with inactive infection, and 28% of 7 with ocular infection; at the same time, however, 25% of patients with schistosomiasis or filariasis had false positive reactions (Gillespie *et al*., 1993). Since larva migrans does not cause pathology in animals, no immunologic tests have been developed for diagnosis, although the tests used for human infection should serve the purpose. Diagnosis of intestinal infection with adult parasites is made by observing the parasite's eggs in feces.

Control: The primary control measure consists of deworming dogs and cats. Since a high proportion of dogs are born infected, newborn pups are especially important in prophylaxis (Barriga, 1991). It is recommended to treat 2-week-old puppies with any anthelmintic that is effective against ascarids and repeat the medication at 4, 6, and 8 weeks of age (Barriga, 1991). This measure eliminates the parasites before they have time to pass on eggs and contaminate the environment. The mothers should be treated at the same time.

Although most adult *T. canis* larvae are eliminated spontaneously from the intestine when dogs reach puberty (about 8 to 10 months of age), between 5% and 30% of adult dogs are infected with the parasite. Therefore, adult dogs should be treated twice a year, or else examined regularly for eggs in feces and treated if they are infected. Although hypobiotic larvae in the bitch are resistant to anthelmintics, treatment can kill the parasites when they renew their migration before they are passed on to the fetuses. For this

purpose, the mother should be given a daily dose of 50 mg/kg of fenbendazole, or 0.3 mg/kg from day 40 of pregnancy to day 14 postpartum (Barriga, 1997).

Since even the best treatment has not been shown to be more than 50% effective (Barriga, 1991), other complementary measures should be used at the same time. One of these is to reduce the population of stray dogs and require all other dogs to have a socially responsible owner. Dogs should not be allowed to run free in public parks, especially where there are sandboxes for children. Owners can walk their dogs on a leash and pick up their feces in a plastic bag; the feces should then be burned or disposed of in the trash at home. Flushing the feces down the toilet is not as effective because some *T. canis* eggs can be resistant to wastewater treatment. Finally, the most important measure is to educate the public about the transmission of toxocariasis and the importance of washing hands and raw food before eating.

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ZOONOTIC ANCYLOSTOMIASIS

ICD-10 B76.0 Ancylostomiasis; B76.8 Other hookworm diseases

Synonyms: Ankylostomiasis, hookworm disease, necatoriasis, uncinariasis.

Etiology: The agents of these diseases are the nematodes *Ancylostoma caninum* (of dogs) and *A. ceylanicum* (of cats). Up until 1982, just six cases of human infection caused by *A. caninum*, which affected the intestine, had been reported (Barriga, 1982). However, based on reports from Australia in the 1990s, it is now known that the parasitosis is common in that region. Human intestinal infection with *A. ceylanicum* has been described, but it is uncommon. In the 1950s, several cases of human intestinal infection due to *A. braziliense* were reported before the difference between *A. braziliense* and *A. ceylanicum* was understood. Since that difference became widely accepted, just one case has been reported (in Portugal in 1970). It is likely, therefore, that the previous reports confused the two species. However, *A. braziliense* seems to be a common agent of cutaneous larva migrans (Cypess, 1982), which is discussed in the respective chapter.

A. malayanum in Argentina and Brazil, *A. japonica* in Japan, *Necator suillis* in Malaysia, and *N. argentinus* in Trinidad and Brazil were once reported as causing infection in the human intestine (Barriga, 1982). Since these species have not been confirmed, their identity is questionable and they will not be addressed here. *Ancylostoma duodenale* and *Necator americanus* are exclusively human parasites, although the former infects dogs and cats under experimental conditions (el-Naggar *et al*., 1994); *N. americanus* infects hamsters (Rose and Behnke, 1990) and mice (Wilkinson *et al*., 1990). The nematode *A. duodenale* was identified in 83% of 1,000 swine in Nigeria, but only by examination of the eggs (Salifu *et al*., 1990). The oldest literature mentions that *A. duodenale* is occasionally found in Old and New World monkeys, swine, and domestic and wild felids; *N. americanus* has been found in Old and New World monkeys, rhinoceri, an African rodent, domestic carnivores,

and a rabbit (Barriga, 1982). Albonico and Savioli (1997) believe that there are probably 1.3 billion people infected with ancylostomes worldwide, and that perhaps 96 million have symptoms.

The life cycles of *A. caninum* and *A. ceylanicum* are essentially identical; therefore, only the former will be described here. The adult parasites are grayish-white to reddish-white, although they may also be dark red. They measure from 11–20 mm in length and 0.3–0.6 mm in diameter (the females are larger) and have three pairs of teeth on the ventral rim of the buccal capsule. The morphology of the bursa copulatrix in males is an aid to identification. They live in the small intestine of the host, and each female lays some 16,000 eggs per day, which are eliminated to the exterior with the fecal matter. Under favorable environmental conditions (humidity above 90%, temperature between 23°C and 30°C, shade, availability of oxygen, and absence of predators), embryogeny is rapid, and the first-stage larva, which has a rhabditiform esophagus, can hatch from the egg in 24 to 48 hours. These larvae are not resistant to low temperatures or a dry environment. In the course of a week, the larva undergoes two molts and develops into a third-stage larva, which is infective for the host. In this stage, the larva has a filiform esophagus, is encysted in the cuticular envelope of the second-stage larva, does not feed, and can survive in the soil for approximately three weeks.

Hosts can become infected through the skin or orally, in the latter case by ingestion of milk from infected mothers or consumption of paratenic hosts. Both methods occur in the case of *A. caninum,* for which dogs are natural hosts. Transmission of this species through the placenta is considered an exceptional situation (Barriga, 1997). When the infection route is through the skin, the infective larvae lodge in the host, attracted by the temperature and chemical substances (Ashton *et al*., 1999), penetrate the skin by means of mechanical and enzymatic phenomena, probably with the aid of a hyaluronidase (Hotez *et al*., 1994), and are carried by the bloodstream to the lungs. Once there, they pass through the capillary and alveolar walls and advance up the tracheobronchial tree to the pharynx, molt into the fourth stage 44 to 48 hours after infection, and are swallowed. The larvae develop into juvenile nematodes in the small intestine prior to the sixth day of infection. Subsequently, they reach maturity and the females begin to lay eggs 14 days after infection. In infections via the oral route, a few larvae may penetrate the digestive mucosa and follow a systemic cycle similar to that of the transcutaneous infection, but most penetrate the gastric or intestinal mucosa and mature there without leaving the gastrointestinal tract. The discovery of adult ancylostomes in human infants suggests the possibility of either transplacental or transmammary transmission. The persistence of infective ancylostome larvae for days or months in rodents, rabbits, or chickens as transport hosts suggests that transmission in man can occur through paratenic hosts.

A. ceylanicum is smaller than *A. caninum* and has just two pairs of teeth. The natural hosts of *A. caninum* are dogs and other wild canids; the natural hosts of *A. ceylanicum* are cats and other wild felids.

Geographic Distribution and Occurrence: The human intestinal infection is very rare almost everywhere in the world. The literature mentions just six cases up to 1982 (Barriga, 1982). However, an epidemic of 93 human cases was reported in northeastern Australia in 1990, with an eosinophilic enteritis that seemed to be caused by this para-

site (Prociv and Croese, 1990). Six years of research confirmed *A. caninum* as the culprit, and a few cases were found in other parts of Australia (Prociv and Croese, 1996). There seems to be no reason why the infection cannot be found in other parts of the world, especially since *A. caninum* is very common in dogs, with prevalences of 20% to 60%. Of 80 stray dogs autopsied in Uruguay, 99% were infected with *A. caninum* and 49% were infected with *A. braziliense* (Malgor *et al*., 1996).

The geographic distribution of *A. ceylanicum* is difficult to determine because of the long-standing confusion with *A. braziliense.* The locations reported since 1967, when the difference from *A. braziliense* was already well known, include eastern Asia, Brazil, the Philippines, Guyana, India, Indonesia (Sumatra), Japan, Liberia, Madagascar, Malaysia, Sri Lanka, Suriname, Thailand, Taiwan, and Zimbabwe. Between 1968 and 1982, 1 human case in Japan and 1 in the Philippines were reported; *A. ceylanicum* was reported in 5 of 140 people examined in Taiwan, 7 of 45 people in Thailand, 2 of 15 soldiers returning to the Netherlands from Suriname, and 16 of 183 ancylostomiasis patients in India (Barriga, 1982). *A. ceylanicum* infection occurs sporadically and, in general, with few specimens: 29 infected individuals had an average of 2.6 specimens of *A. ceylanicum,* with a maximum of 23 specimens. For the most part, the patients are also infected with a large number of human ancylostomes: a study of 16 ancylostomiasis patients found a ratio of 1:25:54 for *A. ceylanicum*, *A. duodenale,* and *N. americanus*.

In India, Japan, Malaysia, and Taiwan, high rates of infection due to *A. ceylanicum* were found in dogs and cats. In Suriname, *A. ceylanicum* was found in 80% of 102 dogs and in 60% of 50 stray cats that were autopsied. In South Africa, autopsies of 1,502 cats found 41% with *Ancylostoma tubaeforme,* 25% with *A. braziliense,* 3.3% with *A. caninum*, and 1.4% with *A. ceylanicum* (Baker *et al*., 1989).

The Disease in Man: The most important signs of nonzoonotic ancylostomiasis are anemia caused by an anticoagulant peptide which inhibits the coagulation factor Xa (Cappello *et al*., 1995) and atrophy of the intestinal villi. These signs are not seen in the zoonotic ancylostomiases because of the limited number of parasites in man. Human infection with *A. caninum* is probably asymptomatic in a large proportion of cases, but it causes eosinophilic enteritis in some. The most common clinical manifestation is abdominal pain, sometimes very intense, with or without eosinophilia. In no case has more than one parasite been found, always juvenile larvae, so the infections did not become patent. The lesions associated with the infection are focal or diffuse eosinophilic inflammation, probably caused by reaction to the parasite's antigens, and aphthous ulcers of the terminal ileum, cecum, or colon, visible on endoscopy. These lesions were found in 5% of patients in northeastern Australia. The clinical manifestations and pathology of this infection are similar to those of anisakiasis (Prociv and Croese, 1996).

In the few confirmed cases of intense infection by *A. ceylanicum,* the symptomatology was similar to that caused by human ancylostomes, and anemia was the main sign. Eight volunteers who received 50 to 150 *A. ceylanicum* larvae via the percutaneous route developed papules at the inoculation site; 15 to 20 days later they complained of epigastric discomfort, headache, fatigue, and eosinophilia. The prepatent period lasted three to five weeks. The early symptoms described were similar to those observed in volunteers who received the human ancylostome *N. americanus* or *A. duodenale* (Wijers *et al.,* 1966).

The Disease in Animals: Animal ancylostomiasis can manifest itself clinically on the skin due to the entry of the parasites, in the lungs due to the migration of the larvae, or in the intestine due to the activity of the adults. The intensity of the infection depends on several factors, such as the number of parasites, nutritional state of the animal, age, or previous infections by these nematodes. Young animals are the most affected. Entry of larvae through the skin in a first infection causes microscopic wounds that heal quickly. Subsequent infections can cause allergic inflammation with extensive pruritus, which can lead to further tissue damage due to scratching and rubbing. The signs are more acute in infection by *Uncinaria stenocephala* than *A. caninum*. In general, migration of the larvae in the respiratory system is asymptomatic. Extensive infections can cause petechiae and foci of traumatic inflammation, and the subsequent infections can cause more intense allergic inflammations, but these rarely have clinical manifestations. In intense infections, enteritis (sometimes with hemorrhagic diarrhea), atrophy of the intestinal villi, and deficiencies in intestinal absorption are frequent. Loss of blood caused by suction and the subsequent bleeding, associated with malnutrition caused by diarrhea and malabsorption, leads to hypochromic microcytic anemia. Eosinophilia, generally 10% to 15%, is lower than in human patients. Mild infections are generally asymptomatic.

It has been confirmed that some *A. caninum* larvae can remain hypobiotic in female dogs and, in gravid animals, become active again toward the end of pregnancy and be passed on to the newborn puppies in the mother's milk (Barriga, 1997).

Source of Infection and Mode of Transmission: There is epidemiological evidence that human infection with *A. caninum* is acquired from infected dogs (Croese *et al*., 1994). The sources of infection for humans are soil and vegetables contaminated with the feces of infected dogs or cats. Soils that retain moisture are the most favorable for the larvae because they prevent desiccation. While the larvae do not develop at temperatures below 12°C, temperatures close to that favor the survival of infective larvae because they do not accelerate the consumption of food reserves. While human ancylostomiasis can be acquired through the transcutaneous or digestive route, infection with *A. caninum* in its normal host occurs more efficiently by the oral route, and there is some evidence that infection of man by *A. ceylanicum* is also more efficient by the oral route.

Diagnosis: As was shown in Australia, infection by *A. caninum* cannot be diagnosed by the presence of eggs in the feces because the nematode does not reach sexual maturity in man. The observation of aphthous ulcers of the terminal ileum, cecum, or colon, associated with the clinical manifestations, can be an aid to diagnosis. The parasite itself is observed in just 10% to 15% of endoscopies. Enzyme-linked immunosorbent assays (ELISA) with secretory and excretory products of the parasite have revealed specific IgG and IgE antibodies. The Western blot technique with a 68 kDa antigen appears to be more sensitive and specific, even though a similar antigen seems to be present in human ancylostomes (Prociv and Croese, 1996).

Infection with *A. ceylanicum* can be confirmed by discovery of the eggs in fecal matter, but it is not possible to distinguish them from the eggs of *A. duodenale*, with which it is frequently associated. Counting the number of eggs (Stoll or Kato-Katz method) indicates the intensity of the infection: less than 2,000 eggs per gram of feces in man corresponds to less than 50 parasites and a subclinical infection; 5,000 eggs per gram of feces are found in infections with clinical significance; and more

than 11,000 eggs per gram are found in cases of frank anemia. However, it is not known whether these figures are valid for *A. ceylanicum.* For specific diagnosis, the patient should be given an anthelmintic (bephenium hydroxynaphthoate, pyrantel pamoate, mebendazole, or thiabendazole), and the expelled parasites identified.

Control: Zoonotic human ancylostomiasis is so infrequent as compared to the nonzoonotic variety that specific control measures are not justified, unless they also help reduce human infection with ancylostomes or other, more prevalent parasites. Since both zoonotic ancylostomes are prevalent in areas in which the nonzoonotic infection also occurs, the recommendations to avoid walking barefoot in areas that may be contaminated with ancylostomes, boil untreated water, avoid eating suspicious foods, and wash the hands before eating can help prevent both types of infection. Seventy years of research have brought about important advances in the development of vaccines against ancylostomiasis (Hotez *et al*., 1996), but it is not known whether a single vaccine can protect against all species of ancylostomes. Mechanical vectors may play a role in ancylostome infection: a study in Nigeria of 5,000 domestic flies found 2.6% to have *Ancylostoma caninum* eggs and 6.2% to have *A. caninum* larvae on their external surface and their digestive system (Umeche and Mandah, 1989). Health education regarding the role of pets in human infection would be the most effective method of controlling this and other zoonoses.

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ZOONOTIC FILARIASES

ICD-10 B74.1 Filariasis due to Brugia malayi; B74.8 Other filariases

Etiology: The agents of these infections are the zoonotic filariae *Brugia malayi* (subperiodic form), possibly *B. pahangi* and *B. leporis*, *Dirofilaria immitis*, *D. (Nochtiella) tenuis*, *D. (Nochtiella) repens*, *Loaina* sp., *Meningonema* sp., *Onchocerca* sp., and several species of unidentified animal filariae, including some that manifest themselves in man and that have been identified only as *Microfilaria semiclarum* and *M. bolivarensis* (Beaver *et al.*, 1984; Orihel and Eberhard, 1998).

The subperiodic form of *B. malayi* infects man as well as monkeys, cats, and dogs in the Orient. While *B. pahangi* infects the same animals as subperiodic *B. malayi* and has been experimentally transmitted to man (Nutman, 1991), its presence in man has not been reported under natural conditions. Eberhard *et al*. (1991) found a *Brugia* microfilaria similar to that of *B. leporis* in 60% of the rabbits on the island of Nantucket, in the state of Massachusetts, US. The authors believe that this microfilaria could be the agent of the 21 cases of human brugiasis reported in the northeastern US. Two years earlier, Orihel and Beaver (1989) had described nine cases of human brugiasis, eight acquired in the US and one in Brazil, and reclassified as brugiasis three other cases whose etiologic agents had been identified as "similar to" *Dirofilaria*, *Dipetalonema*, or *Brugia*. *D. immitis* is a filaria of the heart and great

vessels of dogs, wild canids, and, less frequently, cats. It has also been described in almost 30 other wild species, mainly carnivores, mustelids, and primates (Barriga, 1982). On rare occasions, the dead parasites are found in the lungs of man. The subgenus *Nochtiella* is a dirofilaria of the subcutaneous tissue; it is characterized by fine transversal striations and prominent longitudinal ridges along the cuticulae. *D. tenuis* is a filaria of the subcutaneous tissue in raccoons and man; it is found in the southern US. *D. repens* is a filaria of the subcutaneous tissue of dogs and cats in Africa, Asia, and Europe; it is also found occasionally in man. *Onchocerca* (possibly *O. cervicalis* in horses or *O. gutturosa* in cattle) is a filaria that has been found just six times anywhere in the world in the form of subcutaneous nodules; on the seventh occasion, it was found embedded in the cornea (Burr *et al*., 1998). *Loaina* is a filaria that has been found at least once in the human eye (Beaver, 1989). *Meningonema* (possibly *M. peruzzii*) is a filaria of the nervous system of *Cercopithecus* monkeys; it has been found in man in Cameroon and may also occur in Zimbabwe (Boussinesq *et al*., 1995).

Animals do not participate to a significant extent in the epidemiology of human filariases caused by *Wuchereria bancrofti*, *B. malayi* (periodic form), *B. timori*, *Onchocerca volvulus*, *Loa loa*, *Mansonella ozzardi*, *Tetrapetalonema (Dipetalonema) perstans*, or *T. (Dipetalonema) streptocerca*, which are all considered to be parasites specific to humans (Dissanaike, 1979). Some findings in animals are so limited that zoonotic classification is not practicable. *O. volvulus* has only been found in one gorilla in the Democratic Republic of the Congo and in one spider monkey (*Ateles geoffroyi*) in Mexico (Dissanaike, 1979). The mandrill worm, similar to *L. loa* in man, is considered a different subspecies, *L. loa papionis*, which is transmitted by a different vector, *Chrysops.* Parasites similar to *M. ozzardi* have been observed in neotropical monkeys, but there is no certainty that this is the same species that infects man (Dissanaike, 1979). Also, *T. perstans* and *T. streptocerca* have been found in anthropoid monkeys, but there is not enough information available about their biology to determine their epidemiological importance (WHO, 1979).

One of the prominent features in the biology and epidemiology of filariae is that their life cycle requires an arthropod host. The adult parasites are long, thin nematodes that live in the host's tissues or body cavities. The females are viviparous, incubating their eggs *in utero* and releasing embryos called microfilariae, which live in the blood or lymph, or, sometimes, in the skin. The presence or absence of a sheath (the stretched shell of the egg) around the microfilariae is an important factor in diagnosis. The microfilariae are ingested by an arthropod during feeding and continue their development into a third-stage larva inside the host; then they migrate to the invertebrate host's mouthparts. When the arthropod feeds again, it releases the infective larvae, which enter the body of a vertebrate host and continue their development, reaching sexual maturity and producing microfilariae.

The microfilariae of some species appear in the blood with a marked nocturnal or diurnal periodicity. Those that do not display this phenomenon to a high degree are called subperiodic. *B. malayi* has a nocturnal periodic form in which the microfilariae disappear or are very rare during the day, and a subperiodic form with maximum filaremia during the night, but with filariae also present during the day. *D. repens* is of diurnal periodicity, while *D. immitis* has a nocturnal subperiodicity, with filaremia 5 to 10 times greater in the afternoon or at night than in the morning or at

midday. This phenomenon, which is interpreted as an adaptation of the filariae to the feeding habits of the vectors, is important in the epidemiology and diagnosis.

Geographic Distribution and Occurrence: Periodic *B. malayi* is the cause of most of the human cases of brugiasis *malayi* that occur in Southeast Asia, China, Korea, and India, but it is a parasite exclusive to man that is transmitted only experimentally to cats and monkeys. The subperiodic form is limited to wooded and swampy regions of Indonesia, peninsular Malaysia, Thailand, southern Viet Nam, and three foci in the Philippines. Transmission occurs between jungle animals and man by means of mosquitoes, primarily those of the genus *Mansonia.* The parasite has been found in several species of nonhuman primates, domestic cats, wild felids, and pangolins (*Manis javanica*). *B. pahangi*, whose microfilariae are not easily distinguished from those of *B. malayi*, is a parasite of dogs, cats, wild felids, and less frequently, primates. Experimentally, the infection was transmitted from cat to man, but it is not known if the human infection occurs naturally, given the difficulty in distinguishing the two species. Its vectors are *Armigeres subalbatus* and *Mansonia* spp. mosquitoes; its area of distribution in Malaysia coincides with that of *B. malayi.* In the US, up until the year 2000, 22 cases of human infection by *Brugia* spp. of animal origin were described, but it was not possible to determine the species of filariae. *B. beaveri*, of raccoons, and *B. leporis*, of rabbits, are found in that country. Judging by their geographic distribution, the human cases could be due to *B. leporis* (Eberhard *et al*., 1991). Two cases of a human infection by a zoonotic *Brugia* of unknown species have been described in Colombia (Kozek *et al.*, 1984).

D. immitis is widespread among dogs throughout the world, although the prevalence varies greatly in different areas. In the endemic areas, the prevalence is generally 40% to 70% in dogs and 1% to 4% in cats. Up until 1982, just 44 human cases had been reported (Barriga, 1982), but then Rodrigues-Silva *et al*. (1995) mentioned 229, and Echeverri *et al*. (1999), 150. Of the cases reported between 1995 and 2000, 10 were in Japan, 6 in Germany, 4 in the US, 3 in Italy, and 1 each in Argentina, Brazil, Puerto Rico, and Thailand. Some 87 cases had been reported in the US by 1992 (Asimacopoulos *et al*., 1992), and 5 more were reported by 2000. The human infection was rare in Japan, with just 2 cases reported up to 1968, but an additional 118 cases had been reported by 1995 (Makiya, 1997) and 10 more by the year 2000. Subcutaneous human dirofilariasis is usually due to *D. tenuis*, a parasite of raccoons *(Procyon lotor)*, in the US, and to *D. repens*, a parasite of dogs and felids, in other countries. Many cases of human subcutaneous dirofilariasis have been diagnosed in numerous countries of Africa, the Americas (Argentina, Brazil, Canada, and the US), Asia, and Europe. The greatest numbers of cases have been recorded in Italy, Sri Lanka, and the former Soviet Union (Dissanaike, 1979).

D. repens occurs in Africa, Asia, and Europe. In Europe, it is known to exist in France, Greece, Italy, Spain, and the former Yugoslavia. In the endemic areas, the prevalence in dogs generally ranges from 5% to 20%. Up to 1995, 397 cases of human infection by *D. repens* had been reported worldwide. The highest number of cases, 168, occurred in Italy (Pampiglione *et al*., 1995). There were just 4 human cases in Spain up to 1998. There were about 60 cases in France up to 1996, but only about 30 were well documented (Marty, 1997). While a prevalence rate of 1.4% for *D. repens* was found in 5,000 dogs (Marty, 1997), in some populations of military dogs the prevalence exceeded 20% (Chauve, 1997). In Greece, 20 human cases were

recognized up to 1990, but 20 more cases were identified by 1997 (12 unpublished); 4 cases were ocular and the rest were subcutaneous. There has been just one known human case of *D. repens* in Japan (Makiya, 1997).

Four species are recognized in dogs: *D. repens*, *D. immitis*, *D. reconditum*, and *D. grassii.* The overall prevalence rate is 12% to 37% (Vakalis and Himonas, 1997). The infection is common in Sri Lanka: up until 1997, there were 70 human cases, and the prevalence in dogs was 30% to 60% (Dissanaike *et al*., 1997).

The few cases of zoonotic onchocerciasis reported have been diagnosed in Canada, the US, Japan, Switzerland, and the former Soviet Union (Burr *et al*., 1998). Human cases of cutaneous or ocular infection by filariae "similar to *Dipetalonema*" have been diagnosed in Costa Rica (one case) and in the US (four cases: three in Oregon and one in Alabama) (Beaver *et al.*, 1984).

The Disease in Man: The main symptomatology of filariases due to *B. malayi*, both periodic and subperiodic (zoonotic), consists of lymphadenopathies, lymphangitis, and high eosinophilia. Attacks of lymphadenopathy lasting several days occur at irregular intervals, with fever, malaise, cephalalgia, nausea, swelling of one leg, and sterile abscesses. In advanced cases, elephantiasis of the lower extremities may occur due to obstruction of the lymphatic circulation. Elephantiasis of the scrotum, such as is seen in Bancroft's filariasis *(Wuchereria bancrofti)*, is rare in brugiasis. Many infections among the natives of endemic regions occur asymptomatically in spite of the presence of filaremia. In the cases of human infection by *Brugia* spp. of animal origin in the US, the parasite was unexpectedly found in infarcted ganglia in patients who had no other symptomatology related to this infection (Gutiérrez and Petras, 1982). The two Colombian cases were also characterized by lymphadenopathy (Kozek *et al.*, 1984).

The dirofilariae that infect man (*D. immitis*, *D. repens*, and *D. tenuis*) often cause pulmonary or cutaneous symptoms. *D. immitis* is transmitted by a variety of mosquitoes. In man, it appears that the parasite begins its cycle from the subcutaneous tissue, reaches the heart and dies, and is carried in the bloodstream to the lung, where it forms a thrombus. The parasites are usually found dead, forming a 1–4 cm nodule in the lung. In general, the parasite is a juvenile specimen; mature females have been found on a few occasions, and parasitemia was observed only in the case of a girl who received immunosuppressant therapy (Barriga, 1982). The X-ray image is known as a coin lesion (Echeverri *et al*., 1999). In 39 patients, 22 (56%) were asymptomatic and the infection was discovered during routine examination (Flieder and Moran, 1999). However, the parasite is often removed unnecessarily when it is suspected that it is a neoplasm (Rodrigues-Silva *et al*., 1995). In the symptomatic cases, cough and thoracic pain lasting a month or more have been reported, along with occasional hemoptysis, fever, malaise, chills, and myalgia. X-rays show the coin lesion, and eosinophilia is rarely confirmed.

Subcutaneous dirofilariasis and, frequently, subconjunctival dirofilariasis is due to *D. tenuis* in the US and *D. repens* in Africa, Asia, Europe, and South America. Other, unidentified species of animal dirofilariae may also be involved. Up until 1995, 397 cases of human dirofilariasis by *D. repens* had been reported worldwide. Italy had the highest number of cases (168). The lesion is generally a subcutaneous nodule or submucosal swelling which may or may not be nodular. The nodules and swelling may or may not be painful, and some are migratory. The most frequent

localizations are the head, chest wall, upper extremities, and, occasionally, under the conjunctiva. Sometimes it is internal, mainly in the lung (Pampiglione *et al*., 1995). In general, a single parasite is responsible for the lesion, and on some occasions, it has been retrieved alive. In a few cases, microfilariae have been observed in the uterus of the parasite, and in just one case, in the patient's blood (Marty, 1997). The lesion is inflammatory, with accompanying histiocytes, plasmocytes, lymphocytes, and abundant eosinophils. Blood eosinophilia is unusual (Marty, 1997).

D. tenuis seems to have a greater affinity for subconjunctival localization. It was originally identified as *D. conjunctivae* because of the frequency with which it affected the eyelids. Periorbital dirofilariasis caused by *D. tenuis* is suspected in the presence of migratory swelling in patients who have lived or traveled in the southeastern US. The infection must be differentiated from sarcoidosis, ruptured dermoid cyst, infectious abscesses, neoplasms, and idiopathic pseudotumors (Kersten *et al*., 1994). Some 56 cases of human intraocular filariasis in which the parasite was a specimen of a variety of species, predominantly nonzoonotic worms such as *L. loa* and *W. bancrofti*, have been described (Beaver, 1989). In Oregon, US, there were three cases with actively motile filariae in the anterior chamber of the eye. The causal agent was classified as *Dipetalonema* spp., with morphology similar to that of *D. arbuta* of porcupines (*Erethizon dorsatum*) or *D. sprenti* of beavers (*Castor canadensis*).

The cases of zoonotic onchocerciasis in North America were manifested as fibrotic nodules on the wrist tendon and, in one case, the nodule was embedded in the cornea (Burr *et al*., 1998).

The Disease in Animals: Dogs and cats do not seem to suffer symptoms of infection due to subperiodic *B. malayi* or *B. pahangi*, but in the laboratory, both species—especially *B. pahangi*—can cause changes in the lymphatic circulation, with edema in the hind legs of infected animals. Dogs develop lymphangitis with fibrotic lymphadenopathy similar to that of man (Snowden and Hammerberg, 1989). The infection in domestic carnivores is probably underdiagnosed.

D. immitis lives in the pulmonary artery of dogs and, secondarily, in the right ventricle; it almost always forms a mass that includes numerous parasites. When the number of parasites is small, the infection may be asymptomatic. In cases of more intense or protracted infections, the living or dead filariae cause stenosis of the pulmonary vessels, obstructing the flow of blood. Over time, this causes failure of the right ventricle (Barriga, 1997). The most prominent signs are chronic cough, loss of vitality, and, in serious forms, right cardiac insufficiency. Chronic passive congestion can develop in several organs and produce ascites; thromboses caused by dead parasites can lead to pulmonary infarctions, resulting in sudden death. The acute hepatic syndrome consists of obstruction of the vena cava inferior by a large number of adult parasites that matured simultaneously, with consequent acute congestion of the liver and kidneys, hemoglobinuria, and death in 24 to 72 hours.

D. tenuis and *D. repens* do not cause illness in the animal; they may occasionally cause pruritis and eczema, leading to hair loss and scab formation.

Source of Infection and Mode of Transmission: The reservoirs of subperiodic brugiasis, which occurs in the wooded and swampy regions of Southeast Asia, are monkeys, cats, and wild carnivores. High rates of infection have been found in the monkeys *Presbytis obscurus* and *Macaca irus*. The relative importance of wild and

domestic animals as reservoirs is unknown, but it is likely that the latter serve more frequently as a source of infection for man (Denham and McGreevy, 1977). The infection is transmitted by mosquitoes of the genus *Mansonia* from animal to animal, from animal to human, and from human to human. The maximum concentration of microfilariae in the blood occurs at night to coincide with the nocturnal feeding habits of the vectors. Although *Mansonia* mosquitoes usually feed outside houses, they have also been found inside them, as is demonstrated by the fact that the infection occurs in children. In other zoonotic human infections by *Brugia* spp., *Onchocerca* spp., and *Dipetalonema* spp. (or similar species), the source of infection is wild animals of undetermined species. The main reservoir of *D. immitis* is the dog, and the disease is transmitted by a variety of mosquitoes; man is infected only accidentally. The reservoir of *D. repens* is the dog, and that of *D. tenuis* is the raccoon. Man is an accidental host of zoonotic filariae (with the exception of subperiodic *B. malayi*) and does not play any role in the epidemiology.

Role of Animals in the Epidemiology of the Disease: Of the large number of filariae species that exist in nature, only eight have fully adapted to man, and their transmission is exclusively or mainly person to person (see Etiology). The other species of filariae are parasites of animals, affecting man only occasionally and thus not constituting a public health problem. One exception is subperiodic *Brugia malayi*, which is an important pathogen for man.

Diagnosis: Of all the filariases presented in this section, only subperiodic *B. malayi* infection can be diagnosed in man when microfilariae are detected in the patient's blood; the others are not evident in man. The most common techniques are the blood smear stained with Giemsa stain, the Knott concentration, and Millipore filter concentration. Since microfilaremia takes many months to appear after infection, ganglion biopsy can be useful for early diagnosis.

In man, diagnosis of pulmonary or subcutaneous dirofilariasis is made by morphologic examination of parasites obtained through biopsy or surgery. In dogs and cats, diagnosis is made by identifying microfilariae in the blood, using a smear, the modified Knott method, or Millipore filters. In the case of *D. immitis*, a blood sample should preferably be obtained during the nocturnal hours, when the microfilaremia reaches its maximum level. Microfilaremia by *D. immitis* appears in dogs six months after infection; microfilaremia is not detectable (occult dirofilariasis) in approximately 15% of dogs infected by *D. immitis.* It is also necessary to differentiate the microfilariae of *D. immitis* from those of *D. repens* and *Dipetalonema reconditum. D. reconditum* is a nonpathogenic filaria of dogs, but its microfilariae can be confused with those of *D. immitis.* This need has been the impetus for the development of indirect diagnostic tests. The detection of an antigen of female *D. immitis* in the bloodstream of infected dogs by enzyme-linked immunosorbent assay (ELISA) makes a very sensitive and specific diagnosis possible. In man, it has been found that both *D. immitis* and *D. repens* cause the formation of antibodies and that both parasites have specific antigens. Consequently, it is possible to differentiate the respective infections serologically (Simon *et al*., 1997). The polymerase chain reaction has also been used successfully to differentiate infections caused by *D. immitis* and *D. repens* (Favia *et al*., 1997). However, the polymerase chain reaction and the Western blot technique seem to be more sensitive than ELISA in detecting infections by *D. repens* (Cancrini *et al*., 1999).

Control: Human filariasis is combated by controlling the vector arthropods, mainly with insecticides. Mass therapeutic treatment of human communities has also been successfully used to decrease the source of infection for the vectors. Control of subperiodic brugiasis is more difficult because of the ecologic characteristics of the endemic area and because of the abundance of wildlife reservoirs. In India and Sri Lanka, population levels of the intermediate host and vector of subperiodic *B. malayi* (*Mansonia* mosquitoes) were reduced by eliminating several species of floating aquatic plants to which the mosquito larvae attached. In highly enzootic areas, *D. immitis* infection in dogs can be prevented by periodic administration of an appropriate oral anthelmintic to kill the infective larvae when they are introduced by the mosquito. The drug should not be given to dogs with microfilaremia, as it can destroy the microfilariae and produce anaphylactic shock in sensitized animals. While this preventive treatment is not used against *D. repens* because the infection in dogs is asymptomatic, it could be used to decrease the reservoir of vectors in areas of high human endemicity. The other human zoonotic filariases are very rare, so individual protective measures against vectors are sufficient.

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2. Cestodiases

BERTIELLIASIS

ICD-10 B71.9 Cestode infection, unspecified

Etiology: *Bertiella studeri* (*B. satyri*) and *B. mucronata* are anoplocephalid cestodes whose natural definitive hosts are nonhuman primates. Differentiation of the two species is based on the size of the glandular portion of the vagina, the eggs and their pyriform apparatus, and the number of testes. Some specialists think that these differences are not sufficient to separate *B. studeri* from *B. mucronata,* and accept only the former species name. Others accept geographic and host segregation as additional valid criteria (Denegri *et al*., 1998). Adult cestodes are 10 to 30 cm long and 1 cm wide. The gravid proglottids (segments) are much wider than they are long, detach in groups of about 20, and are eliminated in the feces of the primates. The intermediate hosts are oribatid mites of the genera *Dometorina, Achipteria, Galumna, Scheloribates,* and *Scutovertex.* These mites are about 0.5 mm long, live in the soil and humus, and, since they feed on organic matter, can become infected by ingesting cestode eggs found in soil contaminated by the fecal matter of infected monkeys. The embryo travels to the mites' body cavity and forms a larva known as cysticercoid. When a monkey ingests an infected mite with its food, digestion of the mite releases the cysticercoids, which mature into adult cestodes in the host's intestine.

Geographic Distribution and Occurrence: This parasitosis is rare in man. Up to 1999, 56 cases in humans had been reported: 45 cases of infection by *B. studeri,* 7 by *B. mucronata,* and 4 by *Bertiella* sp. (Ando *et al*., 1996; Denegri and Perez-Serrano, 1997). The cases caused by *B. studeri* occurred in east Africa, Gabon, India, Indonesia, the island of Mauritius, the Philippines, the Russian Federation, Saint Kitts in the Lesser Antilles, Singapore, Spain, Thailand, the US (state of Minnesota), and Yemen. At least two of the three cases caused by *B. studeri* in the New World seem to be associated with Old World monkeys: the monkeys on Saint Kitts are of African origin, and the case in Spain was apparently acquired in Kenya. Three cases caused by *B. mucronata* were reported in Argentina, two in Brazil, one in Cuba, and one in Paraguay. The cases caused by *Bertiella* sp. occurred in the Democratic Republic of the Congo, Great Britain, India, and Saudi Arabia. The natural hosts of *B. studeri* belong to the genera *Simya, Anthropithecus, Hylobates,*

Cercopithecus, Troglodytes, Macaca, Pan, and *Papio*; the natural hosts of *B. mucronata* belong to the genera *Allouata, Callicebus, Cebus,* and *Callithrix*. Infection in monkeys is common. Prevalences of 3.6% to 14.0% have been reported in rhesus monkeys, 1.4% to 5.3% in cynomolgus monkeys, 7.1% in Japanese macaques, and 7.7% in baboons (Flynn, 1973).

The Disease in Man and Animals: The infection causes neither symptoms nor lesions in monkeys (Owen, 1992). It is generally also asymptomatic in man, but some cases with abdominal pain, intermittent diarrhea, anorexia, constipation, and weight loss have been reported. These symptoms seem to be more common in children. In rare cases, severe abdominal pain and intermittent vomiting have been described.

Source of Infection and Mode of Transmission: Nonhuman primates, which constitute the natural reservoir of the cestode, acquire the parasitosis by ingesting infected oribatid mites with their food. Man can become infected by accidental ingestion of food contaminated with soil containing infected mites. This occurs when people are in close contact with monkeys kept at home or in zoos, or when there are large numbers of monkeys in the peridomestic environment.

Diagnosis: Preliminary diagnosis is based on observation of the proglottids eliminated in the feces and is subsequently confirmed by microscopic examination of the eggs obtained from the proglottids. The eggs are slightly oval and thin-shelled, and the embryo is encased in a capsule or pyriform apparatus with two blunt horns. The eggs of *B. studeri* are 49–60 by 40–46 µm and the eggs of *B. mucronata* are 40–46 by 36–40 µm.

Control: Since human infection is accidental and infrequent, its prevention is difficult. Ingestion of food contaminated with soil from environments where monkeys are numerous should be avoided.

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COENUROSIS

ICD-10 B71.9 Cestode infection, unspecified

Synonyms: Coenuriasis, vertigo, gid, sturdy.

Etiology: *Coenurus cerebralis, C. serialis,* and *C. brauni* are larval stages of the cestodes *Taenia multiceps, T. serialis,* and *T. brauni,* respectively. While those names do not correspond to the species of the parasite, and therefore should not be written in italics or in Latin with the first letter capitalized, the custom goes back to the time when the relationship between the larval and adult stages of cestodes was not known. Those species used to be assigned to the genus *Multiceps*, whose identifying characteristic is that the larval stage is a coenurus. Since this property is not evident when the adult cestodes are examined, and since they are morphologically indistinguishable from cestodes of the genus *Taenia*, they are currently assigned to the genus *Taenia*. However, certain authors still reserve the subgenus *Multiceps* for those larval stages (Barriga, 1997). Parasitologists disagree about how to differentiate these species: some attribute the morphological differences observed, especially in the larvae, to factors inherent in the host. For example, Lachberg *et al*. (1990) developed a *C. serialis* that seemed to be a racemose cysticercus in an immunodeficient mouse; Bohrmann (1990) found muscular coenuri in a gazelle, despite the belief that coenuri in ruminants are forms of *T. multiceps* and are almost always found in the central nervous system. Currently, new molecular biology techniques are being used to study cestodes, and these questions will probably be resolved in the near future (Gasser and Chilton, 1995).

The definitive hosts are domestic dogs or wild canids such as coyotes, foxes, and jackals, which harbor the tapeworms in their small intestines. The intermediate hosts of *T. multiceps* are domestic herbivores, mainly sheep. The larval stage, *C. cerebralis*, is found in the central nervous system of these animals, in particular the brain and spinal cord. It is believed that goats can develop this coenurus in the subcutaneous or intermuscular tissue or in other organs. In the past, this parasite was identified in goats as *T. gaigeri*, but the taxonomy of cestodes that form coenuri is too complicated to allow for the acceptance of new species without strong arguments. The intermediate hosts of *T. serialis* are lagomorphs and rodents, especially the domestic rabbit and the hare. The *C. serialis* larva develops in the subcutaneous and intermuscular connective tissue. However, at least one case of fatal infection caused by the *T. serialis* larva in the brain of a cat has been described (Huss *et al*., 1994). The intermediate hosts of *T. brauni* are wild rodents. The *C. brauni* coenuri also develop in the subcutaneous connective tissue.

The life cycle starts with the expulsion of gravid proglottids or eggs with the feces of the definitive host. Intermediate hosts are infected by ingesting the eggs deposited in grass or in water. The oncospheres (embryos) penetrate the wall of the small intestine and, through the blood vessels, are distributed to different tissues and organs. *C. cerebralis* reaches maturity only in the central nervous system; the coenuri of the other two species develop in connective tissue. The only morphological difference between *C. cerebralis* and *C. serialis* is that the former has 500 to 700 scolices distributed in non-linear groups and the latter has 400 to 500 scolices distributed in radial lines (Barriga, 1997). The coenurus reaches full development in the brain in

six to eight months and can grow to a size of 5 cm or more; it forms a cyst that contains a considerable amount of liquid and has a germinal membrane with several hundred scolices. The cycle is completed when a dog or wild canid ingests tissue or an organ containing coenuri. Each coenurus can give rise to numerous tapeworms, which develop in the small intestine of the canids. There is no reliable morphological criterion for distinguishing the species in the adult stage.

Geographic Distribution and Occurrence: *T. multiceps* and its larval stage, *C. cerebralis,* are cosmopolitan in cattle-raising areas but occur primarily in temperate climates. While up until 1950 just five cases of infection with the larva were recognized in man, by 1990, some 55 human cases of cerebral coenurosis had been recorded in the world, most in Africa or South America. There were also a few cases in the US and in the sheep raising areas of western Europe (Pau *et al*., 1990). Up until 1998, six cases were recorded in the US (Ing *et al*., 1998). A study carried out in Ethiopia found that 37 of 37 sheep (100%) that were apparently sick with coenurosis and 5 of 183 sheep (2.7%) that were apparently healthy had *T. multiceps* larvae with diameters ranging from 0.8 cm to 6.5 cm. In 96% of the cases, the larvae were in the brain, and in the rest of the cases they were in the cerebellum. Prediction of the localization of the coenurus based on the direction of the parasite's circular movements or gid or the deviation of the head were accurate in just 62% of the cases. A retrospective study showed that the local prevalence of coenurosis in sheep was 2.3% to 4.5% and that the prevalence of taeniasis in autopsied stray dogs was 47%. Seventy-two percent of infections in sheep occurred when the animals were between the ages of 6 and 24 months (Achenef *et al*., 1999). In Iran, 738 of 7,992 sheep (9.8%) studied were infected with *T. multiceps* larvae (Oryan *et al*., 1994). In Great Britain, *T. multiceps* was found in 4 (0.5%) and *T. serialis* was found in 5 (0.6%) of 875 foxhounds, *T. multiceps* was found in 15 (1.7%) and *T. serialis* was found in 3 (0.3%) of 882 farm dogs, and *T. serialis* was found in 1 of 197 foxes (0.5%) (Jones and Walter, 1992). In Germany, *T. multiceps* was found in 3.3% of 397 foxes (Ballek *et al*., 1992), and in Peru, it was found in 20% of 20 foxes (Moro *et al*., 1998).

T. serialis and its larval stage, *C. serialis,* are also cosmopolitan. Human infection is rare; about 10 cases have been recognized, mostly in Africa (Faust *et al.,* 1974). In man, the coenuri may invade the connective tissue and central nervous system. The frequency of coenurosis in leporids is not known.

T. brauni and its larval stage, *C. brauni,* occur in tropical Africa (central and eastern) and also in South Africa. In central Africa, where this is the only species found, about 25 human cases of coenurosis in connective tissue have been described, as well as one case with ocular localization. The frequency of coenurosis in wild rodents is not known.

The Disease in Man: Most human infections are located in the brain, less frequently, they are subcutaneous, and, in rare cases, they are ocular or peritoneal. The cerebral form is the most serious (Ing *et al*., 1998). Several years may pass between infection and the appearance of symptoms, and the symptomatology varies with the neuroanatomic localization of the coenurus: cerebral coenurosis is manifested by signs of intracranial hypertension, and the disease is very difficult to distinguish clinically from neurocysticercosis or cerebral hydatidosis. Symptoms that may be observed consist of headache, vomiting, paraplegia, hemiplegia, aphasia, and epileptiform seizures. Papilloedema is a sign of increased intracranial pressure. The

coenurus can also develop in the vitreous humor and may affect the retina and choroid. The degree of damage to vision depends on the size of the coenurus and the extent of the choroidoretinal lesion. The prognosis for coenurosis of the nervous tissue is always serious and the only treatment is surgery, although recently, the testing of treatment with praziquantel or albendazole has begun.

Coenurosis of the connective tissue caused by *C. brauni,* which is seen primarily in tropical Africa, is the most benign form. The subcutaneous cysts resemble lipomas or sebaceous cysts.

Interestingly, researchers have discovered that coenuri produce certain components that interfere with the host's immunity and may be responsible for the host's relative tolerance of the larva (Rakha *et al*., 1997).

The Disease in Animals: Cerebral coenurosis occurs primarily in sheep, although it may also occur in goats, cattle, and horses. Two phases can be distinguished in the symptomatology of cerebral coenurosis in sheep. The first phase is associated with the invasion and migration of the parasite. Massive numbers of larva can migrate simultaneously and cause meningoencephalitis and the death of the animal. This acute form is not frequent and occurs mainly in lambs. The second phase corresponds to the establishment of the coenurus in the cerebral tissue. In general, symptoms are not observed until the parasite reaches a certain size and begins to exert pressure on the nervous tissue. Symptoms vary with the location of the parasite and may include circular movements or gid, incoordination, paralysis, convulsions, excitability, and prostration. Mortality is high. Softening of the cranial wall was observed in 42% of 62 sheep with coenurosis. This change occurs most often in young animals and when the coenuri are situated on the surface of the brain.

Source of Infection and Mode of Transmission: The transmission cycle of infection by *T. multiceps* takes place between dogs and domestic herbivores. Man is an accidental host and does not play any role in the epidemiology of the disease. The main factor in maintaining the parasitosis in nature is access by dogs to the brains of dead or slaughtered domestic herbivores that were infected with coenuri. The life cycle of the other two species of *Taenia* that form coenuri depends on predation by dogs on leporids and rodents.

Taenia eggs expelled in the feces of infected dogs or other canids are the source of infection for man and for the other intermediate hosts. In general, the eggs are eliminated by the definitive host in the proglottids. Since these dry out rapidly and are destroyed outside the host, the eggs are released and dispersed by the wind, rain, irrigation, and waterways.

Diagnosis: Diagnosis in the definitive hosts can be made only by recovery and examination of the parasite; even so, identification of the species is doubtful. Neither the proglottids nor the eggs are distinguishable from those of other species of *Taenia*. Diagnosis in the intermediate hosts can be made only by recovery and examination of the parasite. The morphological differences between *C. cerebralis* and *C. serialis* are explained above. The presumptive diagnosis in man is generally made by establishing the existence of a lesion that occupies space; however, since coenurosis is much less common than hydatidosis, coenurosis is rarely considered before the parasite is recovered (Pierre *et al*., 1998). Because of the relative infrequency of human coenurosis, there has been no incentive to develop immunological

diagnostic techniques. However, the tests that are currently available indicate that cross-reactions with other cestodes are common (Dyson and Linklater, 1979).

Control: For man, individual prophylaxis consists of avoiding the ingestion of raw food or water that may be contaminated with dog feces. General preventive measures for cestodiases consist of preventing infection in the definitive host so that it cannot contaminate the environment, preventing infection in the intermediate host so that it cannot infect the definitive host, or changing the environment so that both actors are not found in nature. Some details on the application of these measures for the control of coenurosis can be found in the chapter on Hydatidosis, which has a similar epidemiology.

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CYSTICERCOSIS

ICD-10 B69

Etiology: The agent of this disease is the larval form or cysticercus of *Taenia solium* and *T. crassiceps.* Observation of the *T. solium* larva in man was reported as far back as the sixteenth century; the *T. crassiceps* larva was reported just five times. The *T. saginata* larva does not seem to occur in man (see below). Before the relationship between taeniae and their cysticerci was understood, the larval stages were described with their own scientific names, as if they were separate species. Thus, the *T. solium* larva was called *Cysticercus cellulosae*, the *T. crassiceps* larva was *C. longicollis*, and the *T. saginata* larva was *C. bovis*. This unfortunate situation still exists today.

The definitive host of the *T. solium* and *T. saginata* cysticerci is man; the definitive hosts of *T. crassiceps* are the fox and other wild canids. The natural intermediate hosts of the *T. solium* cysticercus are the domestic pig and the wild boar. These cysticerci are also occasionally found in dogs, cats, sheep, deer, camels, monkeys, and humans. The intermediate hosts of the *T. crassiceps* cysticerci are wild rodents, but the cysticercus has also been found in man and in one dog. The natural hosts of the adult larvae of *T. saginata* are domesticated cattle and, rarely, wild artiodactyls. In the past, cases of human infection by cysticerci with unarmed rostella—identified as *T. saginata* (*C. bovis)*—have been described. Currently, this is not considered a valid criterion for identifying the species because the hooks can detach due to the host's reaction. Current expert opinion holds that there is no reliable proof of human parasitism caused by the larval stages of *T. saginata*. Accordingly, cases of human cysticercosis caused by *C. bovis* have not been mentioned in the literature during the last decade. Individual cases of human infection with the cysticercus of *T. ovis* have been reported in the spinal cord of man in the former Soviet Union and with the cysticercus of *T. taeniaeformis* in the liver of a boy in Argentina; a case of infection with the cysticercus of *T. hydatigena* in the liver has also been reported.

The adult stage of *T. solium* lives in the small intestine of man and regularly eliminates gravid proglottids, which are generally expelled to the external environment with the feces; there they dry out and release the eggs. The eggs remain near the droppings or are disseminated by the wind, rain, or other climatic phenomena, contaminating water or food which may be consumed by pigs or man (for further details, see the chapter on Taeniasis). The eggs are infective from the time they leave the intestine. When a pig or a person ingests them, the hexacanth embryo is activated inside the egg then released from it; it then penetrates the intestinal mucosa, and is spread via the bloodstream. Once lodged in its preferred tissue, the embryo is transformed into a cysticercus which looks like an ovoid vesicle approximately 5 mm by 8–10 mm and contains the scolex of the invaginated adult taenia. The scolex of the cysticercus, like that of the adult taenia, has four suckers and two different-sized rows of hooks. This larva becomes infective for a new definitive host in 60 to 70 days. In pigs, the cysticerci preferentially locate in striated or cardiac muscle; in man, the majority of cysticerci found are located in the nervous system or subcutaneous tissue, although they have also been found in the eye socket, musculature, heart, liver, lungs, abdominal cavity, and almost any other area. The diversity of human localizations may be due more to the ease of detecting the cysticercus in the

infected individual than to an actual tropism. Rarely, a multilobular larva that resembles a bunch of grapes has been found, but with vesicles that have no scolices, at the base of the infected person's brain; it has been designated *Cysticercus racemosus*. The histology of the parasite indicates that it is a taenia larva, and most authors believe it is a degenerative state of *C. cellulosae*, perhaps due to the localization. However, others have posited that it may be a form of coenurus (see the chapter on Coenurosis).

T. crassiceps is a taenia found in wild animals. Its cysticerci are found in foxes and can affect other wild canids, such as coyotes. The adult stage of *T. crassiceps* has been identified in hamsters and mice treated with corticoids. The cysticerci are found in the subcutaneous tissue or the peritoneal or pleural cavities of wild rodents and, very rarely, in man. One case of the adult larva of *T. crassiceps* has been described in a dog.

T. crassiceps seems to be so closely related to *T. solium* that the antigens of the former are used for serologic diagnosis of and vaccination against the latter.

Geographic Distribution: Distribution of the *T. solium* cysticercus is worldwide and coincides with the distribution of infection with the adult taenia (see the chapter on Taeniasis). Human cysticercosis caused by *T. crassiceps* larvae has been reported only in Austria, Canada, France, and Germany, but infection with the adult parasite—and, therefore, the opportunity for human infection with the larva—occurs where foxes are present.

Occurrence in Man: Human cysticercosis occurs worldwide, but is especially important in the rural areas of developing countries, including those of Latin America. Obviously, its prevalence is parallel to that of the adult *T. solium* parasite (see the chapter on Taeniasis). In some areas, the prevalence is very high; for example, cysticercus antibodies were found in 14.9% of 222 blood donors in Mozambique (Vilhena *et al*., 1999), 17% and 10% of the populations of two communities in Guatemala (García-Noval *et al*., 1996), 22% of 41 rural residents and 16% of 363 urban residents in Honduras (Sánchez *et al*., 1998), 9% of 9,254 individuals in Ecuador (Escalante *et al*., 1995), 3.2% of 2,180 people in five Brazilian counties (Lonardoni *et al*., 1996), and 9%, 4.5%, and 2% of 438 inhabitants of three Bolivian settlements (Jafri *et al*., 1998). A recent study conducted in Cuzco, Peru, showed a prevalence of 13% in 365 people and 43% in 89 pigs with the inmunoelectrotransfer test (Western blot) (García *et al*., 1999). Another study carried out in Honduras in 1991 showed 30% positive serology for porcine cysticercosis and 2% of human feces positive for taenia. Four years later, the prevalence of porcine cysticercosis was 35% and that of taeniasis was 1.5% (Sánchez *et al*., 1997). A study carried out in Brazil found that the clinical prevalence of human cysticercosis ranged from 0.1% to 9% and that the serologic prevalence fluctuated between 0.7% and 5.2% (Agapejev, 1996).

Neurocysticercosis, the most serious form of the disease, has been observed in 17 Latin American countries. A 0.43% rate of neurocysticercosis was found in the course of 123,826 autopsies in nine countries that account for two-thirds of the population of Latin America. It has been estimated that out of every 100,000 inhabitants, 100 suffer from neurocysticercosis and as many as 30 from ocular or periocular cysticercosis. The highest morbidity rates are found in Brazil, Chile, El Salvador, Guatemala, Mexico, and Peru (WHO, 1979). The prevalence of neurocysticercosis

seems to be especially high in Central America and Mexico. It was estimated that cysticercosis was the cause of 1% of all deaths in the general hospitals of Mexico City and 25% of the intracranial tumors. Autopsies carried out from 1946 to 1979 on 21,597 individuals who died in general hospitals in Mexico found cerebral cysticercosis in 2.9%, leading to the conclusion that about 3% of the general population was affected by this parasitosis (Mateos, 1982). In the Triângulo Mineiro, Minas Gerais, Brazil, a rate of 2.4% of cysticercosis was found in 2,306 autopsies; of these, 66% were cases of neurocysticercosis, 26.8% had cardiac localization, 25% had musculoskeletal localization, and 7.1% had cutaneous localization (Gobbi *et al.,* 1980).

In India, cerebral cysticercosis is second in importance, after tuberculosis, as a cause of expansive diseases of the skull, and is one of the principal causes of epilepsy. Neurocysticercosis is also common in Indonesia. On the other hand, human cysticercosis has disappeared in western and central Europe; it is also disappearing in eastern and southern Europe.

Just four cases of human cysticercosis caused by *T. crassiceps* larvae have been reported since 1992: one in the anterior chamber of the eye of an apparently healthy girl in Austria (Arocker-Mettinger *et al*., 1992), another in the subcutaneous tissue of an AIDS patient in Germany (Klinker *et al*., 1992), and twice in France (Chermette *et al*., 1995; François *et al*., 1998), both in AIDS patients. Apparently an intraocular case was reported earlier in Canada.

Occurrence in Animals: Information on swine cysticercosis comes from veterinary inspection records at slaughterhouses and packing plants. However, it must be borne in mind that usual inspection methods, which consist of cutting the meat at sites where the parasite preferentially locates, reveal only a portion of infected animals. It is also important to point out that swine raised on small family farms, where they have a greater opportunity to ingest human feces, are generally slaughtered by their owners without veterinary inspection or are sold without restrictions in local markets.

For obvious reasons, in all areas where human taeniasis exists, animal cysticercosis is also found, with variations in prevalence from region to region. In the Americas, only some countries and islands in the Caribbean have not recorded this parasitosis. In Brazil, which accounts for more than 65% of the total swine population in Latin America, 0.83% of 12 million pigs slaughtered in 10 states during 1970–1972 were found to be infected with *C. cellulosae*. Similar rates have been observed in Mexico and several South American countries, such as Chile (0.7%) and Colombia. In a survey conducted in Mexico, 17 of 75 (23%) swine examined were found to be positive for cysticercosis by palpation of the tongue and 26 (35%) by serology (Rodríguez-Canul *et al*., 1999). In Cuzco, Peru, a prevalence of 43% was found in 89 pigs by immunoelectrotransfer (García *et al*., 1999). Another survey conducted in Honduras showed 30% positive serology for porcine cysticercosis (Sánchez *et al*., 1997).

In South Africa, the only African country with more than a million swine, the infection rate in slaughterhouses was under 1.5%. In the Democratic Republic of the Congo, the rate ranges from 0.1% to 8.1%, depending on the region. In Asia, information on the prevalence of animal infection is scarce. Porcine cysticercosis is disappearing in Europe. In the former Soviet Union, the rate of cysticerci in swine was

0.14% in 1962 and only 0.004% in 1970. Similar figures have been reported from Hungary and other countries of eastern Europe. At present, very few endemic foci are found on that continent, as a consequence of modernized swine-raising practices. Economic losses due to the confiscation of bovine and swine carcasses infected by cysticercosis can be significant. In 1963, swine cysticercosis was the reason for 68% of all confiscations in six slaughterhouses in Central America, causing an estimated loss of one-half million dollars. During 1980, 264,000 swine carcasses were confiscated in Mexico, and total losses due to swine cysticercosis were estimated at more than US$ 43 million. Losses due to bovine cysticercosis in Latin America are possibly even greater than those due to swine cysticercosis. The economic impact consists of not only the losses caused by the animal parasitosis, but also the cost of treating human neurocysticercosis, which involves significant expenses for surgery, hospitalization, and work days lost. The cost of medical care in Mexico for a patient with neurocysticercosis has been estimated at more than US$ 2,000.

No information is available on the prevalence of the *T. crassiceps* cysticercus in rodents. In the past decade, the adult parasite was found in 18% to 29% of several thousand red foxes examined in France, Germany, and Spain; cysticercus was also found in Greece, and reported in less than 10% of arctic foxes examined in the state of Alaska, US.

The Disease in Man: Cysticercosis is a disease which varies in severity according to the localization of the parasite. Man can harbor from one to several hundred cysticerci in various tissues and organs. The localization that most often prompts a medical consultation is the central nervous system (neurocysticercosis), followed by the eye and its surrounding tissues (ocular and periocular cysticercosis). Localization in muscles and subcutaneous connective tissue is generally not clinically apparent unless large numbers of cysticerci are involved, causing muscular pain, cramps, and fatigue.

The symptomatology of neurocysticercosis varies with the number of cysticerci, their stage of development (young, mature, intact, degenerate), morphology (vesicular or racemose), location in the central nervous system, and the reaction of the patient. The cysticerci locate most frequently in the meninges, cerebral cortex, and ventricles, and less frequently in the parenchyma. The symptoms generally appear several years after the infection, when the death of the larva causes inflammatory reactions. The symptoms are often not well defined and may resemble those of a cerebral tumor, basal meningitis, encephalitis, intracranial hypertension, and hysteria. In a study of 119 cases, Sousa *et al*. (1998) found that 64% of the patients consulted a doctor because of epileptiform attacks and 22% because of headaches; two patients had an altered mental state. Computerized tomography showed that 44% of the patients had more than five cysticerci and that the parietal lobe was the site most often affected. However, there was no relationship between the severity of the symptoms and the radiographic findings. Of 54 patients under the age of 17 studied in Ecuador (del Brutto, 1999), 89% had convulsions and just 3 had increased intracranial pressure. Computerized tomography revealed parenchymatous cysticerci in 52 patients, 19 (36%) with a single cysticercus. In 122 children in Mexico, the main symptoms were convulsions, intracranial hypertension, and learning difficulties (Ruíz-García *et al*., 1997). A study in Brazil found that the most common clinical

characteristics were epileptic syndrome (22.92%), intracranial hypertension (19% to 89%), and psychiatric symptoms (9% to 23%); 6% of the clinical patients and 48.5% of the autopsies represented asymptomatic cases (Agapejev, 1996). The presence of cysticerci in the central nervous system does not always give rise to clinical symptoms. Rodríguez-Canul *et al*. (1999) identified five asymptomatic cases serologically. Chimelli *et al*. (1998) reviewed 2,522 autopsies in Brazil and found 38 (1.5%) cases of cysticercosis. Of these, 22 (58%) had not been previously diagnosed, and 21 (55%) had been asymptomatic. Data from several Latin American countries show that in 46.8% of the cases in which cysticerci were found in the central nervous system during autopsy, the individual had had no clinical manifestations of the parasitosis during his life.

Ocular and periocular cysticercosis is less frequent, accounting for some 20% of cases. The cysticerci locate primarily in the vitreous humor, subretinal tissue, and the anterior chamber of the eye. The parasitosis may cause uveitis, iritis, and retinitis, as well as palpebral conjunctivitis, and may affect the motor muscles of the eye.

Until recently, no effective chemotherapy was available for cysticercosis. Surgery was the only treatment, and it presented serious risks in the case of neurocysticercosis and was often only palliative. It has been estimated that more than 30% of such patients die during the operation or in the postoperative period. The advent of new drugs, especially praziquantel, in recent years, has resulted in up to a 68% rate of cure or clinical improvement with medical treatment (Robles *et al*., 1997).

The clinical manifestations of cysticercosis are determined by a strong inflammatory reaction that seems to occur only during and after the death of the parasite. While the cysticercus generates significant immune responses, the inflammation around viable cysticerci is quite moderate. It is now known that the live cysticercus produces taeniaestatin and paramyosin, which inhibit complement activation, and sulfated polysaccharides, which activate complement at sites distant from the parasite and may inhibit the proliferation of lymphocytes and macrophages (White *et al*., 1997). These actions probably limit the inflammatory reaction while the parasite is alive.

Cases of human cysticercosis caused by *T. crassiceps* are so scarce that there is no general picture of their symptomatology. The François *et al*. case (1998) was a subcutaneous and intermuscular tumor of the arm, fluctuating and painful, in an AIDS patient. The lesion contained cysticerci that resemble small vesicles surrounded by a granulomatous reaction with fibrocollagenous tissue contained in a caseous material. The Klinker *et al*. case (1992) involved a paravertebral pseudohematoma in an AIDS patient that spread to most of the back in the following weeks and caused a deficiency of clotting factor V and local bleeding that required transfusions. The lesion ruptured spontaneously, releasing blood and spherules 2 to 3 mm in diameter, which were identified as cysticerci of the parasite. Treatment with a combination of mebendazole and praziquantel reduced the lesion and coagulation returned to normal, but the patient suffered a relapse four months later. In this case, there appears to have been asexual multiplication of the cysticerci, as was described in rodents, which are natural intermediate hosts.

The Disease in Animals: Cysticercosis in swine does not usually manifest itself clinically. In isolated cases, infected swine may experience hypersensitivity of the snout, paralysis of the tongue, and epileptiform convulsions, but the useful life of

swine is usually too short for neurologic manifestations to appear. Dogs that ingest human feces and become infected with the eggs of *T. solium* sometimes show symptoms of cerebral cysticercosis which may be confused with those of rabies. Experimental infection of cattle with a high dose of *T. saginata* eggs can produce fever, weakness, sialorrhea, anorexia, and muscular stiffness. Death may occur as a result of degenerative myocarditis.

Source of Infection and Mode of Transmission: Man acquires cysticercosis through *Cysticercus cellulosae* infestation by consuming water or food (e.g., vegetables or fruits) contaminated with *T. solium* eggs that were released into the environment by gravid proglottids eliminated by an infected person. Such contamination also allows for the infection of swine by coprophagy. A person's hands may be contaminated by contact with contaminated soil or water or from eggs from his own feces, and thus transmitted to others. *T. solium* eggs only survive for a few weeks or months outside the host, but, since the taeniae can live for many years in the human intestine and eliminate several hundred thousand eggs every day, environmental contamination can continue for a long time. The risk is particularly high in the rural areas of developing countries, where the lack of adequate excreta disposal systems promotes outdoor defecation and consequent contamination of peridomestic areas. Moreover, taeniae eggs can be spread by rain, wind, and, possibly, by coprophagous insects, and transported over long distances by watercourses and, possibly, also in the intestines of gulls and other birds. Such dispersion facilitates the contamination of produce from the family garden, either through contamination of the area around the house or through irrigation with water that was contaminated farther upstream. In addition, the lack of potable water supply hinders the effective washing of hands and foods. This situation often generates a cycle of autoinfection in the family: it has been shown that the most important risk factor for cysticercosis is the presence of a family member who is infected with taenia. A study of soldiers and their relatives in Mexico, for example, showed that 12.2% of the soldiers had cysticercosis and 0.5% had taeniasis, and that 12% of the soldiers' relatives with cysticercosis had eliminated proglottids in the past. Just 3.7% of the relatives in an uninfected control group had eliminated proglottids in the past (García-García *et al*., 1999).

It is also common for poor peasants to raise some swine under very primitive conditions and sell them locally or slaughter them for big celebrations. Those animals have many opportunities to become infected through human feces and, since they are consumed without veterinary inspection, they are often the source of taeniasis infection in the community. *T. solium* cysticerci can survive for several years in the swine and for more than a month in the carcass.

Food handlers can be of vital importance in transmission: thus, in a Peruvian village, it was found that 3% of the general population was infected with taeniasis and 24% was infected with cysticercosis, while 8.6% of the vendors of a locally-prepared pork dish had taeniasis and 23.3% had cysticercosis (García *et al*., 1998). A survey in Honduras found a 16% to 22% prevalence of human cysticercosis, and it was determined that the most important risk factors were hog-raising in the area around the house, lack of potable water, lack of sanitary excreta disposal, existence of a dirt floor in the house, general lack of education, and ignorance of the parasite's biology (Sánchez *et al*., 1998). In a study in Mexico, the main human risk factors for acquiring cysticercosis were the consumption of cysticercosis-infected swine

and proximity to a taeniasis-infected person. A study on Reunion Island in the Indian Ocean showed that household swine raising—a common practice there—can maintain significant levels of human cysticercosis even if levels of taeniasis are low: 14 of 993 (1.4%) individuals examined serologically for cysticercosis were positive, even though just 0.02% had taeniasis and no swine with cysticercosis were found in the island's slaughterhouses (Chamouillet *et al*., 1997). In addition to these risk factors, a study in China determined that the risk factors for human cysticercosis also included: poor personal hygiene, lack of knowledge about the infection in swine, poor swine breeding practices, and a history of taeniasis.

For swine, the greatest risk of acquiring cysticercosis comes from livestock-raising practices that allow the animals to roam freely and expose them to human feces. Animals confined in corrals had a much lower risk of acquiring the infection than free-roaming swine (Rodríguez-Canul *et al*., 1999).

Likewise, it has been suggested that the gravid proglottids of the taenia could be carried by reversed peristalsis to the stomach, where the eggs could be activated, and from there, once again be carried to the intestine, where the oncosphere would be liberated and give rise to cysticercosis. Despite the fact that most authors rejected that possibility, the recent finding of the oral expulsion of a *T. saginata* in a patient (Gupta *et al*., 1997) necessitates review of this opinion.

Diagnosis: Apart from subcutaneous and intraocular cysticercosis and some cysticercoses of the central nervous system, most cysticercus infections are clinically inapparent. Diagnosis of subcutaneous cysticercosis can be made by biopsy of the nodules or by radiography. Ocular cysticerci may be discovered by ophthalmoscopy. Neurological imaging, and especially computerized tomography, are very useful in the diagnosis of neurocysticercosis because this procedure allows lesions of various densities to be distinguished and absorption coefficients of different tissues to be quantified (Carpio *et al*., 1998). In a study carried out in Ecuador, that procedure discovered 8 cases in 46 subjects examined (17%) in a rural population and 35 cases in 147 subjects examined (24%) in an urban population. In contrast, inmunoelectrotransfer discovered 6 of 42 cases (14%) in the rural population and 28 of 124 cases (23%) in the urban population (Cruz *et al*., 1999). Since the course of treatment of cysticercosis depends on the interpretation of the clinical manifestations, the findings on imaging, and the immunological results, del Brutto *et al*. (1996) developed protocols for diagnosing individual cases as possible, probable, or definite.

The cerebrospinal fluid of those affected by neurocysticercosis shows an increase in the level of proteins, especially the gammaglobulin fraction, and a marked cellular reaction with a high percentage of plasmocytes and eosinophils. Eosinophilia is also generally present.

Serologic tests can be valuable when used in conjunction with other diagnostic procedures. Although some laboratories still recommend the hemagglutination reaction test, the enzyme-linked immunosorbent assay (ELISA) and the immunoelectrotransfer test are more sensitive, particularly with selected antigens. In a study of sera that were positive with ELISA, just 85.4% were positive with hemagglutination (Ferreira *et al*., 1997). Immunoelectrotransfer with 8 kDa and 26 kDa antigens is considered sensitive and specific (Rodríguez-Canul *et al*., 1999). Using the ELISA with recombinant antigens, 96.3% sensitivity and 91.5% specificity have been obtained (Hubert *et al*., 1999). However, serology is not the preferred method of

clinical diagnosis because it indicates contact with the parasite but not necessarily an active infection. In fact, most seropositive individuals are asymptomatic. *T. solium* and *T. crassiceps* share antigens, to the point that the use of *T. crassiceps* antigens to diagnose or vaccinate against *T. solium* is under study.

Diagnosis of swine cysticercosis can be made antemortem by palpation of the tongue, where the cysticerci are felt in cases of intense infection. More often, it is made by study of the cysticerci during postmortem examination in slaughterhouses and packing plants. This method, which only examines certain muscles where the cysticercus commonly locates, is a compromise between cost and efficiency, and many cases of mild infection are not detected. While there is not much incentive for developing serologic methods of diagnosing the swine infection, Rodríguez-Canul *et al*. (1999) used immunoelectrotransfer of 8 kDa and 26 kDa antigens with the swine infection and achieved 93% sensitivity and 100% specificity.

Control: Health education for at-risk populations is the foundation of cysticercosis prevention. A study in China (see Source of Infection and Mode of Transmission) established that control of human cysticercosis required a combination of health education and treatment of taeniases (Cao *et al*., 1997). A study in Mexico evaluated the effects of health education about the disease by measuring the change in knowledge and habits and in the prevalence of swine cysticercosis before and after an education program that promoted knowledge about transmission of the parasite and the appropriate hygiene practices for preventing transmission. After program execution, there were significant changes in knowledge of the parasite's biology, but behavioral changes were short-lived and less impressive. The incidence of human taeniasis decreased from 5.2% to 1.2% (Sarti *et al*., 1997).

In addition to individual protective measures for humans, control measures for cysticercosis consist of interrupting the chain of transmission of the parasite at any of the following intervention points: the production of eggs by an infected person, the dissemination of eggs to the environment, the ingestion of eggs by the intermediate host, the development of the cysticercus in the intermediate host, and the dissemination of the cysticerci to the definitive host (Barriga, 1997). For more details on control, see the chapter on Taeniasis.

Recently, successful attempts have been made to provide mass treatment to a human population with human taeniasis: in an area of Guatemala where *T. solium* is endemic, the prevalence of human taeniasis decreased from 3.5% to 1%, and that of swine cysticercosis decreased from 55% to 7% after 10 months of treatment (Allan *et al*., 1997). García *et al*. (1999) found that cases of human and swine cysticercosis tend to be associated in geographic groups and that their serologies were positively correlated. Swine serology, therefore, is a suitable indicator of environmental contamination by *T. solium* and should be used to estimate the risk of human infection.

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DIPHYLLOBOTHRIASIS

ICD-10 B70.0

Synonyms: Bothriocephaliasis, bothriocephalosis, dibothriocephaliasis, broad tapeworm infection, fish tapeworm infection.

Etiology: The agent of this disease is a cestode of various species of the genus *Diphyllobothrium* (synonyms *Bothriocephalus, Dibothriocephalus*). Nomenclature within the genus is still imprecise because the limits of intraspecific morphologic variation and the factors associated with that variation are not known. The type species, and most important one, is *D. latum*. Some of the species currently considered valid are: a dwarf form of *Diphyllobothrium,* described as *D. parvum* in 1908 and subsequently confirmed as *D. latum, D. parvum* type in two human cases in the Republic of Korea; *D. nihonkaiense*, one of the most common parasites from fish in Japan (Ohnishi and Murata, 1993); *D. klebanovskii*, a highly prevalent species (0.07%) in the northeastern part of the former Soviet Union (Muratov *et al*., 1992); and *D. yonagoense*, which has been reported in human cases in the Republic of Korea. The following species have been described in human cases found in arctic and subarctic communities: *D. dendriticum*, which is found farther north than *D. latum*; *D. ursi* in northern Canada and in Alaska, US; *D. dalliae* in Alaska and Siberia; and *D. klebanovskii* in Siberia (Curtis and Bylund, 1991). *D. pacificum* has been described in Chile and Peru, and *D. dendriticum* has been described in Argentina and Chile.

In this section, *D. latum* is used to describe the life cycle of the cestode. The parasite requires two intermediate hosts: the first of these is a copepod (small, planktonic crustacean); the second, a freshwater fish from one of several species. The adult or strobilar form of the parasite lives in the small intestine of man, dogs, cats, bears, and other wild animals; it has a scolex without hooks or suckers with two sucking grooves or bothria, measures 3 to 12 m long and 10 to 20 mm at its widest part, and may have 3,000 to 4,000 proglottids. The gravid proglottids expel eggs from the intestine through a uterine pore, along with chains of proglottids that are empty or contain just a few eggs, which detach and are eliminated with the feces. A single parasite can shed up to a million eggs per day. The eggs eliminated in the host's feces contain an immature embryo which, after incubating in fresh water for 10 to 15 days at 15–25 °C, forms a ciliated embryo called a coracidium. The coracidium, some 50–100 µm in diameter, emerges from the egg and remains in the water until it is ingested by the first intermediate host, a copepod crustacean. Ingestion must occur within 24 hours of eclosion because the coracidium loses its infectiveness rapidly; however, the embryo of the species that use marine fish as intermediate hosts can tolerate the semi-brackish water of estuaries or briny sea water. This embryo lodges in the coelomic cavity of the crustacean and, in 10 to 20 days, turns into a procercoid, a solid, elongated larva 6 to 10 mm long with a circular caudal appendage. When the crustacean and larva are ingested by the second intermediate host, any one of a variety of fish, the procercoid migrates to the muscles and other organs of the fish and becomes a plerocercoid or sparganum in about a month. If the first fish is eaten by a larger fish, the transport or paratenic host, the plerocercoid simply migrates from one fish to the other. A large fish can harbor up

to 1,000 plerocercoids. When the infected fish is eaten by a definitive host, the plerocercoid lodges in the small intestine and starts to grow until it matures, and it begins to release eggs after 25 to 30 days. Human infections have been known to last up to 30 years (Marquardt *et al*., 2000).

The first intermediate host is an almost-microscopic copepod crustacean of the genera *Diaptomus* (the Americas), *Eudiaptomus* (Asia and Europe), *Acanthodiaptomus* (Alpine region, the Carpathians, Scandinavia, Tibet, and Turkestan), *Arctodiaptomus* (Ural Mountains region), *Eurytemora* (North America), *Boeckella* (Australia), or *Cyclops* (Africa, Asia, and Europe) (von Bonsdorff, 1977). The most important fish that act as second intermediate hosts in the transmission of *D. latum* to man are the pike (*Esox* spp.); the perches (*Perca* spp. and *Stizostedion* spp.); the burbot (*Lota* spp.); and the acerina (*Acerina cernua*). In Chile the agents of *D. latum* transmission are the salmonids introduced from Europe: rainbow trout (*Salmo gairdneri)* and brown trout (*Salmo trutta)*, as well as certain autochthonous fish species. Salmon of the genus *Oncorhynchus* are a source of infection in the US, Eurasia, and Japan. The larvae of *D. dendriticum* are found mainly in salmonid fish and have never been found in pike or perch. In contrast, *D. latum* is rarely found in salmonids. *D. ursi* and *D. klebanovskii* predominate in Pacific salmon. *D. klebanovskii* is found in the eastern part of the former Soviet Union, the Sea of Japan, and the Bering Sea. The usual definitive hosts are carnivores and the intermediate hosts are fish of the genera *Oncorhynchus* and *Salvelinus* (Muratov, 1990). *D. dalliae* has an affinity for local fish, such as the Alaska blackfish (Curtis and Bylund, 1991). In southern Argentina, Revenga (1993) found that 9% of brook trout are hosts to *D. latum* and 27% are hosts to *D. dendriticum*; rainbow trout are also hosts to both species, but perch are host only to *D. latum* (19%), and the mackerel were not infected with any species.

D. latum seems to be a primary human parasite, because it is in humans where the parasite reaches its greatest size and the infections are the most protracted; this appears to be an ancient illness, since eggs thought to be from *D. latum* have been found in Paleolithic mummies. But it also infects other fish-eating mammals, such as dogs, cats, swine, bears, and wild carnivores. The other diphyllobothrids seem to be predominantly zoophilic, because infections in man generally persist a few months and the cestode is expelled by itself. While the most important definitive hosts for *D. dendriticum* are gulls, this role can also be played by other birds and mammals, such as dogs, cats, rats, or man. *D. pacificum* is found on the Pacific coast of the Americas. Its natural definitive hosts are pinnipeds such as the sea lion *Otaria byronia* (*O. flavescens*) on the Peruvian coast. The intermediate hosts, as yet unidentified, would be planktonic copepods and marine fish. The species has also been found in other pinnipeds of the family Otariidae along the northern Pacific coast and in fur seals (*Arctocephalus australis)* on San Juan Fernández Island, Chile. Plerocercoid larvae of *Diphyllobothrium* spp. have been found off the coast of Peru in the following species of marine fish: croakers (*Sciaena deliciosa)*, cocos (*Paralonchurus peruanus), Trachinotus paitensis*, and others (Tantaleán, 1975). The intermediate hosts definitive for *D. ursi* in Alaska, US, and British Columbia, Canada, are the bears *Ursus arctos* and *U. americanus* and, occasionally, man. The second intermediate host is the salmon *Oncorhynchus.* Other human cases in Alaska and northeastern Siberia are attributed to *D. dalliae,* a diphyllobothrid of dogs, foxes, and gulls, whose plerocercoids are found in the blackfish *Dallia pectoralis.*

Geographic Distribution and Occurrence: *D. latum* is a cosmopolitan species found in the temperate zones, between the subarctic and subtropical, particularly in lacustrine regions. The most appropriate biotopes are lakes, river banks, and reservoirs, where the cestode finds the intermediate hosts it needs to continue its life cycle; but for humans to become infected they must eat raw or undercooked fish. The areas of greatest prevalence of this parasitosis are eastern and northeastern Finland, northern Norway, and northern Sweden. The prevalence of infection has decreased notably in almost all Eurasian countries. In Finland, where the prevalence was about 20% in the 1940s, a rate of 1.8% was found in the period 1969–1972. Notwithstanding, it was estimated that in 1973 more than 9 million persons were infected worldwide (5 million in Europe, 4 million in Asia, and 0.1 million in the Americas) (von Bonsdorff, 1977; WHO, 1979). Another endemic area is Karelia, Estonia, and St. Petersburg, Russian Federation, where lakes are abundant; important foci are also found in Siberia. In Hawaii, US, where the parasite does not exist, a case of human infection was found in a boy who had never been off the Islands and who apparently contracted it from imported fish (Hutchinson *et al*., 1997). In the Republic of Korea, 37 cases of diphyllobothriasis were reported in 1997, in addition to 21 cases in which the eggs were found in feces (Chung *et al*., 1997). Examination of the feces of 52,552 patients between 1984 and 1992 in a hospital in Seoul, Republic of Korea, revealed that 0.004% were infected with *D. latum* (Lee *et al*., 1994). In Australia, the cestode has been found only in European immigrants and, apparently, the parasite does not occur naturally in that country.

D. latum appears to have been introduced into North and South America by European immigrants. In North America, the highest prevalence of diphyllobothriasis is found among Eskimos, with rates between 30% and 80% in some localities. The infection is probably caused by several species of *Diphyllobothrium.* Plerocercoids have been found in several species of fish in the Great Lakes in North America, but the infection does not seem to exist in the area. The infection in humans has been described in several areas of the US and in Montreal and Toronto, Canada. The first confirmed case in Cuba was described in 1990 (Bouza Suárez *et al*., 1990). In Peru, the human infection is caused by *D. pacificum*; it was found in 136 of 314 patients with cestodiasis examined between 1962 and 1976. Semenas and Úbeda (1997) reported on 13 cases diagnosed in Patagonia, Argentina between 1986 and 1995. In northern Chile, 13 cases of infection by *D. pacificum* were diagnosed; in addition, plerocercoids of *D. dendriticum* were found in fish, and the adult parasite in gulls in the lake region of the south (Torres, 1982). In the Valdivia River Basin in southern Chile, Torres *et al.* (1989) found a prevalence of 1.2% in 1,295 individuals. All the parasites recovered after treatment were identified as *D. latum*. A study of 1,450 fish revealed plerocercoids of *D. latum* or *D. dendriticum* in two species of imported fish (*Salmo gairdneri* and *Salmo trutta*) and in a few autochthonous species. A retrospective study of 10,758 patients (over a 10-year period) also found, in the Valdivia River area, 11 cases of diphyllobothriasis (Kurte *et al*., 1990).

With respect to animals, in Alaska, US, cestodes of the genus *Diphyllobothrium* spp. were found in 57 of 97 autopsied dogs. Torres *et al*. (1989) found *D. latum* in 5.3% to 9.8% of dogs, but none in cats or swine. They subsequently examined the feces of 159 people, 17 dogs, 19 swine, and 4 cats, and found just one infected cat. Abo-Shehada and Ziyadeh (1991) found *D. latum* in 1.5% of 756 dogs in Jordan. In

1992, Muratov reported the presence of *D. klebanovskii* in 47% of brown bears, 1 of 2 black bears, 1.7% of wolves, 1.6% of dogs, 0.3% of otters, and 2.8% of swine in the northeastern Russian Federation; he believes that the natural definitive hosts are brown and black bears.

The Disease in Man: While humans generally host just a single specimen, multiple parasitism is not uncommon. *D. latum* attaches itself to the mucosa of the ileum and less frequently to that of the jejunum. In most cases, the parasitosis is asymptomatic. When symptoms occur, they generally consist of diarrhea, epigastric pain, nausea, and vomiting (Curtis and Bylund, 1991). Some patients who harbor a large number of parasites may suffer mechanical obstruction of the intestine. The most serious complication of diphyllobothriasis is megaloblastic anemia; in the Baltic countries it occurs in less than 2% of persons with *D. latum* parasites, mainly in individuals with parasites localized in the jejunum. The symptomatology is similar to that of pernicious anemia. It stems from the parasites blocking and competing for the absorption of vitamin B_{12}. The parasite interferes with that vitamin's combination with the intrinsic factor (a normal component of the gastric juice), thus resulting in vitamin B_{12} deficiency. Patients frequently manifest slight jaundice, fever, glossitis, edema, hemorrhage, debility, and paresthesia in the legs. The illness occurs mainly in persons 20 to 40 years of age. Megaloblastic anemia seems to be rare among individuals with diphyllobothriasis in Latin America. For example, Frisancho *et al*. (1994) failed to find the parasite in 45 patients with megaloblastic anemia of unknown etiology studied in Peru. There are no reports of cases of anemia due to diphyllobothriasis other than those caused by *D. latum*.

The Disease in Animals: Infection by *Diphyllobothrium* is not clinically apparent in dogs and cats. Several epizootics in trout have been described in Great Britain and Ireland; they were caused by infection with a large number of diphyllobothrid plerocercoids that may not have been *D. latum.* In general, infection with a small number of larvae causes no major damage, but invasion by a large number of larvae may cause death.

Source of Infection and Mode of Transmission: The cycle of infection is maintained in nature by the contamination of rivers, lakes, and reservoirs with the feces of humans and other fish-eating mammals. Contamination of water with feces containing *D. latum* eggs allows the initial infection of copepods and subsequent infection of fish. Humans become infected by eating fish or its roe or liver raw, lightly salted, or smoked without sufficient heat. An example of the relationship between eating habits and prevalence of the parasite is provided in Finland. While human diphyllobothriasis is common in eastern Finland, where consuming raw fish is an ancestral habit, in western Finland this practice is not followed and infection is infrequent in spite of the existence of similar ecologic conditions (von Bonsdorff, 1977). *Ceviche*, a popular dish made of fish with lemon juice, salt, and hot peppers, which is consumed in several Latin American countries, can be a source of infection for man. The multiple cases of *D. pacificum* infection in Peru are attributed to *ceviche* prepared with marine fish. The Japanese dish sushi, which is also made with raw fish, gave rise to four cases of diphyllobothriasis in California (CDC, 1981). Human infection is not limited to the endemic areas, but can be extended by transport and consumption of refrigerated infected fish. One case of human infection was

found in Hawaii, US, where the autochthonous parasite does not exist. The infection was apparently contracted through imported fish (Hutchinson *et al*., 1997).

Humans are the principal definitive host for *D. latum,* but in their absence other fish-eating mammals can maintain the cycle by a similar transmission mechanism.

There are indications that anadromous fish (which migrate annually from the ocean to fresh water) could serve as a common source of infection by plerocercoids of various species of *Diphyllobothrium* for both land and marine mammals. In this way, freshwater fish that feed on anadromous fish could acquire larvae of marine origin, and land mammals could become infected by eating these fish raw.

Diagnosis: Specific diagnosis is carried out by identifying the eggs of the cestode (55–75 by 40–55 µm, operculate, unembryonated, and with a small lobe on the abopercular end) in the fecal matter. It is not possible to distinguish the species by examining the eggs, but attempts can be made to differentiate them by studying the proglottids passed spontaneously or after treatment. While formalin-ether sedimentation gives the best results in connection with the concentration of eggs in fecal matter, the number of eggs the parasite produces is so high that it is rarely necessary to concentrate them.

Control: Prevention of the infection in humans is based on the following: a) educating the population to abstain from eating raw or undercooked fish and contaminating the lakes with their feces; b) treating cestode carriers to prevent contamination of the environment; c) in endemic areas, cooking fish to 56 °C for 5 minutes or freezing it to –10 °C for 48 hours or to –18 °C for 24 hours to kill the plerocercoids; and d) taking steps to control fecal contamination of lakes and rivers, which is often difficult because of economic conditions in the affected areas. Treatment of domestic dogs in the area of lakes or rivers where fishing occurs may be useful, as may refraining from feeding dogs or cats scraps of raw fish. Most tests show, however, that humans are the principal reservoir of *D. latum* for other humans.

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DIPYLIDIASIS

ICD-10 B71.1

Synonyms: Dipylidiosis, dog cestode infection, dog tapeworm infection.

Etiology: *Dipylidium caninum* is a cestode 10 to 70 cm long and 3 mm at its widest part, with 60 to 175 proglottids; its definitive hosts are the dog, cat, and some wild felids and canids. The intermediate hosts are mainly dog fleas (*Ctenocephalides canis*) and cat fleas (*C. felis*). The human flea (*Pulex irritans*) and the dog louse (*Trichodectes canis*) can occasionally serve as intermediate hosts. The gravid proglottids detach singly or in groups from the strobila or chain of segments or proglottids that make up the body of the cestode; they are mobile and pass to the exterior on their own or with the feces. The proglottids disintegrate in the environment, releasing the eggs, which must be ingested by the flea larvae to continue their development to adulthood. The eggs hatch in the intestine of the flea larva, and the embryos (oncospheres) penetrate the celomic cavity; there they turn into cysticercoids. During this development of the parasite, the flea larva continues its own

development until it becomes an adult insect. Hinaidy (1991) conducted a study in Austria of 9,134 fleas from 198 cats and 182 dogs, and found that 98.5% of the cat fleas and 77.5% of the dog fleas were *C. felis*, and that 2.3% of the cat fleas and 1.6% of the dog fleas contained, on average, not more than two or three cysticercoids per flea. When a dog or cat ingests an infected flea, the cysticercoid is released in the small intestine through digestion, establishes itself in the mucosa, and becomes an adult parasite in about 20 days. The longest survival time recorded for the parasite in cats is three years.

Geographic Distribution: The parasite exists wherever there are dogs and fleas.

Occurrence in Man: There are fewer than 150 cases of human infection reported in the literature; most are in young children, especially in the US and Europe. In Latin America, the infection has been observed in Chile (17 cases), Argentina, Uruguay, Brazil, Venezuela, Guatemala, Mexico, and Puerto Rico. The infection is so rare in humans that, when single cases occur, they are reported in almost all countries (Wijesundera and Ranaweera, 1989; Raitiere, 1992; Reid *et al*., 1992; Neafie and Marty, 1993; Brandstetter and Auer, 1994).

The Disease in Animals: *D. caninum* is the most common dog cestode in urban areas due to the almost universal presence of the intermediate host, the flea. The prevalence of infection with *D. caninum* in dogs is high, but varies worldwide. Prevalences of 45% were reported in 156 dogs autopsied in Nairobi (Wachira *et al*., 1993); 19.8% in 756 samples of dog droppings in Jordan (Abo-Shehada and Ziyadeh, 1991); 13.2% in 303 rural dogs in Uruguay (Cabrera *et al*., 1996); 9.2% in 315 rural dogs in Great Britain (Jones and Walters, 1992); and 1.1% in 3,329 dogs in Germany (Epe *et al*., 1993); also, it was found sporadically in 371 stray dogs in Switzerland (Deplazes *et al*., 1995). Several surveys of foxes conducted in Europe found a prevalence of 0.2% to 3.8%. The infection in cats is as prevalent as or more prevalent than in dogs, but is also variable. Prevalences of 23.8% were found in samples of the droppings of 52 cats in Nigeria (Umeche and Ima, 1988); 23% in 1,502 cats autopsied in South Africa (Baker *et al*., 1989); 20.7% in 58 cats autopsied in Spain (Calvete *et al*., 1998); and 1.4% in fecal samples of 1,147 cats in Germany (Epe *et al*., 1993).

The Disease in Man: Because of its epidemiological characteristics, human dipylidiasis affects mainly infants and young children. The symptomatology consists of digestive disorders, such as diarrhea and colic, irritability, erratic appetite, and insomnia; the infection is often asymptomatic. In a series of patients studied in Chile (Belmar, 1963), abdominal distension was almost always seen. Elimination of motile proglottids is the sign usually noticed by the patients' parents, and is sometimes the only manifestation of the infection. In about 25% of the cases, more than one parasite has been found.

The Disease in Animals: Dipylidiasis, like other cestodiases of dogs and cats, rarely has clinical manifestations. During an epidemiological survey, Barriga (1997) collected 1.1 kg of *D. caninum* upon purging an asymptomatic 13 kg dog with arecoline. Anal irritation or itching has often been attributed to the movement of gravid proglottids in the anal area, because some infected animals rub themselves on the ground as if trying to scratch themselves; however, the presence of inflamed anal sacs, which also causes similar symptoms, has not been confirmed.

Source of Infection and Mode of Transmission: Dogs and cats generally defend themselves against fleas by biting them and, frequently, by ingesting them. This behavior ensures continuation of the parasite's life cycle. Man is also infected by ingesting fleas infected with cysticercoids of *D. caninum.* Almost all cases of human infection are in very young children who live in homes with infected dogs or cats. The child accidentally eats the flea when kissing or biting the pet, or when the flea drops into his food or attaches itself to a wet pacifier.

Diagnosis: In humans and animals, diagnosis is based on microscopic observation of the gravid proglottids. These cestodes have, as a unique characteristic, two genital pores, one on each side of the proglottid. No other human cestode has this characteristic. *D. caninum* is whitish and resembles a melon seed (when expanded) or a grain of boiled rice (when contracted); it is highly motile and can often be seen crawling on the coat of infected animals or on the skin, diapers, or feces of an infected baby. Each proglottid contains a large number of eggs typical of cestodes, but arranged in groups of 5 to 20 in sacs known as oviferous capsules. For observing proglottids or eggs, better results are achieved by examining material collected from the perianal region than by examining the fecal matter.

Control: Prophylactic measures consist of eliminating fleas from the home and cestodes from pets. While recommended, watching small children to keep them from ingesting fleas is difficult.

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HYDATIDOSIS

ICD-10 B67 Echinococcosis

Synonyms: Echinococciasis, hydatid disease, hydatid cyst.

Etiology: The agent of this disease is the hydatid or larval stage of the cestodes *Echinococcus granulosus*, *Echinococcus multilocularis*, *Echinococcus oligarthrus*, and *Echinococcus vogeli.* While other species and subspecies of *Echinococcus* have occasionally appeared in the literature, their taxonomic status is doubtful or uncertain. The definitive hosts of *E. granulosus* are domestic dogs and some wild canids. The adult cestode lives attached deep inside the mucosal crypts of the definitive host's small intestine and is 3 to 6 mm long; it has 22 large hooks and 18 small hooks on the scolex and usually has just 3 proglottids, of which only the last is gravid. The gravid proglottid, containing several hundred eggs, detaches from the strobila, is expelled with the feces, and disintegrates in the environment. Each egg contains an embryo (oncosphere) with six hooks (hexacanth), which must be ingested by an intermediate host to continue its development. Intermediate hosts are sheep, bovines, swine, goats, equines, camelids (Asian and American), cervids, and man. The oncosphere is released in the small intestine of the intermediate host, passes through the intestinal wall, and is carried by the bloodstream to various organs, where it undifferentiates and then differentiates again to develop the larval stage, called the hydatid. After three weeks the hydatid measures 250 μm in diameter and has a central cavity. Around the fifth month, it measures approximately 1 cm and it is apparent that its wall consists of two layers: an external, cuticular or laminar layer, formed by numerous thin nacreous lamina that resemble the cross-section of an

onion, and another, internal layer, germinative or proligerous, which is a delicate cellular syncytium. The larval form of *E. granulosus* typically consists of a single cavity (is unilocular). The interior of the hydatid is filled with liquid. During the same period, brood capsules bud off from the germinative layer, and invaginated protoscolices, which constitute the infective agent of the parasite, develop within them. These capsules either adhere to the wall by means of a peduncle or float freely in the hydatid fluid. The capsules and the protoscolices that float freely in the hydatid fluid are known as "hydatid sand." Some hydatids do not form capsules, and sometimes the capsules do not form protoscolices: these are sterile larvae. In contrast, daughter hydatids with a two-layer wall like that of the mother sometimes form inside the hydatid. As the larva develops and the tissues of the host are compressed, the host responds with a fibrotic reaction, surrounding the larva with dense connective tissue, the adventitial layer. The hydatid surrounded by this connective tissue is the hydatid cyst. The most common localizations of these cysts are the liver (in about two-thirds of the cases) and the lungs (in about a fourth of the cases); on rare occasions they may become situated in some other organ, such as the kidneys, spleen, bones, and brain. The cycle is completed when a dog or other canid ingests the viscera of an intermediate host in which there are fertile hydatid cysts. The scolex attaches to the wall of the dog's small intestine and develops into an adult cestode that begins to produce infective eggs 47 to 61 days after infection. A single cyst can give rise to thousands of adult cestodes because of the large number of scolices. The species *E. granulosus* is polytypic, and morphological, biochemical, and biological variants have been found in different parts of the world. For example, in Great Britain, two strains occur: an equine strain whose development cycle involves horses and dogs, and an ovine strain that circulates between sheep and dogs. In addition to the differences in morphology and development in the different intermediate hosts, the two strains also differ in biochemical and physiological characteristics. Even though dogs are definitive hosts for both, it seems that the equine strain is not transmitted to sheep and vice versa. Doubts also exist about the equine strain's infectivity for man. In Latin America, except around Santa María, Rio Grande do Sul, Brazil, horses are rarely affected by the larval form of *E. granulosus*, in spite of their close contact with dogs. In the boreal region of the northern hemisphere, the strain of *E. granulosus* that circulates between wolves and the large deer *Rangifer* and *Alces* is transmitted with difficulty to domestic ungulates (Schantz, 1982). In Australia, three strains are distinguished; one circulates between the dingo and macropodid marsupials (wallabies, kangaroos), and the other two (one continental and the other from Tasmania) circulate between dogs and sheep but differ in some biochemical, morphological, and biological properties (Thompson and Kumaratilake, 1982). Studies in the former Soviet Union have shown that the strain circulating between dogs and sheep is not infective for swine, and the strain circulating between dogs and swine is not transmitted to sheep. Recent molecular biology studies have confirmed the presence of four genotypes in Argentina: the ovine, circulating between sheep and humans; the ovine from Tasmania, circulating in sheep and humans; the porcine in swine; and the camelid in humans (Rozenzvit *et al*., 1999). Similar work is being carried out on the other species (Rinder *et al*., 1997).

The adult form of *E. multilocularis*, sometimes identified as *Echinococcus alveolaris* or *Echinococcus sibiricensis*, measuring 1.2 to 3.7 mm, is somewhat smaller

than that of *E. granulosus.* It has 27 large hooks and 23 small hooks on the scolex. The species are distinguished by subtle characteristics of the mature proglottid and by the number and shape of the hooks on the scolex. The natural definitive hosts are foxes, chiefly the arctic fox (*Alopex lagopus*) and the red fox (*Vulpes vulpes*). The intermediate hosts are wild rodents, primarily species of the genera *Microtus*, *Clethrionomys*, and *Lemmus.* Domestic dogs and cats may also serve as definitive hosts when they enter the cycle by feeding on infected wild rodents. The rodents develop the hydatid in the liver after ingesting eggs deposited with the fecal matter of definitive hosts; in about 60 days, the hydatid contains infective protoscolices. Unlike the larva of *E. granulosus*, this hydatid has a weak cuticular layer that enables it to constantly form small exogenous brood capsules that invade and destroy the surrounding tissue. The vesicles are filled with a gelatinous liquid and generally lack protoscolices in humans. Due to its spongelike morphology, the cyst of *E. multilocularis* is commonly called a "multilocular" or "alveolar" cyst. The absence of protoscolices seems to indicate that man is not a satisfactory host because, when a cyst is transplanted from man to a suitable rodent, the cyst begins to produce them. When a fox, dog, or cat ingests an infected rodent, the protoscolices give rise to the development of adult cestodes, which begin producing infective eggs that are eliminated in the fecal matter in about 33 days.

The adult form of *E. oligarthrus* is about 2 to 3 mm long and consists of a scolex with 33 large hooks and 26 small hooks, an immature proglottid, a mature proglottid, and a terminal gravid proglottid. The definitive hosts are wild felids such as pumas, jaguars, jaguarundis, and lynxes. The intermediate hosts are wild rodents such as the agouti *Dasyprocta* and possibly other rodents as well. The hydatid of *E. oligarthrus* also forms daughter larvae, which are external, larger, and filled with liquid, with abundant protoscolices in man, and not invasive like those of *E. multilocularis*. This noninvasive cyst, which has multiple external compartments and abundant protoscolices, is generally called "polycystic."

The adult form of *E. vogeli* is 3.9 to 5.6 mm long, has 42 large hooks and 33 small hooks, and has been found in a wild canid (*Speothos venaticus*), which ranges from Panama to northern Argentina. The intermediate host is the local rodent *Cuniculus paca*, known as paca. The hydatid of *E. vogeli* is also polycystic and is differentiated from the hydatid of *E. oligarthrus* by the number and shape of the hooks on the protoscolices.

Geographic Distribution: *E. granulosus* is the most widespread of the species, with areas of high endemicity in southern South America (Argentina, southern Brazil, Chile, Peru, and Uruguay); the Mediterranean coast, especially Bulgaria, Cyprus, southern France, Greece, Italy, Portugal, Romania, Spain, and Yugoslavia; the southern part of the former Soviet Union; the Middle East; southwestern Asia (Iran, Iraq, and Turkey); northern Africa (Algeria, Morocco, and Tunisia); Australia; New Zealand; Kenya; and Uganda. In some of these countries, the incidence has recently diminished notably because of control programs.

The distribution of *E. multilocularis* is limited to the northern hemisphere. The parasitosis occurs in central and eastern Europe, the former Soviet Union, Turkey, Iraq, northern India, central China, some islands of Japan, several provinces of Canada, Alaska, and several north central states of the US. The most important endemic areas are the northern tundras of Europe and Asia and their American

extension, as well as central Siberia, the central Asian republics of the former Soviet Union, and central China. In Europe, infection with *E. multilocularis* occurs in Austria, Belgium, France, Germany, Liechtenstein, Luxembourg, Poland, and Switzerland (Eckert, 1996). Infections caused by *E. granulosus* and *E. multilocularis* may occur together in the same areas, as happens, for example, in some parts of the former Soviet Union, Alaska (US), and Canada.

E. oligarthrus and *E. vogeli* are present only in South and Central America. Although the areas of infection coincide, since the definitive host of *E. vogeli* exists only from Panama to northern Argentina, cases of polycystic hydatidosis outside this area are probably imported or due to *E. oligarthrus.* Moreover, this species was identified recently in northeastern Mexico (Salinas-López *et al*., 1996), and this is the first available report on it in North America.

Occurrence in Man: The prevalence of classic unilocular hydatidosis caused by *E. granulosus* varies considerably between geographic areas. The highest infection rates are recorded in countries with livestock industries, especially sheep raising, in rural areas, and among people of limited economic and cultural means. Information on the prevalence of human hydatidosis is often based on doctors' reports. But studies from Chile (Serra Canales *et al*., 1999) have shown that doctors' reports could represent just a quarter of the cases found by studying hospital admission or surgery records. Consequently, the published figures should be used advisedly. Moreover, it is necessary to distinguish between the infection, which may be asymptomatic, and the disease, which, by definition, is symptomatic. The most reliable sources of information on the incidence of the disease are the hospital records of surgical operations. In Latin America, the highest concentration of cases occurs in the Southern Cone of South America (Argentina, southern Brazil, the mountains of Peru, and Uruguay) (Arámbulo, 1997). In the 1960s, the annual incidence of surgical cases per 100,000 inhabitants was 1.0 in Peru, 2.0 in Argentina, 7.8 to 7.9 in Chile, and approximately 20 in Uruguay. However, these data paint an unrealistic picture, because prevalence refers to the total population of the country and not the rural population, which is the population at real risk for the infection. The prevalence of infection caused by *E. granulosus* in an endemic area of the Peruvian Andes was 9.1% in 407 individuals examined by imaging and immunoelectrotransfer (Western blot), 87% in 117 slaughterhouse sheep, and 32% in 104 dogs. The prevalence of human cases was five times higher than that reported in 1980, when a control program was suspended (Moro *et al*., 1997). In the IX Region of Chile, in the vicinity of the 38th south parallel, between 18 and 48 per 100,000 inhabitants have the human infection, and the prevalence in local slaughterhouses is about 40% for sheep and cattle and 15% for swine. The cost of treatment alone comes to US$ 300,000 a year (Gutierrez *et al*., 1992). According to official sources, the incidence of hydatidosis in Chile has declined in recent years, but a critical study of hospital cases found that the actual incidence in the period 1985–1994 fluctuated between 6.5 and 11.4 per 100,000 inhabitants. In other words, it was four times higher than the official figures reported (Serra Canales *et al*., 1999). The authors believe the apparent decrease is the result of problems in the reporting system. In southern Argentina, a 1994 survey found 16 cases (26.7 per 100,000), with a human serological prevalence of 1.3% and a parasitological prevalence of 2.3% in dogs (Larrieu *et al*., 1996). In southern Uruguay, 156 cases (1.6%) of cystic hydatidosis were recently diagnosed

in 9,515 individuals examined by ultrasound and serology (Carmona *et al*., 1998). The prevalence of infection in the general population can be determined by various diagnostic methods. In Chile, a series of 115,819 autopsies performed between 1947 and 1970 uncovered 359 cases of human hydatidosis (310 per 100,000), and 108 (204 per 100,000) in 53,014 autopsies of individuals who died violent deaths. These figures on the prevalence of the infection are 25 to 40 times higher than the estimated prevalence of the disease for the same period. In the other Latin American countries, hydatidosis is not a health problem; some countries have sporadic cases and others have not reported the disease in humans. There are endemic pockets in the US among inhabitants of Basque origin who breed sheep in the northern California area, among Eskimos in Alaska, and among the indigenous peoples of Arizona and New Mexico. However, a significant percentage of the cases in California may be imported; Donovan *et al*. (1995) found that 25 of 28 patients (89%) in Los Angeles had been born abroad and 19 were immigrants from the Near East or central Asia. The Mediterranean coast of Europe constitutes one of the areas of highest prevalence, comparable only to the Southern Cone of South America. In Asia, the highest prevalences of infection are found in the southwest (Iraq and Turkey), in the southern republics of the former Soviet Union, and in China and Japan. In six provinces of China, 26,065 surgical cases of cystic hydatidosis were reported between 1951 and 1990, the majority after 1980. An extensive survey in agricultural areas found rates of infection of 0.5% to 4.5% in humans by imaging, 3.3% to 90% in sheep, and 7% to 71% in dogs (Chai, 1995). A serologic study in northwestern Mongolia found a 5.2% rate of infection in 334 seminomadic shepherds (Watson-Jones *et al*., 1997). In Africa, the areas with the highest rates of infection are in Kenya and in the northwestern part of the continent. A recent survey carried out in Libya with ultrasound techniques found 339 abdominal infections in 20,220 individuals (1.7%); 233 (69%) of them were also positive with the enzyme-linked immunosorbent assay (ELISA) (Shambesh *et al.*, 1999). Oceania is another area of high prevalence; the morbidity rate in humans in Australia is estimated at 1.2 per 100,000 inhabitants and 2.3 per 100,000 inhabitants in New Zealand before control programs were set up.

Occurrence of the human infection caused by *E. multilocularis* was thought to be sporadic, with low endemicity. From 1970 to 1980, 91 cases were diagnosed in France, equaling a prevalence rate comparable to the prevalences in Germany and Switzerland. The only region with a high prevalence (1% of the population) was Rebun Island, Japan, where effective control measures were established. However, since 1990 there has been a significant increase in the prevalence of human infection caused by this parasite in the northern part of Eurasia (Romig *et al*., 1999). In Europe, the prevalence of *E. multilocularis* in foxes is 1% to 50%. The infection in dogs and cats is rare (<1%), and the prevalence in humans is 0.02 to 1.4 cases per 100,000 persons in most cases. Although it is not a very common infection, it is considered very important because mortality is higher than 90% without treatment, and treatment is very expensive (Eckert, 1996). In 1990, a study of 606 individuals drawn from the general population of the province of Gansu, China, found 8.8% with positive serology for the parasite. A study using ultrasonography and serology conducted the following year confirmed the infection in 65 of 1,312 people (5%). Examination of domestic dogs found *E. multilocularis* in 10% (Graig *et al*., 1992). Subsequently, 584 cases were diagnosed in seven provinces of China; it is estimated

that the prevalence ranges from 2.8% to 19.2%, and morbidity ranges from 2.4% to 5% (Jiang, 1998).

Up to 1998, 86 cases of human polycystic hydatidosis had been diagnosed in Latin America, in the region between Nicaragua and Argentina; 32 were attributed to *E. vogeli*, 3 to *E. oligarthrus* (2 orbital cases in Suriname and Venezuela, and 1 cardiac in Brazil), and 51 whose causal agent could not be determined because the hooks of the protoscolices were not found (Basset *et al*., 1998). The cases of human polycystic hydatidosis reported in Argentina, Chile, Costa Rica, Nicaragua, and Uruguay are probably caused by *E. oligarthrus* or are imported cases of *E. vogeli,* because the definitive host of the latter species does not exist in those countries (D'Alessandro, 1997).

Occurrence in Animals: In all areas where the prevalence of human infection by *E. granulosus* is high, a high rate of parasitism in animals, both the intermediate and definitive hosts, is to be expected. Some specific examples were mentioned in the previous section. In dogs in endemic areas, infection rates greater than 30% are commonly found. In sheep, the most important intermediate host in many parts of the world, rates of infection are also high. The rate of hydatid cysts found in slaughterhouses in hyperendemic areas of Latin America varies from 20% to 95% of sacrificed animals. The highest rates are found in rural slaughterhouses, where older animals are slaughtered. High prevalence rates are also found in cattle, swine, and goats. In Argentina and Uruguay, hydatid cysts have not been found in horses; in Chile, the prevalence is low (0.29%), while in an area of Rio Grande do Sul, Brazil, it is about 20%. According to some parasitologists, the strain that parasitizes horses is a special biotype of *E. granulosus* that has adapted itself to this animal species (see Etiology). In other parts of the world, such as the Middle East, in addition to high rates in sheep, a high prevalence is found in camels, which are intermediate hosts, and in dogs, jackals, and wolves, which are definitive hosts. Buffaloes are important intermediate hosts in some countries.

The prevalence of the infection caused by *E. multilocularis* in the natural definitive host, the fox, can reach high percentages in some localities; in dogs in Alaska, US, it is almost 6%. In rodents, the intermediate hosts of *E. multilocularis*, the infection rate is relatively low and varies from 2% to 10%.

Little is known of the prevalence of *E. oligarthrus* infection in wild felids (the definitive hosts) and rodents (the intermediate hosts). Infection by *E. vogeli* was found in 96 of 425 pacas (*Cuniculus paca*), the main intermediate host, caught in Colombia (Rausch *et al.*, 1981).

The Disease in Man: The hexacanth embryo of *E. granulosus* generally travels in the bloodstream until it colonizes a part of the liver or lung, and remains there for years, growing slowly and silently, without causing major tissular reactions or clinical signs. The symptoms generally appear when the larva grows large enough to compress or erode the neighboring tissues or ducts and interfere with their function. Absorption of parasitic antigens by the host often sensitizes the individual and may cause hypersensitivity phenomena. Because the *E. granulosus* cyst generally has a single compartment, as opposed to those of the other species, human infection by this parasite is usually called "cystic" or "unilocular" hydatidosis. Many cysts are asymptomatic throughout the infected individual's life and are discovered only at autopsy, during surgery, or in radiographs, all related to other causes. A review of

almost 190,000 autopsies performed in Chile from 1947 to 1984 found that 363 of 568 cases of cerebral hydatidosis (64%) and 79 of 116 cases of cerebral cysticercosis (68%) had been discovered during these autopsies. From this it is clear that the symptomatology of unilocular or cystic hydatidosis depends on the location of the cyst and its size. The most common location is the liver (65% to 70% of cases), followed by the lungs (about 25% of cases). There are indications that the localization of the hydatids may depend on the strain of *E. granulosus.* Thus, in the case of wild *E. granulosus* of the boreal region, which circulates between wild cervids and wolves, the lung localization predominates in humans, and the disease is generally more benign than that caused by the *E. granulosus* strain of the domestic cycle. In a small percentage of patients, the cysts localize in other organs or tissue. In locations where growth of the cyst is not restricted by anatomical structures, it can reach a very large size and contain several liters of fluid. For example, rupture of the cyst by external trauma in hypersensitive patients can result in anaphylactic shock and pulmonary edema caused by rapid absorption of the antigen through the peritoneal or pleural serosa. Another serious consequence of cyst rupture is hydatid seeding within the abdominal or pleural cavity, and the formation of many new cysts in the serosa. Rupture of a cyst can also cause arterial embolisms in the lungs and sometimes in other organs. Early diagnosis in man is important for prevention of complications and rupture of the cyst, with its consequent seeding in multiple locations. For inoperable cases, treatment with mebendazole for several years is used, resulting in reduction of the cysts in several cases.

In hepatic hydatidosis, most cysts (approximately 75%) are located in the right lobe; they may be situated either deep in the parenchyma or superficially, below Glisson's capsule. The intraparenchymatous cysts cause atrophy of the surrounding tissue and, through pressure on the veins and biliary passages, provoke congestion and biliary stasis, which may be complicated by a secondary infection. A subcapsular cyst may grow upward (anterosuperior cyst) and adhere to the diaphragm, and the cyst may even cross the diaphragm and open into the thoracic cavity, or it may grow toward the peritoneal cavity, where it can adhere to and empty into the hollow abdominal viscera. In a study of 677 patients who had surgery for hepatic hydatid cysts, Hernando *et al*. (1996) found that the most common clinical manifestations were dyspepsic symptoms (60%), hepatomegaly or a palpable mass in the right hypochondrium (58%), and pain (46%). Most cysts were solitary (66%) and in the right lobe (65%). The most common complication of surgery was a biliary fistula; the average period of hospitalization was 25 days and the mortality rate was 1.6%. The average age of the patients was about 39 and the prevalence was the same in both sexes.

The second most common location is the lungs. The cyst is generally located in the lower lobe, and more frequently in the right lung than in the left. In the lung, as in the liver, a cyst's presence may be asymptomatic, or it may be manifested by symptoms such as pain in the affected side of the chest (especially if the cyst is peripheral), dry cough, hemoptysis, vomiting if the cyst ruptures, and sometimes deformation of the thorax. Expectoration of the cyst (hydatid vomica) occurs with some frequency in pulmonary hydatidosis and may be followed by recovery. Hueto Pérez de Heredia *et al*. (1999) studied the clinical and epidemiological characteristics of 40 patients with thoracic hydatidosis, 32 of whom had pulmonary cysts.

Bone hydatidosis causes destruction of the trabeculae, necrosis, and spontaneous fracture. This localization is estimated to occur in 1% of the cases. Hydatidosis of

vital organs, such as the central nervous system, heart, and kidneys, has a grave prognosis. The latency period of cerebral hydatidosis is relatively short, about eight months in the general population and four months in children. In Spain (Jiménez-Mejías *et al*., 1991), most patients (74%) had a solitary cyst, 74% in the right lobe, and in half the cases the cyst was intraparenchymatous.

The disease caused by *E. multilocularis*, or alveolar hydatidosis, is progressive and malignant. In the vast majority of cases, the multilocular cyst is located in the liver and rarely in other organs. In general, the cyst starts as a small vesicle, which, by exogenous and endogenous proliferation of the germinative membrane, forms multiple vesicles in all directions, producing its multilocular appearance. After a time, the center necroses and the cyst becomes a spongy mass consisting of small irregular cavities filled with a gelatinous substance. Metastasis can occur, giving rise to secondary cysts in different organs. The symptomatology is similar to that of a slowly developing mucinoid carcinoma of the liver. Alveolar hydatidosis is afebrile if there is no secondary infection, but causes hepatomegaly and often splenomegaly. In more advanced stages, ascites and jaundice appear as a consequence of intrahepatic portal hypertension. The course of the disease is always slow, and signs and symptoms appear after many years. The average age in a group of 33 cases in Alaskan (US) Eskimos was 53 years, and the investigators (Wilson and Rausch, 1980) estimate that 30 years had passed from the time of infection to the appearance of symptoms. The most common objective signs were hepatomegaly and a palpable abdominal mass derived from the liver. By the time symptoms were apparent, the majority of the patients could not be operated on. The disease is usually fatal without an organ transplant.

In a study of 72 human cases of *E. vogeli* or *E. oligarthrus* polycystic hydatidosis, D'Alessandro (1997) found that in 80% of the cases the lesions were limited to the liver or other organs. The most frequent signs were palpable, hard, round masses in the liver, hepatomegaly, bulging abdomen, pain, significant weight loss, and fever. All the cases were fatal, and in 25% there were signs of portal hypertension; 10% of the cases were asymptomatic. In a study of seven human cases of polycystic hydatidosis caused by *E. vogeli*, Meneghelli *et al*. (1992) found that the most common signs were abdominal pain, hepatomegaly, jaundice, weight loss, anemia, fever, hemoptysis, palpable abdominal masses, and portal hypertension. In four cases, hepatic calcifications were observed. The most frequent localizations were the liver (six cases), the lungs (two), the mesentery (two), the spleen (one), and the pancreas (one).

To appreciate the importance of hydatidosis in public health, it should be remembered that the principal treatment is surgery, and hospitalization is lengthy; about 60% of those operated on cannot return to work until about four months after leaving the hospital, and approximately 40% are incapacitated for six or more months.

The Disease in Animals: Clinical symptoms are not seen in dogs parasitized by the adult form of *E. granulosus*. Barriga and Al-Khalidi (1986) obtained more than 5,000 parasites from the intestine of an asymptomatic 8.5-kg dog. Infection with a large number of parasites probably causes enteritis. In the domestic intermediate hosts of *E. granulosus*, no definite clinical symptomatology has been found, even in cases of multiple cysts in the liver and lungs. In contrast, some studies indicate that parasitized sheep become fatter, which would make them more attractive to predators and hinder their escape.

The confiscation of viscera with hydatid cysts, especially livers, accounts for significant economic losses. This procedure results in the loss of an estimated 1,500,000 pounds of viscera annually in New Zealand. In Uruguay, approximately 60% of all beef livers are confiscated because of hydatidosis and fascioliasis. It has been estimated that the viscera of 2 million cattle and 3.5 million sheep are confiscated every year in the Southern Cone, causing losses estimated at US$ 6.3 million in Argentina and US$ 2.5 million in Chile. The costs of medical and surgical care of human patients must be added to the losses suffered by the livestock economy. Hospitalization is usually lengthy (about seven weeks). The cost of hospitalization for a surgical case of hydatidosis, without complications, is from US$ 1,500 to $2,000 in Argentina and Chile.

Foxes infected by *E. multilocularis* do not manifest clinical symptoms, even when harboring an enormous number of parasites in their intestines. On the other hand, infection by the larval form in arvicoline rodents is often fatal when the cystic burden is large (Schantz, 1982).

Source of Infection and Mode of Transmission: The dog-sheep-dog cycle is the most important cycle for maintenance of the parasitism in the endemic areas of the southern part of South America and many other areas of the world. Sheep are the most important intermediate hosts of unilocular hydatidosis caused by *E. granulosus* for several reasons: the infection rate is generally high among these animals, 90% or more of their cysts are fertile, they live in close association with dogs, and, since they are often sacrificed for household consumption on ranches, the viscera are customarily fed to dogs. Also the Southern Cone of South America is a region with a high concentration of sheep: approximately 50% of the total sheep population lives on 10% of the total land area of the continent. Finally, the number of dogs on sheep ranches is high.

Sheep and other intermediate hosts contract hydatidosis by grazing on pastures contaminated with dog feces containing eggs of the cestode. Those eggs are deposited directly on the grazing land or are carried by rain or wind. The dogs in turn are infected by eating viscera that contain fertile cysts (with viable protoscolices). Man is an intermediate host and plays no role in the transmission of the parasite, unless he is eaten by a carnivore. Nevertheless, his sanitary habits make him the main agent responsible for perpetuating the infection by feeding dogs viscera that contain hydatid cysts. The adult cestode of *E. granulosus* can live in a dog's intestine for about a year, but it remains fertile for just 6 to 10 months. Therefore, theoretically the infection would die out if man ceased reinfecting dogs by feeding them raw viscera. Domestic animals that serve as secondary hosts could still become infected for a time, since the eggs of *Echinococcus* are resistant to environmental factors, but the infection cycle would be halted if dogs were prevented access to the infected viscera.

A gravid proglottid of *E. granulosus* contains a very small number of eggs (from 200 to 800) compared with those of other tapeworms, which contain many thousands. It is estimated that only one segment of *E. granulosus* is eliminated every two weeks (Lawson and Gemmell, 1983). This low biotic potential of *E. granulosus* is compensated for by the high rate and intensity of infection in the definitive host and by the asexual multiplication of the larva in the intermediate host. The survival time and dispersion of the eggs are of great epidemiological interest. The eggs have little

resistance to desiccation and extreme temperatures. In the laboratory, the eggs of *E. granulosus* can survive in water or damp sand for three weeks at 30°C, 225 days at 6°C, and 32 days at 10–21°C (Lawson and Gemmell, 1983). After 10 days, radial dispersion up to 80 m from the place the feces were deposited has been confirmed for eggs of other taeniids; they may be able to disperse even greater distances with the aid of mechanical vectors such as carrion birds and arthropods. The physical composition of the soil, its porosity, and the kind of vegetation cover also help determine the length of time that the eggs survive.

As we have said, man is an accidental host, and his direct contact with dogs is important. The gravid proglottids are found primarily on the surface of fecal matter, and they can accumulate in the perianal region, where they disintegrate and release the eggs. The dog carries the eggs on its tongue and snout to different parts of its body, and a person's hands can become contaminated by touching the animal. Close contact with dogs and deficient personal hygiene practices, such as failure to wash the hands before eating, are important factors in the transmission of the infection from dogs to humans. Another important source of human infection can be vegetables and water contaminated with infected dog feces. Coprophagic flies may also serve as mechanical vectors of the eggs.

Although hydatidosis is usually an infection of the rural population, infected dogs and human cases of the disease occur in urban areas. The difference in infection rates between religious and ethnic groups is merely a reflection of their relationship with dogs. In Lebanon, for example, a higher prevalence of hydatidosis has been observed among Christians than among Moslems because the Koran asserts that dogs are "dirty" animals. Long-standing cultural and religious habits account for the high and unusual incidence of hydatidosis among the members of the Turkana tribe of northwestern Kenya. This pastoral tribe, which includes about 150,000 persons, has attracted the attention of researchers. A large number of dogs live with the members of this tribe, and the dogs have a high rate of infection. The Turkana use dog feces as a lubricant and as medicine, and they either do not bury dead persons or cover them only with a thin layer of earth, making it possible for the dogs to eat the cadavers (Macpherson, 1983). More than 1,500 Turkana with hydatidosis were operated on between 1965 and 1980; annual incidence, based on hospitalized cases of the disease, varies from 220 per 100,000 inhabitants in the northern part of the district to 18 per 100,000 in the southern part (French and Nelson, 1982). In contrast to findings in 111 patients with pulmonary hydatidosis in Uruguay (Yarzábal and Capron, 1971), whose cysts did not contain protoscolices, 60% of 154 cysts in Turkana patients were fertile.

In the Holarctic region of North America—Alaska (US) and Canada—unilocular hydatidosis exists in a wild cycle that develops between the wolf (*Canis lupus*) and several cervid species. Another wild cycle independent of the domestic cycle has been described in Australia between dingoes and marsupials such as wallabies and kangaroos. The strobilar form of *E. granulosus* has been found in Argentina in three species of foxes of the genus *Dusicyon*, and the larval form has been found in the European hare. In contrast to what is occurring in the northern region of the Americas, wildlife infection in Argentina appears to derive from the domestic cycle.

Alveolar hydatidosis (*E. multilocularis*) has many natural foci in the northern hemisphere; the parasite circulates between foxes of the genera *Alopex* and *Vulpes*, the definitive hosts, and arvicoline and microtine rodents, the intermediate hosts.

Man can come into accidental contact with the eggs of the cestode when handling dead foxes or drinking water from streams contaminated with the feces of infected foxes. Domestic dogs and cats can carry the infection into the home when they hunt wild rodents. A community in which arvicoline rodents and dogs abound can become a hyperendemic focus, as has happened in some Eskimo villages of the North American boreal tundra. Coprophagous flies can act as mechanical transfer hosts of the eggs. A study carried out in Auvergne, France, found the infection in 2.4% of 943 captured *Arvicola terrestris scherman* rodents. In the area where they were captured, the prevalence varied from 0% to 4.6%, which suggests that the distribution is focal. Only 2 of the 23 animals (8.7%) had fertile larvae. In the same region, 8.5% of 70 foxes (*Vulpes vulpes*) harbored the strobilar form, and five human cases occurred in 10 years (Pétavy and Deblock, 1983).

The cycles of *E. vogeli* and *E. oligarthrus* are exclusively wild. Man probably becomes infected accidentally by eggs of *E. vogeli* through the feces of dogs that are fed the viscera of the paca or with eggs of *E. oligarthrus* from the feces of cats that eat infested rodents.

Diagnosis: A diagnosis of human hydatidosis is suspected based on the clinical symptoms and epidemiological circumstances. Imaging methods such as radiography, computerized tomography, ultrasonography, and scintigraphy are used. While they do not confirm the diagnosis, they are very helpful to the specialist. Ultrasonography is the first choice because it is economical, noninvasive, simple, and accurate and reveals developing cysts that generally cannot be found with X-rays (Suwan, 1995). Numerous immunobiologic tests have been used in the diagnosis of human hydatidosis by *E. granulosus*, among them Casoni's intradermal test, complement fixation, indirect hemagglutination, latex agglutination, inmunoelectrophoresis, electrosyneresis, and double diffusion to detect antibodies against the arc 5 antigen. Practically all have been displaced by ELISA and the immunoelectrotransfer or Western blot test. Casoni's intradermal test is not very sensitive and is nonspecific for the diagnosis. While it was once used for epidemiological surveys, the collection of drops of blood on filter paper now makes it possible to use serologic techniques that are much more sensitive and specific on a large scale. The complement fixation, indirect hemagglutination, and latex agglutination tests have no operational advantage over ELISA and are much less specific or sensitive. The techniques based on observation of arc 5 were abandoned when it was found that the respective antigen was specific not for *Echinococcus* but for many cestodes. Navarrete *et al*. (1995) found that ELISA diagnosed 96.6% of hydatidosis patients but cross-reacted with taeniasis and ascariasis; indirect hemagglutination diagnosed 86% of patients but also gave cross-reactions, and the double diffusion test for arc 5 diagnosed 79% of patients but did not give false positives. Only ELISA gave false positives. Moreover, the test with selected antigens is not only highly sensitive and specific but can also distinguish among infections caused by different species of *Echinococcus*. ELISA for *E. multilocularis*, for example, showed a sensitivity of 93% and a specificity of 97%, in contrast to another ELISA for *E. granulosus* that showed a sensitivity of 89% and a specificity of 99% (Helbig *et al*., 1993). But there seem to be wide variations in the sensitivity and specificity of the test among different laboratories. For example, Navarrete *et al*. (1995) found, in Valdivia, Chile, that 28 of 29 patients (96.5%) with hydatidosis confirmed by surgery showed posi-

tive reactions to ELISA, and taeniasis and ascariasis patients showed false positives; but Arienti *et al*. (1996) reported that ELISA was positive in just 62 of 176 surgery patients (35.2%) in Córdoba, Argentina, and they found no false positives. The differences do not seem to be due to a variation in the methods or composition of the antigenic extracts used (Coltorti and Cammarieri, 1993). More recent reports compared ELISA with antigen electrotransfer and attributed an 82% specificity to ELISA and a 94% to 97% specificity to the transfer test (Poretti *et al.*, 1999). More recently, the polymerase chain reaction has also been used to detect nucleic acids from the parasite in patients' bloodstreams (Kern *et al*., 1995).

Results of all the tests vary according to the location of the cyst and its physiological state. The immunodiagnostic tests seem to be less sensitive for detecting pulmonary than hepatic hydatidosis. Several investigators are looking for antigens characteristic of fertile or live cysts, since these cysts are the only ones that can cause secondary hydatidosis. Knowledge of whether a cyst is sterile or dead enables the doctor to be more conservative in treatment.

Even though there is no reason why the immunological methods for diagnosing cysts cannot be adapted to domestic animals, there apparently has been no incentive to do so. The traditional method of diagnosing hydatidosis in these species is postmortem examination in slaughterhouses or packing plants.

Intestinal echinococcosis in the definitive hosts is traditionally diagnosed by administering a strong purgative, generally arecoline hydrobromide, and searching for the parasite in the feces. The maximum effectiveness of this technique is about 65% if both the feces and the vomit are examined. Besides being slow and tedious, this method is dangerous because the eggs of *Echinococcus* are infective when they are eliminated. There is evidence that intradermic reactions may be positive in infected dogs (Barriga and Al-Khalidi, 1986), but the discovery, using ELISA, of circulating antibodies has a sensitivity of just 61% (Gasser *et al*., 1994). In recent years, investigators have attempted to find antigens to the parasite in droppings (coproantigens) by using ELISA with monoclonal antibodies and through polymerase chain reactions. The specificity and sensitivity of the former test were 95% to 99% and 80% to 93%, respectively. The specificity and sensitivity of the latter were 100% and 94%, respectively (Deplazes and Eckert, 1996).

Control: At present, conventional control measures consist of: 1) educating the rural population about hydatidosis and its control; 2) centralizing the slaughtering of animals for food in units with veterinary control; 3) ensuring sanitary conditions for slaughtering done on ranches and preventing dogs' access to raw viscera; 4) reducing the number of dogs on the ranches and treating them for *Echinococcus* on a regular basis. A fifth measure has recently been added: looking for human hydatidosis during primary health care visits. This has made it possible to diagnose many unsuspected cases and interest the population in the control campaign. Recently, joint and coordinated implementation of these health measures, both medical and veterinary, has resulted in noteworthy improvement in the results of the control campaigns.

One of the first examples of organized control was the campaign on Cyprus, which was carried out only in the area controlled by the Government of Cyprus; certain areas of the island remained uncontrolled. The activity was initiated in 1971 with a vigorous attack phase directed essentially at dogs: in two years, two-thirds of the estimated 45,000 dogs were sacrificed, and the rest were treated 3 or 4 times a

year. The parasite disappeared, and the campaign was suspended in 1985. Studies carried out in the period 1993–1996 showed that the parasite had returned in 20% of the communities checked. A consolidation campaign was then initiated, this time emphasizing both control of the intermediate hosts and treatment of dogs. The campaign carried out in Tasmania, Australia, reduced the rate of infection in dogs from 12.6% in 1965–1966 to 0.09% in 1981–1982, and the rate in sheep from 52.2% in 1966–1967 to 0.7% in 1981–1982. New cases of human hydatidosis fell from 19 in 1966 to 4 in 1982; in practice, the disease was no longer found in young people (Australia, 1973). In 1991, however, hydatid cysts were found in cattle in the northern part of the state, where the parasitism was thought to have been eradicated. In Iceland, health education and a highly motivated population were the main factors in the success of the campaign to eradicate the infection. The main objective of the program was to develop an understanding of the problem and a sense of responsibility in the people. The campaign that resulted in the eradication of *E. granulosus* in New Zealand has been described by Gemmell (1990). Campaigns for control on islands, such as Cyprus, Iceland, New Zealand, and Tasmania, in Australia, have shown that the area under control must remain totally closed to the introduction of new definitive or intermediate hosts; otherwise, the initial phase of attacking the problem must be followed by a permanent, indefinite consolidation phase (Economides *et al*., 1998). Observations in Bulgaria also indicate that, even if complete eradication is achieved, control activities should continue to ensure that the infection does not recur. The annual incidence of human hydatidosis in Bulgaria in 1950–1962 was 6.5 per 1,000 inhabitants; that provided the impetus for a control campaign from 1971 to 1982, which decreased the figure to 2 per 100,000. Administrative and economic problems between 1983 and 1995 necessitated suspension of the control measures, and the incidence returned to the previous levels (Todorov and Boeva, 1999). In Peru, suspension of the control programs in a hyperendemic area was associated with a five-fold increase in the incidence of the human infection (Moro *et al*., 1997).

In Latin America and other developing areas where socioeconomic and cultural conditions differ from those in Iceland, New Zealand, and Tasmania (Australia), the relative effect of each known control procedure must be evaluated to adapt them to the environment, or new procedures must be found. Regional programs for the control of hydatidosis are being carried out in four Latin American countries (Argentina, Chile, Peru, and Uruguay). Programs have been organized in several Argentine provinces. For example, in the control program being carried out in Río Negro, in the southern part of the country, the canine population is subject to diagnostic treatment or deparasitization, the infection in sheep is being detected and controlled in the slaughterhouses, classes are being taught in the schools, community health education is being promoted through the media, and human cases are being sought out, reported, and treated. Between 1979 and 1992, canine echinococcosis was reduced from 41.5% to 4.2%, ovine hydatidosis from 61% to 13%, and the human infection in children age 10 and younger from 64 per 100,000 to 4.5 per 100,000 (Larrieu *et al*., 1994). China officially initiated a national program for the control of hydatic disease between 1992 and 1995, based on education, improvement of sanitation in slaughtering livestock, and deparasitization of dogs (Chai, 1995).

While the control of hydatidosis does not include the benefit of a system of immunization of the hosts, a vaccine against development of the larva in intermediate

hosts is in the final stages of evaluation (Lightowlers *et al*., 1996). This vaccine is highly effective, but marketing problems have created a roadblock to its widespread use.

With regard to individual human protection, the following are recommended: avoiding close contact with dogs that may carry the eggs of the parasite on their tongues or coats and avoiding ingestion of raw vegetables and water that may have been contaminated with the feces of infected dogs. This is particularly important in the household gardens of sheep ranches where local dogs roam and sometimes defecate.

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HYMENOLEPIASIS

ICD-10 B71.0

Etiology: The agents of this disease are the cestodes *Hymenolepis nana* and *Hymenolepis diminuta.* Divergent opinions exist among parasitologists with respect to the nomenclature of *H. nana*, which infects man as well as rodents, particularly mice. Some consider *H. nana* in mice a subspecies and assign it the name *H. nana* var. *fraterna*, and *H. nana* var. *nana* in humans; others maintain that both parasites are biological strains of a single species, physiologically adapted to particular hosts but capable of causing cross-infections. Experimental and epidemiological observations support a noteworthy host specificity in both the human and murine parasite. Although children have been infected experimentally with the parasite of rodent origin and rodents have been infected with the parasite of human origin, human infection always occurs more easily with the human cestode. From the epidemiological standpoint, most human infections with *H. nana* come from other people. In fact, there does not seem to be strong evidence of transmission of the infection from rodents to man in nature. Moreover, there is no correlation between the rates of human and rodent infection in the same region. Over the last decade, the names *H. nana* var. *fraterna* and *H. fraterna* have hardly appeared in the literature.

The cycle of *H. nana* is direct in most human infections, not requiring the intervention of an intermediate host. In these cases, man acts as both definitive and intermediate host. The adult parasite is small, very narrow, 2.5 to 4 cm long by 1 mm wide, and translucent, so it is difficult to see. The scolex has hooks (is "armed"), and the body is composed of some 200 proglottids wider than they are long. The terminal gravid proglottids contain 80 to 180 eggs each. These proglottids disintegrate in the intestine of the host, and the eggs, now infective, are carried with the feces to the external environment. When another human host ingests the embryonated eggs, the oncosphere (hexacanth embryo) is released in the upper part of the small intestine, penetrates the villi, and, in about four days, changes into a cysticercoid larva. The larva has an invaginated scolex like the cysticercus, but it is microscopic and solid, not vesicular like the cysticercus. The cysticercoid ruptures the villus, travels to the lumen of the intestine, and attaches itself to the upper ileum, where it reaches the adult phase about 30 days after infection. It then begins to release eggs, reinitiating the cycle. The size of the adult parasites is partly determined by the number of parasites coexisting in the intestine: the more parasites, the smaller is each individual. This is attributed to competition for essential nutrients and is known as the crowding effect. While the adult larva of *H. nana* lives just a few weeks, the infection can continue because the cestode is replaced with new infections or by autoinfection. Endogenous autoinfection is believed to be a common mode of re-infection for man: some of the cestode's eggs hatch inside the intestine, producing cysticercoids which give rise to new adults; the entire cycle occurs without the larva leaving the host. But the actual occurrence of autoinfection in man requires study because it does not occur in rodents (see below). When the eggs eliminated with the feces of a definitive host are eaten by the larvae of fleas or cereal or flour beetles, the cysticercoid develops in the intestine of those arthropods. These intermediate hosts continue their development with the cestode larva, which is infective for the person or rodent that eats it. *H. nana* in rodents grows especially well in mice, with more difficulty in rats, and has the same life cycle described above.

H. diminuta is a cestode of rodents, in particular rats, and, rarely, man. The adult is found in the small intestine of rats and, more rarely, mice. It has a hookless scolex (is unarmed) and approximately 1,000 proglottids, wider than they are long, and measures 20 to 60 mm long and 4 mm wide in the distal portion. The embryonated eggs are eliminated with rodent fecal matter and must be ingested by an intermediate host for the oncosphere to develop further. The principal intermediate hosts are larvae of fleas (*Nosopsyllus* and *Xenopsyllus*) and of cereal beetles (*Tribolium* and *Tenebrio*), but different coprophilic arthropods, as well as several species of coleopterans, lepidopterans, myriapods, and cockroaches can support the larva's development. The egg hatches in the intestine of these arthropods, and the oncosphere penetrates the coelomic cavity, where it changes into a cysticercoid larva. When the infected arthropod is ingested by a rodent, the cysticercoid disinvaginates its scolex, attaches to the mucosa of the small intestine, and develops into an adult cestode in about three weeks.

Geographic Distribution and Occurrence: The two species of *Hymenolepis* that infect man have worldwide distributions. The hymenolepiasis caused by *H. nana* is the most prevalent human cestodiasis in the world. In Chile, 49.6% of 2,426 intes-

tinal cestodiases confirmed between 1961 and 1971 were caused by *H. nana*. However, its prevalence is highly variable. A random sample of reports obtained from all over the world in the last decade yielded the following findings: 24% of the infections in 315 rural children and 18% in 351 urban children examined in Zimbabwe (Mason and Patterson, 1994), 21% in 110 preschool children in Peru (Rodríguez and Calderón, 1991), 16% in 1,800 children in Egypt (Khalil *et al*., 1991), 8.8% in 147 children in daycare centers in Botucatu, São Paulo, Brazil (Guimarães *et al*., 1995), 8.7% in 381 apparently healthy people in Bolivia (Cancrini *et al*., 1988), 8% in 266 rural children in Honduras (Kaminsky, 1991), 2% in 100 children in orphanages in Egypt (Makhlouf *et al*., 1994), 2% in 146 children in a hospital in Canada (Kabani *et al*., 1995), 0.4% in 280 samples from the general population in Nigeria (Agi, 1995), 0.4% in 219 school children in Chile (Navarrete and Torres, 1994), 0.4% in 216,275 fecal samples sent for parasitological examination in the US (Kappus *et al*., 1991), 0.03% in 52,552 patients in a hospital in Seoul, Republic of Korea (Lee *et al*., 1994), and 0.008% in more than 3 million fecal samples taken in Cuba between 1981 and 1995 (Suárez Hernández *et al*., 1998).

In general, the prevalence is higher in urban than in rural environments, and in children's institutions, such as orphanages, daycare centers, boarding schools, and other schools where children are crowded together and at risk for acquiring the infection from their companions. The prevalence in rodents can also be high in certain places: in Santiago, Chile, it was found that 7.8% of 128 samples examined were infected, and in Bombay, India, that 14.5% were infected. But the correlation between the rates of murine and human infection has not been proven.

H. diminuta is a common cestode in rats, less common in mice, and infrequent in man. In the Republic of Korea, the parasite was found in 14 of 43 captured *Rattus norvegicus* (33%). Most texts indicate that about 200 cases of hymenolepiasis caused by *H. diminuta* in man have been reported worldwide. Between 1989 and 1999, six human cases were reported in the literature, one each in India, Italy, Jamaica, Spain, the US, and Yugoslavia. During that same period, one case was found in Chile in more than 70,000 fecal examinations, but prevalences of 0.3% were reported in 1,050 examinations in São Tomé and Príncipe in western Africa, and 4% in 900 examinations in Minas Gerais, Brazil.

The Disease in Man and Animals: Hymenolepiasis occurs mainly in children. The parasitosis is asymptomatic in some cases, but in others it produces clinical signs. Of 200 infected children in Egypt, 84% had symptoms; in 62% of these cases, the patient's body weight was below the third percentile (Khalil *et al*., 1991). A study of 325 infected children in Mexico found that the most important and consistent symptoms in the children infected only by *H. nana* were abdominal pain, decreased appetite, and irritability, but weight loss, meteorism, and flatulence were also present. The symptoms varied very little with the parasite load. In cases of concomitant parasitism with *Giardia intestinalis*, one of the most common symptoms is diarrhea (Romero-Cabello *et al*., 1991). In 250 infected children in Cuba, the major symptoms were abdominal pain, diarrhea, and anorexia (Suárez Hernández *et al*., 1998). Anxiety, restless sleep, and anal or nasal pruritus are frequently attributed to *H. nana* infections; eosinophilia greater than 5% has been observed in about 30% of the cases. The prepatent period lasts from 2 to 4 weeks.

In human infections, *H. diminuta* appears to be less pathogenic than *H. nana.* The

parasitosis does not seem to markedly affect the health of rodents. A large number of parasites may cause catarrhal enteritis.

Source of Infection and Mode of Transmission: The most important risk factors found in infected children were contamination of the environment with human feces, lack of drinking water (Kaminsky, 1991), poor environmental hygiene, and the presence of another infected person in the home (Mason and Patterson, 1994). The reservoir of *H. nana* for human infection is man himself, and transmission between humans occurs by the fecal-oral route. The infection is more common in children because of their deficient hygiene habits, particularly in overcrowded conditions, as in orphanages, boarding schools, and other schools. Autoinfection is believed to be common in man, although studies with rodents do not support this opinion (see Control). The role played by rodents in the epidemiology of the human parasitosis is not well known, but it is thought that, under natural conditions, they play a very limited role. While it has been shown experimentally that animal strains can infect man and vice versa, there is no correlation between the prevalence of human and murine infections in the same area; also, the higher risks of human infection point to infection acquired from another person (see above). Nevertheless, rodents may play a role in fecal contamination of food. Accidental ingestion of arthropods infected with cysticercoids (for example, cereal and flour beetles such as *Tenebrio* and *Tribolium*) is a possible, but probably very rare, mechanism of infection.

H. nana is transmitted among rodents by the fecal-oral route, as it is in man. Coprophagia contributes significantly to the spread of the parasitosis. Ingestion of infected arthropods is probably a more important mechanism among rodents than among human beings.

The natural reservoirs of *H. diminuta* are rodents, mainly rats. Man is infected only accidentally by ingesting insects infected with the cysticercoid, particularly insects that contaminate precooked cereals. Since the parasite's eggs are infective only for arthropods, interhuman transmission of the cestode does not occur. This explains the rarity of human infection. The parasitosis can become established in laboratory rodent colonies, which may create great difficulties in experimentation.

Diagnosis: Infection is suspected on the basis of the symptomatology and the epidemiological circumstances. Specific diagnosis is made by detecting the characteristic eggs in the feces. A single fecal examination is not conclusive and, in the event of a negative result, the examination should be repeated up to three times, with samples taken on alternate days. The eggs of *H. nana* are clear, thin-shelled, oval or round, and 38 μm to 45 μm in diameter; the embryo has small projections, with filaments, on each end. The eggs of *H. diminuta* are 60 μm to 79 μm in diameter and have no filaments. The space between the shell and the embryo is empty and resembles the white of a fried egg; the embryo resembles the yolk.

Inasmuch as fecal examination is simple and unequivocally demonstrates the presence of the parasite, there has been no interest in developing immunological diagnostic tests. However, immunological diagnoses would be possible because the study of antigens of *H. nana* and other cestodes has shown that the parasite has antigens in common with the other helminths as well as exclusive antigens (Montenegro *et al*., 1994). In fact, Castillo *et al*. (1991) showed that the enzyme-linked immunosorbent assay (ELISA) for *H. nana* antibodies in the serum has a sensitivity of 79% and a specificity of 83%. But cross-reactions were quite common: the most

frequent occurred with the sera of cysticercosis (28%) or hydatidosis (35%) patients, and the antibodies disappeared 90 days after successful treatment of the infection. ELISAs to detect *Taenia* spp. antigens in the feces (coproantigens) did not show cross-reactivity with the feces of rodents infected with certain species of murine *Hymenolepis*, including *H. diminuta*, but reacted at low dilutions with the feces of patients with *H. nana* (Allan *et al*., 1990).

Control: Since hymenolepiasis caused by *H. nana* is basically an infection due to contamination of the environment with human feces, prevention of the infection consists of avoiding contamination of the environment and, secondarily, avoiding contact of individuals with eggs from the contaminated environment. Kosoff *et al*. (1989) showed, in Costa Rica, that the infection was significantly more prevalent in poor communities without access to sewer systems than in communities with easy access to them. Mason and Patterson (1994) studied the epidemiological characteristics of groups of patients in urban and rural areas of Zimbabwe and found that, while all indicators suggested that the infection was intrafamiliar in urban patients, the same phenomenon was not present in rural patients.

One dose of praziquantel probably cures 75% to 80% of infections. This level of efficacy, along with the fact that the parasite's eggs survive for just a short time (less than two weeks) in the external environment, indicates that treatment of infected persons would have a strong effect on preventing new infections. However, the periodic treatment of school children with effective anthelminthics has decreased the prevalence of other parasites, but has not definitively reduced the rates of infection with *H. nana* or *G. intestinalis* in the respective groups. Most *H. nana* infections are probably produced through the anus-hand-hand-mouth cycle, as occurs with *Enterobius vermicularis*, so the infective eggs remain in the external environment for a short time. Under these circumstances, consistent hand washing before eating can be of great importance. While there is no information on the role of mechanical vectors in the dissemination of *H. nana* eggs, protection of food from flies, cockroaches, and other arthropods is a good general hygiene practice. Protection of food and water for human consumption to prevent access by rodents is probably more important in the case of *H. diminuta* than in the case of *H. nana*.

Although attempts to vaccinate people at risk for *H. nana* have not been published, this seems to be a possibility, since studies in murines have shown that infection with eggs produces strong, rapid immunity against homologous infections and less rapid immunity against cysticercoid infection. That immunity prevents autoinfection in immunocompetent rodents (Ito, 1997) and raises questions about the occurrence of autoinfection in man.

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INERMICAPSIFERIASIS

ICD-10 B71.9 Cestode infection, unspecified

Etiology: The agent of this infection is *Inermicapsifer madagascariensis* (synonyms: *Inermicapsifer cubensis* and *Inermicapsifer arvicanthidis*). The cestode is 27 cm to 42 cm long and its maximum width is 2.3 mm; it has 350 proglottids. *Inermicapsifer* is distinguished from *Raillietina* (see the chapter on Raillietiniasis) by its hookless (unarmed) scolex and sucker. The gravid segments, in which egg capsules take the place of a uterus, are longer than they are wide (in contrast to the nongravid segments, which are wider than they are long). Each gravid segment encloses 150 to 175 capsules 49 µm to 53 µm in diameter, each containing six or more eggs. Its life cycle is unknown, but by analogy to related parasites of the genus *Raillietina,* it is believed that an arthropod acts as intermediate host. Kourí *et al*. (1963) discuss this rare parasite in detail.

Geographic Distribution and Occurrence: *I. madagascariensis* is a parasite of rodents (*Arvicanthis*) in eastern Africa, where it very occasionally affects man. Outside Africa, it may be exclusively a human parasite. Human cases have been recorded in the Democratic Republic of the Congo, Kenya, Madagascar, Mauritius, Philippines, Puerto Rico, Thailand, and Venezuela. The highest number of cases (more than 100 up until 1949) has been recorded in Cuba, mainly in children 1 to 2 years old. Since 1989, two more cases have been reported in a Havana hospital (González Núñez *et al*., 1996).

The Disease and Diagnosis: The parasitosis is generally unaccompanied by clinical symptoms. Specific diagnosis is based on microscopic examination of the proglottids. To differentiate *Inermicapsifer* from *Raillietina,* the scolex of the cestode, which may be expelled spontaneously or following treatment, must be examined.

Source of Infection and Mode of Transmission: The intermediate host is not known, but, by extension of what occurs in related genera, is probably an arthropod. The larval stage would develop in an arthropod that ingests cestode eggs deposited with the fecal matter of the definitive host (rodent or man). The cycle would be completed when the definitive host ingests an intermediate host infected with the larva. In Africa, the transmission cycle would be rodent-arthropod-rodent, and, rarely, rodent-arthropod-man. Outside the African continent, transmission would occur from human to arthropod to human.

Control: Since the life cycle of the parasite and consequently the mode of transmission are unknown, the only preventive measures that can be recommended consist of rodent control and personal and environmental hygiene.

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MESOCESTOIDIASIS

ICD-10 B71.9 Cestode infection, unspecified

Etiology: The agents of mesocestoidiasis are the cestodes *Mesocestoides lineatus* and *Mesocestoides variabilis.* Their life cycle is not well known. The adult parasites measure 40 cm or longer and not more than 2 mm wide, with proglottids shaped like melon seeds, similar to those of *Dipylidium caninum*, but with each one having a single set of reproductive organs. The nomenclature of the genus is uncertain because there is a great deal of variation and the morphological characteristics are not well established. The definitive hosts are foxes, dogs, cats, and different species of wild carnivores. The first intermediate host may be a coprophagous arthropod that ingests the eggs of the gravid proglottids eliminated by the definitive host. Oribatid arthropods have been experimentally infected and have developed cysticercoids. The second intermediate hosts harbor a larval form known as tetrathyridium in the peritoneal or pleural cavities, liver, or lungs. The tetrathyridium is similar to a plerocercoid, thin with variable length, but the scolex has four acetabula or invaginated suckers on the thicker end, instead of the plerocercoid's two bothria (grooved suckers). Moreover, the tetrathyridium can multiply asexually in the host by dividing lengthwise. The intermediate hosts are mainly rodents, but also dogs, cats, birds, amphibians, and reptiles. Some mammals, such as cats and dogs, can harbor both the adult cestode and the tetrathyridium. When a definitive host ingests the meat of an animal infected with the larval form, the larval form develops into an adult cestode in the host's intestine in two to four weeks.

Geographic Distribution and Occurrence: *M. variabilis* occurs in Central and North America; *M. lineatus* is found in Africa, Asia, and Europe. Mesocestoidiasis is rare in man: about 20 cases have been described, including 7 in Japan, 2 in the US, 2 in Rwanda and Burundi, 1 in Greenland, and 1 in the Republic of Korea. Just two human cases have been reported since 1989: one in the Republic of Korea (Eom *et al*., 1992) and the other in the US (Schultz *et al*., 1992). The limited space devoted to it by textbooks on veterinary medicine notwithstanding, infection caused by adult *Mesocestoides* in carnivores, especially red foxes, seems to be common. In Malawi, *Mesocestoides* spp. was found in 34% of 120 native dogs at autopsy (Fitzsimmons, 1967). Between 1997 and 1999, *Mesocestoides* sp. was found in the intestines of 73% of 342 red foxes in Greece, 54% of 1,300 in Germany, 24% of 68 in the Netherlands, and 23% of 201 in Spain. In eight localities in Alaska, US, infection rates of 0% to

58% were found in 254 arctic foxes; in Spain, 37% of 8 lynxes were found to be infected at autopsy, as were 14% of 58 autopsied stray cats. In endemic areas, peritoneal infection caused by tetrathyridia is common in domestic animals (Crosbie *et al*., 1998) as well as snakes and frogs. Massive infection can cause illness.

The Disease and Diagnosis: In man, the main symptoms are digestive disturbances, abdominal pain, diarrhea, and a massive discharge of small proglottids, a constant reminder to the patient that he has a foreign living being inside him (Eom *et al*., 1992). The adult parasite does not produce symptoms in dogs and cats. Diagnosis is based on microscopic examination of the gravid proglottids. These segments are barrel-shaped, like those of *Dipylidium caninum*, but with a single set of reproductive organs, and they contain eggs with a double membrane grouped in a central, thick-walled parauterine organ. A large number of larval forms in the serous cavities can cause peritonitis and edema in cats and dogs. The clinical symptoms of the peritoneal infections in 11 dogs were recently published (Crosbie *et al*., 1998). The animals had distended abdomens and dysuria; while lesions were not found with radiography, ultrasonography did show abnormal structures; microscopic examination of the abdominal fluid showed structures compatible with the tetrathyridium, and polymerase chain reaction confirmed the diagnosis.

Source of Infection and Mode of Transmission: Dogs, cats, and wild carnivores contract the parasitosis by eating birds, amphibians, reptiles, and small mammals infected with the tetrathyridium. Man is occasionally infected by the same mechanism when he eats the meat of insufficiently cooked intermediate hosts. In Japan, several cases were caused by eating the raw livers of snakes, to which popular belief attributes curative powers. The human case that occurred in Africa was probably due to ingestion of raw partridge meat. In the same locality, tetrathyridium infection was found in chickens, guinea fowl, and partridge; the case that occurred in the Republic of Korea was probably due to the ingestion of chicken viscera.

Control: Human infection is so infrequent that large-scale control measures are not a consideration. Individual control of human infection in endemic areas consists of not eating the raw or insufficiently cooked meat of wild animals. Tetrathyridium infections should be eradicated as quickly as possible to prevent multiplication in the tissues.

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RAILLIETINIASIS

ICD-10 B71.9 Cestode infection, unspecified

Etiology: *Raillietina celebensis* and *Raillietina demerariensis* are the main species described as agents of the disease in man. The other species of the genus *Raillietina* found in man, such as *R. asiatica*, *R. formosana*, *R. garrisoni*, *R. madagascariensis*, and *R. siriraji*, are thought to be identical to one of these two. The natural definitive hosts of *R. celebensis* are rodents, especially rats. It measures up to 40 cm in length by 2.5 mm wide, at a maximum, and has more than 500 proglottids. The suckers are not spinose, which is uncommon in this genus. The gravid proglottids contain 300 to 400 egg capsules with up to 4 eggs each. *R. demerariensis* has been found in both rodents and howling monkeys. The original specimen described in the first human case (1895, in Guyana) measured 23 cm and had 320 proglottids. The specimens mentioned most often in the literature are those recovered in 1925 in Ecuador: they measured up to 12 m and had up to 5,000 proglottids. The gravid proglottids are shaped like grains of rice; they contain 75 to 250 egg capsules with 7 to 9, and sometimes up to 12, eggs each. The length of this parasite is unusual for the genus *Raillietina*. The biological cycle of the species that affect man is not known, but the intermediate host is assumed to be an arthropod, probably an ant or beetle, as it is for other species of the genus. About 225 species of *Raillietina* parasitize birds and mammals. The intermediate hosts of the species for which the life cycle is known are beetles, flies, and ants. When these insects ingest the *Raillietina* eggs, they develop into cysticercoids in their tissues and generate new adult worms when a suitable definitive host eats the insect.

Geographic Distribution and Occurrence: *R. celebensis* has been recovered from children in southeastern Africa, Australia, Iran, Japan, Mauritius, the Philippines, Taiwan, Thailand, and the Turkestan region of Asia. Some 20 human cases have been reported in the Philippines, and 11 in Thailand. The infection is common in rodents: 54% of *Rattus norvegicus* and 9% of *Rattus rattus* in Taiwan were found to be infected, as were 5% of *R. rattus* and 7% of *Bandicota bengalensis* in Bombay, India. The situation does not seem to have changed in recent years; 37% of rats in Thailand were infected in 1997.

R. demerariensis is a neotropical species that has been found in human infections in Cuba, Ecuador, Guyana, and Honduras. *Raillietina quitensis*, *Raillietina equatoriensis*, *Raillietina leoni*, and *Raillietina luisaleoni* are considered to be synonymous with this species. The largest endemic focus is found in the parish of Tumbaco, near Quito, Ecuador, where the infection rate in school-age children varied from 4% to 12.5% during the period 1933 to 1961. The parasitosis was diagnosed in 0.14% of 8,148 children in the Children's Homes in Quito and in 0.08% of the patients in another hospital in the same city. Outside of Ecuador, human infection is very rare.

The Disease in Man: The infection occurs primarily in children. In Ecuador, the symptomatology attributed to this parasitosis consists of digestive upsets (nausea, vomiting, diarrhea, colic), nervous disorders (headaches, personality changes, convulsions), circulatory problems (tachycardia, arrhythmia, lipothymia), and general disorders (weight loss and retarded growth). Observations in the Philippines indi-

cated that the human infection is usually asymptomatic and the parasite is expelled spontaneously by the infected individual.

Source of Infection and Mode of Transmission: Rodents are the reservoirs of the infection. By analogy with infections caused by *Raillietina* in other animal species, it is thought that man becomes infected by accidentally ingesting food contaminated with an arthropod infected with cysticercoids.

Diagnosis: Proglottids can be observed in the fecal matter; they resemble grains of rice and are frequently mistaken for such. The gravid proglottids of *R. celebensis* have 300 to 400 egg capsules, each containing 1 to 4 oval eggs measuring 99 µm by 46 µm in diameter. The gravid proglottids of *R. demerariensis* have 75 to 250 egg capsules, each with 7 to 12 subspherical eggs measuring 25 µm to 40 µm in diameter. Free capsules can be found in the feces as a result of disintegration of the proglottid. The proglottids of *Raillietina* are similar to those of *Inermicapsifer*. The two genera are easily differentiated on the basis of the scolex: the scolex of *Raillietina* has hooks, while the scolex of *Inermicapsifer* is unarmed.

Control: The human infection is so infrequent that large-scale control actions are not warranted. However, it has been shown that burning and annual treatment of fields where the cotton rat (*Sigmodon hispidus*) lives can significantly reduce the prevalence and intensity of infection with *Raillietina* sp. in rodents. Individual control measures should include hygienic handling of food, in particular, to prevent its contamination by infected insects.

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SPARGANOSIS

ICD-10 B70.1

Synonyms: Larval diphyllobothriasis, spirometrosis, plerocercoid infection.

Etiology: The agent of this zoonosis is the second larval stage (plerocercoid or sparganum) of the pseudophyllidean cestode of the genus *Spirometra* (*Diphyllobothrium*, *Lueheela*). Several species of medical interest have been described: *Spirometra mansoni*, *Spirometra mansonoides*, *Spirometra erinaceieuropaei*, and *Spirometra proliferum*. But, because taxonomic recognition of plerocercoids in man is extraordinarily difficult (Rego and Schaffer, 1992), there is uncertainty as to whether these names actually correspond to different species. There has been a tendency recently to identify the parasites occurring in the Far East as *S. mansoni*, those of the Americas as *S. mansonoides*, and those of Australia as *S. erinaceieuropaei*. Studies of nucleic acids have made it possible to differentiate *S. erinacei* from *S. mansonoides* (Lee *et al*., 1997). *S. proliferum* is a rare form of branched plerocercoid whose definitive host is unknown; it produces lateral buds and multiplies in the host's tissues. Serologically, it seems to be related to *S. erinacei* (Nakamura *et al*., 1990). Noya *et al*. (1992) have studied its structure.

The definitive hosts of sparganum are domestic and wild canids and felids. The development cycle requires two intermediate hosts: the first is a copepod (planktonic crustacean) of the genus *Cyclops*, which ingests coracidia (free, ciliated embryos) that develop from *Spirometra* eggs when they reach the water with the feces of the definitive host. In the tissues of the copepod, the coracidium turns into the first larva, or procercoid. When a second intermediate host ingests an infected crustacean, the procercoid develops into a second larval form, the plerocercoid or sparganum. According to some researchers, the natural second intermediate hosts would be amphibians, although they may also be other vertebrates, including reptiles, birds, small mammals (rodents and insectivores), swine, nonhuman primates, and man. Fish are not satisfactory hosts for plerocercoids. Numerous species of vertebrates become infected with plerocercoids by feeding on amphibians, but they may also develop plerocercoids after ingesting water with copepods infected by procercoids. Several animal species that are not generally definitive hosts function as paratenic or transport hosts, since the larvae they acquire by feeding on animals infected with plerocercoids encyst again, after passing through the intestinal wall and migrating to other tissues, waiting for a definitive host. This transfer process is undoubtedly important in the life cycle, but the fact that many species that act as secondary hosts can be infected directly by ingestion of copepods containing procercoids is probably no less important. When the sparganum reaches the intestine of the definitive host, it attaches to the mucosa; in 10 to 30 days, it matures into an adult cestode and begins to produce eggs.

The adult parasite reaches about 25 cm in length in the intestine of the definitive hosts: cats, dogs, and wild carnivores. The sparganum varies from 4 to 10 cm long in tissues of the secondary intermediate hosts and the paratenic hosts, including man.

Geographic Distribution and Occurrence: Worldwide. Human cases have been described in Argentina, Australia, Belize, Brazil, China, Colombia, Ecuador,

Guyana, India, Japan, Malaysia, Mexico, Paraguay, Puerto Rico, the Republic of Korea, Sri Lanka, Taiwan, the US, Venezuela, and Viet Nam. But human infection is rare: probably fewer than 500 cases have been reported, mostly in Southeast Asia, China, and the Republic of Korea. Up to 1996, 62 cases had been reported in the US (Griffin *et al*., 1996). Approximately 30 cases have been diagnosed in Africa.

Infections caused by the adult cestode and by plerocercoid larvae are frequent in some areas. Some time ago, surveys in Japan indicated that 95% of the cats and 20% of the dogs were infected with *Spirometra* in some areas; a recent study of 916 dogs over eight years showed that just 0.7% were infected. In Australia, it was found that 15% of the cats were infected. In Maracay, Venezuela, about 3% of the cats were found to be infected, and in other Latin American countries, the adult parasite has been recognized in domestic animals and several wild species, such as foxes, felids, and marsupials.

Sparganosis (infection by the plerocercoid) can be found in a great variety of animal species. In some localities of Florida (US), infection with plerocercoids was found in 50% to 90% of the water snakes. On the outskirts of Brisbane, Australia, 25% of the frogs (*Hyla coeruela*) were found to be infected. In that country, during the period 1971–1972, 100% of the wild pigs captured and fattened for human consumption in a slaughterhouse in New South Wales were confiscated because they contained spargana. Moreover, the infection has been found in crocodile meat for human consumption. A high prevalence of sparganosis has also been found in Yugoslavia. Spargana were found in 49% of 37 *Leptodactylus ocellatus* frogs and in five of six *Philodryas patagoniense* snakes in Uruguay. In Asian countries where parasitological studies were conducted, high rates of infection were found in frogs and snakes.

The Disease in Man: The incubation period, determined in a study of 10 patients who ate raw frog meat, lasts from 20 days to 14 months (Bi *et al.*, 1983). The localizations of the sparganum in man include the brain, spinal cord, subcutaneous tissue, breast, scrotum, urinary bladder, abdominal cavity, eye, and intestinal wall. The most common localization seems to be the subcutaneous connective tissue and superficial muscles, where the initial lesion is nodular, develops slowly, and can be found on any part of the body. The main symptom is pruritus and, sometimes, urticaria. The lesion is painful when there is inflammation. The patient may feel discomfort when the larva migrates from one location to another. In a recent clinical study of 22 cases of sparganosis in the province of Hunan, China, half the patients suffered from migratory subcutaneous nodules, which disappeared and reappeared as the sparganum migrated (Bi *et al.*, 1983). The subcutaneous lesion resembles a lipoma, fibroma, or sebaceous cyst (Tsou and Huang, 1993). Ocular sparganosis occurs mainly in Thailand, Viet Nam, and parts of China. Its main symptoms consist of a painful edema of the eyelids, with lacrimation and pruritus. A nodule measuring 1 to 3 cm forms after three to five months, usually on the upper eyelid.

Migration of the sparganum to internal organs can give rise to the visceral form of the disease. The preferred localizations are the intestinal wall, perirenal fat, and the mesentery; vital organs are rarely affected. When the plerocercoid invades the lymphatic system, it produces a clinical picture similar to that of elephantiasis. Eosinophils are abundant in the areas near the parasite; examination of blood samples reveals mild leukocytosis and increased eosinophilia.

An infrequent but serious form is proliferative sparganosis caused by *S. proliferum.* The sparganum of *S. proliferum* is pleomorphic, with irregular branches and proliferative buds that detach from the larva and migrate to different tissues in the host, where they repeat the process and invade other organs. The life cycle of *S. proliferum* is not known. Nine confirmed and three suspected cases of this clinical form have been described: seven in Japan (Nakamura *et al*., 1990), one in the US, and one in Venezuela; in the three suspected cases the larvae were too undifferentiated for positive identification.

The cerebral form is reported with some degree of frequency in the Republic of Korea. It is especially prevalent in inhabitants of rural areas who have eaten frogs or snakes, it is chronic, and the most common symptoms are convulsions, hemiparesis, and headache (Chang *et al.*, 1992; Kim *et al*., 1996).

The Disease in Animals: The adult cestode, which lodges in the intestine of the definitive host, generally does not affect the health of the animal. In cats, however, it may produce weight loss, irritability, and emaciation, together with an abnormal or exaggerated appetite. Infection by the larvae or spargana can be clinically apparent when their number is large and especially when they invade vital organs. In the intermediate host, the disease is almost always asymptomatic if the number of parasites is relatively small. It has often been noted that rats infected with spargana become extremely fat. This is because the plerocercoid produces a growth factor that, while not equivalent to the mammalian growth hormone, combines with that hormone's receptors and imitates its effect (Phares, 1996).

Source of Infection and Mode of Transmission: Sparganosis is maintained in nature primarily by contamination of natural or artificial bodies of water (lagoons, marshes, lakes, and so forth) with feces from felids and canids infected with *Spirometra* spp. Contamination of water with eggs of *Spirometra* spp. leads to the infection of copepods and of the second intermediate hosts that ingest these crustaceans. An important means of infection is transfer of the second larva (sparganum, plerocercoid) from one secondary host to another, which increases the number of animal species and individuals infected. The infection is acquired through the ingestion of infected meat; various mammal and bird species become infected by feeding on parasitized frogs or snakes. The high rate of infection in wild pigs in Australia may be due to this mechanism, although it may also stem from ingesting copepods in the drinking water from lagoons. In any case, contamination of the water is assured by wild canids that share the habitat.

The infection rate in man is low compared to the rate in other animals. Man acquires sparganosis mainly by ingesting larvae contained in the raw or undercooked meat of animals infected with spargana, such as amphibians, reptiles, birds, and wild mammals. Another mode of infection, also by larval transfer, is by contact. In Thailand and Viet Nam, frogs are popularly believed to have an antiphlogistic effect, and they are applied as poultices. This custom is responsible for ocular sparganosis. It is also probable that man can acquire sparganosis via drinking water, by ingesting copepods infected with procercoids (first larvae).

Man is an accidental host and does not play a role in the life cycle of the parasite. However, under certain ecologic conditions, such as those in some regions of central Africa, it is suspected that man may act as an intermediate host in the epidemiological chain. In those regions, hyenas are the definitive hosts of *Spirometra* and

man is apparently the only host infected with spargana. In these circumstances, the infection cycle is maintained as a result of a tribal custom of letting hyenas devour human corpses.

Diagnosis: Diagnosis is confirmed through the symptoms of the infection and the epidemiological history of the patient. Although magnetic resonance imaging is better than computerized tomography for the clinical study of sparganosis, neither of these techniques is diagnostic (Chang and Han, 1998). Nishiyama *et al*. (1994) showed that enzyme-linked immunosorbent assay (ELISA) serologic studies have high sensitivity and specificity for sparganosis *mansoni* in humans; however, specific diagnosis can be made only by removing the lesion and confirming the presence of the plerocercoid. Sparganum looks like a bright white ribbon with the undulating movement typical of a pseudosegmented cestode and with an invagination at the oral end. Attempts have been made to identify the species of *Spirometra* by infecting dogs and cats via the digestive route, but most of those attempts have not produced adult parasites. Diagnosis in definitive hosts infected with adult cestodes can be made by coprologic examination or autopsy.

Control: Human sparganosis can be prevented by: 1) avoiding ingestion of water contaminated with copepods that may be infected, unless it is first boiled or filtered; 2) making sure that meat that may contain spargana is sufficiently cooked; and 3) avoiding compresses, poultices, or dressings prepared with the meat of frogs, snakes, or other poikilotherms that may be infected.

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TAENIASIS

ICD-10 B68.0 *Taenia solium* taeniasis; B68.1 *Taenia saginata* taeniasis

Etiology: The cestodes *Taenia solium*, *T. saginata,* and *T. asiatica*. *T. solium* and *T. saginata* have been known as human parasites for more than 300 years (Shulman, 1982). *T. asiatica*, a species closely resembling *T. saginata*, was described as a new species in 1993 (Eom and Rim, 1993), although most authors consider *T. asiatica* to be a subspecies of *T. saginata* rather than a new species, and call it *T. saginata asiatica*. This section will use the specific name only to differentiate it from *T. saginata saginata*.

The definitive host of these taeniae is man, in whose small intestine the adult stage lodges. The natural intermediate hosts of *T. solium* are the domestic pig and the wild boar, although dogs, cats, sheep, deer, camels, monkeys, and individuals infected with the larva or cysticercus have occasionally been found (human cysticercus infection is presented in the chapter on Cysticercosis). The natural intermediate hosts of *T. saginata* are bovines of the family Bovidae and some members of the family Cervidae. The natural intermediate hosts of *T. asiatica* are domestic and wild swine (Fan *et al*., 1990a; Fan *et al*., 1990b).

T. solium, or swine taenia, measures 2 to 4 m in length and is made up of 800 to 1,000 proglottids or segments. The gravid proglottids detach from the strobila in groups of 5 or 6, are somewhat motile, are expelled with the feces, and contain from 30,000 to 50,000 eggs. Pigs, because of their coprophagic habits, may ingest a large number of eggs, both those contained in the proglottids and those existing free in fecal matter. The embryos (oncospheres) are released from the egg in the pig's intestine, penetrate the intestinal wall, and within 24 to 72 hours, spread via the circulatory system to different tissues and organs of the body. Complete development of the larva or cysticercus (which was called *Cysticercus cellulosae* when it was thought to be a parasite different from the adult taenia) takes place in 9 to 10 weeks. It is 8–15 by 5 by 10 mm in size, and resembles a fluid-filled bladder; it holds the invaginated scolex equipped with the suckers and hooks of the adult taenia. When a human consumes raw or undercooked pork that contains cysticerci, the larva is released from the surrounding tissue, the scolex is disinvaginated and attaches to the wall of the small intestine, usually in the jejunum, and begins to develop strobila. The first proglottids are expelled in the feces 62 to 72 days after infection. *T. solium* can survive in the human intestine for a long time; cases have been observed in which the

cestode persisted for 25 years. Some authors have observed differences in the size of the hooks on the scolices of cysticerci found in humans, swine, cats, dogs, and baboons, and proposed the existence of different strains or subspecies. A multilobular cysticercus without a scolex has frequently been observed in human cysticercosis in Mexico; it has been designated *Cysticercus racemosus.* Most investigators are inclined to believe that it is a degenerative state of *T. solium* (see the chapter on Cysticercosis). The significance of *T. solium* for public health is that humans can become infected with the eggs of the taenia and develop cysticerci in their tissues.

T. saginata, or bovine taenia, is longer than *T. solium*; it is composed of 1,000 to 2,000 proglottids and is 4 to 10 m long. The gravid proglottids, which can contain more than 100,000 eggs, detach from the strobila one by one; they are motile and often exit actively through the anus. The eggs are either expelled from the proglottid or released when it disintegrates, contaminating the environment. Inside bovines, the viable eggs ingested by grazing cattle develop into cysticerci (still called *Cysticercus bovis)* in a manner similar to the eggs of *T. solium* in swine. Development takes 60 to 75 days. Cysticerci begin to degenerate in a few weeks, and after nine months, many of them are dead and calcified. Humans are infected by ingesting undercooked beef containing viable cysticerci. The adult taenia develops in the intestine in 10 to 12 weeks. Human cysticercosis caused by ingestion of *T. saginata* eggs either does not occur or is extremely rare (see the chapter on Cysticercosis). *T. saginata* eggs can survive several weeks or months in wastewater, bodies of water, or on grass, in moderate climatic conditions.

Geographic Distribution: *T. solium* and *T. saginata* are distributed worldwide. *T. solium* is much more common in developing countries, particularly in Latin America, eastern Europe, northern China, India, and eastern Africa. *T. saginata* is more universally distributed, particularly in eastern and western Africa (where both taenia coexist), North and South America, and Europe. *T. saginata* is approximately 10 times more prevalent than *T. solium*. *T. asiatica*, originally discovered in Taiwan, has since been identified in Ethiopia, Indonesia, Madagascar, the Republic of Korea, and Thailand (Fan *et al*., 1990a; Fan *et al*., 1990b).

Occurrence in Man: It was estimated in 1947 that nearly 39 million people in the world were infected by *T. saginata* and 2.5 million by *T. solium.* A 1973 estimate attributed 45 million cases to *T. saginata* and 3 million to *T. solium* (Strickland, 1991). Although the local prevalences of *T. asiatica* are known, there are no worldwide figures. Taeniases are not notifiable diseases, and the available information is based on isolated studies of specific sectors of the population, such as schoolchildren, recruits, and others. Also, since many studies of prevalence are based on the finding of eggs in feces, and the eggs of *T. solium*, *T. saginata,* and *T. asiatica* cannot be distinguished by conventional methods, the best-known prevalences do not establish differences among the species. A local report in Poland analyzed 736 cases of cestodiasis diagnosed in 1997: 634 were caused by *T. saginata,* 6 by *T. solium*, and 63 by *Taenia* sp. On a college campus in Chile, the 11 cases of taeniasis diagnosed at the species level between 1985 and 1994 were caused by *T. saginata*. In contrast, in Bali, Indonesia, one of every three cases of taeniasis was caused by *T. solium* and two were due to *T. saginata* (Sutisna *et al*., 1999). *T. solium* parasites were identified in 98% of 56 cases of taeniasis in Guatemala (Allan *et al*., 1996). The relative frequency of these species is strongly influenced by local customs. For

example, *T. solium* is absent from Moslem and Jewish population groups that adhere to religious precepts prohibiting the consumption of pork.

In 216,275 fecal samples sent to state diagnostic laboratories in the US in 1987, 0.1% were found to contain *Taenia* sp. eggs (Kappus *et al*., 1991). Based on these findings, any prevalence exceeding 1% in the general population should probably be considered very high. Hinz (1991) estimated that there were 900,000 infections in Germany, for a prevalence of 1.5%. Recent reports on high prevalence indicated a 12.4% infection rate in 1,008 people in a hamlet in Laos (Giboda *et al*., 1991); 10.4% in 300 children in Sudan (Karrar and Rahim, 1995); 8.1% in the residents of 19 Ethiopian communities (Birrie *et al*., 1994); and 2.9% in 171 adults in the general population of Thailand (Supanaranond *et al*., 1990). The countries that historically have the highest prevalences of *T. saginata* (10% of the population) are Ethiopia, Kenya, and the Democratic Republic of the Congo. The endemic areas are the Caucasus region, the former Soviet republics in south and central Asia, and certain countries on the Mediterranean, such as Lebanon, Syria, and the former Yugoslavia. Up to 65% of the children were found to be infected in parts of the former Yugoslavia. South America, southwestern Asia, Europe, and Japan have moderate prevalences, while Australia, Canada, the US, and some countries in the western Pacific have low prevalences.

Infection by *T. solium* is endemic in southern Africa (especially among the Bantu), Latin America, and the non-Islamic countries of Southeast Asia. Little information is available on the prevalence of taeniasis in the Americas. Some studies recorded the following rates of infection by *T. saginata*: 0.6% in Argentina, 1%–2% in Brazil, 1.6% in Chile, 0.1% in Cuba, and 1.7% in Guatemala.

The prevalence of *T. asiatica* seems to be very high in the endemic areas. Fan (1997) reported a prevalence of 11% in the mountainous zones of Taiwan, 6% on Cheju Island in the Republic of Korea, and 21% on Samosir Island in Indonesia. But the natives of these areas engage in food and hygiene practices that greatly encourage the spread of parasites between man and swine (Depary and Kossman, 1991).

Occurrence in Animals: Animals are resistant to infection with the adult parasites. Animal cysticercosis is discussed in the chapter on Cysticercosis.

The Disease in Man: Taeniasis by *T. saginata* is often subclinical and is only revealed by fecal examination or when the infected person consults a physician after feeling the crawling movement of the proglottids in the anal region. In clinical cases, the most common symptomatology consists of abdominal pain, nausea, debility, weight loss, flatulence, and diarrhea or constipation. While a patient may have one or several of these symptoms, experience in Chile showed that only about a third of patients have any of these symptoms before becoming aware of the infection. The gravid proglottids of *T. saginata* sometimes travel to different organs (appendix, uterus, bile ducts, nasopharyngeal passages), causing disorders related to the site in which they settle. In rare cases, there may be intestinal obstruction and even perforation of the colon (Demiriz *et al*., 1995). A high percentage of patients experience a decrease in gastric secretion. Individual reactions to the infection differ and may be influenced by psychogenic factors, since patients often notice symptoms only after they see the proglottids (Pawlowski, 1983).

Taeniasis caused by *T. solium* is more rarely clinically apparent than that caused by *T. saginata* and is usually benign and mild, possibly because its proglottids are

less active and, therefore, less noticeable to the patient. In addition, complications such as appendicitis and cholangitis have not been recorded.

In a survey of 1,661 patients with *T. asiatica* in Taiwan, Fan *et al*. (1992) found that 78% had signs or symptoms. The most common signs were movement of proglottids (95% of patients), going on for years in some of them; anal pruritus in 77%; nausea in 46%; abdominal pain in 45%; dizziness in 42%; increased appetite in 42%; and headache in 26%.

Source of Infection and Mode of Transmission: In contrast to their role in other zoonotic infections, humans constitute an essential link in the epidemiology of taeniasis. Humans are the exclusive definitive host of the three species of *Taenia*; their feces contaminate cow pastures and areas where home-bred swine may eat. Taeniae can live for many years in the human small intestine, and can eliminate hundreds of thousands of eggs in a single day in the gravid proglottids. Consequently, the contamination can be extensive and intense. Sometimes, just one human carrier of *T. saginata* defecating in the grain silos or water reservoirs can infect several hundred cattle in a feedlot. Epizootic outbreaks of the cysticercosis caused by *T. saginata* have been described in Canada, the former Czechoslovakia, and the US. Survival of the eggs in pastures depends on the ambient temperature and humidity; in summer, *T. saginata* can survive for about two months in the environmental conditions found in Europe, while they may survive more than five months in winter. In the highlands of Kenya, eggs of *T. saginata* have been found to remain viable for up to a year. *T. solium* eggs seem to be a little less resistant to environmental factors.

In developing countries, where peasants on poor farms or large ranches often defecate in open fields, both swine and cattle have access to taenia eggs. The use of sewer water for irrigation or of contaminated water from rivers or other sources for watering animals contributes to the spread of cysticercosis. Another factor that has acted to raise the incidence of taeniasis in recent years is the increasing use of detergents that impede the natural destruction of the parasite's eggs in sewer systems. Taenia eggs can be carried several kilometers by river water, and they may be transported over long distances by gulls and other birds. An important role in the dissemination of taeniae eggs is also attributed to coprophagous insects. The cysticerci of *T. saginata* remain viable in live cattle for nine months, and in the tissues of the dead animal for two weeks; those of *T. solium* survive for several years in living swine, and nearly 60% remain viable if the carcass is stored at 4°C for 26 to 30 days (Fan *et al*., 1998).

The distribution and prevalence rates of the human taeniases vary considerably in different geographic areas of the world. Several socioeconomic and cultural factors influence transmission. Taeniasis caused by *T. solium* is much more prevalent in the developing countries than in the industrialized ones. Taeniasis caused by *T. saginata* is prevalent in both developing and developed countries. It has been said that, while taeniasis caused by *T. solium* is especially prevalent in poor populations, taeniasis caused by *T. saginata* is "prevalent in wealthy nations because of their wealth and in the poor nations because of their poverty." Humans acquire *T. solium* taeniasis by eating raw or undercooked pork infected with cysticerci. The infection has almost disappeared from the more industrialized countries, where modern intensive swine-raising practices do not permit access to human feces. In developing countries, on the other hand, the breeding of small numbers of swine by households is still a com-

mon activity among impoverished rural inhabitants. Moreover, since this population group often does not have the benefit of drinking water and sewer systems, the swine have a much higher risk of infection by human feces. Finally, a high percentage of these swine are slaughtered at home for household or local consumption and, therefore, the animals are not subject to veterinary inspection.

In contrast, humans acquire *T. saginata* taeniasis by eating raw or undercooked beef infected with cysticerci. Human infection is closely related to the habit of eating dishes prepared with raw beef or beef cut into thick pieces that are not thoroughly cooked. The infection can also be contracted by tasting meat dishes during their preparation, before the meat is completely cooked. The risk of contracting the infection is five times greater in a family in which there is a carrier of *T. saginata*, which demonstrates the importance of the food handler in transmission of the disease. The risk is 14 times greater among workers involved in processing and marketing raw meat, probably due to their access to meat that is not subject to veterinary inspection or that is discarded during inspection. *T. saginata* taeniasis is widespread among the upper classes because beef costs more than pork and, therefore, is consumed more by the well-to-do, particularly in thick, undercooked portions (with the center still pink) or in sophisticated dishes intended to be eaten raw. However, as far as the poorer classes are concerned, the systems for supplying potable water, excreta removal, and veterinary inspection of slaughterhouses are often deficient, which facilitates the infection of cattle and, subsequently, of man. Man becomes infected with *T. asiatica* by eating the undercooked livers of infected swine.

There is some question about whether man can contract cysticercosis through regurgitation of distal portions of a *T. solium* from his own intestine, followed by activation of the eggs by his own gastric juices. While the majority of authors used to believe that the regurgitation of gravid proglottids from the jejunum or the ileum would be most unusual, the discovery of the oral expulsion of a *T. saginata* in a patient (Gupta *et al*., 1997) requires another look at that opinion.

Diagnosis: *T. saginata* proglottids crawl the length of the intestine in order to exit, and *T. solium* proglottids adhere to the fecal matter. Thus, there is little opportunity for the eggs to be released in the intestine; parasite eggs are found in the feces of just one quarter of patients. Moreover, the various species of the genus *Taenia* cannot be distinguished by microscopic examination of the eggs. This is a major disadvantage because *T. solium* eggs pose a clear risk of cysticercosis to humans. For these reasons, diagnosis of human intestinal taeniasis is generally made by identifying gravid proglottids in the feces. In the case of infection by *T. saginata*, anal swabs should be used rather than direct examination of fecal samples. Proglottids are not eliminated on a daily basis, so the examination must be repeated if results are negative. Differential diagnosis between *T. saginata* and *T. solium* is based on the number of primary lateral branches of the uterus of the gravid proglottids, 16 to 30 in the former species and 7 to 12 in the latter. Differentiation of proglottids with 12 to 16 primary branches is unreliable. When the scolices are expelled (spontaneously or because of treatment), *T. saginata* can be identified by microscopy, since its scolex lacks hooks, but that of *T. solium* has them. Although *Taenia* spp. eggs are indistinguishable by conventional microscopy, techniques have been developed that differentiate the eggs of *T. solium* from those of *T. saginata* and other cestodes by the

enzyme-linked immunosorbent assay (ELISA) (Montenegro *et al*., 1996) and those of *T. saginata* with the polymerase chain reaction (Gottstein *et al*., 1991). An ELISA that uses patients' feces to reveal *T. solium* coproantigens has also been developed (Allan *et al*., 1996). This test is 2.5 times more sensitive than microscopic examination. A survey of 475 persons in a community endemic for *T. solium* in Mexico found no infection using parasitological methods but found 10 by looking for the coproantigen; 7 of these were confirmed by the subsequent discovery of proglottids (Rodríguez-Canul *et al*., 1999).

Control: Human taeniases are not just a threat to public health, but also a factor in economic loss. According to estimates by Fan (1997), taenia infections resulted in an annual loss of US$ 11,327,423 in the mountainous areas of Taiwan, US$ 13,641,021 on Cheju Island in the Republic of Korea, and US$ 2,425,500 on Samosir Island in Indonesia. Almost all actions to control this zoonosis are based on appropriate health education of the at-risk population. Barriga (1997) proposes several control measures that consist of interrupting the epidemiological chain of the parasite at any of the following points of intervention:

1. The production of eggs and the consequent contamination of the environment. These are prevented by early diagnosis and effective treatment of infected persons, since man is the only definitive host. In the former Soviet Union, rates of *T. saginata* infection were reduced through health education of the public and the mass treatment of the population in endemic areas: between 1964 and 1972, the rate of infected bovines fell from 1.09% to 0.38%.
2. Dispersion of the eggs in the environment. This is prevented through an appropriate excreta disposal system, consisting not just of a traditional sewer system, but also well-built and utilized septic tanks and education of the population in their proper use. Unfortunately, the economic and cultural conditions of the rural populations in developing countries often preclude these actions. Also, traditional sewer systems can decrease the viability of taenia eggs up to approximately 8%, but the final solids can still contain significant numbers of viable eggs (Barbier *et al*., 1990).
3. Ingestion of eggs by the natural intermediate host. This is avoided by preventing breeding swine and bovines access to food or drink contaminated with human feces. This is the rule on modern, large farms. However, poor peasants customarily breed a few swine for their own consumption or sale on the local market and, because of ignorance or lack of the means to implement hygienic breeding standards, the animals have easy access to places that have been contaminated with human feces, and they acquire cysticercosis.
4. Development of the cysticercus in the intermediate host. This can be prevented by treating the animals—which is too expensive, insufficiently effective, and not preventive of subsequent infections—or by vaccination. Studies of vaccination of the intermediate hosts of cestodiasis are very far advanced; in the case of bovine cysticercosis, there are just a few practical marketing problems to be resolved before its routine use can be initiated (Lightowlers, 1996). Attempts to vaccinate against porcine cysticercosis in Peru fared less well (Evans *et al*., 1997).
5. The dissemination of cysticerci to the definitive host. This can be prevented by good veterinary inspection in slaughterhouses and educating the population against avoidance of inspection. Household slaughtering of swine and the consumption of pork that has not been subject to veterinary inspection is still very prevalent in eco-

nomically depressed agricultural communities and plays a large part in sustaining the human intestinal infection.

6. Personal human protection. This entails cooking pork and beef well to kill any cysticerci, and taking food hygiene measures such as washing food and washing the hands before eating to avoid ingesting *T. solium* eggs.

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Section A

PROTOZOOSES

AFRICAN TRYPANOSOMIASIS

ICD-10 B56 African trypanosomiasis; B56.0 Gambiense trypanosomiasis; B56.1 Rhodesiense trypanosomiasis; B56.9 African trypanosomiasis, unspecified

Synonyms: Sleeping sickness, trypanosomiasis; *gambiense* trypanosomiasis: infection due to *Trypanosoma brucei gambiense*, West African sleeping sickness; *rhodesiense* trypanosomiasis: infection due to *Trypanosoma brucei rhodesiense*, East African sleeping sickness.

Etiology: African trypanosomiasis in man is caused by two subspecies of *Trypanosoma (Trypanozoon) brucei*: *T. brucei gambiense* and *T. brucei rhodesiense*, both of which are transmitted by the bite of tsetse flies (genus *Glossina*) (Bales, 1991; Dumas and Bouteille, 1996; Chimelli and Scaravilli, 1997). These trypanosomes are considered to belong to the salivarian group because of the way in which they are transmitted through the vector's bite. Infection caused directly by a bite is considered inoculative, or via the anterior station, as opposed to contaminative, or via the posterior station, when the infection is transmitted by means of the fly's excrement (see the chapter on Chagas' Disease).

The two subspecies that affect man, *T. b. gambiense* and *T. b. rhodesiense*, as well as *T. b. brucei*, are morphologically indistinguishable. The latter species, while it does not affect man, is pathogenic for domestic animals in Africa, such as donkeys, horses, goats, camels, mules, sheep, dogs, and cattle. The forms that are present in blood, cerebrospinal fluid, and lymph are pleomorphic trypomastigotes (see Chagas' Disease). The forms range from long, thin parasites (measuring 30 μm by 1.5 μm on average, with a subterminal kinetoplast, a long flagellum extending from the anterior tip of the body, and an undulating membrane between the flagellum and the body) to short, fat parasites (averaging 15 μm by 3.5 μm, with a near-terminal kinetoplast and no external flagellum). The long forms multiply in the fluids of the definitive host by binary longitudinal division. The short forms are the infective elements for the vector and do not divide in the human host.

For a long time, the three subspecies *T. b. brucei, T. b. gambiense*, and *T. b. rhodesiense* were distinguished on the basis of their infectivity and pathogenicity for rats, their sensitivity to the drug tryparsamide, and their pathogenicity for man. To make a definitive distinction between *T. b. brucei* and the human trypanosomes, human volunteers were employed, with the consequent risks. In practice, differentiation

between the two human pathogens is still fundamentally based on the course and geographic distribution of the infection. Now more precise techniques are available for identifying the parasites. The blood incubation infectivity test (BIIT) consists of incubating the trypanosomes in human serum or plasma and then inoculating them in rats. In this procedure, *T. b. brucei* loses its infectivity for rats whereas the subspecies that affect humans maintain it. Nevertheless, studies have revealed wide variation in the susceptibility of these trypanosomes to the effects of human serum, and some evidence exists that *T. b. brucei* can become resistant to the action of the serum. This would mean that *T. b. brucei* could become infective for man when flies infected by animals feed on human blood (Minter, 1982). Another important and increasingly used method is characterization of the trypanosomes according to the electrophoretic movement of their isozymes, which makes it possible to distinguish the different zymodemes (see definition under Chagas' Disease). Truc and Tybayrenc (1993) have described 23 zymodemes in Central Africa, which can be divided into two groups, one corresponding to *T. b. gambiense* and the other to *T. b. brucei*. Recent findings suggest that the different zymodemes are related not only to the species but also to the geographic distribution and clinical characteristics of the infection (Smith and Bailey, 1997). Also, the use of polymerase chain reaction has made it possible to identify *T. b. gambiense* (Schares and Mehlitz, 1996).

In man, the trypanosomes of African trypanosomiasis multiply in the blood, lymph, cerebrospinal fluid, and intercellular spaces, but they do not penetrate cells. In the vector, the short, fat trypanosomes consumed in the process of ingesting a blood meal multiply in the lumen of the mid and hindgut for about 10 days, after which they turn into thin forms and migrate toward the proventriculus, where they multiply for another 10 days; from there they travel to the salivary glands, where they attach themselves to the epithelial cells and turn into epimastigotes (see Chagas' Disease). The epimastigotes continue to multiply and are rapidly transformed into short, fat, metacyclic trypomastigotes, sometimes without a flagellum, which are the forms that are infective for man. Although the complete cycle of the trypanosome inside the tsetse fly can range from 15 to 35 days (average 21 days), the infection cycle up to the formation of metacyclic trypomastigotes is completed in only about 10% of the flies that ingest the parasite. The infected flies remain so for the rest of their lives and inoculate trypanosomes every time they take a blood meal.

Geographic Distribution: African trypanosomiasis in man occurs between 15° N and 20° S Latitude in Africa, which is the vector's area of distribution. *T. b. rhodesiense* is found in multiple foci in eastern Africa over an area stretching from Ethiopia to Botswana, while *T. b. gambiense* is found in central and western Africa, from northwestern Senegal to northeastern Sudan in the north to Angola in the south. Outside the endemic area, there are occasional cases in tourists and immigrants from endemic countries.

Occurrence in Man: In the past, there were devastating epidemics of *gambiense* trypanosomiasis, brought on by the migration of settlers during colonization. At the beginning of the twentieth century, 500,000 people died within a decade in the Congo basin alone, and there were about 200,000 fatalities (two-thirds of the population) in the province of Busoga, Uganda (Goodwin, 1970). Following the implementation of control measures, by 1950 and 1960 prevalence of the disease had dropped to very low levels in some areas (0.1% to 2%) and annual incidence was

estimated at less than 10,000 cases. In 1972, there were 4,126 new cases in the Democratic Republic of Congo (formerly Zaire) and 3,000 in the rest of Africa (De Raadt, 1976). However, starting in the 1970s, the disease flared up again alarmingly in some of its old foci (Kusoe, 1993; Cattand, 1994; Jusot *et al*., 1995). This increase was a reflection of the massive new movements of people both within and outside the endemic areas as a result of wars and social and political instability in many African countries. The situation was aggravated by shortages of human and material resources for surveillance and medical care programs in the affected countries (Mhlanga, 1996). In 1982, the World Health Organization (WHO) reported that *gambiense* trypanosomiasis was endemic in 23 African countries, 45 million inhabitants were at risk, and that every year there were nearly 10,000 new infections (*Bull World Health Organ*, 1982). Currently, African trypanosomiasis in man is endemic in 36 African countries south of the Sahara; the two forms of the disease together pose a risk for approximately 50 million people; and about 25,000 new cases are being reported annually, with the likelihood that not all cases were being notified (Bales, 1991; Kusoe, 1993).

Gambiense trypanosomiasis, which is chronic, tends to occur in epidemics, whereas *rhodesiense* trypanosomiasis, which has a more acute course, occurs sporadically, and gives rise to far fewer epidemics. The latter infection is endemic among livestock-raising tribes in eastern Africa and frequently affects hunters, fishermen, and travelers. Overall incidence is rather low because the people avoid areas infested by the vector.

The Disease in Man: The human disease usually has three phases: the primary lesion, parasitemia, and invasion of the central nervous system. Two or three days after the bite of an infected fly, a painful inflammation (chancre) appears at the inoculation site, and it disappears after two to three weeks (McGovern *et al*., 1995). The primary lesion is observed more frequently in infections caused by *T. b. rhodesiense* than in those produced by *T. b. gambiense.* From the chancre site, the trypanosomes invade the bloodstream, and the patient suffers from irregular and intermittent fever, mirroring the waves of parasitemia. Other signs during this acute period are painless adenopathies, especially in the posterior cervical lymph nodes, as well as edema of the eyelids and joints. The most common symptoms of the acute phase are cephalalgia, insomnia, arthralgia, weight loss, and generalized erythema and pruritus, particularly in the sternal region. In later stages of the disease, the symptomatology is related to the affected organ. Invasion of the central nervous system is common, and a large variety of psychological, motor, and sensory perturbations may be seen. Following the meningitis that develops early in the course of the infection, a rupture occurs in the choroid plexus which allows the parasites to invade sites in the brain. The result is encephalitis, consisting of generalized inflammation with perivascular infiltrations of B and T lymphocytes, plasmocytes, and macrophages. The blood-brain barrier becomes permeable, and this condition may give rise to vasogenic cerebral edema. Astrocytes and microglia are activated, and, together with immune cells, they begin to produce cytokines, which also contribute to progression of the disease (Pentreath *et al*., 1994). There is irritability, paresthesia, and insomnia, and later on, cerebral edema can cause severe headaches and edema of the optic papillae. There can also be neurologic manifestations such as epileptic seizures, chorea, psychotic episodes, euphoria, somnolence, lethargy, and coma.

As it was noted earlier, *gambiense* trypanosomiasis usually follows a slow and chronic course. Weeks or months may elapse between the first and second phase, and months or years may elapse between the second and third phase. *Rhodesiense* trypanosomiasis has a more acute course and its phases are less marked; death may come within a few months, in contrast to patients with *T. b. gambiense* infection, who can live for many years. Cardiac complications are more common in *rhodesiense* trypanosomiasis, and some patients die before reaching the neurologic phase (Greenwood and Whittle, 1980; WHO, 1979).

Both forms of African trypanosomiasis severely alter the patient's immune system. The main characteristics are synthesis of large amounts of gamma globulin, autoantibody formation, and immunodeficiency (Vincendeau *et al*., 1996). The parasites in the bloodstream are covered with variable glycoprotein surface antigen (VGSA), which generates powerful immune responses that rapidly suppress parasitemia. These responses include antibody production and activation of macrophages that produce tumor necrosis factor alpha (TNF-α) and nitric acid (NO). Some parasites, however, manage to express another of the more than 1,000 genes coded for this antigen and are covered with a different glycoprotein, thereby initiating a new wave of parasitemia. These waves recur every 7 to 15 days until the patient, if left untreated, dies. The succession of new antigens is a powerful stimulus for the immune response, which participates in both the defense and the pathology of the disease. Although there is epidemiologic evidence of protective immunity in *gambiense* trypanosomiasis (Khonde *et al*., 1995), individual antigenic variation is effective protection for the parasite against the immunity of the host. In terms of immunopathology, there is no evidence that high gamma globulin levels or an abundance of immune complexes play an important role in pathology of the human disease. Nevertheless, there is experimental evidence suggesting that autoantibodies to components of the central nervous system, such as anti-galactocerebrosides and tryptophan anti-analogous antibodies, may play a part in the development of encephalitis (Hunter *et al*., 1992). Although T lymphocytes diminish the parasite's capacity to proliferate, they continue to produce gamma interferon (IFN-γ). The macrophages and astrocytes, for their part, produce TNF-α. Although IFN-γ and TNF-α, together with their specific antibodies and the NO of the macrophages, have powerful properties to fight the trypanosomes, it has been demonstrated that TNF-α levels are directly related to the severity of the disease (Okomo-Assoumou *et al*., 1995).

The Disease in Animals: Infections caused by African trypanosomes in animals have a variety of local names, but they are most often referred to as *nagana*. *T. b. gambiense* has been inoculated in or isolated occasionally from animals, including laboratory animals, antelopes, swine, chickens, dogs, and cows, but there is no evidence that it causes disease or sustained parasitemia. However, *T. b. rhodesiense* can cause an infection, which is usually asymptomatic, in domestic animals such as cattle and sheep; wild animals, including antelopes, hyenas, and lions; and also laboratory animals. *T. b. brucei*, on the other hand, infects a wide variety of animals, including carnivores, swine, equines, ruminants, and laboratory animals. It causes an important disease in camels, equines, cats, dogs, and small ruminants. The disease is chronic and occasionally fatal in cattle; it is rarely fatal in swine. Man is resistant to the infection. There are other African trypanosomes of great importance

for domestic animals, but none of them infects man (Levine, 1985): *T. congolense* affects carnivores, swine, equines, and ruminants; *T. vivax* affects equines and ruminants; and *T. simiae* affects camels and swine. The primary symptoms in animals are lymphadenopathy, intermittent fever, anemia, and progressive emaciation (Urquhart, 1980). Depending on the species, the age of the host, and the parasite load, the disease may be acute or chronic.

Trypanosomiasis in animals has played a role in configuring African societies: awareness of the parasite's fatal effect on horses protected the original inhabitants from foreign invasions, while its effect on cattle has prevented ranchers from taking advantage of 7 million km^2 of pastureland to raise high-yield European cattle. Another form of trypanosomiasis that occurs both in Africa and outside the continent is caused by *T. evansi.* It is transmitted by tabanid flies and is especially pathogenic for camels, equines, and dogs.

Source of Infection and Mode of Transmission: Man is the main reservoir of *T. b. gambiense* and the source of infection for the vector. Because the infection is prolonged and includes intervals between febrile attacks during which the patient feels relatively well, affected individuals may move about and propagate the infection in new areas where the vectors exist. There is no evidence that lower animals play a role in human *T. b. gambiense* infection, even though animal-to-animal transmission has been demonstrated in the laboratory (Molyneux, 1983) and parasites from swine, sheep, and dogs have been shown to be identical to human parasites in their sensitivity to human sera or their isoenzymatic profile (Scott *et al*., 1983; Schares and Mehlitz, 1996). The success of control programs aimed exclusively at eliminating the human parasite would indicate that animal reservoirs are not important in *gambiense* trypanosomiasis. Nevertheless, the presence of animal reservoirs could account for maintenance of the *T. b. gambiense* infection in areas where isolated human cases have occurred with long intervals between them.

The main vectors of *T. b. gambiense* infection are the tsetse flies *Glossina fuscipes, G. palpalis*, and *G. tachinoide.* These species belong to the *palpalis*, or riverine, group of flies, which inhabit dense vegetation along the shores of rivers and lakes. Human infection occurs almost always in the vicinity of watercourses or places where water pools in rural settings; tourists are rarely affected. The male and female tsetse flies are biological vectors, but they can transmit the infection mechanically during epidemics, when there are many patients with parasitemia. In general, the infection rate in the vectors is low. In addition, according to some reports, congenital transmission can occur in man.

By contrast, in the case of *rhodesiense* trypanosomiasis, lower animals, especially cattle, play an important role as reservoirs. *T. b. rhodesiense* has been isolated from a number of wild and domestic animals; but only antelopes, hyenas, lions, sheep, and cattle develop sufficiently high and prolonged parasitemia to serve as effective reservoirs. These animals are responsible for persistence of the parasite in areas that have not been inhabited by humans for years.

The main vectors in eastern Africa are *Glossina morsitans*, *G. pallidipes*, and *G. swynnertoni.* These species belong to the *morsitans* group of flies, which inhabit savannahs and forested areas and prefer to feed on cattle and wild animals. The more acute nature of the human infection, coupled with the fact that the habitat of the vectors is not near homes, makes *rhodesiense* trypanosomiasis more sporadic than the

gambiense form and less capable of causing epidemics. The main victims of the *rhodesiense* form are hunters, tourists, and persons who have contact with wild animal habitats where the infection is enzootic.

Diagnosis: The disease may be suspected when its main symptoms and signs are present, in particular intermittent fever, enlarged posterior cervical lymph glands, and cutaneous erythema. Biochemical tests do not reveal any remarkable alterations except higher cell counts and increased IgM in cerebrospinal fluid, which are considered pathognomonic of invasion of the central nervous system (Bisser *et al*., 1997). The infection is confirmed by demonstrating the presence of the parasite in aspirate from the chancre or the lymph glands, in bone marrow, or in blood taken during the acute phase, or cerebrospinal fluid during the chronic phase. The sample to be observed may be either fresh or fixed and stained. In acute-phase patients, aspiration of the lymph glands is more effective for detecting *T. b. gambiense* than *T. b. rhodesiense*. On the other hand, peripheral parasitemia is higher in *rhodesiense* than in *gambiense* trypanosomiasis, and it is therefore easier to demonstrate the presence of *T. b. rhodesiense* by examining thick blood films. In both cases, however, the levels of parasitemia fluctuate and are higher during febrile attacks. It is easier to find parasites in blood by centrifugation in hematocrit tubes and examination of the leukocyte layer, or by minifiltration in DEAE-cellulose, centrifugation, and examination of the exudate (Bailey and Smith, 1994). To demonstrate the presence of *T. b. rhodesiense,* samples of blood or cerebrospinal fluid can be inoculated intraperitoneally in mice, which develop detectable parasitemia within the second week. It is difficult to infect rodents with *T. b. gambiense*. When the foregoing methods have been unsuccessful, an attempt may be made to examine bone marrow or culture it in special media such as glucose, lacto-albumin, serum, hemoglobin, or GLSH. Sediment from cerebrospinal fluid should be examined immediately after it is collected. Serologic reactions such as the card agglutination test, indirect hemagglutination, enzyme-linked immunosorbent assay (ELISA), and indirect immunofluorescence are useful for epidemiologic studies, but they are of limited value for individual diagnosis: healthy individuals may have developed antibodies to animal trypanosomes inoculated by tsetse flies which did not produce infection, and these antibodies can cross-react with the antigens of *T. b. gambiense* and *T. b. rhodesiense*.

Control: The two main approaches to controlling the African trypanosomiases are to reduce the principal reservoirs of infection and the presence of the vectors. In diminishing the reservoirs of *gambiense* trypanosomiasis, detecting and treating the human infection should be emphasized to reduce the source of infection for the vectors. The challenge is greater with *rhodesiense* trypanosomiasis, because measures must also be taken to control the livestock population, both wild (e.g., antelopes) and domestic (e.g., cattle). The latter can be reduced by converting the savannahs where livestock graze into cropland, which is not propitious for the proliferation of tsetse flies. Reduction of the vector population, which is much more efficient in controlling *rhodesiense* trypanosomiasis, can be achieved either through the targeted destruction of the flies' habitats or the use of insecticides. Both approaches, however, can cause major ecologic changes. Moreover, the mass use of insecticides is costly and not very efficient, because the flies are protected by vegetation in their habitats. Tsetse fly traps have been developed that are very effective, especially when they are impregnated with insecticides (Langley, 1994). Another approach

would be to saturate the natural environment with male flies sterilized in the laboratory, which was successful in eradicating the fly *Cochliomyia hominivorax* in Libya in 1991. Empirical observations and mathematical models suggest that reducing the vector population is most efficient during epidemics, while reducing the human reservoir is more effective in endemic situations (Gouteux and Artzrouni, 1996). Other appropriate measures include preventing host-vector contact by the use of protective clothing, netting that keeps out flies, repellants, or simply not going into areas where there are high densities of tsetse flies. In highly endemic areas, the indiscriminate donation of blood should be prohibited. Chemoprophylaxis for visitors to endemic areas is not recommended because pentamidine and suramin are only effective against *T. b. gambiense*, they are somewhat toxic, their use can mask symptoms of the disease until it invades the central nervous system, and generalized application promotes parasite resistance to the drugs. Moreover, most tourists are more exposed to *T. b. rhodesiense* than to *T. b. gambiense.* Wery (1990) considers that the most important advances in the control of *gambiense* trypanosomiasis have been the improvements in serologic diagnosis, the demonstration of parasitemia, and the introduction of low-cost, efficient traps for tsetse flies.

The problem of antigenic variation in the African trypanosomes has impeded the production of a vaccine, but there is epidemiologic evidence that the disease generates protective immunity: while 30% of the uninfected population in the Democratic Republic of Congo is at risk of contracting the infection, only 15% of those previously infected run a similar risk (Khonde *et al*., 1995). These facts suggest that a vaccination is possible.

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AMEBIASIS

ICD-10 A06

Synonyms: Amebiosis, amebic dysentery, entamebiasis.

Etiology: Of the numerous species of the genus *Entamoeba* found in mammals, only *E. histolytica* and *E. polecki* are of zoonotic interest. *E. dispar* was recently identified as a separate species, but knowledge about it is still quite limited. *E. histolytica* is essentially a human parasite which is also capable of infecting a number of nonhuman primates. In addition, it has been occasionally isolated from dogs, cats, swine, and rats, and it has produced experimental infection in rabbits and other rodents (Tsutsumi, 1994). *E. polecki* was isolated from swine and goats in 1912 and has also been identified in humans (Giboda *et al*., 1988), although Levine (1985) contends that the original description was inadequate to distinguish it from *E. histolytica*. Another human species, *E. dispar*, was thought for many years to be a "small race" of *E. histolytica* because it is very similar in appearance but does not have the same pathogenic power; it has now been identified as a separate species (Jackson, 1998).

Amebas have two developmental stages: the trophic (or vegetative), during which the trophozoite is formed, and the cystic (or resistant) stage, when the cyst appears. The trophozoites live in the large intestine of the host, moving around by means of pseudopodia and multiplying by binary fission. As they progress through the host intestine toward the outside, they divide into smaller forms, cease taking in nourishment, and develop a thin, resistant wall around themselves in preparation for turning into cysts. At first the cysts are mononuclear; they then subdivide by two consecutive mitoses, producing two and ultimately four nuclei. At that point the cysts are eliminated in the feces of the host. If they are ingested by another host via contaminated food or water, upon reaching the small intestine they break up into four new trophozoites which then migrate to the large intestine, where the multiplication process resumes.

Geographic Distribution: Worldwide.

Occurrence in Man: *E. histolytica* infection is especially prevalent in tropical and subtropical areas, and it is more frequent in developing countries than industrialized ones. An estimated 400 to 500 million people in the world are infected, and between 5% and 10% of them present symptoms (García and Bruckner, 1997). In recent decades, prevalence of the infection has declined notably in the industrialized countries. In the US, for example, the rate in the general population fell from 7% in 1961 to approximately 2% at the end of the 1990s. On the other hand, in the developing world the disease continues to be an important cause of morbidity and mortality. According to reports published in 1996–1997, the infection was found in 0.3% of 1,917 apparently healthy children in Spain, 7.8% of 862 children with diarrhea in Kenya, 19.4% of 33,253 hospital fecal samples in Beirut and 1.2% of 11,611 similar samples in Tripoli, between 20% and 29% of 980 normal adults in Egypt, 18.6% of 1,267 individuals in Nicaragua, and 8.7% of a group of 342 persons in Venezuela.

The prevalence of *E. dispar* is unknown because laboratories only rarely distinguish it from *E. histolytica*. Its frequency may be high, however, since symptoms are present in only 5% to 10% of the infections attributed to *E. histolytica*.

E. polecki infection is rare in humans, and most reports refer to individual cases. However, the prevalence of this species may be greater than has been reported so far because of the difficulty of distinguishing it from *E. histolytica* (Levine, 1985). It would appear to be more frequent in southeastern parts of Asia: the parasite was found in 19% of 184 children in Papua New Guinea (Desowitz and Barnish, 1986); 4.6% of 1,478 refugees from Cambodia, the Lao People's Democratic Republic, and Viet Nam arriving in the US (DeGirolami and Kimber, 1983); and 3.2% of 435 refugees from Cambodia and Viet Nam arriving in France (Chaker *et al.,* 1982).

Occurrence in Animals: Infection with *E. histolytica* is relatively common in nonhuman primates. The parasite has been isolated from dogs and rats, and on occasion from naturally infected cats and swine; it has also been reported in cattle (Levine, 1985). Experimental infections have been produced in numerous rodents (mice, rats, guinea pigs, hamsters, and jerboas) and also in rabbits (Tsutsumi, 1994).

Infection with *E. polecki* appears to be common in swine. Pakandl (1994) reported high prevalence of this parasite among newly weaned swine in the former Czechoslovakia. It is rarely identified in diagnostic laboratories.

The Disease in Man: Most *E. histolytica* infections are asymptomatic, but they should be regarded as potentially pathogenic because there is always the danger that they could develop into a progressive and invasive disease (WHO, 1981). Amebiasis is particularly common in young adults and may be manifested by an invasion of the small intestine, liver, or, more rarely, other tissues. In the intestinal disease, the parasite invades the tissues and produces small ulcers in the intestinal mucosa which spread underneath in the submucosal tissue by means of lysis. On rare occasions it can cause perforation of the intestine or produce granulomas in the wall of the large intestine. The symptoms range from mild abdominal discomfort with bloody mucous diarrhea, alternating with periods of constipation or remission, to acute or fatal dysentery with fever, chills, and bloody or mucous diarrhea (amebic dysentery) (Benenson, 1995). Hematogenic dissemination may carry the parasites to the liver, where they produce a focal necrosis which is often incorrectly referred to as an amebic liver abscess. The symptoms of intestinal amebiasis correspond to febrile and painful hepatosplenomegaly. However, unlike hepatic fascioliasis, there is no peripheral eosinophilia. Occasionally, the parasite may invade the lungs, skin, genital organs, spleen, brain, or pericardium.

Human infection with *E. polecki* is usually asymptomatic. In the few cases of intestinal disease that have been described, the symptoms were considerably milder than those produced by *E. histolytica* and there was no invasion of extraintestinal tissues.

The Disease in Animals: Like human infections, animal infections with *E. histolytica* are usually asymptomatic. Both the clinical intestinal form and the hepatic form occur in lower primates, and spider monkeys are particularly susceptible (Amyx *et al.,* 1978). It is not known whether the disease occurs in swine. In dogs, there have been reports of occasional cases of intestinal disease and, more rarely, invasion of the liver and other tissues. Shimada *et al*. (1992) described a case of *E. histolytica* disease in a cat. Among laboratory rodents, the hamster and the jerboa are susceptible to hepatic invasion, but the guinea pig and the rat are resistant. Although combined immunodeficient mice are fully susceptible to hepatic amebiasis, normal mice are highly resistant.

E. polecki does not appear to be pathogenic for swine (Dunlap, 1975).

Source of Infection and Mode of Transmission: Humans are the reservoir of *E. histolytica*. There is no evidence of animal-to-human transmission. The infection is acquired by the ingestion of products contaminated with the fecal matter from infected persons. Although contaminated water (Marshall *et al.*, 1997) and raw vegetables (Monge and Arias, 1996) are sources of infection, well-documented risk factors include persons who handle contaminated food and those with poor hygienic habits who may contaminate the household food supply. In addition, flies are efficient vectors of the cysts. The trophozoites, which are virtually the only forms present in diarrheic stools, are of little importance as transmitters of the infection because they are not very resistant to desiccation or the action of gastric juices. The cysts, which are found in abundance in pasty or formed feces, are the principal elements of transmission, since they survive in the soil for eight days at temperatures between 28°C and 34°C and for 40 days at 2°C to 6°C. For this reason, the chronic patient and the healthy carrier are more effective sources of infection than the acute patient. In the last two decades it has also been documented that sexual practices which include anal-oral or anal-genital-oral contact are an important risk factor for infection.

Except in the case of monkeys, it is believed that animals acquire the infection from human reservoirs. Apparently *E. histolytica* can be propagated among lower primates: of 29 chimpanzees admitted to a particular colony, only 2 had *E. histolytica* on the day of their arrival, whereas 4 years later 10 of the 29 were infected (Miller and Bray, 1966).

The reservoir of *E. polecki* is swine, and the human infection is contracted either by the ingestion of protozoan cysts in contaminated water or food or via the hands of a person who has been in contact with fecal matter from this reservoir. Human-to-human transmission is also suspected: of three patients diagnosed in Venezuela, two had not had any contact with animals (Chacin-Bonilla, 1983).

Diagnosis: Clinical manifestations alone are not sufficient to differentiate dysentery caused by amebiasis from other causes of dysentery. Laboratory diagnosis is based on three fecal examinations, each taken half a day apart, and serologic tests in special cases. Direct examination of diarrheic feces almost always reveals trophozoites, whereas cysts and occasional trophozoites are found in formed and pasty feces. Samples of diarrheic fecal matter should be examined as soon as possible after collection unless steps are taken to preserve the trophozoites, for which purpose trichromic or iron hematoxylin stain is recommended (García and Bruckner, 1997). Samples from formed or pasty feces may be examined using stool concentration methods and direct microscopic observation of cysts. The diagnosis of *E. histolytica* requires carefully performed procedures and personnel well trained in distinguishing between the macrophages, leukocytes, trophozoites, and cysts of this and other parasites.

The clinical manifestations of extraintestinal amebiasis are not sufficient for a definitive diagnosis. Tests such as the enzyme-linked immunosorbent assay make it possible to identify 90% of all cases, although this technique only detects 10% of intestinal cases (Restrepo *et al*., 1996). Tests designed to identify foreign bodies, such as radioisotopic imaging, ultrasound, and computerized tomography, may help to locate the lesion, but they are not diagnostic of the disease.

Differential diagnosis between *E. histolytica* and *E. polecki* is difficult and can only be accomplished by studying the cysts. Although the distinction between the pathogenic species *E. histolytica* and the nonpathogenic *E. dispar* cannot be made on the basis of morphological criteria alone, there are immunologic and isoenzymatic differences which have recently made it possible to identify the species in specialized laboratories (Jackson, 1998). The *E. polecki* cysts have a single nucleus, unevenly distributed chromatin in the nuclear periphery, rare glycogen vacuoles in the cytoplasm, usually an opaque cytoplasmic inclusion body which is much larger than the nucleus, and up to 30 chromatoidal bars. On the other hand, mature *E. histolytica* cysts have four nuclei, uniformly distributed chromatin, frequent glycogen vacuoles in the cytoplasm, no cytoplasmic inclusion body, and fewer than 10 chromatoidal bars (Levin and Armstrong, 1970). Giboda *et al*. (1988) have established additional criteria.

Control: Basically, amebiasis is controlled by avoiding contamination of the environment with human feces and educating the general public—children in particular, in order to reach the people in the household who handle food—and commercial food handlers about proper hygiene to prevent transmission of the infection. The following measures are essential in order to avoid contamination: proper disposal of human excreta, protection of water sources from fecal contamination, treatment of chronic patients and healthy carriers who are spreading cysts, and supervision of food preparation in public places where raw food is eaten. Food should be covered when there are flies or dust in the air. Health education should stress the danger of drinking water or eating raw vegetables that might be contaminated, as well as the importance of washing one's hands after defecating and before preparing food. Education programs should be targeted toward high-risk groups such as homosexuals and swineherds in order to prevent infections caused by *E. polecki*. In endemic areas, water and food should be either boiled or treated with nine drops of 2% tincture of iodine per liter of water for 30 minutes. Travelers visiting endemic areas should consume only bottled water (including ice made from bottled water) and cooked food.

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BABESIOSIS

ICD-10 B60.0

Synonyms: Piroplasmosis, babesiasis.

Etiology: Of the 73 species of *Babesia* that have been described as parasites of mammals, only slightly more than a dozen are important for domestic animals and only five occasionally infect man: 1) *B. microti,* a parasite of rodents; 2) *B. divergens*, a parasite of cattle in Europe; 3) a species related to the dog parasite *B. gibsoni*, isolated in Africa and Asia (but undistinguishable from *B. microti*) and also in the state of Washington, US, where it was given the preliminary designation WA1; 4) a species related to *B. divergens* isolated in Missouri, US, and assigned the preliminary designation MO1; and 5) a species related to *B. microti* isolated in Taiwan and identified preliminarily as TW1 (Barriga, 1997; Herwaldt *et al*., 1996; Shih *et al*., 1997). Since the diagnosis of *Babesia* is still based mainly on the morphology of the parasites, it is possible that man may be infected by other species which have not yet been identified with certainty.

Babesias parasitize the red blood cells of vertebrate hosts and are transmitted in nature by ticks. When an infected tick bites a mammal, pyriform parasites (sporozoites measuring 1.5–3 μm long) are introduced through the tick's saliva and rapidly penetrate the host's erythrocytes. The majority of the parasites grow inside the red blood cells as pyriform trophozoites or merozoites, the rest as gametocytes. The trophozoites or merozoites often divide asexually into two organisms, forming a "V." *B. microti* sometimes divides into four parasites that form a tetrad or Maltese cross. When they achieve full growth and measure between 1 μm and 5 μm in length, the parasites break free of the erythrocytes, often destroying them in the process, and invade new ones. This cycle is repeated until either the infection is brought under control or the host dies. The gametocytes, on the other hand, develop inside the host's erythrocytes until they become an oval or round parasite, at which point they stop growing. These gametocytes are the precursors of the parasite's sexual stage, which continue to multiply inside the tick.

Babesiosis is typically a chronic infection. Even after the infection is controlled, the parasite usually maintains a low-level presence in the host erythrocytes for a very long time. In domestic animals, this period often lasts for the rest of their life.

When a tick vector—*Ixodes scapularis* (formerly *I. dammini*) in the case of *B. microti*, or *I. ricinus* in the case of *B. divergens*—sucks blood containing the parasites, the merozoites are destroyed in the digestive tract, but the gametocytes mature and become male and female gametes, which fuse and form mobile zygotes. The latter in turn become kinetes, which migrate to the hemocele and from there invade numerous organs of the tick, where they divide asexually and invade even more organs. Some of the kinetes invade oocytes; once inside the egg, they can be passed on to the next generation of ticks via transovarial transmission. Other kinetes invade the salivary glands, where they are transformed into sporozoites after the gland has undergone certain developmental changes that take place while the arthropod ingests its blood meal. Because of the time required for this process to occur, sporozoites are not inoculated until a few days after the infected tick begins to feed (Mehlhorn and Schein, 1985).

Geographic Distribution: Animal babesias occurs almost everywhere in the world where ticks exist, including both the tropical zones and many temperate areas as well. In the US, human infections have been identified and attributed to the following: *B. microti* (especially in New England), WA1 (in Washington State and northern California), and MO1 (in Missouri). In Europe, cases of babesiosis caused by *B. divergens* have been reported in Belgium, France, Ireland, Russia, Scotland, Spain, Sweden, and the former Yugoslavia. In Taiwan, cases due to TW1 were identified. Osorno *et al*. (1976) found antibodies to an undetermined species of *Babesia* in 38 of 101 samples taken from residents in a rural area of Mexico, and they successfully isolated the parasite from three of the samples by inoculation in hamsters.

Occurrence in Man: Clinical human babesiosis is infrequent. The first case was confirmed in the former Yugoslavia in 1957 and attributed to *B. divergens*. Since 1990, there have been reports in the US of 100 cases in the states of Massachusetts and New York; 2 in the midwest in the states of Wisconsin and Minnesota; 10 in the states of Washington and California; and 1 in the state of Missouri. In addition, some 22 cases have been identified in Europe and there has been 1 case in Taiwan. The total number of cases described in the world is estimated to be fewer than 200. Although

most of the cases in Europe and the first cases in the US occurred in splenectomized individuals, in the last decade numerous cases have been described, especially in the US, in patients who were immunodeficient for other reasons or previously healthy. However, there is evidence that the infection is much more frequent than the disease. For example, 6.3% of 1,285 residents of Connecticut were found to be seropositive for *B. microti* (Krause *et al*., 1991), 9% of 574 residents of Rhode Island were also seropositive for *B. microti* (Krause *et al*., 1992), and 17.8% of 230 semirural residents of northern California were seropositive for WA1 (Fritz *et al*., 1997).

Occurrence in Animals: Animal babesiosis is widespread throughout the world, with the highest prevalence in the tropics. It is one of the most important diseases of cattle in Africa, the Middle East and other parts of Asia, Australia, Central America, and the northern half of South America. The disease poses a risk for 50% to 70% of the cattle in the world and causes heavy economic losses, and has been compared to malaria in man. *B. divergens* occurs only in Europe and some parts of the former USSR. It is distinguished from the other major babesias of cattle (*B. bigemina, B. bovis*, and *B. major*) by its relatively smaller size, measuring only 1.5 μm x 1.0 μm, compared with at least 2.0 μm in length in the case of all the others (Barriga, 1997). *B. microti* is found on numerous wild rodents in the US and Europe, and it is a common laboratory research model. In the US, blood examinations of the white-footed mouse (*Peromyscus leucopus*) on Nantucket Island, Massachusetts, revealed *B. microti* in 35.4% of the blood smears examined and 67% of the specimens inoculated in hamsters (Spielman *et al.,* 1981). In Germany, it was found in 38% of 255 field voles (*Microtus agrestis*) (Krampitz, 1979). Nevertheless, the only known cases of human infection due to this species have been found on the eastern coast of the US.

The Disease in Man: The cases in Europe of *B. divergens* infection usually occur in splenectomized individuals (80%). They are characterized by severe illness, often with pyrexia, chills, anemia, muscular pain, prostration, hemoglobinuria, and jaundice. The case fatality rate is about 50%. The spleen plays a very important role in resistance to the parasite, and splenectomy is undoubtedly a predisposing factor. By the same token, the disease may be more severe in immunodeficient individuals. In the Americas, the nonsplenectomized patients infected with *B. microti* had a disease that developed gradually, with anorexia, fatigue, fever, sweating, and generalized muscle pain. Some patients may have mild splenomegaly and hepatomegaly, and mild to severe hemolytic anemia is common as well. Parasitemia may affect fewer than 1% or up to 10% or more of the erythrocytes. In blood smears, it is difficult to distinguish the predominant form of *B. microti* from the small ring forms of *Plasmodium*, which they closely resemble. Recovery is slow, with malaise and fatigue persisting for several months (Ruebush, 1984). *B. microti* rarely causes death, even in splenectomized or immunodeficient patients. The incubation period between the tick bite and the appearance of symptoms can range from 7 to 28 days.

Because of epidemiologic similarities with infections caused by *Borrelia burgdorferi* and *Ehrlichia* spp., human babesiosis in the US can coexist with infections caused by these other agents (Mitchell *et al*., 1996).

The Disease in Animals: In the affected domestic species the symptomatology of babesiosis is similar, characterized by the triad of fever, anemia, and jaundice.

Anemia occurs when the parasites emerge from the erythrocytes and cause the immunologic destruction of these cells. The increased amount of free hemoglobin in plasma often produces hemoglobinuria. *B. bovis* tends to attach itself to the capillary endothelium in much the same way that *Plasmodium falciparum* does in man, thereby blocking circulation. The sensitivity of nervous tissue to anoxia often results in symptoms of agitation and convulsions. Babesiosis in cattle can range from mild to fatal, and those animals that recover usually harbor a subclinical infection and act as healthy carriers. Calves and young equines 6 to 9 months of age are relatively resistant to the infection and disease. In endemic areas, most animals acquire an asymptomatic infection when they are young that confers premunition (i.e., resistance to subsequent infections). By contrast, animals arriving from parasite-free areas usually develop a severe form of the disease.

B. microti in rodents appears to be asymptomatic, but no extensive studies have been done on the subject.

Source of Infection and Mode of Transmission: The reservoirs for domestic animals and rodents are other infected animals, which are often healthy carriers. The reservoirs for man are wild rodents, especially the white-footed mouse *P. leucopus* and meadow vole *Microtus pennsylvanicus*, both of which have been demonstrated to be infected with *B. microti* in the US, and cattle infected with *B. divergens* in Europe. The *B. microti* infection is transmitted in nature by the tick *I. scapularis* and the *B. divergens* infection, by *I. ricinus*.

In the case of *B. microti*, the larva of *I. scapularis* acquires the infection from wild rodents and the nymph, which acquires the infection via transstadial transmission from the larva, passes the infection along when it bites a human host. In a study on Nantucket Island, Massachusetts, US, 5% of the *I. scapularis* nymphs collected were infected. However, the protozoan is not passed from the nymph to the adult tick. Since the adult tick feeds on deer that are not susceptible to *B. microti*, it does not have the opportunity to become infected and therefore does not transmit the infection (Lane and Crosskey, 1993). The *B. microti* enzootic areas are characterized by an abundance of rodents, which serve as hosts for the larvae and nymphs of the vector, while deer serve as the host for adult ticks. Most of the human infections in the US occur in July and August, when nymphs are most abundant (Ruebush *et al*., 1981).

In the case of *B. divergens*, only the adult *I. ricinus* tick feeds on cattle and is capable of acquiring the infection. However, *B. divergens* is transmitted to the next generation of ticks both through the egg (transovarial transmission) and subsequently during the different developmental stages of the tick (transstadial transmission). Thus, *I. ricinus* can transmit *B. divergens* at any stage in its life cycle.

There have been about eight reports of human *Babesia* infection due to blood transfusion (Mintz *et al*., 1991). Asymptomatic donors carry the infection for up to 12 months after they initially acquire the infection themselves.

Diagnosis: A diagnosis of babesiosis should be suspected when the clinical symptoms coincide with an epidemiological history of tick bites or visits to enzootic areas. It is confirmed in febrile or acute cases when parasites are seen inside erythrocytes on Giemsa-stained thin or thick blood smears. Differentiation from *Plasmodium*, especially *P. falciparum*, may require the help of experts. Unlike *Plasmodium*, *Babesia* does not produce pigment (hemozoin) in the parasitized red

blood cells. In more chronic cases with low parasitemia, a diagnosis can be made using serologic examinations such as the indirect immunofluorescence test or the inoculation of blood into susceptible animals. In chronic cases, or before babesias appear in the blood in detectable numbers, the polymerase chain reaction can be used to detect the specific nucleic acids of the parasite (Krause *et al.*, 1996).

Control: For domestic animals in endemic areas, the most effective control measure is to prevent intense infestation by the tick vectors. There is now a vaccine that invokes an immunologic response against *Boophilus microplus* infestation in cattle; as this tick is the main vector of babesiosis in cattle, the reduction of tick infestation also reduces the transmission of the disease (de la Fuente *et al*., 1998). Cattle introduced into endemic areas may be protected by the administration of commercially available live vaccines or by artificial premunition, i.e., inoculating them with blood from healthy carrier cattle to induce a mild infection and then treating them subcuratively. Since the human infection is usually sporadic and occurs only after visits to endemic areas, it is recommended that on such occasions people use protective clothing or tick repellents, and following the visit, that they examine themselves closely for nymphs, which are very small. Those living in endemic areas should control rodents inside the home and cut down shrubbery surrounding the dwelling to control the presence of nymphs.

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BALANTIDIASIS

ICD-10 A07.0

Synonyms: Balantidiosis, balantidial dysentery.

Etiology: *Balantidium coli* is a ciliated protozoan that affects swine, primates (including humans) and, rarely, guinea pigs, dogs, and rats. It has been isolated from 27 species of vertebrates (Wenyon, 1926), but its identification is dubious in many cases. The vegetative form (or trophozoite) measures 30–150 μm in length and 25–120 μm in width; it is ovoid, with a slightly elongated end in which there is a triangular cell mouth, or cytostome, and it is covered with short cilia in a spiral pattern. Osmoregulatory and food vacuoles are frequently found in its cytoplasm. The infective form (the cyst) measures 45–65 μm in diameter, is round, and contains the ciliated organism, sometimes mobile and often with vacuoles, within a thick but transparent double wall (Neva and Brown, 1994). As is characteristic of ciliates, both forms have a large kidney-shaped nucleus, or macronucleus, which is responsible for vegetative functions, and a smaller spherical nucleus, or micronucleus, which is not always visible and is responsible for sexual reproduction, when it occurs. Unlike other protozoa, the parasite does not multiply inside the cyst. Hence, the *Balantidium* cyst possesses the same number of nuclei as the trophozoite (García and Bruckner, 1997).

The trophozoites live in the lumen of the large intestine and, occasionally, invade the mucosa and other tissues. They replicate by transverse binary fission and, sometimes, by budding or conjugation. As they move towards the outside of the body, many become encysted. The cysts form in the fecal matter as it passes through the intestine or in the soft feces that are excreted.

Geographic Distribution: *B. coli* is found throughout the world, but it is more prevalent in tropical and temperate regions. In man, it is most often found in individuals who are in contact with swine and those exposed to poor environmental hygiene conditions.

Occurrence in Man: Balantidiasis is an uncommon disease in humans. Worldwide, only 772 cases of balantidial dysentery had been reported up to 1960. Asymptomatic infection is less rare, but it is not frequent, either. Four surveys carried out between 1988 and 1996 in apparently healthy populations found prevalences of 0.05% in Mexico, 0.3% in Venezuela, 0.5% in children in Argentina, and 1.8% in children in Bolivia. Of 18,512 people examined in Benin, only 0.26% were infected. Wittner and Tanowitz (1992) report that the infection is extremely uncommon in travelers returning to the US from developing countries. Occasionally, however, circumstances arise that facilitate the infection of a sizable segment of population. A study conducted in Ecuador during a gastroenteritis epidemic found that 19.3% of the children examined were infected. In studies in indigenous communities of Bolivia and Peru and in isolated rural populations in Chile, presumably with poor sanitary conditions, the infection was detected in 8%, 6%, and 4.5%, respectively, of those surveyed.

Occurrence in Animals: The infection is very frequent in swine. Prevalences of 60% to 90% have been reported in animals in a single herd and in 60% or more of the herds examined. Based on the form of the parasite and its macronucleus, a separate species, *B. suis*, has been described in swine, but most authorities do not accept this species as different from *B. coli*. Natural infection in dogs and rodents seems to be exceptional.

The Disease in Man: Disease from *B. coli* in man usually affects the mucosa of the large intestine, but it can also invade the liver and the lung, though this rarely happens (Vidan *et al*., 1985; Ladas *et al.*, 1989). In symptomatic infections, the parasite first causes congestion and hyperemia of the mucosa and then small ulcers, which may spread and ultimately destroy large areas of epithelium. The organisms generally invade the intestinal crypts and cause inflammation due to lymphocytes and eosinophils, as well as microabscesses and necrosis. They may spread into the muscularis mucosae and, on rare occasions, perforation of the intestinal wall has occurred. Secondary bacterial infection is common. In acute cases, the patient presents with severe diarrhea, often with mucus, blood, and pus in the stools. In chronic cases, the patient may alternate between diarrhea and constipation and suffer from abdominal pain, anemia, and cachexia. The pathology and symptomatology for *B. coli* are similar to those associated with *Entamoeba histolytica*.

The Disease in Animals: The parasite is apparently not pathogenic in swine. It invades the intestinal mucosa only when prior damage enables its entry and, even in these cases, it does not appear to cause any reaction in the tissues. Infection of dogs and rats is rare, and invasion of the tissues in these species is even less frequent. Primates may possess some natural resistance to *B. coli* infection and disease. Yang *et al.* (1995) reported that two monkeys treated with hydrocortisone and infected with cysts of human origin developed diarrhea, while two untreated monkeys developed only the asymptomatic infection.

Source of Infection and Mode of Transmission: In many cases, the infection in man has been conclusively linked to contamination of water and food by feces of infected pigs or to close contact with pigs. However, the infection exists in Muslim countries where pigs are not raised (Geddes, 1952), and epidemics have occurred in mental hospitals where no pigs were present (Faust *et al.*, 1970). Hence, it appears

that person-to-person transmission is possible where environmental sanitation conditions are poor.

The *B. coli* trophozoite cannot survive for very long in a dry environment, so it is unlikely that infection would be acquired through ingestion of viable trophozoites. The cyst is a much more efficient means of transmission than the trophozoite, since it can survive outside the body for two weeks or more at ambient temperatures. Ingested cysts excyst in the intestine and begin to multiply as trophozoites.

Diagnosis: The symptomatology of balantidiasis is such that it cannot be differentiated clinically from other causes of dysentery. Similarly, it is not possible to distinguish it from amebiasis through endoscopic observation of intestinal lesions. Diagnosis is based on detection of trophozoites, which are most commonly found in watery diarrheal stools, or cysts, which are particularly abundant in formed stools. The trophozoite, obtained from stool specimens or endoscopic samples, can be seen by microscopic examination of wet mounts at low magnification (100X). Permanent stained preparations are not recommended because the parasite, owing to its size and thickness, stains deeply and its internal structures then cannot be observed. The cysts can be visualized by means of fecal parasite concentration methods.

Control: The most efficient control method is probably to educate the public about basic personal hygiene practices in areas in which contact between humans and swine is common. On pig farms, care should be taken to prevent animal waste from contaminating water used for drinking or irrigation, and manure should not be used as fertilizer on crops of vegetables that are eaten raw. Suspicious water or food should be boiled because normal chlorination will not kill the cysts. Where there is a potential for person-to-person transmission, the usual personal hygiene practices for preventing infections of fecal origin, combined with effective treatment of infected individuals, should reduce the risk of transmission.

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CHAGAS' DISEASE

ICD-10 B57

Synonyms: American trypanosomiasis, Chagas-Mazza disease, infection due to *Trypanosoma cruzi*.

Etiology: Chagas' disease is produced by the flagellate protozoan *Trypanosoma (Schizotrypanum) cruzi*. This protozoan has a complex developmental cycle that involves mammals and an arthropod vector. In mammals, *T. cruzi* is found in two forms: extracellular trypomastigotes (formerly "trypanosomal forms") in the bloodstream, and intracellular amastigotes (formerly "leishmanial forms") in tissue. In the vector, it also exists in two forms, both of them extracellular: epimastigotes (formerly "crithidial forms") in the intestine and *in vitro* cultures, and trypomastigotes or metacyclic trypanosomes in the insect's rectum. Thin blood smears prepared with Giemsa's stain show that the trypomastigotes are fusiform, doubled over in the shape of a "U" or "C"; some of them are narrow and about 20 μm long, while others are wider and shorter, measuring about 15 μm long. Near the tip of the parasite there is a large bulging kinetoplast with an attached flagellum that protrudes from the rear end of the body. Between the flagellum and the body is a thin, wavy membrane with two or three undulations. The nucleus, located near the center of the body, is large and bulky. The amastigotes are oval, measuring about 2 μm by 3 μm, and have a nucleus, a kinetoplast, and a short intracellular flagellum which can be seen only at high levels of magnification. The epimastigotes are fusiform and about 20 μm long; the kinetoplast is in front of the nucleus, and the membrane and flagellum are shorter. The metacyclic trypanosomes are longer, thinner, and straighter than the trypomastigotes seen in the bloodstream.

Electrophoresis of isozymes of various *T. cruzi* isolates has made it possible to group the strains of the parasite according to their predominant isozymes, known as zymodemes. Miles (1983) introduced this technique for the study of *T. cruzi* and identified 3 zymodemes in Brazil, each of them with different epidemiological characteristics. Subsequent studies have identified 7 zymodemes in Brazil, 11 more in Bolivia, Chile, Colombia, and Paraguay (Bogliolo *et al*., 1986), and 12 in Argentina (Blanco and Montamat, 1998). Some authors have suggested that there is a correlation between zymodemes and the epidemiological or clinical characteristics of the parasites, but others have not been able to confirm this hypothesis (Lauria-Pires and Teixeira, 1996). The species *Trypanosoma (Herpetosoma) rangeli* is found in some parts of Central America and northern South America; like *T. cruzi,* it is transmitted to man and a variety of mammals by the bite of certain reduviid bugs. Although this species does not cause disease in man or animals, it produces prolonged parasitemia and can be mistaken for *T. cruzi*. The bloodstream trypomastigotes of *T. rangeli* are narrower and longer than those of *T. cruzi*, measuring about 30 μm, with a smaller nucleus and a much smaller kinetoplast, which is located farther from the posterior tip of the parasite.

Some 150 mammal species are susceptible to *T. cruzi*, ranging from marsupials such as the opossum (*Didelphis marsupialis*) to primates. Prevalence can be high in

cats, dogs, rodents, and both domestic and wild lagomorphs, which taken together constitute an important reservoir for human infection. Birds and cold-blooded vertebrates are refractory to *T. cruzi* infection, but domestic birds are important food sources for the vector.

The vectors are reduviid bugs of the family Triatomidae. It has been confirmed that about a hundred species are susceptible to the infection, but the most important vectors are *Triatoma infestans* in southern Peru; *Panstrongylus megistus* in northern Argentina, southern Brazil, and Paraguay; and *Rhodnius prolixus* in northern South America, parts of Central America, and Mexico. The vector becomes infected when it feeds on the blood of an infected mammal and ingests trypomastigotes. These forms reach the midgut of the insect, turn into epimastigotes, and divide abundantly by binary fission. After the bug has been infected for 15 to 30 days, the infective metacyclic trypanosomes begin to appear in its rectum. The bug usually remains infected for several months or the rest of its life.

Unlike the African trypanosomes (see the chapter on African Trypanosomiasis), which produce infection through the bite of a vector, *T. cruzi* infects its definitive host through the vector's excrement. This modality is referred to as contaminative infection, or transmission from the "posterior station," as opposed to inoculative infection, or transmission from the "anterior station." Animals may also become infected by ingesting infected vectors. The metacyclic trypanosomes penetrate the organism either through normal healthy mucosa or broken skin, often caused by scratching; they then invade the macrophages of the dermis or subcutaneous tissue, transform into amastigotes, and multiply by binary fission. Between four and five days after infecting the host cell, the amastigotes then turn into trypomastigotes, which destroy the original cell and invade neighboring cells or spread through the bloodstream to the cells of other organs, especially macrophages, cardiac and striated muscle fibers, and the neuroglia. The trypomastigotes do not multiply in the bloodstream; instead, they turn into amastigotes once again inside the cells and repeat the cycle of intracellular multiplication and destruction of the cell. Some authors have described intermediate forms between trypomastigotes and amastigotes (promastigotes, epimastigotes) when the parasite abandons the cells, but if such forms exist, they are rarely seen in a mammal host. At the beginning of the infection, there are large numbers of trypomastigotes in the bloodstream, but over time, the frequency of the blood-cell cycles tapers off, and as a result, after a few weeks the level of parasitemia drops considerably and the parasite remains restricted to tissue.

Geographic Distribution: *T. cruzi* infection exists only in the Americas, within an area extending from 42° N latitude in the US (from California to Maryland) to approximately 34° S in Chile and 42° S in Argentina. Vectors and wild reservoirs have also been found throughout much of the Caribbean, which was previously considered free of the infection (PAHO, 1984). Autochthonous Chagas' disease has not been confirmed outside the Americas (Marsden, 1997).

Occurrence in Man: Chagas' disease is essentially a problem affecting southern Mexico and Central and South America. According to estimates based on seroepidemiologic studies, at the beginning of the 1980s, 10 to 20 million people in Latin America were infected and 65 million were at risk for the infection; in addition, 10% of those infected in South America could be expected to develop symptoms and clinical signs of chronic Chagas' disease (PAHO, 1984). By the mid-1990s, it was esti-

mated that the disease had affected between 16 and 18 million people, that 50 million were at risk, and that up to 30% of those infected would develop the chronic disease, with a fatal outcome (Moncayo, 1992; Wanderley and Correa, 1995).

The highest prevalence of vector-borne infection is found in rural and periurban areas, but the distribution is uneven and depends on the presence of the vector, whether it lives in dwellings, and whether conditions in the home facilitate contact between the vector and man. In three rural villages in northwestern Argentina, the level of serologic prevalence was 34% (Gurtler *et al*., 1998). In a rural community of São Paulo State, Brazil, cross-sectional studies found a seroprevalence rate of 16.6% (ranging from 2.9% to 61.9%) in 1971–1972, but after a long campaign to control the vector, by 1989–1991, the level had dropped to 10.1% (with a range from 0.4% to 44.8%). In both studies, the lowest prevalence was found in children, and the highest, in the elderly (Passos *et al*., 1997). Jaramillo *et al*. (1997) found a prevalence of 7.1% in Belize; 8.2% in El Salvador; 5.1% in Guatemala; and 6.2% in Honduras. In the southern US, where the infection exists but there are no domiciliary vectors and conditions do not exist for vectors to invade human homes, five acute vector-borne infections have been reported (Benenson, 1995).

Although to a lesser extent, transmission by transfusion also contributes to maintaining the infection. In endemic areas, the importance of this mechanism depends on the prevalence of the infection in the population: in Mexico, it was found that 17% of blood donors had antibodies to *T. cruzi* (Rangel *et al*., 1998), while in the US, there have been 3 cases of *T. cruzi* infection by transfusion, and in some areas of Los Angeles and Miami, where there are large numbers of immigrants from Latin America, 34 of 49,565 blood donors were serologically positive for the infection (Leiby *et al*., 1997).

Congenital transmission has been documented in several studies: in Paraguay, 3% of 172 mothers who were serologically positive for *T. cruzi* transmitted the infection to their babies (Russomando *et al*., 1998); in Argentina, 5.3% of 62 mothers (Arcavi *et al*., 1993), 4% of 149 (Zaidenberg and Segovia, 1993), and 2.6% of 341 (Streiger *et al*., 1995) did so; and in Bolivia, 9.5% of 910 mothers also passed the infection on (Azoge, 1993). In the US, Di Pentima *et al*. (1999) found that 0.3% of 3,765 pregnant women in the city of Houston had antibodies to *T. cruzi* and speculated that congenital infection could occur in this area. Leiby *et al*. (1999) found two blood donors with antibodies to *T. cruzi* who had been born in the US and had never traveled to endemic areas. Since these donors had a family history of heart disease and complications, the authors suggested that the infections might have been congenital.

Attention has often been called to the public health importance of Chagas' disease, particularly because of the high rate of cardiopathy in chronic patients. In central Brazil, visceromegalies such as megacolon and megaesophagus are also a consequence of the chronic disease. In some areas, Chagas' disease is the most frequent cause of myocardiopathy and even the leading cause of death. Deaths from Chagas cardiopathy were confirmed in 7 of 10 Latin American cities studied in an investigation of mortality (Puffer and Griffith, 1967). The mortality rate was exceptionally high in the city of Ribeirão Prêto, Brazil: Chagas' disease was the cause of 13% of all deaths in the population aged 15 to 74 years—29% of 25-to 44-year-old men and 22% of the women in the same age group. Chagas' disease is primarily a rural affliction, but its sequelae in chronic patients are also seen in cities. Vector transmission

occurs in cities as well, as migrants from the countryside bring the disease and even the vector along with them.

Occurrence in Animals: The natural infection has been found in 150 species of mammals, both domestic and wild. However, because of the difficulty in identifying the agent, it is not certain that all the strains that have been isolated correspond to *T. cruzi.* Several animal species serve as reservoirs in different ecologic settings. In Paraguay, the direct agglutination test was positive for *T. cruzi* in 3 of 37 cattle (8.1%), 2 of 20 swine (10%), 16 of 44 dogs (36.4%), and 3 of 8 cats (37.5%), while 3 equines, an opossum, and 3 armadillos were negative (Fujita *et al*., 1994). Among domestic animals, dogs and cats are common and important hosts of the parasite. In a group of towns in northwestern Argentina, 41.2% of 68 dogs and 39.3% of 28 cats were positive on xenodiagnosis (Gurtler *et al*., 1993). In Texas, US, 11 symptomatic cases of Chagas' disease in dogs were reported between 1987 and 1996 (Meurs *et al*., 1998). Several studies have confirmed that in endemic areas the prevalence of infection is higher in these species than it is in man. In the Yaracuy Valley in Venezuela, 70 of 140 dogs (50%) tested were positive on xenodiagnosis. In Chile, 9.1% of 3,321 dogs and 11.9% of 1,805 cats were positive. Xenodiagnosis also revealed that 8.4% of the human population was positive. Other domestic animals can also serve as reservoirs (Miles, 1983). In a serologic survey of 34 rural localities in Region IV of Chile, the hemagglutination test showed antibodies for *T. cruzi* in 7.8% of 232 goats, 11.7% of 145 rabbits, and 4.8% of 42 sheep, and high rates of infection were also confirmed in dogs and cats (Correa *et al.,* 1982). The guinea pig *Cavia porcellus,* a common domestic animal in the high Andean plateau, plays a very important epidemiologic role in the transmission of Chagas' disease in that region, with infection rates ranging from 10.5% to 61% in different localities in Bolivia.

Natural infection has also been confirmed in a large number of wild animal species. Although any mammal in contact with infected vectors can acquire the infection, not all species are equally preponderant in maintaining the Chagas enzootic in the wild. Studies conducted in Brazil and Venezuela have shown that opossums of the genus *Didelphis (D. albiventris* and *D. marsupialis)* play a very important role. Xenodiagnosis of 750 mammals representing 31 species from the dry tropical forests in the highland plains of Venezuela was positive in 10 species; in all, 143 infections were found, and 83% of them were in *D. marsupialis,* even though the infected animals represented only 30% of the mammals in the sample. Seasonal fluctuations were observed, with the infection rate rising at the end of the rainy season and affecting more than 80% of the opossum population (Telford *et al.,* 1981). These marsupials have prolonged parasitemia, which can last for more than 12 months (Mello, 1982). Opossums are important because of their tendency to approach human homes, thus serving as a link between the wild and domestic cycles of the infection. Armadillos, which are common in Latin America, have been found to be parasitized in a number of countries. In Georgia, US, parasitemia was found in 13 of 30 (43%) raccoons tested. The cardiac muscle was examined histopathologically in 10 of the cases; in each case a mild, multifocal interstitial inflammation was observed, and a parasitic cyst was found in one of them. Apparently the infection does not cause pathology in this species (Pietrzak and Pung, 1998).

The Disease in Man: In cases of vector transmission, the incubation period lasts 7 to 14 days and sometimes longer. When the infection is transmitted by infected

blood, incubation takes between 30 and 40 days. Three phases of infection are distinguished: acute, indeterminate, and chronic. The acute phase can range from an asymptomatic course, which is most common, to a severe or fatal disease. In 59 acute-phase patients treated in Venezuela between 1988 and 1996, the disease presented 19 different forms. In its most frequent manifestation, the symptomatology included fever, myalgia, cephalalgia, and Romaña's sign (unilateral eyelid swelling which seems to be mainly an allergic reaction to the bite), observed in 20% of the patients (particularly children). Fifteen percent of the cases were asymptomatic, and 11.9% manifested fever only. Nearly 50% of the children had an inoculation chagoma (swelling with involvement of a satellite lymph node, apparently caused by local multiplication of the parasite), but in about 25% of the patients no signs of a portal of entry were observed. The case fatality rate for the acute form is about 8%, and the deaths occur mainly in children with cardiac or central nervous system complications (Anez *et al*., 1999).

The indeterminate phase consists of a period of latent infection with low parasitemia and no clinical symptoms, which can last indefinitely or progress to the chronic disease. This period is characterized by positive serology or xenodiagnosis without any clinical cardiac, digestive, or central nervous system manifestations and no electrocardiographic or radiologic alterations. In endemic areas, this form is seen especially in the first three decades of life (Dorea, 1981). Autopsies of persons dying from an accident who were in this phase have revealed foci of myocarditis and a reduced number of neurons in the parasympathetic plexus.

The chronic form is seen in 10% to 30% of infected individuals, usually appearing 10 to 15 years after the acute phase. Chagas cardiopathy is the most important chronic form. After the first manifestations, which almost always consist of extrasystoles and precordialgia, an electrocardiogram will show complete or partial blockage of the right branch of the bundle of His. Signs of heart failure are seen during this phase, and autopsies show a weakened ventricular wall with aneurysms. Often the chronic phase is manifested only by abnormalities in the electrocardiogram, with no clinical symptomatology. Histopathologic examination reveals areas of fibrosis and infiltration of mononuclear cells but not the presence of parasites, conditions not usually found in the chronic form of the disease (see hypotheses presented below). The heart lesion corresponds to a microfocal, diffuse, fibrosing myocarditis. At the same time, there is a significant reduction in the number of parasympathetic ganglia (González Cappa and Segura, 1982). In Argentina, it is estimated that about 20% of all Chagas patients suffer from myocarditis. In several endemic areas of Latin America, there is a digestive form of Chagas' disease that produces visceromegalies such as megacolon and megaesophagus, and less frequently, neurologic, myxedematous, and glandular forms. Patients with acquired immunodeficiency syndrome may experience reactivation of the disease, with nervous (75%) or cardiac (44%) involvement, or myositis of the esophagus and stomach (Ferreira *et al*., 1997).

The pathogenesis of the chronic phase is not yet understood. The lack of correlation between the lesions in the myocardium or digestive apparatus and the presence of parasites has given rise to three main hypotheses to account for the pathogenesis of these manifestations: 1) when the pseudocysts rupture, *T. cruzi* "toxin" is released and destroys the muscle cells or the neurons; 2) antigen from the *T. cruzi* pseudocysts is absorbed by the adjacent cells, inducing an immune response that destroys

these cells; or 3) the parasite and the muscle cells or neurons share antigens in common; therefore, immune reactions to the parasite also destroy the host cells. Since no toxin has been found that might account for the damage, the autoimmune hypotheses have been gaining ground in recent years, even though the supporting evidence is only circumstantial (Kierszembaum, 1999). Some investigators have proposed that the lesions may be due to inflammatory reactions to parasites that remain inside the tissues (Brener and Gazzinelli, 1997).

When immunocompetent individuals acquire the infection from a blood transfusion, there are usually no symptoms of the disease, but these people may develop prolonged fever, adenopathies, and later, splenomegaly. In immunodeficient patients, however, the infection can cause a high fever and progressively compromise their general state of health.

In the congenital disease, the most frequent signs are hepatosplenomegaly, premature birth (weight under 2.5 kg), changes in the retina, meningoencephalitis, and cardiac insufficiency with alterations in the electroencephalogram. Fever is unusual.

The Disease in Animals: It is generally believed that *T. cruzi* infection is asymptomatic in wild animals, but this impression may be largely due to the lack of detailed clinical examination. Electrocardiographic studies and ventricular angiograms of rats (*Rattus rattus*) naturally infected with *T. cruzi* have revealed auricular and ventricular arrhythmias, second degree AV block, blockage of the right outflow tract, and dilation of the right chambers. The same alterations are seen in dogs with chronic *T. cruzi* infections (Blandon *et al*., 1995). The acute phase, which begins after an incubation period of 5 to 42 days, is characterized by moderate fever, palpebral edema in some cases, pronounced hepatomegaly, multiple adenopathies, cardiac perturbations, and alterations in the nervous system. The acute phase lasts from 10 to 30 days and sometimes longer, following which the disease passes to the indeterminate phase, which can extend for years without clinical manifestations. Dogs with acute experimental infections have exhibited alterations in the neurons of the Auerbach plexus and myositis in the lower third of the esophagus (Caliari *et al*., 1996), but they did not have any visceromegalies. As in man, the chronic form is characterized by myocarditis. Of 26 dogs experimentally infected with blood trypomastigotes, 13 died spontaneously during the acute phase, while 12 of 38 dogs infected with metacyclic trypanosomes survived to the chronic phase and lived for 1 or 2 years. These animals had the same cardiac alterations that are seen in man during the acute and chronic phase (Lana *et al*., 1992). Clinical, electrocardiographic, and echocardiographic manifestations in dogs with chronic Chagas' disease were compatible with right heart disease. Six dogs survived less than 6 months, while 5 of them lived more than 30 months, the outcome varying according to the age of the animal at the time of initial examination (Meurs *et al*., 1998). There have also been occasional reports of alterations in the brain and the peripheral nerves during the acute and chronic phases. The infection was found in a female dog and seven of her eight pups in Virginia, US, suggesting that in dogs the infection can be transmitted either via the placenta or through the mother's milk.

Source of Infection and Mode of Transmission: The source of Chagas' infection is always the infected mammal. In the case of vector transmission, the reservoir may be any peridomestic animal that infects the vector, which in turn, infects other animals, including man. In nature, Chagas' disease appears to exist preferably in the

wild, invading the domestic environment only when there are domiciliary vectors and ecological conditions that enable them to live in human homes. Since these conditions do not exist in the US, the infection has remained in the wild in that country. However, in many poor rural areas of Latin America, there are vectors that live exclusively or preferably inside houses, or at least have the potential to do so, and the dwellings have the kind of cracks that the insect needs in order to reproduce and hide during the day. The infection is particularly prevalent in these areas. Migrants who move from the countryside to the outskirts of cities can carry the vectors in their personal effects and infest new residential areas. Often, migrants or *T. cruzi*-infected vectors settle in periurban areas where Chagas' disease is already endemic. Several studies have shown that one of the major risk factors for human infection is the presence and number of dogs in the home, and some studies have implicated cats as well, especially when these animals are infected. This observation would indicate that dogs are a primary source of food and infection for the vectors (Gurtler *et al*., 1998). Chickens in the household are also a risk factor because, even though these animals are not susceptible to *T. cruzi*, the vector feeds on them. *T. cruzi* can also be introduced in the human environment through peridomestic wild animals such as armadillos, guinea pigs, opossums, and others. Rats have visible and prolonged infections, and they can also be a source of infection (Blandon *et al*., 1995). Moreover, even in the chronic phase of the disease, a human can be a potential source of infection, as revealed in a 13-year follow-up study of 202 chronic-phase patients: xenodiagnosis showed that the levels of parasitemia were consistently maintained in 146 of the patients and actually rose in 14 of them, while in 42 of the cases did these levels decline (Castro *et al*., 1999). These results notwithstanding, there are statistical studies indicating that the presence of infected dogs is much more important in the infection of vectors than is the presence of infected humans (Gurtler *et al*., 1991).

A number of the vectors are fully adapted to cohabiting with humans—for example, *Triatoma infestans*, which has a wide area of distribution that encompasses Argentina, Bolivia, Brazil, Chile, Paraguay, Peru, and Uruguay. Such species play a key role in human infection because of their facility of contact with people. Then there are species, found both in homes and in the wild, that are important because they introduce *T. cruzi* into the domestic environment; an example is *Rhodnius prolixus*, which is widely active in Colombia, Ecuador, Venezuela, much of Central America, and Mexico. Still other species are in the process of domiciliary adaptation—for example, *Triatoma sordida* in Argentina, Bolivia, and Brazil; *Panstrongylus megistus* in the eastern part of Brazil; *T. brasiliensis* in the Brazilian northeast; and *T. maculata* in Venezuela. Finally, there are species that are fundamentally wild and rarely invade the peridomestic environment; examples are *T. spinolai* in Chile, *T. protracta* in North America, and *T. sanguisuga* in the US. Although these species do not play a significant role in human infection, they maintain the endemicity of Chagas' disease in the wild. Some of the vectors, such as *T. infestans*, defecate while they feed, thus easily contaminating the skin or mucosae of the host and facilitating transmission of the infective agent. These species are most important in transmission to man. Other species, such as *T. protracta,* defecate later and are therefore less significant for human infection, but they can play a role in the case of animals that chew and eat them in an effort to get rid of them.

The ecology of Chagas' disease is closely linked to underdevelopment and poverty in rural and marginal urban areas of Latin America. Precariously built

dwellings made of adobe and mud, as well as roofs of palm thatch or straw, afford ideal conditions for triatomine colonization. The bugs also take up residence in chicken houses, rabbit hutches, corrals, pigsties, aviaries, sheds, and wood piles in areas surrounding the homes.

Although less prevalent than vector transmission, congenital transmission and transmission via blood transfusion are also important sources of human infection (see The Disease in Man), especially because they introduce the agent in areas where the vectors do not exist. Unlike toxoplasmosis, Chagas' disease can be passed on congenitally when the mother is in the chronic phase of the infection. Although transmission can also occur from the ingestion of food contaminated with the excrement of infected triatomines, the importance of this route in the epidemiology of the disease remains to be assessed. There have also been accidental infections in laboratories and from organ transplants from infected donors.

Diagnosis: The specific diagnostic methods for Chagas' disease are direct identification of the parasite and testing for immunologic reactions. Recent efforts have focused on detection of the parasite's DNA using the polymerase chain reaction (PCR) technique. Since *T. cruzi* remains in the blood for only a short time, direct demonstration is used mainly in the acute phase, whereas the immunologic tests are used in the indeterminate and chronic phases.

In direct observation, fresh blood is examined either between slide and coverslip or in thin or thick films stained using Giemsa's method. However, the effectiveness of these diagnostic procedures is limited except in very acute cases and with congenital infection in children under 6 months old. Microscopic examination of tissues often fails to yield any parasites. A technique that is more efficient is the Strout method (Flores *et al.,* 1966), in which the blood sample is allowed to coagulate, the serum is centrifuged at a low speed (200 G) to eliminate the rest of the blood cells and then at a high speed (600 G) to concentrate the trypanosomes, and finally, the sediment is observed. All the procedures mentioned become less effective as the level of parasitemia declines. For borderline cases, the most effective direct methods are xenodiagnosis, hemoculture (Anez *et al*., 1999), and inoculation in animals, in all of which the few parasites present in the patient's blood are multiplied. In xenodiagnosis, the patient is bitten by uninfected vectors that have been produced in the laboratory and fed on chickens (to prevent accidental *T. cruzi* infections), and the insects' feces are examined 30 and 60 days later to detect the presence of the parasite. This method is 100% effective in acute-phase patients, but less than 50% effective with those in the indeterminate and chronic phases. Culture of blood or tissue samples is done preferably using Novy-MacNeal-Nicolle medium, and incubation takes 30 days. Finally, another method of diagnosis consists of inoculating samples in uninfested mice or rats and subsequently observing these animals for parasitemia.

As the patient progresses to the indeterminate or chronic phase, the presence of parasites in the bloodstream is too low to apply direct methods and indirect immunologic methods must be used. The complement fixation test (or Guerreiro Machado reaction) was common in the past, but it is now considered that the most sensitive and specific tests are direct agglutination, indirect immunofluorescence, and the enzyme-linked immunosorbent assay (Anez *et al*., 1999). Specificity, and to some extent sensitivity, depends on the antigens used, and recombinant antigens are being studied for this purpose (Umezawa *et al*., 1999). Also being investigated is PCR,

which detects parasite DNA and should obtain reactions that are both highly specific and sufficiently sensitive (Gomes *et al*., 1999).

Cases of congenital infection in infants up to 6 months of age can be considered acute cases; thereafter, they should be considered indeterminate or chronic cases. When serology is used in congenital cases, the focus should be on finding IgM or IgA antibodies, because the mother's IgG antibodies cross the placenta and can simulate an infection in healthy children.

Although *T. rangeli* can be mistaken for *T. cruzi*, the two can be differentiated by morphology, immunologic techniques based on selected antigens (Acosto *et al*., 1991), or PCR.

Control: The drugs available for the treatment of acute-phase Chagas' disease are toxic and unreliable in terms of eradicating the infection, and there is no curative treatment for chronic infection (Levi *et al*., 1996); therefore, it is highly important to control transmission. A number of countries, Brazil in particular, have independently undertaken control campaigns (da Rocha e Silva *et al*., 1998). In 1991, six Southern Cone countries (Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay) launched a regional control initiative with the support of the World Health Organization (Schofield and Dias, 1999). By 1999, vector transmission had been interrupted in Uruguay and significantly reduced in Argentina, Chile, and Brazil, but it had not yet been curtailed in Bolivia or Paraguay.

To ultimately control vector transmission, homes must be improved by eliminating the cracks and crevices in which the vectors establish their colonies. However, since this is a costly, long-term undertaking, a more immediate alternative is to treat the surfaces of infested dwellings with residual insecticides. Synthetic pyrethroids are most often used, and the employment of synthetic insect hormones is under study. It is desirable to remove dogs and cats from the human environment because they are not only an important food source for the vector but also a major reservoir for *T. cruzi* (Gurtler *et al*., 1998). The areas to be treated are identified through reports received, observation of the vector's presence in homes (often found after the spraying of repellents), and detection of persons with positive serology for *T. cruzi*. Although the last approach is the most efficient and reliable, its drawback is that it only identifies a Chagas endemic area after the people have become infected. The verification of *T. cruzi*-positive serology in domestic dogs appears to give similar results (Castanera *et al*., 1998). One possible approach to identifying endemic areas prior to the appearance of *T. cruzi* infection might be by detecting antibodies to the vector (instead of the protozoan) in humans or domestic animals (Barriga, 2000). It is necessary to maintain surveillance following initial eradication of the domiciliary vectors; it has been shown that they can establish foci outside the home after the application of insecticides and return to their original densities in one to six years. Moreover, wild species can occupy the habitats abandoned by the domestic vectors.

Transmission by blood transfusion is prevented through the presumptive identification of blood donors using questionnaires to find out if they come from Chagasic areas, through blood tests, or by treating the donated blood with gentian violet (250 mg/L) for 24 hours or longer, with or without the addition of ascorbic acid and exposure to light (Morães-Souza and Bordin, 1996).

Congenital infection is combated through timely treatment of infected mothers, but there are no reliable reports on the effectiveness of this method.

Although numerous studies have been conducted with a view to producing a vaccine against Chagas' disease, success has been impeded by the difficulty of distinguishing between protective antigens and those that might generate pathology in the long term.

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CRYPTOSPORIDIOSIS

ICD-10 A07.2

Synonym: *Cryptosporidium* infection.

Etiology: The genus *Cryptosporidium*, together with *Isospora, Cyclospora, Sarcocystis,* and *Toxoplasma*, contains protozoa of the coccidia group in the phylum Apicomplexa (formerly Sporozoa). Since the genus was recognized in 1907 by Tyzzer, more than 20 species of *Cryptosporidium* have been described, but at present only 6 are accepted as valid. The only species that affects both humans and other mammals is *C. parvum* (Barriga, 1997). However, it appears that some varieties of this parasite infect only humans and other varieties infect humans, cattle, and mice. *C. parvum* normally lives in the small intestine, where it forms oocysts that are excreted in the host's feces. Each oocyst contains four small banana-shaped sporozoites, which are the infective stage of the parasite. When a susceptible host ingests

the oocysts, the sporozoites shed their protective cover and penetrate the epithelial cells of the new host's intestine. Each sporozoite differentiates into a spherical parasite, the trophozoite, which in turn multiplies asexually to form two types of meronts (formerly called schizonts), each about 5 μm in diameter. Type I meronts produce six to eight new banana-shaped parasites (merozoites). Type II meronts form four oval-shaped merozoites, the gametocytes. Once mature, the merozoites leave the host cell and invade new epithelial cells, where they produce more merozoites (type I) or gametocytes (type II). The gametocytes also invade new intestinal cells, where they differentiate into male cells (microgametocytes) and female cells (macrogametocytes).

The microgametocytes produce numerous filamentous microgametes 1–2 μm in length, which leave the host cell and fertilize the macrogametocytes, forming a zygote. The zygote matures in the host cell and produces four naked sporozoites—i.e., not inside sporocysts—which are already infective. Most of the mature zygotes (around 80%) develop a tough outer cover measuring 2.5–5 μm in diameter and become infective oocysts. These oocysts are excreted by the host in feces and contaminate the environment. The rest of the mature zygotes have only a thin outer membrane. Because these thin-walled oocysts are easily ruptured, their sporozoites remain in the intestine, reinfecting the same host (Fayer and Ungar, 1986).

Geographic Distribution: Worldwide. Cases of human cryptosporidiosis have been reported from more than 50 countries on 6 continents (Benenson, 1997).

Occurrence in Man: The first two clinical cases of human cryptosporidiosis were identified in 1976 in two immunodeficient patients. Since then, many cases and numerous epidemics have been recognized. Various surveys have indicated that the oocyst prevalence in feces ranges from 1% to 2% in Europe, 0.6% to 4.3% in North America, and 10% to 20% in the developing countries. However, serologic evidence of past infections has shown positivity rates of 25% to 35% in industrialized countries and up to 65% in developing countries. The most well-known epidemic occurred in 1993 in Milwaukee, Wisconsin, US, where a total of 1.6 million people were exposed, 403,000 were infected, and 7 died (Lisle and Rose, 1995). Infection is much more common than the clinical disease and most frequently occurs in children under 2 years of age, contacts of infected individuals, livestock handlers, travelers to developing countries, homosexuals, and, especially, immunodeficient individuals. In Australia, *Cryptosporidium* was found in 4.1% of stool samples from 884 patients with gastroenteritis, but not in samples from 320 patients without gastroenteritis (Tzipori *et al*., 1983). In the US, however, while *Cryptosporidium* was similarly found in the stool samples of around 4% of patients with gastroenteritis, it was also found in 13% of samples from healthy individuals.

Occurrence in Animals: Several species of *Cryptosporidium* infect both warm- and cold-blooded animals. *C. parvum* infects numerous mammals in addition to humans, in particular other primates, cattle and other ruminants, horses, carnivores, and rodents. In all the affected domestic species, very young unweaned animals are more susceptible to the infection and the disease than adults, and calves appear to be most susceptible. The first clinical case of cryptosporidiosis in animals was identified in a calf in 1971. Subsequently, the infection has been found in up to 80% of calves under 1 month of age and up to 62% of apparently healthy adult cattle. In horses, the

infection has been found in 15%–31% of suckling foals, but only 0.6% of adult horses. Of calves with diarrhea studied in the US, 25% were found to be infected.

The Disease in Man: In individuals with healthy immune systems, cryptosporidiosis may be asymptomatic or may occur as a self-limiting disease. The illness is characterized by profuse watery diarrhea that begins explosively one or two weeks after infection and generally lasts 8–20 days, often accompanied by abdominal pain, nausea, vomiting, low-grade fever (under 39°C), and weight loss. In immunodeficient individuals, the symptoms are more severe and may include as many as 71 evacuations per day, with fluid loss of up to 25 liters (Ryan, 1994). Rather than being self-limiting, the disease may persist until the individual's death. In such patients, the parasite has sometimes been found to invade the respiratory and biliary tracts (Clavel *et al.*, 1996).

The Disease in Animals: Cryptosporidiosis is fairly common in young calves. The infection generally appears during the first three weeks of life and affects animals between 3 and 35 days of age. The clinical manifestations are diarrhea, tenesmus, anorexia, and weight loss. It is difficult to distinguish diarrhea caused by *Cryptosporidium* from diarrhea caused by other agents. Anderson (1982) reported that in calves aged 1–15 days from 47 herds, only 17 out of 51 were found to be excreting *Cryptosporidium* oocysts, although all had diarrhea. In horses, swine, and domestic carnivores, the disease has occasionally been reported in very young or immunodeficient animals (Barriga, 1997). Infected rodents do not appear to develop signs of disease. Birds are rarely affected by the species of the parasite that infect mammals.

Source of Infection and Mode of Transmission: The sources of infection for humans are other infected people and infected cattle. There is no solid evidence that other animals are an important source of human infection. Although *Cryptosporidium*-infected cats have been found in association with AIDS patients, it is not clear who infected whom. However, recent studies indicate that *C. parvum* exhibits genetic polymorphism, with one genotype infecting only humans and another infecting humans, cattle, and mice (Peng *et al*., 1997). These genotypes might represent different species, but unequivocal identification of *Cryptosporidium* species is difficult.

The source of infection for domestic animals is other domestic animals. Cross-transmission studies have demonstrated that parasites isolated from humans, goat kids, deer, lambs, and calves can infect and cause diarrhea in pigs, lambs, and calves, while they produce an asymptomatic infection in chickens, colts, and laboratory animals (Tzipori, 1983). Isolates from humans and calves have also been transmitted to kids, puppies, cats, mice, and calves (Current, 1983). *Cryptosporidium* species that infect birds do not infect mammals, and species that infect mammals rarely infect birds.

The infection is transmitted through ingestion of foods and water contaminated with fecal matter from an infected individual, direct contact with infected feces, or ingestion of water from sources contaminated by effluents from sewerage systems or cattle farms. Children, childcare workers who change diapers, bed-ridden patients and their caregivers, people who work with cattle, and individuals who engage in anal sex have a high risk of being infected through direct contact with fecal matter.

Diagnosis: Diarrhea from *Cryptosporidium* is hard to distinguish clinically from diarrheal illnesses due to other causes. Diagnosis of cryptosporidiosis is suspected

on the basis of both clinical symptoms and epidemiological history and is confirmed by demonstrating the presence of oocysts in the patient's feces. However, because oocysts are small (2.5–5 μm in diameter), they are difficult to see with direct microscopic examination of fecal samples. They are therefore more easily detected by means of techniques involving concentration in sugar solutions, such as Sheather's solution, and by phase contrast microscopy. Giemsa or methylene blue staining makes the oocysts more visible but also turns yeast contaminants the same color, making it impossible to distinguish them from the parasite. Ziehl-Neelsen stain, on the other hand, turns oocysts red but does not stain yeast. Auramine-rhodamine and safranine-methylene blue are also useful for distinguishing oocysts. A recently developed technique uses fluorescent monoclonal antibodies specific to *Cryptosporidium* to visualize the parasites in fecal or environmental specimens. The specificity of serologic diagnosis by means of immunofluorescence assay or enzyme-linked immunosorbent assay was initially dubious, but the tests have been refined and now show satisfactory levels of sensitivity and specificity. Although serologic diagnosis is useful for epidemiological studies, the antibodies may appear too late for clinical purposes in immunocompetent patients or may not appear in sufficient quantities in immunodeficient patients.

Procedures for recovering and identifying *Cryptosporidium* in environmental waters are highly variable, inefficient, and time-consuming. The currently recommended practice involves passing large volumes of water through special filters, centrifuging the material trapped by the filters to concentrate it, purifying the concentrate in a Percoll-sucrose gradient, staining with fluorescent antibodies, and, finally, examining the material microscopically.

Control: For an individual, prevention of cryptosporidiosis consists of avoiding the ingestion of raw foods or water that may be contaminated with human or animal feces and avoiding contact with feces (Juraneck, 1995). Cooking high-risk foods and washing hands carefully before eating should also reduce the danger of infection. People should avoid immersion in water containing effluents from sewerage systems or cattle farms. *Cryptosporidium* oocysts are highly resistant to all disinfectants. For example, the CT value (concentration of disinfectant in milligrams per liter multiplied by contact time in minutes) for killing 99% to 99.9% of the *Cryptosporidium* oocysts present in water is 6 to 10 for ozone and 9,600 for chlorine. In contrast, the corresponding values for *Giardia intestinalis* are 0.17 and 15. Exposure to water temperatures of 25°C and 8°C for 4 weeks kills only 50% and 25% of oocysts, respectively (Barriga, 1997). Under favorable conditions, they are probably capable of surviving for several months in nature.

Treatment of drinking water in well-run plants with good filters removes around 99.9% of oocysts.

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CUTANEOUS LEISHMANIASIS

ICD-10 B55.1

Synonyms: Chiclero ulcer, espundia, pian-bois, uta, and buba (in the Americas); oriental sore, Aleppo boil, Baghdad sore, Delhi sore, and other local names (in the Old World).

Etiology: Leishmaniasis is caused by flagellate protozoa of the family Trypanosomatidae, genus *Leishmania*. The life cycle of leishmanias is relatively simple. The flagellate forms of the parasite—oval amastigotes measuring 2 to 5 μm in diameter (see the chapter on Chagas' Disease)—exist within macrophages of a definitive vertebrate host, including humans. Small flies of the family Phlebotomidae (genus *Phlebotomus* in the Old World and *Lutzomyia* in the Americas) ingest the parasites when they feed on the host's blood. Once in the fly's intestine, the amastigotes become promastigotes—extracellular forms with a flagellum emerging from the anterior end, which are fusiform and measure 14 to 20 μm long and 2 to 4 μm wide. The promastigotes then multiply in the intestine of the vector. In the insect, two promastigote forms can be observed: a wider, relatively immotile form that attaches to the wall of the intestine, and another, thinner, motile form that moves freely in the insect's intestinal lumen and proboscis. The first form incubates easily in human serum; the second does not. Presumably, the latter are metacyclic infective forms for the vertebrate which, by regurgitation from the intestine, are inoculated by the fly through the proboscis at its next blood meal (Kettle,

1995). Once inside the vertebrate, the promastigotes become amastigotes, invade the cutaneous macrophages, and multiply in a parasitophorous vacuole. These parasites are equipped with several adaptation mechanisms that enable them to overcome the lethal effects of macrophages and lysosomes on microorganisms (Antoine, 1995). Their multiplication eventually causes the host cell to rupture, and the released amastigotes then invade new macrophages.

Though there have been reports of morphological differentiation of *Leishmania* by computerized image analysis (Youssef *et al*., 1997), it is virtually impossible to distinguish between species by means of conventional microscopy. Moreover, leishmanias seem to be undergoing an active process of evolution: isolates from parasites that cause identical diseases have shown different biochemical characteristics, while isolates from parasites that cause different diseases have similar biochemical features (Barral *et al.*, 1991). Some authors have proposed dividing the genus into two subgenera: *Leishmania*, encompassing forms that multiply in the foregut of their vectors (suprapylaria reproduction), and *Vianna*, comprising leishmania that develop in the midgut and hindgut (peripylaria reproduction). It is widely accepted that very similar groups of leishmanias exist. Those groups have been classified as species or complexes, which in turn comprise various lesser categories or subspecies. The complexes associated with cutaneous or visceral leishmaniasis in the Americas have been identified by polymerase chain reaction (Harris *et al.*, 1998). The species or subspecies of each complex are distinguished mainly by their geographic distribution, the clinical manifestations of the disease they cause, and epidemiologic characteristics.

Current efforts are endeavoring to classify leishmanias by means of serologic methods (agglutination, specificity of excretory antigens, and fluorescence with monoclonal antibodies), biochemical methods (enzymatic profile, nuclear and kinetoplast DNA (kDNA) density, and metabolic characteristics), and molecular biology techniques (genomic DNA sequencing and karyotype analysis), as a result of which new species are being proposed (Kreutzer *et al.*, 1991). Investigators now speak of serodemes (populations that are differentiated by their reactivity, using antibody batteries), zymodemes (populations distinguished by the composition of their isozymes), and schizodemes (populations that can be distinguished by the size of their DNA fragments when they are treated with batteries of restriction enzymes). For example, Chouicha *et al*. (1997) studied 10 enzymatic systems from 137 isolates of *L. braziliensis* obtained in Bolivia, Brazil, and Colombia, and were able to identify 44 closely related zymodemes. Kapoor *et al.* (1998) distinguished *L. tropica* from *L. donovani,* the agent of visceral leishmaniasis in Africa and Asia, and identified different isolates of *L. donovani* using cDNA probes and kDNA fragments.

The complexes that produce cutaneous leishmaniasis in the Americas are *L. mexicana* (which encompasses the species *L. mexicana*, *L. amazonensis*, and *L. venezuelensis*); *L. braziliensis* (*L. braziliensis*, *L. panamensis*, *L. guyanensis*); and *L. peruviana*. In the Old World, the agents of the disease belong to the *L. tropica* complex (*L. tropica*, *L. major*, and *L. aethiopica*) (Chulay, 1991). The complexes that cause American cutaneous leishmaniasis can be distinguished by such characteristics as vector, parasite localization in the insect's intestine, the pathogenicity of the agent on hamster skin, and the growth in culture media (Lainson and Shaw, 1974). The vectors of the *L. mexicana* complex leishmanias are phlebotomines of the group *Nyssomyia*. These parasites undergo suprapylaria development. When inoculated in hamster skin,

they reproduce quickly, forming histiocytomas in which amastigotes are abundant and metastasis is common. They grow profusely in Novy, MacNeal, and Nicolle (NNN) culture medium. In contrast, leishmanias of the *L. braziliensis* complex, for which the vectors are phlebotomines of the groups *Psychodopygus* and *Nyssomyia*, undergo peripylaria development and multiply very slowly in hamster skin, producing small nodules or ulcers with few amastigotes that do not metastasize and whose growth in NNN culture media is slow or moderate (Bonfante-Garrido, 1983).

Geographic Distribution (Table 1): Some leishmanias appear to be indigenous to the Americas, while others were most likely imported from the Old World. Momen *et al*. (1993) found similarities between the isozymes of *L. chagasi* in Central and South America and those of *L. infantum* in the Mediterranean and Asia. They also found zymodemes characteristic of *L. major* from Africa and Asia in parasites isolated in the Americas.

Human cutaneous leishmaniasis in the Americas occurs from southern Mexico to northern Argentina, with sporadic cases in permanent residents and travelers who visit northern Mexico (Melby *et al.*, 1992). In the Caribbean islands, indigenous leishmaniasis exists only in the Dominican Republic (Zeledón, 1992). In South America, on the other hand, only Chile and Uruguay are free of the parasite. Detailed information on the distribution of leishmanias in the Americas can be found in Grimaldi *et al.* (1989). In the Old World, there are known endemic areas along the Mediterranean coast and in the Middle East, several countries of Asia (Azerbaijan, Kazakhstan, Tajikistan, Turkmenistan, and Uzbekistan), northern China, and northwestern India. In Africa, in addition to the foci on the Mediterranean coast, others exist in the western-central, eastern-central, and southern parts of the continent.

Within the *L. mexicana* complex, the subspecies *L. mexicana* is distributed in Belize, Brazil (Vale do Ribeira in the state of São Paulo) (Machado *et al.*, 1983), Guatemala, Mexico (Yucatan Peninsula and foci in Veracruz and Oaxaca), and the US (Texas, Oklahoma, Ohio, and possibly Michigan) (Sellon *et al.*, 1993). *L. amazonensis* is distributed in Mato Grosso in the Amazon Basin of Brazil, and *L. venezuelensis* was described in 1980 and isolated in Venezuela on the banks of the Turbio River in the state of Lara (Bonfante-Garrido, 1984).

Within the *L. braziliensis* complex, the distribution area of *L. braziliensis* encompasses eastern Bolivia, jungle areas of Brazil, Colombia, Ecuador, Paraguay, Peru, and Venezuela (Bonfante-Garrido, 1983). *L. guyanensis* is distributed north of the Amazon in Brazil and in French Guiana, Guyana, and Suriname. *L. panamensis* is present in Costa Rica, Honduras, Panama, and possibly in other Central American countries. *L. peruviana* is limited to the Peruvian Andes and is found only at altitudes of 900 to 3,000 m. In several regions of the Americas, *L. braziliensis* coexists with *L. mexicana*.

As for the complex *L. tropica* in the Old World, the subspecies *L. tropica* is found in some Mediterranean countries (Greece, Tunisia, and Turkey) and in Afghanistan, Iran, Iraq, Israel, Kuwait, and Uganda. In many other countries, such as the former Soviet Union, its identification is dubious owing to lack of information over the last 15 years or because it was eradicated (WHO, 1984). *L. major* exists in the Arabian peninsula, Afghanistan, Algeria, Burkina Faso, Egypt, India, Iran, Iraq, Israel, Jordan, Libya, Mali, Morocco, Mauritania, Pakistan, Senegal, Sudan, Syria, and Turkey. *L. aethiopica* is found in Ethiopia and Kenya (WHO, 1984).

TABLE 1. Features of *Leishmania* infections.

Species	Syndrome	Geographic distribution	Principal reservoir	Principal vector
Leishmania mexicana complex				
L. mexicana	Cutaneous, rarely diffuse	Belize, Brazilian Amazon, Guatemala, Mexico, Venezuela	Rodents	*Lutzomyia olmeca*
L. amazonensis	Cutaneous and diffuse	Brazilian Amazon	Rodents and marsupials	*Lutzomyia flaviscutellata*
L. venezuelensis	Cutaneous	Venezuela	Unknown	*Lutzomyia olmeca*
L. braziliensis complex				
L. braziliensis	Cutaneous and mucocutaneous	Bolivia, Brazil, Colombia, Paraguay, Peru, Venezuela	Rodents, dogs	*Lutzomyia wellcomei*
L. panamensis	Cutaneous, rarely mucocutaneous	Colombia, Costa Rica, Panama	Sloths	*Lutzomyia trapidoi*
L. guyanensis	Cutaneous	French Guiana, Guyana, Suriname	Sloths, anteaters	*Lutzomyia umbratilis*
L. peruviana	Cutaneous	Argentina, Peru	Dogs	*Lutzomyia peruensis* *Lutzomyia verrucarum*
L. tropica complex				
L. tropica	Cutaneous	Middle East, Mediterranean coast, Southeast Asia	Man, dogs	*Phlebotomus sergenti* *Phlebotomus papatasi*
L. major	Cutaneous	Middle East, Southeast Asia, Sub-Saharan Africa	Gerbils	*Phlebotomus papatasi* *Phlebotomus caucasicus*
L. aethiopica	Cutaneous and diffuse	Ethiopia, Kenya	Hyraxes	*Phlebotomus longipes* *Phlebotomus pedifer*
L. donovani complex				
L. donovani	Visceral	India, Nepal, Pakistan, Sub-Saharan Africa, Western Africa	Man, dogs, rodents	*Phlebotomus argentipes* *Phlebotomus orientalis* *Phlebotomus martini*
L. infantum	Visceral	Mediterranean coast, Central Asia, China, Middle East	Domestic and wild canids	*Phlebotomus perniciosus* *Phlebotomus major* *Phlebotomus caucasicus* *Phlebotomus chinensis* *Phlebotomus sergenti*
L. chagasi	Visceral	Central and South America	Canids	*Lutzomyia longipalpis*

Occurrence: Leishmaniasis is believed to be endemic in 88 countries—72 of them developing countries—on four continents. It is estimated that every year between 1.5 and 2 million new cases occur, of which only 600,000 are officially reported. An estimated 320–350 million people are at risk of acquiring the infection and 12 million are already infected (Desjeux, 1992; WHO, 2003). Ninety percent of all cases of cutaneous leishmaniasis occur in Afghanistan, Brazil, Peru, Saudi Arabia, and Syria (WHO, 2003). Despite some local successes in controlling the infection, it seems to be expanding in range and increasing in prevalence. Cutaneous leishmaniasis prevalence rates vary considerably, but most endemic countries are reporting an increase in cases or an expansion in the disease's distribution. For example, in 1972, a total of 22,368 human cases of leishmaniasis (cutaneous and visceral) were reported in the Americas, 20,348 of them from Mesoamerica, especially Guatemala (29.6 per 100,000 population), and 2,020 from South America (2.9 per 100,000 population) (PAHO, 1975). Since 1987, Brazil has been reporting between 23,000 and 26,000 cases of cutaneous leishmaniasis annually, with 2,511 cases of visceral leishmaniasis in 1985 alone (Lacerda, 1994). Although part of this increase may be due to improved reporting, Jorquera *et al.* (1998) found a prevalence of 16.7% in three communities in Venezuela, and prevalences of 47% were recorded in Ecuador (Armijos *et al.*, 1997), 34% in Brazil (Pignatti *et al.*, 1995), 10.7–20% among 11,517 children in Iran (Sharifi *et al.*, 1998), and 64.8% in 4 communities in Iran (Yaghoobi-Ershadi and Javadian, 1995).

The Disease in Man: Cutaneous leishmaniasis is a polymorphous disease that may affect only the skin or both the skin and the mucous membranes. It manifests initially as itchy erythematous lesions, which later form papules and then painless ulcers. The incubation period is between one week and several months. There may be one or many lesions, and they may sometimes be nonulcerative and diffuse. Though the lesions generally heal spontaneously within weeks or months, they may persist for as long as a year, or more. Spontaneous healing of leishmaniasis in man has been shown to depend on cell-mediated immunity and production of gamma interferon (Carvalho *et al.*, 1995). In AIDS patients, the manifestations are atypical and relapses are frequent (Agostoni *et al.*, 1998). In the Americas, the disease occurs in several clinical forms, depending mainly, but not solely, on the species of the etiologic agent involved.

a) Leishmaniasis due to *L. mexicana mexicana* predominates in Central America and southeastern Mexico. It causes a benign infection with only one or a few skin ulcers, known as chiclero ulcer, chiclero ear, or bay sore. The lesion is usually located on the earflap or, less often, on the face or extremities. It begins with an erythematous papule that then ulcerates and, when the scab comes off, bleeds easily. The lesions on the earflap are deforming, tend to be chronic, and may last many years, while those on other parts of the body heal spontaneously in about six months. A distinctive feature of this form of cutaneous leishmaniasis is that it may spread to the lymph nodes, though this very rarely occurs. In Mexico, no cases of mucocutaneous leishmaniasis have been detected, but two or three cases of cutaneous lesions that invaded the contiguous mucosa have been reported. The vectors are not especially attracted to man, and the main victims tend to be people who spend a lot of time in the forest, the vector's habitat, such as the gum tappers (*chicleros*) who work there during the rainy season when phlebotomine flies are plentiful.

b) *L. mexicana amazonensis* leishmaniasis occurs in the Amazon basin of Brazil and neighboring countries. Human cases due to this agent are rare because the vectors are nocturnal and not normally anthropophilic, and they inhabit marshy areas where man does not ordinarily live. The infection causes single or multiple lesions that rarely heal spontaneously. Around 30% of patients have diffuse cutaneous lesions characterized by thickening of the skin in the form of scattered plaques, papules, or nodules, found mainly on the face and legs.

c) *L. mexicana pifanoi* causes a diffuse cutaneous leishmaniasis similar to lepromatous leprosy, with which it is often confused. This diffuse form of leishmaniasis has been described in Venezuela, but it also occurs in other areas. Outside the Americas, cases have been reported from Ethiopia and Kenya. This form appears in individuals with immune system deficiencies. Patients with diffuse cutaneous leishmaniasis are anergic and do not react to the Montenegro skin test. The lesions harbor a large number of parasites. Healthy volunteers inoculated with parasites from patients with diffuse cutaneous leishmaniasis developed a localized lesion at the inoculation site which healed without sequelae. For that reason, the occurrence of this form is believed to be due more to deficient immune response in the host than to some special property of the parasite. Human cases of diffuse cutaneous leishmaniasis are infrequent.

d) *L. mexicana venezuelensis* leishmaniasis causes ulcerous lesions and, less frequently, nodules or ulceronodular lesions.

e) *L. braziliensis braziliensis* causes the mucocutaneous form of leishmaniasis known as espundia. The disease begins with a papular lesion on the face or extremities that may develop into a painless ulcer that seldom heals spontaneously. A characteristic feature of this form is metastasis to the mucocutaneous parts of the body. A sizable proportion of untreated patients develop lesions on the nasal septum, mouth, nasopharynx, and, sometimes, even the anorectal region, penis, scrotum, and vulva. These metastases may occur simultaneously with the primary lesion or, more often, much later, and may cause severe destruction of the affected tissue, disfiguring the patient. The secondary lesions are ulcerous or indurated.

f) Leishmaniasis due to *L. braziliensis guyanensis* occurs in Guyana, French Guiana, Suriname, and northern Brazil; it causes characteristic lesions on the skin, which frequently spread via the lymph vessels and produce ulcers known as pian bois all over the body.

g) *L. braziliensis peruviana* leishmaniasis exists in villages in Andean valleys of Peru and causes a form of cutaneous leishmaniasis called uta, characterized by a single lesion that tends not to metastasize and heals spontaneously. The disease mainly affects children.

h) *L. braziliensis panamensis* causes ulcerous skin lesions and, occasionally, affects the mucosa.

Despite these descriptions, most clinical physicians indicate that it is very difficult to differentiate between subspecies of leishmanias based only on the lesions they cause.

In the Old World, cutaneous leishmaniasis occurs in three main forms:

a) *L. major* causes the rural or wet form of leishmaniasis that occurs in semidesert and desert regions. The lesion begins as a papule on the exposed parts of the body (face and extremities), which develops into a wet ulcer. The lesions may

spread, either directly or via the lymph system. The disease lasts two to eight months, and fibrosis during spontaneous healing leaves a permanent scar.

b) *L. tropica* causes the dry form of leishmaniasis, which occurs in urban and peri-urban areas primarily in the Middle East. The initial papule develops slowly, and ulceration, when it occurs, is also slow to develop. The disease has a long course—a year or more—and leaves a permanent scar. In contrast to the wet form, the lesions contain large numbers of parasites.

c) *L. aethiopica* causes three types of lesions: the oriental button or furuncle, the mucocutaneous form, and diffuse cutaneous leishmaniasis. The lesions develop slowly and may or may not ulcerate later. Spontaneous healing occurs after one to three years, or sometimes longer (WHO, 1984).

The Disease in Animals: In the Americas, until recently only *L. braziliensis peruviana*, the agent of human cutaneous leishmaniasis, and *L. donovani chagasi*, the agent of human visceral leishmaniasis, had been identified in dogs. However, *L. braziliensis* has since been found in dogs in São Paulo, Brazil. Owing to the difficulty of identifying the parasite species, the etiologic agent of leishmaniasis in dogs is sometimes called simply *L. canis* (Santos *et al.*, 1998). The prevalence in dogs may be high. In 270 dogs from endemic areas of Rio de Janeiro, Brazil, Santos *et al*. (1998) found that 31.5% had acute or chronic lesions, results of indirect immunofluorescence were positive in 25.1%, and the skin test yielded positive results in 40.5%.

In the Old World, dogs are affected by *L. tropica*, which causes a cutaneous disease in man, and by subspecies of *L. donovani*—except for those isolated in India—which causes a visceral disease in humans. Regardless of which species causes the infection, dogs often exhibit both cutaneous and visceral manifestations. In endemic areas, leishmaniasis may also occur in equines, which develop nodular lesions and sometimes scabs or ulcers, but only on or around the earflap.

In Venezuela, of 116 donkeys examined, 28 had one or more ulcerous lesions and 17 (15%) had positive microscopy. Based on its behavior in hamsters and culture media, the authors classified the agent as *L. braziliensis* (Bonfante-Garrido *et al.*, 1981). In general, infections in wild animals are inapparent. In rodents and other wild animals, apparent infections by the agents of the *L. mexicana* complex produce skin alterations, mainly at the base of the tail and, occasionally, on the ears and toes. Lesions consist of swellings with hair loss and, sometimes, ulcers, in which the presence of amastigotes can be demonstrated. Infection in these hosts is prolonged. *L. mexicana amazonensis* infection has also been found in the rodent *Proechimys guyannensis* and other animals in the Amazon Basin. In these cases, the skin remains normal in appearance but the parasites are dispersed in the dermis. The parasites of the *L. braziliensis* complex produce a systemic infection in wild animals, but skin lesions are rarely seen. The parasites can be cultured from blood, viscera (spleen, liver), and apparently normal skin.

Source of Infection and Mode of Transmission: In the Americas, the reservoirs of cutaneous leishmaniasis are generally rodents or edentate animals (Table 1). The infection is transmitted from one wild animal to another by means of phlebotomine flies of the genus *Lutzomyia*. Humans are infected accidentally by the bite of these phlebotomines when they enter enzootic areas in the jungle. Recent studies have shown that a large number of wild mammal species are infected, but not all of these

animals can be considered primary hosts, either because they are not very abundant or their infection rate is too low for them to play that role. The exception is dogs, the only known nonhuman hosts of *L. b. peruviana.* However, Lainson (1983) suspected that dogs are actually a secondary host of this infection (uta) and that the primary host is a wild animal. Infected domestic rats (*Rattus rattus*) have been found in Brazil. In Manaus, Brazil, opossums of the species *Didelphis marsupialis* may also serve as a link between the wild enzootic and the peridomestic cycles (WHO, 1984). It is possible that the infections produced by the *L. mexicana* complex are maintained in nature not by a single specific host, but by a wide variety of species associated with a particular type of habitat (WHO, 1984). In some areas of the Americas, the relative roles of the various infected animal species have not been clearly defined.

In the Old World, the vectors belong to the genus *Phlebotomus*. The main reservoir of *L. major* in the former Soviet Union is the great gerbil *Rhombomys opimus*. Infected colonies of this desert or semidesert rodent have been found in Iran, the southern part of the former Soviet Union, and from northern Afghanistan to Mongolia. In northwestern India and in Israel and Morocco, the reservoirs are *Meriones* spp. The infection in these rodents is quite prolonged. In Algeria, northwestern Libya, and Israel, *Psammomys obesus* serves as the reservoir, while in Ethiopia and Senegal, the reservoirs are species of *Mastomys*, *Tatera*, and *Arvicanthis*.

The agent *L. tropica* has been isolated from dogs and from *Rattus rattus*, but most investigators believe that the maintenance host is man. Lainson (1982) does not share that opinion, however, pointing out that person-to-person transmission is unlikely, since this agent causes few skin lesions in humans and those lesions contain only scant numbers of amastigotes.

In Ethiopia and Kenya, *L. aethiopica* infection is maintained by hyraxes, such as *Procavia capensis*, *Heterohyrax brucei*, and *Dendrohyrax arboreus*.

Cutaneous leishmaniasis is a zoonosis. Humans are accidental hosts who acquire the infection when they enter enzootic forest areas for occupational purposes (e.g., lumberjacks, gum tappers, oilfield workers, cattlemen, and farmers). Cutaneous leishmaniasis may be a serious problem in rural settlements within the jungle. Permanent human settlements in enzootic areas generate significant ecological changes, especially deforestation, replacement of wildlife with domestic animals, and replacement or modification in the prevalence of some insects as species better adapted to the new environment become dominant. These ecological changes also modify the epidemiology of cutaneous leishmaniasis: in Vale do Ribeira, São Paulo, Brazil, 80% of cutaneous leishmaniasis patients worked near their homes and had no contact with the jungle. The devastation of the natural environment altered the species composition of the phlebotomine population in that region and *Psychodopygus intermedius*—a species that prefers secondary growth, enters human dwellings, and is anthropophilic—became dominant (Tolezano *et al.*, 1980).

In the western-central region of Venezuela, the disease used to occur exclusively among the inhabitants of villages located near mountainous areas with dense vegetation. However, cases have been diagnosed in several neighborhoods on the outskirts of the city of Barquisimeto (Bonfante-Garrido *et al.*, 1984). It is not yet known whether this was due to some ecological change, but the appearance of the disease in an urban environment shows that cutaneous leishmaniasis is not always sylvatic or rural and that its epidemiology is changing. Among the American cutaneous leishmaniases, uta in Peru is exceptional because no wild reservoirs of the parasite

are known. In the Old World, *L. major* infection is a rural zoonosis, whereas *L. tropica* infections appear to be transmitted between humans in an urban environment.

Diagnosis: The simplest specific diagnostic method consists of confirming the presence of amastigotes in lesions. For that purpose, the lesion is cleaned with 70% alcohol to remove any necrotic matter. Then, a sample is taken from the edge or base of the lesion (nodule or ulcer of the skin or mucosa) by aspiration, scraping, or biopsy. The sample is mounted on a slide and stained using the Giemsa or Wright technique. Numerous amastigotes may be seen in the case of lesions that are recent or active, but in lesions that are chronic or healing, it can be difficult or impossible to demonstrate the presence of parasites by direct smear microscopy or biopsy. Parasitologic diagnosis is especially difficult in the mucocutaneous form (Cuba Cuba *et al.*, 1981).

Isolation of the agent can be accomplished by culturing the sample in an appropriate medium, such as NNN or Schneider's Drosophila, with a supplement of 30% fetal bovine serum. The promastigotes grow in these media and can be observed within a week. Another procedure is intracutaneous or intranasal inoculation of the suspicious material into hamsters, but it may take two months or more to obtain a positive result. The best results are obtained by culturing and inoculating hamsters simultaneously. Parasites of the *L. mexicana* complex grow abundantly in laboratory media. When inoculated into the nose of a hamster, a histiocytoma containing many amastigotes forms within a few weeks, and the infection spreads by metastasis. In contrast, parasites of the *L. braziliensis* complex grow poorly in artificial culture media, and when inoculated in hamsters produce a small nodule or ulcer that takes six months or more to form. These lesions contain few amastigotes and do not metastasize.

Numerous immunologic tests have been used to diagnose cutaneous leishmaniasis, including the Montenegro skin test, immunofluorescence, direct agglutination, latex agglutination, gel immunodiffusion, and enzyme-linked immunosorbent assay (ELISA). The Montenegro skin test is a delayed hypersensitivity reaction, which is read 48–72 hours after intradermal injection of a suspension of promastigotes. It is group-specific but not species-specific, and it is useful in epidemiologic surveys. Though frequently positive in the cutaneous and mucocutaneous forms, the Montenegro test is ordinarily negative in the visceral and diffuse cutaneous forms. It does not produce cross-reactions with the agents of American or African trypanosomiasis, and its application will not affect the titer for any subsequent serologic reactions (Amato Neto *et al.*, 1996). The indirect immunofluorescence test, perhaps the most widely used of the serologic reactions, yields better results with an amastigote antigen than with a promastigote antigen; however, there is no correlation between the titer required to produce a reaction and clinical manifestations, duration, or number of lesions (Cuba Cuba *et al.*, 1981). An IgA conjugate proved superior to IgG when used to diagnose the mucocutaneous form (Lainson, 1983).

Serology for the cutaneous leishmaniases of the Old World is generally negative (WHO, 1984). In general, serology is positive in only 70% to 80% of cases, at low titers—except in the mucosal forms—and only after two to three months following initial infection. Polymerase chain reaction had a sensitivity of 86% when used alone and 93% when used in combination with Southern blotting. In contrast, microscopy of histological sections and impression smears exhibited a sensitivity of only 76% and 48%, respectively (Andresen *et al.*, 1996).

Control: Cutaneous leishmaniases in the Americas are mainly diseases of forest areas, with sylvatic reservoirs and vectors. Hence, it is impossible to control them by eliminating reservoirs and vectors. The only effective method of prevention is to avoid endemic areas or use repellents and protective clothing to avoid being bitten by the insect vectors. In special circumstances, the environment may be modified by means of deforestation to eliminate vector habitats. In camps or in domestic and peridomestic areas where *L. peruviana* and *L. tropica* exist, the walls of rooms can be sprayed with insecticide and windows can be covered with fine mesh to control the vectors. Use of insecticides in antimalaria campaigns in Southeast Asia led to virtual disappearance of visceral and cutaneous leishmaniasis from the region. Patients infected with *L. b. braziliensis* should be treated as soon as possible to prevent development of the mucocutaneous form, as should those infected with *L. mexicana amazonensis* to prevent the occurrence of diffuse cutaneous leishmaniasis. It is believed that uta could be prevented by eliminating infected dogs in the endemic areas of Peru. However, the elimination of reservoirs has not generally been effective against the urban cutaneous leishmaniasis in the Old World.

In Iran, Israel, and the former Soviet Union, immunization with virulent strains of *L. major* has been practiced to prevent infection with that agent and with *L. tropica.* The inoculation is intended to prevent later infections that cause deforming lesions on the face, and it is applied on a part of the body where the scar will not be visible or unattractive. Inoculated individuals are advised to remain outside endemic areas until immunity is established. This type of immunization is not recommended, though it may be useful for people who must enter high-risk areas. Armijos *et al*. (1998) achieved 72.9% protection in Ecuadorian children by administering a killed promastigote vaccine with BCG adjuvant.

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CYCLOSPORIASIS

Etiology: Cyclosporiasis is caused by *Cyclospora cayetanensis*, a coccidium related taxonomically to the genus *Eimeria* and clinically to the genera *Cryptosporidium* and *Isospora*. The earliest reports of the disease—from Peru in 1986—referred to cyanobacteria-like bodies found in human feces. Subsequent studies revealed their coccidial nature. Apparently, similar organisms had been observed in New Guinea in 1977 and had been confused with *Isospora* (Sterling and Ortega, 1999).

The life cycle of *Cyclospora* is not yet fully known, but various observations, as well as the organism's similarities to other coccidia, suggest that parasites ingested

in mature oocysts lodge in the epithelial cells of the duodenum and jejunum, where they multiply asexually to form merozoites. It is not known whether these forms must leave the host cell and invade new cells to begin the next phase of sexual multiplication, which concludes with the formation of oocysts. The oocysts, which must sporulate in the external environment to become infective, are passed from the body in feces. The mature oocyst contains two sporocysts, each of which contains two sporozoites (Ortega *et al.,* 1998).

Geographic Distribution: Probably worldwide. The first cases were seen in Nepal, New Guinea, and Peru, but since then the infection has been confirmed in the Americas, North Africa, Southeast Asia, Australia, Bangladesh, Western Europe, Indonesia, Pakistan, Papua New Guinea, the UK, and the Middle East (Drenaggi *et al*., 1998).

Occurrence in Man: The distribution of *Cyclospora* is similar to that of *Cryptosporidium*, although it is only a third to a half as prevalent (various surveys have found prevalence rates of 1% to 20%). It infects mainly children between 2 and 4 years of age, and the prevalence diminishes rapidly with age. Approximately one-third of infected individuals are symptomatic. Although the infection does affect travelers and immunocompromised patients, it does not appear to be predominantly associated with these groups.

Occurrence in Animals: Animals do not appear to be susceptible to cyclosporiasis. Eberhard *et al*. (2000) attempted to infect nine strains of mice (including some immunodeficient animals), rats, chickens, ducks, rabbits, hamsters, ferrets, pigs, dogs, and various monkeys with oocysts obtained from Guatemala, Haiti, Nepal, Peru, and the US. None of the animals manifested clinical signs of infection or disease.

The Disease in Man: The disease in humans is characterized by watery diarrhea, which begins abruptly after an incubation period of 12 hours to 11 days. In immunocompetent individuals, it lasts from six to eight weeks, while in immunodeficient patients it may persist for up to three months (Looney, 1998). In a study in Egypt, the diarrhea lasted 28±8 days in children and 37±12 days in adults, with more than 5 evacuations per day (Nassef *et al.*, 1998). Of 63 infected individuals in Peru, 68% were asymptomatic and the highest prevalence occurred among children aged 2 to 4 years. The prevalence decreases in winter and with age (Madico *et al.*, 1997). Patients usually experience anorexia and weight loss. Examinations have shown malabsorption, atrophy of villi, and crypt hyperplasia (Connor, 1997). Not all infected individuals develop the disease. In Haiti, 15%–20% of the population examined were found to be carriers of *Cyclospora* oocysts, but few had diarrhea (Eberhard *et al.*, 1999).

The Disease in Animals: *Cyclospora* does not appear to infect animals (see Occurrence in Animals).

Source of Infection and Mode of Transmission: Cyclosporiasis is acquired through ingestion of raw fruits and vegetables and contaminated water. The second outbreak of cyclosporiasis in the US affected 1,400 people and was attributed to consumption of raspberries from Guatemala (Katz *et al.*, 1996). A later study, in which 5,552 stool samples were collected from workers on raspberry farms in Guatemala, found infection rates of between 2.3% and 6.7%, with children showing

the highest rates (Bern *et al.*, 1999). The highest prevalence occurred during the warm months. In Peru, Ortega *et al*. (1997) found that 14.5% of vegetables obtained from markets were contaminated with *Cryptosporidium* and 1.8% with *Cyclospora*. In two outbreaks in the US, basil seems to have been the vehicle (López *et al.,* 1999), while in Spain, cases have been attributed to consumption of raspberries, buffalo milk, and raw fish (Gascon *et al*., 2001). The study by Bern *et al.* (1999) in Guatemala revealed that the principal risk for infection among those affected was consumption of untreated water. A study of the water in domestic containers in Egypt showed that 56% was contaminated with *Giardia*, 50% with *Cryptosporidium*, 12% with *Blastocystis*, 9% with *Cyclospora*, and 3% with microsporidia (Khalifa *et al*., 2001). Using microscopy and molecular biology techniques, Sturbaum (1998) identified *Cyclospora* oocysts in wastewater.

Diagnosis: *Cyclospora* infection is suggested by the patient's symptoms and by epidemiological circumstances, especially in travelers who have visited endemic areas. The diagnosis is confirmed by detection of the double-walled oocysts measuring 8–10 microns in diameter in stool samples. The oocysts are concentrated by formol-ether sedimentation and flotation in Sheather's sucrose solution. They can be detected by staining, autofluorescence under ultraviolet light, phase contrast microscopy, or polymerase chain reaction (Ortega *et al.*, 1998). The stains used most frequently (to make it easier to visualize the organisms and to differentiate them from yeasts) are trichrome stains, Ziehl-Neelsen, Giemsa, safranin with methylene blue, calcofluor white, and auramine phenol. Safranin has been found to be the most effective and appropriate stain for use in diagnostic laboratories (Negm, 1998).

Control: Cyclosporiasis can be prevented by applying the classic measures for control of parasitoses transmitted via the fecal-oral route: washing foods that are eaten raw, boiling suspicious water, and washing hands before eating. Treatment of water contaminated with *Giardia*, *Cryptosporidium*, *Blastocystis*, *Cyclospora*, or microsporidia with chlorine at 4 or 8 parts per million (ppm) or with ozone at 1 ppm showed that ozone was more effective in destroying the parasites, but that it did not totally inactivate *Cyclospora* or *Blastocystis* (Khalifa *et al.*, 2001).

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GIARDIASIS

ICD-10 A07.1

Synonyms: Lambliasis, *Giardia* enteritis.

Etiology: The taxonomy of the species of the genus *Giardia* is still controversial. Three morphological forms are currently accepted: *G. intestinalis,* which affects man, domestic animals, and other mammals; *G. muris*, which affects birds, rodents, and reptiles; and *G. agilis*, which affects amphibians (Barriga, 1997; Meyer, 1990). Although in the past many species were described and named according to the host in which they were found—for example, *G. canis, G. bovis,* and *G. caviae*—there are no clearly defined criteria for differentiating them. Giardia infection in man is caused by *G. intestinalis,* also called *G. duodenalis, G. lamblia*, and, sometimes, *Lamblia intestinalis.* Although *Lamblia* was the original name given to the genus by Lambl when he first described it in 1859, Stiles changed it to *Giardia* in 1915. It is possible, however, that *G. intestinalis* is a complex of several species or subspecies (Adam, 1991).

G. intestinalis is a flagellate protozoan whose life cycle includes trophozoites in the vegetative stage and cysts in the transmission stage. The trophozoites are pyriform and measure 10 µm to 19 µm long, 5 µm to 12 µm wide, and 2 µm to 4 µm thick. They have four pairs of flagella which extend towards the rear part of the

organism, two nuclei, two claw-shaped median bodies in the middle of the body, and a convex ventral disk in the front half of the body, with which they cling to the intestinal mucosa. Those forms live in the anterior portion of the host's small intestine, particularly in the duodenum, where they multiply by binary fission. Many of the trophozoites are carried to the ileum, where they secrete a resistant wall and become ovoid cysts measuring 7 µm to 10 µm by 8 µm to 13 µm. After encysting, the parasite's organs divide again. The mature cyst thus has four nuclei, four median bodies, and eight flagella. Division of the cytoplasm does not occur until the parasite excysts. The cysts leave the host in feces. They can survive for more than two months in water at 8°C and around one month at 21°C; however, they are sensitive to desiccation, freezing, and sunlight. They are also relatively sensitive to ordinary disinfectants. Solutions of quaternary ammonium recommended for disinfecting the environment will kill them in one minute at 20°C, but normal concentrations of chlorine in drinking water do not affect them. The mature cyst is the infective element for a new host. Once ingested, the parasite excysts in the duodenum, divides, and begins to multiply normally.

Geographic Distribution: Worldwide.

Occurrence in Man: Giardiasis is endemic throughout the world. Its prevalence generally ranges from 2% to 4% in industrialized countries, but it may be over 15% among children in developing countries. Both the infection and the disease are more common in children than in adults. Giardiasis may also occur in epidemic form. Of 25 and 22 disease epidemics spread through ingestion of drinking or recreational waters, which affected 2,366 and 2,567 people in the US in 1993–1994 and 1995–1996, respectively, *G. intestinalis* was the most common pathogen. In the first epidemic, together with *Cryptosporidium*, it caused 40% of the cases, while in the second epidemic, together with *Shigella sonnei*, it was responsible for 9% of the cases (Kramer *et al.,* 1996; Levy *et al*., 1998). In 1974, in a population of 46,000 inhabitants in the state of New York, US, 4,800 people (10.4%) contracted clinical giardiasis as a result of contamination of drinking water supplies. In epidemic situations, all age groups are affected equally. In previously uninfected populations, morbidity rates may be as high as 20% or more of the total population (Knight, 1980). Outbreaks are relatively common in institutions for children, such as orphanages and daycare centers. *G. intestinalis* is also frequently a cause of "travelers' diarrhea." In a group of 21 people whose feces tested negative for *Giardia*, the protozoan's cysts were later found in those of 15 out of 17 who became ill after visiting Leningrad (Kulda and Nohynková, 1978). The infection is less frequent in AIDS patients, perhaps because the virus interferes with the parasite's activity in the intestinal mucosa (Lindo *et al*., 1998).

Occurrence in Animals: The infection has been confirmed in a wide variety of domestic and wild mammal species. Surveys from all over the world have found prevalences of 20% to 35% in young dogs; 10% to 15% in young cats; 5% to 90% in calves; 6% to 80% in lambs; 17% to 32% in foals; and 7% to 44% in young pigs (Xiao, 1994). As with man, the infection is less frequent in adult animals. In a study in which feces of 494 dogs were examined for parasites, the infection was detected in 3.4% of adult males, 7% of adult females, and 53.2% of puppies. A study in Colorado, US, found cysts of the parasite in 10% of the cattle, 18% of the beavers,

and 6% of the coyotes examined. A giardiasis outbreak among nonhuman primates and zoo personnel was recorded in Kansas City, Missouri, US. High rates of infection have also been found in rats and other rodents, both synanthropic and wild, but whether the agent was *G. intestinalis* or *G. muris* has not been determined (Meyer and Jarroll, 1982).

The Disease in Man: The majority of infections are subclinical (Flanagan, 1992; Farthing, 1996). Rajeshwari *et al*. (1996) found that impairment of the humoral immune response was the deciding factor in whether or not the infection was symptomatic in children. In symptomatic individuals, the incubation period is generally 3–25 days (Benenson, 1997). The symptomatology consists mainly of diarrhea and bloating, frequently accompanied by abdominal pain. Nausea and vomiting occur less frequently. The acute phase of the disease lasts 3–4 days. In some persons, giardiasis may be a prolonged illness, with episodes of recurring diarrhea and flatulence, urticaria, and intolerance of certain foods. These and other allergic manifestations associated with giardiasis disappear after treatment and cure. Meloni *et al*. (1995) examined 97 isolates of *G. intestinalis* from humans and various animals and differentiated 47 zymodemes. In another study, Cevallos *et al*. (1995) found a correlation between certain zymodemes and the pathology caused by the parasite in rats. However, Rajeshwari *et al*. (1996) demonstrated that neither the zymodeme of the parasite nor the presence of associated bacterial infections influenced the occurrence or the pathogenicity of the infection in children.

The Disease in Animals: As in man, the infection is usually asymptomatic. The manifestations of the disease in dogs and cats are also similar to those in man. However, experimental infections in ruminants produced only mild diarrhea in calves and weight loss in lambs (Zajac, 1992; Olson *et al*., 1995). The disease is more frequent in young animals.

Source of Infection and Mode of Transmission: Man is the principal reservoir of human giardiasis. The source of infection is feces containing the parasite's cysts, which often contaminate water. Although the infection in individuals is often self-limited and disappears within a few months, continuous transmission to other hosts in endemic areas ensures the agent's persistence. The existence of asymptomatic infected individuals and chronic patients, coupled with the cysts' resistance to environmental factors, are important factors in the epidemiology. The median infective dose (ID_{50}) of giardiasis for man is only 10 cysts, but infected individuals may later excrete up to 900 million cysts per day in their feces. Elimination of cysts can be intermittent and the quantity can vary greatly (Knight, 1980).

The most frequent mode of transmission appears to be ingestion of water contaminated with cysts (Hill, 1993). Direct hand-to-hand or hand-to-mouth transmission of cysts from an infected person to a susceptible person is also common, especially among children, personnel in institutions that care for children or adults, and food-handlers. Rezende *et al*. (1997) studied 264 food-handlers in 57 schools in Minas Gerais (Brazil) at various times of the year and found 8%, 2%, and 3% to be infected. Indirect transmission from fecal contamination of food is less frequent than direct transmission from infected food-handlers, but it may occur as a result of irrigating or washing foods with contaminated water or by means of mechanical vectors. However, as the cysts are susceptible to environmental factors such as desicca-

tion, high or low temperatures, and sunlight, they cannot survive for long on foods. All the epidemics that have occurred in various cities have been due to contamination of drinking water or water in pools, lagoons, and ponds. An association has been described between giardiasis, hypochlorhydria, and pancreatic disease among children suffering from protein-calorie malnutrition, which is very frequent in developing countries. Giardiasis and hypochlorhydria are more common in people of blood type A than in people of other types (Knight, 1980).

Some animals probably also serve as reservoirs for human infection. The giardias that infect man and domestic and wild animals are morphologically identical, and several experiments have demonstrated that cross-species infections can occur. *G. intestinalis* cysts of human origin have produced infection in several animal species, including dogs, raccoons (*Procyon lotor*), rats (*Rattus norvegicus*), gerbils (*Gerbillus gerbillus*), guinea pigs, mouflon sheep (*Ovis musimon*), bighorn sheep (*Ovis canadensis*), and pronghorn antelope (*Antilocapra americana*). In another experiment, two of three human volunteers and four of four dogs were infected with *Giardia* cysts from beavers, but hamsters, guinea pigs, mice, and rats did not become infected. A human volunteer who ingested cysts from a blacktail deer was infected, but dogs similarly exposed were not (WHO, 1981). However, neither positive nor negative results are completely reliable: the former may be due to resurgence of a previous infection and the latter to resistance acquired through earlier infections (Meyer and Radulescu, 1979). The most extensive outbreak of human giardiasis attributed to an animal source occurred in 1976 in Camas, a city of 6,000 inhabitants in the state of Washington, US, where 128 cases of giardiasis were confirmed. Part of the Camas water supply came from two remote mountain streams, and though epidemiologic investigation revealed no human source of contamination, several infected beavers were found in the area of the streams. Specific-pathogen-free puppies have also been infected with *Giardia* cysts from beavers. Another apparent example of cross-transmission occurred in 1978 in a zoo in the US, where six primates and three female employees contracted the infection from an infected gibbon that had been placed in a special care unit (Armstrong *et al*., 1979). Meloni *et al*. (1995) found certain similarities between isolates from humans and those from other animals, as well as extensive genetic variation in human *Giardia* isolates. The authors interpreted this discovery as evidence of zoonotic transmission of the parasite.

Diagnosis: Diagnosis is generally made by identifying parasites in the patient's feces. Cysts prevail in formed feces, while trophozoites are more commonly found in diarrheal stools. Different methods should be used in each case to preserve and process samples. Concentration methods are useful for the detection of cysts. As cysts are eliminated intermittently, at least three samples, taken every other day, should be examined to rule out the infection. Excretion of trophozoites is also irregular. The recommended procedures for detecting them are simultaneous examination of fresh stool samples, in which the parasite can be identified by its characteristic flagellar movement, and examination of fixed and stained samples, in which the parasite can be identified by its characteristic morphology. Some experts recommend taking up to six samples and looking for trophozoites in fixed and stained preparations, even in formed feces (García and Bruckner, 1997). Aspiration of duodenal fluid or duodenal biopsy can also be performed to reveal the presence of trophozoites. Specific fluorescent antibodies have been used as a diagnostic method

for detecting cysts, as these techniques facilitate visualization under the microscope with a sensitivity 2.3 times greater than observation without fluorescence (Winiecka-Krusnell, 1995). The enzyme-linked immunosorbent assay (ELISA) has also been used to demonstrate the presence of *G. intestinalis* antigens in feces (Hill, 1993). Although the presence of antibodies and cell-mediated immune responses have been reported in patients, immunobiological procedures are not very specific (Isaac-Renton *et al*., 1994) and do not indicate whether an infection is current or residual. The possibility of using polymerase chain reaction to detect specific DNA sequences in patients' feces or blood is currently being studied. In any event, it should be borne in mind that there is not always a causal relationship between symptoms and the discovery of giardias in an ill person, and it is therefore necessary to rule out infections due to other intestinal microorganisms or other pathologies.

Control: As the cysts of *G. intestinalis* can live for long periods in water, public water supplies should be protected against contamination by human and animal fecal matter. Adequate systems of sedimentation, flocculation, and filtration can remove *Giardia* from water, allowing the use of surface water supply systems (CDC, 1977). Sanitary elimination of feces is another important measure. In developing countries, prevailing socioeconomic conditions make it difficult to prevent infection in children. Instruction in personal hygiene is essential in institutions for children. Individual prevention measures include boiling or filtering suspicious water. Tourists should drink only bottled water in places where the purity of tap water cannot be guaranteed. Although there is no evidence that domestic animals are a significant source of infection for man, dogs and cats with giardiasis should be treated because they may frequently come into contact with children (Meyer and Jarroll, 1982).

Whereas treatment of infected individuals, coupled with prophylactic measures, has reduced the prevalence of parasitic infections caused by other organisms, it has not been successful in the case of giardiasis (Dorea *et al*., 1996). Studies have shown that vaccinated dogs develop some resistance to the disease (Olson *et al*., 1996). These results may be promising for humans as it has been shown that people with natural infections also develop a certain degree of resistance, which lasts at least five years (Isaac-Renton *et al*., 1994). Most methods for testing suspicious water are tedious, complicated, and not very efficient; however, some highly effective and sensitive techniques have been developed (Bielec *et al*., 1996; Kaucner and Stinear, 1998).

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INFECTIONS CAUSED BY FREE-LIVING AMEBAE

ICD-10 B60.1 Acanthamebiasis; B60.2 Naegleriasis

Synonyms: Naegleriasis, primary amebic meningoencephalitis, acanthamebiasis, granulomatous amebic encephalitis, amebic conjunctivitis, and amebic keratoconjunctivitis.

Etiology: Three genera of free-living amebae are capable of infecting man and other mammals: *Naegleria* (*N. fowleri*), *Acanthamoeba* (*A. astronyxis, A. castellanii, A. culbertsoni*, and *A. polyphaga*), and *Balamuthia* (*B. mandrillaris)*. *Balamuthia* was included under the order Leptomyxida (the leptomyxid amebae) until Visvesvara *et al*. (1993) created this new genus and species in 1993. All three genera have both trophozoites and cystic forms in their respective life cycles (Martínez and Visvesvara, 1997). Although free-living amebae belonging to the genera *Hartmanella* and *Vahlkampfia* have been isolated from human nasal passages, they apparently do not cause pathology.

The trophozoites of *N. fowleri* can exist in either ameboid or flagellate form. The ameboid form is elongated (more rounded on the anterior end and more pointed on the posterior) and measures between 7 μm and 20 μm. The cytoplasm is granular, contains vacuoles, and forms blunt lobular pseudopodia at its widest point. The nucleus has one large nucleolus at the center and does not have peripheral chromatin. The flagellate form occurs when ameboid forms in tissue or culture are transferred to fresh water, especially at temperatures between 27°C and 37°C. It is pear-shaped and slightly smaller than the ameboid form, with two flagellae at its broader end. The cytoplasm and nucleus are similar to those of the ameboid form, but it does not reproduce. The cysts are round, measuring between 7 μm and 10 μm, with a nucleus similar to that of the trophozoites, and they are surrounded by a smooth thick double wall. Both the trophozoites and the cysts are present in water and soil; only the ameboid forms and the cysts grow in cultures; and only the ameboid forms are found in host tissue and cerebrospinal fluid.

The trophozoites of *Acanthamoeba* spp. occur only in the ameboid form, which is elongated and can vary widely in size, from 15 μm to 25 μm or longer. The nucleus is very similar to that of *Naegleria*, but the pseudopodia are long and narrow, and they are often distally bifurcated. The cysts are similar to those of *Naegleria*, but they are slightly larger and have an undulated wall. Both trophozoites and cysts are observed in host tissue, and both forms live in water and soil as well.

The trophozoites of *B. mandrillaris* have branches extending in all directions and they can measure between 15 μm and 60 μm. Sometimes they have two nuclei, and they have a central nucleolus. They do not have flagellate forms. The pseudopodia

have secondary branchings. The cysts, which can measure from 15 μm to 30 μm, also have a single nucleus, and the outer wall is undulated. Both trophozoites and cysts can be found in host tissue. Little is known about the natural reservoir of *Balamuthia*.

Geographic Distribution: Free-living amebae appear to exist throughout the world. Clinical cases have been recorded in widely distant locations, including Australia, Brazil, US, Europe, India, and Zambia (Strickland, 1991).

Occurrence in Man: Infections with free-living amebae have only been known since the 1960s. As of 1996, there had been 179 reported cases of primary amebic meningoencephalitis caused by *N. fowleri,* 103 cases of granulomatous amebic encephalitis caused by *Acanthamoeba* spp., and 63 cases of granulomatous amebic encephalitis caused by *B. mandrillaris* (Martínez and Visvesvara, 1997). In addition, as of 1993, there have been 570 known cases of keratitis caused by *Acanthamoeba* spp. (Benenson, 1995).

Occurrence in Animals: *Naegleria* is capable of infecting experimentally inoculated mice and sheep. *Acanthamoeba* can infect sheep (Van der Lugt and Van der Merve, 1990) and dogs (Pearce *et al*., 1985) in nature, and in the laboratory, it can infect the cornea of swine, rabbits, and mice. The invasive capacity of this protozoan appears to vary. Other researchers have found that it does not attack the cornea of horses, guinea pigs, rabbits, chicken, mice, rats, or cows, but that it can produce severe damage in the cornea of man, swine, and Chinese hamsters (Niederkorn *et al*., 1992). *Balamuthia* has been isolated from fatal infections in horses, gorillas, mandrills, and sheep (García and Bruckner, 1997). The range of susceptible animals is probably greater, but there have been few reports of infection because of the difficulty of diagnosing this genus and because the disease in animals receives less attention than its human counterpart.

The Disease in Man: *Naegleria* mainly affects young, immunocompetent, healthy individuals. The ameba penetrates the host via the nasal cavity, where it causes local inflammation and ulceration, and goes on to invade the olfactory nerves and ultimately the meninges, where it multiplies and produces an acute inflammation with abundant neutrophils and monocytes along with hemorrhagic necroses (primary amebic meningoencephalitis). The disease is fatal. After an incubation period of three to seven days, the initial symptoms include sore throat, blocked nasal passages, and intense cephalalgia, subsequently followed by fever, vomiting, and stiff neck. Mental confusion and coma develop three to four days after the first symptoms, and death occurs between three and four days later.

Acanthamoeba spp. preferentially attack individuals who are immunodeficient, undernourished, or weakened by other conditions. This ameba usually invades the host through the skin, the respiratory tract, or the genitourinary tract, spreading through the bloodstream until it reaches the brain and the meninges. The exact length of incubation is unknown, but central nervous system symptoms apparently do not develop until weeks or even months after the primary infection. Often there is a slow-growing cutaneous or pulmonary granulomatous lesion which tends to follow a subacute or chronic course (granulomatous amebic encephalitis). The predominant lesions are foci of granulomatous inflammation, necroses, thromboses, and hemorrhages. The most prevalent symptoms include cutaneous papules, nod-

ules, ulcers or abscesses, congestion, secretion from or ulcers in the nasal passages, sinusitis, cephalalgia, mental or motor disturbances, meningeal signs, or sensory deficiencies. Occasionally the parasite is recovered from other organs such as the skin, kidneys, liver, or pancreas. *Acanthamoeba* often infects the ocular cornea, causing keratitis, uveitis, and chronic corneal ulcers, which can lead to blindness, especially in persons who wear contact lenses. Both *Acanthamoeba* and *Naegleria* are capable of ingesting microorganisms in their environment such as *Legionella* and acting as vectors of the respective infections (Tyndall and Domingue, 1982).

Less information is available about *Balamuthia*, which was not identified until 1993. It can attack both previously healthy and weakened individuals. Although its mechanism of penetrating the host is still unknown, it can produce a subacute or chronic illness similar to that associated with *Acanthamoeba* (Denney *et al*., 1997) and it can also cause granulomatous amebic encephalitis.

The Disease in Animals: Very little information is available about the disease in animals, but the cases reported so far have resembled the disease in humans (Simpson *et al*., 1982; Pearce *et al*., 1985; Niederkorn *et al*., 1992; Visvesvara *et al*., 1993).

Source of Infection and Mode of Transmission: The source of *Naegleria* and *Acanthamoeba* infections appears to be contaminated water and soil. Muñoz *et al*. (1993) examined 100 freshwater samples collected from different sources and found *Naegleria* present in 7.6% and *Acanthamoeba* in 31.5%. The main source of *Naegleria* infection is poorly maintained swimming pools, lakes, etc. The ameba enters the nasal passages of swimmers, especially in summer or when the water has been artificially heated. This ameba is destroyed when pools are adequately chlorinated. The flagellate trophozoite forms probably play the most important role in infection, since they are more mobile and appear to predominate in warm water. The cysts are capable of overwintering, and it is believed that the arrival of warm summer weather causes them to break open and assume the form of flagellate trophozoites. Contaminated water is also the source of infection caused by *Acanthamoeba,* and probably by *Balamuthia* as well. However, the fact that some patients have had no history of contact with suspicious water would indicate that the infection can also be acquired from contaminated soil through breaks in the skin, by the inhalation of dust containing parasite cysts, or by the inhalation of aerosols containing cysts or trophozoites. An important source of the ocular infection is the use of contact lenses that have been poorly disinfected or kept in contaminated cases. *Acanthamoeba* is more resistant to environmental agents than *Naegleria*, as evidenced by the fact that it can tolerate conventional chlorination. It has been determined that 82% of all samples of cysts survive 24 years in water at 4°C, and in vitro cultures have been known to retain their virulence for mice as long as eight years. The reservoir and mode of transmission of *Balamuthia* are unknown.

Diagnosis: Diseases caused by free-living amebae cannot be differentiated from other etiologies on the basis of clinical manifestations alone. Under the microscope it is difficult, though possible, to identify the parasites in tissue on the basis of their morphology; however, at low levels of magnification they can be easily mistaken for macrophages, leukocytes, or *Entamoeba histolytica*. *E. histolytica* has a thin nuclear membrane and a small nucleolus that stains only faintly, unlike the free-living amebae, which have a very distinct nuclear membrane and a larger nucleolus that stains

brightly. In lesions caused by *Naegleria*, the only forms present are ameboid trophozoites, which are often perivascular, and polymorphonuclear cells are abundant in the reaction. On the other hand, in lesions produced by *Acanthamoeba* and *Balamuthia* there are both trophozoites and cysts, vasculitis is present, and the reaction is characterized by an abundance of mononuclear cells, either with or without multinucleate cells (Anzil *et al*., 1991). The wall of *Acanthamoeba* cysts found in tissue turns red with periodic acid-Schiff stain and black when methenamine silver is used. The morphology of the amebae in cerebrospinal fluid can be observed by conventional or phase-contrast microscopy in fresh preparations or those to which Giemsa or Wright's stain has been applied. *Naegleria* grows on non-nutrient agar cultures in the presence of *Escherichia coli* and in sodium chloride at less than 0.4% solution, while *Acanthamoeba* grows in the absence of bacteria and in sodium chloride at less than 0.85% solution. Because *Naegleria* trophozoites are destroyed at cold temperatures, the samples should never be refrigerated. The diagnosis of *Balamuthia* is not yet well defined. Although the trophozoite is characterized by its branching, the cysts are very similar to those of *Acanthamoeba*; only the occasional presence of binucleate *Balamuthia* cysts makes it possible to use conventional microscopy to differentiate *Balamuthia* from *Acanthamoeba*. *Balamuthia* does not grow well on agar in the presence of bacteria, but it does proliferate in mammal tissue cultures. Immunologic reactions with patient sera have not been successful. However, it has been possible to identify exact genera and species using immunofluorescence with monoclonal or polyclonal antibodies at reference centers such as the US Centers for Disease Control and Prevention. Recently, there have been encouraging results with the use of molecular biology techniques to identify and separate species.

Control: Infections caused by free-living amebae are not sufficiently common to justify general control measures. Education of the public regarding appropriate swimming-pool maintenance and the importance of not swimming in suspicious water should reduce the risk of infection. To prevent the parasites from invading the nasal passages, those practicing aquatic sports should avoid submersing the head in water or else use nose clips. In addition, persons who are immunodeficient or have debilitating diseases should be careful not to let broken skin come in contact with natural water or damp soil and avoid breathing dust or aerosols. Contact-lens wearers should not swim with their lenses on to avoid contamination, and lenses should be disinfected either by heating them to a temperature of at least 70°C or by using hydrogen peroxide solutions, which are more effective against *Acanthamoeba* than conventional sodium chloride solutions. Control to protect against animal cases does not appear to be necessary. There is no evidence of human-to-human transmission or transmission from animals to humans. These infections mainly occur in humans and in animals that transmit them from one to another.

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MALARIA IN NONHUMAN PRIMATES

ICD-10 B53.1 Malaria due to simian plasmodia

Synonyms: Monkey malaria, monkey paludism.

Etiology: Malaria is a disease caused by protozoa of the phylum Apicomplexa, genus *Plasmodium*. The four species that infect man are *P. falciparum, P. malariae, P. ovale*, and *P. vivax.* Some 20 species are presumed to infect nonhuman primates: the large simians are affected by 4 species of the family Pongidae, gibbons by 4 species of the family Hylobatidae, Old World monkeys by 8 species of the family Cercopithecidae, New World monkeys by 2 species of the family Cebidae, and lemurs by 2 species of the family Lemuridae (Collins and Aikawa, 1977). However, the taxonomy of some species is uncertain. Table 2 shows some characteristics of the most common species.

Seven of the species that affect nonhuman primates have been transmitted experimentally to humans: *P. brasilianum*, *P. cynomolgi*, *P. eylesi*, *P. inui*, *P. knowlesi*, *P. schwetzi*, and *P. simium.* In addition, some species, such as *P. cynomolgi*, *P. knowlesi*, *P. simium*, and, possibly, *P. eylesi*, have been found in natural or accidental infections, though this rarely occurs. Nonhuman primates can also be infected

TABLE 2. *Plasmodium* species that infect primates.

Species	Host	Geographic range	Periodicity	Relapses
P. brasilianum	New World monkeys	Central and South America	Quartan	Uncertain
P. coatneyi	Old World monkeys	Malaysia	Tertian	No
P. cynomolgi	Old World monkeys	Southeast Asia	Tertian	Yes
P. eylesi	Gibbons	Malaysia	Tertian	Uncertain
P. falciparum	Humans	Tropics	Tertian	No
P. fieldi	Old World monkeys	Malaysia	Tertian	Yes
P. gonderi	Old World monkeys	Central Africa	Tertian	No
P. hylobati	Gibbons	Malaysia	Tertian	No
P. inui	Old World monkeys	India and Southeast Asia	Quartan	No
P. knowlesi	Old World monkeys	Malaysia	Quotidian	No
P. malariae	Humans	Tropics and subtropics	Quartan	No
P. ovale	Humans	Asia and Africa	Tertian	Yes
P. reichenowi	Chimpanzees	Central Africa	Tertian	No
P. schwetzi	Gorillas and chimpanzees	Tropical Africa	Tertian	Yes
P. simiovale	Old World monkeys	Sri Lanka	Tertian	Yes
P. simium	New World monkeys	Brazil	Tertian	Uncertain
P. vivax	Humans	Tropics and subtropics	Tertian	Yes

with natural or adapted strains of the plasmodia that normally affect humans: *Aotus* and *Saimiri* monkeys with *P. falciparum* or *P. vivax*, and chimpanzees with *P. ovale*.

For many years, it was believed that the plasmodia of man did not have a common origin (monophyletic) but rather were descended from different ancestral species (polyphyletic), and the relationship of some species that infect man to some species that infect simians was frequently the subject of speculation. Escalante *et al*. (1998) compared cytochrome *b* gene sequences from 4 species of human parasites, 10 species of simian parasites, 1 species of rodent parasite, and 2 species of avian parasites. They concluded that the plasmodia of man are indeed polyphyletic. *P. falciparum* and *P. reichenowi* are closely related to one another and share a common ancestor with avian malaria parasites. *P. vivax* forms a different but closely related group with the plasmodia of Old World monkeys, especially *P. simium. P. ovale* and *P. malariae* form a separate group, although there is very little relationship between them. An interesting finding is that, contrary to widely held opinion, no inverse relationship exists between virulence of the parasite and length of the plasmodium-host association. Neither is there any relationship between phylogenetic proximity of the parasites and certain characteristics of malarial disease, such as virulence, periodicity, and occurrence of relapses. Notwithstanding the foregoing, biologic and pathogenic similarities have led to the use of certain nonhuman primate *Plasmodium* species as the preferred models for *Plasmodium* species that infect man: *P. cynomolgi* for *P. vivax, P. brasilianum* for *P. malariae*, *P. fieldi* and *P. simiovale* for *P. ovale*, and *P. coatneyi* for *P. falciparum.* In addition, Lal *et al*. (1988) demonstrated that the immunodominant repeat domain was the same for *P. brasilianum* and *P. malariae* and for *P. reichenowi* and *P. falciparum.*

The life cycle of plasmodia of nonhuman primates, like that of the plasmodia that infect man, includes host mammals and insect vectors. An infected mosquito of the genus *Anopheles* injects sporozoites of the parasite into a susceptible host when it

takes a blood meal. In less than an hour, the sporozoites disappear from the blood and enter the cells of the hepatic parenchyma. There, they begin to multiply by multiple fission to form thousands of filamentous parasites, the merozoites, which leave the host cell after five days or more. In some species, there is a single generation of hepatic merozoites, but in others, dormant forms, hypnozoites, are produced. The hypnozoites may become active again months or years later and cause reinfection (Cogswell, 1992) (Table 2). This stage of replication in the liver is known as the exoerythrocytic cycle. The growth and asexual division of the sporozoites to form merozoites is termed merogony (formerly called schizogony).

Once released, the merozoites invade the erythrocytes to form a trophozoite within a vacuole. The trophozoite is originally ovoid, but then it forms a ring structure with a vacuole in the center. At this stage, the trophozoite begins to feed on the cytoplasm of the erythrocyte, and a dark pigment, hemozoin, is deposited into its food vacuoles. As the trophozoite matures, the central vacuole disappears and the nucleus begins to divide by successive mitosis, forming a multinucleate cell, the meront (formerly called the schizont). Later, the cytoplasm of the erythrocyte divides into portions that envelop each nucleus to form numerous merozoites. The mature merozoites rupture the blood cell and enter the bloodstream, where they invade other erythrocytes, and the same cycle is repeated. This multiplication in the erythrocytes is known as the erythrocytic cycle. Like the process that occurs in the liver, the growth and asexual division of the original parasites to form merozoites is known as merogony. The cycle of merozoite formation in the red blood cells takes 24 hours in some species (e.g., *P. knowlesi*) and 48 or 72 hours in others. As the recurrent fevers of malaria coincide with the mass release of merozoites from the red cells, they occur daily or every third or fourth day. Malaria is classified as quotidian, tertian, or quartan, respectively, according to the periodicity of these febrile attacks (Table 2).

After several rounds of asexual reproduction in the erythrocytes, some merozoites become female cells, or macrogametocytes, and male cells, or microgametocytes, which are the infective forms for the vector. The process of gamete formation is known as gametogony. When an *Anopheles* mosquito ingests the gametocytes during a blood meal, they mature in the insect's alimentary tract and become macrogametes (ova) and microgametes (sperm). A sperm fertilizes each ovum, forming a motile zygote, the ookinete, which penetrates the epithelium of the insect's midgut, is engulfed by a membrane, and forms an oocyst in the intestinal wall. Inside the oocyst, the zygote multiplies by successive mitosis to produce an enormous number of filamentous parasites, the sporozoites, which ultimately break out of the oocyst and are distributed in the hemocele of the insect. The process of sporozoite formation is known as sporogony. The sporozoites invade all of the mosquito's tissues, and those that reach the salivary glands may be passed to a vertebrate host with the saliva of the insect at its next blood meal.

Geographic Distribution: Although the prevailing opinion is that the plasmodia of simians originated in Southeast Asia, Escalante *et al*. (1998) suggest that the origin of primate malaria parasites is African and posit that from there they spread to Southeast Asia with their host mammals and vectors. Their current geographic distribution coincides with that of their preferred hosts (Table 2). In the Americas, *P. brasilianum* is widely distributed among the neotropical monkeys of Brazil,

Colombia, Panama, Peru, and Venezuela, while *P. simium* is found in the southern and eastern regions of Brazil.

Occurrence in Man: Infection of man with plasmodia of nonhuman primates is considered very rare. The literature records only two confirmed human cases acquired under natural conditions: one caused by *P. knowlesi* in Malaysia and another by *P. simium* in Brazil. Two other cases have been reported but not confirmed: one by *P. knowlesi* and the other by *P. eylesi*, both in Malaysia. All these cases occurred prior to 1970. However, it was subsequently discovered that more than 90% of the adults in four tribes in northern Brazil had antibodies against *P. brasilianum* or *P. malariae* (these species cannot be differentiated using conventional serology), although the incidence of malaria was very low and parasitemia was below 0.02% (de Arruda *et al.,* 1989). The presence of *P. brasilianum* was confirmed in numerous monkeys and in *Anopheles darlingi* mosquitoes in the area. This finding suggests that *P. brasilianum* infection is occurring in the indigenous population.

P. knowlesi was transmitted experimentally to human volunteers through the inoculation of blood or the bite of infected mosquitoes. After 170 serial passages, however, the infection became so virulent that the passages were stopped (Collins and Aikawa, 1977). *P. cynomolgi* was inoculated accidentally into humans and was then transmitted to man and monkeys by infected mosquitos. Although the level of parasitemia in humans was low, the disease was moderately serious. Infection by *P. brasilianum*, *P. inui*, or *P. schwetzi* in volunteers produced low levels of parasitemia and mild symptoms (Collins and Aikawa, 1977). *P. schwetzi* was also transmitted experimentally to man and produced a mild disease. Transmission of *P. reichenowi* to man was attempted, but without success (Flynn, 1973). Deane (1992) reported an accidental human infection with *P. simium* in southeastern Brazil.

Occurrence in Animals: *P. brasilianum* has been found in numerous monkey species of the family Cebidae in neotropical regions. The infection rate is close to 15% in howler monkeys of the genus *Alouatta*, spider monkeys of the genus *Ateles*, and capuchin or white monkeys of the genus *Cebus*. Natural infection by *P. simium* has been found in brown howler monkeys (*Alouatta fusca*) and in woolly spider monkeys (*Brachyteles arachnoides*). The prevalence of malaria has been reported to be 10% among simians in the Amazon region and 35% and 18% in the southeastern and southern regions of Brazil, respectively. Although *P. brasilianum* is present in all those areas, *P. simium* is found only along the southeastern and southern coast. Virtually all the parasites were detected in monkeys of the family Cebidae (Deane, 1992). Among nonhuman primates in Asia and Africa, the prevalence of the infection seems to be high in areas with large numbers of monkeys and appropriate anopheline vectors. Conversely, there are areas with sparse monkey populations in both the New World and the Old World where the infection does not occur.

The Disease in Man: Human malaria caused by plasmodia of simian origin resembles a mild and benign infection caused by human plasmodia (see Occurrence in Man). In general, the disease is of short duration, parasitemias are low, and relapses are rare. Recuperation is spontaneous, and very few patients require treatment. The periodicity of malarial attacks depends on the parasite species (Table 2).

The Disease in Animals: In general, malaria in simians is a mild disease that resolves spontaneously in the parasite's natural hosts. However, *P. knowlesi* infec-

tion is serious in rhesus monkeys and in baboons. *P. brasilianum* can cause acute disease in American monkeys and, occasionally, may even be fatal for spider, howler, and capuchin monkeys. *P. eylesi* causes high parasitemia in mandrills. *P. gonderi* has a chronic course, *P. georgesi* produces a relapsing malaria, and *P. petersi* causes a brief infection in *Cercocebus* monkeys, which are the natural hosts for these species (Poirriez *et al.,* 1995). In rhesus monkeys (*Macaca mulatta*), *P. coatneyi* and *P. fragile* cause neurological signs similar to those that occur in humans infected with *P. falciparum* (Aikawa *et al.,* 1992; Fujioka *et al*., 1994). *P. cynomolgi* causes placentitis in rhesus monkeys (Saxena *et al.,* 1993). After infection with *P. ovale*, monkeys of the genus *Saimiri* develop parasites in the liver but do not progress to erythrocytic stages (Millet *et al.,* 1994).

Source of Infection and Mode of Transmission: Malaria of both humans and nonhuman primates is transmitted by the bite of infected anopheline mosquitoes. Which species of mosquitoes transmit malaria of nonhuman primates in the forests of Africa, the Americas, and a large part of Asia is still not well known. In northwestern Malaysia, the vector of *P. cynomolgi* has been shown to be *Anopheles balabacensis balabacensis,* which also transmits human malaria in that region. However, the cycles of disease transmission in humans and nonhuman primates are generally independent of one another because the vectors of human plasmodia feed at ground level, while those of simian plasmodia feed in the treetrops. In northern Brazil, *P. brasilianum* has been found in *Anopheles darlingi* mosquitoes. It has been demonstrated that the distribution of *P. simium* and *P. brasilianum* in that country is governed by the presence of the mosquitoes *A. cruzi* and *A. neivai*, which feed in the forest canopy. This explains the rarity of human infection by plasmodia of simian origin. Nevertheless, in some regions of Brazil, such as the mountainous and wooded coastal areas of the state of Santa Catarina, *A. cruzi* is the vector of human malaria and possibly also of simian malaria, while in other regions it is exclusively a vector of the simian disease. In Santa Catarina, however, it was found that *A. cruzi* feeds both at ground level and in the treetops. In such conditions, human infection caused by simian plasmodia may occur naturally. In western Malaysia, a similar situation exists: the vector is the same for the human and nonhuman cycles, and zoonotic infections may thus occur. However, the risk appears to be limited to those who live in or enter jungle areas, and it is unlikely that the infection could spread to other human communities. In tropical Africa, where chimpanzees are infected by *P. malariae*, *P. rodhaini*, and *P. schwetzi*, humans might become infected when they enter the habitat of these primates. However, malariologists point out that the plasmodia of nonhuman primates pose little risk for the human population, since *P. malariae* from chimpanzees cannot infect *Anopheles gambiae*, the vector of human malaria, and *P. schwetzi* does not develop fully in that mosquito.

Diagnosis: Routine diagnosis in man and in monkeys is done by examining the parasite in thick blood films stained with Giemsa stain. Differentiation of the species of *Plasmodium* that infect nonhuman primates is based mainly on morphologic features of the parasite's various stages of development. Another criterion is host specificity. Specific diagnosis is very difficult, for example in the case of *P. brasilianum* and *P. simium*, which are similar to the human plasmodia *P. malariae* and *P. vivax*, respectively. Because the routine diagnostic techniques for differentiating *Plasmodium* species are imprecise, it is possible that some human malaria cases of

simian origin have been diagnosed erroneously as being caused by human malarial agents. Another difficulty in diagnosis by microscopic examination of blood preparations is the low parasitemia that occurs in nonhuman primates. To get around this difficulty, inoculation of blood into susceptible monkeys is recommended. Although serologic reactions are useful as a means of confirming malarial infection, they are rarely specific enough to identify the *Plasmodium* species involved.

Control: Malaria experts agree that malaria of nonhuman primates does not constitute an obstacle for programs to control and eradicate human malaria. The human infection has been eradicated from some parts of Brazil, although high rates of infection in monkeys persist. Given the small number of confirmed cases of human infection by plasmodia of simian origin and the benign nature of the clinical manifestations, special control measures are not justified.

To prevent the disease, nonimmune persons who must go into the jungle should use insect repellents on exposed body parts and on clothing. Regular use of chemoprophylaxis would be justified only if the nonimmune person had to live in an area where human malaria is endemic.

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MICROSPORIDIOSIS

ICD-10 B60.8 Other specified protozoal diseases

Etiology: Microsporidiosis is an emerging human infection caused by protozoa of the family Microspora. Although there are some 700 species that infect vertebrates and invertebrates, the species identified to date as parasites of man are *Enterocytozoon bieneusi, Encephalitozoon intestinalis* (formerly *Septata intestinalis*), *Encephalitozoon hellem, Encephalitozoon cuniculi*, and some species of the genera *Nosema, Pleistophora, Trachipleistophora*, and *Vittaforma* (Scaglia *et al.*, 1994). *Enterocytozoon* causes intestinal infections almost exclusively, while *Encephalitozoon* may cause intestinal or systemic infections which may spread to various organs. Parasites of the genera *Nosema, Pleistophora, Trachipleistophora*, and *Vittaforma* are uncommon in man and do not affect the intestine (Field *et al.,* 1996). The first known human infection was by *E. bieneusi* in 1985. Differentiation of genera and species requires experience and is generally based on ultrastructural morphology, antigenic composition, or DNA sequencing. Proof of the existence of isolates with genetic differences exists, at least within *E. bieneusi,* but it is not yet known if those differences are associated with differences in clinical or epidemiological conditions (Rinder *et al.,* 1997). The genera *Cryptosporidium, Isospora*, and *Cyclospora* belong to a completely different phylum: Apicomplexa (formerly Esporozoa). However, because they are also transmitted by elements commonly

called "spores" and because they cause intestinal pathology, they are frequently grouped with the microsporidia under the name "intestinal spore-forming protozoa" (Goodgame, 1996).

Microsporidia are small intracellular protozoa that undergo a phase of asexual multiplication—merogony—followed by a phase of sexual multiplication—sporogony—during which they produce spores, or oocysts, inside the infected cell. The spores are released from the host cell and are eliminated into the external environment, where they may infect other individuals. They are small, double-walled bodies measuring 1 µm to 3 µm which contain a parasitic cell, or sporoplasm, with one or two nuclei. At their anterior end, they have an extrusion apparatus, the polaroplast, which everts the polar tube or filament that is coiled around the polaroplast and sporoplasm within the spore. Infection takes place when the polar tube is extruded and penetrates the host cell, allowing the sporoplasm to pass through it and enter the host.

Geographic Distribution: Apparently worldwide. Cases have been reported in Argentina, Australia, Botswana, Brazil, Canada, Czech Republic, Germany, France, India, Italy, Japan, New Zealand, Netherlands, Spain, Sri Lanka, Sweden, Switzerland, Thailand, Uganda, UK, USA, and Zambia (CDC, 2003).

Occurrence in Man: Microsporidiosis is one of the most frequent complications occurring in immunodeficient patients, but it is rare in immunocompetent individuals. It has also been reported in transplant patients (Rabodonirina *et al.*, 1996). As of 1994, more than 400 cases had been recognized, most in immunodeficient patients. The most frequent microsporidium is *E. bieneusi,* followed by *E. intestinalis,* which is about 10 times less prevalent. Other species are even less frequent. In North America, Australia, and Europe, prevalences of 12% to 50% have been reported in AIDS patients (Voglino *et al.*, 1996). The infection generally causes chronic diarrhea in immunodeficient patients. Coyle *et al.* (1996) found the infection in 44% of AIDS patients with diarrhea but in only 2.3% of AIDS patients without diarrhea. In Germany, microsporidia were identified in 36% of 50 AIDS patients with diarrhea and in 4.3% of 47 AIDS patients without diarrhea. The parasites were detected in 60% of patients with chronic diarrhea but in only 5.9% of patients with acute diarrhea. In 18 of the patients, the agent was *E. bieneusi* and in 2, it was *E. intestinalis* (Sobottka *et al.,* 1998). In Spain, Del Aguila *et al*. (1997) found the infection in only 1.2% of HIV-positive children, whereas the percentage among HIV-positive adults was 13.9%. In Niger, Bretagne *et al*. (1993) found the infection in 7% of 60 HIV-positive children and in 0.8% of 990 asymptomatic HIV-negative children. In Zimbabwe, van Gool *et al*. (1995) found the infection in 10% of 129 adults with AIDS, but in none of 106 children with AIDS and none of 13 adults and 12 children without AIDS.

Occurrence in Animals: Microsporidiosis occurs in a great number of vertebrate and invertebrate species, but as it is not generally pathogenic for vertebrates, its discovery is accidental, and there are thus no reliable statistics on its frequency. Only *E. cuniculi* has been proven to be zoonotic (Deplazes *et al.,* 1996). However, *E. bieneusi* has been found in macaques (Chalifoux *et al.,* 1998) and *E. intestinalis* in donkeys, cows, goats, pigs, and dogs (Bornay-Llinares *et al.,* 1998), and it is therefore believed that these species could also be zoonotic. In addition, *E. bieneusi* has been transmitted to macaques with AIDS and to immunodeficient pigs (Kondova *et al.,* 1998), and *E. hellem* has been transmitted to mice (Snowden, 1998).

The Disease in Man: *E. bieneusi* infects the small intestine and, sometimes, the hepatobiliary tract in immunodeficient individuals. The clinical manifestations include chronic diarrhea with passage of watery or semi-watery stools numerous times (2–8) a day, but without evidence of intestinal hemorrhage; malabsorption with atrophy of the microvilli, which is aggravated by the ingestion of food; and subsequent progressive and irreversible weight loss. Spontaneous remissions are sometimes seen, but they are short-lived. The diarrhea can ultimately lead to dehydration and malnutrition. Although the causes of the intestinal disease are not well understood, it is presumed that it is due to loss of microvilli and enterocytes. *E. intestinalis* also causes chronic diarrhea and malabsorption, and it may spread to the nasal sinuses and the kidneys (Dore *et al.,* 1996; Moss *et al.*, 1997). *E. hellem* has been isolated from the corneal epithelium and the conjunctiva and has been found in generalized infections. As in the lower animals, the few human cases of *E. cuniculi* have been systemic and have affected mainly the brain and the kidneys. *Trachipleistophora hominis* may affect the skeletal musculature, the cornea, and the upper respiratory tract (Field *et al.,* 1996); *Vittaforma* may infect the cornea.

The Disease in Animals: Most infections in vertebrates seem to be asymptomatic, except for *E. cuniculi* infection, which occasionally causes disease with foci of micronecrosis and formation of granulomas in the brain, kidneys, endothelia, and other organs of rabbits, rats, mice, and dogs.

Source of Infection and Mode of Transmission: The presence of microsporidia spores in the host stools and urine suggests that the infection could be transmitted by fecal or urinary contamination of the environment, especially water. Recent studies have demonstrated the presence of *E. bieneusi, E. intestinalis*, and *Vittaforma corneae* in surface and underground waters and in effluents from sewerage systems (Dowd *et al.,* 1998), which supports that presumption. *E. cuniculi* can be transmitted by parenteral inoculation in rabbits and rodents, and it is believed that it is transmitted congenitally in mice.

Diagnosis: Diagnosis of microsporidiosis is difficult owing to the small size of the spores. Specimens are obtained, inter alia, from body fluids, feces, duodenal aspirates, urinary sediment, and corneal scrapings, and they are then stained using methods that facilitate microscopic examination. Fluorescence with calcofluor white is the most sensitive method but, as it also stains yeast cells, it may give false positive results. Weber's modified trichrome stain is almost as sensitive as calcofluor white, but it is more specific because it does not stain yeasts; however, it is slower. The slowest and least sensitive test is indirect immunofluorescence using polyclonal antibodies (Didier *et al.*, 1995). In biopsies, the parasites can be detected by means of Gram or Giemsa stains or fluorescent antibodies; however, these procedures must be performed by experienced personnel. Microsporidia have been grown in cell cultures to which stains are applied to reveal the parasitized cells (Croppo *et al.*, 1998). Systemic immunologic reactions are of little use from a clinical standpoint because they do not indicate whether the infection is recent or active. Polymerase chain reaction has also been used successfully to identify microsporidia in feces and biopsies (Gainzarain *et al.*, 1998). This method may also replace electron microscopy as the only reliable procedure for differentiating species (Croppo *et al.*, 1998).

Control: Because it is not fully understood how microsporidia are transmitted,

there is not yet an effective control protocol. However, the discovery of microsporidia spores in surface and underground waters and sewage by Dowd *et al*. (1998) suggests that immunodeficient individuals should avoid oral exposure to water from suspicious sources such as pools, streams, and lakes, and that questionable drinking water should be boiled.

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SARCOCYSTOSIS

ICD-10 A07.8 Other specified protozoal intestinal diseases

Synonym: Sarcosporidiosis.

Etiology: Of more than a hundred species of *Sarcocystis* that infect mammals, only two are known to parasitize the human intestine: *S. suihominis* and *S. hominis* (also known as *S. bovihominis*). For many years the oocysts of these species were mistakenly assigned to the genus *Isospora* and referred to as *Isospora hominis*. A third species appears to have been found in the intestines of five immunodeficient patients in Egypt (el Naga *et al*., 1998). A presumed sarcocyst, *S. lindemanni*, was observed for the first time in human muscle in 1968; the ecologic relationship between this species and man is uncertain.

Sarcocysts are coccidia belonging to the phylum Apicomplexa. Although these coccidia are related to *Isospora, Cryptosporidium, Cyclospora*, and *Toxoplasma*, they require both an intermediate and a definitive host. The definitive host of *S. hominis* and *S. suihominis* is man, and the intermediate hosts are cattle and swine, respectively (Markus, 1978).

The life cycle of sarcocysts appears to be similar in all the species. The definitive host acquires them upon ingesting meat infected with the parasite. The infected striated muscle contains mature, whitish-colored cysts (sarcocysts), which are usually oval and range in size from microscopic to clearly visible by direct observation. The sarcocyst has a wall around it with internal septa that divide the cyst into compartments filled with hundreds or thousands of slowly dividing fusiform parasites, called bradyzoites. Once the cyst is ingested, the bradyzoites are released into the intestine and invade the cells of the lamina propia, where they are immediately transformed by gametogony into sexuated parasites, which in turn fuse and form oocysts by sporogony. There is no asexual multiplication phase in the intestine of the definitive host. The oocysts mature in the intestine, destroy the host cell, and then exit the body in the feces. When they are eliminated they already contain two sporocysts, each with four sporozoites.

The intermediate host acquires the infection upon consuming oocysts or mature sporocysts. The sporozoites are released into the intestine, penetrate the intestinal mucosa, invade the bloodstream, and multiply asexually by merogony in the endothelial cells of the small blood vessels for one or two generations. These forms, called tachyzoites, do not form cysts; instead, they multiply rapidly, invade the fibers of striated muscle, form the sarcocyst wall, and multiply asexually by merogony for several generations into intermediate forms known as merozoites, the forms that generate the infective bradyzoites (Rommel, 1989).

Geographic Distribution: Human intestinal sarcocystosis appears to occur worldwide. Muscular sarcocystosis has been reported only in Egypt, India, Malaysia, and Thailand.

Occurrence in Man: The human intestinal infection is found in most parts of the world, with an incidence of 6% to 10% (WHO, 1981). However, these figures are affected by the custom of eating raw meat. For example, in the Lao People's Democratic Republic the prevalence of *S. hominis* was higher than 10% in adults, and in Tibet the rate for *S. hominis* was 21.8%, while that for *S. suihominis* ranged from 0.06% to 7%. About 30 cases of human muscular sarcocystosis have been reported, most of them in Malaysia, where the prevalence of sarcocystosis in general was 21% in routine autopsies (Wong and Pathmanathan, 1992).

Occurrence in Animals: The prevalence of muscular infection caused by *Sarcocystis* spp. in cattle and swine is very high, sometimes reaching more than 90%. Cattle also harbor the species *S. cruzi* (alternatively referred to as *S. bovicanis*) and *S. hirsuta* (or *S. bovifelis*), whose definitive hosts are dogs and cats, respectively, while swine are associated with *S. miescheriana* (or *S. suicanis*) and *S. porcifelis*, the definitive hosts of which are dogs and cats, respectively. Since it is difficult to differentiate species in the intermediate host, it is not known what percentage of prevalence corresponds to the parasites that are infective for man. The World Health Organization (1981) estimates that nearly half the muscular cysts in cattle and swine correspond to *S. hominis* or *S. suihominis*. Indeed, in India it was found that the prevalence of *S. suihominis* in swine was 47% and that of *S. miescheriana* was 43% (Saleque and Bhatia, 1991). Other studies have shown that rhesus monkeys can be infected with *S. hominis* and maintain an intestinal infection for at least a week.

The Disease in Man: Intestinal sarcocystosis is usually asymptomatic. Experimentally infected volunteers experienced nausea, abdominal pain, and diarrhea 3 to 6 hours after eating raw or undercooked beef containing *S. hominis*. Abdominal pain and diarrhea recurred 14 to 18 days after ingestion of the beef, coinciding with the maximum elimination of sporocysts in feces. Clinical symptoms were more pronounced after the subjects ate pork containing cysts of *S. suihominis.* Symptomatic infection is generally observed when the meat consumed contains a large number of merozoites. In Thailand, several cases of sarcocystosis involved acute intestinal obstruction, requiring resection of the affected segment of the small intestine. Histopathological examination of the resected segments revealed eosinophilic or necrotizing enteritis. It is possible that a bacterial superinfection also may have been involved in the necrotizing enteritis (Bunyaratvej *et al.,* 1982).

Human muscular sarcocystosis is usually discovered fortuitously during examination of muscle tissue for other reasons. Although the infection is nearly always asymptomatic, in some cases muscular weakness, muscular pain, myositis, periarteritis, and subcutaneous tumefaction have been observed. However, in none of these cases was there conclusive proof that the muscular cysts were the definite cause of the clinical symptoms.

The Disease in Animals: There are several species of sarcocysts in nonhuman mammals, which can occasionally cause intestinal or systemic disease. However, *S. hominis* does not cause disease in cattle, and *S. suihominis* only rarely causes severe disease in swine (Barriga, 1997). When 29 suckling pigs were given 50,000 to 500,000 sporocysts of S. *suihominis*, severe pathologic manifestations were observed 12 days after inoculation, and about half the animals died.

Source of Infection and Mode of Transmission: The source of infection for human intestinal sarcocystosis is beef or pork containing mature sarcocysts. Only the bradyzoites, which appear about two and a half months after infection of the intermediate host, are infective for the definitive host. The mode of transmission is through the ingestion of raw or undercooked infected meat. The sources of infection for cattle and swine are the oocysts or sporocysts of *S. hominis* and S. *suihominis*, respectively, shed in the feces of infected individuals. The mode of transmission is through contamination of pastures or feedlots with feces and the eventual ingestion thereof by cattle or swine. The sarcocysts have strict host specificity, so it is clear that other vertebrate species are not directly involved in transmission.

The epidemiology of human muscular sarcocystosis has not yet been clarified. It may be that *S. lindemanni* is a parasite of man, albeit an infrequent one, with an unknown carnivorous or omnivorous definitive host that has the opportunity to consume human cadavers. Some authors have suggested that the reports of human cases of sarcosporidia are based on erroneous diagnoses. Taking into account the morphology of the sarcocysts, Beaver (1979) and Kan and Pathmanathan (1991) have suggested that man might be an aberrant host of sarcocysts that normally infect the musculature of monkeys. The relative frequency of the infection in areas where there are large numbers of monkeys gives some credence to this hypothesis.

Diagnosis: Human intestinal sarcocystosis can be diagnosed by confirming the presence of oocysts or mature sporocysts in feces starting on day 9 or 10 following the ingestion of infected meat. The outer wall of the oocysts is very thin and often

ruptures, which accounts for the presence of sporocysts in feces. The most efficient way to recover them from feces is by zinc sulfate flotation. *S. hominis* sporocysts measure 13 to 17 µm by 10.8 µm, and those of *S. suihominis*, 11.6 to 13.9 µm by 10 to 10.8 µm (Frenkel *et al.,* 1979). Both exhibit interior residue, but neither of them has a Stieda body.

Muscular cysts in cattle and swine are found along the length of the muscle fiber and are whitish in color, often microscopic in size, and have the shape of a long cylinder. The cyst wall forms internal septa that separate the bradyzoites into banana-shaped compartments measuring 6 to 20 µm by 4 to 9 µm (Gorman, 1984). The cysts are found most often in the cardiac muscle, esophagus, and diaphragm of adult cattle and swine. They can be observed by trichinoscopy and, more effectively, by microscopy following tryptic digestion of the infected meat. The sarcocysts are similar to those in man, but they can sometimes be as long as 5 cm and are visible to the naked eye.

Serologic tests (indirect immunofluorescence and ELISA) are not considered useful in diagnosing the intestinal infection (WHO, 1981), but studies are being done to assess their effectiveness in the diagnosis of muscular infection (Habeeb *et al*., 1996).

Control: Cattle or swine should be prevented from ingesting infected human feces, and humans should avoid eating raw or undercooked meat. In the first case, measures should be taken to properly dispose of human waste in rural settings where there are large numbers of cattle and swine. Except in areas where there are high rates of human infection, it is probably not necessary to treat infected individuals in order to reduce contamination of the environment. The population should be educated about the risk of infection when raw meat is consumed, and veterinary inspection of slaughterhouses should be improved. Freezing of meat reduces the number of viable cysts.

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TOXOPLASMOSIS

ICD-10 B58 Toxoplasmosis; P37.1 Congenital toxoplasmosis

Etiology: The agent of these infections is *Toxoplasma gondii*, a coccidium belonging to the phylum Apicomplexa and related to *Sarcocystis*. *T. gondii* can complete its evolutionary cycle in the intestine of the cat and other felines, which are the definitive hosts. In addition, it can, and usually does, take advantage of an intermediate host, which may be any of some 200 species of vertebrates. The fact that man is an intermediate host makes it medically important.

When the parasites are ingested by a cat (see Source of Infection and Mode of Transmission), they invade the feline's intestinal cells and multiply asexually by merogony for several generations. They then multiply sexually by gametogony and produce immature oocysts that cause the host cells to rupture, after which they are eventually evacuated in the feces. The oocysts measure 10 µm by 12 µm and have a single zygote inside. The cat sheds the oocytes for a period of 1 or 2 weeks, and then the cat develops immunity. Outside the host, the oocysts mature in 1 to 5 days, depending on the temperature and humidity of the environment, at which point they form sporulated oocysts (11 µm by 13 µm), each containing two sporozoites (6 µm by 8 µm) without a Stieda body and each of the latter containing four more sporozoites (2 µm by 6–8 µm) inside it (Dubey and Beattie, 1988).

In the intermediate host, which can include man and the cat, parasites are released in the small intestine and invade the epithelial cells, where they multiply until they rupture the cells. They are then disseminated by the lymphatic system or the bloodstream, either as free forms or inside macrophages or leukocytes. Although most of the parasites are captured by the lymph nodes, they can also be found inside macrophages or monocytes, and in some cases they bypass the lymph nodes and spread throughout the rest of the organism. These parasites, or tachyzoites, are banana-shaped and measure 6 µm by 2 µm. They are very active, and their cycles of invasion, multiplication, and cell rupture continue for one to two weeks, until the host develops a degree of immunity. At that point they begin to be replaced in the tissues by bradyzoites (7 µm by 1.5 µm, also banana-shaped), which are more slow-moving. The bradyzoites accumulate in the cytoplasm of the parasitized cells and encase themselves in a membrane, forming a cyst. Tachyzoites, also referred to as

proliferative forms or trophozoites, are typical of the acute, or active, phase of the infection, while bradyzoites, also known as cystic forms or cystozoites, are typical of the latent, or chronic, infection and can persist in tissue throughout the life of the host. These forms can parasitize any nucleated cell, but tachyzoites show a preference for macrophages and monocytes, while bradyzoites are seen more often in muscle and nerve tissue.

Geographic Distribution: Worldwide. This is one of the most widespread of all the zoonoses.

Occurrence in Man: The infection is very common, but the clinical disease is relatively rare. Studies have shown that between 16% and 40% of the population in the US and Great Britain and from 50% to 80% of the people in continental Europe and Latin America have antibodies to the parasite, indicating that they have been infected at some time (Barriga, 1997). Most of those with bradyzoite cysts, given that they often persist for the life of the host, have a latent infection. The prevalence rate is usually higher in warm, humid climates than in cold, dry ones, and it is also higher at lower elevations and in older persons. The seropositivity rate in human populations, for whom the cause of infection is mainly the consumption of infected meat (see Source of Infection and Mode of Transmission), is low in children up to 5 years of age, but then it begins to increase and reaches its highest levels in the population 20 to 50 years old. In areas where the main cause of infection is the ingestion of contaminated soil, the infection rate is also high in children because of their inclination to get dirt on their hands.

The clinical disease usually occurs sporadically and has low levels of incidence. However, occasionally there are small epidemics attributed to the consumption of infected meat (Choi *et al.*, 1997) or contaminated water (Mullens, 1996). The epidemic reported by Mullens (1996) affected more than 110 persons and it may be the largest one on record. In 1979, an outbreak of acute toxoplasmosis affected 39 of 98 soldiers in a company that had been practicing maneuvers in the jungles of Panama. The source of infection was deemed to be the consumption of water from a stream that may have been contaminated with the feces of wild felines (Benenson *et al.*, 1982).

The infection or disease also occurs in recipients of organ transplants. Gallino *et al.* (1996) studied 121 heart transplant patients in Switzerland and found that 16 had recent *T. gondii* infections, 5 of them with clinical manifestations; 61% of the cases were infections that had been transmitted along with the transplanted organ and 7% were reactivations of a latent infection that the recipient had had before.

The congenital infection is particularly important because of the severity of the sequelae in both the fetus and the newborn. In the US, some 3,000 babies are born every year with congenital toxoplasmosis and the annual cost of treating this disease is between US$ 31 and US$ 40 million. The frequency of toxoplasmosis has been calculated at 1 per 4,000 births in the US, and in France the rate is 1 per 1,500. In Norway, Jenum *et al.* (1998) found that 10.9% of 35,940 pregnant women had been infected before pregnancy and that 0.17% became infected during pregnancy, most notably in the first trimester. Twenty-three percent of those who were infected gave birth to infected babies: 13% of the fetuses became infected during the first trimester, 29% in the second trimester, and 50% in the third. In Great Britain, a study found the infection in 6.8% to 17.8% of pregnant women, and 0.4% of these infec-

tions were recent. It is estimated that the rate of congenital infection is about 10 newborns for every 10,000 deliveries. In Spain, the infection affects 56.7% of the general population, but primary infection in pregnant women is only 0.056% (Rodríguez *et al.*, 1996). In a region of Colombia, the rate of congenital infection has been estimated at between 30 and 120 for every 8,000 pregnancies (Gómez-Marín *et al.*, 1997).

Toxoplasmosis is more severe in immunodeficient individuals, whose condition appears to facilitate the infection. Bossi *et al*. (1998) found that 399 (24.5%) of 1,628 AIDS patients had encephalitis caused by *Toxoplasma*, which is rare in immunocompetent persons; 97% of the patients had antibodies to the parasite, 13% had relapses, and 84% died during the course of the study. A study in Thailand revealed an infection rate of 13.1% in pregnant women who were HIV-negative and 21.1% in women who were HIV-positive (Chintana *et al*., 1998).

Occurrence in Animals: The infection has been confirmed in some 200 species of vertebrates, including primates, ruminants, swine, equines, carnivores, rodents, marsupials, insectivores, and numerous avian species. Wild, as well as domestic, felines have been infected with *Toxoplasma*. In Córdoba, Argentina, when 23 specimens of wild cats (*Oncifelis geoffroyi*, *Felis colocolo*, or *Felis eira*) were studied using both serologic and parasitologic tests, oocysts were found in 37% of the animals and positive serologic reactions in 59% (Pizzi *et al.*, 1978). Among domestic animals, high reactor rates have been found in cats, sheep, goats, and swine; lower levels in horses and dogs; and low levels in cattle. In some places, 25% to 45% of the cats are seropositive. For example, studies conducted in Costa Rica using either serologic tests or isolation of the parasite showed that 60 of 237 cats (25.3%) were infected. In 55 of the animals (23%) the parasite was identified by isolation from feces and inoculation in mice, and 82% of the isolations corresponded to cats under 6 months of age. It is of interest to point out that 60% of the cats found to have oocysts in their feces were negative in the serologic tests, which indicates that they were suffering from a primary infection (Ruiz and Frenkel, 1980). In the US, two studies of cats demonstrated the presence of the parasite in the brain of 24.3% and 11% of the felines, respectively (Dubey, 1973). In animals, as in man, the seropositivity rate increases with age.

Confirmation of the parasite's presence in the meat of food animals is of special interest for public health, since undercooked meat is one of the principal sources of infection for man. In Europe, parasitism rates in excess of 50% have been found in the meat of sheep and swine slaughtered in abattoirs. In Canada, the infection was found in 3.5% to 13.2% of pigs that underwent federal inspection, while in Japan the rates are much lower. Cattle, on the other hand, are more resistant to the infection: they have low, brief serologic titers, and parasites are isolated from them only rarely (Dubey and Streitel, 1976). Although there have been sporadic reports in the past of abundant *T. gondii* isolations from cattle, it is now believed that the organism was actually *Neospora caninum*, a tissue coccidium discovered in 1988, which has been found in ruminants, equines, and dogs (Barriga, 1997).

Most infections in animals are clinically inapparent. The clinical forms are similar to those seen in man. The cases occur sporadically, with the following exceptions: in sheep and goats the congenital infection is common, and in swine there have been infrequent epizootic outbreaks in several parts of the world. Dogs can

develop manifestations that are mistaken for distemper, but such cases are rare. The greatest damage caused by toxoplasmosis in sheep and goats, and sometimes swine, is abortion and the birth of infected offspring, in which perinatal fatality can be as high as 50%.

The Disease in Man: Toxoplasmosis acquired postnatally is usually a mild disease. Most of the infections are inapparent, and of the symptomatic infections, about 90% produce mild fever, persistent lymphadenopathy in one or more lymph nodes, and asthenia. Toxoplasmosis can easily be mistaken for influenza or infectious mononucleosis. As a rule, the patient recovers spontaneously in a few weeks or months. About 4% of symptomatic patients have neurological manifestations ranging from cephalalgia, lethargy, and facial paralysis to hemiplegia, severe reflex alterations, and coma. A small proportion of symptomatic patients may exhibit muscular signs with myositis and weakness. There are also reports of myocarditis and pneumonitis caused by *Toxoplasma*, but such cases do not appear to be common. Unlike the foregoing manifestations of acute toxoplasmosis, an ocular form with subsequent uveitis may be seen in adolescents, either as a reactivation of congenital toxoplasmosis or as a delayed manifestation of postnatally acquired toxoplasmosis. Encephalitis caused by *T. gondii* is common in immunodeficient patients but rare in immunocompetent individuals. Ferrer *et al*. (1996) reviewed 63 cases and found that the most frequent clinical manifestations were focal neurological signs (80.9%), cephalalgia (53.3%), and fever (42.4%). Only 6% of the patients had new infections; 87.3% of the cases were reactivations of an earlier infection. The average survival was 11.5 months. Retinitis and pneumonitis caused by *Toxoplasma* are also common in AIDS patients.

Although congenital toxoplasmosis is not very frequent, it can cause severe disease and sequelae. Fetal infection occurs only when the pregnant mother acquires an acute or primary infection, either symptomatic or not, that generates parasitemia and permits transplacental transmission. Since the infection confers lifelong immunity, intrauterine transmission of the parasite does not occur in subsequent pregnancies except when the mother is severely immunocompromised. Observations indicate that the seriousness of the congenital infection depends on the duration of the fetal infection and that the most severe cases stem from infection in the first trimester of pregnancy (WHO, 1979). Early transmission causes few cases of fetal infection, but the risk of severe fetal illnesses is great. Only about 13% of children with toxoplasmosis acquired the infection during the first trimester *in utero* (Jenum *et al*., 1998), but an estimated 80% of them can be expected to suffer severe disease. Of the approximately 29% who become infected in the second trimester, 30% will have serious disease. Of the 50% who become infected in the third trimester, 70% to 90% are born with an inapparent infection, but they may develop ocular or neurological sequelae after several weeks or months. The symptoms of congenital toxoplasmosis are highly varied. Early infection can cause pre- or postnatal death or severe damage to the fetus. Later infection can cause generalized disease *in utero*, subsequent invasion of the nervous system, and the birth of children with sequelae such as hydrocephaly, chorioretinitis, or cerebral calcifications. Even later infection may result in the birth of a child already in the active stage of chorioretinitis or encephalitis. When the infection occurs shortly before delivery, the child may be born with an inapparent infection; or with fever, eruptions, hepatomegaly, splenomegaly, or pneu-

monia; or with a generalized infection that compromises the hematopoietic, reticuloendothelial, or pulmonary systems.

Ocular toxoplasmosis deserves special mention. The most common manifestation of this form is retinochoroiditis (more than 80% of the cases), but there can be other lesions and alterations, such as strabismus, nystagmus, and microphthalmia. Ocular lesions are common in newborn infants with toxoplasmosis, and they are almost always bilateral. Later manifestations of the lesion tend to be unilateral.

Most of the pathology of toxoplasmosis appears to involve the destruction of host cells during the multiplication of tachyzoites. It has also been shown that the production of cytokines during the immune response to the parasite can influence the pathology.

The Disease in Animals: As in man, the infection is very common but the clinical disease is relatively infrequent. Its effects are particularly important in sheep and goats because it causes abortions and disease in newborns, resulting in serious economic losses, especially in Australia, Great Britain, and New Zealand. In Tasmania, Australia, *T. gondii* was believed to have been the etiology in 46% of the outbreaks of abortion and neonatal mortality in sheep between 1962 and 1968 (Munday, 1975). Congenitally infected lambs lack muscular coordination, they are physically weak, and they are unable to feed themselves. Congenital toxoplasmosis occurs in lambs only when the ewe is infected during pregnancy. When the fetus is infected between days 45 and 55 of gestation, it usually dies; if the infection is acquired in the third month of pregnancy, the lambs are born but they are sick; if it occurs after 4 months, the lambs may be born with the infection but they are asymptomatic. Disease in adult sheep is rare. Some authors have defended the use of sheep rather than mice as animal models for the human infection, because the clinical characteristics of ovine congenital toxoplasmosis are similar to those seen in man. In swine, there have been reports of outbreaks with manifestations such as pneumonia, encephalitis, and abortion (Dubey, 1977).

Dogs have a high infection rate, and the clinical picture can resemble distemper. Cats also have a high infection rate. Both the intestinal and the systemic infections tend to be asymptomatic in cats, but cases have been reported with generalized, intestinal, encephalic, and ocular manifestations, particularly in young animals. Artificially infected young cats have developed diarrhea, hepatitis, myocarditis, myositis, pneumonia, and encephalitis. Toxoplasmosis has also been observed in rabbits, guinea pigs, and other laboratory animals, sometimes with fatal outcome. Because toxoplasmosis is a strong trigger for helper lymphocyte type 2 immune reactions (cell-mediated immunity), the infection may interfere with experimental results.

Toxoplasmosis in birds can be very common, but it is rarely symptomatic. In Costa Rica *T. gondii* was isolated from 54% of 50 chickens even though no antibodies were found. In acute cases, necrotic foci have been observed in the liver, spleen, lungs, and lymph nodes.

Source of Infection and Mode of Transmission: The human infection can be acquired *in utero* or postnatally. In the US, it is estimated that fewer than 0.1% of infected adults have acquired the infection congenitally. After birth, the intermediate hosts, including man, can be infected by eating raw or undercooked meat, especially pork or lamb, or by ingesting mature oocysts from earth, water, or food con-

taminated with the feces of infected cats. In Thailand, a study of 1,200 pregnant women showed that 13% were infected. The rate was 19.5% in women who ate undercooked meat and only 9.6% in those who did not. When this factor was excluded, the rate was 31.8% for women who had cats in their home and 19.3% for those who did not (Chintana *et al*., 1998). In Ireland, Taylor *et al*. (1997) found an infection rate of 12.8% in 1,276 children between 4 and 18 years of age. Presumably, infection acquired from infected earth or food played an important role, because the rate was higher in rural areas (16.6%) than in cities (10.2%); these results correlated with titers for *Toxocara canis*, which is acquired from ingesting contaminated earth. As in other studies, no correlation was found with the presence of domestic cats. This result may be due to the fact that the populations studied were mainly infected through the consumption of contaminated meat, or else because cats shed oocysts for only 1 or 2 weeks; hence, the infection correlates more with the existence of a contaminated environment that with the presence of these animals.

Cats and other felines are very important links in the epidemiology of toxoplasmosis. Unlike man, other omnivores and carnivores can become infected by ingesting food, especially meat, contaminated with oocysts. Sheep, which are one of the main sources of human infection, become infected only by ingesting oocysts. It appears that cats are a significant factor in the contamination of pastures, because a single infected cat produces millions of oocysts, which survive in the ground for almost a year as long as they are protected from the sun and from drying out. The results of studies conducted on islands near Australia lend credence to this idea: only 2% of the sheep raised on the islands without cats had antibodies to *T. gondii*, whereas antibodies were found in 32% of the sheep on the islands with cats. Apparently, the main sources of infection for cats are rodents or birds infected with bradyzoite cysts: some experiments have shown that oocysts infect a smaller proportion of cats than do cysts and that most cats develop antibodies against the parasite at around the age when they begin to hunt. Although there have been reports of cats infected with tachyzoites, these forms cannot be very efficient because they are destroyed by gastric acid. At some point between 3 and 21 days after the initial infection, the cat begins to shed oocysts in its feces for a period of 1 or 2 weeks, thus contaminating the environment. The infection generates sufficient immunity to stave off any future clinical infections for the rest of the cat's life. However, the oocysts can remain viable for about a year in environments that are cool, humid, and shady. Even though it is difficult to diagnose clinical infection in a cat, positive serology indicates that the animal has already had an infection, and in that case it poses no risk of contamination because it will no longer shed any oocysts.

It has been pointed out that there is a correlation between meat handling and the prevalence of seropositivity. In a serologic survey of 144 employees and workers at a slaughterhouse in Belo Horizonte, Brazil, the prevalence of positive reactors was 72%, with the highest rate among meat inspectors (92%) and the lowest rate among workers in the corrals (60%) (Riemann *et al.*, 1975). Higher reactor rates have also been found in housewives who handle meat in the kitchen compared with the general population. Presumably, their hands become contaminated by infected meat and transmission occurs via the oral route. Recent studies have suggested that coprophilic flies and cockroaches may act as transport hosts carrying cat fecal oocysts to human food, which would account for infections in vegetarians. Contamination of the soil with oocysts from wild felines would account for infec-

tions contracted by indigenous peoples living along the banks of the upper Xingú River in Brazil, who do not keep domestic cats and do not eat raw meat.

The literature also cites a few cases of transmission to man through raw milk (Riemann *et al.*, 1975; Chiari and Neves, 1984), eggs, transfusions, and accidental inoculations in the laboratory, but these cases are not significant from the epidemiologic standpoint. Congenital transmission in humans, despite its clinical significance, is also unimportant epidemiologically, both because it is relatively rare and also because the infected person is a source of infection only for the fetus during the acute phase. Congenital transmission is infrequent in all animals except sheep and goats. Because the latter are a source of infection for man, they are the only species that are epidemiologically significant.

Diagnosis: Specific diagnosis can be made in acute-phase patients by directly visualizing the parasite in fluid or tissue, but this is a difficult and low-yield process. The parasite can also be isolated from organic fluid or tissue by intraperitoneal inoculation in mice. In chronic cases, samples of muscle or brain tissue may be subjected to peptic digestion before inoculation (this procedure is not recommended in acute cases because the tachyzoites are destroyed by gastric acid). During the first week after inoculation, tachyzoites may appear in the peritoneal exudate of the mice. At 6 weeks, serologic diagnosis is performed on the surviving animals, and, if the result is positive, the mice are sacrificed to confirm the presence of cysts in the brain.

A diagnosis may also be obtained with serologic tests. The following procedures are generally used: Sabin-Feldman (S-F) dye test, indirect immunofluorescence (IIF), indirect hemagglutination (IHA), complement fixation (CF), direct agglutination (DA), and enzyme-linked immunosorbent assay (ELISA). The S-F dye test is based on the fact that live tachyzoites do not ordinarily stain with methylene blue but they do stain if they have been subjected to the lethal action of antibodies and complement; if the patient is infected, the serum to be studied provides the anti-*Toxoplasma* antibodies. With membrane antigen, the S-F test, IIF, and ELISA are sensitive, specific, and often preferred over clinical tests because they give earlier results and make it possible to diagnose active infection. However, the S-F test is being replaced by IIF, even though the results are equivalent, because the former entails manipulating live parasites and breeding mice. Positive results from IHA can be obtained later and over a longer period, but it is of little use during the acute phase of the infection. CF is a more difficult test to perform and does not offer any advantages over the ones already mentioned; consequently, its use is in decline. DA with membrane antigen is a simple, low-cost technique that diagnoses acute infections. It was recently introduced to test for infections in patients with AIDS. Some of these serologic tests, particularly ELISA, have been modified for use in diagnosing infection in food animals. Polymerase chain reaction has been used to confirm the presence of parasite DNA in adult or fetal fluids.

Clinicians are especially interested in developing a test that can distinguish between the acute and chronic forms of the infection, given the importance of the former in congenital transmission. IIF and ELISA are particularly appropriate for this purpose because they make it possible to determine the presence of IgM antibodies, which appear and disappear before the IgG antibodies. In acute acquired toxoplasmosis, IgM antibodies peak during the first month of the disease and persist for an average of eight months, although in some patients they may be present for

years. In the case of acute infection, it is believed that the study of IgG antibody avidity (the total combined power of an antibody molecule and its antigen, which depends on the number of binding sites and the affinity of each) and the presence of IgA antibodies give better results than merely verifying the presence of IgM antibodies (Rodríguez *et al.*, 1996).

Because IgM does not cross the placenta, the presence of these antibodies in the serum of newborns is reliable evidence that the fetus developed them *in utero* and that the infant was born with the infection. In the US, the Food and Drug Administration recently studied six commercial kits to ascertain the presence of IgM antibodies for toxoplasmosis and found that they all had greater than 93% sensitivity; however, the specificity of three of them was lower than 90% (Wilson *et al.*, 1997). For diagnosing toxoplasmosis in the fetus, the most useful tests are ultrasound, demonstration of specific IgM antibodies in the umbilical cord, and verification of parasite DNA in amniotic fluid (Beazley and Egerman, 1998).

It has also been proposed to investigate the presence of IgE antibodies for *Toxoplasma* as an indicator of acute infection, even though they appear after the infection and persist for only three to five months. Unfortunately, the specificity of the antibodies is high (98%), but their sensitivity is low (76%); hence, the absence of IgE antibodies does not rule out acute infection (Gross *et al.*, 1997). Another procedure used for determining the presence of acute infection is the evolution of IgG antibody titers, for which purpose a quantitative serologic test is used and is repeated after two to four weeks. If the titers increase after more than three dilutions, it may be speculated that the patient's immune system is responding actively to the parasite and therefore he or she must be in the active phase of the infection.

The toxoplasmin skin test reveals past infections and is mainly useful in epidemiologic studies. The reaction demonstrates type IV delayed hypersensitivity. The positive response appears several months after the initial infection and may last for life.

The intestinal infection in cats is diagnosed by feces flotation procedures, which permit observation of the small immature oocysts that are characteristic of the parasite. However, it is difficult to find positive cats with this test because they shed oocysts for only 1 to 2 weeks starting 3 to 21 days after primary infection. In the US, it has been estimated that, even though the infection affects 15% to 40% of the feline population, fewer than 1% of the cats are shedding oocysts at any given moment. Nevertheless, the infection in cats can be diagnosed remotely by serology. If a cat is serologically positive, it has already had the infection. Since feline toxoplasmosis leaves strong immunity against reinfection, the animal will not contaminate the environment by shedding oocysts in the future.

Control: Two circumstances facilitate human postnatal *Toxoplasma* infection: the ingestion of bradyzoites in infected undercooked meat, and the ingestion of oocysts via hands or food contaminated with the feces of infected cats. Hence, the control of human toxoplasmosis consists of avoiding these circumstances. Although the measures apply to everyone, pregnant women and immunodeficient individuals merit special attention, the former because of the possibility of congenital infection and the latter because of the risk of developing a severe case. Sanitary education should be directed particularly toward high-risk populations, and it should focus on teaching people to avoid eating raw or undercooked meat and, in the case of food

handlers, to prevent their hands from becoming contaminated. Meat, particularly pork and lamb, should be cooked until there is no reddish color left. Just as it is not recommended to use microwave ovens to kill *Trichinella*, the same is true for *Toxoplasma*, because these ovens do not cook meat evenly. Alternatively, freezing the meat for more than three days at −15°C or for more than two days at −20°C has been shown to kill most of the bradyzoite cysts. Food handlers should avoid tasting raw meat, and they should wash their hands carefully after touching it because water destroys the tachyzoites.

Populations at risk should also be taught to prevent infection from oocysts. People who keep cats in their homes, especially young animals that are just beginning to hunt, should dispose of the cat's fecal matter daily and rinse out the receptacles for the feces with boiling water, thus eliminating the oocysts before they have a chance to sporulate and become infective. These cats should be kept indoors and fed canned, cooked, or previously frozen food to keep them from hunting and catching infected rodents and birds and thus becoming infected. A serologically negative cat in the home of a pregnant woman should be removed from the household because it could acquire a primary infection and contaminate the environment with oocysts. It has been shown in the laboratory that the addition of monensin (a carboxylic ionophore produced by *Streptomyces cinnamonensis*) to dry cat food can suppress the excretion of oocysts in feces (Frenkel and Smith, 1982). Pregnant women and immunodeficient individuals should not perform tasks that expose them to potentially contaminated soil (for example, gardening) unless they use waterproof gloves and wash their hands carefully afterward. Fruit and vegetables that grow near the ground should be washed or cooked, since they might be contaminated. Flies and cockroaches should be controlled to prevent them from serving as transport hosts for the fecal oocysts of cats.

It would appear that an effective means of controlling infection in newborns is to identify pregnant women with acute infection and treat them. In Switzerland, 10 of 17 mothers treated during pregnancy had babies with antibodies to *T. gondii* and only 1 of them was infected, while 4 of 7 untreated mothers had infected babies (Berger *et al*., 1995).

Preventing infection in sheep and swine requires eliminating cats and wild felines from stables and pastures, which would be a major challenge. Veterinary inspection of slaughterhouses, which has been effective in controlling trichinosis and teniasis, is not being done for toxoplasmosis.

For some years, work has been under way to develop vaccines against toxoplasmosis for cats (Freyre *et al*., 1993), sheep (Wastling *et al*., 1995), and swine (Dubey *et al*., 1998). So far, the only successful effort has been a modified live parasite vaccine for sheep, which is administered before impregnation to prevent congenital infections.

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VISCERAL LEISHMANIASIS

ICD-10 B55.0

Synonyms: Kala-azar, black fever, Dum-dum fever, Sikari disease, Burdwan fever, Shahib's disease, infantile splenic fever, febrile tropical splenomegaly, post-kala-azar dermal leishmaniasis.

Etiology: Although visceral leishmaniasis is generally caused by *Leishmania chagasi* in the Americas and by *L. donovani* or *L. infantum* in the Old World (Wilson and Streit, 1996), cases of visceral leishmaniasis due to *L. amazonensis* have been reported (Barral *et al*., 1991), as have cases of cutaneous leishmaniasis due to *L. infantum* (Giudice *et al*., 1998). Moreover, *L. donovani* often causes cutaneous lesions in man, and some subspecies of *L. braziliensis* and *L. major* are viscerotropic in lower animals. Parasites characterized as *L. tropica* have also been isolated from patients with visceral leishmaniasis in India and Israel (Lainson, 1982).

Leishmania chagasi, *L. donovani*, and *L. infantum* are considered subspecies or members of a principal species or species complex called *L. donovani sensu lato*. The leishmanias that cause the visceral form of the disease are indistinguishable morphologically from those that cause the cutaneous and mucocutaneous forms (see classification and taxonomy of leishmanias in the chapter on Cutaneous Leishmaniasis).

The subspecies of *L. donovani sensu lato* were distinguished initially by differing ecological, clinical, and epidemiological characteristics. Later, serologic, enzy-

matic, and molecular biology methods began to be used to differentiate them (Minodier *et al*., 1997). Among the serologic techniques, the most well-known is the Adler, or Noguchi-Adler, test, which relies on the fact that leishmanias clump together and become immobilized when cultured in the serum of patients who have suffered homologous infection. By means of this test, *L. d. donovani* can be distinguished from *L. d. infantum* and from the species that cause cutaneous leishmaniasis in the Americas and in the Old World. However, *L. d. infantum* cannot be differentiated from *L. d. chagasi.*

In humans and other mammal reservoirs, the parasite takes the form of intracellular amastigotes within the macrophages. In the phlebotomine vectors and in culture, it occurs as a flagellate form, or the free promastigote, which is found in the intestinal lumen and in the proboscis of the vector. Its life cycle is similar to that described for cutaneous leishmaniasis, with the difference that the parasites do not concentrate in the subcutaneous or submucosal macrophages but rather are distributed throughout the body with the circulating macrophages, and they multiply preferentially in the spleen, the bone marrow, and the liver.

Geographic Distribution: Ninety percent of new annual cases of visceral leishmaniasis come from five countries: Bangladesh, Brazil, India, Nepal, and Sudan (WHO, 2003). However, there are endemic areas and foci of kala-azar in several places in the world. *L. d. donovani* occurs in Bangladesh and India and possibly in China and Nepal. *L. d. infantum* is distributed across eastern, western, and central Africa; the former Soviet republics of Central Asia; the Mediterranean coast of Europe and Africa; Afghanistan; Saudi Arabia; north and northwest China; Egypt; Iran; Iraq; Israel; and Yemen. *L. d. chagasi* is found in the northeastern region and parts of the eastern region of Brazil, although small foci have also been confirmed in the northern and center-west regions. Sporadic cases of the disease have been diagnosed in northern Argentina, Bolivia, Colombia, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Paraguay, Suriname, Venezuela, and on the islands of Guadeloupe and Martinique. Some reports indicate that the infection could be spreading to new areas in some countries, such as Brazil, Israel (Baneth *et al*., 1998), and Sudan, and that the number of cases and the geographic distribution of both visceral and cutaneous leishmaniasis is expanding in several countries that border the Mediterranean (Gradoni *et al*., 1996; Harrat *et al*., 1996; Lagardere *et al*., 1992).

Occurrence in Man: In most countries, visceral leishmaniasis occurs sporadically; however, it may sometimes reach epidemic proportions. In 1978, in northern Bihar, India, some 50,000 cases occurred, and the infection spread to western Bengal, with 7,500 cases reported in the first eight months of 1982. The largest number of cases occurred in a village in the same area in 1984 and 1985, but, with treatment, the number then declined steadily until 1988, when no more cases were reported (Dhiman and Sen, 1991). In China, the number of cases has declined, thanks to rigorous control efforts. Prior to 1960, as many as 600,000 cases were reported in the northeastern and northwestern parts of the country, whereas in 1979, only 48 cases were reported, most of them in the northeast. As of 1990, the figures remained at the same level (Guan, 1991). In Iraq, 1,969 clinical cases were reported in 1974, but in the following years, the number decreased to about 500 cases a year. In Sudan, between 3,000 and 5,000 cases a year were reported, although the prevalence was estimated to be much higher. However, between 1984 and 1994 an epi-

demic of visceral leishmaniasis broke out in a region of southern Sudan where the disease had not previously occurred, causing 100,000 deaths in a population of 280,000 inhabitants, with average mortality ranging from 38%–57% (Seaman *et al*., 1996). In Brazil, endemicity is highest in the states of Ceará and Bahia; 3,078 cases were reported in that country between 1971 and 1980, 44.6% of them occurring in Ceará (WHO, 1984). Between 1989 and 1991, a survey of 243 people in a village of Bahia confirmed a new leishmaniasis focus: cutaneous tests were positive in close to 30% of those surveyed and serologic tests indicated recent infection in 14%. Of 460 dogs examined, serologic tests were positive in 6% (Cunha *et al*., 1995). Information for the country as a whole indicates that visceral leishmaniasis in Brazil peaked in 1985, when 2,511 cases were reported, and that it had decreased significantly by 1991.

Although the exact incidence of visceral leishmaniasis is not known, the number of cases occurring each year around the world is estimated in the tens of thousands. In the Americas, the western Mediterranean, and northern Africa, those most affected are children under 1 year of age (infantile kala-azar), while in other areas, children over the age of 5 and young adults are most affected (Marinkele, 1981).

Occurrence in Animals: Studies of the prevalence of leishmaniasis in animals generally focus on dogs because they constitute the main source of infection for humans in many areas and because they are the most frequent victims of the infection in southern Europe. However, both wild canids and rodents can also be reservoirs in specific areas.

In the state of Ceará, Brazil, a survey conducted between 1953 and 1962 found the infection in 1.9% of 35,272 dogs with clinical symptomatology and in 1.5% of 285,592 apparently healthy dogs (Deane and Deane, 1962). In the state of Bahia, 10,132 dogs were examined between 1962 and 1969 and 1.7% were positive; in the known foci of human kala-azar, prevalence rates were as high as 25% (Sherlock and Almeida, 1970). In another study of 1,681 dogs in the state of Bahia, 23.5% were found to have antibodies against *Leishmania* and *L. chagasi* parasites were isolated from eight dogs (Paranhos-Silva *et al.,* 1996). Infection rates of 4% and 12% were also found in *Lycalopex vetulus* foxes in Brazil. In northern Iran, 4 of 161 jackals and 3 of 100 dogs whose viscera and skin were examined for parasites tested positive, and for 6 of 48 jackals and 6 of 34 dogs results of immunofluorescence tests were seropositive (Hamidi *et al*., 1982). In a leishmaniasis focus in Tuscany, Italy, 2.9% of 103 dogs were seropositive and 1% showed clinical symptoms. In another focus, 23.9% of 250 dogs examined were seropositive, 10% had lesions, and 7% had positive microscopy (Gradoni *et al*., 1980).

The Disease in Man: The incubation period is generally two to six months, but it may range from 10 days to several years. The promastigotes inoculated by a phlebotomine into human skin are engulfed by macrophages, where they become amastigotes. In some patients, especially in Africa, a primary granuloma of the skin, called a leishmanioma, forms several months before systemic symptoms appear. Leishmanias multiply slowly by binary fission in the macrophages. Some parasitized macrophages spread to the local lymph nodes. From there they enter the bloodstream and reach the viscera, particularly the spleen, the liver, and the bone marrow, where the leishmanias then multiply rapidly in the fixed macrophages, producing reticuloendotheliosis, which ultimately destroys the macrophages.

In inhabitants of endemic areas, the disease's onset is insidious and its course is chronic. However, in persons from areas free from the disease, onset may be abrupt. Fever is prolonged and undulating, often with two daily peaks. Some patients experience cough, diarrhea, and symptoms of intercurrent infections. The disease is characterized by splenomegaly and, later, by hepatomegaly. Lymphadenopathy is common in some regions, such as Africa and the Mediterranean. Other symptoms may include anemia with leukopenia, edema, darkening of the skin, and emaciation. The abdomen sometimes becomes distended from the splenomegaly and the hepatomegaly. Petechiae and hemorrhage of the mucous membranes are frequent and are indicative of clotting problems. Secondary infections are also common. Mortality is very high in untreated patients. *L. donovani* infection is not always accompanied by serious symptoms; it may occur asymptomatically or produce only mild symptoms, depending on the host's degree of resistance. The immune system of some patients is able to control the infection, but the proportion of people who recover spontaneously is not known.

In the infection foci studied in Ceará, Brazil, 67% of the patients were 0 to 4 years old. In the Mediterranean basin, the prevalence of infections caused by *L. d. infantum* by age group is similar. In India, in contrast, the infection is more prevalent in young adults.

In the Americas, cutaneous kala-azar lesions are very rarely seen, but the parasites have been found in macroscopically normal skin. In India, in contrast, the skin of patients often takes on a gray hue (the name kala-azar means "black fever"), especially on feet, hands, and abdomen. In Kenya and Sudan in Africa, and in the Mediterranean and China, patients may develop nodular lesions. Another type of lesion that frequently appears about a year after treatment with antimony is post–kala-azar dermal leishmaniasis. These sequelae are common in the Old World, occurring in up to 56% of cases (Zijlstra *et al*., 1995); however, they are rare in the Americas.

There is solid evidence from both experimental animals and man that the immune response of the T helper 1 lymphocytes (cell-mediated immunity)—especially the production of gamma interferon and tumor necrosis factor alpha—protects against leishmaniasis, and the infection may resolve spontaneously or remain asymptomatic. There is also some evidence that these reactions might contribute to tissue damage in cutaneous leishmaniasis (Ribeiro de Jesus *et al*., 1998).

Visceral leishmaniasis in AIDS patients is similar to the disease in immunocompetent individuals, but it is more severe and far more prevalent, recurs more frequently, and is more often resistant to antimonials (Altes *et al*., 1991; López-Vélez *et al*., 1998). In several organ transplant recipients, the disease recurred after treatment, resulting in the death of some patients (Berenguer *et al*., 1998).

The Disease in Animals: Visceral leishmaniasis in domestic dogs also occurs in geographic foci. Frequently, but not always, the prevalence in man and dogs in the same area is similar, although there may be areas of canine infection where no human infection exists. The disease causes cutaneous and systemic lesions, but the former are more evident. The incubation period is three to seven months. The severity of the disease varies. The cutaneous lesions are non-pruritic and include areas of alopecia, desquamation, and inflammation. They occur mostly around the eyes, ears, face, and feet. Although the lesions may evolve and become nodules, ulcerations,

and scabs, it is uncommon for pustules to form. The most frequent systemic manifestations are intermittent fever, anemia, hypergammaglobulinemia, hypoalbuminemia, lymphadenopathy, splenomegaly, lethargy, and weight loss. Episodes of diarrhea, glomerulonephritis, and polyarthritis sometimes also occur. Antimonial treatment is not very effective and recurrences are frequent (Barriga, 1997). Severity of clinical symptoms does not appear to be related to parasite load, as very heavily parasitized dogs may have mild symptomatology. In Brazil, more than 30% of infected dogs had no apparent clinical symptoms (Hipólito *et al*., 1965). Infection in the fox *Lycalopex vetulus* in northeast Brazil is similar to that of dogs. Some animals may have clinically inapparent infections, while others manifest different forms of the disease, including very serious and even fatal cases.

Source of Infection and Mode of Transmission: The epidemiology of the disease varies from region to region and from one area to another. In the Americas, the reservoirs of visceral leishmaniasis are dogs and the wild canids. The infection is spread among canids and from these animals to man by the bite of the phlebotomine fly *Lutzomyia longipalpis*. The epidemic significance of the man-dog link seems to vary from area to area; while some authors have found no correlation between the prevalence in humans and in dogs (Paranhos-Silva *et al*., 1996) or no change in the human prevalence after removal of infected dogs (Dietze *et al*., 1997), other authors believe that elimination of infected dogs does reduce the prevalence of the infection in humans (Ashford *et al*., 1998).

The most important endemic area in the Americas is in northeastern Brazil; the main foci are distributed across a semiarid region that is subject to prolonged droughts. The disease is basically rural, with a few cases occurring in populations or places on the outskirts of cities. The distribution of kala-azar is focal. The largest concentration of cases occurs in foothill areas or in mountain valleys, where the disease is endemic with periodic epidemic outbreaks. In the flatlands, on the other hand, cases are sporadic and occur primarily in the most humid areas, near rivers.

In Brazil, the geographic distribution of the disease coincides with that of the vector. The main, and possibly the only, vector in the endemic area of northeastern Brazil is the phlebotomine *L. longipalpis*, an abundant insect that reaches its highest density about two months after the heaviest rains and is resistant to drought. The vector is found both outdoors and indoors. It feeds on dogs, wild animals, and, less often, man.

Dogs are an especially suitable reservoir because they offer the vector direct access to the parasitized macrophages of their cutaneous lesions. In studies conducted in Ceará, Brazil, parasites were detected in the skin of 77.6% of 49 dogs with visceral leishmaniasis but only in 16.3% of 43 human patients examined. In addition, humans have been found to have a lesser number of parasites in their skin than dogs. Amastigotes are scarce in human skin and only rarely serve as a source of infection for the vector.

A wild host of visceral leishmaniasis in northeastern Brazil is the fox *Lycalopex vetulus*, which often comes near houses to hunt chickens. Amastigotes are abundant in the fox's skin, and it is a great source of infection for the vector (Garnham, 1971). In the tropical rain forest region of the lower Amazon, such as the state of Pará, where the number of cases in humans and domestic dogs is low, the reservoir of the parasite is suspected to be a wild canid. In this region, *L. donovani* has

been isolated from the fox *Cerdocyon thous (*Lainson *et al.,* 1969; Silveira *et al*., 1982).

In the Mediterranean basin, dogs are also the principal reservoir, while several species of the genus *Phlebotomus* serve as vectors. In the Middle East, jackals and dogs are the hosts and the main sources of infection for phlebotomines. In India, by contrast, no dogs or other animals have been found to be infected, and man is the main reservoir (Bhattacharya and Ghosh, 1983). Prevalence of the disease was very high in the country's large cities, but it was reduced significantly as a result of an antimalaria campaign that eliminated both mosquitoes and phlebotomines. When the campaign was discontinued, Bihar experienced an epidemic resurgence of kala-azar (see Geographic Distribution and Occurrence in Man). In the absence of an animal reservoir, subclinical human infections may play an important role in maintaining the disease (Manson and Apted, 1982). Person-to-person transmission takes place by means of *Phlebotomus argentipes*, an eminently anthropophilic insect which feeds solely on humans. In India, the number of parasites circulating in human blood was found to be sufficient to infect the vector. Transmission occurs inside houses, which constitute microfoci of infection (Manson and Apted, 1982). In Sudan, the infection has been found in wild rodents of the species *Arvicanthis niloticus* and *Acomys albigena*, domestic rats *Rattus rattus*, and carnivores *Felis philippsi* and *Genetta sangalensis*. It is believed that rodents are the primary hosts for the agent and that carnivores are secondary reservoirs. The vector is *P. orientalis.* Humans develop parasitemia and, under epidemic conditions, can be a source of infection for the vectors.

Numerous investigators believe that visceral leishmaniasis was originally an infection that circulated enzootically among wild animals (canids and perhaps rodents), and that later, domestic dogs were included in its cycle; eventually, the disease became an infection transmitted between humans without the intervention of an animal reservoir, as is the case of kala-azar in India. An argument in favor of this hypothesis is dogs' low degree of adaptation to the parasite and their susceptibility to the clinical disease, which suggests that they are a rather new host in the natural history of the disease. In the Americas, it has been suggested that the fox *Cerdocyon thous*, which becomes infected without becoming ill, could have been the original reservoir. However, more research is needed, especially concerning rate of infection, to confirm that this animal is the original reservoir (Lainson, 1983).

Diagnosis: Confirmation of visceral leishmaniasis is made by identifying the parasite. In the form of visceral leishmaniasis that occurs in the Americas, the parasite can rarely be seen in films of peripheral blood; however, this technique can yield positive results for kala-azar in India. The most sensitive procedure (98% positivity) is splenic aspiration, but this technique entails high risk, especially in patients with anemia and clotting problems. Aspiration of sternal or iliac bone marrow can detect the presence of parasites in 54% to 86% of cases and lymph node aspiration can detect them in 64% of cases (WHO, 1984). In the early stages of the disease, when parasites are scarce, culture in Novy-McNeal-Nicolle or another appropriate medium or intraperitoneal inoculation in hamsters can be used. Often, simultaneous application of both methods yields better results. Polymerase chain reaction has begun to be used more recently. This technique is as sensitive as microscopy of lymph node and bone marrow aspirates in confirmed patients, but it offers the added

advantage of confirming the disease in suspected patients who have negative microscopy. Although blood samples on filter paper can be used, the sensitivity of the test increases if lymph node or bone marrow aspirates are used (Osman *et al*., 1997). In dogs and other canids, the parasites can be observed or isolated by culture or hamster inoculation, using material from cutaneous lesions or the viscera of dead animals.

When the usual methods for detecting the parasite do not produce results or the media needed to perform them are not available, immunologic tests are generally used. The immunofluorescence test is useful, and although cross-reactions with *T. cruzi* are a drawback, these can be avoided by the use of specific antigens. The direct agglutination test to detect visceral leishmaniasis has a sensitivity of over 99% and a specificity of 96% if the appropriate dilution is used (Boelaert *et al*., 1999). The enzyme-linked immunosorbent assay (ELISA) for IgG antibodies has exhibited 93.4% sensitivity and 93.6% specificity in Sudan (Elassad *et al*., 1994). In Portugal, the ELISA test showed 100% sensitivity, 90.5% specificity, and 91.4% predictability in man, with an adsorption cut-off value of 0.100; in dogs, it showed 80% sensitivity, 94.3% specificity, and 96.6% predictability, with a cut-off of 0.200. However, the reproducibility of the test was not entirely satisfactory (Mauricio *et al*., 1995).

Since in active visceral leishmaniasis there is a prevalence of T helper 2 lymphocyte response, which includes the production of IgE, the ELISA test for IgE antibodies can indicate active infection. Atta *et al*. (1998) found these antibodies in 23 patients with visceral leishmaniasis, but did not find them in persons with subclinical *L. chagasi* or *T. cruzi* infections or in healthy individuals. The values fell markedly after treatment. A dot-ELISA test showed 98.5% sensitivity and 96.7% specificity for detecting antigens of *L. donovani* in the circulation, and 98.5% sensitivity and 98.9% specificity for detecting antibodies against *L. infantum.*

Control: Leishmaniasis control measures are directed against the vectors and reservoirs. Application of residual insecticides such as DDT in and around dwellings produced excellent results when use of this insecticide was permitted. The incidence of kala-azar in India decreased markedly in the wake of the antimalaria campaign, and the infection has virtually disappeared from the districts that were sprayed. Spraying should not be limited to dwellings, but should also be done around animal dens, stone walls, refuse dumps, and other places where the vector breeds.

In regions in which the infection is of zoonotic origin, it is considered important to systematically eliminate infected dogs and, to the extent possible, control the fox population. On the Greek island of Crete, destroying infected dogs brought down the incidence of the disease in humans significantly. However, vigorous campaigns in northeastern Brazil have not borne out the effectiveness of controlling dog populations and experimental studies have shown that eliminating dogs does not reduce the incidence of human infection (Dietze *et al*., 1997). As no other important reservoirs of *L. chagasi* have been found in those areas, the human infection apparently comes from other humans. In regions in which the infection is of human origin, human cases should be detected and treated. Although vaccination against leishmaniasis is considered impractical because the infection inhibits immunity, experimental studies have demonstrated that partial protection was achieved in mice injected with *L. donovani* promastigote antigens incorporated into liposomes (Ali and Afrin, 1997). Mathematical models suggest that the most effective method for controlling visceral

leishmaniasis is insecticide application when the vector is accessible. The next most effective control method is reduction of host susceptibility through improved nutrition for children and vaccination of people and dogs. Elimination or treatment of dogs that serve as reservoirs is considerably less effective than either of these methods (Dye, 1996).

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Section B

HELMINTHIASES

1. Trematodiases
2. Cestodiases
3. Acanthocephaliases and Nematodiases

1. Trematodiases

CERCARIAL DERMATITIS

ICD-10 B65.3

Synonyms: Swimmer's itch or dermatitis, bather's dermatitis, clam digger's itch, schistosome dermatitis.

Etiology: The agents of this disease are cercariae of avian schistosomes (mainly species of the genera *Australobilharzia*, *Bilharziella*, *Gigantobilharzia*, *Microbilharzia*, *Ornithobilharzia*, and *Trichobilharzia*) or of nonhuman mammals (species of the genera *Heterobilharzia*, *Orientobilharzia*, *Schistosoma*, and *Schistosomatium*). All belong to the family Schistosomatidae. Man is an aberrant host for these species and does not sustain the development of the parasite beyond its cutaneous site.

Although there are differences in the details, all schistosomes share basically the same life cycle (see the chapter on Schistosomiasis). The eggs contain a pre-adult stage, the miracidium, when they are eliminated with the definitive host's feces or urine. When the egg reaches the water, the miracidium is released and swims in search of an appropriate intermediate host, which is usually a snail belonging to *Bulineus*, *Lymnaea*, *Nassarius*, *Physa*, *Planorbis*, *Stagnicola*, or another genus. The miracidia penetrate the body of the mollusk and invade the digestive gland (hepatopancreas), where they develop into another pre-adult stage, the sporocyst. Another pre-adult stage forms within the sporocyst, the redia, which, in turn, gives rise to yet another pre-adult stage, the cercaria. After several weeks, the fork-tailed cercariae mature and leave the snail, swimming in search of a definitive host. Their infectivity decreases quickly and they generally die if they fail to find a host within 24 hours. Unlike the cercariae of other trematodes, schistosomes do not form metacercariae, but rather invade the definitive host's skin directly, at which time they lose their tails and undergo histological changes in their tegument, becoming juvenile parasites called schistosomula. The schistosomula penetrate the blood or lymph vessels and travel to the lungs, where they remain for several days. They then continue on to the liver, where they reach maturity and mate. From there, they migrate to their final site, where they begin laying eggs.

The definitive hosts of the schistosomes that cause cercarial dermatitis in man are generally geese, ducks, and other waterfowl, or domestic or wild mammals, such as

raccoons, otters, and rodents. In man, the cercariae are usually destroyed in the skin before reaching the circulatory system. The species of schistosomes specific to man (*Schistosoma haematobium*, *S. japonicum, S. mansoni*, and others of limited distribution) also cause a cutaneous syndrome as part of the natural infection, but it is generally less serious. Of a group of 28 Dutch tourists who became infected with human schistosomes in Mali (West Africa), 10 (36%) had symptoms of cercarial dermatitis (Visser *et al*., 1995).

Geographic Distribution and Occurrence: Cercarial dermatitis occurs worldwide in all climates, and in all places where people, through their recreational or occupational activities, come into contact with contaminated waters in rivers, lakes, floodlands, irrigation canals, and oceans near the coast. Swimmers, clam-diggers, washerwomen, fishermen, and rice-field workers are the groups most likely to be exposed. Although cercarial dermatitis normally occurs as isolated cases, epidemics have been reported—for example, an outbreak among 11 children who contracted the disease while swimming in a park in the US (Anon., 1992) and one involving 58 rice-field workers in Thailand (Kullavanijaya and Wongwaisayawan, 1993).

As a precise diagnosis is difficult, many cases are probably never recognized as cercarial dermatitis. However, the disease appears to be much more common than official statistics indicate: in a survey carried out in the area of Lake Michigan, in the US, 317 human cases of cercarial dermatitis were identified in a single summer (Lindblade, 1998); in another survey conducted among 555 swimmers in Lake Geneva in Switzerland, 153 probable cases were identified (Chamot *et al.*, 1998).

The Disease in Man: Cercarial dermatitis is basically a defense reaction to an aberrant parasite, which the host almost always successfully destroys, but which causes allergic sensitization.

When a person is exposed to cercariae for the first time, the symptomatology is usually mild and may pass unnoticed. Between 10 and 30 minutes after exposure, the affected person feels a transitory itching and macules appear but vanish within 10 to 24 hours. After 5 to 14 days, small papules appear, accompanied by temporary itching where the macules had been. As no immunologic reactions are expected in the first few days of a primary infection and the cercariae are destroyed within approximately 30 minutes in the malpighian layer, the symptoms that occur in the first few days are presumed to be the result of the damage caused by the parasite and the chemical substances it releases. The clinical manifestations that appear towards the end of the first week suggest an allergic reaction to the dead parasite. Baskin *et al.* (1997) observed that cercarial dermatitis patients produced four times more IgE than controls without dermatitis. This finding supports the hypothesis that the cause of the disease is an early hypersensitivity reaction.

The secondary response in individuals sensitized by previous exposures is faster and more intense than the primary reaction. The symptomatology varies somewhat, depending on the parasite species and the affected individual's response capacity. First, red spots develop on the exposed skin, which begins to itch within 30 to 90 minutes after infection. After 6 to 12 hours, the individual develops a macular rash and experiences intense itching (Narain *et al.*, 1994). This rash is replaced 10 to 20 hours later by papules or, in some people, by marked urticaria. The papular eruption normally subsides within about a week, though it may last for up to a month. Complications may occur as the result of secondary bacterial infection caused by scratching.

Experiments with ducks and mice infected with cercariae of the avian cercaria *Trichobilharzia szidati* (Horak *et al.,* 1998) have shown that the antigens that cause the cutaneous reaction are present in the invasive cercariae but not in the schistosomula that result from their differentiation.

The Disease in Animals: Occasional cases of cercarial dermatitis in cats and dogs have been reported, mostly in association with the occurrence of the disease in their owners. Its occurrence in domestic animals appears to be much less frequent than in man, but this may be because animals are less able to communicate their symptoms and because the lesions are concealed by their fur. Moreover, it is difficult to distinguish cercarial dermatitis from hookworm dermatitis caused by nematodes of the family Ancylostomatidae.

Source of Infection and Mode of Transmission: The sources of infection for man are the banks of bodies of fresh or salt water where the snails that release the cercariae live. Epidemiologists have identified three situations in which the infection typically occurs. In the first, the infection originates in freshwater bodies frequented by waterfowl (geese, ducks, etc.) or wild mammals (raccoons, otters, etc.). In these cases, the parasites are generally species of the genera *Australobilharzia*, *Gigantobilharzia*, or *Trichobilharzia*, which infect fowl and develop in snails of the genera *Lymnaea*, *Nassarius*, or *Physa*, or the genera *Heterobilharzia* or *Schistosomatium*, which infect mammals and develop in *Lymnaea*, *Physa*, or *Stagnicola* snails. In the second situation, the infection is acquired on the banks of saltwater bodies. In these cases, the parasites generally belong to the genera *Australobilharzia*, *Gigantobilharzia*, *Microbilharzia*, or *Ornithobilharzia*, which infect marine or migratory birds and develop in marine snails such as *Ilyanassa*. In the third case, the infection is acquired in rice fields and floodlands inhabited by parasites of domestic animals and wild rodents, such as *Schistosoma spindale*, a species that affects bovines and wild rats (Inder *et al*., 1997); *Schistosoma bovis*, a bovine schistosome; *Schistosomatium douthitti*, which affects rodents; and *Heterobilharzia americana*, which affects dogs. Often, the intermediate hosts are snails of the family Planorbidae.

The mode of transmission is direct penetration of the cercariae into the host's skin within 24 hours of its formation.

Diagnosis: Diagnosis is difficult and is based mainly on observation of the patient's clinical symptoms and a history of recent exposure to watercourses in which hosts of nonhuman schistosomes exist. As treatment is purely symptomatic and does not exclude the existence of other allergic conditions, successful treatment does not help to confirm the infection. Although various serum immunologic tests can establish the diagnosis (fluorescence test, cercarial Hullen reaction, circumoval precipitation, etc.) (Pilz *et al.*, 1995), all require specimens of the parasite and give positive results only 10 to 14 days after infection. Indirect immunofluorescence and enzyme-linked immunosorbent assay, employing commercially available human schistosome antigens, have been used to diagnose the infection, but the results are less sensitive (Kolarova *et al.*, 1994).

Control: Apart from the obvious risk posed by the presence of definitive and intermediate hosts of the agents of cercarial dermatitis, a study in the area of Lake Michigan (United States) found that the risk of infection depended on the age of the

individual, the time of day when he/she was exposed to contaminated water, the month in which the exposure took place, and the high algae content and shallowness of the water (Lindblade, 1998). Few of these elements are really susceptible to modification. The population of snails in pools, rice fields, or irrigation canals can be controlled with molluscicides (Kolarova *et al*., 1989), but their use in natural watercourses would probably cause too much ecological damage. In the case of small natural ponds, clearing the vegetation from the banks will create a less favorable environment for snails and removing the mud from the bottom will eliminate them. Use of praziquantel baits has been recommended to eliminate the mature parasites of fowl, but three 200 mg doses daily per duck are needed to produce a permanent reduction in the excretion of eggs. During the pre-patent period, one dose of 22.5 mg per duck daily is sufficient to prevent patency permanently (Muller *et al*., 1993). In Japan, rice-field workers and other individuals have been protected with copper oleate, which is applied to the skin and allowed to evaporate. Dimethyl phthalate cream can also be used for this purpose. It is recommended that swimmers dry off vigorously as soon as they emerge from the water, since the cercariae are better able to penetrate the skin when it is allowed to air dry slowly.

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CLONORCHIASIS

ICD-10 B66.1

Synonyms: Chinese liver fluke disease, oriental liver fluke disease, infection due to *Clonorchis sinensis*.

Etiology: *Clonorchis sinensis* is a small trematode measuring 12–20 mm long and 3–5 mm wide, with a reddish, translucent body. It lives in the bile ducts of humans, pigs, cats, dogs, rats, and several other species of fish-eating mammals. Some authors place it in the genus *Opisthorchis* because adults of the genera *Clonorchis* and *Opisthorchis* are similar in appearance, but there are clear differences in the pre-adult stages. Moreover, the name *Clonorchis* has been used in the medical literature since 1907, so retaining it seems justified. The parasite requires two intermediate hosts to complete its life cycle. The first is any of several operculate aquatic snails, such as species of *Alocinma*, *Bulimus*, *Melanoides*, *Parafossarulus*, and *Semisulcospira*. Among them, *P. manchouricus* seems to be the most important host. The second intermediate host is any of more than 100 species of freshwater fish (often members of the family Cyprinidae), only about a dozen of which are regularly consumed by humans. Three species of freshwater shrimp can also serve as second intermediate hosts.

The infected definitive host eliminates fully embryonated eggs in its feces. If the eggs reach fresh water (rivers, lakes, lagoons, reservoirs, ponds) and find appropriate intermediate hosts, their development continues. The snail ingests the eggs, which hatch in the intestine and release ciliated larvae, or miracidia. The miracidium penetrates the intestinal wall, invades the digestive gland (hepatopancreas), and becomes a sporocyst, which produces other larvae, the rediae. After a redia leaves the sporocyst, it produces still other pre-adult larvae, the cercariae. Multiplication of larvae in the pre-adult stages is called pedogenesis, and is characteristic of trematodes. The cercariae—juvenile stage larvae with a tail—emerge from the snail when they are mature and seek a second intermediate host, which they must find within 24–48 hours or they will die. A cercaria penetrates the skin of a fish, loses its tail, and forms a resistant wall around its body. This cyst, called a metacercaria, lodges under the fish's skin or in the connective tissue or underlying muscles. The metacercariae become infective for the definitive host in approximately one month.

When the definitive host consumes infected raw fish, the metacercariae excyst in the host's duodenum. The juvenile parasite penetrates the ampulla of Vater and moves against the bile flow towards the bile ducts. After three to four weeks, the parasite reaches sexual maturity and begins to lay eggs, and the life cycle begins anew. In rats, it has been shown that 32% of the metacercariae that enter the host reach the

liver and that the parasite grows quickly during the first 30 days and then slowly during the following 60 days (Kim, 1995). The entire life cycle is completed in around three months, but the mature parasites can live for up to 40 years.

Geographic Distribution: The endemic area of clonorchiasis is limited to China, Japan, Malaysia, Republic of Korea, Singapore, Taiwan, Vietnam, and possibly Cambodia and the Lao People's Democratic Republic. Human cases have also been found in Hawaii, US, among people who had never traveled elsewhere, but those cases may have been due to consumption of infected fish imported from endemic areas. In several countries of the world, sporadic cases have been diagnosed in immigrants from and in people who had visited the endemic area. For example, a prevalence of 26% was found among 150 Chinese immigrants in New York City, US, and the infection rate was 15.5% among 400 immigrants examined in Montreal, Canada (Sun, 1980).

Occurrence: Human infection appears to be ancient, as eggs of the parasite have been found in human remains 2,600 years old. The prevalence among humans is estimated at between 7 and 30 million cases in the endemic area, with some 20 million people believed to be infected in southeastern China alone. In the Chinese province of Hubei, the infection was found in 5.8% of human inhabitants, 36.4% of cats, 16.7% of pigs, 12.2% and 3.8% of two snail species, and 48.1%, 18.2%, and 17.2% of three fish species (Chen *et al.,* 1997). Although the first human case in the Republic of Korea was not diagnosed until 1915, *C. sinensis* is now the most prevalent human parasite there (Rim, 1990). In 1997, stool sample examinations in that country showed a human infection rate of 11.3%, while intradermal tests detected the infection in 27.6% of those examined. Of 25 fish species tested, 7 were infected, with prevalences ranging from 2.8% to 30%. Nevertheless, this situation represents an improvement over that of several decades ago (Joo *et al*., 1997). In 1987, for example, a study found that 80.3% of a sample of 76 people were excreting an average of 27,781 eggs per gram of feces (Hong *et al*., 1994). In Vietnam, the infection was found in 13.7% of humans, 13.3% of snails, and 53.4% to 100% of farm-raised fish, and it was determined that the largest fish were most frequently infected (Kino *et al.*, 1998). In some areas of Japan, 20.6% of dogs and 45.5% of cats examined were infected. In all the endemic areas, the infection has been found to be more prevalent among males than females and among adults than children. These findings are attributed to the fact that the most affected groups are those that eat raw fish most often.

The Disease in Man and Animals: The symptomatology of the disease depends on the number of parasites, the length of time the infection has persisted, and whether continuous reinfections have occurred. In general, when the infection is mild and recent, there are no manifestations of disease. When the infection is more intense and of longer duration, the patient may exhibit loss of appetite, diarrhea, a sensation of intra-abdominal pressure, fever, and eosinophilia. In the heaviest and oldest infections, there may also be enlargement and tenderness of the liver, obstruction of the bile ducts, and even cirrhosis, with edema and ascites. Chen *et al*. (1989) described three stages of the infection in cats: an acute stage of up to 5 weeks' duration, in which specific IgM, IgG, and IgA antibodies are found; a subacute stage that lasts up to 28 weeks, during which only IgG and IgA antibodies are present; and a

chronic stage, in which only IgG antibodies are detected. Based on these criteria, the authors found that 3.9% of 74 patients examined were in the subacute stage and 96.1% were in the chronic stage.

Light recent infections cause little harm. The principal types of damage produced by chronic clonorchiasis are hyperplasia of the mucus-secreting epithelium of the bile ducts, localized dilation of the ducts, and lymphocytic and eosinophilic inflammation of the periductal region, which eventually leads to fibrosis. The changes are attributed to irritation and to a 24-kD cysteine proteinase produced by the parasite (Park *et al.,* 1995). A common complication is recurrent pyogenic cholangitis, which results from obstruction of the bile ducts. Mild pancreatitis is also frequent. Clonorchiasis is often cited as a predisposing factor for the formation of gallstones, but Hou *et al*. (1989) found no clinical evidence to substantiate this assertion. However, it was demonstrated that the combination of *C. sinensis* infection and excessive alcohol consumption does predispose one to cholangiocarcinoma (Shin *et al.,* 1996).

Source of Infection and Mode of Transmission: Studies conducted in China, where the distribution of the parasitosis is uneven, have shown that human infection with *C. sinensis* depends primarily on the presence of intermediate hosts, the existence of reservoirs of the infection, and the customary consumption of undercooked fish by the population (Fang, 1994). The primary factor limiting the distribution of the disease is availability of the first intermediate host because only a small number of snail species are susceptible to the parasite. *Parafossarulus manchouricus* is the main host in China, Japan, the Republic of Korea, and Vietnam, but some other species are also susceptible. The second intermediate host is less of a limiting factor, since more than 100 species of freshwater fish and several species of shrimp can harbor the developing parasite. The reservoirs of the parasite are humans, swine, cats, dogs, rats, and several other fish-eating mammals. Persistence of the infection in nature is fostered by the presence of these reservoirs in the same ecological environment as the intermediate hosts—without which they would not have become infected—and the fact that they eliminate several thousand eggs per gram of feces every day. The use of human feces to fertilize carp ponds, a common practice in China, has also helped keep the infection active.

Diagnosis: Specific diagnosis of the infection is made by finding the parasite's eggs in fecal matter or by means of a duodenal probe following administration of a strong solution of magnesium sulfate to produce a reflex contraction of the gallbladder. When the parasite burden is light, it is advisable to use egg concentration methods to examine stool samples. Some authors recommend the zinc sulfate flotation method, but many operculate eggs tend to sediment in saline solutions. The parasite burden can be evaluated by counting the eggs in feces by means of the Stoll dilution method (Rim, 1982). In humans, up to 100 eggs per gram of feces constitutes a light infection; between 100 and 1,000 eggs, a moderate infection; and more than 1,000 eggs a heavy infection (Manson and Apted, 1982). The eggs of *C. sinensis* are considered quite characteristic: they are small (28–35 μm long and 12–19 μm wide), oval, operculate, and embryonated, with a thick, yellowish wall and a pronounced border around the operculum. However, several other trematodes in Southeast Asia that occasionally infect man (e.g., *Heterophyes heterophyes*, *Metagonimus yokogawai*, and *Opisthorchis viverrini*, the first two of which are

intestinal parasites) have eggs that are virtually indistinguishable from those of *C. sinensis (*Ditrich *et al.,* 1992). Examination of the surface structure of the egg by electronic microscopy is a more reliable way to identify the parasite but is difficult to perform in the clinical environment.

Clinical imaging studies, such as cholangiography, sonography, and computerized tomography, may show shapes that suggest infection (Lim, 1990). However, the sensitivity and specificity of these techniques, at least in the case of sonography, appear to be inadequate. Using sonography, Hong *et al*. (1998) found 52% positivity among patients who were excreting eggs and 49% positivity among patients with negative stool samples.

The use of several immunodiagnostic tests has been proposed. The intradermal test shows immediate hypersensitivity and is simple, but it does not indicate if the infection is current. In a sample of 3,180 people examined by means of this technique, 26.2% tested positive, but when stool samples from 598 of the latter group were examined, only 21.6% were found to be excreting eggs (Kim *et al.*, 1990). In one study, immunoenzymatic staining and indirect immunofluorescence using frozen sections of the parasite showed sensitivities of 92% and 88%, respectively, and high specificity: 2% false positives with the first technique and 4% with the second (Liu *et al.*, 1993). Cross-reactions with cases of acute schistosomiasis, chronic schistosomiasis, and paragonimiasis were observed in 14%, 5%, and 0% of cases using immunoenzymatic staining, and in 14%, 10%, and 0% using indirect immunofluorescence. In another study (Lin *et al*., 1995), use of enzyme-linked immunosorbent assay (ELISA) to detect total Ig, IgG, and IgA showed specificity and sensitivity of 100%, 100%, and 87%–90%, respectively. IgA antibodies were found to have decreased significantly after a month of successful treatment, which indicates that this test can be used to evaluate the results of treatment.

Control: The most effective control measure is probably to refrain from eating undercooked fish in endemic areas. Human clonorchiasis does not exist in northern China, where people do not eat raw fish, although it is prevalent in pigs, cats, dogs, and rats in that region. However, it is very difficult to modify deeply ingrained eating habits that are part of the population's culture. Freezing or salting fish is not a very effective control measure because the metacercariae remain infective for 10 to 18 days at –12°C, for 3 to 7 days at –20°C, and for 5 to 7 days in brine (Fan, 1998). The minimum doses of radiation needed to kill metacercariae are 0.05 kGy when they are isolated outside a host and 0.15 kGy when they are in fish (Duan *et al.*, 1993).

Fish infections can be reduced by allowing human fecal matter to ferment for several weeks before it is used to fertilize fish-culture ponds, as the fermentation process kills *C. sinensis* eggs. Treating the population with praziquantel every six months also significantly reduces the passage of eggs into the environment. Hong *et al.* (1998) showed that this treatment reduced the prevalence of infection from 22.7% to 6.3% in 24 months among inhabitants of a community in which the disease was endemic.

Use of molluscicides is not recommended because these chemicals can kill fish. However, elimination of vegetation from the edges of ponds during the spring and summer will benefit predators that eat snail larvae, which in turn will reduce the population of first intermediate hosts. A possible biological control method involves

introducing *Notocotylus attenuatus*, an intestinal trematode of ducks, whose cercariae affect the gonads of snails and render them sterile.

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DICROCELIASIS

ICD-10 B66.2

Synonyms: Dicroceliosis, dicrocoeliasis, lancet fluke infection, infection due to *Dicrocoelium dendriticum*.

Etiology: The agents of this disease are *Dicrocoelium dendriticum* (*D. lanceolatum*) and *D. hospes,* small, translucent, lancet-shaped trematodes, measuring 5–15 mm long by 1.5–2.5 mm wide. They live in the bile ducts of sheep, goats, cattle, and, less frequently, other domestic and wild ruminants. They rarely infect pigs, dogs, rabbits, rodents, or humans.

D. dendriticum requires two intermediate hosts for its development. The first is a land snail (38 species, among them *Cionella lubrica* in North America, *Zebrina detrita* and *Helicella candidula* in Europe, and *Bradybaena similaris* in Malaysia), and the second is an ant (12 species, among them *Formica fusca* in Germany and North America, *F. cinerea* and *F. picea* in the Russian Federation, and *F. gigantis* and *F. rufibarbis* in the Middle East).

The adult parasites deposit small oval eggs (38–45 µm x 22–30 µm), which are brown in color, thick-walled, operculate, and embryonated at the time they are excreted by the host. They are transported by bile and fecal matter to the exterior, where the first intermediate host ingests them. The egg, which is quite resistant to desiccation, releases the miracidium only when it is ingested by a snail. The miracidium forms two generations of sporocysts in the digestive gland of the snail, the second of which produces numerous cercariae, which are expelled from the snail through the respiratory chamber after about three to four months. The cercariae that leave the snail are stuck together in the form of a viscous mass ("slime ball"), measuring 1–2 mm in diameter. Infection with the parasite affects the snail's fertility and longevity (Schuster, 1992). Each slime ball may contain 100 to 400 cercariae, which, after being ingested by the second intermediate host, migrate into the ant's coelom and nervous system and become metacercariae. Each ant may contain between 38 and 76 metacercariae, depending on the species and size of the insect (Schuster, 1991).

The presence of metacercariae in the ant's brain often alters its behavior: instead of returning to the nest as dusk approaches and the temperature drops, an infected ant will climb to the top of a blade of grass. It will then bite down and suffer a spasm of the jaw musculature, making it impossible for the ant to let go. Thus trapped high on the vegetation, the ant is likely to be eaten by a definitive host. When herbivores consume infected ants while grazing, the metacercariae excyst in the duodenum and the juvenile parasites travel against the bile flow to the bile ducts. The parasites

mature and begin to lay eggs after 10–12 weeks. The life cycle of *D. hospes*, which has been determined more recently, is similar to that of *D. dendriticum.* The first intermediate host is a pulmonate land snail of the genus *Limicolaria*, and the second is an ant of the genus *Camponotus*, in which the metacercariae develop. The definitive hosts are domestic herbivores (cattle, sheep, goats) and probably also wild ruminants (Frank *et al.,* 1984).

Geographic Distribution and Occurrence: *D. dendriticum* is a widely distributed parasite found in many parts of the world, including North Africa (Egypt), South America (Brazil and Colombia), Asia, Australia, the Caribbean islands, Europe, the Middle East, and parts of the eastern US and Canada. Prevalence rates of 40% have been reported in domestic animals in France, 80% in Poland, 46% in Switzerland, 100% in Yugoslavia, and 75% in goats in the Russian Federation. In Greece, parasite eggs were found in 2 of 232 dogs, but there is some doubt as to whether these were true *D. dendriticum* infections (Haralabidis *et al.*, 1988). *D. hospes* is restricted to the sub-Saharan savannas of Africa. In Côte d'Ivoire and Niger, 50% and 94%, respectively, of cattle and sheep have been found to be infected (Frank *et al.,* 1984).

Human dicroceliasis also occurs worldwide. Since 1988, cases have been reported in Saudi Arabia, the former Czechoslovakia, Spain, Kenya, Nigeria, Somalia, the former Soviet Union, and the US, although it is likely that most cases are not reported. The presence of *Dicrocoelium* spp. eggs in human feces is not unusual, though it does not always indicate true infection: in Nigeria, 2 (0.4%) of 479 human stool samples were found to contain *Dicrocoelium* eggs (Reinthaler *et al.,* 1988), and in a hospital in Saudi Arabia, eggs were found in the stools of 208 patients over a three-year period (el-Shiekh Mohamed and Mummery, 1990). However, many of these cases are due to spurious parasites ingested with the infected liver of domestic animals, and the eggs merely pass through the human digestive tract. Of the 208 cases in Saudi Arabia, at least 7 patients had a true infection, while 34 were spurious cases.

The Disease in Man and Animals: Dicroceliasis generally produces no signs of disease in animals, unless the infection is very heavy or of long standing. When this occurs, there is a general decline in health status, the animals tend to remain prostrate, their temperature decreases, and they exhibit some degree of malnutrition and anemia, though it is not certain that the latter is caused by the parasite infection. Theodoridis *et al*. (1991) found no proof of significant loss of blood or plasma protein in experimentally infected sheep with parasite loads of up to 4,000. Liver enzymes and blood biochemistry are generally within normal ranges. Autopsy, however, reveals hundreds or thousands of parasites in the bile ducts and gallbladder, duct inflammation and proliferation, progressive development of fibrosis in the hepatic parenchyma, and, occasionally, granulomas and abscesses (Camara *et al.,* 1996). The disease is more severe in New World camelids (Wenker *et al.,* 1998). Hamsters infected experimentally showed an increase in bile secretion and an accumulation of oxidizing molecules in the liver, which produced liver damage (Sánchez-Campos *et al.,* 1999).

In most human cases, the main symptoms are dyspepsia and flatulence, although there may occasionally be constipation alternating with diarrhea, vomiting, and abdominal pain. Peripheral eosinophilia is seen in some cases. Laboratory analysis

of blood and urine generally reveals no abnormalities. Ectopic localization of parasite eggs in the brain may cause neurological symptoms in rare instances.

Source of Infection and Mode of Transmission: The source of infection for both animals and man is ants infected with metacercariae of the parasite. Animals ingest these insects while grazing. Humans are accidental hosts who are occasionally infected by nibbling on grass containing infected ants or by consuming fruits or vegetables contaminated with these insects. In at least one case, an AIDS patient became infected by consuming a drink contaminated with ants. The infection in snails occurs most frequently in the spring, decreases in the summer, and increases again in the fall. Infected ants are found only when the temperature is below 20°C (Schuster and Neumann, 1988).

Diagnosis: Diagnosis is based on the detection of the eggs of the parasite in feces or bile from the individual suspected to have the infection. Examination of the bile is much more sensitive: of 49 bovines with adult *D. dendriticum* in their livers, eggs were found in the bile of 44 (89.8%) but in the feces of only 13 (26.5%) (Braun *et al.,* 1995). Of the techniques available for demonstrating the presence of eggs, flotation of experimentally contaminated sheep feces, using a solution of mercury iodide mixed with potassium iodide with a specific density of 1.44, yielded an egg recovery rate of 91.2±9.4%, regardless of flotation time. In contrast, solutions of zinc sulfate with specific densities of 1.3 and 1.45, or potassium carbonate with a specific density of 1.45 yielded an egg recovery rate of only 9.0±7.1%, 26.7±24.9%, and 13.0±11.6%, respectively, and more than 3–5 minutes of flotation time were needed to improve the yield. Sedimentation revealed 41.2±1.5% of the infections (Rehbein *et al.*, 1999). To distinguish genuine infections from spurious parasites, it is necessary to ensure that the patient does not eat animal liver for several days and then reexamine the feces for eggs during that period. Although the *Dicrocoelium* spp. eggs are considered distinctive, they cannot be differentiated by means of conventional microscopy from the eggs of *Eurytrema pancreaticum,* a trematode of the pancreas of ruminants and monkeys that develops in land snails and grasshoppers. *E. pancreaticum* has been found in humans in China and Japan on approximately eight occasions.

Immunologic techniques have also been used to diagnose the infection in domestic animals. Counterimmunoelectrophoresis, passive hemagglutination, and agar gel precipitation detected 69.8%, 50.0%, and 23.8% of infections, respectively, in sheep and goats (Jithendran *et al.,* 1996).

Control: Control of dicroceliasis in domestic animals is difficult owing to the variety of intermediate host species (38 snail species and 12 ant species) and to their distribution over wide land areas (in contrast to trematodes with aquatic intermediate hosts, which have a more localized distribution on pasturelands). Although pesticides may be used to control mollusks and ants, their cost and the attendant risk of ecological damage make this an impractical solution. A recommended alternative is to destroy the parasites by treating the definitive hosts, but this, too, is expensive and there are still no drugs available that will totally eliminate the parasite. When possible, cultivation of grasslands can eliminate a very high proportion of the snail population. Similarly, it has been recommended that chickens be introduced in infected areas because they eat snails. The low frequency of human infection probably does not justify mass control measures. It should be sufficient simply to educate the pop-

ulation about the risk of eating, nibbling, or sucking on blades of grass that may be contaminated with ants.

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ECHINOSTOMIASIS

ICD-10 B66.8 Other specified fluke infections

Synonym: Echinostomatidosis.

Etiology: The agents of this trematodiasis are various species of several genera of the family Echinostomatidae. They are trematodes of small but variable size, measuring 5–15 mm long, 1–3 mm wide, and 0.5–0.6 mm thick, which live in the intestine of mammals (generally carnivores, swine, or rats), fowl, and, occasionally, humans. The most remarkable morphologic characteristic of the mature parasite is a collar of spines surrounding the dorsal and lateral sides of the oral sucker. The number, size, and position of the spines are taxonomically significant. The eggs are large (85–125 µm x 55–70 µm), thin-walled, and operculate, and are eliminated before the embryo forms. As the nomenclature of the group is still uncertain, studies are examining their nucleic acids to determine the relationships among some members of the family. The family Echinostomatidae comprises approximately 30 genera. Some 16 species, most of the genus *Echinostoma*, have been recovered from humans (Carney, 1991). The most important causes of zoonosis are the species *E. echinatum* (*E. lindoense*), *E. hortense, E. ilocanum, E. malayanum, E. revolutum, E. trivolvis*, and *Hypoderaeum conoideum.* Radomyos *et al.* (1994) examined fecal matter from 681 individuals in northern Thailand and found 8.3% to be infected with *E. malayanum,* 8.1% with *E. ilocanum*, and 0.8% with *E. revolutum.*

The life cycle differs from species to species, but in general two intermediate hosts are required. The cercariae always develop in a freshwater snail (first intermediate host), but they may encyst as metacercariae in another snail, a bivalve mollusk, a tadpole, or a freshwater fish (second intermediate host) (Table 1). The definitive host, including man, becomes infected by consuming raw foods (intermediate hosts) containing metacercariae (see Source of Infection and Mode of Transmission).

Geographic Distribution and Occurrence: Human echinostome infections are confined mainly to the Far East. However, sporadic clinical cases occur in countries such as the US, where more than a million immigrants from that region reside (Liu and Harinasuta, 1996).

E. malayanum is found in India, Indonesia (Sumatra), Malaysia, the Philippines, Thailand, and Singapore, where it infects dogs, cats, pigs, mongooses, rats, and, rarely, humans. *E. ilocanum* is distributed in the Philippines, Indonesia (Java and Sulawesi), parts of southern China, India, and Thailand. In addition to man, it infects murid rodents, dogs, and cats. Prevalences of 1% to 50% have been found among humans in the Philippines, and of 14% among dogs in China. *E. hortense* is found in Japan and the Republic of Korea, where the infection was detected in 3 (0.5%) of 642 human stool samples on one occasion and in 11 (9.5%) of 116 samples on another (Son *et al.*, 1994). Their life cycle has been replicated in the laboratory using *Lymnaea* and *Radix* snails as the first intermediate hosts, tadpoles as the second hosts, and rats as the definitive hosts (Lee *et al.*, 1991). *E. revolutum* is distributed in the Far East and Europe, where it infects ducks, geese, and other fowl. Human infections have been diagnosed in Indonesia (Java and Sulawesi), Thailand, and Taiwan. The prevalence of human infection in Taiwan is estimated at 2.8%–6.5%. *E.*

TABLE 3. Intermediate hosts and geographic distribution of the main zoonotic echinostomes.

	Intermediate hosts		
Species	**First**	**Second**	**Distribution**
Echinostoma echinatum (E. lindoense)	*Planorbis* snails	Clams, snails	Brazil, India, Indonesia (Java), Malaysia, Philippines
E. hortense	*Lymnaea, Radix* snails	Tadpoles, fish	Japan, Republic of Korea
E. ilocanum	*Gyraulus, Hippeutis* snails	Snails	China, India, Indonesia (Java and Sulawesi), Philippines, Thailand
E. malayanum	*Indoplanorbis, Lymnaea,* and other snail species	Snails, tadpoles, fish	India, Indonesia (Sumatra), Malaysia, Philippines, Singapore, Thailand
E. revolutum	*Lymnaea* snails	Clams	Indonesia (Java and Sulawesi), Taiwan, Thailand
E. trivolvis	*Heliosoma* snails	Snails, clams, tadpoles, fish	North America
Hypoderaeum conoideum	*Lymnaea, Planorbis* snails	Snails, tadpoles	Thailand

trivolvis, which for many years was confused with *E. revolutum*, is found in North America, where it infects 26 fowl species and 13 mammalian species (Marquardt *et al.*, 2000). *E. echinatum* is a parasite of anseriform fowl in Brazil, India, Indonesia (Java), Malaysia, and the Philippines. It used to also be quite prevalent on the island of Sulawesi (24% to 96%), but no human cases have been detected there in recent decades (see Control). *H. conoideum* is a trematode parasite of fowl that is frequently found in the human population of northern Thailand, where people often eat raw snails.

The Disease in Man and Animals: Most human echinostome infections seem to be of little clinical importance. In the Republic of Korea, for example, although human stool sample examinations have revealed *E. hortense* prevalences of 0.4%, 0.5%, and 9.5% (Lee *et al.,* 1994; Son *et al.*, 1994), only 75 cases had been reported in that country as of 1994 (Huh *et al.*, 1994). The disease's clinical features have not been well studied (Huffman and Fried, 1990). In general, echinostomes are not very pathogenic, and mild and moderate infections often go unnoticed. Heavy infections may cause some degree of diarrhea, flatulence, and colic pain, however. In children, anemia and edema have also been reported and, in at least one case, duodenal ulcers have been observed at the site of parasite attachment (Chai *et al.,* 1994). Studies of

E. hortense in rats have demonstrated that, although the parasites remain mostly in the intestinal lumen, the activity of their suckers destroys the epithelium and causes villus atrophy and crypt hyperplasia (Lee *et al.,* 1990). In fowl, severe enteritis due to *E. revolutum* and *H. conoideum* has been reported.

Source of Infection and Mode of Transmission: The first intermediate host of the echinostomes of zoonotic importance is always a freshwater snail (Table 1). The source of infection for man and other definitive hosts is the second intermediate host, which harbors the metacercariae. In many cases, the metacercariae form in snails; in other cases, they may develop in bivalve mollusks or tadpoles and even freshwater fish. Humans acquire the infection by ingesting an undercooked secondary intermediate host. Among the snails that harbor metacercariae, the genera *Pila* and *Viviparus* are important because they are often eaten raw in the Philippines and on the island of Java. Among the bivalves, clams of the genus *Corbicula* are important for the same reason. A wide variety of freshwater fish have been shown to be suitable hosts for echinostome metacercariae.

From the ecological standpoint, echinostomiasis occurs in regions with an abundance of freshwater bodies, which allow the intermediate hosts to survive. The endemicity of the parasitosis is due to the custom of consuming raw mollusks or fish.

Diagnosis: Diagnosis is based on confirmation of the presence of eggs in fecal matter (see the chapter on Dicroceliasis). The size of the eggs differs, depending on the species of equinostome, and these eggs must be distinguished from the unembryonated eggs of other intestinal or biliary trematodes.

Control: The relatively minor clinical importance of this parasitosis does not justify the establishment of special control programs. In endemic areas, it is recommended that the population be educated about the risks of and warned against eating raw or undercooked mollusks or fish, though changing this long-standing eating habit may be difficult. An interesting example of involuntary ecological control that resulted in the disappearance of the human infection occurred in Lake Lindu, on the island of Sulawesi. The incidence of *E. echinatum* in humans ranged between 24% and 96% in some communities in that region, but introduction of the fish *Tilapia mossambica* into the lake interfered with reproduction of the clam *Corbicula lindoensis*, which was the main source of human infection. As a result, the human infection ceased to occur when this species of clam disappeared. However, the wildlife cycle—between rodents as definitive hosts and freshwater snails as intermediate hosts—persists.

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FASCIOLIASIS

ICD-10 B66.3

Synonyms: Hepatic distomiasis, fasciolosis, sheep liver fluke disease.

Etiology: The agents of this disease are *Fasciola hepatica* and *Fasciola gigantica,* trematodes that live in the bile ducts of wild and domestic ruminants and other herbivores and occasionally infect man.

F. hepatica is a flat fluke, shaped like a laurel leaf, which measures 20 to 40 mm long by 10 to 15 mm wide. It is greenish brown in color. The adult parasite lays about 3,000 eggs a day, which are carried to the host intestine by bile and eliminated in feces before they become embryonated. In order to mature, the eggs need to have suitable conditions of humidity, oxygenation, and temperature. They can survive for about two months in feces that are moist but sufficiently compacted to keep out oxygen, but they will not hatch. The eggs can withstand temperatures from 0°C to 37°C, but they only develop at 10°C to 30°C. In freshwater bodies, the first juvenile stage (miracidium) develops and emerges from the egg in 10 to 12 days at temperatures between 20°C and 26°C, but the process takes 60 days or longer at 10°C. Since the energy reserves of the miracidium are limited, once it has been released it has to invade a snail intermediate host within eight hours in order to stay alive. It is guided to its intermediate host in part by the chemical attraction of the snail's mucus.

The intermediate hosts are amphibious snails of the family Lymnaeidae. In the past, most of the species in question were classified under the genus *Lymnaea*, but a number of these have been reassigned to other genera, including *Fossaria*,

Pseudosuccinea, and *Stagnicola* (Barriga, 1997). Since traditional morphological classification is difficult with the family Lymnaeidae, molecular methods are being used to study phylogenetic relationships (Bargues and Mas-Coma, 1997). The most important species are *Fossaria bulimoides, Fossaria modicella*, *Pseudosuccinea columella, S. caperata,* and *S. montanensi* in North America; *Fossaria viatrix* and *L. diaphana* in a large part of South America; *L. tomentosa* in Australia and New Zealand; *L. truncatula* in Africa, Asia, and Europe; and *L. viridis* in Asia, the state of Hawaii (USA), and Papua New Guinea (Boray, 1982). *Fossaria cubensis and P. columella* are the main intermediate hosts in the Caribbean, Colombia, and Venezuela (Cong *et al*., 1991).

The miracidia take 30 minutes to penetrate the snail using both enzymatic and mechanical means, following which they become sporocysts. Rediae (sometimes two generations) develop within the sporocysts, and within the rediae, cercariae. It takes between three and seven weeks, depending on the temperature of the water, for the sporocyst to develop inside the snail to the point of producing cercariae. This multiplication of preadult parasite stages inside the snail, known as pedogenesis, is characteristic of the trematodes and may compensate for the comparatively few eggs laid by the adults. It has been estimated that a single *F. hepatica* miracidium can produce 320 cercariae, and an average of 418 cercariae are recovered from one infected snail (Barriga, 1997). The cercariae abandon the snail when it becomes more active, often when more fresh water is available following rainfall. Once they are free, the cercariae swim in the water for about two hours and then attach themselves to aquatic plants, where they secrete a protective envelope, or cyst, around them. Some cercariae may encyst in water, where they usually remain suspended, attached to bubbles. This encysted organism is called a metacercaria. It measures about 0.2 mm in diameter and becomes infective for the definitive host in two days. In order to survive, the metacercaria requires a relative humidity level of under 70% and moderate temperatures. Few of them can withstand the ice of winter, and none can survive a hot, dry summer. All of them live for 6 months at temperatures between 12°C and 14°C, but only 5% live for 10 months. Their maximum survival in nature is probably about one year.

The definitive hosts become infected by ingesting metacercariae along with plants or water. The cystic envelope is digested in the small intestine of the host, and the parasite becomes active, traverses the intestinal wall, moves around in the peritoneal cavity for a couple of days, and, finally, penetrates the hepatic parenchyma. The parasite, which is only 0.3 mm long at this stage, continues to pass through the liver for the next six or seven weeks and then invades the biliary canaliculi, by which time it measures 4 mm to 14 mm. The parasite matures and eggs begin to appear in feces between 56 and 90 days after the initial infection. The infection lasts approximately four to six years in sheep and between one and two years in cattle.

F. gigantica has a life cycle similar to that of *F. hepatica.* However, its intermediate hosts are different aquatic snails belonging to the superspecies *Lymnaea (Radix) auricularia*, and which live in larger bodies of water. These snails hibernate but do not tolerate long summers. In India and Pakistan, the intermediate host is *L. a. rufescens*; in Malaysia, *L. a. rubiginosa*; in Iran, *L. a. geodrosiana*; and in Iraq, *L. lagotis euphratica.* The main intermediate host in Africa is *L. a. natalensis* (Malek, 1980). The development cycle of *F. gigantica* is longer than that of *F. hepatica.* In countries where both trematodes exist, such as Pakistan, their co-occurrence is deter-

mined by the presence of appropriate intermediate hosts. *F. hepatica* cannot complete its larval cycle in *L. auricularia*, while *F. gigantica* cannot do so in *L. truncatula.* The definitive hosts of *F. gigantica* are cattle, goats, zebras, sheep, and occasionally man. The prepatent period lasts 9 to 12 weeks. This trematode is distinguished from *F. hepatica* by its larger size (25–75 mm by 12 mm), smaller cephalic cone, less prominent shoulders, more transparent body, and slightly larger eggs (156–197 μm by 90–104 μm for *F. gigantica* and 130–150 μm by 63–90 μm for *F. hepatica*).

Geographic Distribution: *F. hepatica* is found in almost all temperate regions where sheep and other ruminants are raised. Virtually all these areas have sufficient humidity and adequate temperature conditions, at least during part of the year, to sustain a snail population. *F. gigantica*, on the other hand, occurs mainly in tropical areas such as Africa, Asia Minor, Southeast Asia, southern Europe, the state of Hawaii (USA), the former USSR, and possibly southern US.

Occurrence in Man: Human fascioliasis caused by *F. hepatica* has been found mainly in Australia, Bolivia, Cuba, Ecuador, England, Egypt, France, Iran, Peru, and Portugal (García and Bruckner, 1997). The frequency of the parasite in animals does not appear to be closely correlated with its occurrence in man. For example, although the infection is common in cattle in western and southeastern US, only one human case has been reported in that country. The situation is similar in China: although the infection is frequently seen in animals, only 44 human cases were known to have occurred as of 1991 (Chen, 1991). Human fascioliasis can occur sporadically or in outbreaks. The largest epidemics on record were in France, near Lyon in 1956–1957, with some 500 cases, and in the Lot Valley in 1957, with about 200 cases. The common source of infection was watercress contaminated with metacercariae (Malek, 1980). In England, the largest known outbreak affected 40 persons in 1972. In Egypt, one study revealed 40 cases in children in one year (el-Karaksy *et al*., 1999) and another, a 3% infection rate in children (Curtale *et al*., 1998). The frequency of human infection in Latin America has been underestimated in the literature. In Cuba, over 100 cases were recorded by 1944 (to which numerous subsequent reports should be added), and in Chile, 82 as of 1959. In 1978, 42 clinical cases were diagnosed in the canton of Turrialba in Costa Rica (Mora *et al.,* 1980). A series of 31 surveys conducted in the Bolivian highland plateau revealed an overall prevalence of 15.4%, with local variations ranging from 0% to 68% (Esteban *et al*., 1999). In a hyperendemic area of that Bolivian region, the prevalence was found to be 75% in children and 41% in adults—probably the highest figures in the world (Esteban *et al*., 1997). A study carried out in Cuba revealed an outbreak involving 67 persons, 59 of whom had prepatent infections and were identified initially by coproantigenic investigation. None of the prepatent cases had *Fasciola* antigen in the bloodstream (Espino *et al*., 1998). A study of 5,861 rural subjects in central Chile showed a prevalence of 0.7% in humans, 13.5% in horses, 6.1% in rabbits, and 20.6% in swine (Apt *et al*., 1992). There is increasing reliance on immunologic diagnosis to study epidemics and find cases in unsuspected contacts (Bechtel *et al*., 1992).

Occurrence in Animals: Hepatic fascioliasis is a common disease of cattle, goats, and sheep in many parts of the world. It can also affect swine, rabbits, equines, and other mammals. Morbidity and mortality rates vary from one region to another. In endemic areas, it is not usual to find infection rates of 30%, 50%, or even

higher. A study conducted in the central highlands of Peru revealed an infection rate of 18.6% in sheep in the foci of origin and 95.8% in the foci of dissemination. In Puerto Rico, 32% of slaughterhouse cattle were found to be infected. The losses caused by hepatic fascioliasis are difficult to calculate, but in the US, it is estimated that US$ 5.5 million are lost each year because of mortality and morbidity, as well as US$ 2.5 million on account of livers that were confiscated because they failed inspection. According to one estimate, the productive efficiency of cattle with mild infections declines by 8% and in cattle with more serious infections, by more than 20%. In the sheep-raising industry, losses in wool production alone can range from 20% to 39%. Indeed, there are losses from delayed development of the animals; reduced wool, milk, and meat production; lower market prices; and the confiscation of livers. Moreover, when the parasites invade an animal's liver, they pave the way for invasion by *Clostridium novyi*, which can cause infectious necrotic hepatitis.

F. gigantica reaches high levels of prevalence in endemic areas. In China, rates of 50% in cattle, 45% in goats, and 33% in buffalo have been reported. In Iraq, rates of 71% were found in buffalo, 27% in cattle, 19% in goats, and 7% in sheep. In Thailand, the average prevalence of infection was 12% in cattle and buffalo, with local variations from 0% to 85% (Srihakim and Pholpark, 1991).

The Disease in Man: The effect of fascioliasis on human health depends on the parasite burden and the duration of the infection. The migration of young fasciolae across the intestinal wall and through the peritoneal cavity does not cause clinical manifestations, but their final journey across the hepatic parenchyma can lead to traumatic, necrotic, and inflammatory lesions, whose severity depends on the number of parasites. In the bile ducts, the adult *Fasciola* produces pericanalicular inflammation and fibrosis, and adenomatous proliferation in the ductal epithelium. Massive infections can cause biliary stasis due to obstruction of the duct, atrophy of the liver, and periportal cirrhosis. Cholecystitis and cholelithiasis occur with some frequency in chronic cases. The most common manifestations during acute fascioliasis, when the young parasites migrate across the hepatic parenchyma, are abdominal pain, fever, hepatomegaly, eosinophilia, and mild anemia. In a study of 53 patients with eosinophilia of probable parasitic origin, 30 of the cases proved to be due to fascioliasis (el Zawawy *et al*., 1995). Elsewhere, *F. hepatica* was the parasite most frequently associated with reduced hemoglobinemia in a group of highly parasitized individuals (Curtale *et al*., 1998). This parasite was also found in 24% of 187 patients with fever of unknown origin (Abdel Wahab *et al*., 1996).

In the chronic phase, which occurs once the parasite has become localized in the bile ducts, the common signs are biliary colic and cholangitis. The acute-phase eosinophilia usually persists, although sometimes the chronic infection can be asymptomatic (el-Nehwihi *et al*., 1995). In a study of 47 patients in Chile, the main symptoms were abdominal pain, dyspepsia, weight loss, diarrhea, and fever. Ten of the 47 patients had jaundice. The eosinophil count was normal in 9 and elevated in 38 cases (Faiguenbaum *et al.,* 1962). In Spain, the most common symptoms in 6 fascioliasis patients were eosinophilia (100% over 1,000 cells/mm^3), abdominal pain (100%), fever (83%), weight loss (83%), and generalized myalgia (67%) (de Gorgolas *et al*., 1992).

As they pass through the peritoneal cavity, the larvae may be diverted to aberrant sites in different parts of the body. Hence it is not unusual for patients to have extra-

hepatic abnormalities, such as pulmonary infiltrates, pleuropericarditis, meningitis, or lymphadenopathy caused by these parasites (Arjona *et al*., 1995).

The Disease in Animals: Fascioliasis is a disease of herbivores. Sheep are the most susceptible domestic species, followed by cattle. The disease has both an acute and a chronic form (Soulsby, 1982).

The acute form occurs when the sheep ingests a large number of metacercariae at once, with consequent invasion of a multitude of young parasites in the hepatic parenchyma. The migrating parasites destroy the hepatic tissue, causing hemorrhages, hematomas, necrotic tunnels, and peripheral inflammation. In massive infections, the affected sheep may die suddenly without any clinical manifestations, or they may exhibit weakness, loss of appetite, and pain when palpated in the hepatic region and then die a couple of days later. In less acute cases there may be weight loss and accumulation of fluid in the abdomen (ascites). Other frequent manifestations are eosinophilia, anemia, hypoalbuminemia, and high alanine aminotransferase (ALT) and aspartate transaminase (ASL) levels in serum. In sheep harboring *C. novyi* spores in the liver, the invasion of juvenile fasciolae can lead to infectious necrotic hepatitis with fatal outcome. Cattle rarely suffer from acute fascioliasis.

The chronic form occurs when the host ingests moderate but sustained doses of metacercariae. Instead of sudden, massive invasion and destruction of the liver, the parasites accumulate over time and eventually reach a pathogenic number after they are already localized in the bile ducts. The symptoms are progressive anemia, weakness, loss of appetite, submandibular edema ("bottle jaw"), ascites, diarrhea, and weight loss. The symptomatology depends on the parasite burden. In sheep, 200 to 700 parasites cause chronic disease and in some cases death, while 700 to 1,400 cause subacute disease and certain death. In cattle, the manifestations of fascioliasis are usually constipation, diarrhea in extreme cases, weakness, and emaciation, especially in young animals. Cattle are more resistant than sheep and can tolerate a larger parasite burden without having any significant clinical manifestations: about 1,400 parasites will cause symptoms in 60% of the animals and a few deaths (Barriga, 1997). The animals' condition worsens when pasturage is scarce and improves when it is abundant, but they are never cured, and the parasitosis has a cumulative effect over the years. In swine, fascioliasis is usually asymptomatic and becomes clinically apparent when debilitating factors, such as malnutrition or concurrent illnesses, are present. The parasitosis has also been described in equines and rabbits.

The pathogenesis, pathology, and symptomatology of the infection caused by *F. gigantica* are similar to those of the parasitosis caused by *F. hepatica.* Both acute and chronic forms are seen in sheep, but cattle have only the chronic form.

Source of Infection and Mode of Transmission: The ecology of fascioliasis is linked to the presence of water, which enables the snails that serve as intermediate hosts to survive, and appropriate temperatures, which allow the parasites to complete their life cycle. Physiographic characteristics, soil composition, and climatic factors determine the reproduction rate of *Lymnaea* and hence the epidemiologic dynamics of the disease. Specimens of *Lymnaea*, as well as cases of fascioliasis, can be found in pasturelands in widely diverse settings throughout the world, from sea level flatlands to Andean valleys at elevations of over 3,700 meters. From the ecologic standpoint, the habitat of *Lymnaea* can be divided into two broad types: primary foci, or reservoirs, and areas of dissemination. The primary foci are located in

permanently wet environments such as streams, lakes, lagoons, or canals. The snails are found near the banks, where water flows slowly. They begin to lay their eggs in springtime when temperatures rise above 10°C and continue to do so as long as the thermometer remains above this level. At 9°C the eggs hatch in one month; at 17°C to 19°C, in 17 to 22 days; and at 25°C, in 8 to 12 days. Since new snails begin to lay eggs at 3 weeks of age, they can produce up to three generations in a single season as long as they have enough water. It has been calculated that a single specimen of *L. truncatula* can produce up to 100,000 new snails in one season.

Many snails die during dry, hot summers, but a few of them estivate and resume their development when the temperature falls and moist conditions return. Many of them also die during very cold winters, but some go into hibernation and resume their development when temperatures once again rise above 10°C. The snails that manage to survive dry conditions, heat, and cold are the seeds for the next season's crop of snails. Temperature above 10°C is a key factor in the epidemiology of fascioliasis because when it is any colder the *Fasciola* eggs fail to develop, the snails do not reproduce, the stages do not develop inside the snail, and the cercaria do not encyst. Areas of dissemination are characterized by the alternation of flooding and droughts, and they have large concentrations of *Lymnaea.* Snails may reach these areas directly from original foci carried by rising waters, or they may be reactivated after estivation during dry spells. Seasonal foci of this kind turn pastures into enzootic areas in which serious outbreaks occur. *Fasciola* eggs transmitted by infected animals in springtime and early summer develop inside the snails and produce cercariae and metacercariae until the end of summer. The animals that ingest them begin to show signs of the disease at the end of autumn and during winter. The eggs transmitted by these animals infect more snails, but eggs do not develop until sufficiently warm temperatures return in the spring. Hence the metacercariae from this new cycle appear at the end of spring or in early summer. When ingested by animals, these metacercariae produce symptoms in summer and autumn.

The most important definitive host is the sheep. It has been estimated that a sheep with a mild subclinical infection can contaminate a pasture with more than 500,000 eggs a day, and one with a moderate infection can shed 2.5 to 3 million eggs a day. Sheep are followed in importance by cattle, but their production of *Fasciola* eggs declines rapidly. Many other species of domestic and wild herbivores, including lagomorphs, can also serve as definitive hosts. However, studies done in Australia suggest that some of these latter animals are only temporary hosts and cannot maintain the cycle by themselves for any length of time. Such would be the case with rabbits, which do not contaminate pastures to any significant extent.

Man is infected mainly by eating watercress *(Nasturtium officinale)* infested with metacercariae. In France, where watercress is a popular salad ingredient (10,000 tons are consumed each year), human infection is more frequent than in other European countries. Sometimes raw lettuce and other contaminated plants that are eaten raw can also be a source of infection, as can water from irrigation ditches or other receptacles. Alfalfa juice has also been implicated in places where people drink this beverage.

Role of Animals in the Epidemiology of the Disease: Man is an accidental host. The infection cycle in nature is maintained between animals (especially sheep and cattle) and snails of the family Lymnaeidae. Animals, therefore, serve primarily as a

reservoir of infection for man. The epidemiological picture of human fascioliasis appears to have changed in recent years. In the last two decades, the number of human cases has increased in places that are geographically unrelated to areas in which the animal disease is endemic. Mas-Coma *et al*. (1999) believe that this infection has ceased to be a secondary zoonosis and propose a new classification for the epidemiology of the human infection.

Diagnosis: The disease is suspected on the basis of clinical manifestations (painful and febrile hepatomegaly coupled with eosinophilia) and is confirmed by the finding of characteristic eggs in feces. During the acute phase, no eggs can be seen because the parasites have not yet matured, and therefore immunologic tests are often used. However, positive reactions may not appear at such an early stage. In this phase, it is important to distinguish fascioliasis from acute hepatitides due to other causes. Epidemiologic antecedents (abundance of cases in the area, custom of eating watercress) and the presence of peripheral eosinophilia assist in identification. In animals, the diagnosis of acute fascioliasis is often made at autopsy based on observation of hepatic lesions and the presence of immature parasites. The most effective method for finding eggs in feces is sedimentation. Sometimes the parasite can be seen using biliary endoscopy. Ultrasound does not show the migrating parasites during the acute phase and reveals only 50% of the patent cases (Fawzy *et al*., 1992).

Consumption of beef or lamb's liver may cause trematode eggs to appear in feces and consequently give a false positive result in the coprologic examination. A correct diagnosis can be made after excluding liver from the patient's diet for several days. If fecal observation is negative, bile can be examined by duodenal probe. In a series comparing the two approaches, coprologic observation revealed 68% of the cases, whereas the study of the bile aspirate identified 98% of the cases. In Latin America, there have been cases of unnecessary and prolonged hospitalization of hepatic patients, and sometimes even surgical interventions have been performed, because differential diagnosis failed to take fascioliasis into account. A number of immunobiologic tests have been used in an effort to diagnose the infection during the prepatent period, including a skin test, complement fixation, immunofluorescence, immunoelectrophoresis, counterimmunoelectrophoresis, enzyme-linked immunosorbent assay (ELISA), and immunoelectrotransfer. The prepatent period of fascioliasis lasts for so long (more than two months in humans), that it is one of the few parasitic diseases in which immunology is useful for diagnosis. The search for appropriate antigens has improved the specificity and sensitivity of these tests, but there are still cross-reactions, especially with schistosomiasis. ELISA, used on cysteine proteinase regurgitated by the parasite, has yielded sensitivity levels of 89% to 95% and specificity levels of 98% to 100% (Cordova *et al*., 1999). Early diagnosis of fascioliasis makes it possible to start treatment before liver damage is too far advanced.

Control: Individuals can prevent fascioliasis by not eating raw watercress of wild or unknown origin. Watercress can be cultivated under controlled conditions that prevent access by animals, and therefore fecal contamination, as well as infestation by snails. However, most watercress sold in markets has been gathered by persons who are unaware of the sanitary conditions under which the plant was grown. Rinsing the greens for 10 minutes in running water washes away only 50% of the

metacercariae, but citric acid (10 ml/L), commercial vinegar (120 ml/L), liquid soap (12 ml/L), or potassium permanganate (24 mg/L) will detach or kill them all (el-Sayad *et al*., 1997).

A modern plan for the control of animal fascioliasis, which would ultimately forestall human infection, would include: a) preventing the consumption of metacercariae, b) strategically administering fasciolicides to the definitive hosts, and c) eliminating the intermediate hosts. Preventing the ingestion of *Fasciola* metacercariae involves fencing in contaminated areas, which is difficult, expensive, and not very effective. The strategic administration of fasciolicides, unlike curative treatment, is aimed at interrupting the life cycle of the parasite by treating animals according to a regimen that will prevent the initial infection, the formation of eggs, and, finally, contamination of the environment. There are now highly sophisticated methods for calculating the best time to administer such treatments (Yilma and Malone, 1998). Previously, some of the chemical compounds against *Fasciola* killed only the adult or juvenile specimens, but now broad-spectrum treatments are available. Controlling snails involves ecologic, chemical, and biologic methods. The ecologic approach consists of modifying the environment to interrupt the life cycle of the snails. Drainage of the land, where this is technically and economically feasible, is the one permanent way to control or eliminate the mollusks. It is also beneficial to smooth the banks of watercourses and remove marginal vegetation to prevent the formation of backwater pools where the snails flourish. The chemical approach consists of applying molluscicides. Given the impressive capacity of *Limnaea* spp. for reproduction and recuperation, molluscicides should be applied regularly to keep down the snail population. This approach is very costly and therefore cannot be applied on a large scale on most livestock-raising establishments in the developing countries. However, it can be used on small farms. In temperate climates, molluscicides should be applied for the first time in spring, when the snails are beginning to reproduce. Application can be repeated in mid-summer to kill the snails before the cercariae are released, and again in autumn, to reduce the population going into hibernation. In climates with only two seasons (dry and rainy), molluscicides should be applied at the beginning and end of the rainy season. Many traditional molluscicides are inactivated by organic materials and elevated pH levels. The biologic approach involves enlisting the natural enemies of the snails that serve as intermediate hosts. Although there are many known competitors, predators, and parasites of snails, this subject has not been fully studied. Vaccination against *Fasciola* might be an appropriate control method, but most researchers have found that sheep do not produce significant protective immunity against this parasite.

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FASCIOLOPSIASIS

ICD-10 B66.5

Etiology: The agent of this infection is *Fasciolopsis buski,* a large, thick, reddish trematode (up to 75 mm long, 20 mm wide, and 3 mm thick) that lives attached to the mucosa of the duodenum and jejunum in humans and swine. The eggs eliminated in the feces must incubate for 16 to 18 days in still water at 30°C to form the first juvenile stage (miracidium) (Soulsby, 1982). Studies in China have found that the eggs need oxygen (they do not tolerate anaerobic conditions) and survive for three to four months at 4°C. The miracidium emerges from the mature egg and penetrates small planorbid snails, mainly of the genera *Gyraulus, Segmentina, Helicorbis, Hippeutis*, and *Polypylis.* In mollusks, the miracidium passes through the sporocyst stage and two generations of rediae. The second generation of rediae gives rise to large numbers of cercariae, which emerge from the snails and encyst as metacercariae on aquatic plants. The studies in China have found that almost 4% of the metacercariae encyst in the water. The definitive hosts, humans or swine, become infected by consuming aquatic plants or water with metacercariae. In the intestine, the metacercaria is released from its envelope, and after about three months, the parasite reaches maturity and reinitiates the cycle by oviposition.

Geographic Distribution and Occurrence: The infection is common in southeast Asia (Waikagul, 1991). The parasitosis occurs in Bangladesh, central and southern China, India, the Indochina peninsula, Indonesia, and Taiwan. Cases have also been reported, many of them among immigrants, in the Philippines, Japan, and several Western countries. Some 10 million people are estimated to have this parasite. Prevalence is very variable but generally low in humans and is thought to be higher in the areas where swine are raised. In some Thai villages, the infection affects up to 70% of the population. In several areas of Chekiang and Kiangsi Provinces, China, the prevalence can be as high as 85%; in contrast, in other areas of the country infection rates ranging from less than 1% to 5% are found. The prevalence of *F. buski* and other geohelminthiases (amebiases) has declined strikingly in this country, but the prevalence of foodborne parasites (trichinosis, cysticercosis, clonorchiasis, paragonimiasis) has increased. In a study of 5,479 randomly chosen persons in China in 1995, 0.8% were infected. Approximately half of all human infections are believed to occur in China (Malek, 1980). The most affected age group is 4- to 13-year-olds. A study conducted in an endemic area of Thailand found that the prevalence of infection in humans was similar to that of the swine population. The swine

were also found to harbor fewer parasites, which produced fewer eggs than those lodged in the human intestine (Manning and Ratanarat, 1970). In some areas of China with high rates of human infection, the parasitosis in swine has not been confirmed. This would seem to indicate that, at least in some areas, humans are the parasite's preferred host.

The Disease in Man and Animals: This parasite produces few or no symptoms in most hosts. Perhaps because it is the largest trematode affecting man, traumatic, toxic, and obstructive effects have been attributed to it, with epigastric pain, nausea, diarrhea, undigested food in the feces, and edemas of the face, abdomen, and legs. Yet a clinical study of a group of mostly young persons in Thailand who were eliminating *F. buski* eggs and of a control group found that both groups showed mild gastrointestinal symptoms (Plaut *et al.*, 1969). The severe disease described in the literature seemingly corresponds to cases with a large parasite burden (Liu and Harinasuta, 1996).

Only 3 to 12 parasites are usually found in naturally infected pigs. By and large, the health of the pigs is not affected, and the symptoms of the disease occur only in cases of massive parasitosis.

Source of Infection and Mode of Transmission: The source of infection for humans and swine is aquatic plants and water containing metacercariae. Epidemiological research in China suggests that between 10% and 13% of persons and from 35% to 40% of swine are infected more from drinking water contaminated with metacercariae than from eating plants. Endemic areas offer the ecological conditions necessary for the growth of both the intermediate hosts and the edible aquatic plants. In central Thailand, these conditions occur in flooded fields, where edible aquatic plants are cultivated near dwellings. These fields receive human excreta directly from the houses, which are built on pillars. Human and animal excreta promote the development of mollusks and plants and provide the infective material (the parasite's eggs) for the host. The hosts are the snails *Hippeutis umbilicalis* and *Segmentina trochoideus* in Bangladesh, in addition to *Polypylis hemisphaerula* in China, Thailand, and Taiwan (Gilman *et al.*, 1982). It has also been found that *Helicorbis umbilicalis* is an intermediate host in Laos (Ditrich *et al.*, 1992). The epidemiologically important aquatic plants, whose fruits, pods, roots, bulbs, or stems are eaten by humans, are "water chestnuts" (*Eliocharis* spp., *Trapa* spp.), the lotus *Nymphaea lotus*, and others of the genera *Eichhornia, Ipomoea, Neptunia,* and *Zizania.* Certain parts of these plants are eaten raw, and the teeth and lips are often used to peel the pods and bulbs. In areas where people customarily boil the plants or their "fruits" (water chestnuts) before eating them but give them raw to swine, the infection rate is much higher in these animals than in humans. In general, the prevalence of human infection is higher in areas where the aquatic plants are cultivated and lower in distant towns, since metacercariae attached to the plants are not resistant to desiccation when some time elapses between harvest and marketing. The pig is considered a reservoir of the parasite that could maintain the infection in the human population even if the sanitary elimination of human excreta were achieved. In Muslim countries, such as Bangladesh, swine do not play any role as a reservoir; man is practically the only reservoir and only source of infection for snails (Gilman *et al.*, 1982). The infection can be imported by patients into regions where intermediate hosts exist; one study found that 3 of 93 Thai workers in Israel were infected by *F. buski*.

Diagnosis: The infection is suspected on the basis of symptoms and epidemiological conditions and is confirmed by the discovery of *F. buski* eggs in fecal matter. The eggs are very similar to those of *Fasciola gigantica* and *Fasciola hepatica*; experts say that the eggs of *F. buski* (128–140 μm by 78–85 μm) cannot be distinguished from those of *F. hepatica* (128–150 μm by 60–90 μm) (Zeibig, 1997). The parasite itself can easily be identified when found in vomit or fecal matter. There are no reports on attempts at immunological diagnosis, but the parasite has shown cross-reactions in tests for *Fasciola hepatica*, the larva of *Taenia solium*, and *Trichinella spiralis*.

Control: The simplest way to prevent human parasitosis is to refrain from eating fresh or raw aquatic plants, peeling them with the teeth, or drinking water from contaminated areas, but this recommendation requires changing a habit, which is difficult to achieve. Studies conducted in China have shown that immersing contaminated plants in boiling water for 1 to 2 minutes is sufficient to kill the parasite. Other measures to combat the parasitosis, in addition to health education, are to use molluscicides, to treat the affected population, to treat the human excreta in septic tanks or with quicklime, to prevent the fertilization of fields with human feces, and to prohibit swine raising in endemic areas.

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GASTRODISCOIDIASIS

ICD-10 B66.8 Other specified fluke infections

Synonym: Amphistomiasis.

Etiology: The agent of this infection is *Gastrodiscoides (Amphistomum) hominis*, a bright-pink, pear-shaped trematode 5–14 mm long by 4–66 mm wide; it lives in the cecum and ascending colon of swine and humans, although it has also been found in monkeys and field rats (Soulsby, 1982). The anterior part of the parasite is conical, but the posterior opens into a disc with a suction cup. The eggs leave the host without embryonating and take 16 to 17 days, at 27°C to 34°C, to form the first juvenile stage (miracidium) and hatch (Neva, 1994). In experiments in India, miracidia were able to produce infection in the planorbid snail *Helicorbis coenosus*, which may be the natural intermediate host. Details of development in the snail are not known, but judging from the cycle of other members of the same family, they are presumed to form oocysts, one or two generations of rediae, and cercariae. Depending on the ambient temperature, the cercariae begin to emerge from the snails 28 to 152 days after infection. Like those of other species of Gastrodiscidae, the cercariae are thought to encyst on aquatic plants and develop into metacercariae. The definitive hosts are infected by ingesting the metacercariae. It has been suggested that *G. hominis* in humans and swine could be different strains or varieties.

Geographic Distribution and Occurrence: This parasitosis occurs primarily in India (states of Assam, Bihar, Orissa, and West Bengal) and in Bangladesh, but has also been recorded in the Philippines, the Indochina peninsula, and in animals in Indonesia (Java), Malaysia, Myanmar, and Thailand. It has been observed in Indian immigrants in Guyana. The geographic distribution may be wider, since the parasite was found in a wild boar in Kazakhstan. Human infection rates vary and can be very high, as in a village in Assam, India, where 41% of the population, mostly children, had the parasite's eggs in their stools. Oddly enough, swine are not abundant in this area.

In a slaughterhouse in India, the parasite was found in 27% of 233 pigs examined. The infection is also found in rodents and several species of nonhuman primates in Asia: rhesus monkeys (*Macaca mulatta*) and cynomologus monkeys (*M. fascicularis, M. irus,* and *M. philippinensis*). The infection rate in 1,201 cynomologus monkeys (*M. fascicularis*) was 21.4%. The infection rate in swine in India is higher in late summer and early autumn, reaching its peak between June and September (Roy and Tandon, 1992).

The Disease in Man and Animals: The infection is clinically apparent probably only when the parasite burden is large. In these cases, there reportedly may be alterations of the mucosa of the colon and cecum, colitis, and mucoid diarrhea (Strickland, 1991).

Source of Infection and Mode of Transmission: The natural definitive host appears to be swine, in which high rates of infection have been found. The parasite has also been found in monkeys and rodents. In general, man is considered to be a secondary definitive host. However, the true relationship between the human and animal trematodes is not yet well known, nor has it been determined experimentally

whether the animal parasites are transmitted to man. In some areas in India, the human infection occurs without infection in swine. The reverse situation has also been observed (Malek, 1980). The definitive hosts acquire the infection through the digestive tract, perhaps by ingesting aquatic plants or untreated water containing metacercariae.

Diagnosis: Diagnosis is based on detection of the presence of eggs in feces or, more easily, on identification of the trematode following administration of an anthelminthic to the affected person. The eggs of *Gastrodiscoides* (150–170 μm by 60–70 μm) resemble those of *Fasciolopsis buski*, but are narrower and greenish.

Control: Since the lifecycle of the parasite is not known, it is difficult to recommend control measures. Nonetheless, for individual protection it is suggested that people in endemic areas not consume aquatic plants or untreated water. For prevention through treatment of the animal reservoir, the best time is mid-summer, before the infection reaches its highest prevalence (Roy and Tandon, 1992).

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HETEROPHYIASIS

ICD-10 B66.8 Other specified fluke infections

Synonyms: Heterophydiasis, heterophyes infection (small intestine).

Etiology: The agents of this infection are trematodes of the family Heterophyidae, which infect the intestine of man and other vertebrates. As of 1980, Malek (1980) had recognized 10 species in the world that were infective for man, the most common being *Heterophyes heterophyes*, *Heterophyes nocens*, *Metagonimus yokogawai*, and *Stellantchasmus falcatus.* The others on this list were *Cryptocotyle (Tocotrema) lingua*, *Haplorchis calderoni*, *Haplorchis taichui*, *Haplorchis vanissima*, *Haplorchis*

yokogawai, and *Stamnosoma armatum*. In 1991, Chai and Lee (1991) added six more species that had infected man in the Republic of Korea: *Centrocestus armatus*, *Heterophyes dispar*, *Heterophyopsis continua*, *M. takahashii*, *Pygidiopsis summa*, and *Stictodora fuscatum*. Later *Metagonimus miyatai*, which for a while had been considered a type of *M. yokogawai*, was described in patients in the Republic of Korea and Japan (Saito *et al*., 1997). Genetic studies have differentiated the two species (Yu *et al*., 1997). The most important species from the medical standpoint are *H. heterophyes* and *M. yokogawai.* For example, in a study carried out in Korea, 5 patients under treatment produced a total of 3,007 specimens of *M. yokogawai*, 120 of *H. nocens,* and 46 of *S. falcatus* (Chai *et al*., 1998).

All the heterophyids have a similar biological cycle: the first intermediate host is an appropriate aquatic snail (*Cerithidea, Cleopatra, Melania, Pironella, Semisulcospira, Tympanotomus*), which ingests the mature eggs, and in which the cercariae are produced. In addition, there is a second intermediate host in which the metacercariae are produced—usually one of a large variety of fish that live in fresh or brackish water. The second intermediate hosts of *C. armatus*, *M. takahashii*, and *M. yokogawai* are freshwater fish; those of *H. continua, H. nocens, P. summa, S. falcatus*, and *S. fuscatum* are found in brackish water (Chai and Lee, 1991); and those of *H. heterophyes*, in estuaries and fresh or brackish water. Because of their public health importance, *H. heterophyes* and *M. yokogawai* are covered here in detail.

H. heterophyes is a very small pyriform trematode measuring 1–1.7 mm long by 0.3–0.4 mm wide that lives in the small intestine of humans, cats, dogs, foxes, and other fish-eating mammals or birds. When observed in host feces, the eggs contain a completely developed miracidium, which must be ingested by an appropriate aquatic snail (first intermediate host) in order to continue its development cycle. Once inside the snail (in Egypt, *Pirenella* spp.; in Japan, *Cerithidea cingulata* and *Semisulcospira libertina*), the miracidia give rise to sporocysts, which in turn give rise to one or two generations of rediae, and the last in turn to cercariae. The cercariae invade the second intermediate host, which may be one of about a dozen species of fish from fresh or brackish water that customarily spawn in brackish or salt water. The cercariae form cysts under the scales or in the musculature of these fish and transform into metacercariae. In Egypt, metacercariae are found primarily in mullet (*Mugil*), *Tilapia*, and a few other species, and in Japan, in several species of goby belonging to the genus *Acanthogobius.* When man or another definitive host eats raw fish containing metacercariae, the parasites are released from the cystic envelope and develop inside the intestine until they turn into adult trematodes, which start to lay eggs in about nine days.

M. yokogawai measures 1–2.5 mm long by 0.4–0.8 mm wide and lives in the small intestine of humans, dogs, cats, swine, pelicans, and possibly other piscivorous birds. The development cycle is similar to that of *H. heterophyes.* The first intermediate hosts are snails of the genera *Semisulcospira, Hua*, or *Thiara*; the second intermediate hosts are fish belonging to the salmon and trout families.

Geographic Distribution and Occurrence: *H. heterophyes*, and probably *H. dispar*, are found in Southeast Asia, the Near and Middle East, Turkey, the Balkans, and Spain. The largest endemic focus is in the Nile Delta, where conditions are especially favorable for propagation of this parasitosis: enormous numbers of *Pirenella* snails live at the bottom of the delta's brackish lagoons, mullet is abundant, the pop-

ulation traditionally eats raw fish, and facilities for sanitary waste disposal are inadequate. Most of the mullet contain metacercariae, with counts as high as 6,000 metacercariae per fish, and almost all the dogs and cats are infected. In one locality, it was estimated that 65% of the schoolchildren had parasites. In addition to the endemic and hyperendemic areas already mentioned, a very low prevalence of *H. heterophyes* has been recorded in western Africa.

A high prevalence of *H. nocens* was reported in Yamaguchi Prefecture in Japan. However, subsequent surveys in other prefectures showed prevalence rates of less than 1% (Malek, 1980). In 1994, Chai *et al*. (1994) found a large focus of *H. nocens* in the Republic of Korea: 43% of 98 persons were infected.

M. yokogawai is found primarily in the Far East and the northern provinces of Siberia. It is seen less often in central Europe and has also been reported in Spain. In a hospital in Seoul, Korea, a total of 52,552 fecal samples were examined between 1984 and 1992, and the only heterophyid observed was *M. yokogawai*, which was present in 1.2% of the samples (Lee *et al*., 1994). Also, a 1991 study in Korea found *Metagonimus* spp. in 12% of the males and 6% of the females examined, with more intense infections in males. The prevalence was higher in persons over 30 years old, but there was no correlation between age and intensity. Eight species of freshwater fish were found to be infected with metacercariae. In 1993, 465 persons and 68 fish were studied along the Hantan River in Korea and it was determined that 3.4% of the people and 21% of the fish were infected with *M. miyatai* (Park *et al*., 1993). Ahn (1993) found *Metagonimus* infection in 7.8% of 1,067 individuals examined in Korea, with rates ranging between 3.8% and 12.8% in 5 different riverbank areas. In fish, the infection rate was 81% in the 318 specimens studied.

The range of *S. falcatus* includes Australia, Hawaii (USA), Indonesia, Japan, the Philippines, Thailand, and the Middle East.

The Disease in Man and Animals: Mild infections are usually asymptomatic. A large parasite burden can cause irritation of the intestinal mucosa with excessive secretion of mucus, superficial necrosis of the epithelium, chronic diarrhea, colic, and nausea. Aberrant eggs of the parasite sometimes enter the bloodstream and produce granulomatous foci in various tissues and organs, including the myocardium and brain. In the Philippines, it is believed that 15% of the cases of fatal myocarditis may be caused by the eggs of these parasites (García and Bruckner, 1997). Nevertheless, most human cases are benign. In *M. yokogawai* infections, parasites have been found both free-living in the lumen and encrusted in the intervillous spaces. Other observations have included massive infiltrations of lymphocytes, plasmocytes, and eosinophils in the stroma, erosion of neighboring enterocytes, depletion of globet cells, and occasionally, edema of the villi (Chi *et al*., 1988).

The picture is similar in animals. The infection is clinically apparent only when the number of parasites is large. In 1962, a metacercarial organism similar to *S. falcatus*, provisionally labeled "agent SF," was isolated in Japan from dogs in which it was causing mild disease. It is now known that the RNA sequences of this agent are 99.1% homologous with *Ehrlichia risticii*, the organism that causes Potomac horse fever, and 98.7% homologous with *E. sennetsu*, which infects humans in western Japan (Wen *et al*., 1996). Its transmission would be similar to that of the canine rickettsia *Neorickettsia helminthoeca* via the trematode *Nanophyetus salmincola* (Soulsby, 1982).

Source of Infection and Mode of Transmission: The source of infection for man, other mammals, and birds is fish (from fresh, brackish, or salt water) infected with the parasite metacercariae. The custom of eating raw or undercooked fish is the main cause of the human infection. The critical host, because of its specificity, is the snail. The parasite is less selective regarding the second intermediate host, which can be one of a number of fish species found in fresh, brackish, or salt water, and even certain shrimp. Contamination of the water with human or animal excreta ensures completion of the parasite's development cycle. The primary definitive hosts vary depending on the parasite species: for some it is piscivorous birds; for others, dogs, cats, or man. Other definitive hosts include numerous species of birds and wild animals that feed on fish.

Diagnosis: Diagnosis is based on the microscopic observation of parasite eggs in fecal matter. The eggs of *H. heterophyes* and *M. yokogawai* (Zeibig, 1997), as well as those of *Clonorchis* and *Opisthorchis*, are all virtually indistinguishable. The surface structure of the eggs is a more reliable criterion than traditional morphology, but it is more difficult to visualize (Ditrich *et al*., 1992). The species can be identified by examining the adult trematodes following anthelminthic treatment. There is no information on the diagnosis of heterophyiasis using immunologic tests, but experimental infection has demonstrated cross-reactions: 10% with antigens of schistosome eggs, and 35% with raw extract of *Fasciola* (Hassan *et al*., 1989).

Control: The human infection can be prevented through education aimed at promoting the thorough cooking of fish and the proper disposal of excreta. Metacercariae survive up to seven days in fish preserved in brine and for several days if they are marinated in vinegar. Dogs and cats should not be fed raw fish or scraps containing raw fish because they can become infected, contaminate the environment, and thus maintain an ongoing infection cycle.

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NANOPHYETIASIS

ICD-10 B66.8 Other specified fluke infections

Synonyms: Elokomin fluke fever, salmon poisoning (in animals).

Etiology: The agent of this disease is *Nanophyetus* (*Troglotrema*) *salmincola*, a small digenetic intestinal trematode of several carnivores that also infects man. On the basis of several biological differences and their geographic distribution, two subspecies are recognized: *N. salmincola salmincola* in the northwestern US and *N. salmincola schikhobalowi* in Siberia, Russian Federation.

The adult trematode lives in the small intestine of coyotes, cats, lynxes, raccoons, nutrias, dogs, minks, foxes, and other carnivores. It can also infect fish-eating birds and humans. Thirty-two species can be natural or experimental hosts of the trematode. The parasites are tiny (0.8–2.5 mm by 0.3–0.5 mm) and require two intermediate hosts to develop. The first is a snail of the family Pleuroceridae. In the US, it has been identified as *Goniobasis plicifera, Juga* sp., *Oxytrema plicifer* var. *silicula*, and *O. silicula*, but its classification still appears uncertain. In Siberia, it has been identified as *Semisulcospira cancellata, S. laevigata*, and *Juga* sp. (Besprozvannykh, 1994). The second host is a specimen of the salmon family (*Onchorhynchus, Salmo, Salvelinus*, etc.) and, less frequently, of other families (Cottidae, Cyprinidae, lampreys, and even the Pacific giant salamander) (Soulsby, 1982). The eggs eliminated in the feces of the definitive hosts are not embryonated and must remain in the water

for 87 to 200 days for the miracidium to form completely. It then leaves the egg, penetrates a snail, and multiplies through two generations of rediae to form the cercariae that leave the snail. These swim around and penetrate the skin of an appropriate fish and ultimately encyst in the kidneys, muscles, fins, and secondarily, any other organ. The metacercariae measure between 0.11 mm and 0.25 mm in diameter, become infective to the definitive host in 10 or 11 days, and can survive up to five years in live fish. When a definitive host ingests raw fish with metacercariae, they de-encyst, reach maturity in the intestine, and begin oviposition in five to eight days.

Geographic Distribution and Occurrence: *N. s. salmincola* is distributed along the Pacific coast of the US, mainly in Oregon. Until 1989, about a dozen human cases had been reported in that country (Fritsche *et al.*, 1989). *N. s. schikhobalowi* is distributed in the northern part of Sakhalin Island and along the mountain tributaries of the Amur River in eastern Siberia. The rate of human infection in some of the villages along these tributaries can reach 98%. The distribution of nanophyetiasis is determined by the presence of the species of the first intermediate host, the snail. In the US, the snail is *Oxytrema silicula*, and in Siberia, *Semisulcospira cancellata* and *S. laevigata*.

The Disease in Man: The infection causes clinical manifestations only when there are abundant parasites (Fang *et al*., 1991). Half of the patients studied by Fritsche *et al.* (1989) showed only eosinophilia, but the other half complained of gastrointestinal symptoms. The most frequent symptoms were chronic diarrhea, nausea, abdominal pain, and high peripheral eosinophilia (Harrell and Deardorff, 1990).

Mild infections by *N. s. schikhobalowi* are asymptomatic. Patients with a parasite burden of 500 or more flukes experience diarrhea (43%), gastric pain (32%), constipation (16%), and nocturnal salivation (16%).

The Disease in Animals: In canines the de-encysted parasite attaches to the mucosa of the small intestine. In the US, different parasites can produce superficial enteritis that could even cause bleeding, but they commonly cause few or no symptoms. The principal significance of the parasite in the US, however, is that in all of its states it can harbor the agent of "salmon poisoning" or Elokomin fluke fever.

The name "salmon poisoning" is unfortunate because the disease is actually a rickettsiosis caused by *Neorickettsia helminthoeca*, not a poisoning. This rickettsia affects only canines. The organism is released when the parasite de-encysts and attaches to the canine intestine, but the eggs of the trematode emerge infected and maintain the infection until the metacercariae form and while they remain in the fish. In dogs, the disease manifests itself 5 to 7 days after infection with high fever, complete anorexia, vomiting, bloody diarrhea, thrombocytopenia, general lymphadenopathy, severe weight loss, and mortality of up to 90% in 7 to 10 days if not treated in time.

Elokomin fluke fever affects canines, ferrets, raccoons, and bears, and can occur in conjunction with "salmon poisoning." It is caused by the *Neorickettsia elokominica* rickettsia, which is antigenically distinct from *N. helminthoeca*, although it is transmitted the same way. Although weight loss is also severe, adenopathy is more prevalent than diarrhea, and the mortality among untreated cases is only 10%.

In Siberia, according to observations by Russian researchers, the infection in cats, dogs, brown rats, and badgers by *N. s. schikhobalowi* can cause a severe, fatal dis-

ease. On the other hand, it is not known whether the parasites in Siberia transmit any other microorganism.

Fish infected with the trematode can also become sick. Different species of salmonids experimentally exposed to *N. salmincola* showed different degrees of susceptibility. In general, species from the enzootic area were more resistant than those from other areas. Death among fish subjected to massive infections occurred mainly in the first 24 hours, in other words, during the penetration and migration of the cercariae. Although gradual infection probably does not cause as much pathology, most researchers agree that the parasites have pathological effects on fish, especially if vital organs such as the heart and gills are invaded by a large number of migrating cercariae. Infected fish also show stunted development and an impairment in swimming ability (Millemann and Knapp, 1970).

Source of Infection and Mode of Transmission: Both humans and animals contract *N. salmincola* infection by ingesting raw or undercooked fish, especially salmonids, infected with metacercariae of the parasite. Yet there is at least one case of infection from the handling of infected fish, without evidence that there was ingestion (Harrell and Deardorff, 1990).

The source of "salmon poisoning" and Elokomin fluke fever infection is fish infected by the trematode, which in turn is infected by the respective rickettsiae. As indicated, these infections occur only in the US. In areas in both the Russian Federation and the US where the trematode exists, a high rate of infection by metacercariae is found in fish, especially in salmonids.

Diagnosis: Diagnosis is confirmed by observation of the parasite eggs in human or animal feces. The eggs measure 87–97 μm by 35–55 μm, and have a small, indistinct operculum and a small lobe in the opposite end. Rickettsial infections are confirmed by a microscopic examination of biopsies of affected lymphatic ganglia, where intracellular bodies with the typical structure of rickettsiae are seen.

Control: The main prevention measure is to educate the population not to consume undercooked fish or give it to their dogs. Salting or pickling fish does not appear to be very effective because the metacercariae are very resistant: they can survive up to 165 days in fish kept at 3°C.

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OPISTHORCHIASIS

ICD-10 B66.0

Etiology: The agents of this disease are *Opisthorchis viverrini*, *O. felineus*, and *Amphimerus pseudofelineus* (*Opisthorchis guayaquilensis*), trematodes that lodge in the bile ducts of humans, cats, dogs, and other animals that eat raw fish. It is often difficult to differentiate between the genera *Opisthorchis* and *Clonorchis* and between the species *O. viverrini* and *O. felineus* because the adult specimens are indistinguishable. However, there are clear differences in the excretory system during the preadult stages. The development cycle of *Opisthorchis* is similar to that of *Clonorchis* (see Clonorchiasis), requiring two intermediate hosts: aquatic snails are the first, and various species of freshwater fish are the second.

O. viverrini measures 7–12 mm by 1.5–2.5 mm and is reddish in color when it is fresh. The eggs, each of which contains a fully formed miracidium when it leaves the adult parasite, must be ingested by an appropriate first intermediate host, in which they form rediae and cercariae within four to six weeks (Adam *et al*., 1995). The first intermediate host may be any of four species of snails: *Bithynia siamensis goniomphalus*, *B. s. siamensis*, *B. (Digoniostoma) funniculata*, or *B. laevis.* The cercariae, which average about 280 per snail, swim until they find a second intermediate host and penetrate its skin. They then become encysted, mainly in subcutaneous tissues and often at the base of the fins, in the form of metacercariae. By the end of six weeks, they are infective for the definitive host. The role of the second intermediate host is assumed by any of several cyprinid fish (carp), such as *Cyclocheilicthys*, *Hampala*, and *Puntius*. The definitive hosts of this species are man, the civet *Felis viverrina*, dogs, domestic and wild cats, and other animals that eat fish or fish scraps. When these hosts ingest a fish containing metacercariae, the parasites excyst inside the duodenum and new juvenile parasites migrate via the choledochus to the smaller bile ducts, where they mature and begin to lay eggs within four weeks. They can live for up to 20 years.

O. felineus cannot be distinguished from *O. viverrini* in the adult stage. Its life cycle is similar to that species, but it uses the snails *Bithynia (Bulimus) leachi, B. infata*, or possibly *B. tentaculata* as its first intermediate host. Freshwater fish of the genera *Barbus*, *Blicca*, *Leuciscus*, or *Tinca* serve as the second intermediate host. The definitive hosts are humans, swine, cats, dogs, and foxes.

A. pseudofelineus measures 4 mm in length by 2 mm in width. The definitive hosts are the coyote *(Canis latrans)*, dogs, and cats.

Geographical Distribution and Occurrence: *O. viverrini* is found in Laos, northeastern Thailand, and Viet Nam, where it affects some 8 million individuals

(Khamboonruang *et al*., 1997). In northeastern Thailand, an estimated 3.5 million people were infected with *O. viverrini* in 1965; 5.4 million in 1981 (Bunnag and Harinasuta, 1984); and 6–7 million in 1991 (Loaharanu and Sornmani, 1991). In some hyperendemic regions, the infection rates have reached as high as 72%–87% of the population. In 1981, the prevalence of human opisthorchiasis in northeastern Thailand was 35%; however, a decade after the establishment in 1988 of a national control program involving diagnosis, treatment, and education, the rate had fallen to 18.5%, with fluctuations ranging from 5% to 56% in different localities (Jongsuksuntigul and Imsomboon, 1997). In Laos, a study conducted in the early 1990s showed that 90% of the males in the villages surveyed were infected with the adult parasite, as were 36% of the domestic or stray cats tested, while 0.5% of the snails *B. s. goniomphalus* had cercariae and 7 species of carp had metacercariae. Only 0.6% of the human infections were serious, while 66% were mild (Giboda *et al*., 1991). In a subsequent study, it was found that 37.5% of 128 children in the villages of southeastern Laos were infected (Kobayashi *et al*., 1996).

O. felineus is found near lakes and in river basins of the former USSR, such as those of central Siberia, Kazakhstan, the lower Dnieper, and the Kama River. There are smaller foci in eastern, southern, and central Europe, the Democratic People's Republic of Korea, and possibly India, Japan, and the Philippines. It is estimated that more than 1 million people are infected with this trematode. In some hyperendemic areas, such as Siberia, the infection rate is very high not only in the nomadic population but also among people living in some urban areas. A study carried out in the city of Tobolsk (Siberia) a few years after World War II estimated that 83% of the human population was infected, as were 100% of the cats and 90% of the dogs tested. In Kazakhstan, 100% of the specimens of some species of fish were found to have metacercariae. The snails that serve as the first intermediate host are very abundant in certain endemic regions, and their infection rate is high. A study carried out in the Ural region between 1986 and 1991 revealed infections in 10% to 30% of the human population tested, 0.2% of the snails of the genus *Codiella*, and 12% to 73% of the carp (Tsybina, 1994).

A. pseudofelineus was first found in humans and described as *Opisthorchis guayaquilensis* in Pedro P. Gómez Parish, Manabí Province, Ecuador. Eggs of the parasite were found in 7.3% of fecal samples from 245 persons in the area (with the rate ranging from 4% in the town center to 32% in peripheral outlying locations). In the same parish, 3 of 100 dogs examined had parasites, whereas none of 80 swine tested had the parasite. The trematode has been found in several animal species in Brazil (Santa Catarina), Ecuador, Panama, and the US (Artigas and Pérez, 1962), but since 1988, there have been no further reports of this species.

The Disease in Man and Animals: The infection causes hepatomegaly, and in most cases, pericholangitis. These changes are restricted to the medium-sized and large bile ducts, which are the sites occupied by the parasite. The small interlobular ducts do not exhibit changes. The most common damage is dilation of the ducts, with hyperplasia, desquamation, proliferation, and adenomatous transformation of the epithelial cells, and infiltration of the wall with connective tissue. Dilation of the gallbladder, chronic cholecystitis, and carcinomas occur only in adults (Riganti *et al*., 1989). The symptomatology of the disease is similar to that of the hepatic distomiasis caused by *Clonorchis sinensis* and depends on both the parasite burden and

the duration of the infection. In general, when only a few parasites are present, the infection is asymptomatic, even though there may be appreciable damage to the bile capillaries. With a parasitosis of medium intensity there is fever, diarrhea, flatulence, moderate jaundice, asthenia, cephalalgia, hepatomegaly, and passive congestion of the spleen. In chronic cases with a large parasite burden, there may be mechanical obstruction and biliary stasis, as well as secondary infections with cholangitis, cholangiohepatitis, and formation of micro- and macroabscesses. When the parasitosis is massive, there may also be invasion of the pancreas, producing catarrhal inflammation of the pancreatic ducts. Infections caused by *O. felineus* often produce erythematous papular eruptions. It is thought that *Opisthorchis* may play a role in the development of hepatic carcinomas, especially cholangiocarcinomas. Although a close correlation has been observed between the infection and this type of cancer in the parasite's endemic areas, there are also areas with high prevalence of the cancer in which the parasite is not present (Sinawat *et al*., 1991; Holzinger *et al*., 1999). In a study conducted in an endemic area, the levels of antibody to the parasite were lower in individuals who had parasite eggs in their feces than in those who were not shedding eggs. This finding was interpreted as evidence that the infection produces protective immunity (Akai *et al*., 1994). However, the prevalence rate, number of eggs in feces, and number of parasites in the liver become stabilized in adults (Sithithaworn *et al*., 1991) rather than decline with age, as might be expected if there were protective immunity.

Source of Infection and Mode of Transmission: Man and other definitive hosts become infected by eating raw or undercooked fish containing metacercariae. Human opisthorchiasis occurs only where appropriate intermediate hosts, especially snails, are found, and where people customarily eat raw, lightly salted, or sun-dried fish. However, infected travelers can carry the parasite to other areas. High rates of infection have been found among Thai workers in other Asian countries. In the US, a 1987 study revealed a 0.6% prevalence of *Opisthorchis* and *Clonorchis* infections in 216,275 fecal examinations (Kappus *et al*., 1991). In highly endemic areas, it is thought that man is primarily responsible for maintaining the cycle, since people contaminate rivers and lakes with fecal matter containing the eggs of the parasite. The main species of fish that transmit *O. felineus* to man, and those that also have the highest prevalence of metacercariae, are *Idus melanotus, Tinca tinca*, and *T. vulgaris*. In Thailand, the fish most often found to be infected with *O. viverrini* metacercariae are *Cyclocheilicthys siaja*, *Hampala dispar*, and *Puntius orphoides*, with infection rates ranging from 51% (in the first species) to 74% (in the second).

Animals can maintain a natural cycle independent of man. In one area in the former USSR, 85% of the cats examined were found to be infected, but no cases were detected in the human population, since the people there do not eat raw fish. Fecal matter deposited by animals on riverbanks is washed into watercourses by rain.

Diagnosis: Laboratory diagnosis is based on demonstrating the presence of parasite eggs in feces either by sedimentation techniques or by duodenal probe. *Opisthorchis* eggs are rather heavy (specific gravity: 1.2814) and do not float readily in a saturated solution of sodium nitrate, which has a higher specific gravity (1.4) (Harnnoi *et al*., 1998). Of the immunologic tests, enzyme-linked immunosorbent assay (ELISA) is used most often. Assays to detect circulating antibodies for *O. viverrini* have shown moderately high sensitivity (91% to 92%), but specificity of

only 70% to 80%. Cross-reactions have been seen in patients with a wide range of other infections: *Ascaris lumbricoides, Blastocystis hominis, Paragonimus heterotremus, Plasmodium* spp., *Schistosoma* spp., *Strongyloides stercoralis, Taenia* spp., *Trichinella spiralis,* and *Trichuris trichiura,* as well as ancylostomes and yeasts (Sakolvaree *et al*., 1997). The use of monoclonal antibodies in an ELISA test to detect an *O. viverrini* metabolic antigen in stool samples yielded slightly greater sensitivity than the observation of eggs in feces and proved to be capable of detecting infections on the basis of a single specimen (Sirisinha *et al*., 1995).

Control: Opisthorchiasis is an infection that needs to be controlled. It is estimated that in Thailand, one-third of the population (6–7 million individuals) are infected, of whom 60% are 15- to 60-year-olds in the workforce. The income lost by this population is estimated at US$ 65 million a year, and the direct cost in terms of medical care has been calculated at US$ 19.4 million (Loaharanu and Sornmani, 1991).

Control of opisthorchiasis entails three interrelated strategies: diagnosis and treatment of patients with symptomatic infections to reduce contamination of the environment; health education of the population at risk to discourage the consumption of raw fish and unsanitary disposal of feces; and the improvement of facilities for the adequate disposal of excreta (Jongsuksuntigul and Imsomboon, 1998). These strategies have been applied in endemic areas in the northern and northeastern parts of Thailand. Although prevalence of the infections was reduced in the northeast from 35% in 1981 to 18.5% in 1991, with variations ranging from 5% to 56% (Jongsuksuntigul and Imsomboon, 1997), it increased considerably in the north. The weakest link appears to be education: the regular consumption of raw fish declined from 14% to 7% of the population between 1990 and 1994, but 42% continued to eat it occasionally. Another weak link is the continued lack of sanitary excreta disposal systems, since opisthorchiasis predominates in low-income rural areas where it is difficult to implement this strategy.

For individual protection, the cooking of fish is effective. Temperatures of –10°C and lower kill the metacercariae within 5 days, and saline solutions of 5%, 10%, or 15% destroy them in 10 to 3 days, depending on the strength. Russian investigators have reported that incubation of carp in 6% acetic acid (household vinegar) for four hours prior to salting considerably increases the capacity of salt to kill the metacercariae of *O. felineus.* It has also been proposed to irradiate fish with a radioactive dose of 0.1 kGy, which has been shown to be effective in destroying the cercariae without affecting the organoleptic properties of the food (Loaharanu and Sornmani, 1991). On the other hand, since humans are often reinfected soon after treatment, Hinz *et al*. (1994) propose that therapy be administered during the month of March, when the risk of infection is minimal.

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PARAGONIMIASIS

ICD-10 B66.4

Synonyms: Pulmonary distomiasis, endemic hemoptysis, lung fluke disease, infection due to *Paragonimus* species.

Etiology: This disease is caused by trematodes of the genus *Paragonimus*. In a highly detailed review, Blair *et al*. (1999) refer to 50 species in this genus, although not all of them are valid. The following nine species of *Paragonimus* have been reported in humans:

1. *P. africanus*, in Cameroon, Côte d'Ivoire, Equatorial Guinea, and Nigeria, since 1976; it also parasitizes monkeys and, experimentally, dogs and rodents.
2. *P. heterotremus*, in China, Lao People's Democratic Republic, and Thailand, since 1970; it also parasitizes cats, rodents, and, experimentally, dogs and rabbits.
3. *P. kellicotti*, in the US, since 1986; it also parasitizes canids, felids, other carnivores, swine, goats, and, experimentally, rodents.
4. *P. mexicanus* (synonyms: *P. peruvianus, P. ecuadoriensis*), in Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela, since 1983; it also parasitizes marsupials, monkeys, wild carnivores, and, experimentally, dogs and cats.
5. *P. miyazakii*, in Japan, since 1992; it also parasitizes wild carnivores, swine, and, experimentally, dogs, cats, and rodents.
6. *P. ohirai*, in Japan, since 1988; it also parasitizes wild carnivores, swine, and, experimentally, dogs, cats, rodents, and rabbits.
7. *P. skrjabini*, in China, since 1975; it also parasitizes monkeys, wild carnivores, and, experimentally, dogs, cats, and rodents.
8. *P. uterobilateralis*, in Cameroon, Côte d'Ivoire, Gabon, Guinea, Liberia, and Nigeria, since 1973; it also parasitizes monkeys, dogs, wild carnivores, and, experimentally, dogs, cats, and rodents.
9. *P. westermani* (partial synonym: *P. philippinensis*), in China, Gabon, India, Indonesia, Japan, Lao People's Democratic Republic, Nepal, Papua New Guinea, the Philippines, Republic of Korea, Russian Federation, Samoa, Taiwan, and Viet Nam, since the nineteenth century; it also parasitizes macaques, wild and domestic carnivores, swine, rodents, galliform and anseriform birds, and, experimentally, rabbits.

Most of these species were described in the 1960s, and their association with man has been recognized since the 1970s and 1980s, and, in one case, the 1990s. The notable exception is *P. westermani*, which was recognized as a human parasite in 1880. The fact that *P. westermani* was discovered so early reflects its greater abundance and also explains why most of the information on human paragonimiasis refers to this species. Because of its wide distribution, high prevalence, and notable pathogenicity, *P. westermani* is considered the *Paragonimus* species of greatest importance for human health. It is followed by *P. heterotremus*, and, in third place with somewhat lower frequency, by *P. mexicanus* (García and Bruckner, 1997). However, there are still species that remain to be assessed in terms of their importance. For example, a recent study in western Africa found four species of *Paragonimus* in humans: *P. africanus*, *P. uterobilateralis*, a specimen similar to *P. westermani*, and a previously unrecognized species of the genus *Euparagonimus*

(Cabaret *et al*., 1999). Moreover, diploid and triploid forms of *P. westermani* have been observed in Asia, and it has yet not been determined whether they constitute different species (Blair *et al.*, 1999). Finally, DNA sequence analysis has revealed that there are two groups within the species *P. westermani*, a northeastern one found in China, Japan, Republic of Korea, and Taiwan, and a southern one found in Malaysia, the Philippines, and Thailand (Blair *et al*., 1997).

Paragonimus trematodes are reddish brown, oval parasites measuring about 4–8 mm wide, 7–16 mm long, and 2–5 mm thick, which lodge in the lungs of the definitive hosts. Their development cycle requires two intermediate hosts: the first is a snail, and the second, an appropriate freshwater crab or crayfish. Man and other mammals, particularly carnivores, are the definitive hosts, and they harbor the parasite in their lungs. The parasite lays 1,000–2,000 eggs a day, which are shed via expectoration, or in feces if bronchial secretions are swallowed. If the eggs reach water, they continue to develop and form a ciliated larva, or miracidium, which hatches in about three weeks and swims around in search of a snail in which to carry on its cycle. Only certain species of snails allow the cycle to continue: for *P. westermani*, they are species of the genera *Semisulcospira*, *Brotia*, and *Melanopides* in Southeast Asia and *Juga* in the Russian Federation; for *P. heterotremus*, the genera *Oncomelania* and *Neotricula* in Thailand and the genus *Tricula* in China; and for *P. mexicanus*, the genera *Oncomelania* and *Aroapyrgus* in Costa Rica, Ecuador, Mexico, and Peru.

Since the miracidium usually invades the snail by active means, it needs to find an intermediate host within a day or two before its energy is exhausted. Once it penetrates an appropriate snail, the miracidium is transformed into a sac called a sporocyst, within which juvenile trematodes, referred to as rediae, are generated. The rediae give rise to a second generation of rediae inside the first, and from the latter, new juvenile forms, called cercariae, emerge. This multiplication of juvenile stages within the snail, referred to as pedogenesis, greatly increases the number of parasites produced by each egg, and hence its biotic potential. A large number of parasites can be lethal for the snail. The cercariae abandon the snail after 9 to 13 weeks, depending on the temperature and humidity, and seek a crustacean in which to encyst. For *P. westermani,* it can be a species from the genera *Cambaroides*, *Candidiopotamon*, *Ceylonthelphusa*, *Eriocheir*, *Geothelphusa*, *Huananpotamon*, *Isolapotamon*, *Macrobrachium*, *Malayapotamon*, *Oziothelphusa*, *Parapotamon*, *Parathelphusa*, *Potamiscus*, *Potamon*, *Procambarus*, *Siamthelphusa*, *Sinopotamon*, *Sundathelphusa*, or *Varuna*; for *P. heterotremus,* the genera *Esanthelphusa*, *Larnaudia*, *Malayapotamon*, *Potamiscus*, *Potamon*, *Siamthelphusa*, or *Sinopotamon*; for *P. mexicanus*, the genera *Hypolobocera*, *Odontothelphusa*, *Pseudothelphusa*, *Ptychophallus*, or *Zilchiopsis.* In rare cases, metacercariae of *P. skrjabini*, which is infective for dogs and cats, have been found in the frog *Rana boulengeri* in China. The cercariae can actively penetrate the crustacean, and the crustacean can also become infected from eating infected snails. Once lodged in the muscles or gills of the crustacean, the parasite surrounds itself with a resistant envelope and turns into a metacercaria. It remains there for several weeks until it becomes infective for the definitive host.

The definitive host becomes infected upon eating freshwater crabs or crayfish that contain metacercariae. Once in the intestine, the metacercariae are released from their envelope and penetrate the intestinal wall, remain in the peritoneal cavity for several days, and then migrate through the diaphragm into the pleural cavity. There they form pairs and invade the lungs, where they encyst in the conjunctival tissue of

the airways and begin to lay eggs 8 to 10 weeks after the initial infection. Although *Paragonimus* trematodes are morphologically hermaphroditic, functionally they are unisexual and, with the exception of the triploid forms of *P. westermani*, they do not self-fertilize. Juveniles that do not find a mate usually continue to move around in the pleural cavity or the lungs and cause further damage, while the adults in the pulmonary cysts are usually found in pairs. When metacercariae are ingested by an inappropriate host—for example, a wild boar, rabbit, or rodent—the parasites remain inside without developing further and utilize the animal as a transfer, or paratenic, host. The wild boar (*Sus scrofa leucomystax*) appears to serve as a paratenic host for *P. westermani* and *P. miyazakii*. On the island of Kyushu in Japan, the human infection has been attributed to the ingestion of raw wild boar meat containing juvenile forms of the parasite (WHO, 1979).

Geographic Distribution and Occurrence: *Paragonimus* is found throughout the world. Human infections occur in Africa, the Americas, and Asia. The geographic distribution of species that affect humans is indicated above in the section on etiology. The most important endemic areas are East and Southeast Asia, China, Japan, Lao People's Democratic Republic, the Philippines, Republic of Korea, Thailand, Taiwan, and the maritime provinces of the former USSR, and there are also isolated foci in India and Viet Nam. The main etiologic agent in all these areas is *P. westermani,* but in some countries, other species occur either concurrently or separately. Toscano *et al*. (1995) have calculated that 20 million people in the world are infected, several million of them in Asia. In the Republic of Korea, the infected population was estimated at 1 to 1.5 million. A study conducted in several provinces of Thailand revealed an infection rate of 6.5% in 503 persons examined. In Taiwan, the average infection rate in schoolchildren was 1.6% (Malek, 1980). A sizable endemic area was identified in Vietnam, in which 44 of 155 patients (28%) with chronic pulmonary disease were found to be infected with *Paragonimus* (Queuche *et al*., 1997). The prevalence in Japan, which rose during World War II and immediately thereafter, has declined sharply (Nawa, 1991). In a survey conducted in an endemic region of Cameroon, examination of sputum or feces revealed *P. africanus* eggs in 5.6% of 900 persons examined, with the highest rates in the population under 20 years of age (Kum and Nchinda, 1982). In eastern Nigeria, cases of *P. uterobilateralis* infection tend to occur sporadically, but the number of paragonimiasis cases increased considerably during and after the civil war of 1967–1970, and 100 cases were diagnosed in one university hospital (Nwokolo, 1972). Sputum specimens from 69 patients revealed that 66 had eggs of *P. uterobilateralis* and 3 had eggs of *P. africanus* (Voelker and Nwokolo, 1973). Isolated cases have been observed in Liberia and Guinea.

The main species that infects man in Latin America is *P. mexicanus*. Human cases of the disease have been seen in Colombia, Costa Rica, Ecuador, El Salvador, Honduras, Mexico, and Peru (in Cajamarca and along the coast north of Lima). In Ecuador, between 1921 and 1969, a total of 511 cases were reported, and between 1972 and 1976, there were 316 cases in four provinces of that country, most of them in the province of Manabí (Arzube and Voelker, 1978). In a study carried out in northwestern Ecuador, 43% of the crayfish examined were found to be infected, and 62% of the streams proved to be harboring infected crustaceans (Vieira, 1992). About 20 cases have been diagnosed in Cajamarca, Peru, and some have also been reported in Mexico.

The parasite's range of distribution in lower mammals is much broader than the corresponding human infection, since the spread of human infection depends on the eating habits of the population.

The Disease in Man: *Paragonimus* trematodes reside mainly in the lungs. A long time elapses between the ingestion of metacercariae and the appearance of symptoms, though the duration of this period is variable. The parasites can cause damage as they migrate toward the lungs and seek a mate in the pleural cavity, while they are encysted in the lungs, and sometimes when they become lodged in ectopic sites. Indeed, experimental studies in dogs have shown that migration toward the lungs can produce considerable damage. During this phase, there can be abdominal pain, fever, and diarrhea. Pleural pathology, often with effusion, is common in *P. westermani* infections. The prominent symptoms of pulmonary paragonimiasis are chronic productive cough, thoracic pain, blood-tinged viscous sputum, and sometimes fever (Im *et al*., 1993; Kagawa, 1997). Intense physical exercise can induce hemoptysis, which is the most notable sign. Eosinophilia is common. Small numbers of parasites in the lungs do not significantly affect the health of the patient and do not interfere with routine activity. The triploid forms of *P. westermani* are larger, produce bigger cysts, and cause more damage. About two-thirds of the shadows revealed by radiography are located in the middle and lower portions of the lungs; they are rarely seen in the apex. The most frequent and serious ectopic localization of *P. westermani* is the brain, but the parasite may also be found in the spinal cord, thoracic muscles, subcutaneous tissue, and abdominal cavity and organs. According to reports of cases in the Americas, the brain has also been parasitized by species other than *P. westermani*. In the Republic of Korea, which is a hyperendemic area, an estimated 5,000 cases of cerebral paragonimiasis occur each year. The symptomatology is similar to that of cerebral cysticercosis, with cephalalgia, convulsions, jacksonian epilepsy, hemiplegia, paresis, and visual disorders. Abdominal paragonimiasis produces a dull pain in that region, which may be accompanied by mucosanguineous diarrhea when the intestinal mucosa is ulcerated. In other localizations, the symptomatology varies depending on the organ affected.

The subcutaneous nodular form, characterized by intense eosinophilia, is predominant in infections caused by *P. skrjabini* in China and *P. heterotremus* in Thailand. This form is clinically similar to cutaneous larva migrans. In addition to migratory subcutaneous nodules, the most common manifestations of *P. skrjabini* infection in China are pleural, ocular, cerebral, pericardial, and hepatic lesions, while pulmonary symptoms are relatively infrequent. Cases of ectopic paragonimiasis in the brain, liver, and perivesical and cutaneous fat have been observed in Latin America. Twelve cases of cutaneous paragonimiasis occurred in the same family in Ecuador; in addition, there was a single isolated case in that country and another in Honduras (Brenes *et al.,* 1983).

The Disease in Animals: Animals parasitized by *P. westermani* frequently have cysts in the lungs, which pass to the respiratory tract and the pleural cavity. The symptoms are similar to those of human pulmonary paragonimiasis, with coughing and bloody sputum.

In the laboratory, trematodes appear in the lungs of dogs 23 to 35 days after experimental infection. The parasitosis begins as pneumonitis and catarrhal bronchitis, which are followed by interstitial pneumonia and the formation of cysts.

Source of Infection and Mode of Transmission: The source of *Paragonimus* infection for man and other definitive hosts is freshwater crabs and crayfish containing parasite metacercariae. Transmission results from the ingestion of raw or undercooked crustaceans, raw crabs marinated in wine ("drunken crabs"), or crustacean juices. Paragonimiasis is a public health problem in countries where it is customary to eat raw crustaceans or use them for supposedly therapeutic purposes. However, the disease is a problem in Japan as well, even though crustaceans are well cooked before they are eaten; in this case, the main source of infection is hands and cooking utensils contaminated during the preparation of crustaceans.

It is possible that man may also become infected by eating meat from animals that are paratenic hosts carrying immature parasites, as evidenced by cases on the island of Kyushu, Japan, that occurred following the consumption of raw wild boar meat. The hypothesis that there are paratenic hosts is reinforced by the fact that paragonims have been observed in carnivores such as tigers and leopards that do not eat crustaceans (Malek, 1980). Wars and internal conflicts that force people to relocate and cause shortages of normal protein food sources can also contribute to sharp increases in the prevalence of the infection, as was seen in Nigeria during its civil war and in Japan during World War II (see Geographic Distribution and Occurrence).

Transmission is always cyclic—the infection cannot be transmitted directly from one definitive host to another. The parasite must complete its natural cycle, and in order for this to happen the two intermediate hosts must be present—appropriate species of both snails and crustaceans.

The reservoir of *Paragonimus* spp. comprises man, domestic animals, and many species of wild animals (see Etiology). In endemic areas of eastern Asia, the human infection rate is high enough that man can maintain the infection cycle alone through ongoing contamination of freshwater bodies with human feces. In such areas, the role of animal definitive hosts may be of secondary importance. In certain areas of Japan, mass administration of bithionol to the human population led to a considerable reduction in the infection rate in crustaceans (WHO, 1979). This experience bears out the importance of human infection in maintaining the endemic. In other parts of Asia, wild animals have been parasitized by *P. westermani* in areas where there were no known human cases, which suggests that there may be a wild cycle independent of the domestic one. On the other hand, in several parts of Africa, Latin America, and Asia, wild animals are more important than man or domestic animals in maintaining the infection cycle. For example, the main natural reservoir of *P. uterobilateralis* is the African civet (*Viverra civetta*): parasite eggs were found in 26 of 28 fecal specimens examined (Sachs and Voelker, 1982).

Diagnosis: In endemic areas, paragonimiasis may be suspected if the typical symptoms are present and the consumption of raw or undercooked crustaceans is a local custom. Radiographic examination is useful, but the findings may be negative even in symptomatic patients. Moreover, interpretation of the results can be difficult in nonendemic areas because the images may be mistaken for those of tuberculosis. Computerized tomography may give a more reliable view of the lesions (Im *et al*., 1993; Kagawa, 1997). Specific diagnosis of pulmonary paragonimiasis is based on the identification of eggs in sputum, fecal matter, pleural effusions, or biopsies. The eggs are reddish brown, operculate, and enlarged at the end opposite the operculum. Published sources report the following egg sizes: *P. westermani*, 85 μm by 47 μm,

with abopercular enlargement; *P. heterotremus,* 86 μm by 48 μm, with no enlargement; *P. mexicanus*, 79 μm by 48 μm, with an undulated shell; *P. africanus,* 92 μm by 48 μm, with an undulated shell; *P. miyazakii,* 75 μm by 43 μm, with no enlargement; *P. skrjabini,* 80 μm by 48 μm, with no enlargement; and *P. uterobilateralis,* 68 μm by 41 μm, with abopercular enlargement. It is important to differentiate the eggs of *Paragonimus* from those of other trematodes, as well as cestodes of the order Pseudophyllidea, such as *Diphyllobothrium*. The cerebral forms can be mistaken for tumors or cysticercosis, and the cutaneous forms, for other migratory larvae—hence the interest in developing indirect tests. An intradermal test that was only weakly sensitive and of questionable specificity was widely used in the past for epidemiologic purposes. In a province of China, a 1961 study found that 24% of the persons examined had positive skin tests, and almost half of those cases were confirmed. In 1991, following a control campaign, 9% of the cases were positive and only 0.4% of them were confirmed. Currently, the most common test is the enzyme-linked immunosorbent assay (ELISA) using 32 and 35 kDa specific antigens. This assay can distinguish infections caused by different species of *Paragonimus* (Kong *et al*., 1998). In addition, the polymerase chain reaction is being used to diagnose paragonimiasis (Maleewong, 1997).

Control: In endemic areas, control efforts should be directed at interrupting the infection cycle by the following means: a) education of people to prevent the consumption of raw or undercooked crabs or crayfish; b) mass treatment of the population to reduce the reservoir of infection; c) elimination of stray dogs and cats for the same purpose; d) sanitary disposal of sputum and fecal matter to prevent the contamination of rivers; and e) controlling snails with molluscicides in areas where this approach is feasible. For a control program to be effective, it should encompass the entire watershed area and adjacent regions.

In Latin America, where the transmission cycle appears to occur predominantly in wildlife and where human cases are sporadic, the only practical measure is to educate and warn the population about the danger of eating raw or undercooked crustaceans. A study in China investigated the possibility of destroying metacercariae in crustaceans by irradiation with cobalt-60. No parasites could be recovered from mice infected with metacercariae irradiated at 2.5 kGy, but the fact that the mice developed antibodies indicates that the parasites had managed to colonize their tissues. Some of the metacercariae irradiated at 2 kGy excysted and survived in the mice for up to 30 days. Metacercariae irradiated at 0.1 kGy did not reach the adult stage in cats (Song *et al*., 1992).

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SCHISTOSOMIASIS

ICD-10 B65

Synonyms: Bilharziasis, Katayama syndrome (acute schistosomiasis).

Etiology: The primary agents of human schistosomiasis are the small blood trematodes *Schistosoma mansoni*, *S. japonicum*, and *S. haematobium*, which measure 0.5–2.5 cm in length and live in pairs inside blood vessels. In certain restricted

geographic areas, the species *S. intercalatum, S. mekongi*, and *S. malayensis* also affect humans. There have also been reports of human infections caused by the bovine parasite *S. mattheei*, although most of these may be caused by the hybridization of *S. mattheei* and *S. haematobium* (Kruger and Evans, 1990). *S. mansoni* and *S. haematobium* are considered strictly human species, although *S. mansoni* has occasionally been observed in rodents, monkeys, and insectivores, and *S. haematobium* has been seen in monkeys. *S. japonicum* can infect seven other mammalian orders, including domestic herbivores and carnivores, swine, and rats; *S. mekongi* can infect dogs; *S. malayensis* affects wild rats (Greer *et al*., 1989); *S. intercalatum* is a primary parasite of ruminants; and the bovine *S. mattheei* also infects other ruminants and rodents. DNA comparisons have demonstrated that *S. mekongi* is closely related to *S. japonicum* and *S. malayensis*, and observations in nature have shown that *S. intercalatum* and *S. mattheei* can hybridize with *S. haematobium* and produce fertile offspring (Jusot *et al*., 1997; Tchuem Tchuente *et al*., 1997). This phenomenon raises doubts regarding the specificity of these species (WHO, 1980). There are 19 recognized species of *Schistosoma*, but their phylogenetic relationships are complex (Rollinson *et al*., 1997).

Unlike the other digenic trematodes, which are hermaphrodites, the schistosomes have both male and female forms. The males are shorter and broader than the females, and they have a gynecophoral canal running along the ventral surface in which the female, which is long and thin, is permanently accommodated. Adults live in the venous system of their definitive hosts, where they mate and lay 100 to 3,500 eggs a day, depending on the species. Although all the species have a similar life cycle, there are variations in their required intermediate hosts and in the final localization of the adults in the circulatory system. *S. mansoni* is found primarily in the mesenteric veins that drain the large intestine, especially in the sigmoid branches; *S. japonicum* is found mainly in the mesenteric venules of the small intestine; *S. haematobium,* in the plexuses of the vena cava system that drains the bladder, pelvis, and uterus; and *S. intercalatum* and *S. mekongi*, the portal and mesenteric veins. In man, *S. mattheei* granulomas are found in the large intestine and the liver, but the eggs may be found in both feces and urine.

The eggs are transported by the venous circulation until they form a thrombus, at which point they secrete enzymes that enable them to traverse the wall of the organ and take up residence in the lumen. From the lumen they are eliminated in feces, urine, or other secretions or excretions of the affected organ. The eggs are deposited with a zygote inside, and before leaving the host they develop a larva (miracidium). When they reach water, most of the eggs hatch within eight hours, stimulated by light and water temperatures of 5°C to 36°C (Ye *et al*., 1997). The released miracidia swim in search of a suitable intermediate host, but they lose their infectivity if they fail to find one within about 10 hours. The snail intermediate hosts belong to the following genera: *Biomphalaria* and *Tropicorbis* in the case of *S. mansoni*; *Oncomelania* for *S. japonicum*; *Bulinus, Physopsis*, and *Planorbarius* for *S. haematobium* (Marquardt *et al*., 2000), *S. mattheei*, and *S. intercalatum*; *Tricula* and *Lithoglyphopsys* for *S. mekongi*; and *Robertsiella* for *S. malayensis*. The miracidium penetrates the snail and turns into a mother sporocyst, which forms daughter sporocysts inside it, and the latter, in turn, produce fork-tailed cercariae. The time lapse between penetration of the miracidium and emergence of cercariae can be as short as 20 days, but it is usually 4 to 7 weeks. The number of cercariae produced depends

on the parasite and snail species in question, as well as the size of the snail: *Biomphalaria glabrata* can generate between 30,000 and 180,000 cercariae of *S. mansoni*; *Bulinus globosus*, 12,000 to 24,000 cercariae of *S. haematobium*; and *Oncomelania*, 450 to 9,000 cercariae of *S. japonicum* (Marquardt *et al*., 2000).

Unlike the cercariae of other digenic trematodes, the schistosome cercariae do not form a metacercaria but instead invade the skin of the definitive host directly, often penetrating via the hair follicles or sebaceous glands by enzymatic and mechanical means. This process has to be completed within 36 hours or the cercaria loses its infectivity. Penetration takes only a matter of minutes; the cercaria drops its tail in the course of penetration, and within a few hours, it transforms into a juvenile schistosome (schistosomulum), which differs from the cercaria in morphology, antigenicity, and physiology. The schistosomula travel through the bloodstream to the lungs, where they stop briefly, and then move through the circulatory and porta systems to the liver, where they reach sexual maturity and mate. About three weeks after the initial infection, the parasites travel against the blood flow to the mesenteric, vesical, or pelvic venules, depending on the species. Oviposition begins at 5 to 7 weeks (*S. japonicum*), 7 to 8 weeks (*S. mansoni*), or 10 to 12 weeks (*S. haematobium*). The parasites live for several years, and there have been reports of infections lasting up to 30 years.

Geographic Distribution and Occurrence: Schistosomiasis is endemic in 74 developing countries, and more than 80% of the infected persons live in sub-Saharan Africa (WHO, 2003a). Direct mortality is relatively low, but the infection poses a public health problem because of the chronic pathology and disability that it produces. Despite control efforts in a number of countries, approximately 200 million people are still infected, of whom 120 million are symptomatic and 20 million have severe disease (WHO, 2003b).

S. mansoni has the widest geographic distribution; it is found in 52 countries of Africa (western and central parts of the continent, Egypt, and almost all the countries south of the Sahara except for a strip on the west running from Cameroon to South Africa), the Eastern Mediterranean, the Caribbean, and parts of South America. The range of *S. mansoni* is coextensive with that of *S. haematobium* in large areas. In Senegal, for example, there are places in which the prevalence of *S. mansoni* infection is nearly 100% and that of *S. haematobium* is 28% (De Clercq *et al*., 1999). There are also isolated foci in Egypt, Saudi Arabia, and Yemen. *S. haematobium* infection is found on some islands of the Lesser Antilles, the eastern coast of Brazil (north of São Paulo), and the coast of Venezuela, and in the Dominican Republic and Puerto Rico. It is believed that schistosomiasis was introduced to the Americas by slaves from Africa. *S. haematobium,* the agent of vesical schistosomiasis, is endemic in 53 countries of Africa as well as the Middle East, Madagascar, the southwestern Arabian peninsula, and along the Tigris and Euphrates rivers. In Tanzania, it is the most abundant helminth in children (Booth *et al*., 1998). *S. japonicum* infection is found in eight countries of Southeast Asia and the Western Pacific (Cambodia, China, Indonesia, the Philippines, and several small foci in Japan, Laos, Malaysia, and Thailand). *S. intercalatum* infection occurs in Cameroon, the Democratic Republic of Congo, Gabon, and other parts of central and western Africa, and prevalence in different areas ranges from 2.5% to 21.2%. The parasite causes bleeding intestinal lesions (Jusot *et al*., 1997; Tchuem Tchuente *et al*., 1997). Since its intermediate hosts (*Bulinus globosus*, *B. forskalii*) are found throughout

Africa, this species has been tending to spread. *S. mekongi* occurs in northern Cambodia, Laos, and Thailand, especially along the Mekong River, where in one area the prevalence was 40% in a group of 2,391 schoolchildren and 49.3% in 1,396 persons in the general population. Young persons 10 to 14 years of age were most affected, and the pathology was often severe (Stich *et al*., 1999). *S. malayensis* occurs in the Malay Peninsula (Greer *et al*., 1989). Human infection caused by *S. mattheei* has been reported in South Africa. Eggs of this parasite are often found in human feces and urine, with infection rates as high as 40% (WHO, 1979).

In China, infection caused by *S. japonicum* is found in the Yangtze River valley and to its south over an area inhabited by 100 million people, most of whom work in the rice fields. Before the current control program was undertaken, it was estimated that more than 10 million people were infected. In Japan, the human infection is largely under control and only a few hundred carriers remain. In the Philippines, an estimated 600,000 people are infected.

In the Americas, Brazil alone has an estimated 8 to 12 million infected individuals. In that country, tests carried out during preparations for its schistosomiasis control program revealed a positivity rate of 22.8% in 739,995 fecal samples from schoolchildren in 6 endemic states (Machado, 1982). In some localities in northeastern Minas Gerais, Brazil, 100% of the population was found to be infected. In the Caribbean area, the rates per 100,000 population in 1972 were 4.8 in the Dominican Republic, 39.2 in Guadeloupe, 1.3 in Puerto Rico, and 375.7 in Saint Lucia. In the US, an average of 170 imported cases were reported annually between 1969 and 1972, most of them from the Caribbean islands. Mahmoud (1977) estimated that, even though the parasitosis is not transmitted in the US for lack of intermediate hosts, some 400,000 infected persons were living there. The infection has spread in some areas because of new irrigation projects and the migration of infected populations. In Brazil, schistosomiasis has spread to the states of Goiás, Maranhão, Pará, Paraná, Santa Catarina, São Paulo (where there are several isolated foci), and from the northeast to southern Minas Gerais (Katz and Carvalho, 1983). In Paraguay, there have been no reports of infection, but more than 100 *S. mansoni*-infected Brazilian immigrants have been found, and the snail *Biomphalaria tenagophila*, which could serve as an intermediate host, is present there.

Despite the fact that several countries have managed to reduce the occurrence of schistosomiasis through vigorous control programs, its prevalence has changed little in recent decades because of the expansion of irrigation and the human migrations mentioned earlier. Reports published in 1999, based on research in selected communities from different countries, gave the following prevalence ranges for *S. mansoni*: 34%–58% in Egypt, 1% in Puerto Rico (down from 21% in 1993), 53%–76% in Senegal, 88% in Tanzania, 2% in Togo, 30%–84% in Uganda, and 1.4% in Venezuela (down from 14% in 1943). In addition, there were an estimated 2 million infected persons in Madagascar. For *S. haematobium*, the ranges were as follows: 7%–11% in Egypt, 97% in Kenya, 46% in Niger, 17% in Nigeria, 53%–64% in Senegal, and 25% in Togo. In addition, there are an estimated half million infected persons in Madagascar. In 1998, two surveys carried out in different municipalities of São Paulo State in Brazil showed 0.4% and 43% positive serology for *S. mansoni*, but only 4.3% and 8.5% of the individuals were shedding eggs.

With regard to the infection in animals, in Brazil *S. mansoni* infection has been found in many rodents, other wild species, and cattle; in eastern Africa, in baboons,

rodents, and dogs; and in Egypt, in gerbils (genus *Gerbillus*) and Nile rats. The infection rates are often quite high. In some areas of eastern Africa infection rates of more than 50% have been seen in baboons (WHO, 1979). Natural infection with *S. japonicum,* in turn, has been found in many animal species, and in some areas the rates are high (see Source of Infection and Mode of Transmission). *S. haematobium* has been known to infect nonhuman primates, rodents, and swine on rare occasions, and the prevalence has been low (WHO, 1979).

The Disease in Man: Approximately 90% of schistosome infections in humans are asymptomatic. However, some patients suffer acute respiratory abnormalities with radiographic signs and unspecific symptoms similar to those of influenza. There can be more significant morbidity, and even mortality, from fibrotic reactions to parasite eggs laid in host tissue, leading especially to portal hypertension in the case of *S. mansoni* or *S. japonicum,* and urinary tract obstruction in the case of *S. haematobium* (El-Garem, 1998). However, the disease's clinical presentation has changed over the last 10 to 15 years thanks to specific chemotherapy for schistosomiasis and to environmental changes in many countries, and its earlier hepatosplenic and other manifestations (ascites, gastric hemorrhage, splenomegaly, cor pulmonale, glomerulopathy) are now less severe (Andrade, 1998). Between 6% and 27% of infected women suffer from genital lesions, but the nature and treatment of these lesions is not yet understood (Feldmeier, 1998). In less than 5% of those infected with *S. mansoni*, the obstruction of pulmonary circulation causes pulmonary hypertension and cor pulmonale (Morris and Knauer, 1997). Occasionally, the eggs reach the central nervous system and produce a granulomatous reaction. When there are only a few eggs and they are widely scattered, no signs are observed, but large granulomas can cause increased intracranial pressure and focalized signs, often in the lumbosacral spinal cord (Ferrari, 1999; Pittella, 1997).

The seriousness of the disease is dictated by the parasite burden and the length of time the patient has been infected; both factors affect the number of eggs that settle in host tissues, which is the main determinant of chronic pathology. School-age children and occupational groups that spend time frequently and for long periods in water, such as fishermen and rice growers, have more intense infections because of the accumulation of parasites from repeated infections. However, there is a limit to this accumulation because the schistosomes generate concomitant immunity; in other words, the adult forms of the parasite partially protect against new infections by schistosomula.

The symptomatology of schistosomiasis may be divided into four phases, according to the evolution of the parasitosis. The first phase corresponds to the penetration of cercariae. It is commonly manifested by a cutaneous allergy to the parasite's products, which occurs with greater frequency and intensity in reinfections. At first there are petechiae with edema and pruritus; these are followed by urticaria, which can become vesicular and last from 36 hours to 10 days. Unlike birds, humans do not always have cutaneous manifestations. The second phase occurs when the schistosomula invade the pulmonary capillaries. In most cases there are no clinical manifestations, although massive infections can produce pneumonitis with coughing and asthma-like crises, along with eosinophilic infiltration. The third phase develops when the parasite matures inside the liver and oviposition begins to take place in the corresponding venules. This phase does not usually produce damage to the tissues

or clinical manifestations, but in the case of massive infections there may be fever, diarrhea, abdominal pain, urticaria, and prostration. It is believed that these symptoms represent an acute immune response to antigens released by the eggs, with the formation of abundant cytokines. The fourth, or chronic or granulomatous phase, reflects the tissue response to the deposition of eggs. The antigens of the eggs that are retained in the tissues generate a cell-mediated immune response that forms granulomas around the eggs. When the granulomas become abundant in a tissue, they converge and can invade an important part of the organ. Prior stimulation of the patient by antigens of the adult parasite and the intervention of tumor necrosis factor alpha seem to play an important role in the formation of granulomas (Leptak and McKerrow, 1997).

In *S. mansoni* infection, the main lesions are found in the intestinal wall. Over time, they spread to the liver and produce interlobular fibrosis and portal hypertension, ascites, and splenomegaly. In advanced stages, there may be pulmonary lesions and respiratory symptoms. In the chronic phase, the following clinical forms can be distinguished: intestinal, hepatointestinal, hepatosplenic, and pulmonary. In a study of *S. mansoni* morbidity in three rural villages on an island off Tanzania, prevalence was 86% and the average parasite burden was 176 eggs per gram of feces, while 80% of those infected had abdominal pain, 43% had melena, and 35% had diarrhea. The disease was more serious in children and adolescents. Ultrasound revealed hepatomegaly in 35% of the infected individuals and splenomegaly in 80%, both of which were associated with a high parasite burden and were less notable in those who had already been treated with praziquantel. Mild periportal fibrosis was common, and signs of portal hypertension were observed in 2% of the subjects. Serum procollagen-IV-peptide levels were elevated in patients with severe periportal fibrosis, suggesting that this might be a marker of hepatic schistosomiasis (Kardorff *et al*., 1997). The most indicative signs of acute *S. mansoni* infection are fever, diarrhea, abdominal pain, weight loss, and eosinophilia. The signs of chronic disease are usually persistent diarrhea and abdominal pain with hepatomegaly or splenomegaly.

The symptoms of disease caused by *S. japonicum* are similar to those caused by *S. mansoni*, but they are usually more severe, the period of incubation is shorter, and the early lesions are typically located in the small intestine rather than the colon. Intestinal and hepatic fibrosis develop much more rapidly because *S. japonicum* lays more eggs.

In infections caused by *S. haematobium,* the lesions and symptoms correspond primarily to the urogenital tract, and, to a lesser degree, the intestine. Papillomatous folds, pseudoabscesses, and miliary pseudotubercles develop in the wall of the bladder, and sometimes there is total fibrosis of the organ. Obstruction of the urethra and the ureters is common. The main symptoms are painful and frequent urination, terminal hematuria, suprapubic pain, and recurrent urinary infections. The hepatopathies are less serious than those seen in *S. mansoni* infections. The eggs may also travel to the intestine, especially the venules that drain the rectum, and they may be eliminated in the feces. Evidence suggests that vesical schistosomiasis may be a predisposing condition for malignant tumors because of the continuous irritation produced by the eggs. In a survey of more than 1,000 persons infected with *S. haematobium* in two hyperendemic localities in Mali, half the subjects did not have clinical manifestations and only 30% had pathologic lesions. Both infection and morbidity rates were higher in children aged 7 to 14 years old. Use of the dipstick

test to measure microhematuria proved to be more sensitive in detecting the disease than the infection. Treatment with praziquantel resolved more than 80% of the urinary tract lesions within a year (Traore, 1998).

In human infections caused by *S. mattheei* or *S. intercalatum*, the lesions and symptoms are usually mild. As a rule, *S. mattheei* is found in persons simultaneously infected by *S. mansoni* or *S. haematobium.* Infection caused by *S. intercalatum* occurs primarily in young people and tends to gradually disappear in older age groups as the population acquires resistance to the parasite. About 90% of patients infected by *S. intercalatum* complain of intestinal disorders, and some 70% have bloody feces. Hepatomegaly occurs in approximately 50% of the cases, but portal hypertension is not seen. Other species of nonhuman schistosomes, such as *S. bovis* and *S. rodhaini*, produce an abortive infection in man because the parasite does not reach maturity.

There is also an acute form of schistosomiasis, often referred to as Katayama fever, which develops four to six weeks after a massive primary infection with *S. japonicum*, and sometimes, *S. mansoni.* The clinical manifestations are similar in some respects to those of serum disease: fever, eosinophilia, lymphadenopathy, hepatosplenomegaly, and sometimes dysentery. Because of the clinical manifestations and the fact that the disease occurs at the beginning of oviposition, it is believed that this syndrome is caused by the formation of antigen-antibody complexes in the bloodstream.

The Disease in Animals: Schistosomiasis can be quite common in animals. Prevalence rates in cattle have been found to be as high as 62% (Bangladesh), 90% (Sudan), and 92% (Zimbabwe). The species that are most pathogenic for domestic ruminants are *S. bovis* and *S. japonicum*. *S. mattheei* and *S. spindale* are less pathogenic, and sometimes the former is eliminated spontaneously over time. As in man, schistosomiasis in cattle has an acute phase, caused when recently matured parasites release large quantities of eggs in the intestinal mucosa, and a chronic phase, during which the damage is caused by the reaction to antigens produced by eggs trapped inside tissues. The former, referred to as the intestinal syndrome, occurs seven to nine weeks after a massive initial infection and causes severe hemorrhagic lesions in the intestinal mucosa, with infiltration of eosinophils, lymphocytes, macrophages, and plasmocytes, along with profuse diarrhea or dysentery, dehydration, anorexia, anemia, hypoalbuminemia, weight loss, and retarded development. The duration of the disease varies depending on the parasite burden, and recovery is spontaneous. The chronic phase, or hepatic syndrome, is a cell-mediated immune response to antigens from the trapped eggs. As in man, the reaction leads to the formation of inflammatory foci, granulomas, fibroses, and ultimately, the obstruction of portal irrigation. The chronic disease occurs in animals that have been repeatedly exposed to infections with large numbers of cercariae, and the principal manifestations are emaciation, anemia, eosinophilia, and hypoalbuminemia (Soulsby, 1982). Unlike man, animals do not appear to be susceptible to splenomegaly or esophageal varices, but the presence of dead parasites can cause them to develop enlarged follicles or lymph nodes, as well as venous thromboses, with infarct of the organ. In addition to the liver, the schistosome eggs can settle in the intestinal wall, lungs, kidneys, bladder, and other organs, where they cause damage and symptoms in proportion to the parasite burden. Cattle have also been reported to have obstructive phlebitis caused by the presence of adult parasites in the veins.

Source of Infection and Mode of Transmission: Schistosomiasis is one of the main human parasitoses and is very important to public health because of its debilitating effect on people throughout large areas of the world. Geographic distribution of the infection appears to be undergoing a change. While some areas are making progress through vigorous control campaigns, the infection is spreading to others in the wake of new irrigation projects or carried by individuals. Moreover, the geographic range of the intermediate hosts is greater than that of the human infection. The Aswan Dam in Egypt provides an example of how environmental change can impact on the disease. Although construction of the dam has resulted in important economic benefits for the country, it has also brought about profound ecological changes in the region and created favorable conditions for the survival of the mollusks that act as intermediate hosts of *S. mansoni*, but not for those of *S. haematobium.* Before construction of the dam, *S. mansoni* schistosomiasis was common in the Nile Delta but infrequent in the region from Cairo to Khartoum, Sudan. The dam reduced the flow rate of the Lower Nile and held back the alluvial sediment, thereby favoring penetration of the mollusks by the miracidia and also facilitating human contact with the cercariae that emerge from them. At the same time, there was an increase in human activities, such as fishing and washing clothes and utensils, along the Nile River. All these factors contributed to an increase in the prevalence of *S. mansoni* infection in Upper Egypt. The ecology of Lower Egypt (the Nile Delta) also underwent changes favorable to the vectors of this parasitosis. The absence of alluvial sediment promoted the growth and spread of aquatic plants as well as the microflora on which the mollusks feed, with a consequent increase in their population and greater possibility of transmission of the parasite to the human host (Malek, 1975). The situation in Egypt, which has been repeated in several other countries of Africa, the Americas, and Asia, shows that knowledge of ecological conditions is essential to understanding the variability of the human infection. The growing rate at which dams are being constructed in the developing countries, sometimes without prior ecologic and epidemiologic studies to serve as a basis for implementing disease prevention measures, is helping to bring about the spread and intensification of schistosomiasis.

The primary intermediate hosts of *S. mansoni (Biomphalaria)* and *S. haematobium (Bulinus)* are aquatic snails that flourish in irrigation canals, lagoons, river backwaters, and small shaded natural pools of water under 2 meters deep with a flow rate of less than 15 m per minute. *Bulinus*, unlike *Biomphalaria*, can survive in mud after the water has dried up. The intermediate host of *S. japonicum (Oncomelania)*, on the other hand, is an amphibious snail that can live for several months in a relatively dry environment, maintaining the larval stages of the parasite. These mollusks become infected when their water becomes contaminated with fecal matter from definitive hosts, especially humans, or urine in the case of *S. haematobium*.

Man acquires the infection by the cutaneous route by entering water that contains mollusks infected with the parasite. For this reason, schistosomiasis is essentially a rural infection. Studies in endemic areas have shown that the prevalence of infection in the snails concerned is generally lower than 5% and that the density of free-living cercariae is extremely low because they are dispersed over a large volume of water. Moreover, the latter are infective for only a few hours. These low rates suggest that the intense infections needed to cause disease require relatively prolonged exposure to contaminated water. Thus, it follows that the population likely to have

the highest prevalence rates and parasite burdens (and consequently more severe disease) is children and young adults aged 5 to 25 years, who spend the most time in water. In some regions, schistosomiasis is also an occupational disease of farm laborers who work in irrigated fields (rice, sugarcane) and fisherman who work in fish culture ponds and rivers. Another highly exposed group is the village women who wash clothing and utensils along the banks of lakes and streams. The infection can also be contracted while bathing, swimming, or playing in the water.

Man is the main definitive host of *S. mansoni*. Patent *S. mansoni* infections have also been seen in rodents, monkeys, and insectivores. Studies in the Americas have shown that rodents alone cannot maintain prolonged environmental contamination, but perhaps baboons (*Papio* spp.) in Africa can do so. Nevertheless, for epidemiologic purposes, *S. mansoni* is regarded as an exclusively human species. *S. haematobium* is also an exclusively human parasite; observations of infection in monkeys have been scarce and epidemiologically insignificant. However, *S. japonicum* is an entirely different matter: at least 31 mammalian species belonging to seven orders, including virtually all domestic animals, are capable of having patent infections caused by this parasite. These species play an important epidemiologic role because they contaminate the water, enabling man to become infected. In Taiwan, there is a strain of *S. japonicum* that is widespread in rodents and domestic animals, but it causes only an abortive infection in man because the parasite does not reach maturity. In addition, *S. mekongi* can infect dogs, and *S. malayensis* is a parasite of wild rats (Greer *et al*., 1989), but the precise influence of the animal reservoir on human infection is unknown in both instances. *S. intercalatum* and *S. mattheei* are animal parasites that secondarily infect man (the former is a parasite, *inter alia*, of sheep, goats, and rats, and the latter, of cattle, sheep, goats, equines, and rodents). They are usually found in mixed infections along with *S. mansoni* or *S. haematobium*, so that the true importance of these species for human health is unclear. DNA comparisons have shown that *S. mekongi* is closely related to *S. japonicum* and *S. malayensis*, and observations in nature have shown that *S. intercalatum* and *S. mattheei* can hybridize with *S. haematobium* and produce fertile offspring (Jusot *et al*., 1997; Tchuem Tchuente *et al*., 1997).

It has been observed that persons infected with abortive animal schistosomes or those that have little pathogenicity for man develop a degree of cross-resistance that protects them against subsequent human schistosome infections. It is even thought that resistance produced by abortive infections of the zoonotic strain *S. japonicum* in Taiwan has spared the island from being invaded by the human strain. In light of this heterologous or cross-immunity, some researchers have proposed vaccinating humans with the antigens or parasites of animal species (zooprophylaxis).

The influence of factors involving the parasite, host, and environment on the persistence of schistosomiasis has been studied using *S. mansoni* in rats (Morand *et al*., 1999).

Diagnosis: Schistosomiasis is suspected when the characteristic symptoms occur in an epidemiologic environment that facilitates its transmission. Specific diagnosis is based on demonstrating the presence of *S. mansoni* or *S. japonicum* eggs in feces and those of *S. haematobium* in either feces or urine. The eggs of all the human schistosome species are long and nonoperculate. Those of *S. mansoni* are brownish-yellow, measure 110–180 µ long by 40–70 µ wide, and have a characteristic lateral spine. Those of *S. haematobium* are about the same size and have a very pronounced

terminal spine, while those of *S. japonicum* are smaller and have a rudimentary subterminal spine. *S. intercalatum* eggs are difficult to differentiate from those of *S. haematobium* (Almeda *et al*., 1996). The eggs may begin to appear five weeks after the initial infection. The ease with which their presence is confirmed depends on the intensity and duration of the infection; mild and long-standing infections produce few eggs. Whenever schistosomiasis is suspected, samples should be examined over a period of several days, since the passage of eggs is not continuous. Direct, unenriched examination of the samples is not a very sensitive method. The Kato-Katz thick smear technique offers a good balance between simplicity and sensitivity, and it is commonly used in the field (Borel *et al*., 1999).

Among the feces concentration techniques, formalin-ether sedimentation is considered one of the most efficient. In chronic cases with scant passage of eggs, the rectal mucosa can be biopsied for high-pressure microscopy. Also, the eclosion test, in which the feces are diluted in unchlorinated water and incubated for about four hours in a centrifuge tube lined with dark paper, can be used. At the end of this time, the upper part of the tube is illuminated in order to concentrate the miracidia, which can be observed with a magnifying glass. In addition to the mere presence of eggs, it is important to determine whether or not the miracidia are alive (which can be seen from the movement of the miracidium or its cilia) because the immune response that leads to fibrosis is triggered by antigens produced by the miracidium. In cases of prepatent, mild, or long-standing infection, the presence of eggs is difficult to demonstrate, and diagnosis therefore usually relies on finding specific antigens or antibodies (Tsang and Wilkins, 1997). However, searching for parasite antigens is not a very efficient approach when the live parasite burden is low. The circumoval precipitation, cercarien-Hullen reaction, miracidial immobilization, and cercarial fluorescent antibody tests are reasonably sensitive and specific, but they are rarely used because they require live parasites. The enzyme-linked immunosorbent assay (ELISA) and immunotransference (Western blot) tests are now preferred. A recombinant protein of *S. mansoni* (Sm22.3) has been produced that recognizes antibodies to *S. mansoni* or *S. haematobium* with 80% sensitivity and 95% specificity, but it still cross-reacts with serum from malaria infections (Hancock *et al*., 1997). IgM and IgG antibodies from all acute patients recognized the *S. mansoni* SM31/32 antigen, but only 10% of the IgM antibodies from chronic patients reacted. Hence, the reaction of this antigen to IgM antibodies may be a marker of acute disease (Valli *et al*., 1999).

A questionnaire administered to students and teachers from schools in urinary schistosomiasis endemic areas revealed a surprisingly large number of *S. haematobium* infections (Partnership for Child Development, 1999). In many cases, centrifugation and examination of the urine sediment is sufficient to find eggs, although filtration in microporous membranes is more sensitive. Examination of the urine sediment for eosinophils reveals more than 80% of all infections. The use of strips dipped in urine to detect blood or proteins also reveals a high number of infections, even though the test is nonspecific. Also, there are now strips impregnated with specific antibodies that reveal the presence of *S. haematobium* antigens when dipped in a urine specimen (Bosompem *et al*., 1997). Although this method is less sensitive than the ELISA test, it is easy to use in mass studies. Searching for antibodies or antigens in serum was substantially more sensitive than looking for eggs in urine (Al-Sherbiny *et al*., 1999).

Control: The measures available for controlling schistosomiasis are: 1) diagnosis and treatment of patients; 2) selective or mass chemotherapy; 3) health education; 4) control of the intermediate hosts; 5) adequate water supply and sanitary excreta disposal systems; and 6) modification of the environment.

Chemotherapy of infected individuals is not only curative but also preventive in that it halts the production of eggs that contaminate the environment. Clinical trials with praziquantel to treat *S. mansoni* infection in Brazil, *S. haematobium* in Zambia, and *S. japonicum* in the Philippines and Japan have given excellent results in terms of both parasitologic cure and the reduction of eggs being eliminated (WHO, 1980). In a three-year study carried out in Madagascar, 289 individuals from a village in which *S. mansoni* was hyperendemic were treated systematically with praziquantel and prevalence declined from 66%, with an average of 202 eggs per gram of feces, to 19% and 27 eggs per gram (Boisier *et al*., 1998). In most cases, it is not recommended to treat the entire community; a more effective approach is to perform parasitologic examinations and treat only the infected individuals. When the intensity of infection declines in a given population, it may be necessary to resort to serologic diagnosis, which is more sensitive. In communities that have a high prevalence of infection but limited economic resources, treatment can be restricted to the groups with the highest parasite burdens, such as children between 7 and 14 years old. In the case of schistosomiasis caused by *S. japonicum*, however, Olds *et al*. (1996) recommend mass treatment or treatment aimed at large, high-risk groups because there are many animal reservoirs, parasitologic diagnosis is not very sensitive, the disease is more serious, and there is no apparent correlation between severity of the disease and parasite burden.

Health education consists essentially in teaching people to avoid contact with contaminated water and not to contaminate water with their own excreta. However, many of the populations most affected by schistosomiasis are communities with low levels of schooling and such limited resources that they often have no alternative but to use contaminated water or to contaminate the environment with their excreta. The intermediate hosts have been controlled in a number of areas by draining or filling in swampland, removing vegetation from water bodies, and improving irrigation systems. In Japan, excellent results were achieved by lining irrigation canals with concrete. The use of molluscicides, though expensive, is a rapid and effective means of reducing transmission if it is combined with other prevention measures, especially chemotherapy. The cost-benefit ratio is more favorable where the volume of water to be treated is small, and for rivers or lakes where transmission is focal (limited to a relatively small habitat). Selection of the molluscicide to be used should take into account the nature of the snail's habitat, the cost of the chemical compound, and any harmful effects it might have on fish and other forms of aquatic life. The introduction of snails that compete with the intermediate hosts of the schistosome has been successful in some areas. In Puerto Rico, for example, introduction of the snail *Marisa cornuarietis,* coupled with chemical control, has eliminated *B. glabrata* almost entirely from the nearby island of Vieques. However, *M. cornuarietis* is not effective in ecosystems with dense vegetation or in swamps or rivers (WHO, 1980). In Saint Lucia, *B. glabrata* was apparently eliminated from swampy areas and streams between 6 and 22 months after the introduction of *Tiara granifera*, a snail from Southeast Asia. Unfortunately, this snail can serve as the intermediate host of *Paragonimus westermani* (Prentice, 1983). Environmental sanitation

(especially the provision of potable water and sanitary waste elimination systems) in rural areas is costly and therefore difficult to implement in the short term and on the needed scale. Moreover, changing the environment entails an improved standard of living for the population, more education, and healthier surroundings—objectives that are difficult to achieve.

The measures described above are useful when they are incorporated realistically within the framework of a control program. In Venezuela, the Schistosomiasis Control Program was launched in 1945 and prevalence of the infection has fallen from 14% in 1943 to 1.4% in 1996. Up until 1982, active cases were diagnosed by fecal examination, which was then followed by treatment, but starting that year, serologic surveys were added because many infections were too mild to be diagnosed by parasitology. Nevertheless, the true prevalence is believed to be underestimated. Given that 80% of infected individuals pass fewer than 100 eggs per gram of feces, it is possible that these people maintain foci of infection, thereby undermining control efforts. Biological control using snails that compete with the intermediate hosts has not been totally successful, since *B. glabrata* has managed to reinfect some areas and increase the prevalence of infection in others. Indeed, infected snails have been found over an expanse of approximately 15,000 km^2 in which the infection was believed to have been eradicated several years ago. As a result, the entire schistosomiasis control strategy in Venezuela has been revised (Alarcón de Noya *et al*., 1999). In Brazil, chemotherapy has been a very important tool for reducing morbidity, incidence, and prevalence in endemic areas, but the provision of potable water, sanitary disposal of excreta, and health education still remain the essential requirements for definitive and permanent control (Katz, 1998).

Although chemotherapy has been very successful in controlling schistosomiasis, reinfection makes it necessary for people to take the treatment often, sometimes annually. Hence the search for a vaccine. Despite reasonable success in domestic and laboratory animals, vaccines for human use are still far from being effective, both because man does not respond to vaccination the same way that animals do and because the methods used with animals (such as infection with irradiated cercariae) are not directly applicable to man. Indeed, vaccination was not considered a viable alternative for the control of schistosomiasis until recently, when the identification of certain protective antigens and the possibility of producing them as recombinant molecules raised hopes for success in this endeavor (Bergquist, 1998).

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Section C

ARTHROPODS

DERMATITIS CAUSED BY MITES OF ANIMAL ORIGIN

ICD-10 B88.0 Other ascariasis

Etiology: In addition to the mite that causes sarcoptic scabies, or mange (see the chapter on Zoonotic Scabies) and ticks (see the chapter on Tick Infestations), there are other acarid parasites that can infest the skin of man and cause a temporary dermatitis, although they are incapable of becoming established on this aberrant host. These parasites belong to the families Cheyletiellidae, Dermanyssidae, and Macronyssidae.

In the family Cheyletiellidae, only the genus *Cheyletiella* is of importance for present purposes. The members of this genus are obligate ectoparasites of lagomorphs, dogs, cats, wild animals, and, occasionally, man. The species transmissible to man are *C. parasitovorax*, a parasite of rabbits; *C. yasguri*, associated with dogs; and *C. blakei*, found on cats. The mites of this genus are grayish white and measure approximately 0.4 mm by 0.3 mm. Each palp has a claw directed toward the mouth, and at the end of the legs is a double row of hairs instead of suckers. The entire life cycle takes place on the host and is completed in about 35 days. The female attaches her eggs (0.2 mm by 0.1 mm) to the animal's hair about 2 mm or 3 mm from the skin. The hexapod larvae develop within the egg and then go through two nymphal stages before becoming adults. They are superficial parasites of the skin and fur and do not dig galleries into the host. They feed on keratinized skin cells and occasionally suck lymph. Off the host, the adult female and the eggs can survive up to 10 days in a cool place, but the larvae, nymphs, and adult males are less resistant and die in about 2 days in the open environment. Because of their appearance and the way they move, they are popularly referred to as "walking dandruff."

The family Dermanyssidae includes hematophagous ectoparasitic mites of birds and mammals. They measure approximately 0.8–1.0 mm in length and are grayish white when fasting and reddish when engorged. The zoonotic species are *Dermanyssus gallinae*, a parasite of chickens, turkeys, pigeons, canaries, and wild fowl, and *Liponyssoides* (*Allodermanyssus*) *sanguineus*, found on small rodents. *D. gallinae* live in hens' nests and nearby cracks, where the female lays her eggs. At night, they come out of their hiding places and feed on the birds. The females initiate oviposition 12 to 24 hours after feeding. The eggs can hatch in two to three days, releasing a six-legged larva that goes through two nymphal stages before becoming an adult. Under favorable environmental conditions, the entire life cycle can be completed in a week. The adults can live up to 34 weeks without feeding, and hence their

spontaneous elimination is difficult. *L. sanguineus* has a similar cycle in rodents, but it takes 18 to 23 days, and the female can survive up to 51 days without feeding.

The family Macronyssidae includes hematophagous ectoparasites of birds, mammals, and reptiles. The potentially zoonotic species are *Ornithonyssus bacoti*, which parasitizes rodents and small marsupials, and *O. bursa* and *O. sylviarum*, found on birds. The genus *Ornithonyssus* has undergone several name changes, and its species are sometimes considered to belong to the genera *Liponyssus* or *Bdellonyssus. O. bacoti* lays its eggs in the burrows or nests of rodents, and in the case of laboratory animals such as mice, rats, and hamsters, in the cracks and corners of the cages. Under ideal conditions, the parasite can complete its life cycle in only 11 to 16 days, going from egg to larva and then through two nymphal stages, the adult stage, and finally, oviposition. Hence, it can generate large populations in a short time. *O. bursa* infests chickens, turkeys, pigeons, sparrows, and other fowl. It lives mostly in the birds' nests, where it goes through its life cycle, but it spends more time on fowl than do *D. gallinae*, and less time than *O. sylviarum*. It does not survive more than 10 days in the absence of an avian host. Unlike the other species, *O. sylviarum* is for the most part a permanent ectoparasite which lays its eggs, develops, and spends most of its life on its host. It can complete its life cycle in only seven days and survive for three to four weeks off the host.

Geographic Distribution and Occurrence: Mites of the genus *Cheyletiella* and the species *Dermanyssus gallinae* are distributed worldwide. *Liponyssoides sanguineus* is found in northern Africa, Asia, Europe, and the US. *Ornithonyssus bacoti* is found throughout the world, especially in association with the black rat, *Rattus rattus*. It appears to be common in the Russian Federation because the local literature reports that 36 foci were identified and eradicated in Moscow between 1990 and 1991. *O. bursa* is found mainly in tropical and subtropical regions, and *O. sylviarum*, in temperate regions of the northern hemisphere and also in Australia and New Zealand. The prevalence in man is difficult to determine accurately because these infestations occur only in special circumstances that enable the arthropod to transfer from its usual host to man.

C. yasguri has been found in dog kennels and, occasionally, in veterinary practices. Many cases of *C. blakei* infestations on cats have been detected because their owners were also affected and had sought medical care (Paradis, 1998). Sometimes the infestation is discovered in a coprologic examination, as happened in a laboratory in the US when very large eggs (0.23 mm by 0.11 mm) were found in the feces of a cat. This finding prompted examination of another 41 cats from the same supplier, and 10 of them were found to be infested; at the same time, 28 cats from two other suppliers were negative (McKeevar and Allen, 1979). *C. parasitovorax*, found on rabbits, can invade laboratory colonies and affect a large number of animals. *D. gallinae* is rarely present in modern establishments where fowl are raised in cages; the species is more commonly seen on rural poultry farms and rustic hen houses that afford suitable hiding places for the arthropod. Human homes can be invaded by mites from nearby hen houses or pigeon cotes, especially when the birds leave their nests and the mites have to look for a new source of food. In Rotterdam, Netherlands, 23 individuals from 8 families were found to be infested. *L. sanguineus* is an abundant parasite of mice (*Mus musculus*), but when it needs food, it can readily feed on other rodents or man. *O. bacoti* is frequent wherever the black rat exists in large numbers, and it can be quite common in poorly maintained laboratory

rodent colonies. It tends to invade human dwellings when campaigns to eliminate rats have not included treatment to suppress the arthropods. Like *D. gallinae*, *O. bursa* is not often seen on modern farms, which do not provide suitable hiding places. Humans experience only a passing infestation because the mite cannot survive more than 10 days without feeding on its natural host. *O. sylviarum* is more common, even on modern farms, because it lives mainly on the fowl and does not need nests or cracks to hide in.

The Disease in Man: Human infestation with *Cheyletiella* spp. results from close contact with infested animals. The disease consists of an unspecific papular, pruriginous dermatitis on the arms, thorax, waist, and thighs. In man, the infestation is transitory and disappears spontaneously once the reservoir animals in the household—the source of infestation and reinfestation—are treated. The bite of *D. gallinae* is painful, and the infestation usually causes a papular, pruriginous urticaria, although sometimes the only manifestation is persistent pruritus. *L. sanguineus* infestation is similar, but this mite can also transmit *Rickettsia akari*, the agent of vesicular rickettsiosis in man. *O. bacoti* causes a similar condition, with painful bites and sometimes allergic dermatitis. *O. sylviarum* attacks man in the absence of its natural hosts, and it can sometimes cause immediate irritation, followed by erythema, edema, and pruritus. The other avian mite, *O. bursa*, frequently attacks man as well, causing a mild skin irritation. In the laboratory, several of these mites have been infected with organisms that are pathogenic for man, but none except *R. akari* is known to transmit pathogens to man in nature.

The Disease in Animals: The symptoms of animal infestation with *Cheyletiella* spp. are variable. In dogs, an exfoliative and a crusted form have been described. In the former, there is abundant formation of dandruff on the back, which is more noticeable in the fur than as a scaly condition of the skin. There is pruritus to varying degrees, alopecia, and inflammation, which is mainly the result of scratching. In the crusted form, the noticeable manifestation is multiple circular areas of alopecia on the back and sides of the trunk, crusted with no inflammation underneath, which bear a resemblance to tinea. In cats, the infection is often asymptomatic, and when it is manifested, it usually assumes a crusted form very similar to tinea, except that it appears on the trunk and neck instead of the face and paws.

D. gallinae does not appear to cause dermal lesions that can be detected, but in birds it produces anemia and irritation. When the infestation is very intense, it can cause lowered egg production and even an interruption in oviposition, and blood loss can be so severe that the birds die of anemia. In Australia, *D. gallinae* is a vector of *Borrelia anserina*, the agent of fowl spirochetosis. *L. sanguineus* is likely to cause irritation, anemia, and debility in mice. It is the vector of *R. akari*, the agent of human vesicular rickettsiosis, for which the reservoirs are mice and rats. An intense infestation of *O. bursa* in chickens, and even more so, of *O. sylviarum*, gives the plumage a dirty appearance because of the presence of mites, their eggs, and their excrement. A large concentration of mites around the cloaca can cause the skin to crack and form scabs. *O. bacoti* infestation in laboratory rodents can result in debility, anemia, reduced reproduction, and even death (Flynn, 1973).

Source of Infestation and Mode of Transmission: Man is an accidental host. These mites do not colonize permanently in the human skin and, in fact, they stay there for

only a short time. Man becomes infested with *Cheyletiella* spp. as a result of close contact with cats, dogs, or rabbits carrying the mites. The infestation usually results from handling infested animals, but it can also be acquired indirectly because the females can survive off the animal's body for about 10 days. It has been pointed out that this latter mode of transmission could occur when infested cats are allowed to sleep on people's beds. *Cheyletiella* females have been found stuck to fleas and louse flies (Hippoboscidae), and it is believed that this may also be a transmission mechanism in certain hosts. *D. gallinae* and the other avian mites can also cause human infestation as a result of contact with infested birds. *D. sylviarum* is found abundantly on birds' eggs, and the handling of them can often cause infestation. Both avian mites and those of rodents may invade human habitations simply because of the proximity of the animals' nests on roofs, between floors, underneath the dwelling, or in the vicinity. The situation becomes worse when the birds leave their nests or the rodents are eliminated, leaving the arthropods to search for new sources of food.

Diagnosis: In the absence of the parasite itself or epidemiologic background, diagnosis of the infestation in man is very difficult because the condition can be mistaken for pediculosis, scabies, or a flea infestation (Engel *et al*., 1998). For a definitive diagnosis, it is necessary to find the arthropod that caused the lesion. This is important because, even though human dermatitis due to zoonotic mites does not require treatment, it is often recurrent if the source of infestation is not eliminated. Dermatologists recommend that zoonotic mites be taken into account in the differential diagnosis of any cutaneous eruption of unexplained etiology (Blankenship, 1990).

Mites of the genus *Cheyletiella* are too small to be seen by the naked eye, but they can be detected on animals by microscopic examination of impressions, comb residue, or skin scrapings, or by coprologic examination, since they are often ingested. Impressions are made using strips of transparent cellophane tape: the tape is pressed against the animal's skin to capture dandruff and any mites that may be present, and it is then examined under a microscope. Dandruff and mites may be collected by combing or superficial scraping and then studied microscopically. These methods are not as effective in man because the skin has no fur, frequent bathing dislodges the mites (Miller, 1983), and their numbers are limited since they do not reproduce on the human skin. *D. gallinae* and other avian and rodent mites can be seen with the naked eye as a red dot on the skin when they are feeding, or as rapidly running dots in the cracks where they hide. To determine whether they are present in a dwelling, the dust in the home can be vacuumed up, especially in the areas where pets sleep or where birds might enter from outdoors, and examined by flotation: the mites will rise to the surface because they have numerous hairs that trap the air and allow them to float easily in water. Taxonomic differentiation of the species is easy as long as sufficient clues are present.

Control: To prevent human infestation with *Cheyletiella*, pets such as dogs, cats, and rabbits that are suspected of being infested should be treated with appropriate acaricides. In cases of intense infestation, it is necessary to vacuum and apply powdered acaricides in the areas they frequent; however, a veterinarian should be consulted because many of these compounds can be toxic for both man and the pets. To avoid infestations with avian or rodent mites, contact with these animals should be avoided. Repellants should be used on visits to rural areas, or else clothing should protect the body and leave no openings by which the mites could enter. When homes are infested with unwanted birds or rodents, these animals and their nests should be

eliminated, and insecticides or acaricides should be applied as part of the treatment to destroy any surviving arthropods.

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MYIASES

ICD-10 B87 Myiasis

Myiases are conditions caused by the infestation of animal tissues or open cavities by dipteran larvae. The flies that produce myiases are classified as: a) obligate or specific parasites, when the larvae require a host in order to develop; b) facultative or semispecific parasites, when the larvae normally develop in dead tissue (human or animal remains) or decomposing animal or vegetal matter but can also develop in necrotic tissue of live animals (these flies are usually secondary invaders, attracted by fetid odors of purulent or contaminated wounds); and c) accidental parasites, when the larvae normally develop in excrement, decomposing organic matter, or food, and the flies only accidentally invade wounds, the gastrointestinal system, or the urinary tract of live animals or humans. Numerous species of flies can cause myiases, but only the most important ones will be covered in this chapter, namely: *Cochliomyia hominivorax*, *Chrysomya bezziana*, *Cordylobia anthropophaga*, *Dermatobia hominis*, *Cuterebra* spp., *Gasterophilus* spp., *Hypoderma* spp., *Oestrus ovis*, *Rhinoestrus purpureus*, and *Wohlfahrtia* spp. In addition, reference will be made to some of the semispecific and accidental parasites that cause myiases.

1. Myiasis Caused by Larvae of *Cochliomyia hominivorax*

Synonym: Screwworm.

Cochliomyia hominivorax (synonyms *Cochliomyia americana* or *Callitroga americana*), of the family Calliphoridae, is a bluish green fly with three dark bands

on its back that measures about 10–15 mm in length. It is found almost exclusively in the Americas. In 1988, a focus of myiasis appeared in Libya, but the fly was eliminated in May 1991 thanks to an eradication program based on an approach similar to the sterile insect technique used in the US (Barriga, 1997). *C. macellaria*, a species which is morphologically very similar, is not a parasite. Differentiation of these two species used to be a problem, but now they can be distinguished rapidly using low-cost molecular biology techniques (Taylor *et al*., 1996).

The larva of this fly (screwworm) is an obligate parasite that can invade the tissues of any warm-blooded animal. It is one of the main agents of myiasis over an area ranging from the southern US to northern Argentina. This species and *Dermatobia hominis* appear to be the principal obligate agents of myiases in Latin America. *C. hominivorax* causes the largest number and most serious cases of human myiases in the Americas. Animal myiases cause heavy economic losses in terms of cattle, sheep, goats, and equines. Prior to an eradication campaign in southern and southeastern US, annual losses in that country due to animal myiases were estimated at between US$ 50 million and US$ 100 million.

The females of *C. hominivorax* mate only once, and they deposit packets of 12 to 400 eggs, overlapped like roof tiles, on the skin of the host. A single female can produce up to 4,000 eggs. The larvae emerge after 11 to 21 hours, penetrate any preexisting wound, and begin to feed on the surrounding tissue. Between four and eight days later, they fall to the ground, bury themselves about 2 cm deep, and turn into pupae. The adult flies emerge a little less than a week afterwards if the weather is warm and humid, or longer if the climate is cooler. The flies mate within three or four days, and in a few more days, the females begin to lay eggs. In summer the entire development cycle can be completed in just over three weeks, so that several generations of flies can be born in a single season. Adult flies live for about two weeks and feed on plant juices. Females can travel about 50 km from their birthplace under their own power, and they are also carried considerable distances by automobiles on which they alight. These facts suggest that eradication programs based on the sterile insect technique need to cover extensive areas in order to achieve a lasting effect.

In the temperate zones, myiases occur in the hot season, from the end of spring to the beginning of autumn, whereas in the tropical zones, they occur all year long and are more frequent in summer (Amarante *et al*., 1992). The larvae, which are screw-shaped and measure about 12 mm in length, destroy the tissue in which they lodge and become covered by exudate from the wound. The profuse reddish brown exudate from the wound stains the skin, fur, or wool, and attracts other flies of both the same and other species, which deposit more eggs or larvae. The larvae of *C. hominivorax* can invade and produce myiases in all types of accidental wounds regardless of their size, surgical incisions (from castration, dehorning, docking, or other procedures), shearing cuts, umbilical wounds, and even skin abrasions and tick bites. It has been demonstrated that the larvae can penetrate the intact skin of rabbits and guinea pigs. Secondary bacterial infections are common in wounds invaded by the larvae of *C. hominivorax* and aggravate the clinical picture, both by their own action and by the attraction of other flies that are semispecific parasites, which in turn deposit eggs and larvae in the lesion. Larval invasions are not limited to tegumentary wounds; they can also occur in open cavities of the body such as the nostrils, mouth, eye socket, outer ear, and vagina.

The clinical manifestations are severe pain in the affected region and intense pru-

ritus obliging the animal or person to scratch. If the animals are not treated, continuous tissue destruction produces pain and restlessness, which interferes with grazing and leads to weight loss. Sometimes prostration and death ensue, and when the flies are very abundant, the fatality rate can be as high as 20%. The most serious clinical pictures are usually seen in sheep, goats, and equines, which often develop secondary infections.

Human myiases occur in rural populations, especially in areas and at the times when there is an abundance of *C. hominivorax*, which depend mainly on domestic animal hosts in order to reproduce. When myiases are abundant in animals, many cases can occur in man. Human myiasis is clinically similar to that of animals. In addition to the invasion of wounds and ulcers (varicose ulcers of the legs), myiasis also occurs in a furuncular form characterized by a nonmigratory cutaneous nodule. Most of the myiases seen in natural cavities are also due to the larvae of *C. hominivorax.* Invasion of the nasal fossae (rhinomyiasis) is most frequent, and it usually occurs as a complication of ozena. The larvae of *C. hominivorax* often destroy the cartilage and palatine vault, and they can penetrate the nasal sinuses and even the cranial cavity. The ocular form can destroy the eye (Chodosh and Clarridge, 1992).

To prevent this myiasis, care should be taken to keep domestic animals from giving birth during the season when the flies are abundant. The navel of animals born during the hot season should be treated with fly repellents. In addition, castrations, dehorning, docking, branding, and other interventions that leave tegumentary lesions should be avoided during this season. All accidental wounds, whether affected by myiasis or not, should be cleaned and properly treated as soon as possible and covered with an effective repellent or insecticide.

Regional eradication programs based on the sterile insect technique have yielded good results. The technique consists of releasing large numbers of artificially bred males sterilized with gamma rays, which are intended to compete with fertile males in the natural population and mate with the females. Since the females mate only once, they do not become fertilized if they copulate with the sterile males. The first pilot program was initiated in Curacao in 1954 and was successful in eradicating the infestation. The island remained free of the fly until 1975, but then, in the first nine months of that year, there were 261 cases of myiasis, including 14 in humans. The animals most affected were dogs, with 179 cases. The southeastern US was freed of *C. hominivorax* in 1959, as were Puerto Rico and the Virgin Islands in 1974. On the other hand, despite application of this measure, the southwestern US continued to remain infested, especially because of the steady introduction of fertile males from the Mexican side of the border. For this reason, a joint initiative was undertaken with Mexico in 1972 to establish a barrier of sterile males across the isthmus of Tehuantepec. This program has led to eradication of the screwworm in the US and Mexico, and it is expected to extend its impact southward. In 1991, *C. hominivorax* was declared eradicated in Mexico, and campaigns were intensified or initiated in Central America. In 1988, the technique proved to be effective in Africa, when the fly that had appeared in Libya was eradicated (Krafsur and Lindquist, 1996).

The sterile insect campaign is not a universal panacea, and it is very expensive: for example, in the US-Mexico border campaign, some 200 million sterile males were released each week. The campaign must be kept up continuously to prevent the introduction of fertile males or the reproduction of residual local males; otherwise,

the epizootic often reappears. The technique only works with species that can be bred in the laboratory in massive numbers and are still able to mate despite sterilization, and it is only effective when the density of fertile males is low (Reichard, 1999). For this reason, an additional measure has been introduced whereby insecticide-saturated bait is distributed to reduce the natural population of *C. hominivorax* before releasing the sterile males.

2. Myiasis Caused by Larvae of *Chrysomya bezziana*

The fly *Chrysomya bezziana* is a species similar to *C. hominivorax* and produces similar lesions. It is found in the tropical regions of Africa, Asia (India, Indonesia, Philippines, Taiwan), the Pacific islands, and Papua New Guinea. Moreover, climatic simulation studies indicate that it could possibly spread to Australia and the Americas (Sutherst *et al*., 1989). The animals most often attacked are cattle, but it also infests sheep, goats, buffalo, equines, swine, and dogs. The human myiasis is more frequent in India and other parts of Asia than in Africa. Like *C. hominivorax,* this fly deposits its eggs near wounds, ulcers, and natural openings (genitals, nose, labial commissure, eyes). The lesions produced on the face can be deforming, and they are fetid and frequently subject to secondary infections. Invasion of the eye is uncommon, but when it occurs, it can destroy the eyeball in two days (Sachdev *et al*., 1990).

3. Furuncular Myiasis Caused by Larvae of *Cordylobia anthropophaga*

Cordylobia anthropophaga ("tumbu fly" or "mango fly") is another fly belonging to the family Calliphoridae. It is found in sub-Saharan Africa, and a few human cases were reported in Saudi Arabia which were believed to have been autochthonous (Omar and Abdalla, 1992). Imported cases have been seen in persons and dogs from Europe and the US who visited Africa (Jelinek *et al*., 1995). The larvae mature in about one week and abandon the host in order to pupate for three to four weeks and give birth to the adult fly. The dog is the domestic animal most affected, but this fly can infest many other domestic and wild species. *Cordylobia rodhaini*, a species of African fly that attacks man less often, produces more intense and more severe infestations. A case was reported in which 150 *C. rodhaini* larvae were recovered from a single individual. Its main hosts are the antelope and the giant rat (Soulsby, 1982).

4. Furuncular Myiasis Caused by Larvae of *Dermatobia hominis*

Synonyms: Torsalo (Central America), moyocuil (Mexico), berne (Brazil), mucha (Colombia), mirunta (Peru), ura (Argentina, Paraguay, and Uruguay).

Dermatobia hominis is a large fly, about 12–18 mm long, which belongs to the family Cuterebridae. It has an opaque, dark blue, hairy thorax that contrasts with its bright blue abdomen. *D. hominis* is widely distributed in tropical America, from Mexico to Paraguay and northeastern Argentina. Several dozen imported cases have been described in Canada and the US (Sampson *et al.*, 2001). It attacks a wide variety of mammals, both domestic and wild, as well as several avian species, and causes heavy economic losses, especially in the case of cattle.

The fly lives in moist forest and underbrush. Its life cycle begins when the female lays its eggs on the abdomen of a hematophagous insect (any of some 50 zoophilic species), which it captures in flight. This nonparasitic transport relationship is known as phoresy. From 15 to 20 eggs are deposited in this manner, and the incubation period lasts 7 to 10 days. When the insect transporting the incubated eggs comes into contact with an animal, the larvae hatch, penetrate its skin (often via the lesion created by the bite of the carrier insect, but they can also penetrate healthy skin), and a few minutes later reach subcutaneous tissue, where they produce a furuncular lesion with an orifice on the top through which to breathe. This outlet to the exterior facilitates the development of secondary infections. The larvae do not migrate; they live in the animal for a period of 4 to 18 weeks, at the end of which they abandon their furuncles early in the morning and fall to the ground in order to pupate. The pupae remain in the ground for 28 to 77 days before developing into adult flies. They mate 24 hours after emerging, and the female lives only 1 to 9 days, during which it does not eat because it has only a vestigial mouth. As a rule, each lesion contains a single larva, but there may be several furuncles, depending on the number of larvae deposited. In cattle, the preferred sites are the forequarters and the back. In man, the lesions are found most often on exposed parts of the body, such as the scalp, legs, arms, hands, face, and neck. Besides causing myiasis in the skin, the larvae of *D. hominis* can invade the eyelids, eye sockets, and mouth. Such cavity myiases are seen primarily in children.

Cattle and dogs can be afflicted by large numbers of parasitic furuncles. Often, these nodules are invaded by the larvae of other flies or bacteria, giving rise to abscesses. The hides of heavily parasitized animals lose much of their value. It has been estimated that Brazil loses about US$ 200 million a year from lowered meat, milk, and hide production as a result of this myiasis.

In man, pain in the affected areas is intermittent; it is especially intense in furuncular myiasis of the scalp. In some regions, human myiases caused by *D. hominis* can be quite common. In Brazil, for example, 41.3% of 363 people living on a eucalyptus plantation had parasitic nodules. In Venezuela, 104 cases of myiasis caused by this fly have been described. In Panama, several palpebral cases were reported, as well as one cerebral case in which larvae on the scalp penetrated through the fontanelle of a child. The number of larvae invading a given person is variable.

The primary objective of a control program should be to prevent myiases in domestic animals by applying insecticides or repellents. In the event of an infestation, care should be taken to keep the larvae from falling to the ground, where they can then transform into pupae. Larvae on animals can be destroyed by systemic insecticides. However, since the flies cover a large range of territory, a control program needs to cover an extensive area in order to be effective. The success of a program also entails the collaboration of cattlemen and control of animal movement. Use of the sterile insect technique to control and eradicate the fly has been tested in large-scale breeding studies, but this approach has a disadvantage in the case of *Dermatobia* because, unlike *C. hominivorax*, the female mates several times in the course of her life.

5. Furuncular Myiasis Caused by the Larvae of *Cuterebra* spp.

Flies of the genus *Cuterebra* resemble bees and measure 20 mm or longer. Their larvae are obligate parasites of rodents and lagomorphs in North America.

The adult females deposit eggs on vegetation in the habitat of their hosts. The lar-

vae are born at intervals, invade the host via natural cavities or penetrate intact skin, and apparently travel extensively throughout the body. They finally appear as third-stage larvae under the skin, where they form subcutaneous furunculoid nodules. Approximately one month after the initial infestation, these nodules rupture, and the larvae fall to the ground and begin to pupate.

The larvae of *Cuterebra* spp. cause subcutaneous cysts in rodents and lagomorphs. *C. emasculator* often parasitizes the scrotum of mice and chipmunks, destroying their testicles. In addition to their natural hosts, the larvae of *Cuterebra* spp. occasionally invade humans, cats, dogs, and domestic rabbits. In cats, the larvae may be found in subcutaneous pruriginous lesions, frequently in the nape of the neck or the submandibular region. In addition, there have been serious or fatal cases in which the parasite was found in the eyeball or surrounding tissue, trachea, or central nervous system of cats (Glass *et al*., 1998).

In 1989, Baird *et al*. (1989) reviewed 54 human cases in the US, plus an additional 8 cases that had been reported as of mid-2001. Most of these cases involved second- or third-stage larvae that had formed furuncular lesions in the neck, chest, or back, and they occurred at the end of summer or in early autumn. It is unusual to recover first-stage larvae; when this happens, the parasite is found in the vitreous humor or the upper respiratory tract, and the lesions appear at the end of spring or in early summer. The same pattern has been reported in cats. The times of the year when the first-, second-, and third-stage larvae of *Cuterebra* appear would suggest that the parasite migrates through the lungs and the head before maturing in subcutaneous tissue.

6. Furuncular Myiasis Caused by Larvae of *Hypoderma* spp.

This myiasis is caused by the larvae of two fly species, *Hypoderma lineatum* and *H. bovis*, which belong to the family Oestridae. Both are parasites of cattle and are found in the Northern Hemisphere (Canada, the US, Europe, and certain parts of Asia and northern Africa). Parasitized cattle have occasionally been introduced in Australia, South Africa, and several South American countries, but the species did not become permanently established.

The flies resemble bees. In cattle, they lay their eggs on hairs on the lower part of the body, preferentially the feet. *H. lineatum* deposits a row of eggs, and *H. bovis* lays isolated eggs. The larvae are born after two to six days and invade the subcutaneous connective tissue, from which they migrate to the rest of the body. The first-stage larvae of *H. bovis* migrate along the nerves and settle in the epidural fat of the spinal canal. The larvae of *H. lineatum* settle in the submucosa of the esophagus. In both cases, the larvae remain for a while in their respective sites, and then in winter (January and February), they finally migrate to the subcutaneous tissue of the dorsolumbar region, where they arrive as second-stage larvae and mature into third-stage larvae within 10 to 11 weeks. During this time, they form cysts about 3 cm in diameter, with a pore through which to breathe. The larvae spend about 10 months of their 11- to 12-month development cycle inside the animal's body. In their final stage, the larvae emerge through the hole in the cyst, fall to the ground, and pupate. The pupal stage lasts from one to three months, depending on climatic conditions. Once the adult flies emerge, they mate very quickly and begin to lay eggs. The adult flies live only eight days at most.

The animals most affected are calves. Adult animals suffer less, since some resistance is acquired with age. The number of furuncles on a given animal can range from one to hundreds. Secondary infection usually leads to the formation of abscesses. The migration of *H. bovis* larvae in the epidural fat along the spinal canal can produce inflammation and necrosis of the adipose tissue of the periosteum, as well as neurologic alterations. The larvae of *H. lineatum*, in turn, can produce inflammation of the tissue underlying the esophageal mucosa and stenosis of the esophageal tract. An abundance of adult flies causes restlessness in cattle and can provoke stampedes and interfere with their feeding. In some regions, the larvae of *Hypoderma* take a heavy economic toll. Annual losses attributable to this myiasis in cattle have been estimated at US$ 35 million in France, US$ 192 million in the US (in 1956), and UK£ 13 million in Great Britain (Soulsby, 1982). These losses are due to delayed growth, lowered milk and meat production, and damage to the hides.

Man is an accidental and aberrant host of the larvae of *H. bovis*, *H. lineatum*, and, less often, *H. diana* (whose larvae parasitize European deer). Development of the parasite in humans is usually arrested in the first larval stage and rarely reaches the third, or mature, stage. A serologic study of more than 100 cases in France led to the conclusion that the species that most frequently affects man is *H. bovis* (Doby and Deunff, 1982). The myiasis it causes is subcutaneous and only occasionally conjunctival or palpebral-conjunctival. Endophthalmias are rare. The cutaneous forms can be manifested as a serpiginous myiasis, similar to cutaneous larva migrans, or as a subcutaneous myiasis with moving furuncles that appear and disappear. The parasitosis can cause pruritus, restlessness, pain, and stomach upset. Children are affected more frequently than adults. The cutaneous myiasis associated with *Hypoderma* spp. would appear to be less common in humans than those caused by other species; Jelinek *et al*. (1995) found only 1 case in a series of 13 myiases reviewed. Authors have described several cases of eosinophilic syndrome with fever and muscle pain, as well as respiratory, muscular, cardiac, dermal, or neurologic symptoms, in patients who turned out to have myiasis caused by *H. lineatum*. In several of these cases, the diagnosis was made when furuncular lesions appeared, usually in the scalp, and the symptoms disappeared spontaneously after they were excised (Navajar *et al*., 1998; Starr *et al*., 2000). In addition, two cases of cerebral *H. bovis* invasion were observed in human patients (Kalelioglu *et al*., 1989). It is possible that the human parasitosis is more common than has been believed in the past, but that it goes unnoticed.

The use of insecticides or repellents in animals at risk can be successful if they are applied at the appropriate time of year, since the season for adult infestation is relatively brief. Most of the development of *Hypoderma* takes place inside the animal (10 months to a year), and hence the larval phase is a good point at which to attack the fly. Control consists of treating cattle with larvicides at the beginning of autumn to prevent the larvae from completing their development cycle and becoming established under the skin. Treatment at this point interrupts the life cycle of the fly and at the same time avoids damage to the hide. To prevent neurological damage to the animals, the larvicide should not be applied in late autumn, when *H. bovis* larvae have reached the spinal canal. In animals being raised for food, the application of insecticides should take into account the time lapse required between administration of the insecticide and use of the meat or milk. Also, delayed treatment can be given in the spring when the subcutaneous larvae are first noticed; in this case, topical insecticides are used, reaching the larvae through the furuncular orifices.

Several European countries—Cyprus, Denmark, Germany (Bavaria), the Netherlands, and Sweden—have succeeded in eradicating the infestation. Promising results have also been obtained in Ireland, where the infestation rate has been reduced to very low levels.

7. Myiasis Caused by Larvae of *Oestrus ovis* and *Rhinoestrus purpureus*

The adult fly of *Oestrus ovis* is gray and measures 10–12 mm in length. It is larviparous and deposits its larvae in the nostrils of sheep, goats, and, occasionally, man. Its distribution is worldwide, and it is found wherever sheep are raised. *Rhinoestrus purpureus* is similar to *O. ovis* in its morphology and development cycle. The larval forms are obligate parasites of equines—in whose nostrils and larynx they develop—found in Africa, Asia, and Europe.

The first-stage larvae enter the nasal fossae, where they feed on mucus and desquamated cells, and they then move on to the frontal or maxillary sinuses, where they mature. After 2 to 10 months, the mature larvae return to the nasal fossae, where they are expelled by sneezing, fall to the ground, and pupate for four to five weeks. The fly that emerges from the pupa lives for 2 to 28 days. The adult flies are annoying to the animals, and when they are very abundant, they cause the animals to become restless. The larvae cause chronic rhinitis and sinusitis. The morbidity rate in a flock may be very high, but mortality is nil. The most prominent symptom is a mucopurulent nasal discharge. Breathing is sometimes difficult because of swelling of the nasal mucosae. The pathology of this condition has been attributed to the mechanical effect of the size of the larvae and the irritation caused by their spines on the mucosae of the nose, pharynx, and sinuses. Some findings indicate that hypersensitivity, probably IgE-mediated, plays an important role. The examination of human cases, however, has not demonstrated the presence of hypersensitivity in man (Dorchies, 1997).

Human cases of myiasis caused by *O. ovis* have been described in several countries of the world, including Chile, Ecuador, Uruguay, and the US. The parasitosis occurs most often in sheep herders and is also seen in urban dwellers who keep sheep in residential areas (Dar *et al.,* 1980). Man is an accidental and aberrant host, but apparently not an uncommon one. The form for which people most often seek treatment is invasion of the conjunctiva, evidenced by lacrimation and the sensation of a foreign body in the eye. Of 112 sheep herders interviewed in Italy, 80% stated that they had had the infestation at some time, and 54% reported that more than one site had been infected at the same time. The sites where larvae were found most frequently were the larynx (77 times), the conjunctiva (56 times), and the nasal fossae (32 times). They were also found in the ears (1 time). The most common sign was pain, sometimes accompanied by fever and general malaise (Pampiglione *et al*., 1997). In Benghazi, Libya, 80 cases of external ocular myiasis were diagnosed over a two-year period, representing an estimated incidence of 10 per 100,000 population (Dar *et al.*, 1980). In a case in Thailand, eight larvae were recovered from the palpebral conjunctiva (Nacapunchai *et al*., 1998). Human oestriasis is usually a benign condition that lasts only a few days because the larvae cannot develop beyond the first stage in man. Serious cases, with destruction of the eye and perforation of the orbital walls, are rare. In Africa, cases of oral and nasal myiases have been described in which the larvae have entered the nasal fossae and frontal sinuses, causing local-

ized pain, frontal cephalalgia, and insomnia over a period of 3 to 10 days. There have also been reports of invasion of the outer ear (otomyiasis). *R. purpureus* appears to be an uncommon parasite, having been described only once in burros (Zayed, 1992) and once in man (Rastegaev, 1980).

Treatment with modern systemic insecticides is effective against all the larval phases, and, if it is applied annually, it can greatly reduce the populations of these flies at livestock-raising establishments.

8. Myiasis Caused by Larvae of *Gasterophilus* spp.

The three most important species of this genus are *Gasterophilus intestinalis*, *G. nasalis*, and *G. haemorrhoidalis*, which are widely distributed on all continents. The species *G. inermis*, *G. pecorum*, and *G. nigricornis* are found only in the Old World. The normal hosts of these flies are horses and other equines, in which the larvae lodge in the stomach. Larval infestation rates are high in equines in many parts of the world. *G. intestinalis*, which is the most common, deposits its eggs primarily on the lower part of the animals' forelegs; *G. nasalis*, on the submaxillary region; and *G. haemorrhoidalis*, on the lip hairs. The first-stage larvae hatch in two to seven days and are carried to the mouth when the animal licks itself, or they can travel there on their own. From there they invade the oral or lingual mucosa, where they develop for three to four weeks until they become second-stage larvae. They are then swallowed, travel to the lumen, and attach themselves to the mucosa of the stomach, where they remain for 8 to 10 months. It has been estimated that fewer than 1% of the larvae lodge in the glandular portion of the stomach. Finally, when they mature, these larvae are shed in the animal's feces, pupate in the ground for about one month, and give rise to adult flies, which reinitiate the cycle. The adult flies live for only a few days, but since the flies do not all emerge from the pupal stage at the same time, populations of *Gasterophilus* spp. can be present from mid-spring until mid-summer.

Little is known about the effect of stomach infestation by *Gasterophilus* larvae on the health of equines. According to some observations, it can cause anorexia and mild colic. Ulceration of the nonglandular portion of the stomach was the most frequent lesion. Abscesses, rupture of the stomach, and peritonitis can occasionally occur (Soulsby, 1982).

Adult flies frighten and disturb the animals.

Human infestation is apparently rare; only a single case was reported during the period from 1989 to 2001 (Royce *et al*., 1999). The larvae rarely develop beyond the first stage, and only exceptionally do they reach the stomach. The common clinical form is a dermal affliction similar to cutaneous larva migrans, with superficial serpiginous tunnels within the tegument that look like red stripes on the surface of the skin. The lesion is characterized by intense itching. The species that most often attacks man is *G. intestinalis*, and the lesions are almost always located on the extremities. The persons most affected are those who are in close contact with equines.

Since the larvae remain for a long time in the horse's stomach, this stage poses a good point of attack for interrupting the life cycle and reducing the population of *Gasterophilus* spp., but it is difficult to determine the optimum time to administer treatment. For example, in Kentucky, US, it has been found that the second-stage

larvae of *G. intestinalis* continue to arrive in the stomach until April, while the third-stage larvae abandon the host to pupate starting in August. Accordingly, the best time for treatment is May, June, or July (the end of spring and beginning of summer) because two generations can be eliminated at once. However, the third-stage larvae of *G. nasalis* become detached between March and August, while the new second-stage larvae reach the stomach in July. In this case, the treatment needs to be applied in February (winter) to eliminate the previous generation and in August (summer) to eliminate the new generation.

9. Furuncular Myiasis Caused by Larvae of *Wohlfahrtia* spp.

Specific myiases are also caused by the larvae of *Wohlfahrtia vigil* and *W. magnifica*, flies belonging to the family Sarcophagidae. Both species are larviparous.

W. vigil is found in Canada and the US, where its larvae parasitize rodents, lagomorphs, foxes, mink, dogs, and other carnivores, and occasionally man. The adult flies feed on plant nectar. The larvae are deposited in packets, either on the animals or in their vicinity, and they then penetrate intact skin and produce a furuncular lesion. The larvae mature in 7 to 9 days, abandon the animal, and pupate for 10 to 12 days. When the adults emerge 11 to 17 days later, the females lay their eggs, and thus the cycle is completed. *W. vigil* is a pest of mink and fox farms in Canada and northern US. Newborn and young animals are the most vulnerable. In rodents, this fly can cause severe tissue destruction. In humans, the infestation is found only in children who spend time outdoors, in whom it causes small subcutaneous abscesses, irritability, fever, and dehydration.

W. magnifica is found in China, the African and European areas of the Mediterranean, the Middle East, and the Russian Federation. The fly is attracted by skin wounds, where it deposits its larvae, but it also does so in natural orifices of humans, sheep, bovine cattle, and other domestic animals, including fowl (especially geese). The myiasis caused by *W. magnifica* is an important disease of sheep in the southern part of the Russian Federation. Human infestation does not appear to be frequent; during the 1990s, only five cases were reported. The following sites were involved: the eye (one case), vulva (in an elderly woman), orotracheal region (in an elderly intubated man), ear (one case), and scalp (in a child) (Ciftcioglu *et al.*, 1997; Delir *et al*., 1999; Iori *et al*., 1999).

Facultative or Semispecific Myiases

A large variety of dipterans can be facultative parasites of animal and human tissue. These flies, which normally lay their eggs or larvae on decomposing meat or animal or human remains, can sometimes invade the necrotic tissue of wounds in live animals. The larvae of these dipterans do not penetrate healthy skin and rarely invade recent wounds that have been kept clean. Their medical importance lies in the fact that the larvae of some species do not always restrict themselves to feeding on necrotic tissue but can occasionally penetrate deeply and damage healthy tissue. One such species is *Lucilia* (*Phaenicia*) *sericata*, whose larvae do not usually cause serious damage but can sometimes destroy healthy tissue surrounding wounds and can also invade the human nasal fossae in large numbers.

Most of the dipterans that cause semispecific myiases in man belong to the families Sarcophagidae (*Sarcophaga* and *Parasarcophaga*) and Calliphoridae (*Lucilia*, *Phormia*, and *Paraphormia*). The larvae of the latter are agents of "calliphorine myiasis" ("blowfly" or "fleece-fly strike" in Australia), which can cause heavy economic losses in sheep in certain areas. The most susceptible breed is the merino, and the highest incidence rates are in Australia, Great Britain, and South Africa. In hot, humid summers, when the population of calliphorine flies is at its peak, this myiasis often affects the development of sheep and causes losses in both wool and meat production. Invasions by the larvae of these flies can also lead to high mortality. In Australia, the most important flies are *Lucilia cuprina*, *L. sericata*, and several species of the genus *Calliphora*, while in Canada and the US, the prominent species are *Phormia regina* and *Protophormia terraenovae.* The most common site of larval invasion is the ano-vulvar or ano-preputial region, where the skin often becomes excoriated from soft feces and urine, the smell of which attracts the flies. Any accidental or surgical wound can be the site of calliphorine myiasis. According to some authors, a lesion is not required in order for invasion to occur; during hot summers with abundant rain followed by sunshine, the matted wool can become rotten and attract swarms of flies. When the density of calliphorine flies is low, their larvae breed in carcasses or garbage containing scraps of meat. The situation changes when climatic conditions favor a rapid increase in the fly population, at which point the larvae also invade contaminated wounds and damp, dirty wool. The development cycle of these flies can be completed in a few weeks, and, under highly favorable conditions, within a single week. As a result, many generations of flies are born in the course of one season. In areas where calliphorine flies are a problem for sheep, all wounds should be treated immediately and the animals should be protected with larvicides or repellents.

According to reports published in different parts of the world between 1989 and 2001, the most common larvae that produce facultative human myiases belong to the genera *Lucilia*, *Sarcophaga*, *Parasarcophaga*, *Phormia*, and *Paraphormia*. *Lucilia* larvae appear to be the most frequent: of 14 human myiases reported over approximately two years in Brisbane, Australia, 10 were caused by *L. cuprina* and 2 by *Parasarcophaga crassipalpis*, while 2 were unidentified (Lukin, 1989). These myiases, because of their nature, affect wounded, bedridden, or otherwise debilitated people who are unable to take care of themselves. There have been a number of reports of nosocomial infestations caused by *L. sericata*: in the former Czechoslovakia, one case in the tumor of a dying 87-year-old woman, and two cases in the mouth and nose of patients with multiple traumas (Daniel *et al*., 1994); in Korea, one case in the nasopharyngeal tube of a paraplegic patient; in Israel, one case in an extreme premature newborn; and in Spain, one case in the cutaneous orifice of an osteoplastic tibial extension (Mateos *et al*., 1990). Cases have also been reported in apparently healthy individuals, such as a cattle-rancher in Korea who had five larvae in the auditory canal which did not appear to be bothering him, and an urban case acquired in Spain.

The larvae of *Sarcophaga* also appear to be a frequent cause of facultative human myiases. Two nosocomial infestations were described in Spain: one in a 77-year-old woman with radionecrotic wounds and another in an 87-year-old man with dementia (Merino *et al*., 2000). One infestation was reported in Japan, with nine larvae in the eye of a debilitated patient. Also, in Spain, one case of vulvar myiasis in an 86-

year-old woman living in a home for the elderly was reported. In India, 64 cases of myiases in the nasal cavity, hands, and toes of leprosy patients were reported, from whom the larvae of *Sarcophaga haemorrhoidalis*, *Chrysomya bezziana*, *Callitroga americana*, and *Musca domestica* were recovered (Husain *et al*., 1993). Also in India, a case of cutaneous myiasis with *Sarcophaga* sp. and *Chrysomya bezziana* larvae was observed in a drug addict. In Japan, two cases of intestinal myiases caused by *S. peregrina* were reported: one was in an 8-month-old girl with hemorrhagic mucous feces, and the other was asymptomatic. In Morocco, a case of intestinal myiasis caused by *S. haemorrhoidalis* in a 15-year-old girl produced abdominal pain, hematemesis, and vomiting of the larvae (Abkari *et al*., 1999). In Israel, larvae from the same fly were found in the auditory canal of four children, resulting in pain, pruritus, and secretions. A case of *Parasarcophaga argyrostoma* larvae in the gangrenous toe of an elderly man was described in England, and in Japan, an intestinal myiasis caused by *Parasarcophaga crassipalpis* was reported. *Phormia regina* was identified in a case in Pennsylvania and another in Florida, US.

In ancient times, the larvae of *L. sericata, L. illustris*, or *P. regina* were used to get rid of necrotic tissue in wounds. The technique is still being applied successfully using sterilized *L. sericata* larvae with infected wounds that are resistant to antibiotics and difficult to treat with surgery (Fleischman *et al*., 1999). In forensic medicine, the larvae of *Phormia regina*, *L. sericata*, *Eucalliphora latifrons*, *Lucilia illustris*, *Calliphora vicina*, and other flies found on cadavers help to determine the time elapsed since death. Since the identification of some of these larvae is difficult, polymerase chain reaction techniques have been developed for this purpose (Vincent *et al*., 2000).

Accidental Myiases

Accidental myiases are caused by numerous species of flies that normally lay their eggs or larvae on decomposing organic matter and accidentally deposit them on the food or wounds of humans or animals, giving rise to intestinal or cutaneous myiases. Most eggs or larvae ingested in this way are destroyed in the digestive tract, but some of them survive and continue their larval development. The larvae of *Musca domestica*, *Fannia canicularis*, *F. scalaris*, and *Muscina stabulans*, as well as several species of Calliphoridae and Sarcophagidae, can produce intestinal myiases.

Often, the ingested larvae are eliminated in feces without causing any damage or symptoms. In other cases, however, there can be abdominal pain and nausea, and, in very intense infestations, damage to the intestinal mucosa and bloody diarrhea. Myiases have been described in the urinary tract (cystomyiasis), but they are rare. In India, Gupta *et al.* (1983) reported that a bedridden hospital patient had developed a case of urethral myiasis (associated with necrosis of part of the glans) from the larvae of a domestic fly. Cases of urogenital myiasis have also been seen in other parts of the world. These infestations have occurred mainly in immobilized elderly patients suffering from incontinence. In rural areas, there have been cases caused by the larvae of *Fannia* spp., which are frequently found in the vicinity of latrines. In some cases of urogenital myiasis, the larvae do not go beyond the first stage—in other words, they cannot feed or develop ("pseudomyiasis"). In other cases, however, second- and third-stage larvae have been found in the bladder. A urinary myi-

asis caused by *Fannia canicularis* was identified in France. Finally, two cases of cutaneous myiasis caused by *Musca domestica* were described in England, as was a third case, attributed to the same species, in a leprosy patient in India.

Role of Animals in the Epidemiology of the Disease: Animals play an essential role in the epidemiology of the flies that cause obligate myiases; without their animal hosts, the flies could not exist. Man is only an accidental host of these larvae, and in some myiases, such as those caused by *O. ovis* and *Gasterophilus* spp., an aberrant host in which the larvae cannot complete their development. The obligate myiases occur in humans when there is a high incidence of animal myiases, typically in the spring or summer. The victims are usually people who live in rural areas where both the flies and the natural hosts of their larvae are abundant. With the facultative myiases, the role of animals is much less significant—indeed, debatable: it could be argued that most of the flies that produce facultative myiases normally develop in the feces of domestic animals, so that the humans living in the proximity of domestic animals increase their risk of becoming infested with facultative myiases.

Control: Human obligate myiases are controlled by eliminating or reducing infestations in the animal reservoirs. The primary means of achieving this goal is preventive treatment of the animals at risk with insecticides or repellents to keep them from becoming infested, or, once they are infested, curative treatment with insecticides to eliminate the larvae before they abandon the host and begin to pupate. With both animals and humans in areas where myiases are common, any wound should be treated as soon as possible and watched closely until it forms a scar. Particular care should be taken with bedridden patients who have wounds and cannot protect themselves from flies. To prevent the disease in man, both personal and environmental hygiene should be observed, including steps to eliminate the breeding sites of flies.

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PENTASTOMIASES

ICD-10 B88.8 Other specified infestations

Synonyms: Tongue worm infection, porocephalosis, porocephaliasis.

Etiology: There are two genera of pentastomids that are of medical interest: *Linguatula* and *Armillifer*, both of the family Porocephalidae. On rare occasions, *Porocephalus* (a snake parasite, with rodents as intermediate hosts), *Leiperia* (a crocodile parasite, with fish as intermediate hosts), and *Raillietiella* (a lizard parasite, with cockroaches as intermediate hosts) have been mentioned as human parasites.

Owing to the morphological and biological peculiarities of the pentastomids, their taxonomy and phylogenetic status are not yet well defined. On the basis of ultrastructural, embryologic, and genetic studies, they can be considered a class related to the arthropods (Self, 1982). Interestingly, almost all the adult parasites infest a host higher on the phylogenetic scale than the hosts of the larval forms, which suggests that the parasite evolved along with the host. The fact that the reverse is true in the case of certain pentastomids is difficult to explain, however.

In their adult stage, pentastomids are commonly parasites of the respiratory system of reptiles or carnivores, and in their larval stages, of herbivores. However, although their specific hosts seem to be limited, infections have been found in many animals. Except for a few epidemiological studies, human infection by pentastomids is infrequent: only eight cases had been reported in the United States up to 1991 (Guardia *et al*., 1991), and nine cases had been reported worldwide from 1989 to mid-2001.

1. Infection due to *Linguatula serrata*

Synonyms: Linguatuliasis, linguatulosis.

Etiology: *Linguatula serrata* is a linguiform parasite with discreet transverse segmentation. The adult female measures about 10 cm long, and the male barely 2 cm. In its adult form, *L. serrata* lodges in the nasal passages, frontal sinuses, and tympanic cavity of dogs, other canids, and felids, where it ingests mucus and blood. Few cases of adult specimens have been found in man.

The development cycle of the parasite requires herbivorous intermediate hosts, mainly sheep, goats, and lagomorphs. Bovines, deer, equines, swine, and various other mammals can also serve as intermediate hosts. Man is an accidental and aberrant intermediate host. *Linguatula* lays its eggs in the upper respiratory passages of the host, and they are then expelled into the environment by sneezing or splitting, or if swallowed, with the feces. The eggs ingested by the intermediate host with food or water release the first-stage larvae in the intestine; they possess four clawed feet and an apparatus that enables them to perforate the intestinal wall. The larvae migrate through the blood to the internal organs and encyst in the lymph glands, the liver, spleen, lungs, and other organs, where they form small pentastomid nodules that are discovered during the veterinary inspection of meat. Between 250 and 300 days after infection and after some 12 molts within the cyst, the larva reaches the nymph, or infective stage. It is about 5 mm and resembles the adult parasite. The nymph can break the cystic envelope, migrate through the peritoneal cavity, and penetrate different tissues. If a carnivore consumes the tissues or organs of an infected intermediate host, the infective nymph migrates through the stomach and esophagus to the nasopharynx, where after several molts it reaches maturity and begins oviposition.

Geographic Distribution and Occurrence: *L. serrata* is widely distributed throughout the world, but human infection is infrequent. Most cases have been reported in several countries of North Africa, Europe, and the Middle East. In the Americas, human linguatuliasis has been diagnosed in Brazil, Canada, Chile, Colombia, Cuba, Panama, and the US. From 1989 to mid-2001, only one ocular case, in Ecuador, was reported worldwide (Lazo *et al.*, 1999).

The infection rate in dogs is very high in some areas. *L. serrata* was found in 43.3% of stray dogs in Beirut, Lebanon, in 38% in parts of India, and in a high percentage in Mexico City. The highest rates are seen in areas where dogs are fed raw viscera from sheep and goats. Infected dogs have been found in the Midwest and in Georgia, US, but the prevalence rate obtained by coprologic examination was very low (Ehrenford and Newberne, 1981). Data on the frequency of nymphal infection in domestic herbivores are not available. In Lebanon, 4 of 10 goat livers acquired in

randomly selected butcher shops had larvae in the hepatic lymph nodes, and 2 of 10 sheep livers were parasitized. In the US, the principal intermediate hosts seem to be wild rabbits, which have been found infected in several southern and southeastern states (Gardner *et al.*, 1984). A study conducted in eight southeastern states found that 2% of 260 *Sylvilagus floridanus* rabbits had nymphs of *L. serrata*, but the infections were mild (Andrews and Davidson, 1980).

The Disease in Man: Man can become infected by ingesting either eggs or nymphs. When the infection occurs from the ingestion of eggs, the larvae become encapsulated in various organs, where they can survive up to two years. When the larvae die, they are absorbed or the cyst can calcify. The larvae locate mainly in the liver, either below Glisson's capsule or in the parenchyma and, to a lesser extent, in the mesentery and intestinal wall. The encysted nymphs do not produce clinical symptoms, and the infection is almost always discovered during surgery, radiological examination, or autopsy. Clinical cases of prostatitis, ocular infection (anterior chamber of the eye), and acute abdomen have been described; their origin is a parasitized, inflamed lymph node adhering to the intestinal wall. The "halzoun" and "marrara" syndromes (infection of the human nasopharynx) are attributed to infection caused by the nymph of *L. serrata* ingested with the raw or undercooked liver or lymph glands of infested goats and sheep. Halzoun occurs in Greece, Lebanon, and Turkey, and marrara in Sudan. The symptoms appear a few minutes to a half-hour after the infective food is eaten. The variation in the incubation period probably depends on the place where the nymphs are released from their cysts, since the ones that are swallowed require more time to migrate to the tonsils and nasopharyngeal mucosa than the ones that become free in the mouth. The most prominent symptoms are throat irritation and pain. Sometimes there is congestion and intense edema of the region, which may extend to the larynx, eustachian tube, conjunctiva, nose, and lips. Lacrimation and nasal discharge are common. At times, there is also dyspnea, dysphagia, vomiting, headaches, photophobia, and exophthalmia. The most serious symptomatology is believed to occur in persons sensitized by visceral infections with *L. serrata*. The course of the disease is rapid and benign. About half of the patients recover in less than one day; in others the illness may last one to two weeks.

The Disease in Animals: The adult parasite causes a mucopurulent nasal catarrh, with sneezing, copious nasal discharge, and sometimes epistaxis in dogs. However, in mild infections no lesion is found in the nasal conchae. Larval infection in domestic herbivores and omnivores (intermediate hosts) is asymptomatic. Only heavy parasite burdens can damage the affected organs.

Source of Infection and Mode of Transmission: The natural reservoirs are wild and domestic canids and, rarely, felids. Carnivores acquire the infection by ingesting viscera and tissues of infected intermediate hosts. In endemic areas, the cycles between dogs and goats and between dogs and sheep are of special interest. Hunting dogs become infected when they catch infected lagomorphs. In the wild cycle, the infection circulates between wild herbivores and their carnivore predators. Herbivores become infected by ingesting pasture contaminated with feces or nasal secretions of the canids.

Man acquires the visceral form by consuming vegetables or water contaminated

with parasite eggs shed with the fecal matter, saliva, or nasal discharge of dogs or other definitive hosts. Man contracts halzoun or marrara by consuming raw liver or lymph nodes from sheep, goats, or other infected domestic herbivores.

Diagnosis: The visceral form (small pentastomid nodules) caused by nymphs is rarely diagnosed in living persons or domestic animals, except during surgery. X-rays showing calcified cysts may arouse suspicion of the infection's presence. Specific diagnosis is effected by identification of the nymph in a biopsy specimen. Histopathological examination reveals a granulomatous reaction with multiple eosinophilic abscesses, at the center of which degenerated nymphs are found. In very old cases, there may not be pathological findings around the calcified cysts. In cases of halzoun or marrara, the nymph should be obtained for identification. In dogs with suspicious nasal catarrh, diagnosis can be confirmed by detecting eggs in the nasal secretion or feces.

Control: Visceral infection from ingestion of the eggs can be prevented by guarding against contamination of untreated water or raw food with carnivore depositions and washing hands carefully before eating. Halzoun and marrara or nasal infection with the adult parasite can be prevented by not consuming raw or undercooked viscera. Likewise, dogs must not be fed the raw viscera of goats, sheep, or other herbivores.

2. Infection due to *Armillifer* spp.

Etiology: *Armillifer armillatus* is the agent of this infection. Human infection by *A. moniliformis* (three cases in China, the Philippines, and the Indonesian island of Java) and by *A. grandis* has been reported rarely. In 1996, a local Chinese journal described the first human case of infection with larvae of *A. agkistrodontis*. These pentastomids have a cylindrical body and well defined segmentation. In the adult stage, they live in the respiratory tract of snakes. The pre-adult stages are found in rodents, livestock, and many other animals, including man.

The life cycle of *Armillifer* is similar to that of *Linguatula*, but the definitive hosts are snakes and the intermediate hosts are rodents and other wild mammals. The female of *Armillifer* deposits eggs in the respiratory cavities of snakes, and the eggs are expectorated or swallowed and then eliminated with the feces. In the cases that are known, the life cycle of the other species is similar (for example, *Porocephalus crotali* in the rattlesnake).

Geographic Distribution and Occurrence: *A. armillatus* and *A. grandis* are African species; *A. moniliformis* is found in Asia, and *A. agkistrodontis* has been described in China. Armilliferiasis occurs mainly in West Africa (Nigeria, Democratic Republic of Congo) and South and Southeast Asia; it seems to be infrequent in eastern and southern Africa, and no cases have been diagnosed in the Americas. Encysted larvae were found in 22.5% of adults autopsied in a hospital in Kinshasa, Democratic Republic of Congo, in 8% of the autopsies in Cameroon, and in 1.4% of the radiographs taken in a university hospital in Ibadan, Nigeria. In addition, autopsies found a 45.4% infection rate in Senoi natives in Malaysia. The most frequent localizations are the liver and lungs. Between 1989 and mid-2001, eight cases were described in the world: one in Benin during a diagnostic laparoscopy, one

fatal case in France, three cases of abdominal calcification and one fatal case in Nigeria, one case in the autopsy of a Nigerian in Canada, and one case of *A. agkistrodontis* in China. The three cases of calcification in Nigeria were found during radiographic examination of 214 patients, thus revealing a prevalence of 1.4% in this population (Nzeh *et al.*, 1996).

The Disease in Man: Man is infected only with the larval forms; no cases of infection caused by the adult are known. The infection is similar to the visceral form of linguatuliasis and generally asymptomatic. The infected person usually harbors few nymphs (from 1 to 12). Severe infections can give rise to serious illness, especially when the larvae lodge in vital organs where they can produce multifocal abscesses, tumors, or obstruction of ducts. In the case in China, high fever, abdominal pain, diarrhea, moderate anemia, eosinophilia, hepatosplenomegaly, and polyps in the colon were observed. In the ocular case, the patient complained of pain, conjunctivitis, and vision problems. The autopsy of the Nigerian in Canada, in which death was due to a longstanding infection, found nodules in the liver, lungs, pleura, and peritoneum, but there was no inflammatory or degenerative reaction around the nodules. In the case of an 18-year-old woman in Nigeria, the patient suffered from fever, dizziness, weakness, jaundice, hypotension, and a confused mental state. She died shortly after being admitted, and the autopsy revealed disseminated infection encompassing the thoracic and abdominal serous membranes and internal organs (Obafunwa *et al.*, 1989). The diagnostic laparoscopy of a woman from Benin who had abdominal pain for 10 years found hundreds of calcified masses 1 to 2 cm in diameter in the abdominal cavity. Microscopy of the nodules revealed questionable remains of parasites, but the X-ray showed crescent- or horseshoe-shaped calcifications that were attributed to *Armillifer* (Mulder, 1989).

The Disease in Animals: Nonhuman primates are also accidental hosts of the infection. The larvae of *Armillifer* spp. are found mainly in Old World primates and less commonly in those of the Americas. The infection is usually asymptomatic.

Source of Infection and Mode of Transmission: The reservoirs and definitive hosts of *Armillifer* spp. are snakes, probably including all members of the families Boidae and Viperidae (Self, 1982). Snakes become infected when they ingest wild mammals infected with the nymph.

Man contracts the infection by consuming water or vegetables contaminated with eggs eliminated in the feces or saliva of infected snakes, by consuming raw or undercooked snake meat, or by placing hands to the mouth after handling contaminated snake meat. The other intermediate hosts also become infected by ingesting the parasite eggs. *Armillifer* eggs are very resistant to environmental factors.

Diagnosis: Some cases can be diagnosed by radiographic examination, which reveals the calcified, half-moon-shaped larvae. In the overwhelming majority of cases, however, the encapsulated nymphs of the pentastomids are found during autopsies or laparotomies performed for other reasons. Jones and Riley (1991) identified a protein of *Porocephalus crotali* that combined with rat immune serum in the Western blot test; an enzyme-linked immunosorbent assay can thus presumably be designed for the diagnosis of pentastomiasis.

Control: Preventive measures for humans consist of observing the rules of food

hygiene: not consuming suspect water or raw vegetables, and washing the hands after handling suspect meat and before eating.

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TICK INFESTATIONS

ICD-10 B88.8 Other specified infestations

Etiology: The agents of these infestations are various species of the genera *Argas*, *Amblyomma*, *Boophilus*, *Dermacentor*, *Haemaphysalis*, *Hyalomma, Ixodes*, *Ornithodoros,* and *Rhipicephalus*. Man is not affected by specific ticks, but can occasionally be infested by ticks of other vertebrates that transmit various infections (Table 4). Ticks are divided into two groups: the family Argasidae, comprised of soft ticks whose bodies are covered by a coriaceous tegument, with the mouthparts located on the ventral surface, and the family Ixodidae, comprised of ticks which have an enlargement of the shield-shaped cuticle on their backs, and mouthparts on the anterior end. That shield covers the entire back in the males, but just the anterior half of the back in females, to permit their bodies to engorge while feeding.

The only soft ticks that are important in human medicine are those of the genus

TABLE 4. Ticks that infect man, and organisms and infections they transmit.

Tick	Transmission area	Organism transmitted
Amblyomma americanum	Southern US and Mexico	*Francisella tularensis* *Rickettsia rickettsii* *Ehrlichia* spp.
Amblyomma cajennense	Texas (US) to tropical South America	*Rickettsia rickettsii*
Amblyomma hebraeum	South Africa	*Rickettsia conorii*
Amblyomma triguttatum	Australia	*Coxiella burnetii*
Amblyomma variegatum	Caribbean	*Rickettsia africae*
Boophilus decoloratus	South Africa and tropical Africa	*Rickettsia conorii* Bunyaviruses of the tick-borne hemorrhagic fevers
Dermacentor spp.	Asia	*Rickettsia sibirica*
Dermacentor andersoni	Western Canada and US	*Francisella tularensis* *Rickettsia rickettsii*
Dermacentor marginatus	Siberia	Flaviviruses of the tick-borne arboviral encephalitides[a]
Dermacentor reticulatus	Siberia	Flaviviruses of the tick-borne arboviral encephalitides[a]
Dermacentor variabilis	Western Canada, US, and Mexico	*Francisella tularensis* *Rickettsia rickettsii*
Haemaphysalis spp.	Asia	*Rickettsia sibirica*
Haemaphysalis bispinosis	Southern China	*Borrelia burgdorferi*
Haemaphysalis leachi	South Africa	*Rickettsia conorii*
Haemaphysalis spinigera	India	Flaviviruses of the tick-borne arboviral encephalitides[a]
Hyalomma aegyptium	South Africa	*Rickettsia conorii*
Hyalomma anatolicum	Eurasia and South Africa	Bunyaviruses of the tick-borne hemorrhagic fevers
Hyalomma excavatum	Somalia	Bunyaviruses of the tick-borne hemorrhagic fevers
Hyalomma impeltatum	Somalia	Bunyaviruses of the tick-borne hemorrhagic fevers
Hyalomma marginatum	Eurasia and South Africa	Bunyaviruses of the tick-borne hemorrhagic fevers
Ixodes cookei	Eastern Canada and US	Flaviviruses of the tick-borne arboviral encephalitides

TABLE 4. Continued.

Tick	Transmission area	Organism transmitted
Ixodes granulatus	Southern China	*Borrelia burgdorferi*
Ixodes holocyclus	Australia	*Rickettsia australis*
Ixodes ovatus	Japan	Virus of tick-borne Asian encephalitis
Ixodes pacificus	Western US	*Borrelia burgdorferi*
Ixodes persulcatus	Asia, northern China, eastern Russian Federation	*Borrelia burgdorferi* *Ehrlichia* of the *Phagocytophila* group Flaviviruses of the tick-borne arboviral encephalitides
Ixodes ricinus	Europe	*Babesia divergens* *Borrelia burgdorferi* *Ehrlichia* of the *Phagocytophila* group Flaviviruses of the tick-borne arboviral encephalitides
Ixodes scapularis (I. dammini)	Central and eastern US	*Babesia microti* *Borrelia burgdorferi* *Ehrlichia* spp.[a]
Ornithodoros hermsi	US	*Borrelia recurrentis*
Ornithodoros hispanica	Africa	*Borrelia recurrentis*
Ornithodoros moubata	Africa	*Borrelia recurrentis*
Ornithodoros rudis	Latin America	*Borrelia recurrentis*
Ornithodoros talaje	Latin America	*Borrelia recurrentis*
Ornithodoros tholozani	Middle East	*Borrelia recurrentis*
Ornithodoros turicata	US	*Borrelia recurrentis*
Rhipicephalus appendiculatus	South Africa	*Rickettsia conorii*
Rhipicephalus sanguineus	Mediterranean and South Africa	*Ehrlichia* spp. *Rickettsia conorii*

[a] Confirmation needed.

Ornithodoros, which transmit the relapsing fevers in man caused by strains of *Borrelia recurrentis*, and several species of *Argas*, in particular those of chickens, pigeons, and other birds that attack man when they cannot find their natural host. The species of *Ornithodoros* that infest man live hidden in the ground, in tools and equipment, and in the cracks of shack or cabin walls, and emerge at night to suck blood from people or chickens that take shelter there. The females measure 7–8 mm in length before feeding and up to 11 mm immediately thereafter; they produce groups of 20 to 100 eggs on alternate days, for a total of 500 to 2,000 in a lifetime. After approximately eight days at 30°C, the eggs hatch and hexapodal larvae, which do not feed, emerge and molt into nymphs in four days. The nymphs that go through four stages molt into adult males; those that go through five stages molt into adult females. Each nymph has one blood meal lasting 20–25 minutes. Adult specimens emerge about four months after oviposition. The female mates and produces eggs 10

to 15 days after each blood meal, and can mate up to 40 times before dying. Also, more than half of the females can survive between 9 and 56 months without feeding. The cycle of *Argas* is similar to that of *Ornithodoros*, but the larvae feed by day as well as by night and can remain attached to the host's skin, sucking blood, for several days.

Among the hard ticks, the species of the genera *Amblyomma*, *Boophilus*, *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Ixodes,* and *Rhipicephalus* are important in human medicine. The life cycle of all these ticks is similar, with small variations among the genera. The female produces several thousand eggs at a time for a few days, and then dies. Hexapodal larvae emerge from the eggs; they measure about 1 mm in length, feed on blood for a few days, and molt into nymphs a few days thereafter. Similarly, the nymphs feed on blood and molt into adults. The adults mate, the female sucks blood in amounts that can exceed 10 times her body weight for several days—an engorged hard tick is the size of a pea—and falls to the ground, seeks out a protected place, and begins to produce eggs. Hard one-host ticks remain with a host from the larval stage until adulthood; two-host ticks remain with one host during the larval and nymph stages, but molt on the ground and the adults have to seek out another host; three-host ticks molt on the ground and need a different host in each stage—larva, nymph, and adult. These differences are important in the spread of disease and the design of tick control plans.

Geographic Distribution and Occurrence: The transmission areas of tick-borne infections are shown in Table 4. The distribution of the ticks themselves is diverse; those of the genus *Amblyomma* are mainly parasites of small and large mammals distributed throughout the tropical and subtropical areas of the Americas and sub-Saharan Africa. Ticks of the genus *Boophilus* are parasites of cattle, and, exceptionally, of other herbivores, and are distributed in tropical to temperate zones throughout the world. Human infection is exceptional. Ticks of the genus *Dermacentor* are parasites of rodents and large mammals ranging from the tropical zone of Latin America to Canada. Ticks of the genus *Haemaphysalis* are parasites of small mammals and birds and are found throughout the world. Those of the genus *Hyalomma* are mainly parasites of domestic animals found in the Old World below the 45th parallel North. Ticks of the genus *Ixodes* are parasites of birds as well as large and small mammals and are distributed worldwide. *Rhipicephalus* are ticks of a variety of African and Eurasian animals; only *Rhipicephalus sanguineus* is distributed worldwide.

Humans can be infested by 12 species of Argasidae (*Argas* and *Ornithodoros*) and 22 species of Ixodidae (4 of the genus *Amblyomma*, 7 of *Dermacentor*, 3 of *Haemaphysalis*, 2 of *Hyalomma,* and 6 of *Ixodes*) (Estrada-Pena and Jongejan, 1999). In the US, 44 species of ticks have been found on humans: 11 species of soft ticks and 33 of hard ticks. But four of the former were acquired outside the country and are not species native to the US. The most common were *Amblyomma americanum* in the south and near the Atlantic Ocean; *Dermacentor variabilis* and *Ixodes scapularis* in the east; *Dermacentor andersoni* in the west; *Ixodes pacificus* near the Pacific; and *Ornithodoros* spp. mainly in the west (Merten and Durden, 2000). North Carolina reported human infestations with *Otobius megnini, Amblyomma maculatum*, *Haemaphysalis leporispalustris*, *Ixodes cookei*, *Ixodes dentatus,* and *R. sanguineus*. *O. megnini* was the first specimen of this species found in North Carolina in over 50 years (Harrison *et al*., 1997).

Since tick infestations in man are occasional, their frequency is difficult to assess. In one locality in Italy, during 1995 and 1996, 240 infested individuals were found, with an average of 1.3 ticks per person; 89% were infested with *Ixodes ricinus* in all stages; 10% with *R. sanguineus* nymphs and adults; and 1% with *Dermacentor marginatus* adults. Eleven percent of the cases occurred in children, 26% in students, 22% in workers, and 24% in retired persons. During the period studied, the prevalence of bites was 5 per 1,000 residents (Manfredi *et al*., 1999). A report from a medical school in the state of Georgia, US, indicates that 521 infestations were recorded in two and a half years, with an average of 1.3 ticks per person (Felz and Durden, 1999). In Chile, 2.2% of 1,384 patients referred to a university clinic for "spider bites" between 1955 and 1995 really had tick bites.

The Disease in Man: Ticks cause damage directly by biting and by sucking blood, since they cause allergic reactions by injecting toxins and transmit infections. It has also been found that ticks cause a depressed immune response (Barriga, 1999), but the importance of that is probably minimal. It may be that the direct damage ticks cause is slight in human beings because the majority of infestations are due to a single arthropod and the patient does not notice it. The case of *Amblyomma testudinarium* of Japan is noteworthy, since it caused infestations with more than 100 larvae (Nakamura-Uchiyama *et al*., 2000). The mouthparts that remain in the wound when the tick is removed can cause a granuloma that looks like a pustule and lasts for several weeks. Despite the fact that *O. megnini*, the ear tick of many animals, is exceptional in man, cases of otocariasis in man are described with some frequency (Indudharan *et al*., 1999).

Ticks are generally not included among the arthropods that cause allergies; however, there are reports of severe allergic reactions. For example, symptoms have been reported ranging from erythematous reactions to ulcerative lesions caused by *Argas reflexus* (pigeon tick) (Veraldi *et al*., 1998), very extensive urticarias, caused particularly by *Argas* (Basset-Stheme *et al*., 1999), cases of anaphylaxia caused by the genera *Argas* and *Ixodes* (Lavaud *et al*., 1999), and even cases of anaphylactic shock caused by *I. ricinus* (Moneret-Vautrin *et al*., 1998).

A paralysis caused by the female of certain ticks feeding on their hosts has been described in both animals and humans; approximately 20 species have been identified: *D. andersoni* and *D. variabilis* in Canada and the US; *Haemaphysalis*, *Hyalomma,* and *Ixodes* in Europe; *Ixodes* and *Rhipicephalus* in South Africa; *Ixodes holocyclus* in Australia; and *Argas persicus* in chickens in many countries (Barriga, 1997). While it is suspected that the paralysis is due to a toxin, it has been identified only in the case of the Australian tick *I. holocyclus*. Grattan-Smith *et al*. (1997) described six cases of paralysis caused by ticks in Australian children. The patients experienced an ascending symmetrical flaccid paralysis that causes respiratory paralysis after about a week; the illness ends when the arthropod is removed, but recovery is slow. In the state of Washington, US, a review was conducted of the 33 cases (with two deaths) reported between 1946 and 1996 (Dworkin *et al*., 1999).

Transmission of infection is the most serious concern in connection with tick infestation of humans. Walker (1998) conducted a review of the problem in the US, and Benenson (1995) conducted a worldwide review. Table 4 presents a summary of the state of knowledge up to the year 2000.

The Disease in Animals: The disease in animals has the same four pathogenic components as the disease in man. Since the number of ticks that attack a single animal can be very high, inflammation, pain, and pruritis are intense, due either to the trauma or hypersensitivity, and distract the cattle from feeding, in addition to causing weight loss. Also, the wounds caused by the ticks can ruin the skins for industrial use and attract fly attacks that result in myiasis. The sucking of blood can be significant when the infestation is intense and can also promote weight loss, since the cattle have to expend energy to replace the blood loss. The combined effect of these factors is often called "tick worry." Paralysis caused by ticks is no longer a widespread problem in cattle, as it was 70 years ago, but cases are still reported regularly in the scientific publications. With respect to the transmission of disease, ticks play a role as important for animals as mosquitoes play for humans. Some of the most severe cattle diseases are tick-borne, such as babesiosis (see chapter on Babesiosis), theileriosis, cowdriosis (hydropericardium), and anaplasmosis (Uilenberg, 1997).

Source of Infestation: The source of infestation is the environment contaminated with ticks; in the case of hard ticks, the vegetation where the hungry larvae are found in large numbers; in the case of soft ticks, the dwellings with cracks where they can find shelter during the day. While infested animals are the source of contamination of the environment, they are rarely a direct source of infection for man or other animals.

Diagnosis: Diagnosis is made by removing and studying the tick. Studying them should not be difficult because even the tick larvae measure more than 1 mm, and they are red or dark after feeding. However, the tick is often located on parts of the body where the infested person cannot see it, including behind the ears, where even the doctor can miss it if he or she is not specifically looking for it. When removing a tick, it is important to extract the mouthparts from the skin to prevent the formation of granulomas; to ensure this, the body must be pulled continuously for one minute, without excessive force, in a direction perpendicular to the patient's skin, until the grip is loosened. It is advisable to remove the tick with tweezers or a plastic sheet to avoid contact with its blood if it should explode, since the fluid may contain pathogenic organisms. Taxonomic identification is rarely necessary but, if it is desired, the specimens should be packaged in 70% alcohol and sent to the Department of Agriculture or university veterinary services.

Control: Control of animal ticks is based essentially on the periodic application of acaricides to animals at risk for infestation. An inevitable consequence of this method is the development of strains of ticks resistant to the acaricide. This situation is common in cattle-raising countries with high rates of tick infestation, such as Brazil and South Africa. Modification of the environment to make it unsuitable for the proliferation of ticks is complicated, and not enough is known about their ecology to ensure success. A large number of biological control experiments have been carried out employing the natural enemies of ticks (Samish and Rehacek, 1999), but practical solutions have not been found. Many experiments have also been conducted in an attempt to develop breeds of cattle with a natural resistance to these arthropods, but, despite encouraging results, a meaningful solution has not been found. In an attempt to increase the host's resistance, Australian investigators devel-

oped a vaccine against the *Boophilus microplus* tick; this inhibits by about 75% the fertility of the ticks that feed on vaccinated animals. However, in the short term, the ticks continue to bite and transmit infections; over the long term, that reduction in fertility could be insufficient to decrease the proliferation of arthropods in the pasturelands. The European Union supports a project for the integrated control of ticks and tick-borne disease, with the objective of increasing livestock productivity through the control of ticks, vaccination, and the comprehensive diagnosis of the diseases (Jongejan, 1999). Also, techniques involving remote sensors and geographic information systems are starting to be used to help control these pests (Thomson and Connor, 2000).

From the standpoint of human infestations, attempts are rarely made to eliminate ticks from an entire area—although it could be tried in the endemic area for Lyme disease in the US. Rather, efforts are directed at protecting hunters and tourists who enter areas populated with ticks. For this, it is sufficient to wear clothing that covers the body completely, including high boots with pants legs closed around the boot tops. The use of repellents is also recommended. DEET (N, N-diethyl-m-toluamide) is an excellent insect repellent, although less effective against ticks than permethrin. The concomitant use of both is particularly effective (Mafong and Kaplan, 1997). The US Army recommends this combination for soldiers on maneuvers.

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TUNGIASIS

ICD-10 B88.1 Tungiasis [sandflea infestation]

Synonyms: Chigoe, jigger flea, burrowing flea, sand flea, dermatophiliasis.

Etiology: The agent of this infestation is *Tunga (Sarcopsylla) penetrans*, a small flea. The ovigerous female is an obligate parasite of warm-blooded animals, including swine, man, nonhuman primates, and dogs. It is easy to identify because it is small (about 1 mm long), it does not have pronotal or genal combs, and it has an angular head.

The fertilized female becomes encrusted in the skin of the host, where she feeds continuously. Her abdominal segments gradually enlarge over a period of about two

weeks until she reaches the size of a pea (approximately 5 mm in diameter). As she increases in size, the host epidermis surrounds and encloses her in an excrescence similar to a wart that encloses inflammatory cells. This formation usually ulcerates and can develop secondary infections. Meanwhile, the female expels her eggs through an orifice on top of the excrescence. If the eggs fall on sandy soil, the larvae are born in three or four days. These larvae molt twice within 10 to 14 days and are transformed into pupae that bury themselves in the soil for another 10 to 14 days. At the end of the pupal stage, the adult fleas emerge. The female lays about 200 eggs and then dies. Both the young males and females feed on the blood of animals. After mating, the male dies and the female penetrates the skin of an animal and reinitiates the cycle with oviposition.

Geographic Distribution and Occurrence: *T. penetrans* is believed to be native to the tropical and subtropical regions of Central America, the Caribbean, and South America. It was first reported in the American tropics in 1526 and in Africa in 1732. It was probably carried from America to Africa in the seventeenth century and reintroduced in 1872 by a British ship that arrived from South America and unloaded its sand ballast on the beaches of Angola. Whether by this means or because some members of the crew were infested with *T. penetrans*, the flea was introduced into Angola. From there it spread through the entire western coast of Africa and ultimately reached eastern Africa and Madagascar. Outside Africa and the Americas, *T. penetrans* is present in western India and Pakistan, where it was probably introduced by workers returning home from Africa (Connor, 1976).

Thus, infestations occur in Central and South America, the Caribbean, tropical Africa, India, and Pakistan (Lowry *et al*., 1996). To cite examples from studies carried out near the end of the twentieth century, infestations were reported in 11 (25%) of 44 children examined in the Republic of the Congo (Obengui, 1989); 49 (22.5%) of 280 in Nigeria (Nte and Eke, 1995); 32 (31.4%) of 102 in the West Indies (Chadee, 1994); and, in a subsequent report, 267 (20.4%) of 1,307 in the West Indies (Chadee, 1998). By contrast, in the rest of the world the infestation is so rare that individual cases are worthy of publication. Between 1989 and mid-2001, 1 case each was reported in Australia, Brazil, Chile, Denmark, France, Germany, New Zealand, and Switzerland; 2 cases were reported in Great Britain, 2 in Israel, 5 in Italy, 4 in Mexico, 2 in the Netherlands, and 6 in the US (in addition to 14 reported previously) (Sanusi *et al*., 1989). In addition, Caumes *et al*. (1995) found 16 cases in French nationals who had traveled abroad, and Matías (1989) reported an epidemic of unknown magnitude in Rio Grande do Sul, Brazil. In all these cases except Brazil and Mexico, the infestation was contracted outside the country. In Mexico, the last cases of human tungiasis prior to those mentioned above were reported in 1948; authors believe that those 4 new cases are an indication that the parasite is reappearing in that country.

In some regions of Africa, human *T. penetrans* infestation can reach very high prevalence rates. In a village in the state of Lagos, Nigeria, 41.5% of 373 children 6 to 14 years old were found to be harboring the fleas between their toes. Prevalence declines with age, probably because the skin is thicker and also because footwear is used more often (Ade-Serrano and Ejezie, 1981).

Little information is available about the frequency of infestation in animals. Outbreaks have been described in Tanzania and the Democratic Republic of Congo

among swine (Cooper, 1967; Verhulst, 1976), and in French Guiana, among dogs (Rietschel, 1989).

The Disease in Man and Animals: The flea usually penetrates the human epidermis on the sole of the foot, the toes, under the edge of the toenails, and in the interdigital spaces, but it can lodge in any exposed part of the body. Upon penetration, the insect produces a mild but persistent pruritus and later, as it increases in size, a chronic proliferating inflammation that completely surrounds the site, except for a small orifice on the top. Ulceration and secondary infections are common. When the flea finally lays its eggs, its body collapses and is expelled by tissue reaction, usually in the form of a draining abscess, leaving behind a crateriform ulceration. At first, the lesion looks like a black spot on a taut area of skin, but later it assumes the appearance of a wart, then an ulcer, and finally it turns into a small oozing abscess. The lesions originated by *Tunga* sp. offer favorable conditions for secondary infections. A study conducted in the West Indies found 7 different bacteria (*Streptococcus pyogenes*, non-group A beta-hemolytic *Streptococcus*, *Klebsiella aerogenes*, *Enterobacter agglomerans*, *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus* sp.) in infections associated with *Tunga* lesions (Chadee, 1998). In Senegal, 11 cases of tetanus infection were found in 44 cases of tungiasis (Obengui, 1989).

In Nigeria, the most common symptoms seen in 49 children with tungiasis were pruritus and ulceration. In all cases, the infestation was in the feet, but no case had been considered serious enough to take the child to a clinic (Nte and Eke, 1995). The pain is particularly intense when the flea penetrates under a nail. Usually only one or two lesions are found on a single individual, but sometimes there can be hundreds. In a series of 102 patients, the highest prevalence of infestation was found in the groups 5 to 9 years of age, 10 to 14, and over 55, with averages of 9, 5–6, and 12 fleas per person, respectively (Chafee, 1994).

In the outbreak among swine in Tanzania, infestations were observed on the scrotum, feet, snout, and teats, but they had not caused any marked inflammation, pruritus, or pain (Cooper, 1967). The outbreak in the Democratic Republic of Congo was characterized especially by agalactia in the sows and consequent death of the suckling pigs, which could not feed because the intense concentration of *T. penetrans* in the maternal nipples compressed or obstructed the lactiferous ducts (Verhulst, 1976).

Source of Infestation and Mode of Transmission: *T. penetrans* is found primarily in dry, sandy places, inside and around precarious human dwellings, and in pigsties, stables, and hen houses. Humans contract tungiasis by walking barefoot in soil containing fleas that originated from infested dogs or swine. Dogs, and sometimes swine, can carry the infestation inside huts with earthen floors. Conversely, man can introduce the flea into the animal environment.

Diagnosis: In areas where *T. penetrans* is common, diagnosis can be based on the finding of the characteristic lesions. Specific diagnosis can be made by extracting the flea from the skin and examining it microscopically.

Control: The application of pesticides (insecticides, development regulators, hormonal analogs, etc.) in contaminated environments can eliminate the source of infestation. The application of pesticides on infested animals can eliminate the

source of the infestation. Flea control has been greatly facilitated by the development of new insecticides and chitin formation inhibitors, which are now being used systemically in domestic animals. Humans can protect themselves individually by wearing shoes. However, this simple preventive measure is difficult to apply because of the low economic level of the population and the tropical climate in affected regions. Indeed, it has been recommended for the control of the ancylostomiases for more than 70 years, so far with very little effect.

Tungiasis by itself is a mild condition; the risk lies in secondary infections. For that reason, the flea should be extracted and the wound should be treated with disinfectants and kept clean until a scar forms.

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ZOONOTIC SCABIES

ICD-10 B86 Scabies

Synonyms: Scabiosis, mange, sarcoptic acariasis, sarcoptic itch, seven-year itch.

Etiology: The agent of human scabies is *Sarcoptes scabiei* var. *hominis*, an oval mite. The female measures up to 450 μm by 350 μm and the male, up to 240 μm by 200 μm. This species has varieties that infest some 40 species of mammals, from primates to marsupials (Elgart, 1990). By and large, each variety is strongly host-specific, although some can infest other species and cause temporary illness. Since the varieties on the different hosts are morphologically indistinguishable, until recently their identification was based solely on empirical testing. However, Lee and Cho (1995) proposed that *Sarcoptes* in humans and swine belonged to different varieties but that the dog mite was a different species. Serological (Arlian *et al.,* 1996) and genetic (Walton *et al.*, 1999) differences that have been found, at least in some varieties, could provide more solid grounds for differentiating them.

Other mites that cause zoonotic scabies in man are *Notoedres cati* (also of the Sarcoptidae family), which produces head scabies in cats, and *Cheyletiella*, the dog, cat, and rabbit mite (see the chapter on Dermatitis Caused by Mites of Animal Origin). In contrast, *Otodectes cynotis* (family Psoroptidae), which causes dog ear scabies, does not seem to affect man (Park *et al.*, 1996).

The mites of sarcoptic scabies lodge in furrows that they excavate in the epidermis of the host and lay their eggs there. The six-legged larvae emerge from the eggs after two days and dig lateral tunnels to migrate to the surface; there they hide under the epidermic scales or in hair follicles. Two to three days later, the larvae give rise to eight-legged, first-stage nymphs, or protonymphs, which transform into tritonymphs; lastly, they reach the adult stage. The adults mate on the surface, and the females begin building tunnels (from 0.5 to 5 mm a day), where they lay their eggs. The entire life cycle can take 10 to 14 days.

The life cycle of *Notoedres* is similar to that of *Sarcoptes*, although a bit slower; the cycle from egg to adult usually takes about 17 days. Unlike *Sarcoptes*, the larvae and nymphs of *Notoedres* move about freely on the skin of the host. Notoedric scabies affects the head of cats and occasionally causes temporary dermatitis in humans.

Sarcoptic scabies affects humans and a large number of domestic and wild animals. Specific names used to be assigned to the mites of each animal species, such as *S. scabiei* for the human parasite, *S. equi* for the horse parasite, and *S. ovis* for the sheep parasite. Now only one species—*S. scabiei*—is recognized, and the mite of each animal species is regarded as a subspecies.

Geographic Distribution and Occurrence: *Sarcoptes* is distributed worldwide. Human scabies is prevalent primarily among socioeconomic classes whose members are poor and often, malnourished, and who have inadequate hygiene; overcrowding promotes the spread of the mite and poor hygiene is conducive to its persistence. However, in the US and Europe, there has been a wave of human infestations unrelated to socioeconomic status, hygiene level, age, sex, or race. Epidemiologists have observed that epidemics of human scabies occur every 30 years and have speculated that a considerable portion of the human population is protected by a certain level of immunity during periods between epidemics.

All animals raised by man for food or transportation are susceptible to *S. scabiei*. Among pets and laboratory animals, the mite is found in dogs, rabbits, hamsters, and some nonhuman primates. The infestation is also seen in zoo animals.

Man is affected by sarcoptic scabies of dogs, cattle, goats, swine, and horses, by notoedric scabies of cats, and by cheyletiellosis of dogs, cats, and rabbits (Beck, 1996; Mitra *et al*., 1993; Parish and Schwartzmann, 1993). Skerratt and Beveridge (1999) reported that man can also acquire the scabies of the Australian wombat. For further information on *Cheyletiella* spp., see the chapter on Dermatitis Caused by Mites of Animal Origin.

Sarcoptes of goats seems not to be very host-specific, inasmuch as there was a report of one epidemic in goats that then spread to cattle, sheep, and dogs, and eventually affected 42 persons. Nineteen goats and one cow died, but the infestation was self-limiting in some human cases (Mitra *et al.*, 1993). The sarcoptic scabies of swine also seems to be transmitted easily to man. Of 48 individuals working with swine infested by *Sarcoptes* in India, 30 (65%) had signs of scabies, and mites were recovered on 20 persons (67%) (Chakrabarti, 1990). Dog scabies is also often transferred to man. In most cases, the symptoms in humans disappear when the animals are treated and contagion ceases to be constant (Fontaine, 2000). Owing to the difficulty of identifying the origin of the mites, the frequency of zoonotic scabies in man is not known. Nevertheless, Normaznah *et al*. (1996) found that 25% of 312 aborigines in Malaysia had antibodies to *S. scabiei* var. *canis*. Arlian *et al*. (1996) found that *Sarcoptes* of man, dogs, and swine had both common and exclusive antibodies. Consequently, it may be possible to differentiate them by serology.

The Disease in Man: The disease caused by the homologous (human) variety of *S. scabiei* is characterized by tunnels in the corneous layer of the skin that are between a few millimeters and 2 cm long. The furrows are very thin and sinuous and are difficult to observe without the aid of a magnifying glass; they are generally not very abundant and are situated primarily in the interdigital spaces, back of the hand, elbows, axillae, torso, inguinal region, chest, penis, and navel. Fiminani *et al*. (1997) conducted a detailed morphological study of dermal pathology caused by *Sarcoptes*.

The most prominent symptom is itching, which is especially intense at night, forcing patients to scratch themselves. Such scratching can cause lesions, new foci of scabies and, often, purulent secondary infections. Irritation and pruritis are manifested one or two weeks after infestion and are due primarily to a type I allergic reaction. Scabies can persist for a long time if not treated; in fact, homologous human scabies is unlikely to heal by itself.

It is believed that animal mites do not generally excavate tunnels in human skin and that the infestation is more superficial. This does not, however, explain the sometimes intense itching that zoonotic infestations cause. A researcher who experimentally infested herself with canine *Sarcoptes* was able to confirm by histopathologic examination the existence of mite tunnels in her skin (Kummel, cited in Schwartzmann, 1983). The lesion can vary from a pruriginous papular eruption, which is the most common form, to an intense allergic sensitization with the appearance of vesicles. Excoriations from scratching are also frequent. The location of lesions in 22 patients infested by *S. scabiei* var. *canis* corresponded to the places most exposed to infested dogs, such as forearms, hands, torso, and thighs (Smith and Claypole, 1967). In 35 patients who were in contact with water buffaloes infested

with *S. scabiei* var. *bubalis*, the lesions were distributed on the face, fingers, hands, thighs, and legs (Chakrabarti *et al*., 1981). In 30 persons infested with swine *Sarcoptes*, the lesions occurred on hands and legs (Chakrabarti, 1990). Zoonotic scabies is unlikely to affect the interdigital folds and external genital organs, which are often affected by homologous scabies. In addition, zoonotic scabies heals by itself and does not last more than one to three weeks. Spontaneous healing is attributed to the fact that the parasites do not multiply or only reproduce for a short time on the heterologous host. An infestation that lasts longer is usually due to ongoing exposure and permanent superinfestation. Treatment of the animal species originating the scabies is usually sufficient to eliminate human zoonotic scabies without treatment in a couple of weeks.

The Disease in Animals: Sarcoptic scabies in animals generally starts on the head and on areas of the body with delicate skin (Davis and Moon, 1990). In equines, the lesions are observed on the head and neck; in dogs, on the ear flaps, snout, and elbows. As with the human parasites, the animal mites produce an allergic sensitization with intense itching and the formation of papules and vesicles. Vigorous scratching by the affected animals causes the vesicles to open and become covered with scales and then scabby plaques, which often ooze a serous liquid. Over time, there is a proliferation of the connective tissue and hyperkeratinization, causing the skin to thicken and form creases. Hair loss in the affected areas as a result of scratching is also frequent. Scabies limited to a small area does not particularly affect an animal's health, but when it spreads to large areas of the body it can have an adverse impact and even cause death.

Source of Infestation and Mode of Transmission: *Sarcoptes* is transmitted mainly by recently inseminated females before they begin to build their tunnels. *Notoedres*, in contrast, is transmitted by larvae or nymphs. In both cases, the skin of the susceptible individual must be in close contact with the skin of the infested individual. In the case of interhuman transmission of *Sarcoptes*, the mite has been found on fomites, and thus contagion through contaminated objects seems possible. Since the parasite can survive for several days off an animal's body on clothing, towels, bedclothes, animal bedding, harnesses, and horse blankets, these objects can serve as sources of infestation.

Each animal species is a reservoir of the mite that attacks its own kind, but cross-transmission between species occasionally occurs. Human scabies is transmitted primarily from person to person, but several animals, such as horses, dogs, cattle, bubalids, sheep, goats, swine, camels, and zoo animals, can occasionally transmit it to man. One of the most common sources of zoonotic scabies is the dog. Infestation by *S. scabiei* var. *canis* occurs through close contact with scabietic dogs and can appear in several members of the family at the same time. It has been estimated that almost 1% of the dogs in the UK have scabies; a study of 65 persons who had been in contact with 28 scabietic dogs confirmed the presence of scabietic lesions in 34 of them. In the US Army dermatology clinic at Fort Benning, Georgia, 20 cases of scabies acquired from dogs were observed in the course of one year (Smith and Claypole, 1967). The University of Pennsylvania found that around 33% of dogs with scabies caused infestations in members of their owners' families (Schwartzmann, 1983). The School of Veterinary Medicine of São Paulo, Brazil tracked human infestation among 143 individuals who were exposed to 27 dogs with

sarcoptic scabies; cutaneous lesions compatible with scabiosis were found in 58 (40.6%) of them (Larsson, 1978). When scabies was still common in domestic animals in the Netherlands, around 25% of the veterinarians in rural areas were infested with *Sarcoptes* of zoonotic origin. Scabies of animal origin is also observed in rural inhabitants. Transmission of sarcoptic scabies (*S. scabiei* var. *bubalis*) from water buffaloes to man was described in India. Of 52 persons who had been in contact with scabietic buffaloes, 35 (67.3%) had symptoms of scabies, and the presence of the mite was confirmed in 22 (42.3%). All of the persons who contracted the infestation (people in charge of handling and milking the buffaloes) had intense pruritus a few hours after initial contact with the affected animals (Chakrabarti *et al*., 1981).

Zoonotic scabies is not an important public health problem because it resolves spontaneously and is not transmitted between humans.

Diagnosis: The presence of sarcoptic scabies is suspected because of intense pruritus and typically located lesions. For the specific diagnosis of homologous infestations in man and animals, the recommendation is to cover the papules and a scalpel blade with a thin layer of mineral oil so that the mites and skin scales stick to it, scrape five to seven times until a small amount of blood is drawn, and examine the scrapings under a microscope to detect the presence of mites. A solution of 10% to 15% sodium or potassium hydroxide can be added to the microscope slide, which can then be heated slightly for 5 minutes to clarify the cornified cells that hinder observation. Since this procedure is painful for patients, in human cases the recommendation is to try and remove the mite from the furrows with a needle. However, the sensitivity of this method is so low that it is almost not worth attempting. Direct examination of the skin with an epifluorescent microscope is also recommended, since this method is quick, painless, and sensitive to the diagnosis of scabies (Argenziano *et al*., 1997).

Zoonotic scabies in humans is more difficult to diagnose because the mites are much less numerous and most seem to move about on the skin. Transparent cellophane tape can be applied to the skin and then examined under a microscope in the hope that a mite has been picked up, but this is not very effective because there is no precise method of determining where the mites are.

Control: In order to prevent human scabies of zoonotic origin, infestation of animals must be prevented or contact with animals suspected of being infested must be avoided. It is easier and more effective to treat pets with acaricides in order to eradicate the infestation. When there is professional contact with animals that may be infested (handling of swine, goats, etc.), gloves and high boots of a material that mites cannot penetrate should be used.

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