

PHARMACODYNAMIC  
BASIS OF  
HERBAL  
MEDICINE

SECOND EDITION



Manuchair Ebadi

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*I dedicate this book to my beloved grandchildren,  
Jesse Manu Ebadi,  
Caylin Jane McCormick,  
Christine Pari McCormick,  
and Jolie Manizeh Ebadi.*

*In books lie the soul of the whole past time,  
the articulate audible voice of the past,  
when the body and material substances  
of it have altogether vanished like a dream.*

— *Thomas Carlyle*

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# Preface to the First Edition

Hippocrates (460-377 B.C.), who used many of the herbal medicines described in this book, lamented, “Life is short, and the art long; the occasion fleeting; experience fallacious; and judgment difficult.”

Herbal remedies have become a major component of American health care. Botanicals like **ginseng**, **ma huang**, **St. John’s wort**, and **valerian** are now household words throughout the world, and the sales of herbal medicine are increasing exponentially.

Alternative therapies include acupuncture, energy healing, folk medicines, herbal medicines, homeopathy, massage, and megavitamins, to name only a few. Millions of people in the third world have used and will always use herbal medicines because they believe in them and regard them as “their” medicine, in contrast to the “allopathic” (conventional Western) system of medicine brought in from “outside.” These medicinal herbs are available locally and are prescribed by traditional practitioners of medicine who are part of the community and in whose presence the patient feels comfortable. In Western countries, there is now an increased use of herbal medicines, largely because of a belief that powerful synthetic agents used in Western medicine can exert more unwanted side effects and are too often used indiscriminately and irrationally. Many of our present medicines are derived directly or indirectly from higher plants. Although several classic plant drugs have lost much ground to synthetic competitors, others have gained a new investigational or therapeutic status in recent years. In addition, a number of novel plant-derived substances have entered into Western drug markets.

The word *pharmacodynamic* may be defined as the study of the actions and effects of drugs on organ, tissue, cellular, and subcellular levels. Therefore, pharmacodynamics provides us with information about how drugs bring about their beneficial effects and how they cause their side effects. By understanding and applying the knowledge gained in studying pharmacodynamics, physicians and other members of the health-care delivery team are able to provide effective and safe therapeutic care to their patients. Western physicians prescribing synthetic drugs may want to believe in herbal medicines and use them in their patients, but wish to see scientific documentation as they have learned in their pharmacology and therapeutic courses in medical school. Eastern physicians yearn to find out how their drugs, proven efficacious for thousands of years in ancient civilizations such as Chinese, Indian, Persian, and Egyptian, work and bring about their beneficial effects. This book bridges the past to the present and shows at the molecular level how the herbal medications most often used work. For example:

- This book shows how Eastern physicians used **meadow saffron**, which is good for gout, but also provides evidence that meadow saffron possesses **colchicines**, an **antigoutic medication**, and provides the mechanisms of action for it.
- This book shows how Eastern physicians used **belladonna** alkaloid for **Parkinson’s disease** but also provides evidence that belladonna alkaloid contains **anticholinergic drugs**, which counterbalance the dopamine deficiency syndrome seen in Parkinson’s disease.
- This book shows how Indians used **Rauwolfia serpentina** to reduce blood pressure and as an antipsychotic, but also shows that it contains **reserpine**, which depletes norepinephrine in the periphery bringing about its antihypertensive effects and depletes dopamine in the mesocortical system causing tranquility.
- This book compares the actions of **fluoxetine**, the most frequently used antidepressant in the world, with those of **St. John’s wort**, in altering the uptake of serotonin.

- This book compares the hypnotic and sedative actions of **valerian** used for thousand years to treat insomnia with those of **benzodiazepine derivatives** in altering GABAergic transmission.
- This book describes the existence of drugs isolated from food substances such as **horse-radish, garlic, and rhubarb**, and provides their mechanisms of action.
- This book describes the efficacy of **Shing Jing** in male fertility and **erectile dysfunction** and compares its efficacy with those brought about by levodopa, amylnitrite, vitamin E, and **sildenafil** (Viagra).

The majority of believers in alternative medicine are more educated, but they report poorer health status. They take herbal medicine not so much because are dissatisfied with conventional medicines, but largely because they find these health-care alternatives to be more congruent with their own values, beliefs, and philosophical orientations toward health care and life in general.

**M. Ebadi**  
*Grand Forks, North Dakota*

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# Acknowledgments for the First Edition

The author expresses his appreciation to Liz Covello, the former publisher of life sciences for CRC Press LLC, and Barbara Ellen Norwitz, the current publisher of life sciences for CRC Press LLC for a gracious invitation to prepare a book on herbal medicine. The author acknowledges the support of Tiffany Lane, editorial assistant, and the magnificent contribution of Gail Renard, production editor, for polishing and refining the book.

The author extends his expression of admiration to Debra Jean Kroese, Dawn Halvorson, Lacy Kay Boushee, and HaleyAnn Kroese for gathering reference materials and for typing certain sections of the book.

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The author pays an affectionate tribute and extends his heartfelt gratitude to H. David Wilson, M.D., the eminent Dean and Vice President for Health Affairs, University of North Dakota School of Medicine and Health Sciences, for his unyielding support, Solomonic wisdom, and genuine friendship in facilitating the completion of this book.



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# Preface to the Second Edition

Let food be your medicine and medicine be your food.

— Hippocrates, 400–377 B.C.

Residents of **Okinawa**, Japan, who eat small portions; of **Sardina**, Italy, who drink red wine; and of **Loma Linda**, California, who eat nuts and beans, live longer, are healthier than anyone else on earth (Buettner, 2005), and have some form of spiritual faith. Herbal medicines have been used effectively by ancient Chinese, Egyptian, Hebrew, Indian, Japanese, and Persian cultures in their arts of healing and in sustaining life.

The words *heal* and *health* mean “whole” or “intact.” In a sense, they are closely connected in meaning — **To heal is to make whole**, whereas health is the harmonious functioning of one’s body, mind, and spirit.

Chronic diseases caused by physical inactivity and inappropriate diet consumption are epidemic in modern Western society. Chronic diseases develop over a lifetime, with clinical sequelae occurring many years after the underlying pathogenesis of the disease has occurred. As we move ahead in the 21st century, **cardiovascular diseases** (i.e., coronary artery disease, hypertension, stroke, and heart failure), **type 2 diabetes**, **metabolic syndrome**, and **cancer** are the leading killers in Western society and are increasing dramatically in developing nations.

Chronic diseases present an enormous burden to society by increasing medical costs and human suffering. Recent data estimate that physical inactivity and poor diet caused 400,000 deaths in the year 2000, ranking second only to tobacco, and it is likely that inactivity and diet will soon rank as the leading cause of death in the U.S. This number may be an underestimate given that it reflects deaths attributable only to those with obesity and physical inactivity. These health problems have been virtually nonexistent in underdeveloped countries, but they are on the rise as people change their diets and become more sedentary.

**Free radicals** (reactive oxygen species and reactive nitrogen species) are implicated in aging and all chronic degenerative diseases. The extent and severity of free-radical damage depends on genetic makeup, current health status, nutrition, and stress level of a person. The body has its own innate ability to counteract free radicals through the production of **glutathione** and **metallothionein**, which are two of the most powerful antioxidants. In addition, fresh fruits and vegetables are high in a variety of free-radical-fighting antioxidants.

There are also a number of vitamins, minerals, herbs, and food supplements that are known to serve as powerful antioxidants. Among these are vitamins A, C, E, and the mineral **selenium**. In addition, the flavonoids found in vegetables, berries, citrus fruits, and herbs such as the **amla fruit** (*Emblica officinalis*) from India all possess powerful free-radical-fighting antioxidants. Many herbs are high in flavonoids, including **Ginkgo biloba**, **astragalus**, **hawthorn**, **green tea**, and **turmeric**, to name a few. Other powerful antioxidants include **pycogenol** from grape seed and pine bark, **coenzyme Q10**, lipolic acid, and *N*-acetyl cysteine (NAC). **Echinacea** has been widely used as a herbal remedy for the common cold. An evaluation of *Echinacea angustifolia* in experimental rhinovirus infections has shown that it has no clinical effects on the infection or the clinical illness that results from it.

Reactive-oxygen-species-mediated oxidation of biological molecules are thought to induce a variety of pathological events such as atherogenesis, carcinogenesis, Parkinson’s disease, and even the aging process (which is the progressive accumulation of changes with time associated with or responsible for the ever-increasing susceptibility to disease and death that accompanies advancing age). The aging process may be common to all living things, because the phenomenon of aging



and death is universal. If so, both aging and the rate of the aging process are under genetic control to some extent, as the manifestations of aging and the life span differs between species and individual members of a species. Furthermore, similar to all chemicals and chemical reactions, the manifestations of aging (which reflect chemical composition) and the rate of the aging process should be subject to environmental influences, including diets.

The nature of the aging process has been the subject of considerable speculation. Suggested possibilities include (1) encodement of aging in DNA, (2) progressive breakdown in accuracy in protein synthesis, (3) cross-linkage of macromolecules, (4) “attack” of the immune system on self-antigens in higher organisms, and (5) free-radical reaction damage caused by **reactive oxygen species or reactive nitrogen species**, which can be attenuated by herbal medicines.

Over 90% of the oxygen consumed by a mammal is utilized in the **mitochondria**. Presumably, the rate of O<sub>2</sub> consumption is under genetic control, both nuclear and mitochondrial. It is reasonable to assume that some of the free radicals generated during the reactions involving oxygen, such as the **superoxide radical** (O<sub>2</sub><sup>•-</sup>), would produce changes in the mitochondria at a rate related to the rate of oxygen consumption. Such alterations in the mitochondrial DNA could have an accumulative deleterious effect on mitochondrial functions, leading to the observed mitochondrial changes in number, morphological characteristics, and enzymatic activity. Thus, the relationship between life span and basal metabolic rate — to a first approximation, constant throughout life — may reflect the overall rate of accumulation of mitochondrial damage secondary to free-radical reactions. **Wheat germ containing coenzyme Q<sub>10</sub>, honey containing choline, and tomato containing lycopene prevent premature aging.**

The free-radical theory of aging, proposed by Harman (1960, 1981), predicts that a healthy life span can be increased by minimizing deleterious free-radical reactions while not significantly interfering with those essential to the economy of the cells and tissues. The data now available indicates that this can be done by maintaining body weight at a level compatible with a sense of well-being while ingesting diets (that include fruits and vegetables) adequate in essential nutrients but designed to minimize random free-radical reactions in the body. Such diets would contain minimal amounts of components that enhance free-radical reactions, for example copper and polyunsaturated lipids, and increased amounts of substances capable of decreasing free-radical reaction damage, such as **α-tocopherol, ascorbic acid, selenium**, or one or more synthetic **anti-oxidants**. It is reasonable to expect that this approach will decrease morbidity.

Several minor compounds in legumes and vegetables have been shown to prevent the peroxidative degeneration of plasma lipoproteins and tissue organelles additively or synergistically with endogenous antioxidants. The major candidates for these dietary antioxidants are phenolic compounds and carotenoids. Many spices such as **turmeric** and **rosemary** have been used extensively as natural food additives for flavoring, seasoning, coloring, and antiseptic properties. Several spices are known to exhibit antioxidative activities.

Dietary supplementation with turmeric (active ingredient is **cucuminoid**) or **rosemary** (*Rosmarinus officinalis* L, active ingredients are **carnosol** and **carnosic acid**) significantly reduces triacylglycerol and cholesterol contents in the liver. Because triacylglycerol accumulation in the liver is caused by biochemical modification of the mitochondrial and endoplasmic functions, turmeric and rosemary are able to prevent liver disorders, and the said effect is caused by stimulation of hepatic cholesterol-7α-hydroxylase activity. **Good nutrition, mostly but not entirely containing vegetables and fruits, and caloric restriction are essential to preventive medicine, and helps one lead a happier and healthier life.**

The second and extended edition has attempted to retain the topics that readers found informative, deleted or simplified areas that critics considered esoteric, and introduced new subjects.

It is the author’s fervent hope that the wisdom of Hippocrates will be heeded, that a wise person should consider health as the greatest of human blessings.

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# Acknowledgments for the Second Edition

The author expresses his appreciation to **Barbara Ellen Norwitz**, the publisher of life sciences for CRC Press, for the gracious invitation to prepare the 2nd edition and to **Amber Donley**, the project coordinator, for all her assistance in preparing a state-of-the-art compendium on herbal medicine. The author acknowledges the magnificent contribution of **Gail Renard**, the production editor, for polishing and refining the book. Gail is an extraordinarily perceptive person who is visionary in character, has eagle eyes, is a remarkably intelligent person, and exhibits a Solomonic wisdom in editing scientific works, an attribute which is rarely seen in a production editor. The author remains eternally grateful and in awe of Gail's judgment and titanic and colossal contributions to restructuring and refining in an admirable fashion four books for him.

The author expresses his loving tribute to his two sons **John Ebadi, Ph.D.** (Oriental medicine and Eastern healing art) and **Mark Ebadi, M.D.** (Western medicine and Western healing art) for their input on how to bridge past and present medical wisdom, and how to respect not only the immense contributions of many ancient cultures but also the amazing advances made by physicians today in their quests for preventing diseases, prolonging life, and reducing morbidity.

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The author remains humbled and in awe of the hundreds of scientists who not only read and made the first edition a best seller but also reviewed the book, lighted the path, and gave direction on how to write the 2nd edition.

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# The Author

**Manuchair Ebadi** earned a B.S. in chemistry from Park University (Parkville, Missouri, 1960), an M.S. in pharmacology from the University of Missouri College of Pharmacy (Kansas City, 1962), and a Ph.D. in pharmacology from the University of Missouri College of Medicine (Columbia, 1967). He completed his postdoctoral training in the Laboratory of Preclinical Pharmacology at the National Institute of Mental Health (Washington, D.C., 1970), under the able direction of Erminio Costa, M.D., an eminent member of the National Academy of Sciences.

Dr. Ebadi served as chairman of the Department of Pharmacology at the University of Nebraska College of Medicine from 1970 until 1988 and subsequently as professor of pharmacology, neurology, and psychiatry from 1988 through 1999. In July 1999, he was appointed professor and chairman of the Department of Pharmacology and Toxicology at the University of North Dakota School of Medicine and Health Sciences. In September 1999, Dr. Ebadi became professor and chairman of the newly created Department of Pharmacology, Physiology, and Therapeutics; in November 1999, he became professor of neuroscience; and in December 1999, he was appointed associate dean for research and program development. In September 2000, Dr. Ebadi was appointed director of the Center of Excellence in Neurosciences at the University of North Dakota School of Medicine and Health Sciences, and in March 2002, associate vice president for medical research at the University of North Dakota.

During his academic career, Dr. Ebadi has received 36 awards, including the Burlington Northern Faculty Achievement Award (1987), the University of Nebraska's systemwide Outstanding Teaching and Creative Activity Award (1995), and was inducted into the Golden Apple Hall of Fame (1995) for having received 11 Golden Apple awards. He is a member of 18 research and scholarly societies, including Alpha Omega Alpha Honor Medical Society.

In 1976, Dr. Ebadi became the Mid-America State Universities Associations (MASUA) honor lecturer; in 1987, he received an award for meritorious contributions to pharmaceutical sciences from the University of Missouri Alumni Association; in 1995, he was honored by a resolution and commendation of the Board of Regents of the University of Nebraska for having developed a sustained record of excellence in teaching, including creative instructional methodology; in 1996, he received the Distinguished Alumni Award from Park University, his alma mater. In November 2002, Dr. Ebadi received a recognition award in appreciation of his outstanding contribution to the UND School of Medicine. In May 2003, Dr. Ebadi received the Outstanding Block Instructor Award for outstanding performance "in the encouragement, enrichment, and education of tomorrow's physicians." In 2003, Dr. Ebadi was elected to the prestigious Cosmos Club (Washington, D.C.) for individuals who have distinguished themselves in art, literature, or science.

Professor Ebadi discovered and characterized brain metallothioneins isoforms in 1983 and subsequently showed that they are able to scavenge free radicals implicated in Parkinson's disease. In addition, he showed that metallothionein averts  $\alpha$ -synuclein nitration, enhances the elaboration of coenzyme Q<sub>10</sub>, increases the activity of complex I, enhances the synthesis of ATP, and as an antioxidant is fifty times more potent than glutathione. His research programs have been supported in the past and currently by the National Institute on Aging (AG 17059-06), the National Institute



of Environmental Health Sciences (NIEHS 03949), the National Institute of Child Health and Human Development (NICHD 00370), the National Institute of Neurological Disorders and Stroke (NINDS 08932, NINDS 34566, and NINDS 40160), and the Office of National Drug Control Policy, Counter Drug Technology Assessments Center (DATM 05-02-C-1252).

Dr. Ebadi has written ten books. *Pharmacology* was translated into Japanese in 1987 (Medical Science International Ltd., Tokyo), *Core Concepts in Pharmacology* was translated into Chinese in 2002 (Ho-Chi Book Publishing, Taiwan), and *Pharmacodynamic Basis of Herbal Medicine* (CRC Press, 2002) became a bestseller.

In 2005 Dr. Ebadi along with Professor Ronald F. Pfeiffer, M.D., published a book entitled *Parkinson's Disease*, which received excellent reviews in *JAMA* 293, 2281, 2005, and in *New England Journal of Medicine* 352, 1304, 2005, and won first prize in the neurology category of the 2006 British Medical Association's Book Competition.

On February 26, 2004, Dr. Ebadi received the University of North Dakota Foundation's Thomas J. Clifford Faculty Achievement Award for Excellence in Research and, on September 7, 2004, he received from President Charles E. Kupchella, the designation of Chester Fritz Distinguished Professor of Pharmacology and of Clinical Neuroscience, the highest honor bestowed by the University of North Dakota.

On July 21, 2005, Dr. Ebadi received the Pendelton Honor, from Eugene DeLorme, J.D., Director of Indian Into Medicine Programs; from Dr. David Gipp, President of United Indian Nations; and from Dr. Frank Williams, Vice President of Tribal Board in appreciation of his providing research support for the Indian Nations. Dr. Ebadi has served as a member of the United States Pharmacopoeia Convention since 1970. In February 2006, Associate Vice President Ebadi was appointed Senior Advisor to the President of the University of North Dakota.

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# Introduction

The Lord has created medicines out of the earth and he who is wise will not abhor them.

— *Ecclesiastes*, Chapter 38, Verse 4

In all, 120 medicinal plants are found in the Bible including **aloe**, **rue**, **madder**, **frankincense**, **myrrh**, and **marigold** (*Calendula officinalis*). With its therapeutic efficacy on cough and bronchitis, dyspepsia, liver and gallbladder maladies, and as an appetite stimulant, **marigold**, known in the Persian language as *hamisheh bahar* (meaning “always spring”), is a sacred flower and is respected and honored in Eastern religions such as Buddhism, Hinduism, and Taoism. Marigold always follows the sun, needs little care, and gives so much beauty. Hence, it is used as a garland to adorn dignitaries and religious leaders. The saffron-colored robes of the Eastern monks have the color of marigold.

Traditional Chinese medicines have developed over a period of at least 5000 years. The earliest known work on Chinese herbs is the *Shing Nung Bon Cas Chien*, or the herbal classic of the **divine plowman**. According to this work, Sheng Nung, the divine plowman, tested and recommended a total of 365 herbs — one for each day of the year.

The Chinese are proud of their heritage, especially in the uses of natural substances, plants, chemicals, and animal products, and the application of acupuncture.

For example, **acupuncture** performs certain functions in traditional Chinese medicine as follows:

- It regulates the flow of **chi** through channels and organs.
- It removes blockage.
- It strengthens the body’s protective chi.
- It lessens the virulence of excesses.

The most sophisticated and state-of-the-art science at the molecular level has shown that acupuncture has the following actions:

- It releases pain-killing **endorphin** and **enkephalin**.
- It releases **immunoenhancing cytokines**.
- It releases **neurotrophins** capable of repairing damaged tissue.
- It suppresses the elaboration and release of **inflammatory and necrotizing peptides**.

Physicians and scientists are beginning to appreciate the therapeutic efficacy of acupuncture. Dr. Ted J. Kaptchuk, who holds a doctorate in Eastern medicine and is the author of a book entitled *The Web That Has No Weaver*, tells a story about a Chinese peasant who had worked as a maintenance man in a newly established Western missionary hospital. The peasant took some antibiotics from the hospital and treated people in his village who had fever. Many of them were cured. The peasant knew nothing about the pharmacology of the antibiotics, but that was irrelevant; the sick got better. The physicians of yesteryear could not explain the efficacy of acupuncture, but acupuncture worked. The mighty oak tree stands tall and firm in the ground because of its roots. One does not see the roots but they are there.

In the last 30 years, significant events occurred that have already produced fundamental changes in the attitude of both the public and scientists toward herbal medicines. These are as follows:

- First, laypersons discovered the utility of whole plant drugs or herbs.
- Second, dissatisfaction with the effectiveness and especially the cost of modern medicines caused an appreciation of all things “**natural**” and “**organic**,” which inspired millions of people throughout the world to gain a deep appreciation for the use of classical plant drugs for the treatment of many ailments.

The “**green**” **revolution** in terms of herbal medicine has now achieved astonishing popularity in the U.S., although it is not yet encouraged by an ultraconservative **Food and Drug Administration** that classifies most plant drugs as dietary supplements or food additives, which places severe limitation on labeling. However, in fairness to the FDA, because a plant drug is “natural” does not necessarily mean that it is safe.

Primeval humans in search of food undoubtedly experienced much poisoning. We learned by trial and error that eating certain mushrooms, berries, and roots could produce various degrees of gastrointestinal discomfort or death, whereas others could be ingested safely. Certain lessons were learned quickly, and primitive food-gathering humans soon became toxicologists of no mean ability. Eventually, this knowledge was made to work for humans; we prepared **arrow poisons** from plant extracts to bring down game or foe. We threw crushed leaves of particular plants into water and with little effort quickly obtained a bountiful supply of stupefied fish, and we learned also to wash poison (e.g., cyanide) from a number of common, staple foods to make them edible. It probably took *Homo sapiens* but a short time to learn how to gather food with relative ease and to participate in the good life.

Humans also learned that poisons could be obtained from plants. In classical Rome, for example, mushrooms were the poison of choice and were expertly used by **Agrippina, wife of Emperor Claudius and mother of Nero**. Agrippina had Lollia Paulina put to death because Claudius, in a careless moment, remarked on Lollia’s beauty.

Higher plants were among those studied by **Cleopatra** in her search for a fatal poison. Using her prisoners and slaves as guinea pigs, she was quite systematic. It was reported that she was not satisfied with the effects of either **henbane** (*Hyoscyamus niger*) or **belladonna** (*Atropa belladonna*), for they produced too much pain in spite of their rapid actions. She was further disappointed with ***Strychnos nux-vomica***, from which **strychnine** was eventually extracted. Although its action was instantaneous, it produced convulsions that distorted facial features at death. Finally, she selected the bite of the asp (Egyptian cobra), which produced a serene and prompt death.

The FDA could do better, and there is little doubt that consumer demand will promote an ever-increasing interest in herbal medicine. Although some plants are poisonous, the majority are not and should be used as therapeutic agents.

Alfred North-Whitehead said that “the rejection of any source of evidence is always treason to that ultimate rationalism which urges forward science and philosophy alike.”

Practitioners throughout the world have used **marijuana**. The most sophisticated pharmacological studies have shown for more than two decades that the active ingredients of marijuana are efficacious in the following conditions:

- Cancer chemotherapy
- Glaucoma
- Epilepsy
- Multiple sclerosis
- Paraplegia and quadriplegia
- AIDS
- Chronic pain
- Migraine
- Rheumatic diseases (osteoarthritis and ankylosing spondylitis)

- Pruritus
- Premenstrual syndrome, menstrual cramps, and labor pains
- Depression and other mood disorders

Only recently has marijuana become available as a drug for patients with cancer.

Would the FDA approve chocolate, which is related to cocaine? *Theobroma cacao* or the chocolate tree, named by the great Swedish naturalist Linnaeus (1707 to 1778), gives us chocolate, also known by the Aztec as “**the food of the gods**,” which has acquired immense importance socially, religiously, medically, economically and, of course, gastronomically.

Natural products are extremely important for the following four reasons:

1. In the first place, they provide a number of extremely useful drugs that are difficult, if not impossible, to produce commercially by synthetic means. These include diverse groups of compounds such as the **alkaloids** of opium poppy, **ergot**, and **solanaceous plants**; the cardiotonic glycosides of **digitalis**; most of the antibiotics; and all of the serums, vaccines, and related products.
2. Natural sources also supply basic compounds that may be modified slightly to render them more effective or less toxic. The numerous variations of the morphine molecule serve as examples here.
3. A third role of natural products is their utility as prototypes or models for synthetic drugs possessing physiological activities similar to the original drug. **Procaine** and similar local anesthetics are commonly cited representatives of this category.
4. There is a fourth role for natural products that is quite different from the preceding ones, but which is nonetheless important. Some natural products contain compounds that demonstrate little or no activity themselves but which can be modified by chemical or biological methods to produce potent drugs not easily obtained by other methods. For example, **taxol** may be synthesized from baccatin III, which occurs more or less abundantly in the leaves of various **yew species**, whereas taxol itself is found only in the bark of the scarce **Pacific yew**. Proper chemical and biological treatment of **stigmaterol**, which occurs abundantly in **soybean oil**, permits the large-scale production of **hydrocortisone** or related corticosteroids, compounds that occur in nature in only small amounts. The importance of natural products as precursors of significant drugs cannot be overemphasized.

One should consider that plant-derived steroids alone account for about 15% (\$22 billion) of the \$150 billion world pharmaceuticals market and that the annual market for taxol exceeded \$1 billion in the year 2000. The antineoplastic agents **vinblastine** and **vincristine** have sales amounting to \$100 million per year; the market for **psyllium seed products** amounts to some \$300 million annually; and **nicotine** and **scopolamine** patches now have combined sales of more than \$1 billion per year. It is obvious that natural products continue to play important economic as well as therapeutic roles in modern medicine.

Why then do Western physicians and scientists resist the **chi** vitality and **yin** and **yang** theory? Although yin and yang can be distinguished, they cannot be separated. They depend on each other for definition. And the things in which yin and yang are distinguished could not be defined without the existence of yin and yang qualities. Certainly, in Western sciences, there are millions of examples of yin and yang, such as:

- Adrenergic–cholinergic systems controlling heart beat
- Dopaminergic–cholinergic systems controlling movements
- Glutamatergic–GABAergic systems controlling emotion



Nevertheless, Western culture does not fully understand chi. **Lao Tzu** (Iaozi), the eminent and reputable founder of **Taoism**, says in *Tao-Te-Ching*, the classic of the **Tao** and its virtue, that **yin and yang** control each other as:

Being and nonbeing produce each other;  
Difficult and easy complete each other;  
Long and short contrast each other;  
High and low distinguish each other;  
Sound and volume harmonize each other;  
Front and back follow each other.

Lao Tzu describes the transformation process of yin and yang poetically, thus:

He who stands on tiptoe is not steady.  
He who strides forward does not go.  
He who shows himself is not luminous.  
He who justifies himself is not prominent.  
He who boasts of himself is not given credit.  
He who brags does not endure for long.

**Chi** in Chinese medicine, known in India as **prana** (life force) and in Japan as **ki**, gives us a measure of the vitality of a person, object, or state.

Appropriate drug therapy can improve the quality of life, whereas injudicious drug therapy may be harmful. Medications are given for a variety of diagnostic, prophylactic, and therapeutic purposes. These prescribed medications bring about the desired effects in most patients, but they may also prove to be inert and ineffective in some. They may even evoke totally unexpected responses and precipitate serious reactions in others.

**Pharmacology** can be defined as the study of the selective biologic activity of chemical substances in living matter. Often, but not always, these selective biologic activities are triggered by very small amounts of drugs. Because it is selective, the drug should produce responses in only some of the cells.

The use of drugs in the treatment of a disease is termed **pharmacotherapeutics**. However, the use of drugs is not always necessary in managing a disease. A drug may be used substitutively, supportively, prophylactically, symptomatically, diagnostically, or correctively. For example, in **juvenile-onset diabetes mellitus (type I, insulin-dependent diabetes mellitus)** and **Addison's disease**, **insulin** and **cortisone acetate** are used, respectively, as substitutes or supplements for substances that either were never produced or were once there but are now not produced. In **adult-onset diabetes mellitus**, oral antidiabetic agents support the physiological function of the body by stimulating the synthesis and release of insulin.

**Oral contraceptive** tablets are used to **prevent pregnancy**. **Isoniazid** may be used to prevent the development of active **tuberculosis** in those individuals who have been exposed to the disease but show no evidence of infection, in those who test positively for it but have no apparent disease, and in those with once active but now inactive disease.

Drugs may eliminate or reduce the symptoms of a disease without influencing the actual pathology. For example, fever may be associated with respiratory tract infection, bacterial endocarditis, biliary tract disorders, tuberculosis, carcinoma, cirrhosis of the liver, collagen diseases, encephalitis, glomerulonephritis, Hodgkin's disease, hysteria, malaria, leukemia, measles, mumps, and plague, to name a few. **Aspirin**, found in willow, wintergreen, and birch, can reduce the fever in these disorders but cannot alter the disease processes themselves (see Chapter 59).

A drug may also be used to diagnose a disease. **Histamine** has been used to assess the ability of the stomach to secrete acid and to determine parietal cell mass. If an acidity or hyposecretion

occurs in response to histamine administration, this may indicate **pernicious anemia, atrophic gastritis, or gastric carcinoma**; a hypersecretory response may be observed in patients with **duodenal ulcer** or with the **Zollinger–Ellison syndrome**.

In most cases, drugs do not cure diseases, but do ease or eliminate the associated symptoms. For example, no drugs exist that cure essential hypertension, but there are some that lower blood pressure. In reducing symptoms, drugs never create new functions. They can only stimulate, or depress, the functions already inherent in the cells.

In alleviating symptoms, drugs may also induce adverse effects, which may or may not be acceptable to patients. For example, numerous agents with anticholinergic properties cause dry mouth, which is easily correctable and hence is acceptable to patients. Conversely, some **antihypertensive medications** cause **impotence** in male patients, which they may find unacceptable, and this side effect may thus lead to lack of compliance with the prescribed medication.

Drugs can therefore resemble a double-edged sword in that they can both help and harm the patient. By fully appreciating the nature of **pharmacokinetics, pharmacodynamic** principles, and **drug–drug interactions**, practitioners can drastically reduce unwanted side effects and at the same time enhance the therapeutic efficacy and usefulness of drugs.

**Pharmacodynamics** may be defined as the study of the actions and effects of drugs on organ, tissue, cellular, and subcellular levels. Therefore, pharmacodynamics provides us with information about how drugs bring about their beneficial effects and how they cause their side effects. Pharmacodynamics considers the sites, modes, and mechanisms of actions of drugs. For example, if a patient with multiple fractures receives a subcutaneous injection of 10 to 15 mg of morphine sulfate, analgesia, sedation, respiratory depression, emesis, miosis, suppression of the gastrointestinal tract, and oliguria may ensue. These diversified effects occur at multiple peripheral and central sites and through the influence of numerous modes and mechanisms of actions.

**Site of action** is the receptor site where a drug acts to initiate a group of functions. The central sites of action of morphine include the cerebral cortex, hypothalamus, and medullary center.

**Mode of action** is the character of an effect produced by a drug. Morphine, by depressing the function of the cerebral cortex, hypothalamus, and medullary center, is responsible for decreasing pain perception (**analgesia**), inducing narcosis (**heavy sedation**), depressing the cough center (**antitussive effect**), initially stimulating then depressing the vomiting center, and depressing respiration.

**Mechanism of action** is the identification of molecular and biochemical events leading to an effect. For example, morphine causes respiratory depression by depressing the responsiveness of the respiratory center to carbon dioxide.

Medicinal plants have been used for healing and preventative health for thousands of years all around the world. For example, the therapeutic efficacy of the following herbs are well known (see Kovach, 2001; for additional herbal medicine, see Chapter 9).

### **ALOE VERA LEAF (*ALOE FEROX*, *A. BARBADENSIS*)**

- Heals sunburn and other skin problems
- Eases constipation
- Aids ulcers
- Exhibits antibacterial, antiviral, and antifungal activity

### **ASHWAGANDA (*WITHANIA SOMNIFERA*)**

- Reduces stress
- Has anti-inflammatory effect
- Boosts sexual energy in men (**aphrodisiac**)

### **ASTRAGALUS LEAF (*ASTRALAGUS MEMBRANACEUS*)**

- Enhances immune response
- Heals burns and abscesses
- Relieves effects of chemotherapy
- Helps lower blood pressure
- Acts as a heart tonic, protecting the heart against viral damage

### **BILBERRY FRUIT (EUROPEAN BLUEBERRY — *VACCINIUM MYRTILLUS*)**

- Relieves varicose veins
- Exhibits antidiarrhetic effects
- Enhances circulation
- Improves night blindness, cataracts, and diabetic retinopathy

### **BLACK COHOSH ROOT (*CIMICIFUGAE RACEMOSAE RHIZOME*)**

- Eases menopause
- Relieves premenstrual syndrome
- Aids dysmenorrhea

### **CAT'S CLAW BARK (*UNCARIA TOMENTOSA*)**

- Stimulates immune response
- Exhibits anti-inflammatory effects
- Exhibits antiviral effects

### **CAYENNE PEPPERS (*CAPSICUM SPP.*)**

- Relieves painful muscles
- Acts as a cardiovascular tonic
- Eases stiff, painful arthritic joints
- Exhibits an antibacterial effect
- Aids weight loss
- Hoarseness, sore throat and cough

### **CHAMOMILE (*MATRICARIA RECUTITA*)**

- Is calmative
- Acts as a diuretic
- Promotes wound healing
- Exhibits an anti-inflammatory effect

### **CHASTE BERRY (*VITEX AGNUS-CASTUS*)**

- Relieves menstrual disorders
- Eases symptoms of premenstrual syndrome and menopause
- Helps combat hot flashes
- Suppresses appetite

### **CRANBERRY FRUIT (*VACCINIUM MACROCARPON*)**

- Treats urinary tract infections
- Is a good source of vitamin C
- Cleanses the stomach
- Treats nausea

### **DEVIL'S CLAW ROOT (*HARPAGOPHYTUM PROCUMBENS*)**

- Exhibits an anti-inflammatory effect
- Acts as an analgesic
- Relieves tendonitis, acute lower back pain
- Relieves loss of appetite
- Treats skin lesions

### **EVENING PRIMROSE OIL (*OENOTHERA BIENNIS*)**

- Relieves premenstrual syndrome symptoms
- Reduces cholesterol
- Fights heart disease
- Acts as a liver tonic
- Relieves skin conditions
- Treats upset stomach

### **FLAXSEED OIL (*LINUM USITATISSIMUM*)**

- Aids endometriosis
- Relieves premenstrual syndrome and menopausal symptoms
- Helps psoriasis
- Lowers cholesterol and blood pressure
- Protects against heart attack and stroke

### **GINGER (*ZINGIBER OFFICINALE*)**

- Relieves nausea, vomiting, and motion sickness
- Eases stomach upset
- Exhibits an anti-inflammatory effect
- Treatment of coughs and shortness of breath

### ***GINKGO BILOBA (GINGKO)***

- Combats age-related memory loss
- Eases dizziness
- Relieves tinnitus (ringing in the ears)
- Improves circulation and oxygen delivery to the brain
- Acts as a potent antioxidant, stronger than vitamin E

### ***ASIAN GINSENG ROOT (PANAX)***

- Enhances memory
- Fights fatigue
- Protects against stress damage, both physical and emotional
- Has anti-aging properties

### ***SIBERIAN GINSENG ROOT (ELEUTHEROCOCCUS SENTICOSUS)***

- Is an immunostimulant
- Exhibits anti-inflammatory effects
- Prevents colds and flus

### ***GOLDENSEAL ROOT (HYDRASTIS CANADENSIS)***

- Relieves cold and flu symptoms
- Prevents or treats “traveler’s diarrhea”
- Acts as an antiseptic

### ***GRAPE SEED EXTRACT (VITIS VINIFERA)***

- Potent antioxidant
- Treatment of varicose veins and other vein disorders
- Cardiovascular protectant
- Anti-inflammatory agent
- Antihistamine
- Wrinkle treatment
- Treatment of burns
- Treatment of slow-healing ulcers

### ***GREEN TEA LEAF (CAMELLIA SINENSIS)***

- Acts as an antioxidant
- Exhibits chemopreventative effects
- Stops tooth decay
- Improvement of mental processes

## **HAWTHORN BERRIES AND LEAVES (*CRATAEGUS MONOGYNA*, *C. LAEVIGATA*, AND RELATED SPECIES)**

- Dilates coronary arteries
- Improves blood flow to the heart
- Decreases blood cholesterol levels
- Acts as a hypotensive agent
- Improves digestion

## **LICORICE ROOT (*GLYCYRRHIZA GLABRA*)**

- Soothes sore throat
- Relieves coughs
- Treats peptic ulcers
- Relieves canker sores
- Aids viral infections
- Eases skin conditions
- Helps relieve premenstrual syndrome and menopausal disorders

## **MILK THISTLE FRUIT (*SILYBUM MARIANUM*)**

- Acts as a liver tonic and protectant
- Treats jaundice

## **PEPPERMINT (*MENTHA PIPERITA*)**

- Exhibits antispasmodic effects
- Calms the stomach and intestinal tract
- Relieves the common cold
- Aids muscle pains
- Eases headaches
- Helps irritable bowel syndrome
- Soothes gallstones

## **RED CLOVER BLOSSOMS (*TRIFOLIUM PRETENSE*)**

- Relieves menopausal symptoms
- Exhibits antitumor properties
- Reduces swollen glands
- Acts as an expectorant
- Soothes skin problems

## **SAW PALMETTO BERRIES (*SERENOA REPENS*)**

- Relieves benign prostate hyperplasia (enlarged prostate)

## **UVA URSI (*ARCTOSTAPHYLOS UVA-URSI*)**

- Combats urinary tract infections and inflammation
- Eases kidney and bladder stones
- Reduces heavy, painful menstrual periods

## **VALERIAN (*VALERIANA OFFICINALIS*)**

- Relieves insomnia
- Aids restlessness
- Eases nervous conditions
- Acts as a sedative

Students of herbal medicine should always remember the following points.

Steven Bratman, in a book addressing a realistic evaluation of alternative healing methods, states:

Most proponents of the field would like to define alternative medicine as the art of using safe, natural methods to get to the root of problems, help the body to heal itself, and prevent diseases before they arise. While this definition sounds beautiful, it is a pure romance. Alternative medicine seldom achieves such an idealized standard.

James A. Duke, in a book entitled the *Green Pharmacy* lamenting the therapeutic efficacy of herbal plants, states:

For all herbs, any number of therapeutic claims have been made over the ages. Many have been verified scientifically. Others are supported by centuries of traditional use or by anecdotal accounts that have not been validated scientifically. This doesn't mean that such uses don't hold water. It means that science hasn't bothered to investigate or test these health-promoting claims. By contrast, because of either misinformation, misinterpretation, or outright deception motivated by greed, false claims have been made on behalf of many plants. Those claims have not withstood, or could not withstand, scientific scrutiny.

In spite of the fact that herbal medicines are used extensively in the world, only recently have there been attempts to standardize and characterize the material used in clinical studies. For example, **Echinacea** is a true **Native American medical plant** and is used for a variety of medicinal purposes by American Indian tribes including the **Cheyenne** (sore mouth and gums), **Choctaw** (coughs, dyspepsia), **Comanche** (toothache, sore throat), **Crow** (colds, toothache, colic), **Dakota** (inflammation, bowel complaints, sepsis, tonsillitis, hydrophobia, toothache, snakebite; headache and distemper in horses), **Delaware** (gonorrhea); **Hidatsa** (stimulant), **Kiowa** (coughs, sore throat), **Meskwaki** (stomach cramps, fits), **Omaha** (septic diseases, tings), **Omaha-Ponca** (eyewash, hair comb), **Pawnee** (rattle snakebites), and **Winnebago** (anesthetic).

In Germany, echinacea root products must state on the label that they are used to help the body resist common cold infections affecting the throat, nasal passages, and head. The common cold is a benign and self-limiting illness most commonly caused by rhinoviruses. Although the importance of the common cold derives primarily from its frequency and from the enormous socioeconomic impact it has, it is clear that the common cold in general and rhinovirus infection in particular are associated with significant medical consequences. There are no specific antiviral treatments for rhinovirus infection. Perhaps, because of the lack of specific therapies, concern about the risks relative to the benefits of treatments for symptoms, and the relatively benign nature of the common cold, there is wide interest in the use of alternative medicines for the treatment of this illness.

As stated previously, ***Echinacea angustifolia* roots** were originally used by North American Indians to treat a variety of infections and wounds. In the late 1800s, these echinacea preparations

became popular as remedies for the common cold. There has been renewed interest in echinacea in the U.S. since the Dietary Supplement Health and Education Act in 1994 liberalized the regulation of herbal medicines. There are three species of echinacea, with different phytochemical characteristics, that are used for medicinal purposes. The phytochemical composition of echinacea preparations may also vary owing to differences in the part of the plant used, the method used to extract the material in the preparation, and even the geographic location and time of year that the plant is harvested. In spite of the variability among echinacea preparations, only recently have there been attempts to standardize and characterize the material used in clinical studies.

Turner et al. (2005) evaluated the efficacy of *Echinacea angustifolia* in experimental rhinovirus infections. The results of this study indicate that extracts of *E. angustifolia* root, either alone or in combination, did not have clinically significant effects on the infection or on the clinical illness that results from it. Be that as it may, many believe in echinacea and used it routinely to avert the common cold.

Many herbal medicines are efficacious and their beneficial effects have been established scientifically; for example, the efficacy of the **vinca alkaloids** in childhood leukemia has been proved. The beneficial properties of the **periwinkle plant** (*Vinca rosea* Linn.), a species of myrtle, have been described in medicinal folklore in various parts of the world. Fractionation of these extracts yielded four active dimeric alkaloids: **vinblastine**, **vincristine**, **vinleurosine**, and **vimosidine**. Two of these, vinblastine and vincristine, are important clinical agents for treatment of leukemias, lymphomas, and testicular cancer. Another agent, **vinorelbine**, has activity against lung cancer and breast cancer. The vinca alkaloids are cell-cycle-specific agents and, in common with other drugs such as **colchicine** and **podophyllotoxin**, block cells in mitosis. The biologic activities of these drugs can be explained by their ability to bind specifically to tubulin and to block the ability of the protein to polymerize into microtubules. When cells are incubated with vinblastine, dissolution of the microtubules occurs, and highly regular crystals are formed that contain 1 mol of bound vinblastine per mol of tubulin. Through disruption of the microtubules of the mitotic apparatus, cell division is arrested in the metaphase. In the absence of an intact mitotic spindle, the chromosomes may disperse throughout the cytoplasm (exploded mitosis) or may clump in unusual groupings, such as balls or stars. The inability to segregate chromosomes correctly during mitosis presumably leads to cell death. Both normal and malignant cells exposed to vinca alkaloids undergo changes characteristic of apoptosis.

The 2nd edition of *Pharmacodynamic Basis of Herbal Medicine* has separated facts from myths and has attempted to provide detailed molecular mechanisms on how herbal plants bring about their beneficial therapeutic effects.





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# Contents

<b>Chapter 1</b>	<b>The Pharmacokinetic Basis of Therapeutics</b>	<b>1</b>
Introduction		1
Administration of Drugs		2
Duration of Action		2
Nature of the Drugs		2
Special Circumstances		3
Drug Delivery by Iontophoresis or Phonophoresis		3
Liposomal Drug Delivery System		3
Bioavailability		3
Absorption of Drugs		3
Drug Particle Size		4
Buccal and Sublingual Absorption		4
Intranasal Delivery		4
Rectal Administration		5
Transport Mechanisms		5
Passive Diffusion		5
Carrier-Mediated Transport		5
Facilitated Transport		6
Ion Pair Transport		6
Pinocytosis		6
Receptor-Mediated Endocytosis		6
Other Factors Controlling the Rate of Absorption of Drugs		6
Degree of Ionization		7
Surface Area		8
Blood Flow		8
Gastric Emptying Time		8
Hepatic First-Pass Effect		9
Distribution of Drugs		9
Binding of Various Drugs to Plasma Proteins		10
Albumin		10
Alpha <sub>1</sub> -Acid Glycoprotein		10
Other Glycoproteins		10
Lipoproteins		11
Tissue Localization of Drugs		11
Apparent Volume of Distribution of Drugs		12
The Blood–Brain Barrier		12
The Placental Barrier		12
Drugs in Pregnancy and the Newborn		13
Drug Therapy in Pregnancy		13
Drug Therapy in the Newborn		13
The Site of Action of Drugs		13
Nature and Type of Pharmacologic Receptor Sites		13
Dose–Response Relationship		14
Potency and Efficacy		14

Physiologic and Pharmacologic Antagonism .....	16
Enhancement of Drug Action .....	16
Therapeutic Index.....	16
Biotransformation.....	17
Hepatic Drug Metabolism .....	17
Nonhepatic Metabolism.....	17
Plasma .....	17
Lung .....	18
Intestinal Epithelium.....	18
Molecular Biology of Multiple Isoenzymes of P-450 .....	18
Scheme of the Mixed-Function Oxidation Reaction Pathway .....	18
Consequence of Biotransformation Reactions .....	19
Precursor Activation .....	19
Metabolic Activation of Drugs.....	19
Conversion to Metabolites with Dissimilar Actions .....	19
Conversion to More Active Products .....	19
Lethal Synthesis.....	19
Drug Metabolite Kinetics.....	19
Factors That Modify the Metabolism of Drugs .....	20
Pharmacogenetics .....	20
Liver Disease.....	20
The Influence of Age .....	20
Enzyme Induction and Inhibition .....	20
Clinical Implications of Enzyme Induction and Inhibition .....	21
Renal Excretion of Drugs .....	21
Rate of Excretion of Drugs by the Kidneys.....	21
Significance of Blood Flow for Drug Clearance.....	22
Half-Life of a Drug.....	23
<b>Chapter 2 Pharmacodynamics .....</b>	<b>25</b>
Introduction .....	25
Site of Action .....	25
Mode of Action.....	25
Mechanism of Action.....	25
Structure–Activity Relationship.....	25
Drug Actions Unrelated to Structures .....	26
Drug Receptor-Specific Interaction .....	26
Cellular Sites of Actions of Drugs .....	27
Drug–Coenzyme Interactions.....	27
Isoniazid and Pyridoxal Phosphate.....	27
Folic Acid and Trimethoprim-Sulfamethoxazole .....	27
Drug–Enzyme Interactions.....	27
Allopurinol, Xanthine Oxidase, and Hyperuremic States.....	28
Drugs and Bronchial Asthma .....	28
Drug–Nucleic Acid Interactions .....	28
The Interactions of Drugs with Neuronal Elements .....	29
Interaction of Drugs with the Endocrine System.....	29
Alpha-Methyldopa and Renin .....	29
Drugs and Prolactin.....	29

<b>Chapter 3</b>	<b>Adverse Reactions and Drug–Drug Interactions</b>	<b>31</b>
Introduction		31
Definitions		31
Iatrogenic Reactions		31
Allergic Reactions		31
Idiosyncratic Reactions		32
Tolerance and Tachyphylaxis		32
Supersensitivity		33
Pharmacokinetic Interactions		33
Interaction at the Site of Absorption		33
Alteration of Gastric pH		33
Formation of Complex		34
Alteration in Gastric Emptying Time		34
Interactions at the Plasma–Protein Binding Sites		34
Interactions at the Stage of Drug Biotransformation		35
Interactions at the Site of Excretion		36
<b>Chapter 4</b>	<b>Herb–Drug Interactions</b>	<b>37</b>
Herbs and Drug Effects		37
Potential Interactions between Alternative Therapies and Warfarin		38
Anticoagulants and Thrombolytic Agents		38
Aggregin and Platelet Aggregation		42
Vitamin E and Platelet Aggregation		42
Platelet-Activating Factor		42
Platelet-Inhibiting Drugs		42
Fibrinolysis		43
Hirudin and Thrombin		43
Agents that Interfere with Coagulation		43
Oral Anticoagulants		44
Herbs with Coumarin, Salicylate, or Antiplatelet Drugs		44
Feverfew		44
Garlic		45
Ginger		45
Ginkgo		45
Coenzyme Q <sub>10</sub>		45
Danshen		45
Devil’s Claw		46
Ginseng		46
Green Tea		46
Papain		46
Vitamin E		46
<b>Chapter 5</b>	<b>Natural Products as a Resource for Established and New Drugs</b>	<b>49</b>
The Role of Herbal Medicines in Health Care		49
Drug Therapy in Chinese Traditional Medicine		50
Prescription of Multiple Herbs in CTM		50
Pharmacological Classification of Herbs According to CTM		51
Classic Plant Substances		53
Caffeine		53

Capsaicin.....	53
β-Carotene .....	53
Colchicine .....	53
Nordihydroguaiaretic Acid .....	53
Pilocarpine .....	56
Quinine .....	56
Scopolamine (Hyoscyne) .....	56
Tetrahydrocannabinol .....	56
Theophylline .....	56
Antimalarial Agents .....	56
Cardiovascular Drugs.....	57
CNS Drugs .....	57
Antibiotics .....	58
Antineoplastic Agents .....	59
Cholesterol-Lowering Agents (Hypolipemics).....	60
Immunomodulators .....	61
Recently Evaluated Herbal Products .....	61
Aloe Vera Gel ( <i>Aloe vera</i> ).....	61
American Dwarf Palm ( <i>Serenoa repens</i> ) .....	61
Cranberry juice ( <i>Vaccinium</i> spp.).....	61
Evening Primrose Oil ( <i>Oenothera biennis</i> ) .....	61
Feverfew Leaf ( <i>Tanacetum parthenium</i> ).....	62
Garlic ( <i>Allium sativum</i> ) .....	62
Ginger Root ( <i>Zingiber officinale</i> ) .....	62
Ginkgo Leaf ( <i>Ginkgo biloba</i> ).....	62
Hawthorn ( <i>Crataegus monogyna</i> and <i>C. laevigata</i> ) .....	62
Horse Chestnut ( <i>Aesculus hippocastanum</i> ) .....	62
Ipecacuanha ( <i>Cephaelis ipecacuanha</i> and <i>C. acuminata</i> ).....	62
Ispaghula Husk ( <i>Plantago ovato</i> ) .....	63
Kava-Kava ( <i>Piper methysticum</i> ) .....	63
Marijuana ( <i>Cannabis sativa</i> ).....	63
St. John's Wort ( <i>Hypericum perforatum</i> ).....	63
Tea Tree Oil ( <i>Melaleuca alternifolia</i> ) .....	63
Wheat Bran ( <i>Triticum</i> spp.).....	63
New Uses for "Old" Drugs.....	63
<b>Chapter 6</b> Alternative Therapies.....	65
Introduction .....	65
Why Patients Use Alternative Medicine.....	65
Acupressure .....	65
Acupuncture .....	66
Aromatherapy .....	66
Auricular Therapy .....	66
Ayurveda.....	66
Biodynamic Massage .....	67
Bioenergetic Therapy .....	67
Chi Kung Medicine.....	67
Chinese Herbalism .....	68
Chiropractic Medicine.....	68
Crystal and Gem Therapies .....	68

Cupping Therapy.....	68
Dietary and Nutritional Therapies.....	69
Eastern Herbal Medicine.....	69
Environmental Therapies.....	70
Flower and Tree Remedies.....	70
Food and Diet Therapy.....	71
Geopathic Therapy.....	72
Gestalt Therapy.....	72
Herbal Medicine.....	72
Homeopathy.....	74
Hydrotherapy.....	74
Hypnosis and Hypnotherapy.....	74
Iridology.....	74
Japanese Medicine.....	75
Light Therapy.....	75
Massage Therapy.....	75
Shiatsu.....	75
Therapeutic Massage.....	75
Reflexology.....	76
Sports Massage.....	76
Baby Massage.....	76
Biodynamic Massage.....	76
Moxibustion.....	76
Myotherapy.....	76
Native American Herbal Medicine.....	76
Naturopathy ( <i>Medicatrix Naturae</i> ).....	77
Osteopathy.....	77
Persian Medicine.....	77
Polarity Therapy.....	78
Psychic Healing.....	78
Psychological Therapies.....	78
Analytical Therapy.....	78
Behavioral Therapy.....	79
Humanistic Therapy.....	79
Integrative Therapy.....	79
Meditation Therapy.....	79
Sound Therapy.....	79
Reflexology (Reflex Zone Therapy).....	79
Reiki Therapy.....	80
Relaxation Therapies.....	80
Rolfing Medicine.....	80
Shamanistic Medicine.....	80
T'ai Chi Chuan Medicine.....	81
Therapeutic Diets.....	81
Exclusion Diet.....	81
Vegetarian Diet.....	81
Vegan Diet.....	81
Food Combining Diet.....	81
Anti- <i>Candida</i> Diet.....	81
Liver Diet.....	81

Low Blood Sugar Diet .....	81
Macrobiotic Diet.....	82
Tibetan Medicine .....	82
Transcendental Meditation (TM).....	82
Transpersonal Therapies .....	83
Visualization Therapy .....	83
Yoga.....	83
<b>Chapter 7 Herbal Therapeutics Then and Now .....</b>	<b>85</b>
Introduction .....	85
Agnus Castus.....	85
Agrimony.....	85
Alfalfa.....	85
Aloe .....	85
Aloe Vera.....	86
Angelica .....	86
Aniseed.....	86
Apricot.....	86
Arnica .....	86
Artichoke .....	86
Asafoetida.....	86
Avens .....	86
Bayberry .....	87
Black Cohosh.....	87
Bloodroot.....	87
Blue Cohosh.....	87
Blue Flag .....	87
Bogbean.....	87
Boldo .....	87
Boneset.....	87
Borage .....	88
Broom.....	88
Buchu .....	88
Burdock.....	88
Burnet.....	88
Calamus.....	88
Calendula.....	88
Capsicum.....	89
Cascara .....	89
Cascara Sagrada .....	89
Cassia .....	89
Cat's Claw .....	89
Celery .....	89
Centaury .....	89
Cereus.....	89
Chamomile .....	90
Chamomile (German) .....	90
Chamomile (Roman).....	90
Chaparral .....	90
Cinnamon .....	90

Clivers.....	90
Clove .....	90
Cola .....	91
Coltsfoot .....	91
Comfrey.....	91
Corn Silk .....	91
Couchgrass .....	91
Cowslip.....	91
Cranberry.....	91
Damiana .....	92
Dandelion .....	92
Devil's Claw.....	92
Dong Quai.....	92
Drosera .....	92
Echinacea .....	92
Elder .....	92
Elecampane .....	93
Eucalyptus .....	93
Euphorbia .....	93
Evening Primrose .....	93
Eyebright .....	93
False Unicorn .....	93
Fenugreek .....	93
Feverfew .....	93
Figwort .....	94
Frangula.....	94
Fucus .....	94
Fumitory .....	94
Garlic .....	94
Gentian .....	94
Ginger.....	94
Ginkgo.....	95
<i>Ginkgo biloba</i> .....	95
<i>Ginseng (Eleutherococcus)</i> .....	95
<i>Ginseng (Panax)</i> .....	95
Golden Seal.....	95
Gravel Root .....	95
Ground Ivy .....	96
Guaiacum .....	96
Hawthorn .....	96
Holy Thistle.....	96
Hops .....	96
Horehound (Black).....	96
Horehound (White) .....	96
Horse Chestnut.....	96
Horseradish.....	97
Hydrangea .....	97
Hydrocotyle.....	97
Ispaghula .....	97
Jamaica Dogwood.....	97
Juniper .....	97



Kava.....	97
Lady's Slipper .....	97
Lemon Verbena .....	97
Licorice.....	98
Liferoot.....	98
Lime Flower .....	98
Lobelia.....	98
Ma Huang and the Ephedra Alkaloids .....	98
Marshmallow .....	98
Maté.....	99
Meadowsweet.....	99
Mistletoe.....	99
Motherwort.....	99
Myrrh.....	99
Nettle .....	99
<i>Panax ginseng</i> .....	99
Parsley .....	99
Parsley Piert .....	100
Passionflower.....	100
Pennyroyal.....	100
Pilewort .....	100
Plantain.....	100
Pleurisy Root.....	100
Pokeweed.....	100
Poplar .....	100
Prickly Ash (Northern).....	101
Prickly Ash (Southern).....	101
Pulsatilla .....	101
Quassia .....	101
Queen's Delight.....	101
Raspberry .....	101
Red Clover .....	101
Rhubarb .....	102
Rosemary.....	102
Sage .....	102
Sarsaparilla.....	102
Sassafras .....	102
Saw Palmetto.....	102
Senega .....	102
Senna .....	103
Shepherd's Purse .....	103
Skullcap.....	103
Skunk Cabbage .....	103
Slippery Elm .....	103
Squill .....	103
St. John's Wort.....	103
Stone Root.....	104
Tansy .....	104
Thyme.....	104
Uva-Ursi .....	104
Valerian.....	104

Vervain.....	104
Wild Carrot.....	104
Wild Lettuce.....	105
Willow.....	105
Witch Hazel.....	105
Yarrow.....	105
Yellow Dock.....	105
Yucca.....	105
<b>Chapter 8 Dietary Antioxidants.....</b>	<b>107</b>
Introduction.....	107
The Role of Diet in Curing and Preventing Diseases.....	107
Antioxidant Capacity of Vegetables and Fruits.....	107
Antioxidant Activity in Cereal Grains.....	108
Antioxidant Actions of Du-Zhong.....	108
Oxidative Stress and Chemotherapeutic Effectiveness.....	110
Principle of Cancer Therapy.....	110
Chemotherapy.....	110
Alkylating Agents.....	112
Nitrogen Mustards.....	112
Chlorambucil.....	112
Cyclophosphamide.....	112
Alkyl Sulfonate.....	112
Nitrosoureas.....	113
Triazines.....	113
Antimetabolites.....	113
Folic Acid Analogs.....	113
Pyrimidine Analogs.....	113
Deoxycytidine Analogs.....	114
Purine Antimetabolites.....	115
Natural Products.....	115
Vinca Alkaloids.....	115
Dactinomycin.....	116
Mithramycin.....	116
Daunorubicin and Doxorubicin.....	116
Bleomycin.....	116
Miscellaneous Antineoplastic Agents.....	116
Asparaginase.....	116
Hydroxyurea.....	117
<i>Cis</i> -Platinum.....	117
Carboplatin.....	117
Procarbazine.....	117
Etoposide.....	117
Cancer-Chemotherapy-Induced Emesis.....	117
Oxidative Stress and Interference with the Cytotoxic Effects of Antineoplastic Agents.....	117
Antioxidant Effects on Antineoplastic Activity and Chemotherapy-Induced Side Effects.....	118
Vitamin E.....	118
Vitamin C.....	119
Coenzyme Q <sub>10</sub> (Ubiquinone).....	119
β-Carotene.....	120

Glutathione (GSH) and Glutathione Esters .....	120
<i>N</i> -Acetylcysteine.....	121
Glutamine .....	121
Selenium .....	121
Genistein and Daidzein .....	122
Quercetin.....	122
Conclusions .....	123
<b>Chapter 9</b> Herbal Drugs and Their High Demand in Treating Diseases .....	125
Introduction .....	125
Laws Regulating Herbs and Dietary Supplements.....	126
Food, Drug, and Cosmetic Act .....	126
Nutrition Labeling and Education Act of 1990.....	126
Dietary Supplement Health and Education Act of 1994.....	127
Food and Drug Administration Modernization Act.....	127
Scientists Who Pioneered Herbal Medicine .....	128
<b>Chapter 10</b> Algae.....	139
Introduction .....	139
Kainic Acid .....	140
Domoic Acids.....	141
Toxicity of <i>Caulerpa</i> .....	142
Toxicity of <i>Gracilaria</i> .....	142
<b>Chapter 11</b> Alkaloids.....	143
Introduction .....	143
Classification .....	144
The Group Containing Aliphatic Bases with an Aromatic Nucleus .....	144
The Pyrrolidine Group .....	144
The Pyridine Group.....	144
The Glyoxaline Group.....	146
Alkaloids with Condensed Pyrrolidine and Piperidine Rings.....	146
Derivatives of Quinoline .....	147
Derivatives of Isoquinoline .....	147
Phenanthrene.....	147
Indole Derivatives.....	147
The Purine Bases.....	148
Alkaloids of Unknown Constitution .....	149
<b>Chapter 12</b> Aloe and Colon Function .....	151
Introduction .....	151
Aloe Preparations .....	151
Chemical Composition of Aloe Plants .....	152
The Therapeutic Uses of Aloe.....	152
Aloe and Cancer.....	152
Aloe and AIDS .....	153
Aloe and Asthma.....	153

Aloe and Diabetes .....	153
Aloe Gel and Skin Ailments .....	153
Aloe and Constipation .....	153
Movements of the Colon .....	154
Mixing Movements: Haustrations .....	154
Propulsive Movements: “Mass Movements” .....	154
Initiation of Mass Movements by the Gastrocolic and Duodenocolic Reflexes .....	155
Defecation .....	155
The Defecation Reflexes .....	155
Other Autonomic Reflexes Affecting Bowel Activity .....	157
Constipation .....	157
Definition .....	157
Causes .....	158
Cathartics.....	158
Emodin or Anthraquinone Cathartics.....	159
Cascara Sagrada.....	160
Senna.....	160
Rhubarb.....	160
Aloe.....	160
Castor Oil .....	161
Ricin.....	161
Abrin.....	161
Croton Oil.....	161
Resin of Podophyllum.....	162
Jalap, Scammonium, Ipomea .....	162
Colocynth, Elaterin, and Bryonia.....	162
<b>Chapter 13</b> Banisterine, Selegiline, and Parkinson’s Disease .....	163
Introduction .....	163
The Actions of Acetylcholine and Dopamine .....	163
History .....	164
Selegiline .....	164
Clinical Pharmacokinetics of Selegiline.....	165
Lack of Adverse Interaction between Selegiline and Citalopram or between Selegiline and Cabergoline .....	166
Distribution of Monoamine Oxidases A and B mRNAs in the Rat Brain by <i>In Situ</i> Hybridization .....	167
Inhibition of Monoamine Oxidase B by Banisterine and Selegiline and the Initial Rationale of Using Them in Parkinson’s Disease.....	168
Protection of Dopaminergic Neurons by Rasagiline.....	169
Protection against MPTP-Induced Neurotoxicity by Selegiline .....	171
Protection by Selegiline of Dopaminergic Neurons in Culture from Toxic Factors.....	172
Protection by Selegiline of Dopaminergic Neurons from Glutamate-Induced Excitotoxicity .....	173
Selegiline: A Calmodulin Antagonist .....	175
Induction by Selegiline of Dopamine Release through an ATP-Sensitive Potassium Channel .....	176
Neurotrophic-Like Action of Selegiline: Rescue of Axotomized Motorneurons Independent of Monoamine Oxidase Inhibition .....	177
Restoration by Selegiline of Serum Insulin-Like Growth Factor-I in Aged Rats .....	181

Protection by Selegiline of Dopaminergic Neurons from Toxicity Induced by Glutathione Depletion.....	182
Increase by Selegiline of the Striatal Superoxide Dismutase .....	185
Protection by Selegiline against Peroxynitrite- and Nitric-Oxide-Induced Apoptosis.....	186
Antiapoptotic Actions of Selegiline in a Variety of Neurons.....	187
Stimulation by Selegiline of Biosynthesis of Cytokines Interleukin-1 $\beta$ and Interleukin-6.....	188
Interleukin 1 .....	189
Interleukin 6 .....	189
Banisterine and Selegiline for the Treatment of Parkinson's Disease.....	190
Rigidity .....	191
Hypokinesia .....	191
Abnormal Gait and Posture.....	191
Other Clinical Features .....	191
Summary and Conclusions .....	193
<b>Chapter 14</b> Belladonna Alkaloids: Autonomic Drugs .....	195
Introduction .....	195
Solanaceae or Nightshade Family .....	195
Occurrence.....	196
History .....	196
Chemistry.....	197
Botany of Solanaceae .....	198
Pharmacognosy of Belladonna .....	198
Preparation of the Leaves.....	199
Preparations of the Root.....	199
Atropine and Its Derivatives .....	199
Belladonna Alkaloids and the Autonomic Nervous System .....	199
Comparison of the Somatic and Autonomic Nervous Systems .....	199
Neurochemical Basis of Cholinergic Transmission .....	200
Division and Functions of the Autonomic Nervous System.....	200
Classification of Cholinergic Receptors .....	202
Cholinergic Receptor Blocking Agents .....	203
Dose-Dependent Effects of Atropine.....	203
The Historical Uses of Belladonna Alkaloids.....	203
The Modern Uses of Synthetic Muscarinic Receptor Antagonists.....	204
Contraindications to Anticholinergic Agents.....	205
Hyoscyamine .....	205
Scopolamine.....	205
Synthetic and Semisynthetic Substitutes for Belladonna Alkaloids.....	206
Quaternary Ammonium Muscarinic Receptor Antagonists.....	206
Ipratropium .....	206
Methoscopolamine.....	207
Homatropine Methylbromide .....	207
Methantheline .....	207
Propantheline .....	207
Other Compounds.....	208
Tertiary-Amine Muscarinic Receptor Antagonists .....	208
<b>Chapter 15</b> Blueberry ( <i>Vaccinium</i> ).....	209

<b>Chapter 16</b> Botulinum Toxin.....	213
Introduction .....	213
Botulinum Toxin Type A (Oculinum) .....	213
Botulism Antitoxin, Trivalent (ABE) Equine.....	213
Uses of Botulinum Toxin Injection in Medicine Today.....	213
Rationale for Treatment with Botulinum Neurotoxin.....	214
Ophthalmic Disorders.....	214
Movement Disorders .....	215
Spasticity.....	215
Neuromuscular Disorders.....	215
Pain .....	216
Ear, Nose, and Throat Disorders.....	216
Disorders of Pelvic Floor.....	216
Overactivity of Smooth Muscles.....	216
Hypersecretion of Glands Supplied by Cholinergic Sympathetic or Parasympathetic Neurons.....	216
 <b>Chapter 17</b> Brussels Sprouts .....	 217
Introduction .....	217
Effects of Brussels Sprouts on Oxidative DNA Damage .....	217
 <b>Chapter 18</b> Cannabis .....	 221
Introduction .....	221
The Psychoactive Effects of Cannabis .....	221
Marijuana in History.....	223
Botanical Properties of <i>Cannabis indica</i> or Indian Cannabis (Indian Hemp) .....	224
Marijuana-Induced Inebriation .....	225
Cannabinoid Receptor Subtypes.....	226
Cannabinoid Receptor (CB <sub>1</sub> ).....	227
Cannabinoid Receptor (CB <sub>2</sub> ).....	227
Cannabinoid Receptors and Their Endogenous Agonist, Anandamide .....	227
Central Nervous System Cannabinoid Receptors .....	228
Therapeutic Potential of Cannabinoid Ligands.....	228
Movement Disorders .....	228
Multiple Sclerosis.....	229
Huntington's Chorea.....	229
Neuroprotection .....	229
Cannabis for Migraine.....	230
Antiemetic Effects of Cannabis.....	230
The Physiology of Vomiting .....	230
The Central Control of Vomiting .....	230
Drugs to Control the Vomiting Caused by Cancer Therapy .....	231
Ondansetron.....	231
Dexamethasone.....	231
Metoclopramide.....	232
Phenothiazines .....	233
Cannabinoids.....	233
Benzodiazepines.....	233
Anticipatory Nausea and Vomiting .....	233

Delayed Emesis .....	233
Multiple-Day Cisplatin Chemotherapy .....	233
Summary.....	233
Cannabis for Dyskinesia .....	234
Conclusion.....	236
<b>Chapter 19</b> Capsicum, Rosemary, and Turmeric .....	237
<b>Chapter 20</b> Carotenoids .....	239
Introduction .....	239
Prostate Cancer .....	240
Breast Cancer .....	240
Cancer of the Head and Neck .....	240
Cardiovascular Disease .....	240
Age-Related Macular Degeneration .....	241
<b>Chapter 21</b> Chocolate .....	243
<b>Chapter 22</b> Cinchona Tree.....	245
Introduction .....	245
Cinchona: A Peruvian Bark .....	245
Varieties of Cinchona.....	245
Composition of Cinchona .....	245
Quinine for Treatment of Malaria .....	247
Blood Schizonticides.....	248
Quinine Sulfate: A Classic Drug .....	248
Other Actions of Quinine.....	250
Colloids and Surface Phenomena .....	250
Local Actions.....	251
Ulcers .....	251
Sunburn Prophylaxis .....	251
Quinine as Anesthetic.....	251
Antiseptic Action .....	251
Effect on Digestion.....	251
Antipyretic Action .....	251
Use of Quinine in Colds, Headaches, and Neuralgias .....	252
Skeletal Muscle .....	252
Cinchonism .....	252
Skin Eruptions and Idiosyncrasy .....	252
<b>Chapter 23</b> Coca .....	253
Introduction .....	253
Coca.....	253
Habitat .....	253
Synonym .....	253
Er-y-throx'y-lon L. ....	253
Co'ca.....	253
History .....	253

Plant.....	254
Commercial Properties.....	255
Botanical Properties.....	255
Chemical Composition.....	256
Cocaine as a Local Anesthetic.....	256
General Pharmacology of Local Anesthesia.....	257
Vascular Supply at the Site of Injection.....	257
Systemic Reactions.....	258
Cardiovascular Effects.....	258
Central Nervous System Effects.....	258
Allergic Reactions.....	258
Effect of Cocaine.....	259
Mechanism of Local Anesthetic Action of Cocaine.....	259
Detailed Pharmacology of Cocaine as a Local Anesthetic.....	259
Selective Action on Motor and Sensory Fiber.....	260
Peripheral Paralysis of Special Sense Nerves.....	261
Site of Action.....	261
Combination of Anesthetics.....	261
Potassium Synergism.....	261
Alkalinization.....	261
Other Synergisms.....	262
Epinephrine Anesthetic Combinations.....	262
Local Vascular Action.....	262
Practical Application of Local Anesthetics.....	262
Local Ischemia.....	263
Surface Anesthesia.....	263
Ophthalmic Anesthesia.....	263
Actions of Cocaine on the Eye.....	263
Insoluble Anesthetics for Open Wounds and Ulcers.....	263
Conduction and Infiltration Anesthesia.....	264
Spastic Rigidity of Skeletal Muscles.....	264
Spinal Anesthesia.....	264
Sympathetic Stimulation.....	264
Circulation.....	265
Cerebral Stimulation.....	265
Incoordination, Narcosis, and Convulsions.....	265
Emesis.....	265
Temperature.....	265
Examples of Currently Used Local Anesthetics.....	265
Procaine.....	265
Chlorprocaine.....	265
Tetracaine.....	266
Lidocaine.....	266
Mepivacaine.....	266
Prilocaine.....	266
Bupivacaine.....	266
Etidocaine.....	266
Clinical Uses of Local Anesthetics.....	266
Infiltration Anesthesia.....	266
Field Block Anesthesia.....	266
Nerve Block Anesthesia.....	267



Intravenous Regional Anesthesia (Bier's Block) .....	267
Spinal Anesthesia.....	267
Epidural Anesthesia.....	268
Epidural and Intrathecal Opiate Analgesia .....	268
Safe and Toxic Dosage of Local Anesthetics.....	268
Destruction of Cocaine <i>In Vitro</i> : Sterilization .....	269
Cocaine, A "Nerve Stimulant".....	269
Cocaine Addiction .....	270
Uses of Cocaine in the 18th Century.....	270
Cocaine: A Psychostimulant .....	270
Cocaine Blocks Dopamine Transporter .....	271
Biosynthesis of Dopamine .....	271
Cocaine Withdrawal Symptoms and Signs.....	272
Pharmacological Interventions .....	272
<b>Chapter 24 Colchicine and Gout.....</b>	<b>275</b>
Introduction .....	275
History.....	275
Gout and Hyperuricemia.....	275
Allopurinol .....	276
Uricosuric Agents.....	276
Treatment with Colchicine for Gout.....	277
Pharmacological Properties .....	277
Effect in Gout .....	277
Effect on Cell Division.....	277
Other Effects.....	277
Pharmacokinetics and Metabolism .....	278
Toxic Effects.....	278
Therapeutic Uses .....	278
Acute Attacks.....	278
Prophylactic Uses .....	279
Other Uses of Colchicine.....	279
<b>Chapter 25 Compositae .....</b>	<b>281</b>
Introduction .....	281
Sesquiterpene Lactones.....	281
Sesquiterpene-Induced Neurotoxicity.....	282
Tanacetum Parthenium (Feverfew) .....	282
Other Asteraceae Groups .....	283
Achillea.....	283
Artemisia.....	283
Baccharis.....	284
Elephantopus.....	285
Helenium.....	285
Montanoa .....	285
Packera.....	285
Parthenium.....	285
Tithonia.....	285

<b>Chapter 35</b> Foxglove, Cardiac Glycosides, and Congestive Heart Failure .....	355
Digitalis .....	355
The Digitalis Series.....	355
Chemistry .....	356
Cardiac Glycosides in the Treatment of Congestive Heart Failure .....	358
Biochemical Basis of Myocardial Contraction .....	359
The Positive Inotropic Action of Cardiac Glycosides.....	360
The Modes of Action of Cardiac Glycosides .....	360
Electrophysiological Effects of Cardiac Glycosides .....	360
Digitalis Toxicity .....	361
Symptoms of Digitalis Toxicity .....	361
Cardiac Effects.....	361
Gastrointestinal Effects.....	362
Visual Effects .....	362
Neuropsychiatric Symptoms.....	362
Treatment of Digitalis Toxicity .....	362
General Treatment.....	362
Specific Treatment .....	362
Antidigoxin Antibodies.....	362
Drugs Acting on Peripheral Dopamine Receptors .....	362
Dopamine Receptors .....	362
Drugs Inhibiting Phosphodiesterase .....	363
Vasodilators and Angiotensin Antagonists .....	363
Receptor-Dependent Vasodilation .....	364
Endothelium-Dependent vs. Independent Vasodilators .....	364
 <b>Chapter 36</b> <i>Ginkgo biloba</i> .....	367
Introduction .....	367
<i>Ginkgo biloba</i> Extract and Inhibition of Monoamine Oxidase A and B in Living Human Brain.....	367
<i>Ginkgo biloba</i> and Nitric Oxide .....	368
 <b>Chapter 37</b> Ginseng and Cholinergic Transmission .....	371
Introduction .....	371
Cholinergic Transmission.....	372
Division and Functions of the Autonomic Nervous System .....	372
Neurochemical Basis of Cholinergic Transmission.....	373
Classification of Cholinergic Receptors.....	373
Cholinergic (Cholinomimetic) Receptor Agonists.....	374
Anticholinesterase Agents .....	374
Structure of Acetylcholinesterase .....	374
Classification of Cholinesterase Inhibitors .....	374
Antidote to Irreversible Cholinesterase Inhibitors.....	375
Cholinergic Receptor Blocking Agents.....	375
Dose-Dependent Effects of Atropine .....	376
Synthetic Muscarinic Receptor Antagonists .....	376
Ophthalmology.....	376
Preoperative Uses.....	376
Cardiology.....	376

Gastroenterology .....	376
Neurology.....	377
Contraindication to Anticholinergic Agents.....	377
Other CNS Actions of Ginseng.....	377
Antineoplastic and Immunomodulatory Effects of Ginseng.....	377
<b>Chapter 38</b> Green, White, and Black Teas.....	379
Introduction .....	379
Antioxidant Properties .....	379
The Efficacy of Tea in Attenuating Skin Cancer .....	380
Anticariogenic Effects of Tea .....	381
Pathogenesis of Dental Caries.....	381
Potential Anticariogenic Actions of Tea .....	381
Benefits of White Tea.....	381
<b>Chapter 39</b> Herbal Plants and Tuberculosis.....	383
Antituberculosis Efficacy of Natural Products .....	383
Mycobacterial Diseases.....	384
Tuberculosis.....	384
Leprosy .....	384
Other Diseases .....	385
Antimicrobial Activity of Plants .....	385
<b>Chapter 40</b> Herbal Products for the Chemotherapy of Human Immunodeficiency Virus Infection .....	387
Introduction .....	387
Herbal Products Used in HIV Therapy .....	387
Etiological Agent.....	388
Life Cycle of HIV.....	388
Immunopharmacology .....	390
Immune System Components .....	390
Cyanovirin-N.....	391
Sulfated Polysaccharides.....	392
Ingenol Derivatives .....	392
Flavonoids .....	392
Glycyrrhizin.....	393
Mannose-Specific Plant Lectins.....	393
Siamycins .....	393
Betulinic Acids.....	393
Polyphemosins .....	394
Baicalin.....	394
Avarol, Avarone, Psychotrine, and Phloroglucinol Derivatives (i.e., Mallotojaponin).....	394
Calanolides and Inophyllums.....	395
Illimaquinone .....	395
Curcumin, Curcumin Analogs, Dicafeoylquinic Acid, and L-Chicoric Acid .....	395
Equisetin.....	396
Melittin .....	396
Trichosantin, MAP30, GAP31, DAP31, and DAP32 .....	396

Bellenamine.....	396
Hypericin and Pseudohypericin .....	397
<b>Chapter 41</b> Honey: The Nectar of Life.....	399
Introduction .....	399
Wonder of Honey.....	399
Curative Properties of Honey .....	400
Common Kinds of Honey.....	400
Honey: An Antioxidant .....	403
Honey Enhances Memory Formation.....	403
Neurochemical Basis of Cholinergic Transmission .....	403
Classification of Cholinergic Receptors.....	403
Honey and the Treatment of Wounds and Burns .....	404
Honey for the Treatment of Peptic Ulcers .....	405
Honey for the Treatment of Gastroenteritis .....	405
Honey in Inflammatory Bowel Disease.....	406
Honey Protects against Carcinogenesis.....	406
Honey in the Treatment of Herpes Simplex Lesions .....	407
Treatment of Bullous Keratopathy with Honey .....	407
<b>Chapter 42</b> Horseradish and Antiplatelet Actions.....	409
Introduction .....	409
Antiplatelet Drugs.....	409
Aspirin .....	409
Dipyridamole .....	411
Ticlopidine .....	411
Therapeutic Uses of Anticoagulant, Thrombolytic, and Antiplatelet Drugs .....	412
Venous Thromboembolism.....	412
Myocardial Infarction.....	412
Unstable Angina .....	412
Saphenous Vein Bypass Grafts.....	412
Percutaneous Transluminal Coronary Angioplasty.....	412
Atrial Fibrillation.....	412
Prosthetic Heart Valves.....	412
Valvular Heart Disease.....	413
Cerebrovascular Disease.....	413
Peripheral Vascular Disease .....	413
Primary Prevention of Arterial Thromboembolism .....	413
<b>Chapter 43</b> Hypericum (St. John's Wort) and Depression .....	415
Introduction .....	415
St. John's Wort.....	416
Botanical Name .....	416
Family .....	416
Synonyms .....	416
Common Names .....	416
Commercial Products .....	416
Active Ingredients.....	416

Hypericum (St. John's Wort) in Folk Medicine and Traditional Systems of Medicine.....	417
Antidepressants .....	417
Neurotransmitters and Their Role in Depression.....	419
Classification of Antidepressants .....	419
Dibenzapine Derivatives .....	419
Conversion to Pharmacologically Active Metabolites.....	420
Various Properties of the Tricyclic Antidepressants.....	420
The Sites of Action of Antidepressants .....	420
Side Effects of Antidepressants.....	422
Therapeutic Indications .....	422
Fatal Overdoses .....	423
Monoamine Oxidase Inhibitors .....	424
Indications for Monoamine Oxidase Inhibitors.....	424
Newer, Novel, or Atypical Antidepressants.....	424
Control of Manic Episodes in Manic-Depressive Psychosis Using Lithium .....	425
Pharmacokinetics.....	425
Side Effects.....	425
Pharmacodynamics of Lithium .....	426
Therapeutic Uses of Lithium .....	426
Regulatory Status of Hypericum.....	426
<b>Chapter 44</b> Ipecac.....	427
Ipecacuanha and Emetine .....	427
Ipecac .....	427
History .....	427
Active Principles.....	427
Status and Use .....	427
Drugs That Produce Vomiting (Emetics).....	429
Source, Nature, and Preparations.....	429
Nature of Emetic Action of Ipecac .....	430
Clinical Effects .....	431
Prevention of Further Absorption of Poison .....	431
Emesis.....	431
Syrup of Ipecac .....	432
Monitoring .....	432
Amebiasis .....	433
Treatment of the Asymptomatic Carrier .....	433
Treatment of Acute Amebic Dysentery .....	433
Treatment of Amebic Hepatitis and Abscess.....	433
<b>Chapter 45</b> Manuka and Fungal Disease .....	435
Tea Tree Oils from Australia and New Zealand .....	435
Fungal Diseases.....	436
Antifungal Agents .....	436
Systemic Antifungal Agents.....	436
Amphotericin B .....	436
Pharmacodynamics .....	437
Pharmacokinetics and Proper Usage .....	437
Flucytosine.....	438

Ketoconazole .....	438
Fluconazole.....	438
Griseofulvin.....	438
Nystatin.....	439
Topical Antifungal Agents .....	439
Clotrimazole .....	439
Econazole.....	439
Miconazole .....	439
Terconazole and Butoconazole.....	439
Ciclopirox Olamine .....	440
Haloprogin .....	440
Tolnaftate .....	440
Naftifine .....	440
Undecylenic Acid .....	440
Benzoic Acid and Salicylic Acid .....	440
Aromatherapy Cautions .....	440
<b>Chapter 46</b> Marine Therapeutics.....	441
<b>Chapter 47</b> Morphine: <i>Papaver somniferum</i> .....	445
Introduction .....	445
Opioid Analgesics in History.....	445
Friedrich Wilhelm Adam Sertürner and Opium.....	446
Opium.....	446
Cultivation, Collection, and Commerce .....	447
Morphine and Other Narcotic Analgesics .....	448
Multiple Medications to Treat Painful Conditions.....	448
Endogenous Opioid Peptides .....	449
Opioid Receptors.....	449
The Evidence for Multiple Opioid Receptors .....	449
Distribution of Opioid Receptors.....	450
Proposed Functions of the Opioid Receptor Subtypes.....	450
Morphine and Related Compounds .....	452
Morphine: A Naturally Occurring Analgesic.....	452
Effects on the Central Nervous System .....	452
Analgesic Effects .....	455
Therapeutic Uses of Morphine .....	456
Sedation and Sleep.....	458
Side Effects of Morphine.....	459
Morphine-Induced Addiction.....	460
Withdrawal Symptoms.....	462
Antidiarrheal Effects .....	463
Oliguric Effect .....	463
Morphine-Induced Tolerance.....	464
Natural Opium Alkaloids .....	464
Codeine .....	464
Papaverine.....	464
Noscapine .....	465
Synthetic Derivatives of the Opium Alkaloids.....	465
Heroin (Diamorphine) .....	465

Dihydrocodeinone.....	466
Dihydromorphinone.....	466
Dextromethorphan Hydrobromide .....	466
Levorphanol Tartrate.....	467
Ethylmorphine .....	467
Apomorphine .....	467
Symptoms.....	467
Nonopiate Addicting Analgesics.....	468
Meperidine (Pethidine).....	468
Action.....	468
Undesirable Side Effects.....	469
Metabolism.....	469
Therapeutic Use .....	469
Methadone .....	469
Action.....	470
Mechanism of Action.....	470
Therapeutic Uses.....	470
Alphaprodine Hydrochloride.....	470
Anileridine .....	471
Phenazocine .....	471
Piminodine Ethanesulfonate.....	471
Dextropropoxyphene .....	471
Opioids with Mixed Actions: Agonists–Antagonists and Partial Agonists .....	472
Opioid Receptor Antagonists .....	472
Antitussive Preparations .....	472
<b>Chapter 48</b> Oats ( <i>Avena sativa</i> L.) and Their Antioxidant Activity .....	473
Introduction .....	473
<b>Chapter 49</b> Olives and Olive Oil.....	475
<b>Chapter 50</b> Onion and Garlic .....	477
Introduction .....	477
Active Ingredients in Onion and Garlic .....	477
Inhibition of Platelet Aggregation by Onion and Garlic.....	478
Anticoagulants and Thrombolytic Agents.....	478
Aggregin and Platelet Aggregation.....	478
Vitamin E and Platelet Aggregation.....	479
Platelet-Activating Factor.....	479
Platelet-Inhibiting Drugs .....	479
Eicosanoids.....	479
Pharmacokinetic Properties of the Eicosanoids.....	479
Physiology of the Eicosanoids .....	479
The Pharmacodynamics of Eicosanoids .....	480
The Therapeutic Uses of Eicosanoids.....	481
Agents That Alter Metabolism of Eicosanoids.....	481
Effect of Garlic and Onions on Eicosanoid Metabolism .....	482
Cardiovascular and Lipid-Lowering Effects of Garlic.....	482
Garlic and Cancer Prevention.....	483

Anticlastogenic Effects of Garlic and Onion .....	483
Antimicrobial Effects of Garlic and Onion .....	483
The Antioxidant Actions and Other Therapeutic Effects of Garlic .....	484
Cardioprotective Actions of Wild Garlic ( <i>Allium ursinum</i> ) in Ischemia and Reperfusion .....	484
ACE Inhibitors .....	484
Myocardial Infarction .....	485
Progressive Renal Impairment .....	485
Scleroderma Renal Crisis .....	486
Antioxidant Activity of Allicin, an Active Principle in Garlic .....	486
Attenuation of Ischemic Brain Damage by Aged Garlic Extracts.....	487
Inhibition of Free-Radical Generation and Augmentation of Antioxidant Enzyme	
Activity in Vascular Endothelial Cells by Garlic.....	488
Attenuation of Renal Oxidative Stress with Garlic Oil .....	489
Amelioration of Hyperlipidemia in Chronic Aminonucleoside Nephrosis by Garlic .....	490
Amelioration of Gentamicin Nephrotoxicity by Garlic: Relation to Antioxidant Enzymes.....	491
<b>Chapter 51</b> Immunoenhancing Actions of Plantain .....	493
Introduction .....	493
Immunopharmacology .....	494
Therapies That Enhance or Suppress the Immune System.....	494
Radioimmunotherapy .....	494
Cell Transfer Therapy and Cancer .....	494
Immunosuppressive Agents.....	494
Corticosteroids .....	496
Cytotoxic Compounds as Alkylating Agents .....	496
Antimetabolites .....	497
Cyclosporin A and Dihydrocyclosporin C .....	497
Antilymphocyte Globulin .....	497
Rho (D) Immune Globulin .....	497
Immunomodulating Agents.....	498
Summary .....	498
<b>Chapter 52</b> Plants and Diabetes .....	499
Introduction .....	499
Antidiabetic Agents.....	499
Effects of Food on Insulin Release .....	500
Effects of Fasting on Insulin Release.....	500
Metabolic Consequences of Diabetes Mellitus .....	500
Diabetes Mellitus and Pregnancy .....	501
Classes of Diabetes Mellitus .....	502
Signs and Symptoms of Diabetes.....	502
Complications of Diabetes.....	502
Vascular Complications .....	502
Neuropathy .....	502
The Insulin Receptor.....	502
Structure and Function .....	502
Termination of Insulin Signal .....	503
Clinical Syndromes Associated with Cellular Defects in Insulin Receptor .....	503



Treatment of Diabetes Mellitus .....	503
Dietary Treatment.....	503
Drug Treatment.....	504
Insulin.....	504
Oral Hypoglycemic Agents .....	505
Receptors for Sulfonylurea and Their Mechanism of Action .....	506
Treatment of Diabetic Ketoacidosis .....	506
<b>Chapter 53</b> Pomegranate .....	507
<b>Chapter 54</b> Pycnogenol .....	509
Introduction .....	509
Antioxidant Activity of Pycnogenol .....	509
Vasorelaxant Activity .....	510
Inhibition of Platelet Aggregation .....	510
Enhancement of Microcirculation .....	510
Inhibition of Elastase Activity .....	511
Regulation of Inflammatory Response .....	511
Modulation of Macrophage Activity .....	511
Summary .....	511
<b>Chapter 55</b> <i>Pygeum africanum</i> and Permixon for the Treatment of Patients with Benign Prostatic Hyperplasia .....	513
Introduction .....	513
Urinary Symptoms and Flow Measures .....	514
Permixon in the Treatment of Symptomatic Benign Prostatic Hyperplasia.....	514
<b>Chapter 56</b> Reserpine .....	515
Introduction .....	515
The <i>Rauwolfia</i> Alkaloids.....	515
Chemistry .....	515
Pharmacology.....	516
Mechanism of Action.....	517
Prevention of the Storage of Norepinephrine by Reserpine .....	518
Neurochemical Basis of Adrenergic Transmission.....	518
Catecholamine Metabolism.....	519
Adrenergic Neuronal-Blocking Drugs.....	519
Side Effects .....	519
<b>Chapter 57</b> Rhubarb.....	521
Introduction .....	521
Rhubarb and Its Laxative Properties .....	521
Constipation .....	522
Laxatives and Cathartics .....	523
Irritants.....	523
Bulk Saline Laxatives.....	523
Lubricants .....	523

Other Uses of Laxatives.....	524
Antioxidant Properties of Rhubarb.....	524
<b>Chapter 58 Saffron .....</b>	<b>525</b>
Introduction .....	525
Antioxidant Effect of Saffron .....	525
Effect of Saffron on Learning and Memory.....	525
Possible Molecular Target of Crocin.....	526
<b>Chapter 59 Salicylate.....</b>	<b>529</b>
Introduction .....	529
Source.....	529
Official Salicylates Used in the Early 20th Century.....	529
Analgesics–Antipyretics and Anti-Inflammatory Agents .....	530
Mechanism of Action of Aspirin .....	531
Aspirin and Its Uses.....	531
Aspirin-Induced Analgesia .....	531
Aspirin-Induced Antipyresis.....	532
Uricosuric Effects of Aspirin .....	532
Anti-Inflammatory Effects of Aspirin .....	532
Aspirin and Cardiovascular Disease .....	532
Aspirin and the Premenstrual Syndrome .....	532
Side Effects of Aspirin.....	532
Effects of Salicylate on Respiration.....	532
Treatment of Aspirin Poisoning .....	533
The Gastrointestinal Effect of Aspirin.....	533
The Hematopoietic Effect of Aspirin.....	533
New Uses of Aspirin.....	533
Salicylate Protects against MPTP-Induced Parkinsonism.....	534
Health Effects of Salicylates in Foods .....	535
Aspirin-Induced Asthma .....	535
Aspirin and Other Natural Inhibitors of Tumor Necrosis Factor- $\alpha$ Production, Secretion, and Function.....	540
Inhibition of TNF Production and Secretion .....	540
Inhibitors of TNF-Mediated Cytotoxicity .....	542
<b>Chapter 60 Sex Herbs.....</b>	<b>545</b>
Introduction .....	545
Impotence .....	545
Normal Sexual Function .....	546
Failure of Erection .....	547
Therapy.....	547
Drugs That Stimulate Sexual Behavior .....	549
Levodopa .....	549
Amyl Nitrite.....	549
Vitamin E.....	550
Sildenafil (Viagra) .....	550
Emerging Pharmacological Therapies for Erectile Dysfunction.....	550

<b>Chapter 61 Sponges and Steroids</b> .....	553
Introduction .....	553
Examples of Steroids Found in Sponges.....	553
Polyoxygenated Steroids .....	553
Steroid Sulfates.....	553
Steroids with Unconventional Side Chains .....	554
Adrenal Steroids.....	554
The Synthesis of Cholesterol .....	555
Classification of Adrenal Steroids.....	555
The Glucocorticoids.....	555
The Mineralocorticoids.....	556
The Sex Hormones .....	557
Regulation of Adrenal Steroid Biosynthesis.....	557
Adrenocorticotrophic Hormones .....	558
Actions and Pharmacological Applications of Glucocorticoids.....	558
Central Nervous System Effects.....	559
Calcium Metabolism.....	560
Contraindications to Glucocorticoid Therapy .....	561
Adrenal Disorders — Cushing’s Syndrome .....	561
Reproductive Pharmacology .....	561
Steroid Hormones.....	561
Receptors.....	561
Receptor Antagonists .....	561
Estrogens.....	562
Progesterone .....	564
Antifertility Agents .....	566
Androgens.....	566
 <b>Chapter 62 Taxol (Paclitaxel) and Cancer Chemotherapy</b> .....	571
Introduction .....	571
Chemical Groups of Natural Products with Anticancer Properties .....	571
Cancer Chemotherapy.....	574
Alkylating Agents .....	575
Nitrogen Mustards .....	575
Chlorambucil .....	576
Cyclophosphamide .....	576
Alkyl Sulfonate.....	576
Nitrosoureas.....	576
Triazenes.....	576
Antimetabolites .....	576
Folic Acid Analogues .....	576
Pyrimidine Analogs .....	577
Deoxycytidine Analogs .....	578
Purine Antimetabolites .....	578
Natural Products.....	579
Vinca Alkaloids .....	579
Dactinomycin.....	579
Mithramycin .....	579
Daunorubicin and Doxorubicin.....	580

Bleomycin.....	580
Paclitaxel and Docetaxel.....	580
Miscellaneous Antineoplastic Agents.....	581
Asparaginase.....	581
Hydroxyurea.....	581
<i>Cis</i> -Platinum.....	581
Carboplatin.....	581
Procarbazine.....	581
Etoposide.....	582
Cancer Chemotherapy-Induced Emesis.....	582
<b>Chapter 63</b> Tomatoes and Medicine.....	583
Lycopene and Prostate Cancer.....	583
History of Carotenoids.....	584
Physicochemical Nature of Carotenoids.....	584
Lycopene: An Important Carotenoid in Tumor Suppression.....	584
Carotenoid Content of Fruits and Vegetables.....	584
Distribution of Lycopene in Humans.....	585
Concentrations of Carotenoids in Human Organs.....	585
Tomatoes, Lycopene, and Cancer Risk.....	587
Lung and Pleural Cancers.....	587
Quenching of Reactive Oxygen by Lycopene.....	588
<b>Chapter 64</b> Ulcer Therapy with Herbal Medicine.....	591
Introduction.....	591
Acid-Pepsin Disease.....	591
Pathogenesis of Peptic Ulcer.....	591
Physiology of Gastric Acid Secretion.....	591
Drug Therapy.....	592
Antacids.....	592
Anticholinergic Drugs.....	592
Histamine-Receptor Antagonists.....	593
Inhibitors of H <sup>+</sup> K <sup>+</sup> -ATPase.....	593
Active Herbal Products with Antiulcer Activity.....	593
Flavonoids.....	593
Quercetin.....	594
Naringin.....	595
Anthocyanosides.....	595
Sophoradin Derivatives.....	595
Saponins.....	595
Tannins.....	596
Gums and Mucilages.....	597
Herbal Drugs with Antiulcer Activity.....	597
Licorice.....	597
Aloe Gel.....	598
Capsicum (Chili).....	598
<b>Chapter 65</b> Valerian.....	599

Introduction .....	599
Valerian in the Management of Insomnia .....	599
The Use of Valerian in Folk Medicine and Traditional Systems of Medicine.....	600
Valerian.....	600
$\gamma$ -Aminobutyric Acid.....	600
Basic Mechanisms of Epilepsy.....	601
The Anxiolytic Agents .....	602
Pharmacodynamics of Benzodiazepines.....	602
GABA Receptors .....	603
Benzodiazepine-Binding Sites .....	603
Mode of Action of Benzodiazepine Derivatives .....	604
Antianxiety Effects .....	604
Muscle Relaxant Activity .....	604
Sedative Effects .....	605
Anticonvulsant Activity .....	605
Mode of Actions of the General Anesthetics .....	605
Glycine .....	606
Sedatives and Hypnotics .....	606
The Barbiturates .....	606
Classification .....	606
Pharmacokinetics .....	607
Acute Toxicity.....	607
Addiction.....	608
Selection of Drugs .....	608
Nonbarbiturate Sedatives and Hypnotics — Benzodiazepine Derivatives.....	608
Regulatory Status .....	609
<b>Chapter 66</b> Vitamins and Diet.....	611
Introduction .....	611
Nutritional Actions of Vitamins.....	611
Part One: Fat-Soluble Vitamins.....	611
Vitamin A.....	611
Retinols .....	611
Beta Carotene.....	611
Vitamin K.....	613
Vitamin K Derivatives .....	613
Vitamin D (Calciferol).....	613
Vitamin E (Tocopherols).....	614
Part Two: Water-Soluble Vitamins .....	614
Biotin.....	614
Folate (Folic Acid, Folacin).....	614
Niacin (Vitamin B <sub>3</sub> , Nicotinic Acid, Nicotinamide) .....	614
Pantothenic Acid (Vitamin B <sub>5</sub> ).....	615
Riboflavin (Vitamin B <sub>2</sub> ).....	615
Thiamine (Vitamin B <sub>1</sub> ) .....	615
Vitamin B <sub>6</sub> (Pyridoxine, Pyridoxamine, Pyridoxal).....	615
Vitamin B <sub>12</sub> (Cobalamins) .....	615
Vitamin C (Ascorbic Acid).....	615
The Importance of Vitamin A in Human Nutrition.....	616
Dietary Sources of Vitamin A.....	616

Action of Vitamin A.....	617
Vitamin A and Carcinogenesis.....	617
Vitamin A and Immune Function .....	617
Symptoms of Deficiency .....	618
Eye .....	619
Bronchorespiratory Tract.....	619
Skin .....	619
Genitourinary System.....	619
Gastrointestinal Tract.....	619
Sweat Glands .....	619
Bone .....	619
Miscellaneous.....	619
Therapeutic Uses .....	620
Vitamin A Deficiency Diseases .....	620
Dermatological Diseases.....	620
Cancer and Other Uses .....	620
Excessive Vitamin A Intake (Hypervitaminosis A) .....	620
Vitamin A (Retinol) (Aquasol A).....	621
Aging and Diet.....	621
Basic Dietary Recommendations .....	621
Antioxidants, Protective Plant Chemicals, Preventing Diseases .....	621
Essential Trace Minerals .....	622
Foods That Help.....	623
Apples .....	623
Apricots.....	623
Artichokes .....	624
Asparagus .....	624
Avocados.....	624
Bananas.....	624
Beans.....	624
Bean Sprouts.....	624
Beef and Veal.....	624
Beer.....	624
Beets .....	624
Bioflavonoids .....	624
Blackberries .....	625
Blueberries .....	625
Bread.....	625
Brussels Sprouts .....	625
Buckwheat .....	625
Butter and Margarine .....	625
Cabbage .....	625
Caffeine.....	625
Cakes, Cookies, and Pastries.....	626
Carrots.....	626
Cauliflower.....	626
Celeriac .....	626
Celery.....	626
Cereals .....	626
Cheese.....	626
Cherries.....	627

Chestnuts.....	627
Chilies.....	627
Chocolate and Candy.....	627
Coconuts.....	627
Coffee.....	627
Corn.....	627
Cranberries.....	627
Cucumbers.....	628
Currants.....	628
Dates.....	628
Eggplants.....	628
Eggs.....	628
Fennel.....	628
Fiber.....	628
Figs.....	628
Fruits.....	628
Fish.....	629
Flours.....	629
Garlic.....	629
Ginger.....	629
Gooseberries.....	629
Grains.....	629
Grapefruit.....	629
Grapes.....	629
Guavas.....	630
Honey.....	630
Ice Cream.....	630
Kale.....	630
Kiwi Fruits.....	630
Kohlrabi.....	630
Lamb.....	630
Leeks.....	630
Legumes.....	631
Lemons.....	631
Limes.....	631
Malted Milk, Malt Extracts.....	631
Mangoes.....	631
Mayonnaise.....	631
Melons.....	631
Milk and Milk Products.....	632
Mushrooms and Truffles.....	632
Nectarines.....	632
Nuts and Seeds.....	632
Oils.....	632
Okra.....	632
Olives.....	633
Onions.....	633
Oranges.....	633
Organ Meats.....	633
Papayas.....	633
Parsnips.....	633

Pasta.....	633
Peaches .....	633
Pears.....	634
Peas and Pea Pods.....	634
Peppers.....	634
Pickles and Other Condiments.....	634
Pineapples .....	634
Plums .....	634
Pork.....	634
Poultry.....	634
Prunes .....	635
Pumpkins .....	635
Quinces .....	635
Quinoa.....	635
Radishes.....	635
Raspberries .....	635
Rhubarb.....	635
Rice .....	636
Salad Dressings .....	636
Salt and Sodium .....	636
Sauces and Gravies.....	636
Seaweed .....	636
Shellfish .....	636
Smoked, Cured, and Pickled Meats.....	637
Snacks and Dips .....	637
Soft Drinks .....	637
Soups.....	637
Spinach .....	637
Squash.....	638
Strawberries .....	638
Tangerines .....	638
Tea.....	638
Tomatoes.....	638
Turnips .....	638
Vinegar.....	639
Watercress .....	639
Wine.....	639
Yams and Sweet Potatoes.....	639
Yogurt .....	639
Zucchini .....	639
Zwieback.....	639
<b>Chapter 67</b> Wheat Germ.....	641
Introduction .....	641
Mitochondrial Dysfunction in Neurodegeneration.....	642
Toxin Models of Parkinson’s Disease.....	644
Toxin Models of Huntington’s Disease .....	644
Alzheimer’s Disease.....	644



Increase in Brain Mitochondrial Concentrations and Exertion of Neuroprotective Effects by Coenzyme Q <sub>10</sub> .....	645
Neuroprotective and Neurorestorative Strategies for Parkinson's Disease.....	645
Efficacy of Coenzyme Q <sub>10</sub> in Parkinson's Disease.....	645
The Neuroprotective Role of Vitamin E.....	646
<b>Chapter 68 Wine.....</b>	<b>647</b>
Introduction.....	647
Effects of Red Wine.....	647
Alcohol.....	647
The Pharmacology of Alcohol.....	649
Effects of Ethyl Alcohol.....	649
Central Nervous System.....	649
Acute Intake of Alcohol.....	649
Cardiovascular System.....	649
Gastrointestinal Effects.....	649
Liver.....	650
Endocrine Glands.....	650
Fetal Alcohol Syndrome.....	651
Pharmacokinetics of Ethanol.....	651
Poisoning and Toxicity.....	652
Acute Poisoning.....	652
Delirium Tremens.....	652
Chronic Toxicity.....	652
Treatment of Alcoholism.....	652
Disulfiram: An Alcohol Sensitizing Agent.....	653
<b>Chapter 69 Yogurt and the Immune System.....</b>	<b>655</b>
Introduction.....	655
Immune System Functions.....	655
<i>In Vitro</i> Indexes of Immune Function.....	656
Phagocytic Activity.....	656
Lymphocyte Proliferation Assay.....	656
Cytokine Production.....	657
Yogurt Components with Potential Immunostimulatory Effects.....	658
<b>Specific References.....</b>	<b>661</b>
<b>General References.....</b>	<b>669</b>
<b>Index.....</b>	<b>673</b>

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# 1 The Pharmacokinetic Basis of Therapeutics

Poisons and medicine are oftentimes the same substance given with different intents.

— Peter Mere Latham

## INTRODUCTION

The primary objectives of therapy should be to prevent and cure disease. If these goals are not achievable, the secondary objectives should be to use drugs that mitigate the progressive, devastating, or disabling aspects of disease. The nature of the disease then determines the amount of drug or drugs to be given and the duration of therapy.

The successful prevention, cure, or treatment of a disease depends on using amounts of drugs sufficient to obtain the desirable effects while avoiding harmful side effects.

Advances in our understanding of pharmacology and therapeutics have broadened our appreciation of (1) the mechanisms involved in the disposition of drugs by the body, (2) the inherent ability of drugs to modify the physiologic integrity of the host, and (3) the nature of drug interactions. By being aware of these pharmacologic principles, applying them fully, and remaining vigilant concerning the countless interactions between herbal drugs and the ailing body, the side effects of numerous drugs can be substantially reduced (Brunton et al., 2006).

Pharmacokinetic principles, which deal with the **absorption, distribution, binding, biotransformation, and excretion** of drugs and their metabolites in the body (Figure 1.1), are the topic of this chapter.

Schulz and Schmodt (2003) in a review article described the therapeutic and toxic concentrations of more than 800 drugs. The compilation includes data for hypnotics, benzodiazepines, neuroleptics, antidepressants, sedatives, analgesics, anti-inflammatory agents (e.g., NSAIDs), antihistamines, antiepileptics, beta adrenergic antagonists, antibiotics (penicillins, cephalosporins, aminoglycosides, and gyrase inhibitors), diuretics, calcium-channel blockers, cardiac glycosides, antiarrhythmics, antiasthmatics, ACE-inhibitors, opiate agonists, and local anesthetics, among others. In addition, toxicologically relevant xenobiotics were listed. Data were abstracted from published information, both compilations and primary sources, and were completed with data collected in their own forensic and clinical toxicology laboratories. Wherever possible, ranges for therapeutic plasma concentrations were expressed as trough concentration at steady state. The half-life values given for each drug was chosen to represent the terminal log-linear phase at most. The authors intended to rapidly assess the significance of drug levels for the therapeutic monitoring of patients, and to facilitate the diagnostic and clinical assessment in case of intoxications.

The therapeutic levels and toxic concentrations of active ingredients of many herbal plants have not been determined and hence remain unknown.

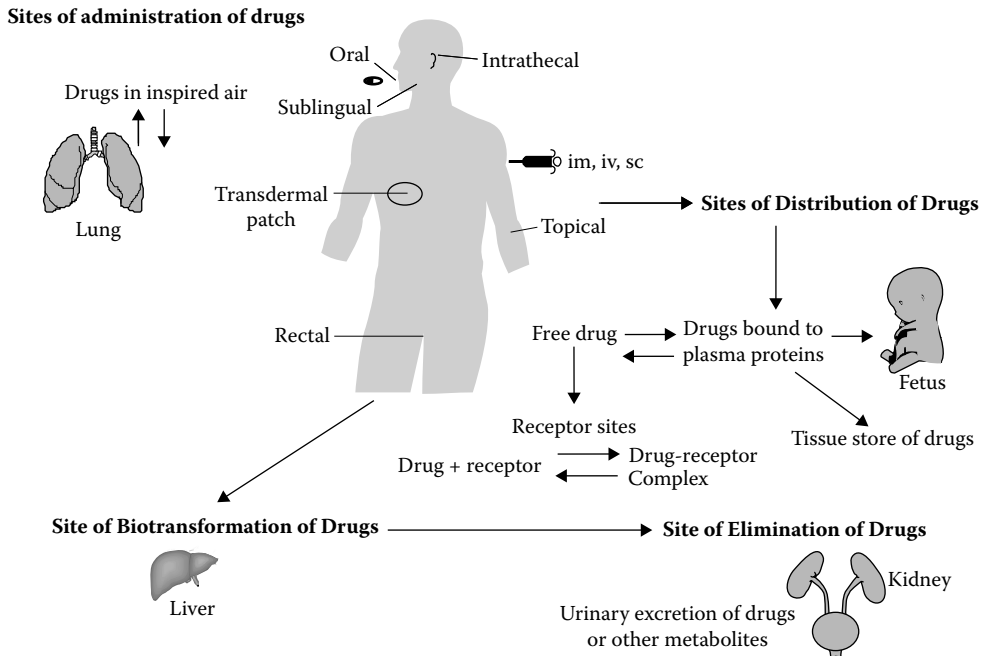


FIGURE 1.1 Pharmacokinetic basis of therapeutics. Im = intramuscular, iv = intravenous, sc = subcutaneous.

## ADMINISTRATION OF DRUGS

Drugs are administered as a **solid** in the form of capsules, tablets, and pills (e.g., clonidine), a **volatile liquid** (e.g., halothane and enflurane), a **solution** (e.g., chlorpromazine), an **aerosol** (e.g., beclomethasone), a **gas** (e.g., oxygen and nitrous oxide), and a **crystalline suspension** (e.g., insulin). The route of administration is chosen based on the desired onset and duration of action of the drug, the nature of the drug, any special circumstances, and the bioavailability of the drug.

In life-threatening conditions or in circumstances requiring an immediate onset of action, drugs must be administered directly into the general circulation. For instance, in diabetic ketoacidosis, large doses of insulin (2 units/kg initially, divided intravenously and subcutaneously, followed by 1 unit/kg subcutaneously every 2 h) are given until the concentration of glucose in the blood approaches normal values. In hypocalcemic tetany, calcium gluconate is administered as a 10% solution delivering 0.45 mEq of  $\text{Ca}^{2+}$ /ml.

## DURATION OF ACTION

If a long duration of action is desirable, one may administer a drug either continuously, or in a long-acting form, or both. For example, in treating pneumococcal meningitis, 20 to 40 million units of penicillin G are either given daily by constant-infusion drip or divided into doses and given by intravenous bolus at 2- to 3-h intervals. Penicillin G procaine suspension (e.g., Crysticillin, Duracillin, and Wycillin), which is soluble in water only to 0.4%, is designed for deep intramuscular injection and slow absorption from the site of injection.

## NATURE OF THE DRUGS

**Proteinaceous drugs** such as insulin for diabetes mellitus, growth hormone for hypopituitary dwarfism, and oxytocin in dysfunctional labor are destroyed in the stomach, and therefore are not given orally. The first drug in milk will be obtained from transgenic goat, owned by **GTC Bio-**

**therapeutics**, headquartered in Framingham, MA. The animal secretes a valuable pharmaceutical protein in its milk. Initially, GTC generated transgenic goats by microinjecting into the developing nucleus of a one-cell embryo a gene encoding the desired human protein (along with DNA that promotes activation of that gene in milk). Such embryos were transferred into female goats, which produced offspring that were then tested for the presence of the newly integrated gene. The milk of these “founder” animals contains the therapeutic protein, which must then undergo a purification process. The mature transgenic animals were bred usually with nontransgenic goats as a first step toward producing a herd (Stix, 2005).

### SPECIAL CIRCUMSTANCES

Drugs are applied to the mucous membranes of the conjunctiva, nasopharynx, and vagina to achieve local effects. On the other hand, the antidiuretic hormone **lypressin** (Diapid) is given by nasal spray, but the intention is to produce systemic effects. For the treatment of meningeal leukemia, **cytosine arabinoside** is injected directly into the spinal subarachnoid space. In osteoarthritis, **corticosteroids** are given by intra-articular injection.

### DRUG DELIVERY BY IONTOPHORESIS OR PHONOPHORESIS

The topical application of drugs may be enhanced by decreasing the barrier function of the stratum corneum, and by using either **iontophoresis** (by electrical field) or **phonophoresis** (by ultrasound). Phonophoresis has been used for the topical application of many medications, including **dexamethasone** (for inflammatory conditions), **zinc oxide** and **tannic acid** (for herpes simplex), **benzylamine** (for sports-related injuries), **benzoic acid** (for fungal infections), **hydrocortisone** (for inflamed digital, joints, and subdeltoid bursitis), **phenylbutazone** (for arthrosynovitis), **thiodyne** (for vertebral osteochondrosis), and **interferon** (for herpetic keratitis).

### LIPOSOMAL DRUG DELIVERY SYSTEM

Utilizing the concept that the key function of the plasmalemma is to exclude the external environment, liposomes were developed to carry **soluble** as well as **lipophilic drugs**.

Clinical studies have shown that liposomes are able to effectively encapsulate and deliver a number of drugs, including **daunorubicin** (an antineoplastic agent), **orgiprenaline** (a bronchodilator), **indium** (a gamma-imaging agent), and **amphotericin B** (for systemic mycosis). A major therapeutic advantage of liposomes is their ability to enhance the bioavailability of a drug, alter the tissue distribution of an agent, or prolong the release of a substance in the body.

### BIOAVAILABILITY

The physiochemical nature of certain drugs may rule out oral administration, and hence these drugs are considered to have subnormal oral bioavailability. For example, nitroglycerin is given sublingually in the treatment of angina pectoris because it is catabolized very rapidly in the liver if it is given orally (see Figure 1.6).

### Absorption of Drugs

The various lipid barriers of the gastrointestinal tract, the kidney tubules, and the central nervous system (CNS) allow the absorption of essential nutrients, guard against the uncontrollable disposal of electrolytes and other substances, and prevent the entrance of potentially toxic materials.

To reach its site of action (the **receptor**), a drug may have to traverse a succession of membranes. For example, **phenytoin**, when administered orally, must cross the gastrointestinal epithelium, the blood–brain barrier, the plasma membrane, and finally the membranes of subcellular organelles of

neurons. An understanding of how drugs traverse various cellular and subcellular membranes is of clinical significance, in terms of attaining the desired therapeutic level of an administered agent.

Multiple **physical and chemical factors** influence the rate and extent of absorption of drugs. These include the following:

#### Physiochemical factors

- Molecular weight

- The degree of ionization under physiologic conditions

- Product formulation characteristics

- Disintegration and dissolution rates for solid dosages

- Drug release characteristics for timed-release preparations

#### Patient factors

- The surface area available for absorption

- Gastric and duodenal pH

- The gastric emptying time

- Bile salt pool size

- Bacterial colonization of the gastrointestinal tract

- The presence and extent of underlying diseases

Lipid-soluble substances traverse the membrane by dissolving in the lipid phase, and the lipid-insoluble substances penetrate only when they are small enough to pass through the pores. The absorption of large lipid-insoluble substances such as sugars and amino acids is accomplished by **specialized transport processes**.

## DRUG PARTICLE SIZE

The rate of dissolution of a drug increases significantly as the size of the drug particle decreases. For example, the reduction in particle size of digoxin from 3 to 1  $\mu\text{m}^3$  increases the **surface area** of drug particles exposed to solution by as much as 300% (Figure 1.2). The more soluble drugs are absorbed faster and more completely than are the relatively insoluble ones. The **oral bioavailability** of numerous drugs has been increased by a reduction in particle size. On the other hand, decreasing particle size is not advantageous for compounds such as **penicillin G** and **erythromycin**, which tend to decompose in the gastrointestinal tract.

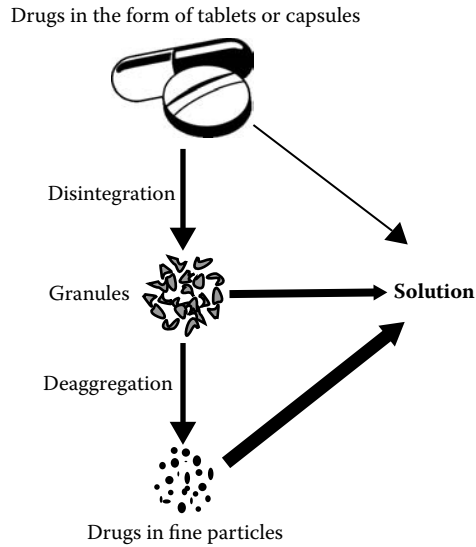
## BUCCAL AND SUBLINGUAL ABSORPTION

Compared with other routes of administration, different mucosa that line the oral cavity (**buccal** and **sublingual** sites of drug administration) offer advantages that include (1) being noninvasive, (2) producing a rapid onset of action, (3) providing high blood levels, (4) avoiding first-pass effects, and (5) circumventing the exposure of drugs to the acidic and digestive fluid of the stomach. In addition, drugs may be easily applied (cheeked), sufficiently localized and, if necessary, readily retrieved.

Drug absorption from the oral cavity occurs through the **passive diffusion** of the nonionized form from an aqueous phase to one that is lipid in nature. In addition, there is also evidence for the **carrier-mediated transport** of drugs, whereby the **levo isomers**, but not the dextro isomers, of many drugs are absorbed.

## INTRANASAL DELIVERY

The intranasal route of administration is best for those drugs that either undergo **extensive degradation** or are **poorly absorbed** after oral administration.



**FIGURE 1.2** A reduction in the particle size of a drug increases its absorption.

Drugs that are routinely administered intranasally include peptides such as **vasopressin** and its analog **desmopressin**, **luteinizing hormone-releasing hormone**, **buserelin**, **leuprolide**, **nafarelin**, and **oxytocin**.

### RECTAL ADMINISTRATION

The oral administration of drugs, which is the route of choice, is impractical or impossible to use under certain circumstances, such as in conditions causing nausea and vomiting, in patients with convulsions, just before surgery, and in uncooperative patients. The rectal route is also desirable for inducing anesthesia in children. However, the relatively smaller surface area for absorption is often less than that available for orally administered drugs. To overcome this problem, absorption-promoting agents such as **surfactants**, **sodium salicylate**, and **enamines** are coadministered with the drugs.

If a drug undergoes an extensive **first-pass metabolism** (e.g., **morphine**, **metoclopramide**, **ergotamine**, or **lidocaine**), rectal administration may produce an even higher plasma level. The prolonged rectal administration of multiple drugs may produce local irritation or even rectal ulceration.

## TRANSPORT MECHANISMS

### PASSIVE DIFFUSION

Passive diffusion takes place when a drug molecule moves from a region of relatively high to low concentration without requiring energy. The diffusion and movement of drugs continue until equilibrium has been achieved on both sides of the membrane. This equilibrium is achieved faster with highly permeable and, hence lipid-soluble, drugs and when the membrane has a large surface area.

### CARRIER-MEDIATED TRANSPORT

A substance to be carried forms a complex with a component of the membrane on one side; the complex is then carried through the membrane, the drug or substance is released, and the carrier returns to the original surface and state to repeat the process. The carrier shows specificity; for instance, **L-dopa** but not **D-dopa** is transported.

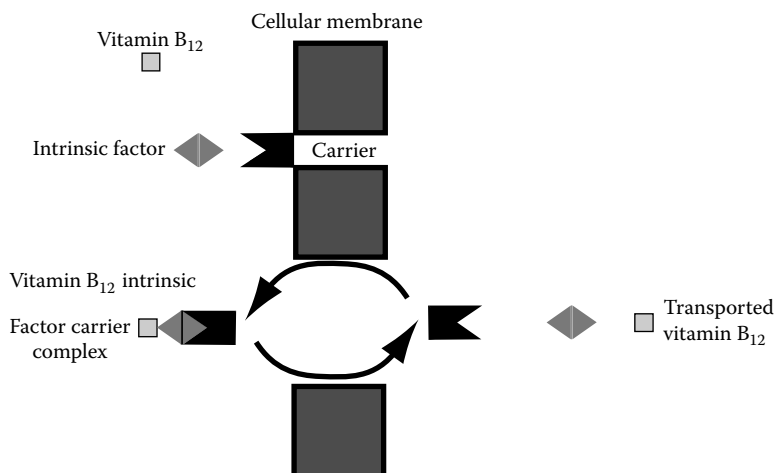


FIGURE 1.3 A carrier-mediated transport of vitamin B<sub>12</sub>.

### FACILITATED TRANSPORT

Facilitated transport is essentially the same as carrier-mediated transport, except that besides a carrier molecule, another transport facilitator is essential. For example, **vitamin B<sub>12</sub>** attaches to the **intrinsic factor**, and the vitamin B<sub>12</sub>-intrinsic factor complex then attaches to the carrier molecule and is transported. This transport process does not require energy and does not proceed against a concentration gradient (Figure 1.3).

### ION PAIR TRANSPORT

For ion pair transport to take place, **organic anions** combine with **organic cations** to form a neutral complex, which is then transported through the membrane by passive diffusion.

### PINOCYTOSIS

In pinocytosis, the transport of water-insoluble substances such as **vitamins A, D, E, and K** is accomplished in the following manner. First, they are engulfed by the membranes, after which they are dissolved in the membranes and released unchanged in the inside compartment.

### RECEPTOR-MEDIATED ENDOCYTOSIS

Receptor-mediated endocytosis is the process of **ligand movement** from the extracellular space to the inside of the cell by the interaction of the ligand with a specific **cell-surface receptor**. Receptors bind the ligand at the surface, internalize it by means of coated pits and vesicles, and ultimately release it into an acidic endosomal compartment (Figure 1.4).

## OTHER FACTORS CONTROLLING THE RATE OF ABSORPTION OF DRUGS

In addition to the **lipid–water partition coefficient**, other factors that control the rate of absorption of drugs are the **degree of ionization**, the **surface area**, **blood flow** through the region, and the **gastric emptying time**.

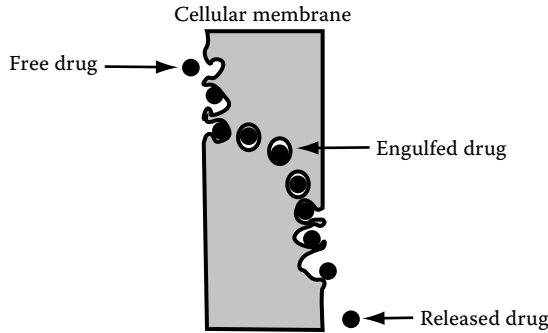


FIGURE 1.4 A mechanism for transport of water-insoluble vitamins.

**DEGREE OF IONIZATION**

The **degree of ionization** of drugs and the **pH of the internal medium** play important roles in the transfer of drugs across biologic membranes. Most drugs are either weak acids or bases. Therefore, in solution, they exist in nonionized and ionized forms. The nonionized forms of various compounds are more lipid soluble and can penetrate the cellular membranes (Figure 1.5). The **rate of passage** of many drugs across various membranes becomes a function of the **negative logarithm of the dissociation constant** ( $pK_a$ ) of the drug and the **pH of the internal medium**. This concept is derived from the **Henderson–Hasselbalch equation**.

For example, **phenytoin** is absorbed primarily from the upper intestinal tract. Phenytoin is an acid with a  $pK_a$  of 8.3 to 9.2 and is insoluble at the pH of gastric juice (pH, 2.0). Therefore, it cannot be absorbed significantly from the stomach. On passage into the small intestine, where the pH is less acidic (7 to 7.5), phenytoin is absorbed in a nonionized form.

At the duodenal pH of 7.0, 96.9% of the phenytoin is in the nonionized form, which favors its absorption. The absorption of phenytoin is greatest in the duodenum and decreases in the lower parts of the small intestine. The absorption from the cecum and the large intestine is several-fold lower than that in the duodenum.

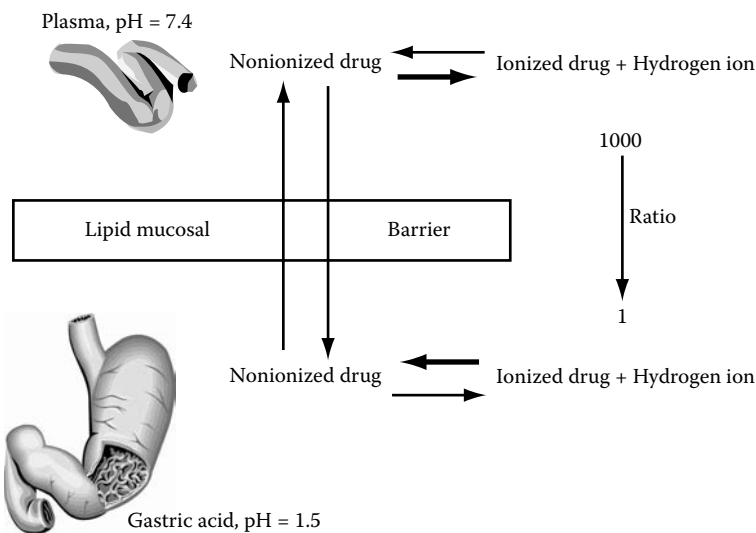


FIGURE 1.5 Drugs are absorbed in nonionized forms.



Again using the Henderson–Hasselbalch equation, one finds that **acetylsalicylic acid** ( $pK_a$ , 3) is 99% and 91% nonionized at the pH of 1 and 2, respectively.

Therefore, according to this model, acetylsalicylic acid (aspirin) is best absorbed when the pH of the stomach is highly acidic. This high acidity, however, limits its aqueous solubility.

### SURFACE AREA

The influence of ionization on drug absorption is important only in circumstances in which biologic pHs vary dramatically, such as those in the stomach (varying from 1.4 to 7.0) and the urine (varying from 4.5 to 7.5). The changes in pH in other biologic fluids are considerably smaller. Because both ionized and nonionized drugs are absorbed from subcutaneous and intramuscular sites of injection, ionization does not appear to play as important a role in the passage of drugs across the capillary wall. Finally, although drugs such as acetylsalicylic acid are best absorbed from an acidic medium such as that in stomach, most of the aspirin is nevertheless absorbed in the upper small intestine, which has a considerably greater absorptive surface. The **total absorptive area** of the small intestine and its microvilli has been estimated to exceed 200 m<sup>2</sup> for the intestine vs. 1 m<sup>2</sup> for the stomach. Similarly, the **perfusion rate** of the intestine is considerably greater than that of the stomach. In fact, most drugs, whether nonionized or ionized and whether acidic, basic, or neutral, are absorbed mostly from the small intestine. Consistent with this is the observation that buffered acetylsalicylic acid preparations are dissolved faster and absorbed better mostly in the intestine. Similarly, patients with **achlorhydria** or those who have undergone gastrectomy have little difficulty with the absorption of orally ingested drugs.

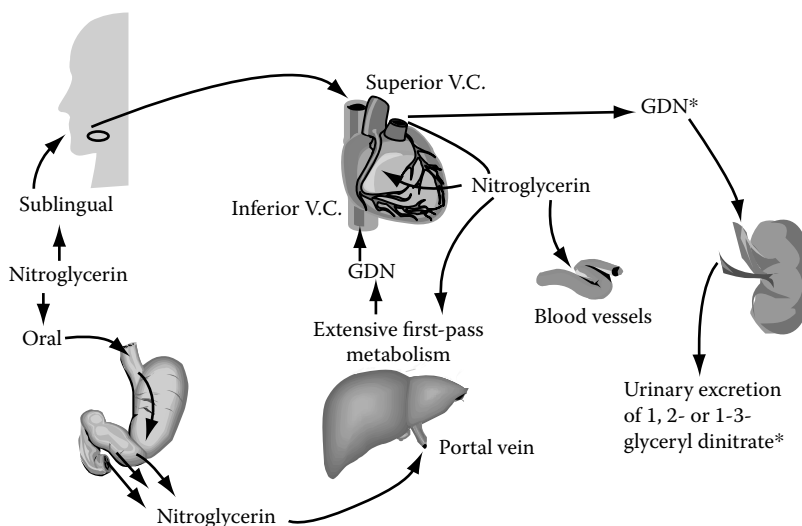
### BLOOD FLOW

The absorption of drugs in solution from intramuscular and subcutaneous sites of injection is limited by the **perfusion rate**. Failure to recognize this important concept has resulted in patient death. For example, **morphine sulfate** is often administered subcutaneously in a dose of 10 mg per 70 kg of body weight. This dose is sufficient to produce analgesia in 70% of patients with moderate to severe pain. However, in the setting of circulatory collapse and shock (e.g., septic shock in bacteremia due to release of endotoxin) in which the peripheral circulation may be impaired, morphine is not absorbed. Cases have been reported in which the lack of analgesia prompted the additional injection of morphine, all of which remained at the injection site and in the subcutaneous capillary bed. When the peripheral circulation improved, the massive amount of morphine that had collected became absorbed and death ensued, which was primarily due to respiratory depression.

Increasing the blood flow enhances the absorption of drugs, whereas decreasing the blood flow reduces absorption. Massaging the site where a drug has been administered therefore increases the rate of absorption, whereas placing an ice pack on the site retards it. One may take advantage of this concept and deliberately retard the absorption of drugs by reducing the peripheral circulation. For instance, local anesthetics are often combined with a vasoconstricting substance such as epinephrine and injected as a mixture. The epinephrine causes vasoconstriction, hence producing a bloodless field of operation. Epinephrine prevents the rapid absorption of local anesthetics and thus both enhances their duration of action and prevents systemic toxicity.

### GASTRIC EMPTYING TIME

Because drugs are mostly absorbed from the upper part of the small intestine, the rate of gastric emptying plays a crucial role in drug absorption. If rapid absorption is desired, drugs should be taken on an empty stomach. Meals, especially those with a high fat content, retard absorption. The desire for rapid absorption of drugs necessitates that the interactions between food and drugs be monitored carefully.



**FIGURE 1.6** In order to avoid extensive hepatic first-pass metabolism, nitroglycerin is given sublingually. \*GDN = 1,2- or 1,3-glyceryl dinitrate; V.C. = vena cava.

Drugs such as **clindamycin** and **lincomycin** should be taken on an empty stomach. Only 20 to 35% of clindamycin and lincomycin is absorbed from the gastrointestinal tract, and taking these agents with a meal further hinders their absorption and produces a plasma concentration of antibiotics that is ineffective.

The **tetracyclines** should be taken orally 1 h before or 2 h after meals. Absorption of these agents is impaired by the presence of milk and milk products and by the concomitant administration of aluminum hydroxide gels, sodium bicarbonate, calcium and magnesium salts, or iron preparations because of the chelation of divalent and trivalent cations by these agents.

**Anticholinergic drugs** such as **proprantheline** should be taken 1 h before meals. Anticholinergic drugs are able to inhibit the secretion of gastric juice, which is ordinarily stimulated by food.

## HEPATIC FIRST-PASS EFFECT

By far the most important reason for an inadequate plasma concentration following the oral or parenteral administration of a drug is the **first-pass effect**, which consists of the loss of a drug as it passes through the liver for the first time. For example, **nitroglycerin**, which is used in the management of patients with angina pectoris, is given sublingually. Taken orally, nitroglycerin is rapidly inactivated in the liver and the resulting concentration is inadequate to be of immediate value to the patient. Sublingually administered nitroglycerin bypasses the liver and enters the superior vena cava, whereupon it perfuses the coronary circulation (Figure 1.6). Besides nitroglycerin, there are other drugs that exhibit extensive first-pass hepatic elimination and hence have a very low oral bioavailability. These include **desipramine**, **morphine**, **propranolol**, **lidocaine**, and **verapamil**. The first-pass effect can at times be overcome by raising the dose, as is done with desipramine and propranolol.

## DISTRIBUTION OF DRUGS

Whether given orally or parenterally, drugs are distributed nonuniformly throughout the body. Factors that regulate this distribution are the **lipophilic characteristics** of the drugs, the **blood supply** to the tissues, and the **chemical composition** of various organs and tissues. The distribution

of drugs not only influences their **onset of action**, but also at times determines their **duration of action**. For example, **thiopental**, an intravenous anesthetic, produces unconsciousness 10 to 20 sec after its administration, and consciousness returns in 20 to 30 min. The rapid onset of action is due to the rapid transport of thiopental to the brain. The short duration of action stems from its subsequent redistribution to other tissues, such as muscle and fat.

## BINDING OF VARIOUS DRUGS TO PLASMA PROTEINS

In an ideal therapeutic regimen, a sufficient amount of the drug should reach the locus of action (receptor site) in order to bring about the desired effect, but not so much as to produce toxicity. Furthermore, the drug should not disappear too rapidly from the locus of action, or the therapeutic effects will be transient and hence of limited value. The binding of drugs to plasma proteins and various subcellular components tends to accomplish these objectives. Human plasma contains over 60 different proteins, and the most abundant one is **albumin**. Other significant proteins include **prealbumin**, **lipoproteins**, and **various globulins**. A number of plasma proteins, especially albumin, have shown a high affinity for binding drugs, so that at a given total plasma concentration only a portion of the total amount of drug is free in the plasma water. The remainder is bound to plasma proteins and in this form does not exert any pharmacologic effects.

The interaction between proteins and a drug is governed by the **law of mass action**, in that the proportion of bound drug remains constant, provided the binding sites are not saturated. With the possible exception of **valproic acid** and **disopyramide**, the saturability of binding sites does not occur within therapeutic ranges.

The interaction between drug and protein is not a chemical one, but a reversible attachment that is achieved by various forces, including **electrostatic**, **London-van der Waals**, and **hydrogen binding**, or some combination of these. This drug-protein complex is readily reversible (the half-life being on the order of milliseconds). There is a continuous shift of bound to unbound drugs (see Figure 1.1), and, unlike receptor binding, no pharmacologic response occurs as a result of the association. The binding site of endogenously occurring acidic substances (e.g., **bilirubin**, **vitamin C**, and **bile acids**) and acidic drugs (e.g., **phenylbutazone**, **penicillins**, **sulfonamides**, **warfarin**, and **salicylic acid**) is the N-terminal amino acid. The basic drugs (e.g., **diphenhydramine**, **streptomycin**, **chloramphenicol**, and **coumarin anticoagulants**) bind nonspecifically.

### ALBUMIN

Albumin has two binding sites: **Site I** binds structurally unrelated substances (e.g., **warfarin**, **phenytoin**, and **sulfonamides**), and **Site II**, which is more selective, binds a smaller number of drugs (i.e., **diazepam**, **phenylbutazone**, and **ibuprofen**).

### ALPHA<sub>1</sub>-ACID GLYCOPROTEIN

Alpha<sub>1</sub>-acid glycoprotein exists in concentrations that are 50 to 100 times lower than those of albumin. **Basic drugs** (**quinidine**, **imipramine**, **propranolol**, and **lidocaine**) bind to the single site present on alpha<sub>1</sub>-acid glycoprotein.

### OTHER GLYCOPROTEINS

**Corticosteroid-binding globulin** and **thyroxine-binding globulin** are both alpha globulins that possess high affinities but low capacities for their respective substrates. **Methadone** (a narcotic analgesic) binds to the gamma-, beta-, and alpha-globulins, as well as to albumin.

## LIPOPROTEINS

Lipoproteins bind a small amount of certain drugs (**imipramine**, **amitriptyline**, **nortriptyline**, **phenytoin**, and **quinidine**), which usually bind to  $\alpha_1$ -acid glycoprotein.

The response to a drug is determined by the unbound fraction that is in the plasma water. The **concentration of unbound drug**, rather than the concentration of total drug, is often a better index of a drug's effective therapeutic level. The clinical laboratory assessment of the plasma level of a drug in most cases involves the measurement of bound-plus-unbound amounts of the agent. The greater the amount of bound drug, the less rapidly will the plasma level of unbound drug decline, as it is continuously being replenished through dissociation of the complex. The binding of drug to plasma protein is not usually a disadvantage; in fact, without such binding the effect of most drugs would be too transient. The drugs would therefore have to be administered so frequently that the plasma concentration would oscillate between toxic and ineffective levels. Therapy is easier to control when a drug is stable in the body and the plasma concentration does not fluctuate widely.

The percentage of protein binding of drugs at therapeutic levels varies dramatically. Some drugs such as **allopurinol**, **heparin**, and **isoniazid** do not become bound. Other drugs such as **antipyrene**, **ethambutol**, and **theophylline** become bound to the extent of only 4 to 15%. Several drugs such as **ampicillin** (25%) and digoxin (23%) show low protein binding, some drugs such as **atropine** (50%) and **meperidine** (40%) show moderate protein binding, and some drugs such as **carbamazepine** (72%), **furosemide** (75%), **nitrofurantoin** (70%), and **rifampin** (85%) show high degrees of protein binding. Some drugs such as **dicumarol** (97%), **diazepam** (96%), **phenylbutazone** (98%), and **diazoxide** (96%) bind extensively to plasma proteins.

The binding sites of the protein are not unlimited and are subject to saturation. When this occurs, toxicity may develop following further drug administration, because the later portion of the drug remains free. Consistent with this view is the observation that toxic manifestations of drugs are quite frequent and considerably higher in individuals suffering from hypoalbuminemia, or altered plasma and tissue protein concentrations, or both.

Drugs may **alter the protein binding** of other agents. For instance, **aspirin** decreases the binding of **thyroxine** and the binding of bilirubin is hindered by many pharmacologic agents. The more tightly bound drugs can displace the less firmly bound agents. The intensity of the effect of displaced drug on the patient will simply depend on the blood level of the free drug and its nature. At times, the effect may be highly undesirable and even fatal. Only the slight displacement of a highly bound drug such as **dicumarol** (an oral anticoagulant) by **phenylbutazone**, which has greater affinity for binding sites, can cause serious hemorrhage. Because only 3% of the anticoagulant is free, an additional displacement of 3% increases its effects by 100%.

## TISSUE LOCALIZATION OF DRUGS

After a drug has been absorbed, the initial phase of its distribution into the tissues is based on **cardiac output** and **regional blood flow**. Highly perfused organs such as the brain, heart, liver, and kidney receive most of the drug. Diffusion into the interstitial compartment occurs rapidly. **Lipid-soluble** and **lipid-insoluble drugs** have different patterns of distribution; for example, **thiopental**, a highly lipid-soluble substance, distributes rapidly into the brain. Because the blood perfusion of the bone is not extensive, local blood flow may not play a role in the accumulation of **tetracycline** in bone. **Active transport** (e.g., the accumulation of **lithium** in bone) and the presence of **specific binding proteins** (e.g., thyroglobulin in the thyroid gland) are responsible for the respective accumulation of these agents at these sites.

## APPARENT VOLUME OF DISTRIBUTION OF DRUGS

**Volume of distribution** ( $V_D$ ) is defined as the amount of drug in the body in relation to the concentration of drug in the plasma:

$$V_D = \frac{\text{Amount of drug in body}}{\text{Concentration of drug in plasma}}$$

For example, if 300 mg of phenytoin is given to an epileptic patient, once equilibrium has been reached and the plasma concentration of phenytoin is 10  $\mu\text{g/ml}$ , the apparent volume of distribution of phenytoin would be 30 l.

The **one-compartment model** of distribution assumes that an administered drug is homogeneously distributed throughout the tissue fluids of the body. For instance, ethyl alcohol distributes uniformly throughout the body, and therefore any body fluid may be used to assess its concentration. The **two-compartment model** of distribution involves two or multiple central or peripheral compartments. The **central compartment** includes the blood and extracellular fluid volumes of the highly perfused organs (i.e., the brain, heart, liver, and kidney, which receive three fourths of the cardiac output); the **peripheral compartment** consists of relatively less perfused tissues such as muscle, skin, and fat deposits. When distributive equilibrium has occurred completely, the concentration of drug in the body will be uniform.

The **rate of distribution** of a drug from the blood to a tissue depends on the extent of binding of that drug to plasma proteins (only free drug is able to distribute), on the ability of that drug to diffuse through tissue membrane (in general, lipophilic drugs are able to diffuse), on the degree of perfusion of that tissue (unit of blood/min/volume of tissue), and on the properties of the tissue membrane. If all other factors remain equal, the higher the tissue perfusion, the higher the amount of drug to be diffused.

In comparing **thiopental** and **penicillin**, it is found that thiopental enters the brain more rapidly than muscle; the reverse is the case for penicillin. Thiopental is a lipophilic substance, which diffuses easily into both muscle and brain. Because the perfusion of brain is higher than that of muscle, thiopental diffuses more rapidly into the brain. Penicillin is a polar substance, which does not enter the brain at all. However, because the muscle capillaries are porous, they allow many drugs, including penicillin, to diffuse rapidly across the membrane.

Drugs that show **extensive tissue binding** are said to have an apparent volume of distribution many times the total body size. For example, **digoxin** (see Chapter 35), which binds to plasma protein to the extent of 23%, has an apparent volume of distribution of 8 l/kg. The volume of distribution of drugs that do not bind to plasma or tissue proteins varies between the extracellular fluid volume (16 liters) and the total body water (42 liters). **Insulin**, **sodium**, and **iodine** are confined to the **extracellular water**, whereas **caffeine** and **ethanol** are distributed in the **total body water**.

## THE BLOOD–BRAIN BARRIER

The brain capillaries are tightly joined and covered by a footlike sheath that arises from astrocytes. Thus, a drug leaving the capillaries in the brain has to traverse not only the nonporous capillary cell wall, but also the membranes of the astrocyte, in order to reach the neurons. Such a structure, frequently referred to as the **blood–brain barrier**, tends to limit the entry of many drugs into the brain.

## THE PLACENTAL BARRIER

The membrane separating fetal blood from maternal blood in the intervillous space, the **placental barrier**, resembles other membranes, in that lipid-soluble substances diffuse readily but water-

soluble substances either do not or diffuse poorly. Thus, for instance, morphine-induced respiratory depression and miosis may occur in both the mother and her newborn infant. The children of narcotic-addicted mothers will be born with an addiction to narcotics.

## DRUGS IN PREGNANCY AND THE NEWBORN

Pregnancy and the first weeks of life represent two physiologic situations in which there is a continual and significant change in the levels of plasma proteins, and it may therefore be necessary to adjust the doses of medications during these times.

### DRUG THERAPY IN PREGNANCY

In pregnancy, the **total body fluid** increases by 8 liters, of which 80% is extracellular water. The plasma volume increases by 40 to 50% (1.2 to 1.5 liters). Consequently, in pregnancy there is an increase in plasma volume, decrease in plasma protein levels, increase in total and extracellular water compartments, and increase in total body fat. These alterations may change the volume of distribution of most drugs.

### DRUG THERAPY IN THE NEWBORN

At birth, a full-term infant has a significantly lower plasma albumin level than does an adult, and therefore the number of drug-binding sites is substantially less. This situation necessitates a reduction in the total amount of drug administered.

## THE SITE OF ACTION OF DRUGS

It is generally accepted that most, but not all, drugs (e.g., antiseptics) exert their potent and specific effects by forming a bond, generally reversible, with a cellular component called a **receptor site**, which should be differentiated from an **acceptor** or **silent site** where drugs are stored. Drugs that interact with a receptor and elicit a response are called **agonists**. Drugs that interact with receptors and prevent the action of agonists are termed **antagonists**. For example, acetylcholine, which causes bradycardia, is an agonist; atropine, which blocks the action of acetylcholine and prevents bradycardia, is an antagonist. The relative effects of drugs are often judged in terms of their **potency**, which is a measure of the dosage required to bring about a response, and their **efficacy**, which is a measure of their inherent ability to exert an effect.

When the pharmacologic properties of two compounds are compared, one may prove to be more potent and efficacious than the other. For instance, as an analgesic, morphine is more potent and more efficacious than acetylsalicylic acid. On the other hand, two compounds may be equally efficacious but one could be more potent. Haloperidol and chlorpromazine are both efficacious neuroleptics in the management of schizophrenia, but haloperidol is more potent.

A drug's **affinity** and **intrinsic activity** also need to be differentiated. Intrinsic activity refers to a drug's ability to bind to the receptor, which results in pharmacologic actions. Affinity is a measure of the degree to which a drug binds to the receptor — whether it exerts a pharmacologic action (as an agonist) or simply blocks the receptor (as an antagonist).

## NATURE AND TYPE OF PHARMACOLOGIC RECEPTOR SITES

The actions of neurotransmitters are mediated mostly through their interactions with receptors located either at **presynaptic** or **postsynaptic sites**. These receptors function in a coordinated fashion to elicit **excitation** (depolarization) or **inhibition** (hyperpolarization) within and between neuronal subsystems. A basic inadequacy in this interplay is believed to lead to pathologic states

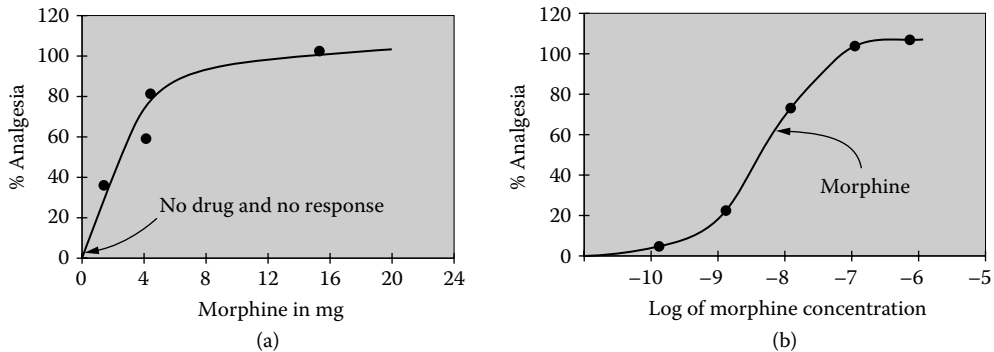


FIGURE 1.7 Examples of dose–response curves.

such as **Parkinson’s disease** (dopamine deficiency), **Huntington’s disease** (dopamine excess), **endogenous depression** (catecholamine deficiency), or **mania** (catecholamine excess).

## DOSE–RESPONSE RELATIONSHIP

The relationship between the amount of drug administered (e.g., morphine), or the concentration of the administered drug in the plasma, and the magnitude of the desired response obtained (e.g., analgesia) is referred to as a **dose–response relationship**. Obviously, for example, no analgesia is obtained if no morphine exists at the receptor site (Figure 1.7A). When all the available receptor sites are occupied, hypothetically the maximum response has been obtained (**Clark’s hypothesis**), and may begin to produce undesirable side effects. This **linear dose–response** relationship, as depicted in Figure 1.7A, may be expressed in a logarithmic scale (Figure 1.7B). A **quantal dose–response** curve relates the frequency with which any dose of a drug evokes a fixed (all-or-none) pharmacologic response.

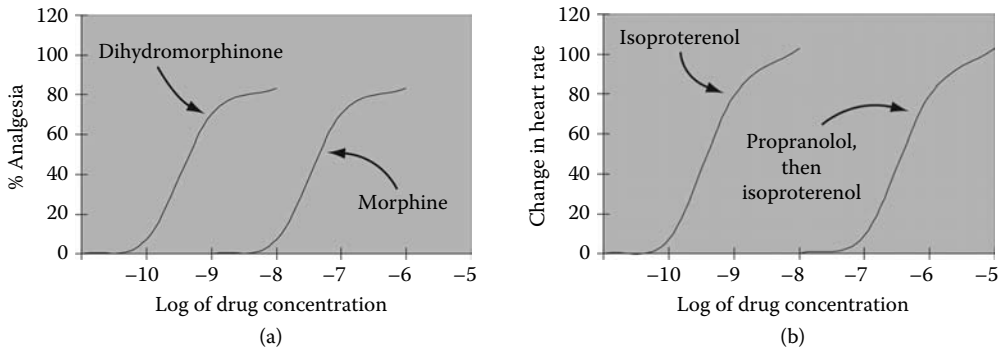
## POTENCY AND EFFICACY

**Potency** refers to the lowest dose that will produce a maximum effect. **Efficacy** refers to the inherent ability to exert an effect. **Morphine** in a dose of 10 mg given subcutaneously produces analgesia but a 2-mg dose of **dihydromorphinone** (Dilaudid) can accomplish the same degree of analgesia. Therefore, morphine and dihydromorphinone are equally efficacious, but dihydromorphinone is more potent than morphine (Figure 1.8).

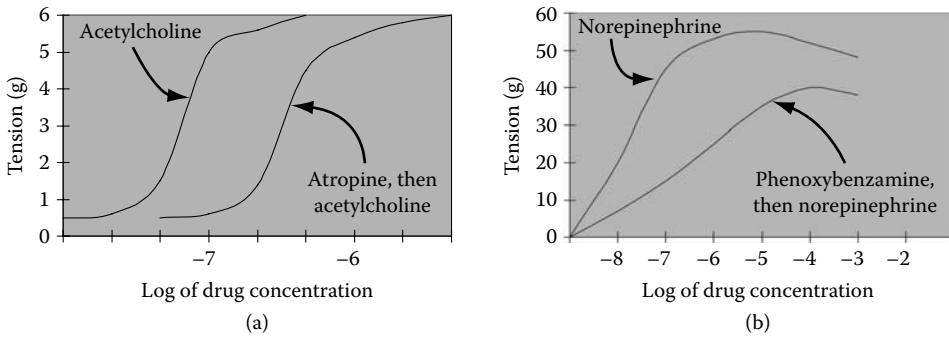
The interaction between a drug and a receptor site is similar to a reversible interaction between a substrate and an enzyme. This antagonism between agonists and antagonists is called **competitive** or **surmountable antagonism** if the inhibition is overcome by increasing the concentration of the agonist (Figure 1.8 and Figure 1.9). For example, **propranolol** (a beta-adrenergic receptor antagonist) is a competitive antagonist for **isoproterenol** (a beta-adrenergic receptor agonist), and **atropine** is a competitive antagonist for **acetylcholine** at the muscarinic cholinergic receptor site. A **partial agonist** produces a lower response than a full agonist. When a maximum response is obtained by an agonist at a concentration that does not occupy all the available receptors, a **spare receptor** or high-efficacy receptor-agonist occupancy mechanism may be involved (Figure 1.10).

In examining the kinetic nature of competitive antagonists, one discovers that parallel dose–response curves possessing the same maximum effect (see Figure 1.8 and Figure 1.9) are produced for the agonists in the presence and absence of a fixed amount of antagonists.

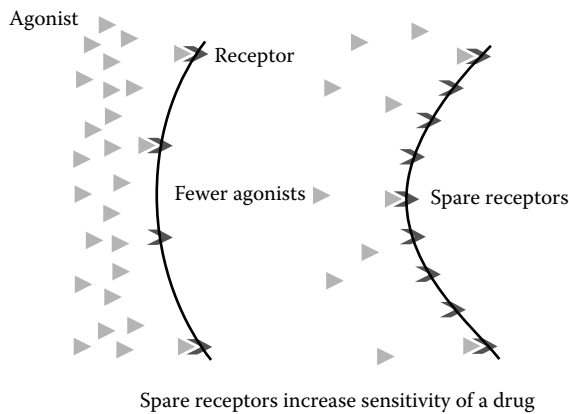
When an antagonist binds irreversibly to the receptor site, thus producing either permanent chemical changes or inactivation of the receptor site, or both, this is referred to as **noncompetitive**



**FIGURE 1.8** a) Dihydromorphinone is more potent than morphine but is equally efficacious. b) Propranolol is a competitive antagonist at adrenergic receptors.

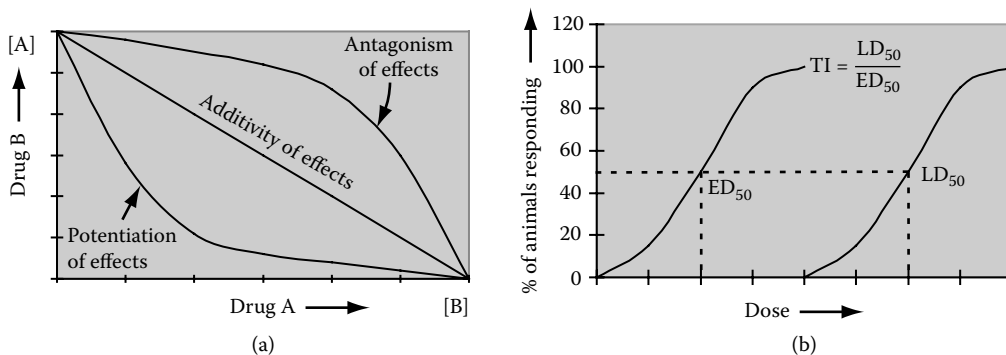


**FIGURE 1.9** a) Atropine is a competitive antagonist at cholinergic receptors. b) Phenoxybenzamine is a noncompetitive antagonist at adrenergic receptors.



**FIGURE 1.10** The concept of a spare receptor.





**FIGURE 1.11** a) The concept of antagonism or potentiation of pharmacologic effects. b) Drugs with higher therapeutic indices are safer. TI = therapeutic index, LD<sub>50</sub> = median lethal dose, ED<sub>50</sub> = median effective dose.

**antagonism or nonequilibrium blockade.** **Phenoxybenzamine**, an alpha-adrenergic receptor blocking agent, noncompetitively and irreversibly blocks the alpha-adrenergic receptor site, preventing **norepinephrine** from exerting its full action (Figure 1.9b).

## PHYSIOLOGIC AND PHARMACOLOGIC ANTAGONISM

If two drugs, one an agonist and another an antagonist, bind to an identical receptor site, either producing or preventing an effect, this association is called **pharmacologic antagonism**. **Naloxone**, **atropine**, and **diphenhydramine** are pharmacologic and specific antagonists of **morphine**, **acetylcholine**, and **histamine** at their respective receptor sites. In **physiologic antagonism**, the drugs do not bind to the same receptor sites but produce functionally opposite results. For example, histamine produces vasodilation, whereas epinephrine produces vasoconstriction; however, they interact with two separate receptor sites.

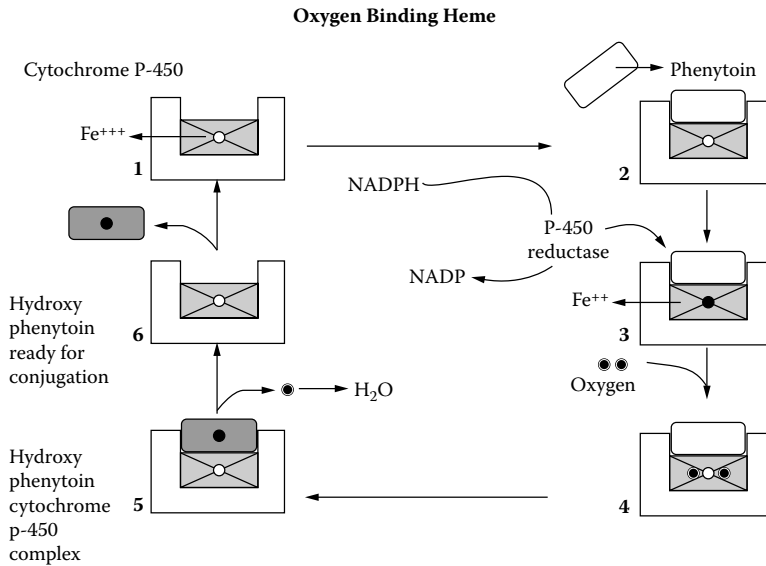
## ENHANCEMENT OF DRUG ACTION

Numerous agents acting at two or more receptor sites may magnify each other's effects, producing responses that are greater than the one produced by either one of the drugs alone. For example, **angiotensin II** enhances the vasoconstricting effects of norepinephrine, and histamine augments the hypotensive effects of acetylcholine. If the quantitative summation of the effects produced by two drugs is greater than the algebraic sum of the effects produced by either drug alone, this phenomenon is called **potentiation**. For example, when taken individually, diazepam, chlorpromazine, and alcohol all cause sedation. However, when alcohol is ingested along with either diazepam or chlorpromazine, pronounced CNS depression may arise and deaths have occurred following the injudicious combined use of these CNS depressants. In this instance, alcohol potentiates the CNS depression induced by diazepam or chlorpromazine. In depicting the potentiation of two drugs, one uses isoboles for plotting their respective effects (Figure 1.11).

## THERAPEUTIC INDEX

The therapeutic index (Figure 1.11) deals with the ratio of lethal doses to 50% of the population (LD<sub>50</sub>) over the median minimum effective dose (ED<sub>50</sub>).

$$\text{Therapeutic index} = \frac{\text{LD}_{50}}{\text{ED}_{50}}$$



**FIGURE 1.12** A simplified scheme for the mechanism of action of cytochrome P-450. NADP = nicotinamide adenine dinucleotide phosphate, NADPH = the reduced form of NADP.

The higher the therapeutic index, the safer the drug; the lower the therapeutic index, the greater the possibility of toxicity. The therapeutic index for barbiturate as a class is 10, whereas the therapeutic index for cardiac glycoside as a class is 3. Because the usual therapeutic dose of cardiac glycoside is 1 mg, death may result if only 3 mg has been administered.

## BIOTRANSFORMATION

Biotransformation may be defined as the enzyme-catalyzed alteration of drugs by the living organism. Although few drugs are eliminated unchanged, urinary excretion is a negligible means for termination of the action of most drugs or poisons in the body. As a matter of fact, the urinary excretion of a highly lipid-soluble substance such as **pentobarbital** would be so slow that it would take the body a century to rid itself of the effect of a single dose of the agent. Therefore, mammalian and other terrestrial animals have developed systems that allow the conversion of most lipid-soluble substances to water-soluble ones, so that they may be easily excreted by the kidney. In general, biotransformation may be divided into two forms of metabolism: hepatic and nonhepatic (Figure 1.12).

### HEPATIC DRUG METABOLISM

By far the major portion of biotransformation is carried out in the liver by **cytochrome P-450** (P-450), which is a collective term for a group of related enzymes or isoenzymes that are responsible for the oxidation of numerous drugs; **endogenous substances** such as fatty acids, prostaglandins, steroids, and ketones; and **carcinogens** such as polycyclic aromatic hydrocarbons, nitrosamines, hydrazines, and arylamines.

### NONHEPATIC METABOLISM

#### Plasma

One of the drugs that is metabolized in the blood is **succinylcholine**, a muscle relaxant that is hydrolyzed by the pseudocholinesterase of liver and plasma to succinylmonocholine. The short duration of action of succinylmonocholine (5 min) is due to its rapid hydrolysis in plasma. Patients

with atypical cholinesterase who cannot metabolize succinylcholine suffer pronounced apnea. **Procaine**, a local anesthetic, is also hydrolyzed by pseudocholinesterase.

### Lung

The lung is involved in both the activation and inactivation of numerous physiologic and pharmacologic substances. For example, **angiotensin I** is converted to **angiotensin II** in the lung.

### Intestinal Epithelium

The intestinal epithelium is capable of removing numerous agents.

## MOLECULAR BIOLOGY OF MULTIPLE ISOENZYMES OF P-450

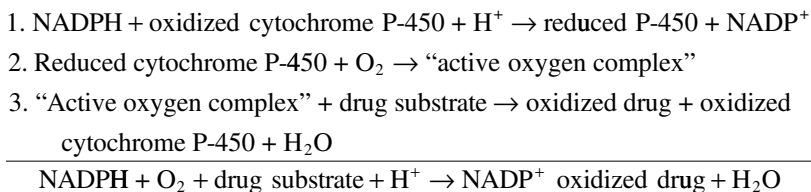
In recent years, an extensive number of complementary DNAs for the P-450 genes for humans have been isolated and sequenced. Genes that encode proteins which are less than 36% similar in their amino acid sequence belong to different families. Currently, eight different families have been identified in humans, each designated by a Roman numeral. The drug metabolizing P-450s belongs to families I, II, III, and IV. P-450s that are 70% or more similar are encoded by genes in the same subfamily. Finally, the individual gene is designated by an Arabic numeral.

During **Phase I**, most drugs are inactivated pharmacologically, some remain unaltered, and the rest become more active and toxic. For example, phenytoin in the liver is first hydroxylated to hydroxyphenytoin (Phase I) and is then conjugated with glucuronic acid (**Phase II**) and excreted by the kidney as phenytoin glucuronide conjugate. During Phase I, besides introducing a polar group such as an  $-OH$  group, a potential polar group may also be unmasked from the drug to be metabolized. For example, compound  $R-OCH_3$  is converted to  $R-OH$  by demethylation. Codeine becomes demethylated to morphine. The free or unmasked polar group is then conjugated with glucuronate, sulfate, glycine, or acetate. With the exception of morphine 6-glucuronide, almost all conjugates lack pharmacologic activity.

## SCHEME OF THE MIXED-FUNCTION OXIDATION REACTION PATHWAY

The hepatic endoplasmic reticulum possesses oxidative enzymes called **mixed-function oxidases** or **monooxygenase** with a specific requirement for both molecular oxygen and a reduced concentration of nicotinamide adenine dinucleotide phosphate (NADPH). Essential in the mixed-function oxidase system is P-450 (Figure 1.12). The primary electron donor is NADPH, whereas the electron transfer involved P-450, a flavoprotein. The presence of a **heat-stable fraction** is necessary for the operation of the system.

A drug substrate to be metabolized binds to oxidized P-450, which in turn is reduced by P-450 reductase. The drug-reduced P-450 complex then combines with molecular oxygen. A second electron and two hydrogen ions are acquired from the donor system, and the subsequent products are oxidized drug and water, with regeneration of the oxidized P-450. This process is summarized as follows:



The overall scheme for the mechanism of action of P-450 is shown in Figure 1.12.

## CONSEQUENCE OF BIOTRANSFORMATION REACTIONS

The process of biotransformation usually inactivates or detoxifies, or both, the administered drugs or the ingested poisons, but other reactions may also taken place.

### PRECURSOR ACTIVATION

Occasionally, an inactive precursor such as **levodopa** is converted to an active metabolite such as **dopamine**.

### METABOLIC ACTIVATION OF DRUGS

Often an active drug is converted to another pharmacologically active substance. The following table lists a few examples of this.

Drug		Active Metabolite
Mephobarbital	is demethylated to	Phenobarbital
Primidone	is oxidized to	Phenobarbital
Imipramine	is demethylated to	Desmethyylimipramine
Prednisone	is reduced to	Prednisolone

## CONVERSION TO METABOLITES WITH DISSIMILAR ACTIONS

In certain instances, the body converts a drug to several active metabolites possessing dissimilar pharmacologic properties. For example, phenylbutazone undergoes **aromatic hydroxylation** to produce a metabolite that has sodium-retaining and antirheumatic activities, and also undergoes **alkyl chain oxidation** to produce a metabolite with a strong uricosuric property. Thus, phenylbutazone has both uricosuric and antirheumatic effects.

### CONVERSION TO MORE ACTIVE PRODUCTS

The conversion of **cyclophosphamide** to **aldophosphamide** and **prednisone** to **prednisolone** are examples of active compounds that are converted to more active substances.

### LETHAL SYNTHESIS

The metabolism of drugs and agents does not always lead to detoxification; occasionally, the metabolites are toxicologically more potent. Some examples of this are **sulfamethazine**, which is metabolized to *N*<sub>4</sub>-acetylsulfamethazine, and **aminopyrine**, with 4-aminoantipyrine as its metabolite.

## DRUG METABOLITE KINETICS

In the majority of cases, drugs are converted to metabolites which, in the more polar and water-soluble forms, are readily excreted. Often the concentration of a metabolite far exceeds the concentration of the drug. For example, orally administered **propranolol** is rapidly converted to 4-hydroxypropranolol, which has a concentration that is several hundredfold higher than that of propranolol. Sometimes the metabolites are able to inhibit the further metabolism of the parent drug. For example, **phenytoin** becomes metabolized to hydroxyphenytoin. When given in higher-than-recommended individual doses, hydroxyphenytoin inhibits the hydroxylase system that metabolizes phenytoin, increasing its concentration in free form and its potential to produce toxicity.

The **enterohepatic circulation** may sometimes prolong the half-life of a drug. A drug that is absorbed from the gastrointestinal tract, excreted in the bile, and resorbed from the intestine is said

to have undergone **enterohepatic cycling**. Drugs are delivered to the liver by both the portal vein and hepatic artery, and returned to the rest of the body by the hepatic vein. The difference between the concentration of drug transported to and removed from the liver accounts for the amount of drug metabolized or excreted, or both, in the bile. For instance, if the liver has conjugated a drug containing glucuronic acid to its metabolite, the conjugated product may appear in the bile and finally be excreted in the small intestine. However, in the intestine, the beta-glucuronidase originating from the resident flora may hydrolyze the glucuronide-drug conjugate back to the parent drug, thus allowing the parent drug to be resorbed. The continuous enterohepatic cycling will therefore increase the half-life of this agent in the body.

## FACTORS THAT MODIFY THE METABOLISM OF DRUGS

Many environmental factors and pathophysiologic conditions inhibit or stimulate the activity of drug-metabolizing enzymes, and hence may alter the outcome of a therapeutic regimen. Pharmacogenetics, the immaturity of drug-metabolizing enzyme systems, and drug-drug interactions (discussed in Chapter 3 and Chapter 4) are a few of the factors that have been shown to alter drug metabolism.

### PHARMACOGENETICS

Pharmacogenetics represents the study of the hereditary variation in the handling of drugs. Pharmacogenetic abnormalities may be entirely innocuous, until the affected individual is challenged with particular drugs. The **hyposensitivity** and resistance of certain individuals to coumarin anti-coagulants and the **hypersensitivity** of patients with Down's syndrome to atropine most probably stem from abnormalities in their respective receptor sites. Acatalsia and the decrease in the activities of **pseudocholinesterase**, **acetylase**, and **glucose 6-phosphate dehydrogenase** are a few examples of enzymatic deficiencies that can result in mild to very severe adverse reactions.

### Liver Disease

The liver is the principal metabolic organ, and hepatic disease or dysfunction may impair drug elimination. Any alteration in the serum albumin or bilirubin levels and in the prothrombin time indicates impaired liver function. Similarly, skin bruising and bleeding tendency indicate decreased production of clotting factors by the liver.

### The Influence of Age

Drug metabolism is qualitatively and quantitatively very deficient in **newborns**. For example, **chloramphenicol**, when used injudiciously, may cause **gray syndrome**. The mechanism of chloramphenicol toxicity is apparently the failure in the newborn to conjugate chloramphenicol with glucuronic acid, because of inadequate activity of hepatic **glucuronyl transferase**. This, in combination with inadequate renal excretion of the drug in the newborn, results in a higher-than-expected plasma level of chloramphenicol. Therefore, a newborn should receive doses of chloramphenicol not greater than 25 to 50 mg/kg of body weight.

The **elderly** are also prone to toxicity from numerous drugs, including cardiac glycosides. A dose of digitoxin, which may be totally therapeutic and innocuous at the age of 60, may produce severe toxicity and even death at the age of 70. The abilities of the liver to metabolize drugs and of the kidney to excrete drug metabolites decline with aging.

### Enzyme Induction and Inhibition

The activities of **microsomal drug-metabolizing enzymes** in humans can be enhanced by altering the levels of endogenous hormones such as androgens, estrogens, progestational steroids, gluco-

corticoids, anabolic steroids, norepinephrine, insulin, and thyroxine. This effect can also be elicited by the administration of exogenous substances such as drugs, food preservatives, insecticides, herbicides, and polycyclic aromatic hydrocarbons. This increase in the activities of drug-metabolizing enzymes appears to stem from an elevated rate of synthesis of the enzyme protein; hence, it is truly an enzyme induction phenomenon.

**Liver microsomal enzyme inducers** that are lipid soluble at the physiologic pH can be classified into two general groups. Some, such as phenobarbital, tend to stimulate all enzymes; others, such as 3-methylcholanthrene, tend to be selective. The administration of phenobarbital increases the amounts of NADPH-cytochrome C reductase and P-450, and the rate of P-450 reduction. In contrast, the administration of 3-methylcholanthrene increases the amount of P-450 but neither the activity of NADPH-cytochrome C reductase nor the rate of P-450 reduction.

### Clinical Implications of Enzyme Induction and Inhibition

Patients are often given several drugs at the same time. The possibility that one drug may accelerate or inhibit the metabolism of another should always be kept in mind. When this phenomenon occurs, the removal of an enzyme inducer could be hazardous. The following examples reveal the consequences of enzyme induction.

**Phenylbutazone** is an analgesic, antipyretic, uricosuric, and anti-inflammatory agent. Among its side effects are activation of peptic ulcer and gastrointestinal hemorrhage. If one gives a dog large amounts of phenylbutazone, side effects such as vomiting and diarrhea with bloody stool ensue. However, if phenylbutazone treatment is continued for several days, these side effects disappear. In this case, phenylbutazone “induces” its own hydroxylation, which results in a lower plasma level of the drug and ultimately the absence of the side effects. Long-term treatment with phenylbutazone and many other drugs should be expected to result in decreased effectiveness and toxicity.

Patients who are on **anticoagulant** therapy may suffer severe hemorrhages several days after discharge from the hospital. Often these patients are sedated with **barbiturates** during their hospitalization, which tends to stimulate the enzymes that metabolize dicumarol. The abrupt withdrawal of barbiturates after discharge tends to revert the activity of the drug-metabolizing enzymes to their prebarbiturate stage, which raises the free circulating level of the anticoagulant and results in hemorrhage. Obviously, treatment with phenobarbital should prompt altering the maintenance dosage of anticoagulants.

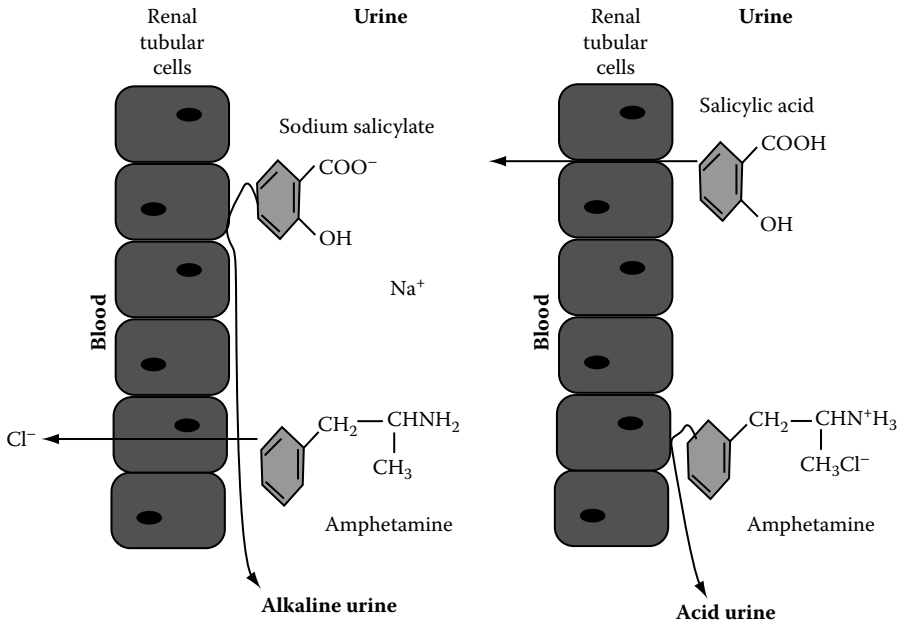
## RENAL EXCRETION OF DRUGS

An orally administered drug will gradually begin to be absorbed. As the amount of drug in the body increases by 50%, the amount of the drug at the absorption site should decrease by the same amount. The absorbed drug will gradually be metabolized or excreted mostly by the kidneys. Besides their renal elimination, drugs and their metabolites are eliminated in bile, breast milk, and sweat, and by the lungs.

### RATE OF EXCRETION OF DRUGS BY THE KIDNEYS

The amount of a drug (and its metabolites) that appears in the urine depends on the amount of drug undergoing glomerular filtration, tubular secretion, and tubular resorption. **Metabolism** plays a major role in drug excretion, because the metabolites are more water-soluble substances, which are excreted. Drugs are excreted when they are in their free form but, plasma-protein-bound drugs and tissue-stored drugs are not excreted.

The excretion of drugs from the kidneys, similar to the absorption of drugs from the gastrointestinal tract, depends on lipid solubility, the degree of ionization of drugs, and the pH of the urine.



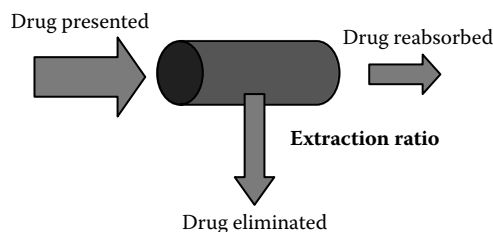
**FIGURE 1.13** Elimination of drug following alkanization or acidification of urine.

Nonionized lipid-soluble drugs are resorbed and not eliminated. Generally, drugs that are bases are excreted when the urine is acidic, whereas acidic compounds are excreted in greater quantities if the urine is alkaline. For example, in **phenobarbital** (weak acid  $pK_a$  of 7.3) poisoning, alkanization of the urine with sodium bicarbonate is helpful in eliminating the phenobarbital. In **amphetamine** toxicity, acidification of the urine with ammonium chloride is required (Figure 1.13).

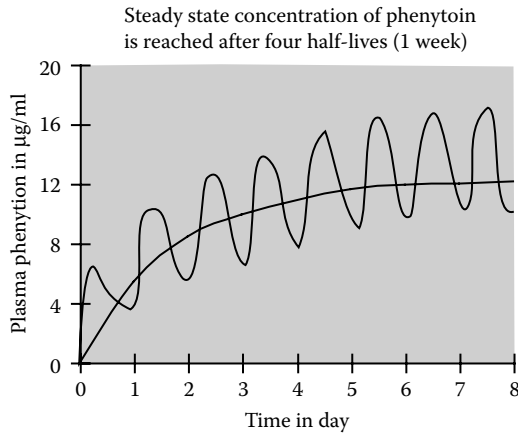
Drugs that undergo both glomerular filtration and active tubular secretion have a very short half-life. **Penicillin** is one such compound, but its half-life is prolonged by the coadministration of **probenecid**, a uricosuric drug that inhibits the tubular secretion of penicillin. Most drugs, however, have half-lives that are relatively longer than penicillin's because they undergo glomerular filtration, partial tubular resorption, and no active tubular secretion.

### SIGNIFICANCE OF BLOOD FLOW FOR DRUG CLEARANCE

In general, the rate of extraction of drug from blood and the rate of clearance by the kidney depend on blood flow and the ability of the kidney to extract the drug (the **extraction ratio**). If the drug is completely removed from the blood as it traverses through the kidneys, the extraction ratio is 1. The higher the blood flow, the higher the rate of excretion of that drug, and the clearance is said to be **perfusion-rate limited** (Figure 1.14). For example, the extraction ratio of digoxin, one of



**FIGURE 1.14** Perfusion-mediated elimination of drug.



**FIGURE 1.15** A steady-state plasma concentration of most drugs is reached following 1 week of continuous administration.

the cardiac glycosides, is low and toxicity is likely to occur in renal failure. Similarly, the hepatic extraction ratio of digitoxin is low, and toxicity is likely to occur in hepatic failure. Consequently, cardiologists have long recognized that **digitoxin** and **digoxin** should be avoided in patients suffering from liver and renal failure, respectively.

### HALF-LIFE OF A DRUG

The half-life of a drug, or its elimination half-life, is the time required for its concentration in the blood to be reduced by one half. For penicillin G, the half-life is 20 min, indicating that only 50% of it remains in the blood 20 min after its intravenous administration. Both the intravenously and orally administered identical drugs have the same half-lives once they reach the general circulation. When given at regular intervals, a drug or its metabolite reaches a plateau concentration after approximately four to five half-lives (Figure 1.15). This plateau changes only if the dose or frequency of administration, or both, are altered.





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# 2 Pharmacodynamics

The desire to take medicine is perhaps the greatest feature which distinguishes men from the animals.

— Sir William Osler

## INTRODUCTION

Pharmacodynamics may be defined as the study of the actions and effects of drugs on organs, tissues, cellular, and subcellular levels. Therefore, pharmacodynamics provides us with information about the beneficial action of drugs and their side effects.

Chapter 1, on **pharmacokinetics**, discussed the processes of absorption, binding, distribution, biotransformation, and excretion of drugs. These processes act efficiently to ensure that a sufficient quantity of drugs reach their receptor sites to elicit the desired therapeutic effects.

**Pharmacodynamics** considers the sites, modes, and mechanisms of action of drugs. For example, if a patient with multiple fractures receives a subcutaneous injection of 10 to 15 mg of morphine sulfate (*Papaver somniferum*, Chapter 47), analgesia, sedation, respiratory depression, emesis, miosis, suppression of the gastrointestinal tract, and oliguria may ensue. These diversified effects occur at multiple peripheral and central sites through the action of numerous modes and mechanisms.

## SITE OF ACTION

The receptor site where a drug acts to initiate a response is that drug's site of action. The central sites of action of morphine include the cerebral cortex, hypothalamus, and medullary center.

## MODE OF ACTION

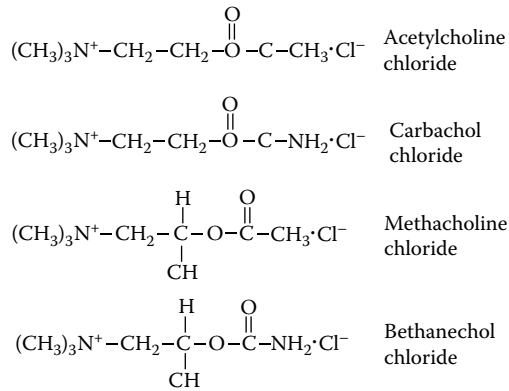
The type of effect produced by a drug is called the **mode of action** of that drug. Morphine, by depressing the function of the cerebral cortex, hypothalamus, and medullary center, is responsible for decreasing pain perception (**analgesia**), inducing narcosis (**heavy sedation**), depressing the cough center (**antitussive effect**), initially stimulating then depressing vomiting, and depressing respiration.

## MECHANISM OF ACTION

The identification of molecular and biochemical events leading to an effect is called the mechanism of action of that drug. For instance, morphine causes respiratory depression by depressing the responsiveness of the respiratory center to carbon dioxide.

## STRUCTURE–ACTIVITY RELATIONSHIP

A definite and strong relationship seems to exist between the molecular structure of most pharmacologic compounds and their inherent pharmacologic properties. For example, modifying the molecular structure of acetylcholine dramatically alters its pharmacologic properties. **Acetylcholine**



**FIGURE 2.1** The structure of various cholinomimetic agents.

mediates cholinergic function at various anatomic sites. By examining the molecular structure of acetylcholine, one notes **quaternary nitrogen** at one end of the molecule and an **ester** at the other end, separated by a two-carbon linkage. Although acetylcholine is an important physiologic agent, it is not useful as a drug, because its short-lived actions are massive and nonspecific. The various synthetic derivatives of acetylcholine differ from it in being more resistant to hydrolysis by cholinesterase (**longer duration of action**) and possessing greater **organ-specific action**. For example, **bethanechol chloride** is useful in treating the urinary retention, megacolon, and delayed gastric emptying that occur following vagotomy for the treatment of severe peptic ulceration. Its molecular structure is shown in Figure 2.1.

## DRUG ACTIONS UNRELATED TO STRUCTURES

In cases in which drugs exert their actions by interacting with specific receptors, structural modification dramatically alters the expected effects. However, not all drugs act by interacting with specific receptors. For example, **general anesthetics** such as **thiopental**, **halothane**, **cyclopropane**, and **nitrous oxide** have vastly dissimilar structures.

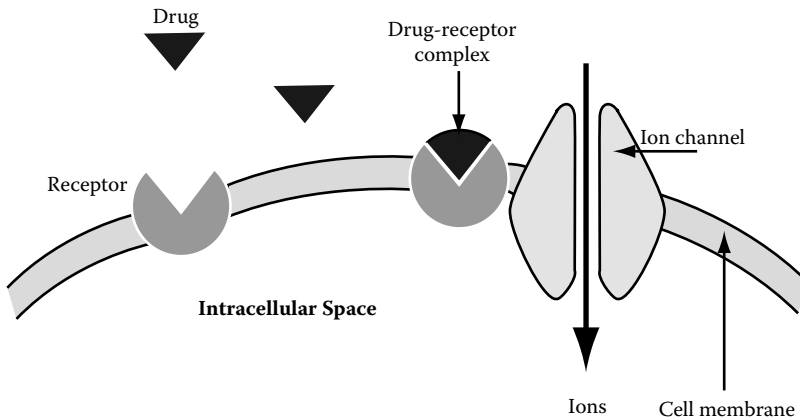
## DRUG RECEPTOR-SPECIFIC INTERACTION

Contemporary ideas of **drug action** and **specificity** are based on the assumption that the initial process in drug action is the formation of a reversible complex between the drug and a cell component generally known as the **drug receptor** (Figure 2.2). The interaction of a drug with a specific receptor site is characterized by at least three factors, namely:

**Chemical and structural specificity:** Any alteration in the structure of a compound alters its pharmacologic properties. For example, **nalorphine**, a narcotic antagonist, differs from **morphine**, a narcotic agonist, by the replacement of the  $\text{CH}_3$  group on the morphine's nitrogen with the allyl radical  $-\text{CH}_2\text{CH}=\text{CH}_2$ .

**Stereoisomeric specificity:** Only the  $\text{L}(-)$  **enantiomorph** of morphine and certain other opioids can interact with (enter) the receptor site. For example, **levorphanol**, a synthetic narcotic, is 5 to 10 times more potent than morphine, but its  $\text{L}(+)$  enantiomorph **dextrorphan** is devoid of analgesic activity.

**Potency:** Drugs that interact with receptor sites may exert their effects in extremely small doses. For example, **etorphine** is 10,000 times more potent than morphine.



**FIGURE 2.2** Most drugs form a reversible complex with their specific receptors.

## CELLULAR SITES OF ACTIONS OF DRUGS

Because drugs are very reactive, many elicit their effects or side effects, or both, by interacting with **coenzymes**, **enzymes**, or **nucleic acids**, as well as other macromolecules and physiologic processes such as transport mechanisms. To gain an appreciation of the complex interactions between drugs and physiologic parameters, some examples are cited.

### DRUG–COENZYME INTERACTIONS

#### Isoniazid and Pyridoxal Phosphate

The primary drugs, first-line agents that combine the greatest level of efficacy with an acceptable degree of toxicity, in the treatment of **tuberculosis** are **Isoniazid**, **ethambutol**, **pyrazinamide**, and **rifampin**. **Isoniazid** is prescribed orally in doses of 4 to 5 mg per kilogram of body weight. If pyridoxine is not given along with the Isoniazid, peripheral neuritis is the most common side effect seen. In toxic doses, optic neuritis, muscular twitching, dizziness, ataxia, paresthesias, and convulsions may occur, especially in malnourished patients. These neuropathies are thought to result from a chemical interaction between Isoniazid and **pyridoxal phosphate**, and the reduced level of this important coenzyme in the body. The coadministration of **pyridoxine** with isoniazid averts these side effects (see Chapter 39).

#### Folic Acid and Trimethoprim-Sulfamethoxazole

In acute and chronic urinary tract infection, the combination of **trimethoprim** and **sulfamethoxazole** (Bactrim, Septra) exerts a truly synergistic effect on bacteria. The sulfonamide inhibits the utilization of ***p*-amino-benzoic acid** in the synthesis of folic acid (Figure 2.3), whereas trimethoprim, by inhibiting dihydrofolic acid reductase, blocks the conversion of dihydrofolic acid to **tetrahydrofolic acid**, which is essential to bacteria in the *de novo* synthesis of purines, pyrimidines, and certain amino acids. Because mammalian organisms do not synthesize folic acid and therefore need it as a vitamin in their daily diets, trimethoprim-sulfamethoxazole does not interfere with the metabolism of mammalian cells.

### DRUG–ENZYME INTERACTIONS

Numerous drugs exert their effects and side effects by interacting with enzymes. Some examples of these interactions are now cited.

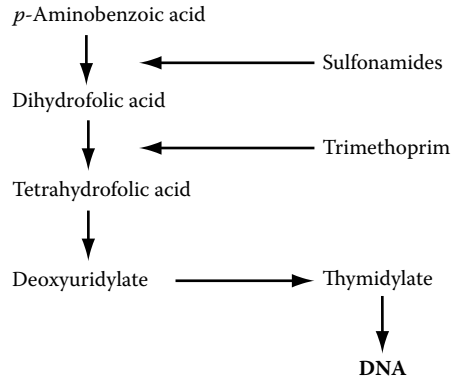
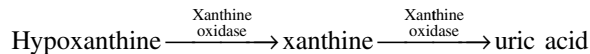


FIGURE 2.3 By inhibiting the synthesis of folic acid, sulfonamides exert their antibacterial activity.

### Allopurinol, Xanthine Oxidase, and Hyperuremic States

Allopurinol is used to lower uric acid levels in the treatment of primary gout, as a prophylaxis in myeloproliferative neoplastic disease, for investigational purposes in Lesch–Nyhan syndrome, and as an adjunct with thiazide diuretics or ethambutol (see Chapter 24). Allopurinol acts by inhibiting xanthine oxidase, which converts hypoxanthine into xanthine and in turn becomes oxidized into uric acid.



When xanthine oxidase is inhibited by allopurinol, the plasma level of uric acid and the size of the urate pool in the body both decrease.

### Drugs and Bronchial Asthma

**Aminophylline** (theophylline ethylenediamine), given intravenously, is used in patients with **status asthmaticus** who do not respond to epinephrine. In addition, epinephrine may be administered subcutaneously for acute asthma attacks. Epinephrine may also be given along with theophylline. It is thought that the bronchodilation is associated with the enhanced concentration of cyclic AMP, which is metabolized according to the following sequence:

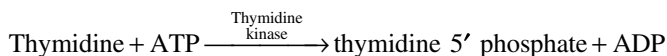


**Epinephrine** stimulates the beta-adrenergic receptors in the bronchioles, which in turn activate membrane-bound adenylyl cyclase to synthesize more cyclic AMP, whereas theophylline inhibits the activity of phosphodiesterase, conserving the previously synthesized cyclic AMP.

## DRUG–NUCLEIC ACID INTERACTIONS

**Chemotherapeutic agents**, useful in the treatment of neoplastic diseases, exert their therapeutic effects by modifying the synthesis or functions of nucleic acids (see Chapter 51 and Chapter 58). For example, **6-mercaptopurine** inhibits purine-ring biosynthesis, **cytarabine** inhibits DNA polymerase, alkylating agents crosslink DNA, and hydroxyurea inhibits the conversion of ribonucleotides into deoxyribonucleotides. However, other pharmacologic agents such as chlorpromazine, a

neuroleptic, also modify nucleic acid synthesis. One of the side effects of chlorpromazine is mild to severe agranulocytosis. **Chlorpromazine** reduces the synthesis of DNA by inhibiting the activity of thymidine kinase according to the following scheme:



In addition to chlorpromazine, the following drugs: phenylbutazone (an analgesic and anti-inflammatory agent), sulfonamides (chemotherapeutic agents), chlorothiazide (a diuretic), thiouracil and methimazole (antithyroid drugs), phenytoin (an anticonvulsant), pyribenzamine (an antihistaminic), and chloramphenicol (an antimicrobial), may cause **agranulocytosis** in susceptible individuals. The incidence of this side effect is highest among individuals with a lower than normal proliferative capacity of the bone marrow.

## THE INTERACTIONS OF DRUGS WITH NEURONAL ELEMENTS

Neuropharmacology is the study of drugs that affect the nervous system and its neuronal components. The functions of the nervous system are intimately linked with the synthesis, storage, release, and uptake of many transmitters and their modulators. The beneficial effects or side effects of an extensive number of drugs are brought about through their interaction with these neurotransmitter-neuromodulator systems.

An example of this interaction is offered by **reserpine** (see Chapter 56). Reserpine may be used in conjunction with a diuretic in the treatment of mild to moderate **hypertension**. It is thought that reserpine produces this antihypertensive effect by preventing the storage of norepinephrine and hence reducing the pool of this neurotransmitter in the body. This amine-depleting action of reserpine causes both beneficial and unwanted effects; for instance, reserpine may act as a tranquilizer, causing depression by depleting the catecholamine content in the brain or sometimes causing bradycardia, miosis, and increased motility of the gastrointestinal tract from the enhanced cholinergic activity resulting from decreased sympathetic activity. Reserpine may also increase the atrioventricular conduction time by prolonging the refractory period of the atrioventricular conduction system, by depleting myocardial norepinephrine stores.

## INTERACTION OF DRUGS WITH THE ENDOCRINE SYSTEM

### ALPHA-METHYLDOPA AND RENIN

Hypotension and decreased renal perfusion pressure promote the release of renin from the juxtaglomerular apparatus of the kidney. **Renin** converts angiotensin I to **angiotensin II**, a potent, endogenously occurring vasoconstrictor. Catecholamine can also release renin, and this effect is blocked by **propranolol**, a beta-adrenergic receptor-blocking agent. Drugs that alter the renin level are able to alter blood pressure. Alpha-methyldopa suppresses renin release, whereas the oral contraceptive medications have the opposite effect. In addition, other antihypertensive medications such as **captopril** specifically inhibit angiotensin-converting enzyme, hence preventing the formation of angiotensin II.

### DRUGS AND PROLACTIN

The release of prolactin from the adenohypophysis is a centrally mediated event involving the **dopaminergic neurons**. Stimulation of these neurons blocks prolactin production, whereas blockade of dopaminergic function causes lactation. **Chlorpromazine**, which blocks dopamine receptors;

**reserpine**, which depletes dopamine stores; and alpha-methyldopa, which forms a false transmitter such as **alpha-methyldopamine**, are all able to cause inappropriate lactation in nonpregnant women.

This discussion clearly demonstrates that drugs do not create functions, but merely stimulate or inhibit functions already inherent in cells. These pharmacodynamic-related interactions occur at various levels of cellular activity, including ion transport, enzymes, coenzymes, nucleic acids, and numerous other biochemical events yet to be delineated.

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# 3 Adverse Reactions and Drug–Drug Interactions

Imperative drugging — the ordering in any and every malady — is no longer regarded as the chief function of the doctor.

— Sir William Osler

## INTRODUCTION

It is commonly found that patients with **multiple medical problems** may be taking as many as 10 to 15 drugs concomitantly. It is also becoming increasingly obvious to physicians, and other members of the health-care delivery team, that many **drug combinations**, when used inappropriately and injudiciously, have the inherent potential to interact adversely, leading to side effects and even death (see Chapter 4).

Whether drugs are given individually or in combination, some side effects or adverse reactions are inevitable and cannot be eliminated. For example, patients undergoing treatment with antineoplastic drugs (see Chapter 62) will experience expected side effects, such as hair loss (Figure 3.1). Nevertheless, many adverse effects of drugs, or **drug–drug interactions**, are either avoidable or may be substantially minimized.

The varied and complex mechanisms involved can be broadly classified as **pharmacokinetic interactions** or **pharmacodynamic interactions**. In pharmacokinetic interactions, drugs interfere with and may alter the absorption, distribution, biotransformation, or excretion of other drugs. In pharmacodynamic interactions, which have been discussed in Chapter 2, drugs modify the intended and expected actions of other drugs. Before elaborating on the pharmacokinetic interactions, some terms will be defined.

## DEFINITIONS

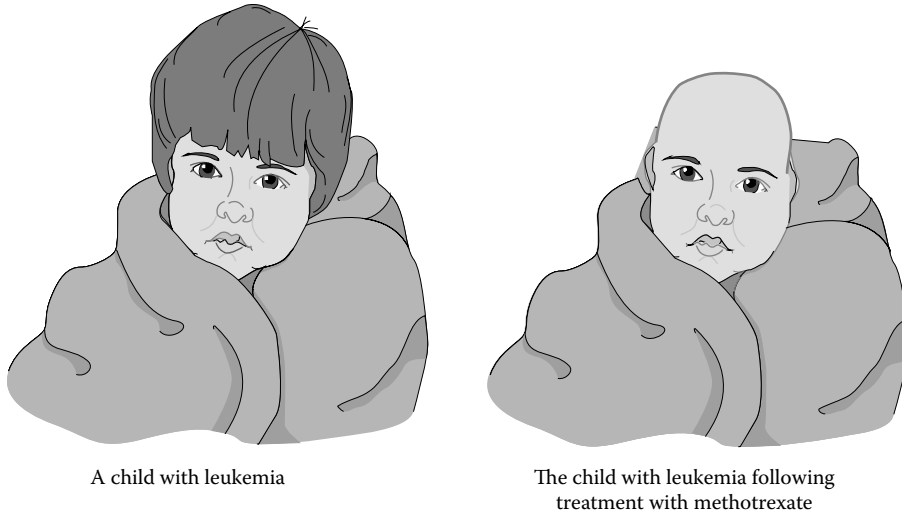
### IATROGENIC REACTIONS

**Iatrogenic Reactions** broadly refer to any adverse reactions that are unintentionally produced by physicians in their patients. For example, one of the side effects of many antihistaminic preparations ( $H_1$  antagonists) such as ethanolamine derivatives (prototype: **diphenhydramine**) is heavy sedation. Although sedation may be desirable for some patients, it may interfere with daytime activities, and this needs to be considered when prescribing such medications. Other antihistaminic preparations (also  $H_1$  antagonists) such as piperidine derivatives (prototypes: **terfenadine** or **astemizole**) have no sedative properties (Figure 3.2).

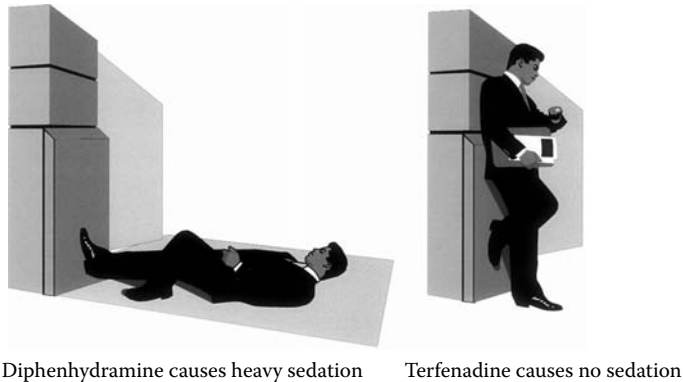
### ALLERGIC REACTIONS

**Drug allergy** refers to drug reactions in a patient who was previously exposed to, or sensitized with, a drug and subsequently developed antibodies to that drug. The underlying immunologic





**FIGURE 3.1** Antineoplastic agents cause alopecia.



**FIGURE 3.2** Terfenadine does not have sedative effects.

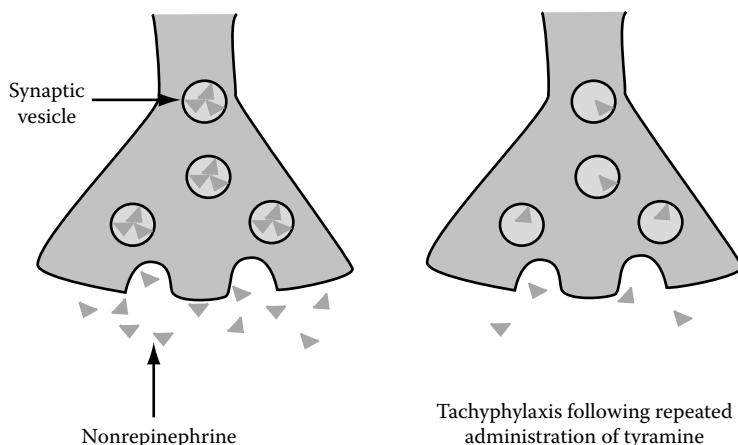
mechanisms may be varied and complex, involving **anaphylactoid immediate reactions** (e.g., penicillin, due to formation of specific immunoglobulin E), **cytotoxic reactions** (e.g., drug-induced hemolytic anemias), and **delayed allergic reactions** (e.g., drug-induced contact dermatitis).

### IDIOSYNCRATIC REACTIONS

**Idiosyncrasy** refers to an abnormal, unexpected, or peculiar reaction seen in certain patients only. For example, **succinylcholine** may cause prolonged apnea in patients with **pseudocholinesterase deficiency**, and **hemolytic anemia** may be seen in patients with **glucose-6-phosphate dehydrogenase deficiency** following the administration of a number of drugs, including sulfonamides. Although these reactions are inevitable when they occur unexpectedly for the first time, they may be circumvented altogether in patients who have previously shown such abnormal reactions.

### TOLERANCE AND TACHYPHYLAXIS

**Tolerance** refers to decreased responses following the long-term administration of drugs. For example, after repeated **morphine** use, tolerance to all of its effects, except for miosis and constipation, occurs, and respiratory depression is also reduced.



**FIGURE 3.3** In the absence of norepinephrine, tyramine is ineffective.

**Tachyphylaxis** refers to a quickly developing tolerance brought about by the rapid and repeated administration of drugs. For example, indirect-acting sympathomimetic agents such as **tyramine**, which exert their effects through the release of norepinephrine, are able to cause tachyphylaxis. If norepinephrine is not present, tyramine fails to act until the supply of norepinephrine in nerve terminals has been replenished (Figure 3.3).

Although tachyphylaxis is innocuous and not regarded as a major clinical problem, not considering tolerance may have devastating consequences. For example, respiratory depression is not seen in a morphine-tolerant patient, and a dosage that far exceeds the normal therapeutic level is required to induce an effect. However, tolerance is lost or lessened following the discontinued administration of morphine. Therefore, in a once-tolerant patient, administering a dose of morphine that was once quite innocuous may prove fatal by causing severe respiratory depression.

### SUPERSENSITIVITY

**Supersensitivity** refers to the increased responsiveness of a patient to a drug, resulting either from denervation or administration of a drug (a receptor antagonist) for a prolonged period. For example, the blocking of dopamine receptors by chlorpromazine may cause supersensitivity by upregulating dopamine receptors.

### PHARMACOKINETIC INTERACTIONS

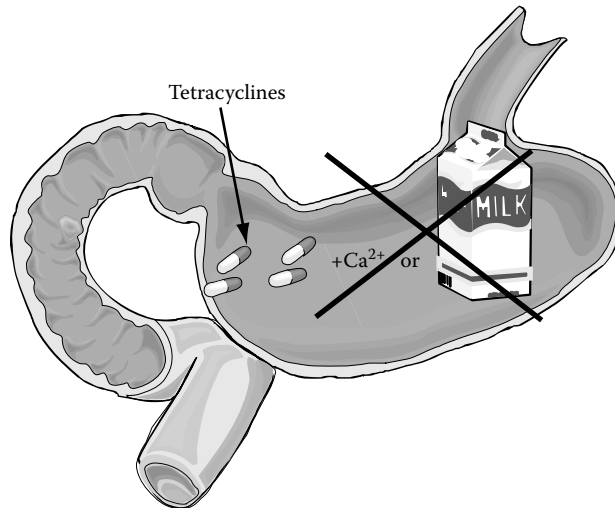
Drugs may affect the absorption, distribution, metabolism, or excretion of other drugs. This includes those interactions in which the gastrointestinal absorption of a drug, plasma protein binding, drug metabolism, and urinary excretion are either enhanced or inhibited.

#### INTERACTION AT THE SITE OF ABSORPTION

The rate or extent of drug absorption from the gastrointestinal tract can be influenced in a number of ways. Examples of these various influences follow.

#### Alteration of Gastric pH

**Iron** poisoning is characterized by vomiting, abdominal pain, gastroenteritis, and shock, and if not properly treated, severe acidosis, coma, and death ensue. **Deferoxamine**, which binds iron, is used as the preferred chelator in treating iron poisoning. The metabolic acidosis may be appropriately



**FIGURE 3.4** Milk products hinder the absorption of tetracyclines.

treated with sodium bicarbonate. However, because deferoxamine chelates iron more effectively in an acidic medium, it should not be administered orally along with sodium bicarbonate. The ideal treatment for iron poisoning consists of gastric aspiration, followed by lavage with a phosphate solution to form insoluble iron salts. Deferoxamine should then be given intravenously or intramuscularly to chelate the iron that has been absorbed. Sodium bicarbonate may be administered intravenously. To absorb any residual iron remaining in the stomach, deferoxamine may then be instilled into the stomach.

### Formation of Complex

**Tetracyclines**, as broad-spectrum antibiotics, are the drugs of choice in treating *Mycoplasma pneumoniae* infections. Most **tetracyclines** are absorbed to various degrees (30 to 100%) from the gastrointestinal tract, primarily from the stomach and upper small intestine. The absorption of tetracyclines is hindered by **milk and milk products**, by numerous **antacids** such as aluminum hydroxide, sodium bicarbonate, and calcium carbonate, and by iron preparations such as ferrous sulfate. Therefore, these and similar substances should not be administered orally together with tetracycline (Figure 3.4).

### Alteration in Gastric Emptying Time

Agents that reduce gastrointestinal motility and prolong gastric emptying time reduce the rate of absorption of drugs whose absorption takes place primarily in the duodenum. Furthermore, by prolonging the time that poorly soluble drugs are kept in the stomach, their bioavailability may be altered. Hence, compounds with strong anticholinergic properties such as **proprantheline** (for peptic diseases), **glycopyrrolate** (for asthma), **benztropine** (for parkinsonism), and **imipramine** (for depression) are potentially able to alter the absorption of other concomitantly administered drugs. The absorption of digoxin and dicumerol is altered by imipramine and other tricyclic antidepressants. On the other hand, some drugs such as antacids may speed the gastric emptying time.

## INTERACTIONS AT THE PLASMA-PROTEIN BINDING SITES

Drugs may **compete** for binding sites on the plasma or tissue protein, or may **displace** previously bound drugs. For example, **phenylbutazone** may compete with **phenytoin** for binding to albumin.

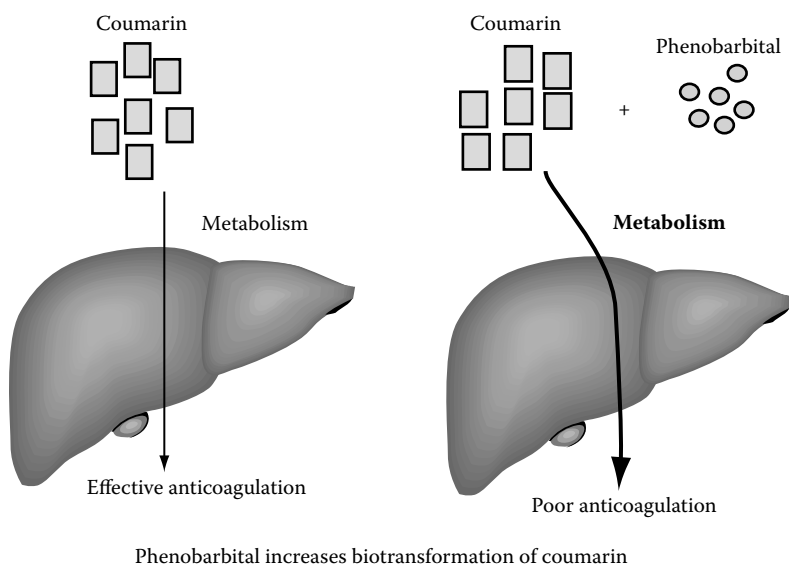
Similarly, phenylbutazone (an anti-inflammatory agent) is able to displace warfarin (an anticoagulant) from its binding site and enhance the free circulating concentration of the anticoagulant. Sulfonamides (chemotherapeutic agents) are able to displace sulfonylureas (oral antidiabetic agents) and cause hypoglycemia.

### INTERACTIONS AT THE STAGE OF DRUG BIOTRANSFORMATION

Drug biotransformation usually converts the nonpolar active drugs into more water-soluble, but pharmacologically inactive, products. Drugs may stimulate or inhibit the metabolism of other drugs. These interactions may be either innocuous or detrimental to the expected therapeutic objectives.

The prolonged ingestion of alcohol or phenobarbital induces drug biotransformation. The maximum inducing effects vary from drug to drug, with the duration between onset and decline usually lasting 7 to 10 d. The sudden withdrawal of an inducing agent in some circumstances can prove fatal. For example, hypnotic sedatives accelerate the rate of metabolism of **coumarin** anticoagulants (Figure 3.5). Increased doses of coumarin may therefore have to be given in order to achieve the desired prothrombin time and therapeutic effects. The sudden withdrawal of a hypnotic-sedative agent may cause the coumarin-catabolizing enzyme to revert to the pretreatment level, and in the presence of large concentrations of free coumarin, **hemorrhage** may ensue. Because physicians anticipate that their patients may not require hypnotic-sedatives after being discharged from the hospital, the maintenance doses of coumarin anticoagulants are gradually reduced 2 to 3 d before discharge (see Chapter 59).

On the other hand, drugs may **inhibit** the metabolism of other drugs. For example, **allopurinol** (a xanthine oxidase inhibitor that inhibits the synthesis of uric acid) increases the effectiveness of anticoagulants by inhibiting their metabolism. **Chloramphenicol** (a potent inhibitor of microsomal protein synthesis) and **cimetidine** (an  $H_2$ -receptor blocker used in acid-pepsin disease) have similar properties. In addition, drugs may **compete** with each other in metabolic reactions. In methyl alcohol (**methanol**) poisoning, **ethyl alcohol** may be given intravenously to avert methanol-induced blindness and minimize the severe acidosis. Ethyl alcohol competes with methyl alcohol for



**FIGURE 3.5** The interaction of phenobarbital with coumarin anticoagulant.

catabolism by liver alcohol dehydrogenase. The unmetabolized and less toxic methanol is excreted unchanged in the urine (see Chapter 68).

### INTERACTIONS AT THE SITE OF EXCRETION

Numerous drugs are able to either enhance or inhibit the excretion of other drugs. For example, **sodium bicarbonate** enhances the excretion of **phenobarbital**. Probenecid interferes with the active secretion of penicillin and hence prolongs its half-life. Probenecid's uricosuric effects are counteracted by acetylsalicylic acid, which also possesses a uricosuric effect. When given concomitantly, both are excreted (see Chapter 24).

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# 4 Herb–Drug Interactions

## HERBS AND DRUG EFFECTS

Oriental medicine, including Chinese medicine (CM), is a complex and holistic system of medical practice with its own philosophy, diagnosis, treatment systems, and pharmacology. CM considers the human body in relation to its own natural, physical, and social environment. The practice of CM involves physical therapy (nonmedication) using acupuncture, moxibustion, and related disciplines such as *Tuina Massage* and *Qi Gong*; and chemical therapy using Chinese medicinal materials (CMM) of animal, mineral, and plant origin in the form of decoctions of combined CMM or related proprietary products. As most of them are from plants, medical books on CMM, throughout the ages, have conveniently referred to them as *Ben Cao* (Herbalism) (Chan, 2005).

Herbal medicines are mixtures of more than one active ingredient. The multitude of pharmacologically active compounds obviously increases the likelihood of interactions taking place. Hence, the likelihood of herb–drug interactions is theoretically higher than that of drug–drug interactions, if only because synthetic drugs usually contain single chemical entities. Case reports and clinical studies have highlighted the existence of a number of clinically important interactions, although cause-and-effect relationships have not always been established. Herbs and drugs may interact either pharmacokinetically (Chapter 1) or pharmacodynamically (Chapter 2). Through induction of cytochrome P-450 enzymes (see Figures 1.1 through 1.12) and/or P-glycoprotein, some herbal products (e.g., **St John’s wort** in Chapter 43) have been shown to lower the plasma concentration (and/or the pharmacological effect) of a number of conventional drugs, including **cyclosporine**, **indinavir**, **irinotecan**, **nevirapine**, **oral contraceptives**, and **digoxin**. The majority of such interactions involve medicines that require regular monitoring of blood levels. To date there is less evidence relating to the pharmacodynamic interaction. However, for many of the interactions discussed here, the understanding of the mechanisms involved is incomplete. Taking herbal agents may represent a potential risk to patients under conventional pharmacotherapy (Izzo, 2004; Butterweck et al., 2004; Chan, 2005).

Herbal medicines follow modern pharmacological principles. Hence, herb–drug interactions are based on the same pharmacokinetic and pharmacodynamic mechanisms as drug–drug interactions (see Chapter 1 to Chapter 3). Pharmacokinetic interactions have been more extensively studied, and *in vitro* and *in vivo* studies have indicated that the altered drug concentrations by coadministered herbs may be attributable to the induction, or inhibition, of hepatic and intestinal drug-metabolizing enzymes, particularly cytochrome P-450 (CYP), (see Chapter 1), and/or drug transporters such as P-glycoprotein (Izzo, 2004).

Concurrent use of herbs may mimic, magnify, or oppose the effect of drugs. Plausible cases of herb–drug interactions include the following:

- Bleeding may occur when **warfarin** (see Chapter 42 and Chapter 59) is combined with **ginkgo** (*Ginkgo biloba*), **garlic** (*Allium sativum*), **dong quai** (*Angelica sinensis*), or **danshen** (*Salvia miltiorrhiza*).
- **Mild serotonin syndrome** occurs in patients who mix **St. John’s wort** (*Hypericum perforatum*) with serotonin-reuptake inhibitors.

- Decreased bioavailability of **digoxin**, **theophylline**, **cyclosporin**, and **phenprocoumon** takes place when these drugs are combined with **St. John's wort**.
- Induction of **mania** may be seen in depressed patients who mix **antidepressants** and **Panax ginseng**.
- Exacerbation of **extrapyramidal effects** is possible with **neuroleptic drugs** and **betel nut** (*Areca catechu*).
- Increased risk of hypertension is imminent when **tricyclic antidepressants** are combined with **yohimbine** (*Pausinystalia yohimbe*).
- Potentiation of oral and topical effects of **corticosteroids** is certain by **licorice** (*Glycyrrhiza glabra*).
- Decreased blood concentration of **prednisolone** occurs when taken with the Chinese herbal product **xaio chai hu tang** (sho-saiko-to).
- Decreased concentrations of **phenytoin** is seen when it is combined with the Ayurvedic syrup **shankhapushpi**.

Furthermore, plants containing anthranoids, including **senna** (*Cassia senna*) and **cascara** (*Rhamnus purshiana*), and soluble fibers, including **guar gum** and **psyllium**, can decrease the absorption of drugs (Fugh-Berman, 2000; Table 4.1).

## POTENTIAL INTERACTIONS BETWEEN ALTERNATIVE THERAPIES AND WARFARIN

Alternative medicine therapies have become increasingly popular, and it has been estimated that one third of all Americans use herbal products. In 1997, herbal medicine sales increased by nearly 59%, reaching an estimated total of \$3.24 billion (see Heck et al., 2000; Izzo, 2004). One particular safety concern is the potential interaction of alternative medicine products with prescription medications. This issue is especially important with respect to drugs with narrow therapeutic indices, such as **warfarin**. More food and drug interactions have been reported for warfarin than for any other prescription medication. Multiple pathways exist for interference with warfarin, and interactions may lead to either hemorrhage or thrombotic episodes by increasing or reducing the effect of this agent. Therefore, close monitoring of therapy and knowledge of potential interactions of herbs with warfarin are extremely important.

### ANTICOAGULANTS AND THROMBOLYTIC AGENTS

Clotting of blood, which protects against hemorrhage, involves the sequential initiation, interaction, and completion of several stages in hemostasis (Table 4.2).

The **adhesion** and **aggregation** of platelets are mediated via the release of **adenosine diphosphate** (ADP). An extensive number of pharmacological agents such as **acetylsalicylic acid**, **indomethacin**, **phenylbutazone**, **sulfinpyrazone**, and **dipyridamole** inhibit both **platelet aggregation** and **thrombus formation**, and thus may be of value in the treatment of **thrombotic disorders**. The **formation of fibrin** itself takes place by means of a cascading group of reactions involving numerous blood-clotting factors and is accomplished in several stages (Table 4.3).

**Hemorrhage** may result from several causes:

- An abnormality or **deficiency of platelets** (thrombocytopenic purpuras)
- A **deficiency of clotting factors** (factors II, VII, IX, or X)
- **Vitamin K deficiency** (necessary for synthesizing clotting factors)
- **Liver diseases** that involve the synthesis of clotting factors

**TABLE 4.1**  
**Herbs Interacting with Drugs**

Herbs and Drugs	Results of Interaction	Comments
<b>Betal nut (<i>Areca catechu</i>)</b>		
Flupenthixol and procyclidine	Rigidity, bradykinesia, jaw tremor	Betal contains <b>arecoline</b> , a cholinergic alkaloid
Fluphenazine	Tremor, stiffness, akathisia	
Prednisone and salbutamol	Inadequate control of asthma	Arecoline challenge causes dose-related bronchoconstriction in patients with asthma
<b>Chili pepper (<i>Capsicum spp.</i>)</b>		
ACE inhibitor	Cough	Capsaicin depletes substance P
Theophylline	Increased absorption and bioavailability	
<b>Danshen (<i>Salvia miltiorrhiza</i>)</b>		
Warfarin	Increased INR, prolonged PT/PTT	Danshen decreases elimination of warfarin
<b>Devil's claw (<i>Harpagophytum procumbens</i>)</b>		
Warfarin	Purpura	
<b>Dong quai (<i>Angelica sinensis</i>)</b>		
Warfarin	Increased INR and widespread bruising	Dong quai contains coumarins
<b>Eleuthero or Siberian ginseng (<i>Eleutherococcus senticosus</i>)</b>		
Digoxin	Raises digoxin concentrations	Patients exhibit unchanged ECG despite digoxin concentration of $5 \times 2$ nM/L.
<b>Garlic (<i>Allium sativum</i>)</b>		
Warfarin	Increased INR	Postoperative bleeding and spontaneous spinal epidural hematoma have been reported with garlic alone; garlic causes platelet dysfunction
<b>Ginkgo (<i>Ginkgo biloba</i>)</b>		
Aspirin	Spontaneous hyphema	Ginkgolides are potent inhibitors of PAF
Paracetamol and ergotamine/caffeine	Bilateral subdural hematoma	Subarachnoid hemorrhage and subdural hematoma have been reported with the use of ginkgo alone
Warfarin	Intracerebral hemorrhage	
Thiazide diuretic	Hypertension	This effect may be an unusual adverse reaction to the drug or herb; ginkgo alone has not been associated with hemorrhage
<b>Ginseng (<i>Panax spp.</i>)</b>		
Warfarin	Decreased INR	
Phenelzine	Headache and tremor, mania	
Alcohol	Increased alcohol clearance	Ginseng increases the activity of alcohol dehydrogenase and aldehyde dehydrogenase
<b>Guar gum (<i>Cyamopsis tetragonolobus</i>)</b>		
Metformin, phenoxymethylpenicillin, glibenclamide	Slows absorption of digoxin, paracetamol, and bumetanide; decreases absorption of metformin, phenoxymethylpenicillin, and some formulations of glibenclamide	Guar gum prolongs gastric retention

*Continued.*



**TABLE 4.1 (Continued)**  
**Herbs Interacting with Drugs**

Herbs and Drugs	Results of Interaction	Comments
<b>Karela or bitter melon (<i>Momordica charantia</i>)</b>		
Chlorpropamide	Less glycosuria	Karela decreases glucose concentrations in blood
<b>Licorice (<i>Glycyrrhiza glabra</i>)</b>		
Prednisolone	Glycyrrhizin decreases plasma clearance, increases AUC, increases plasma concentrations of prednisolone	11 $\beta$ -dehydrogenase converts endogenous cortisol to cortisone; orally administered glycyrrhizin is metabolized mainly to glycyrrhetic acid
Hydrocortisone	Glycyrrhetic acid potentiates of cutaneous vasoconstrictor response	Glycyrrhetic acid is a more potent inhibitor of 5 $\alpha$ -, 5 $\beta$ -reductase, and 11 $\beta$ -dehydrogenase than is glycyrrhizin
Oral contraceptives	Hypertension, edema, hypokalemia	Oral contraceptive use may increase sensitivity to glycyrrhizin acid; women are reportedly more sensitive than men to adverse effects of licorice
<b>Papaya (<i>Carica papaya</i>)</b>		
Warfarin	Increased INR	
<b>Psyllium (<i>Plantago ovata</i>)</b>		
Lithium	Decreased lithium concentrations	Hydrophilic psyllium may prevent lithium from ionizing
<b>St. John's Wort (<i>Hypericum perforatum</i>)</b>		
Paroxetine	Lethargy/incoherence	
Trazodone	Mild serotonin syndrome	A similar case is described with the use of St. John's wort alone
Sertraline	Mild serotonin syndrome	
Nefazodone	Decreased theophylline concentrations	
Theophylline		
Digoxin	Decreased AUC, decreased peak and trough concentrations	Most, but not all, studies indicate that St. John's wort is a potent inhibitor of cytochrome P-450 isoenzymes
Phenprocoumon	Decreased AUC	
Cyclosporin	Decreased concentrations in serum	
Combined oral contraceptive (ethinylestradiol and desogestrel)	Breakthrough bleeding	
Saiboku-to (Asian herbal mixture)		
Prednisolone	Increased prednisolone AUC	Contains all the same herbs as sho-saiko-to, and <i>Porio cocos</i> , <i>Magnolia officinalis</i> , and <i>Perillae frutescens</i>
<b>Shankhapushpi (Ayurvedic mixed-herb syrup)</b>		
Phenytoin	Decreased phenytoin concentrations, loss of seizure control	Multiple coadministered doses (but not single doses) decreased plasma phenytoin concentrations; single doses decreased the antiepileptic effect of phenytoin; Shankhapushpi is used to treat seizures

**TABLE 4.1 (Continued)**  
**Herbs Interacting with Drugs**

Herbs and Drugs	Results of Interaction	Comments
	<b>Sho-saiko-to or Xiao chai hu tang (Asian herb mixture)</b>	
Prednisolone	Decreased AUC for prednisolone	Contains licorice ( <i>Glycyrrhiza glabra</i> ), <i>Bupleurum falcatum</i> , <i>Pinellia ternata</i> , <i>Scutellaria baicalensis</i> , <i>Zizyphus vulgaris</i> , <i>Panax ginseng</i> , and <i>Zingiber officinale</i>
	<b>Tamarind (<i>Tamarindus indica</i>)</b>	
Aspirin	Increased bioavailability of aspirin	Tamarind is used as a food and a medicine
	<b>Valerian (<i>Valeriana officinalis</i>)</b>	
Alcohol	A mixture of valepotriates reduces adverse effect of alcohol	
	<b>Yohimbine (<i>Pausinystalia yohimb</i>)</b>	
Tricyclic antidepressants	Hypertension	Yohimbine alone can cause hypertension, but lower doses cause hypertension when combined with tricyclic antidepressants; effect is stronger in hypertensive than normotensive individuals

*Note:* ACE = angiotensin-converting enzyme; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; ECG = electrocardiogram; PAF = platelet-activating factor; AUC = area under the concentration/time curve.

**Increased clotting** may occur in the presence of **thrombosis** (enhanced formation of fibrin), **stasis**, and **phlebitis** (diminished circulation), or **embolism** (dislocation and lodging of blood clots). Although **heparin** is an extremely effective anticoagulant, it has certain limitations that are not shared by the newer thrombin inhibitors. As a result, these novel inhibitors may have advantages over heparin for use in certain clinical settings.

**Thrombin** activates platelets, converts fibrinogen to fibrin, activates factor XIII, which stabilizes fibrin, and activates factors V and VIII, which accelerate the generation of **prothrombinase**. Therefore, the inhibition of thrombin is essential in preventing and treating **thromboembolic disorders**.

**TABLE 4.2**  
**Stages in Hemostasis**

Stage	Initiator	Response or Outcome
Vascular	Tissue injury	Vasoconstriction
Platelet	Adhesion and aggregation	Plug formation
Plasma	Fibrin generation	Coagulation

*Note:* Hemostasis refers to a complex homeostatic mechanism within blood and on blood vessels that serves to maintain the patency of vessels after injury, while preserving the fluidity of blood.

**TABLE 4.3**  
**Formation of Fibrin**

Stage	Formation	Required Factors or Precursors
One	Plasma thromboplastin	Hageman factor (XII), antihemophilic globulin (VIII), Christmas factor (IX), plasma thromboplastin antecedent (XI), calcium (IV), and platelet phospholipids
Two	Activated thromboplastin	Tissue thromboplastin (III), Stuart factor (X), proconvertin (VII), and calcium (IV)
Three	Thrombin	Prothrombin (II), proaccelerin (V), calcium (IV), and platelet
Four	Fibrin	Thrombin

*Note:* In fibrinolysis, **plasmin**, an endopeptidase that is converted from plasminogen by an activator, hydrolyzes fibrin, fibrinogen, factor V, and factor VIII to their inactive products. **Hageman factor** (factor XII) converts a proactivator to the active activator. Agents such as thrombin, streptokinase, and urokinase therefore enhance the formation of plasmin and hence have fibrinolytic properties. **Epsilon-aminocaproic acid** inhibits the activator-mediated formation of plasmin and hence may be used as an antidote to streptokinase-urokinase, or in a defibrination syndrome when bleeding from a mucous membrane occurs.

## AGGREGIN AND PLATELET AGGREGATION

Platelets circulate in blood without adhering to other platelets or to the endothelium. However, when endothelial cells are disturbed in some way, platelets adhere and undergo a change in shape, and aggregate. **ADP** is known to induce the platelet shape change, aggregation, and exposure of fibrinogen-binding sites.

The platelet surface contains **aggregin**, a membrane protein with a molecular weight of 100 kDa, which has physical and immunochemical properties that differ from those of platelet glycoprotein IIIa.

Binding to aggregin is required for epinephrine-induced platelet aggregation to take place. In turn, **epinephrine** increases the affinity of ADP for its receptor. **Thrombin** stimulates platelet aggregation independent of ADP, but by raising the level of calcium in the cytoplasm, it activates platelet **calpain**, which in turn cleaves aggregin (Figure 4.1).

## VITAMIN E AND PLATELET AGGREGATION

**$\alpha$ -Tocopherol**, a natural antioxidant, inhibits platelet aggregation and release. The effect of vitamin E is due to a reduction in **platelet cyclooxygenase activity** and inhibition of lipid peroxide formation. It is believed that supplementing the diet with vitamin E could play a role in the treatment of thromboembolic disease, especially if it is given in conjunction with an inhibitor of platelet aggregation.

## PLATELET-ACTIVATING FACTOR

A platelet-activating factor, **1-O-alkyl-2-(R)acetyl-sn-glycerol-3-phosphocholine**, is released in the presence of shock and ischemia. The platelet-activating factor antagonist can protect the heart and brain against ischemic injury.

## PLATELET-INHIBITING DRUGS

A combination of **acetylsalicylic acid** and **dipyridimole** has been found to be effective in preventing myocardial reinfarction and occlusion of aortocoronary grafts.

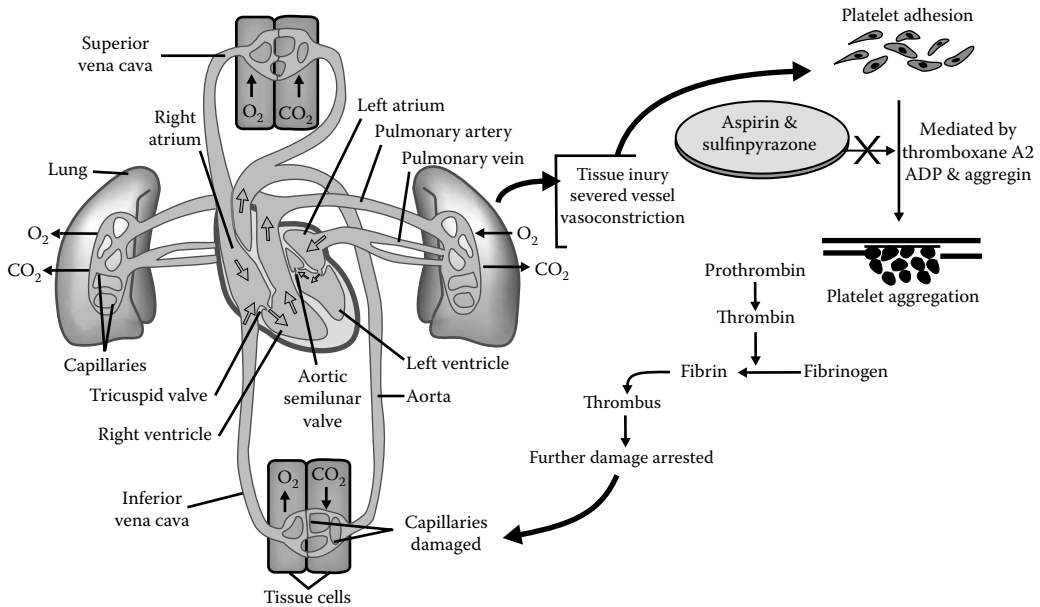


FIGURE 4.1 The role of platelets in arresting tissue injury. ADP = adenosine diphosphate.

## FIBRINOLYSIS

In fibrinolysis, **plasmin**, an endopeptidase that is converted from plasminogen by an activator, hydrolyzes fibrin, fibrinogen, factor V, and factor VIII to their inactive products. **Hageman factor** (factor XII) converts a proactivator to the active activator. Agents such as thrombin, **streptokinase**, and **urokinase** therefore enhance the formation of plasmin and hence have fibrinolytic properties. **Epsilon-aminocaproic acid** inhibits the activator-mediated formation of plasmin and hence may be used as an antidote to streptokinase-urokinase, or in a defibrination syndrome when bleeding from a mucous membrane occurs.

## HIRUDIN AND THROMBIN

The saliva of the **medicinal leech** contains a battery of substances that interfere with the hemostatic mechanisms of the host. One of these compounds is **hirudin**, a potent anticoagulant, which maintains the fluidity of the ingested blood and is the most potent inhibitor of thrombin. Upon binding to thrombin, the cleavage of fibrinogen and subsequent clot formation are prevented. The potency and specificity of hirudin make it a useful antithrombin-III-independent alternative to heparin for the control of thrombosis.

## AGENTS THAT INTERFERE WITH COAGULATION

Therapeutic agents that interfere with blood coagulation fall into four classes:

1. **Anticoagulants**, which include heparin and the **coumadin-inanedione** oral anticoagulants
2. **Thrombolytic** agents such as **streptokinase**, **urokinase**, and **recombinant tissue-type plasminogen activator**
3. **Antiplatelet** drugs, which alter the aggregating ability of platelets
4. **Defibrinogenating** agents, which remove the fibrinogen from circulating blood

## ORAL ANTICOAGULANTS

The **coumarin anticoagulants** include **dicumarol**, **warfarin sodium** (coumadin sodium), **warfarin potassium** (Athrombin-K), **acenocoumarol** (Sintrom), and **phenprocoumon** (Liquamar). The **inanedione derivatives** are **phenindione** (Hedulin), **diphenadione** (Dipaxin), and **anisindione** (Miradon). The pharmacological properties of oral anticoagulants are identical qualitatively, but their pharmacokinetic parameters and their toxicities vary. **Racemic warfarin sodium** is the most widely used anticoagulant. Antithrombotic drugs are used clinically either to prevent the formation of blood clots within the circulation (anticoagulant) or to dissolve a clot that has already formed (thrombolytic).

## HERBS WITH COUMARIN, SALICYLATE, OR ANTIPLATELET DRUGS

Several natural products contain substances that have coumarin, salicylate, or exhibit antiplatelet properties. Therefore, a theoretical risk for potentiation of the pharmacological activity of warfarin exists when these herbs are taken with warfarin. Herbs thought to contain coumarin or coumarin derivatives include the following:

- Angelica root
- Arnica flower
- Anise
- Asafoetida
- Celery
- Chamomile
- Fenugreek
- Horse chestnut
- Licorice root
- Lovage root
- Parsley
- Passionflower herb
- Quassia
- Red clover
- Rue

**Meadowsweet**, **poplar**, and **willow bark** contain high concentrations of salicylates, whereas **bromelain**, **clove**, **onion**, and **turmeric** have been reported to exhibit antiplatelet activity. **Borage seed oil** contains  $\gamma$ -**linoleic acid**, which may increase coagulation time. **Bogbean** has been noted to demonstrate hemolytic activity, and **capsicum** has been reported to cause hypocoagulability. There have been no documented case reports of interaction of warfarin with any of these herbs. However, patients taking any products containing these herbs concurrently with medications that have anticoagulant effects, such as warfarin, should be closely monitored for signs or symptoms of bleeding.

**Sweet clover** also contains coumarin derivatives and therefore poses an increased risk of bleeding if given with warfarin. There have been no reports of an interaction between sweet clover and warfarin or hemorrhagic disease in humans. However, several cases of severe hemorrhage and death have been reported in cattle.

## FEVERFEW

Feverfew (*Tanacetum parthenium*) is commonly used for the **treatment of migraine** headaches, arthritis, and various type of allergies. This herb is thought to exert its pharmacological activity by

inhibiting serotonin and histamine release, prostaglandin synthesis, and platelet release and aggregation. Several studies have shown feverfew to interfere with hemostasis and platelet aggregation by neutralizing platelet sulfhydryl groups, as well as preventing prostaglandin synthesis. **Parthenolide**, one of the many **sesquiterpene lactone** constituents of feverfew extract, has been shown to exert the greatest pharmacological activity.

### **GARLIC**

Garlic (**Allium sativum**) is thought to have several beneficial cardiovascular effects, such as lowering blood pressure and serum lipid, and antithrombotic activity. Garlic oil has been reported to interrupt **thromboxane synthesis**, thereby inhibiting platelet function.

### **GINGER**

Ginger (**Zingiber officinale**), promoted for use in motion sickness and arthritis, has been reported to reduce platelet aggregation through the inhibition of **thromboxane synthetase**. Ginger supplements, containing amounts of ginger much greater than those regularly found in food products, may lead to an increased risk of bleeding when taken with warfarin.

### **GINKGO**

Ginkgo (**Ginkgo biloba**) is a common herbal product available in the U.S. and is advertised to improve **cognitive function**. Ginkgolide B, one component of ginkgo, inhibits platelet-activating factor by displacing it from its receptor-binding site, resulting in reduced platelet aggregation. Several cases of bleeding thought to be secondary to ginkgo ingestion have been reported.

### **COENZYME Q<sub>10</sub>**

Coenzyme Q<sub>10</sub> (also known as **ubiquinone** or **ubidecarenone**), while not a herb, is a provitamin found in the mitochondria of plant and animal cells. It is involved in electron transport and may act as a **free-radical scavenger**, an **antioxidant**, or a **membrane stabilizer**. Coenzyme Q<sub>10</sub> supplementation is primarily promoted as treating a variety of cardiovascular disorders, including the following:

- Heart failure
- Hypertension
- Stable angina
- Ventricular arrhythmias

Many patients with these conditions may also be prescribed warfarin. Coenzyme Q<sub>10</sub> is structurally related to **menaquinone** (vitamin K) and may have procoagulant effects.

### **DANSHEN**

Although not commonly used in the U.S., danshen (the root of **Salvia miltiorrhiza**), also known as **tan seng**, is a very popular herb recommended in Chinese medicine for various cardiovascular diseases. The pharmacological effects of danshen have been described primarily *in vitro* and also in animals and include the following:

- Hypotensive effects
- Positive inotropic effects
- Coronary artery vasodilation
- Inhibition of platelet aggregation

The available evidence contraindicates concurrent use of danshen and warfarin.

### DEVIL'S CLAW

Devil's claw (*Harpagophytum procumbens*) is an expensive herbal product that has been promoted for use as an analgesic in the treatment of arthritis, gout, and myalgia. Until more is known about this possible interaction, patients taking warfarin should be advised to avoid devil's claw.

### GINSENG

Three ginseng species — **American ginseng** (*Panax quinquefolius*), **Oriental ginseng** (*Panax ginseng*), and **Siberian ginseng** (*Eleutherococcus senticosus*) — have been promoted as energy enhancers, stress reducers, and mood improvers. The active components of ginseng are known as **ginsenosides**, more than 20 of which have been identified. The pharmacological activity of each ginsenoside appears to vary depending on where the plant grew and the extraction techniques used. Also, data suggest that the ginsenoside composition varies widely among commercially available ginseng products. This variability makes it difficult to evaluate the safety and efficacy of ginseng products. Although the exact pharmacological actions of ginsenosides in humans are not fully understood, studies suggest that these substances may increase adrenal hormone synthesis, decrease blood glucose concentrations, and promote immunomodulation. Oriental ginseng (Ginsana) may antagonize the anticoagulant effects of warfarin. The possible mechanism for this interaction has not been identified, and it is not known which ginsenoside or ginsenosides may be responsible.

### GREEN TEA

Green tea (*Camellia sinensis*), also known as **Chinese tea**, is a popular beverage purported to prevent various cancers, treat gastrointestinal disorders, and enhance cognition. Although dried green tea leaves have been found to contain substantial amounts of **vitamin K**, brewed green tea is generally not considered a significant source of the vitamin. However, large amounts of brewed green tea may potentially antagonize the effects of warfarin.

### PAPAIN

Papain is a mixture of proteolytic enzymes found in **extract of papaya**, the fruit of the **papaya tree** (*Carica papaya*). It is taken orally in the belief that it reduces edema, inflammation, herpes zoster symptoms, diarrhea, and psoriasis symptoms. The pharmacological mechanisms by which papain may affect coagulation are not known. Patients receiving warfarin should be advised to avoid papain supplementation until further information about this potential interaction becomes available (Table 4.4).

### VITAMIN E

Vitamin E has received much publicity as one of several antioxidants that may be useful in treating a variety of disorders, including cardiovascular disease. Vitamin E may inhibit the oxidation of reduced vitamin K. Vitamin K oxidation is necessary for carboxylation of vitamin-K-dependent clotting factors, which must occur for these clotting factors to be fully functional. Increased prothrombin times, induced by combined vitamin E and warfarin therapy, may be managed by discontinuing vitamin E and, if necessary, by administering vitamin K.

Because nearly 70% of patients who use alternative therapies do not inform their health-care providers about these products, pharmacists and other health-care professionals should question all patients about their use of alternative therapies. Health-care professionals should remain vigilant for potential interactions between alternative therapies and prescription medications, especially medications with a narrow therapeutic index, and should report suspected interactions to the **FDA**

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**TABLE 4.4**  
**Potential and Documented Interactions of Herbs**  
**and Warfarin**

**Potential Increase in Risk of Bleeding**

Angelica root	Ginkgo
Arnica flower	Horse chestnut
Anise	Licorice root
Asafoetida	Lovage root
Bogbean	Meadowsweet
Borage seed oil	Onion
Bromelain	Parsley
Capsicum	Passionflower herb
Celery	Poplar
Chamomile	Quassia
Clove	Red clover
Fenugreek	Rue
Feverfew	Sweet clover
Garlic	Turmeric
Ginger	Willow bark

**Documented Reports of Possible Increase in Effects of Warfarin**

Danshen  
Devil's claw  
Dong quai  
Papain  
Vitamin E

**Documented Reports of Possible Decrease in Effects of Warfarin**

Coenzyme Q<sub>10</sub>  
Ginseng  
Green tea

*Note:* The coumarin anticoagulants include dicumarol, warfarin sodium (coumadin sodium), warfarin potassium (Athrombin-K), acenocoumarol (Sintrom), and phenprocoumon (Liquamar).

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**MedWatch program.** The FDA recently established the Special Nutritionals Adverse Event Monitoring System, a searchable database including information about suspected adverse events associated with dietary supplements or nutritional products. This database includes reports that have been submitted to MedWatch and can be accessed via the Internet (<http://vm.cfsan.fda.gov/~dms/aems.html>). Continued efforts by health-care professionals to recognize and report suspected interactions between prescription medications and herbal and other alternative therapies should ultimately increase knowledge and awareness of interactions and improve the quality of patient care (see Heck et al., 2000; Izzo, 2004; Butterweck, 2004; Chan, 2005).





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# 5 Natural Products as a Resource for Established and New Drugs

## THE ROLE OF HERBAL MEDICINES IN HEALTH CARE

Natural products have served as a major source of drugs for centuries, and about half of the pharmaceuticals in use today are derived from natural products. **Quinine, theophylline, penicillin G, morphine, paclitaxel, digoxin, vincristine, doxorubicin, cyclosporin, and vitamin A** all share two important characteristics: they are cornerstones of modern pharmaceutical care, and they are all natural products. The use of natural substances, particularly plants, to control diseases is a centuries-old practice that has led to the discovery of more than half of all modern pharmaceuticals.

Documentation of the use of natural substances for medicinal purposes can be found as far back as 78 A.D., when **Dioscorides** wrote *De Materia Medica*, describing thousands of medicinal plants. This treatise included descriptions of many medicinal plants that remain important in modern medicine today, not because they continue to be used as crude drug preparations, but because they serve as the source of important pure chemicals that have become mainstays of modern therapy. A few examples will be cited here.

The positive benefits of extracts of two species of *Digitalis purpurea* (foxglove and *lanata*) were recognized long before the active constituents were isolated and structurally characterized. The cardiac glycosides, which include **digoxin, digitoxin, and deslanoside**, exert a powerful and selective **positive inotropic action** on the cardiac muscle (see Chapter 35).

A frequently cited example of an important natural-product-derived drug is the neuromuscular blocker **d-tubocurarine**, derived from the South American plant **curare**, which was used by South American Indians as an arrow poison (see Chapter 26). Tubocurarine led to the development of **decamethonium**, which, although structurally dissimilar to **tubocurarine**, was nevertheless synthesized based on the then prevalent presumption that tubocurarine contained two quaternary nitrogens. Similarly, synthetic local anesthetics, such as **lidocaine, benzocaine, and dibucaine**, were synthesized to mimic the nerve-blocking effect of **cocaine**, a natural alkaloid obtained from the leaves of *Coca eroyllum*, but without the adverse side effects that have led to its abuse.

The **opium alkaloids codeine and morphine** served as models for the synthesis of **naloxone**, an important analog used to treat and diagnose opiate addicts, and also led to the discovery of endogenous opioids (**enkephalins and endorphins**) (see Chapter 47). Similarly,  **$\Delta^9$ -tetrahydrocannabinol (THC)**, the component of *Cannabis sativa* responsible for the central nervous system (CNS) effect, has also been found to reduce nausea associated with cancer chemotherapy (see Chapter 18).

There is no doubt that **antibiotics** are among the most important class of therapeutic agents and have had enormous impact on both life expectancy and quality of life. With the discovery of the natural penicillins as secondary metabolites of the fungus *Penicillium*, the course of medical history was dramatically altered and the antibiotic era began.

Another area in which natural products have had a major impact on longevity and quality of life is in the **chemotherapy of cancer** (see Chapter 62). In fact, most major anticancer drugs are derived from plants or microorganisms. Important examples include **bleomycin, doxorubicin, daunorubicin, vincristine, vinblastine, mitomycin, streptozocin**, and most recently, **paclitaxel**

(Taxol™), **ironotecan** (a camptothecin derivative), and **etoposide** and **tenoposide** (podophylotoxin derivatives).

Some of the most exciting natural products discovered in recent years are the **cholesterol-lowering agents** derived from fungi. These drugs inhibit **3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-COA reductase)**, an enzyme critical in the biosynthesis of **cholesterol**. The first HMG-COA reductase inhibitors were isolated from *Penicillium sp.*

The word *healing* is derived from the Greek “*holos*,” the same word that has given us *whole* and *holistic*. The emotions of life and spiritual flow are as important to health as the state of the body’s organs and tissues. Whether one is concerned with being healthy, regaining health, or becoming healthier, the entire being, physical, mental, and spiritual, is involved in the process.

Although the therapeutic philosophy for plant use varies, plants have demonstrated their efficiency as healing agents for thousands of years. We find them in the Indian **Ayurvedic system**; in Chinese medicine, alongside **acupuncture** and other techniques; they play an important role in the spiritual healing ecology of the **Native North Americans**; and their constituents are also used to manufacture drugs in “**orthodox**” medicine.

## DRUG THERAPY IN CHINESE TRADITIONAL MEDICINE

The origin and development of **Chinese traditional medicine (CTM)**, attributed to **Shen Lon**, is based on the knowledge and experience gained over generations to ensure health and treat disease. It has a history spanning more than 2000 years. Similarly, in ancient Europe, *materia medica* have also been employed for centuries. The use of medicinal herbs is mentioned in ancient Egyptian medical **papyri** that were discovered by **Ebers** in 1862 and translated into English by Ebbell in 1937. More than 800 prescriptions in *Eber’s Papyrus* emphasize that **medicines were originally foods**. Thus, different civilizations discovered the medicinal properties of some food substances in the same way. Herbal medicine usage in the 16th century increased with the introduction of novel Eastern remedies, such as **nutmeg** from the East Indies, **purgative rhubarb** from India, and **camphor** from Japan (Cheng, 2000; Chan, 2005).

The Chinese still believe in the benefits of CTM, and herbal medications remain popular among Chinese societies around the world. One of the main reasons may be the relatively high incidence of side effects associated with Western medicine. This may be why it is used as a last resort, when Western medicine is too toxic or unable to provide the expected benefit.

CTM emphasizes the integrity of the human body and its relationship with the environment. The **yin–yang theory** and the **five-element theory** use ancient cosmology to explain nature, materialism, and dialectics in China. The five-element or phase theory named *Wun Shing* in Chinese, means “five matters.” As shown in Table 5.1, the five-element theory can be applied to a wide range of aspects of humans and the environment, including organs and emotions. The colors in the five-element theory can be applied to symptoms when making a diagnosis. By this theory herbs were also classified depending on taste and sometimes colors. For example, a herb with a black color or salty taste would be assumed to affect the function of the kidney because it is classified under the same group of elements (see Table 5.1). Similarly, a herb with a red color or bitter taste would be associated with the function of the heart.

Significant CTM theories include those developed by **Zhang-Fu** (regarding the pathophysiology of disease), **Bian-Zheng (diagnosis)**, and **Lun-Zhi (treatment)**. Herbal medication has been refined by skilled practitioners over the centuries, and one of its famous experts was **Chang Chon-Zhing**, who practiced during the **Jin** and **Yuan dynasties** (1271–1368).

### PRESCRIPTION OF MULTIPLE HERBS IN CTM

According to experts, several prescriptions were recorded in the ancient CTM books. Therapeutic principles were divided into eight categories, which included the **diaphoretic method** (*Han Fah*),

**TABLE 5.1**  
**Five-Element Theory in Chinese Traditional Medicine**

Indicator	1	2	3	4	5
Taste	Sour	Bitter	Sweet	Pungent	Salty
Color	Blue (dark)	Red	Yellow	White	Black
Evils	Wind	Heat	Damp	Dry	Cold
Organs	Liver	Heart	Spleen	Lung	Kidney
Emotions	Anger	Joy	Worry	Grief	Fear
Senses	Eyes	Tongue	Mouth	Nose	Ear
Expressions	Shouting	Laughing	Singing	Wailing	Groaning
Orientations	East	South	Middle	West	North
Elements	Wood	Fire	Earth	Gold	Water

*Note:* Each element has a correlative connection. For example, impaired function of the liver may produce problems in the eyes; excessive joy is harmful to the “heart,” which includes the functions of the brain; and black, herbs would be likely to affect the function of the kidney.

the **emetic method** (*Tu Fah*), the **purgative method** (*Xia Fah*), the **regulatory method** (*Tee Fah*), the **warming method** (*Wen Fah*), the **heat-purging method** (*Ching Fah*), the **resolving method** (*Xiao Fah*), and the **tonic method** (*Bu Fah*). Except for the emetic method, the other methods were widely used in CTM clinical practice. Sometimes two or more methods were employed together to achieve the desired results. Methods were applied flexibly, depending on individual cases (Cheng, 2000; Chan, 2005).

The prescription of herbs, named *Fang-Chi* in Chinese, may comprise either one or many herbs. The prescription is sometimes named depending on the number of herbs used, such as “**7-component prescription**” (**Chi-Fang**) and “**10-component prescription**” (**Shi-Jie**). The “large” prescriptions refer to the use of several herbs to treat diseases due to virulent pathogens. However, experts in CTM can modify ancient prescriptions by the addition or deletion of herbs or modification of doses depending on the individual’s disease. This is called *Zhia-Gean Fang*. In practice, the CTM experts revise classic prescriptions depending on the symptoms of the patients. Also, differences in the active principles of herbs owing to variation in season or location are also considered.

Herbs contained in the prescription are classified according to four properties depending on their presumed pharmacological activity. The major herb is termed the “**chief**” or the king (**Zhing**) in the prescription. Secondary herbs are called “**adjuvants**” or “**ministers**,” named **Chen** in Chinese. Minor herbs are known as “**assistants**” and named **Zhou**, and additive herbs or “**guiders**” are called **Shi**. Most CTM prescriptions contain these four components. However, each property may not be represented by only one herb. In some cases, two or more herbs may function as the major component or Zhing. Furthermore, in the “small” prescription or monoprescription, one herb may be both Zhing and Chen or even more components. Also, a herb may be Chen in one prescription but Shi in another. The properties of herbs are therefore relative but not absolute, and this is an important trait of CTM. This principle could be explained by the drug interactions in the use of herbs (Cheng, 2000; Chan, 2005).

## PHARMACOLOGICAL CLASSIFICATION OF HERBS ACCORDING TO CTM

Classification of herbs in CTM is different from the modern pharmacological method. Based on their physical properties, either color or taste, each herb can be linked with the theory of five elements (Table 5.2), named *Woo-Wei* in Chinese. Also, the properties of herbs can be classified according to the four-chi principle (*Su-Chi* in Chinese). Four-chi refers to the four properties of

**TABLE 5.2**  
**Pharmacological Classification of Chinese Herbs**

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Herbs for relieving exterior syndrome
Herbs for eliminating heat
Herbs for purgation (cathartics)
Herbs for eliminating wind dampness
Herbs for dispelling dampness
Diuretics
Herbs for warming the interior
Herbs for regulation of chi
Digestives
Anthelmintics
Hemostatics
Herbs for activating blood circulation and removing blood stasis
Expectorants, antitussives, and dyspnea-relieving herbs
Sedatives
Herbs for soothing the liver and suppressing wind
Herbs for promoting resuscitation
Tonics
Astringents

*Note:* Limited toxicological data are available on medicinal plants. However, there exists a considerable overlap between those herbs used for medicinal purposes and those used for cosmetic or culinary purposes, for which a significant body of information exists. There is no reason to doubt the safety of culinary herbs used in herbal remedies, providing the intended dose and route of administration are consistent with their food use. When intended for use in larger therapeutic doses, the safety of culinary herbs requires reevaluation.

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herbs: cold, hot, warm, and cool. Depending on the yin–yang theory, a herb with a cold property is suitable to treat a “hot” symptom. For example, the herb *Rhizoma zingiberis* belongs to the “hot” group and is therefore used in the treatment of diarrhea, which is considered a “cold” disorder.

Two other principles used in CTM are more difficult to understand and reconcile with the practice of modern Western medicine. These are the **attributive meridians** (*Qui Jing*) and the direction of the herb’s action. The direction of a herb is considered important in its application. **Ascending** (*sheng*), **descending** (*jiang*), **floating** (*fu*), and **sinking** (*chen*) are terms used to indicate the directions of herbs and aid practitioners in deciding the best way to combat pathogenic factors. Herbs having a descending property are appropriate to treat vomiting and hiccups that are caused by the “abnormal ascent of the stomach.” Floating herbs can disperse pathogenic factors to treat disorders on the surface of the human body. The direction of herbs corresponds to the four-chi (**Su-Chi**) and the five-element (**Woo-Wei**) theories. Herbs combining acrid and sweet tastes and warm and hot properties are usually ascending and floating in action. Similarly, herbs that taste bitter, sour, and have cool and cold properties are mostly sinking and descending in action. The flowers and leaves of plants and the herbs that are light in weight are mostly ascending and floating, whereas heavy herbs such as seeds and minerals are mostly sinking and descending in action.

The attributive meridian principle (**Qui Jing**) relates to the theory of organs and meridians (**Zhang-Fu**). Meridians are considered to connect the interior and exterior parts of the human body. The most optimum result occurs when the herb meets with the right meridian. This does not necessarily mean that a disorder from a known meridian must be treated by a herb that can only enter this meridian.

In clinical application, herbs are classified into 18 groups, as shown in Table 5.2. Some of these are similar to the therapeutic groups used in Western medicine, such as **digestives**, **anthelmintics**, **purgatives** (cathartics), **diuretics**, **expectorants**, and **antitussives**, which are widely used in herbal medication. However, some groups have no equivalent in the Western system, such as herbs for relieving exterior syndrome, herbs for eliminating heat, herbs for eliminating wind dampness, herbs for dispelling dampness, herbs for warming the interior, and the herbs for regulation of Chi. Hemostatics, dyspnea-relieving herbs, and those used for activating blood circulation and removing blood stasis may have some similarity to Western drugs used to act on the cardiovascular system, but tonics and astringents are applied in a different manner. Although the terms used in the classification may be similar, the main principle is quite different from that of modern pharmacology.

The potential toxicity of herbs has long been emphasized in CTM. *Du-Jing* is the Chinese term used to denote the harmful effects of herbs. The degree of toxicity is generally defined as “**very poisonous**” and “**slightly poisonous**” to indicate caution in the handling of certain herbs. It is important that the practitioner obtain a full understanding of CTM, including the compatibility, indications, and contraindications of herbs (Cheng, 2000; Chan, 2005).

## CLASSIC PLANT SUBSTANCES

Some plant-derived drugs come from lower organisms, such as fungi (e.g., the antihyperlipidemic agent **lovastatin** from *Aspergillus terreus* and the immunosuppressant **cyclosporin** from *Beauveria nivea*) whereas others are obtained from higher plants (see Table 5.3 and Table 5.4).

Over 120 present medicines are derived directly or indirectly from higher plants (Table 5.3 and Table 5.4; De Smet, 1997).

### CAFFEINE

Caffeine continues to be used therapeutically in analgesic combination preparations. It has superseded theophylline as the preferred drug for treatment of neonatal apnea because of its ease of administration and more predictable plasma concentrations.

### CAPSAICIN

This pungent product is responsible for the intense irritant effects of topical *Capsicum* preparations. Repeated application of capsaicin can deplete and prevent reaccumulation of **substance P**, an endogenous mediator of pain impulses from the periphery to the CNS. Since the early 1990s, capsaicin cream has been available in the U.S. as an approved drug for relief of **postherpetic neuralgia** and pain due to **diabetic neuropathy** and **osteoarthritis**.

### β-CAROTENE

In clinical trials, the preventive effect of β-carotene supplementation on cancer or cardiovascular disease could not be demonstrated in a well-nourished population. This apparent ineffectiveness contrasts starkly with the promising results of numerous basic studies and epidemiological observations, which suggest that supplementation with this antioxidant is likely to have a protective effect.

### COLCHICINE

This alkaloid has an active role in the management of **acute gout** (see Chapter 24).

### NORDIHYDROGUAIARETIC ACID

Nordihydroguaiaretic acid occurs as the mesoform in the resinous exudate of the creosote bush (*Larrea divaricata* *syn.* *L. tridentata*). Under the generic name **masoprocol**, it has become available

**TABLE 5.3**  
**Supposed Therapeutic Values of Some Herbal Medicines**

Herbal Medicines	Current Uses	Comments
Aloe vera	Skin moisturizer; minor cuts; sunburn	Sometimes promoted as a laxative or for stomach disorders, but internal use is hazardous
Anise	Cough soother; digestive aid	Generally safe
Arnica	Anti-inflammatory painkiller for sprains, bruises, muscle aches	For external use only; causes cardiac toxicity if ingested; stop using if arnica liniment causes dermatitis
Chamomile	Tea: sedative, digestive aid, reduces menstrual cramps; compress: arthritis, skin disorders	Generally safe in small amounts
Comfrey	Soothes skin wounds, bruises, burns, and boils; reducing swelling of sprains	Should not be taken internally because of possible liver toxicity
Dandelion	Laxative; tonic; diuretic	Generally safe
Echinacea	Compress: skin sores and stings; tea: bladder infections, fever, headache	Generally safe in small doses
Eucalyptus	Nasal and sinus congestion; coughs	Oil irritating to eyes and mucous membranes
Evening primrose	Painkiller; sedative; autoimmune disorders	Can worsen bleeding disorders
Fenugreek	Expectorant; digestive tonic; laxative; poultice: soothes boils and skin ulcers	Generally safe
Fennel	Digestive aid	Generally safe
Feverfew	Painkiller	Generally safe; may cause mouth sores when chewed
Garlic	Antiseptic; reduces high blood pressure and high blood cholesterol	Generally safe, but raw garlic may irritate skin and mucous membranes; should not substitute for prescribed drugs
Ginseng	General tonic; blood thinner; aphrodisiac	Generally safe, but many claims of its healing power are unproved
Licorice	Soothes irritated skin and mucous membranes, ulcers; digestive aid	Generally safe; excessive use raises blood pressure
Peppermint	Digestive aid	Generally safe
Uva-ursi	Diuretic; cystitis; kidney and bladder stones	Generally safe, but should not substitute for antibiotics
Valerian	Sleep aid; relieves stress	Generally safe, but should not be used during pregnancy

*Note:* Some culinary herbs contain potentially toxic constituents. The safe use of these herbs is ensured by limiting the level of constituent permitted in a food product so that it does not represent a health hazard. **Apiole** — The irritant principle present in the volatile oil of **parsley** is held to be responsible for the abortifacient action. Apiole is also hepatotoxic, and liver damage has been documented as a result of excessive ingestion of parsley, far exceeding normal dietary consumption, over a prolonged period.  **$\beta$ -Asarone** — **Calamus rhizome oil** contains  **$\beta$ -asarone** as its major component and has been shown to be carcinogenic in animal studies. Many other culinary herbs contain low levels of  **$\beta$ -asarone** in their volatile oils; therefore, the level of  **$\beta$ -asarone** permitted in foods as a flavoring is restricted. **Estragole (Methylchavicol)** — Estragole is a constituent of several edible herbs but is a major component of the oils of **tarragon**, **fennel**, **sweet basil**, and **chervil**. Estragole has been reported to be carcinogenic in animals. The level of estragole permitted in food products as a flavoring is restricted. **Safrole** — Animal studies involving safrole, the major component of **sassafras oil**, have shown it to be hepatotoxic. The permitted level of safrole in foods is 0.1 mg/kg.

**TABLE 5.4**  
**Examples of Classic Plant Drugs Derived from Higher Plants with and without a Correlation**  
**between Clinical Action and Traditional Use**

Drug Substance	Clinical Action/Use	Botanical Source
<b>With Correlation</b>		
Atropine	Anticholinergic	<i>Atropa belladonna</i>
Caffeine	CNS <sup>a</sup> stimulant	<i>Camellia sinensis</i>
Camphor	Rubefacient	<i>Cinnamomum camphora</i>
Cocaine	Local anesthetic	<i>Erythroxylum coca</i>
Codeine	Analgesic/antitussive	<i>Papaver somniferum</i>
Colchicine	Antigout	<i>Colchicum autumnale</i>
Digitoxin	Cardiotonic	<i>Digitalis purpurea</i>
Digoxin	Cardiotonic	<i>Digitalis lanata</i>
Emetine	Amoebicide	<i>Cephaelis ipecacuanha</i>
Ephedrine	Sympathomimetic	<i>Ephedra sinica</i>
Gossypol	Male contraceptive	<i>Gossypium</i> spp.
Hyoscyamine	Anticholinergic	<i>Hyoscyamus niger</i>
Kawain	Tranquilizer	<i>Piper methysticum</i>
Methoxsalen	Psoriasis/vitiligo	<i>Ammi majus</i>
Morphine	Analgesic	<i>Papaver somniferum</i>
Noscapine	Antitussive	<i>Papaver somniferum</i>
Ouabain	Cardiotonic	<i>Strophanthus gratus</i>
Physostigmine	Cholinesterase inhibitor	<i>Physostigma venenosum</i>
Pilocarpine	Parasympathomimetic	<i>Pilocarpus jaborandi</i>
Podophyllotoxin	Topical treatment for condylomata	<i>Podophyllum peltatum</i>
Quinine	acuminata	<i>Cinchona ledgeriana</i>
Reserpine	Antimalarial	<i>Rauwolfia serpentina</i>
Scopolamine (hyoscine)	Antihypertensive	<i>Datura metel</i>
Sennosides A and B	Sedative	<i>Cassia</i> spp.
Theophylline	Laxative	<i>Camellia sinensis</i>
Tubocurarine	Bronchodilator	<i>Chondodendron tomentosum</i>
Yohimbine	Muscle relaxant	<i>Pausinystalia yohimbe</i>
	Aphrodisiac	
<b>Without Correlation</b>		
Chymopapain	Chemoneucleolysis	<i>Carica papaya</i>
Galanthamine	Cholinesterase inhibitor	<i>Lycoris squamigera</i>
Levodopa	Antiparkinsonian	<i>Mucuna deeringiana</i>
Menthol	Rubefacient	<i>Mentha</i> spp.
Methyl salicylate	Rubefacient	<i>Gaultheria procumbens</i>
Nordihydroguaiaretic acid	Antioxidant (lard)	<i>Larrea divaricata</i>
Quinidine	Antiarrhythmic	<i>Cinchona ledgeriana</i>
Tetrahydrocannabinol	Antiemetic	<i>Cannabis sativa</i>
Vinblastine	Anticancer	<i>Catharanthus roseus</i>
Vincristine	Anticancer	<i>Catharanthus roseus</i>

*Note:* Quality assurance of herbal products may be ensured by controlling the herbal ingredients and by good manufacturing practices. Some products have many herbal ingredients with only small amounts of individual herbs. Chemical and chromatographic tests are useful for developing finished product specifications. The stability and shelf life of herbal products should be established by manufacturers. There should be no differences in standards for the quality of dosage forms of herbal remedies, such as tablets or capsules, from those of other pharmaceutical preparations.

<sup>a</sup> Central nervous system.



in the U.S. as a 10% cream for topical treatment of **actinic keratoses**. Masoprocol is a potent inhibitor of **5-lipoxygenase**, but the exact mechanism of its antiproliferative effect on keratinocytes remains to be established.

### PILOCARPINE

Oral pilocarpine is moderately effective for treating **xerostomia** following irradiation of head and neck cancer. It may also be beneficial in relieving refractory xerostomia associated with chronic graft-versus-host disease (see Chapter 14).

### QUININE

The alkaloid quinine occurs naturally in the bark of the *Cinchona* tree. Apart from its continued usefulness in the treatment of malaria, it can also be taken for the relief of **nocturnal leg cramps** (see Chapter 22).

### SCOPOLAMINE (HYOSCINE)

Transdermal scopolamine (hyoscine) was introduced in the 1980s as a convenient alternative for the prevention of **motion sickness**. It is also effective in reducing of nausea and vomiting after **ear surgery** but was not found to be useful in the prevention of **vasovagal syncope** (see Chapter 14).

### TETRAHYDROCANNABINOL

$\Delta^9$ -Tetrahydrocannabinol is the major psychoactive cannabinoid in **marijuana** (*Cannabis sativa*). Its synthetic form, **dronabinol**, became available in the U.S. in 1985 as an antiemetic for patients receiving **emetogenic chemotherapy**. However, it is seldom used as a first-line antiemetic because of its psychoactive effects, and its use is usually limited to patients who have a low tolerance or minimal response to other antiemetic drugs (see Chapter 18).

### THEOPHYLLINE

The mode of action of theophylline is different from that of Beta<sub>2</sub>-adrenergic agonists and anticholinergic agents, so it is still used in the treatment of selected patients with **asthma** or **chronic obstructive pulmonary disease**.

## ANTIMALARIAL AGENTS

Following the development of synthetic antimalarial agents, such as **chloroquine** and **mefloquine**, the use of *Cinchona* **alkaloid** quinine declined. However, with the emergence of chloroquine-resistant and multiple-drug-resistant strains of malarial parasites, its use has become firmly reestablished. Quinine is the drug of choice for severe chloroquine-resistant malaria due to *Plasmodium falciparum*. In the U.S., the related alkaloid **quinidine** is recommended because of its wide availability and use as an antiarrhythmic agent. In many clinics in the tropics, quinine is the only effective treatment for severe malaria; unfortunately, decreasing sensitivity of *P. falciparum* to quinine has already been reported from Southeast Asia.

In 1972, Chinese researchers began a search for new antimalarial drugs from traditional sources, resulting in the isolation of **artemisinin** (*qinghaosu*) from the leaves of *Artemisia annua* (*qinghao*). This herb has been described in Chinese *materia medica* texts as a treatment for febrile illnesses since 4 A.D. Artemisinin is a **sesquiterpene lactone peroxide** with marked therapeutic activity against malaria. It is effective against *P. vivax* and chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*. Semisynthetic derivatives have greater activity than the parent drug.

Artemisinin compounds clear parasites from the blood more rapidly than any other antimalarial agent, by a unique pharmacodynamic action. They are concentrated in parasitized erythrocytes, and structure–activity relations (see Chapter 2) suggest that their endoperoxide bridge is essential for the antimalarial effect. A critical step in the mechanism of action seems to be a hemin-catalyzed reduction of the peroxide moiety, which results in free radicals and reactive aldehydes that subsequently kill the malaria parasites. The hemin-rich internal environment of the parasites is assumed to be responsible for the selective toxicity of artemisinin toward these organisms.

Another interesting compound, **yingzhaosu**, has been isolated from the roots of *Artabotrys uncinatus* and is used in southern China for treating malaria. A synthetic derivative of yingzhaosu A, **arteflene**, is currently being developed in the West for the treatment of malaria. *In vitro*, this compound has shown activity against drug-resistant strains of *P. falciparum* without signs of cross-resistance toward existing antimalarials. Drug interaction studies have revealed an additive to synergistic effect with **chloroquine**, **mefloquine**, and **quinine** (De Smet, 1997).

## CARDIOVASCULAR DRUGS

The positive benefits of extracts of two species of *Digitalis* (**foxglove**) and *lanata* were recognized long before their active constituents were isolated and characterized structurally (see Chapter 35). The cardiac glycosides, which include **digoxin**, **digitoxin**, and **deslanoside**, exert a powerful and selective positive inotropic action on the cardiac muscle. Digoxin is produced by mass cultivation and extraction of a strain of foxglove (*D. purpurea*) that has been selected for maximum production of the bioactive glycosides. In addition to the cardiac glycosides, a number of naturally occurring alkaloids are important in the control of various cardiovascular conditions. For example, **quinidine**, isolated from the bark of the *Cinchona tree* (see Chapter 22), is an important antiarrhythmic drug and was also one of the earliest and most well-known examples of the critical role of chirality in drug action. Its diastereoisomer, **quinine**, has virtually no cardiac activity but was recognized as one of the first anti-infective agents against malaria. Other important naturally occurring alkaloids active as cardiovascular drugs include **reserpine** (see Chapter 56), once one of the most useful antihypertensive agents known, and **papaverine**, a nonnarcotic peripheral vasodilator (see Chapter 47). In addition, **theophylline**, a xanthine alkaloid, is an important bronchodilator used to control asthma in children. **Ergotamine**, an ergot alkaloid obtained from a fungus that infects rye grass, is an important central vasoconstrictor used to treat **migraine headaches** (see Chapter 30). One of the latest additions to this class of drugs is the dopamine **D<sub>2</sub> receptor agonist cabergoline**, launched in Belgium in 1993 as an **antiprolactin**. This drug is also being evaluated as potential therapy for **Parkinson's disease** (see Chapter 13) and as an anticancer agent for the treatment of **breast cancer** (Clark, 1996).

Research conducted on the pharmacological effects of components in the venom of the **pit viper** (*Bothrops jararaca*) ultimately led to the discovery of the role of **angiotensin converting enzyme (ACE)** in hypertension. As a result, **teprotide**, a specific ACE inhibitor, was discovered and a model system for the interaction of small peptides with the enzyme was developed. Ultimately, **captopril** was designed as a specific, orally effective ACE inhibitor and was introduced to the market in 1981 to help control hypertension (see Chapter 50). The success and utility of captopril led to the design and synthesis of additional ACE inhibitors, such as **enapronil**. The ACE inhibitors constitute an important class of drugs and have played a major role in the management of cardiovascular disease (De Smet, 1997).

## CNS DRUGS

One of the most cited examples of important natural-product-derived drugs is the neuromuscular blocker **d-tubocurarine**, derived from the South American plant curare, which was used by South

American Indians as an **arrow poison** (see Chapter 26). Tubocurarine led to the development of **decamethonium**, which, although structurally dissimilar to tubocurarine, was nevertheless synthesized based on the then presumption prevalent that tubocurarine contained two quaternary nitrogens. Similarly, synthetic local anesthetics, such as **lidocaine**, **benzocaine**, and **dibucaine**, were synthesized to mimic the nerve-blocking effect of cocaine, a natural alkaloid obtained from the leaves of *Coca eroxylum*, but without the adverse side effects that have led to its abuse. The opium alkaloids **codeine** and **morphine** served as models for the synthesis of **naloxone**, an important analog used to treat and diagnose opiate addicts, and also led to the discovery of **endogenous opioids (enkephalins and endorphins)** (see Chapter 47). Similarly,  $\Delta^9$ -**tetrahydrocannabinol (THC)**, the component of *Cannabis sativa* responsible for the CNS effects, has also been found to reduce nausea associated with cancer chemotherapy. As a result, efforts to design semisynthetic or synthetic agents that mimic the desirable antiemetic effects while reducing the CNS effects of THC led to the development and introduction of **nabilone** as an antiemetic. Although nabilone retains some of the less desirable effects of THC, it is an effective and popular antiemetic (see Chapter 18).

Recently, the possibility that several vastly different CNS and peripheral nervous system diseases may be therapeutically controlled by selective **nicotinic acetylcholine receptor (nAChR)** agonists has opened a new area of drug design based on the nicotine molecule. Better treatment for disorders such as **Alzheimer's disease**, **Tourette's syndrome**, **Parkinson's disease**, as well as other **cognitive and attention disorders**, may ultimately be more effectively treated if agonists specific to certain subtypes of nAChRs can be discovered or designed (see Chapter 27). The characterization and understanding of these receptors was based largely on studies using agonists or antagonists, most of which are natural products, such as **acetylcholine**, **arecoline**, **anabasine**, **lobeline**, and **methyllycaconitine**. Recent reports that the nicotine analog **epibatidine**, isolated from the skin of **poisonous frogs**, exhibits exceptional analgesic activity and is a potent nAChR agonist have led to a number of synthetic studies on this molecule, including the synthesis of both pure enantiomers and the remarkable discovery that they are very active. Although the toxicity of this compound probably precludes its development as a therapeutic agent, structure–activity relationship (SAR) studies are likely to be performed in an effort to separate its toxic from its analgesic effects.

**Physostigmine**, a naturally occurring alkaloid, and its carbamate ester, **neostigmine**, are also important acetylcholinesterase inhibitors (see Chapter 14). The cholinesterase inhibitors are used for the treatment of **myasthenia gravis** and as antagonists to neuromuscular blockade by nondepolarizing blocking agents. The acetylcholinesterase inhibitor **galanthamine**, an alkaloid that occurs in the bulbs of **daffodils** (see Chapter 27), is currently being investigated as a possible therapy for cognitive impairment in **Alzheimer's disease** (De Smet, 1997).

## ANTIBIOTICS

There is no doubt that the antibiotics are among the most important classes of therapeutic agents and have had enormous impact on both life expectancy and quality of life. With the discovery of the natural **penicillins** as secondary metabolites of the fungus *Penicillium*, the course of medical history was dramatically altered and the antibiotic era was introduced. Antibiotics are, by definition, natural products or derivatives of natural products. During the 50-year period following **Alexander Fleming's** observations and the subsequent isolation and characterization of the active constituent by **Howard Florey** and **Ernst Chain**, hundreds of antibiotics have been isolated from scores of microorganisms. On average, two or three new antibiotics are introduced each year. Not only are antibiotics important drugs, but explorations into their functioning have led to an understanding of the biology of the target pathogens that would not likely have been possible without these important biochemical probes. With advances in molecular biology, similar advances in the utilization of natural products to probe specific molecular targets in the pathogens are also being made.

The discovery of important anti-infectives is not limited to antibacterial or antifungal antibiotics (see Chapter 45) from microbial sources. Long before the discovery of penicillin, it was known

that the bark of the South American “**fever tree**,” *Cinchona succiruba*, was effective in controlling malaria. **Quinine** was ultimately identified as the active antimalarial constituent of the *Cinchona* **bark**. When the natural source of quinine was threatened during World Wars I and II, massive programs to synthesize quinoline derivatives based on the quinine prototype were undertaken. In fact, it could be said that this effort, if not responsible for the origination, was a major contributor to the early growth of medicinal chemistry based on the synthesis of biologically active compounds modeled after natural products. From this intensive effort emerged two drugs that remained the therapeutic standards for the treatment of malaria until the past decade: **primaquine** and **chloroquine** (see Chapter 22).

Today, new important anti-infectives are being discovered from microbial, plant, and animal sources. For example, the antimalarial agent **artemisinin** was isolated from the Chinese medicinal plant *Artemisia annua*. Commonly known as **Qinghaosu**, this herbal remedy was used in China for centuries for the treatment of malaria. In 1972, the active constituent was isolated and identified as the **sesquiterpene endoperoxide artemisinin**. This compound, in addition to having a structure unlike any known antimalarial agents (i.e., quinolines), also exhibits antimalarial and pharmacological profiles very different from the clinically useful agents. Specifically, its activity against strains of the parasite that had become resistant to conventional chloroquine therapy and the ability, due to its lipophilic structure, to cross the blood–brain barrier, made it particularly effective against deadly **cerebral malaria**. For this reason, several major programs were undertaken to produce artemisinin derivatives with more desirable pharmaceutical properties; and much has been published on synthetic and semisynthetic studies, microbial transformations, biological evaluations, mechanism of action studies, and pharmacological profiles of artemisinin and related analogs. As a result of these studies, **artemether** was discovered, a derivative that is currently approved for the treatment of malaria in most parts of the world.

Another important class of anti-infective natural products introduced in recent years is the **avermectins**, polyketide-derived macrolides that were originally isolated from several species of *Streptomyces*. The major drug in this class, **ivermectin**, was originally developed to treat and control nematodes and parasites in livestock. In recent years, however, the potential of ivermectin for the treatment of human disease has also been realized, and it is now used to treat **onchocerciasis** (**river blindness**), a disease that afflicts 40 million people worldwide (De Smet, 1997).

## ANTINEOPLASTIC AGENTS

Another area in which natural products have had a major impact on longevity and quality of life is in the chemotherapy of cancer. In fact, most major anticancer drugs are derived from plants or microorganisms (see Chapter 62). Examples include **bleomycin**, **doxorubicin**, **daunorubicin**, **vincristine**, **vinblastine**, **mitomycin**, **streptozocin**, and most recently, additions of **paclitaxel** (Taxol™), **irinotecan** (a camptothecin derivative), and **etoposide** and **tenoposide** (podophyllo-toxin derivatives).

The observation that fractions of the **rosey periwinkle**, *Catharanthus rosea*, produced severe leukopenia, resulted in the isolation and development of two major anticancer drugs, **vincristine** and **vinblastine**. These two complex, dimeric indole-indoline alkaloids are important in the treatment of **acute childhood leukemia** (**vincristine**), **Hodgkin’s disease** (**vinblastine**), and **metastatic testicular tumors** (**vinblastine**), and continue to be manufactured today by mass cultivation and processing of their natural source.

Over 40 years ago, the National Cancer Institute initiated a program to explore higher plants as a source of anticancer agents. Although subject to periods of low productivity and little support, the discovery of one of the most exciting new drugs in recent history, **paclitaxel** (Taxol™), was a direct result of this effort (see Chapter 62). This compound, as well as most other anticancer drugs, was discovered using a system of screening several extracts of plants, microorganisms, and, more recently, marine organisms, for inhibition of cancer cells grown in culture. Although the total

synthesis of paclitaxel has been reported, this drug is a complex natural product with many asymmetric centers and is not readily amenable to total synthesis on an economical basis. Although a semisynthetic derivative with improved water solubility, **Taxotere™**, is now available, the unaltered natural product is approved and used clinically. Studies on the mechanism of anticancer action by paclitaxel revealed that it blocks **depolymerization of microtubules**. Because Taxol is the only known compound to exhibit this activity, without its discovery and development this new target for anticancer drug discovery and development would likely not have been identified.

Another important anticancer natural product is **camptothecin**, an alkaloid derived from the Chinese tree *Camptotheca acuminata* Descne. A semisynthetic water-soluble derivative of camptothecin known as irinotecan (**Topotecin™**, **Campto™**) was introduced in Japan in 1994 for the treatment of lung, ovarian, and cervical cancers. Unlike **Taxol**, camptothecin acts by inhibition of the enzyme **topoisomerase I**.

Two important recent additions to the cancer chemotherapeutic arsenal are **etoposide** and **tenoposide**. *Podophyllum peltatum*, used for years as a folk remedy, is the source of **podophyllin**, a crude resin used topically to treat **condylomata acuminata**. Podophyllin contains the **lignan podophyllotoxin**, among other things. Studies directed at preparing a water-soluble derivative of podophyllotoxin ultimately led to the discovery of a minor, but very active, constituent of the podophyllin resin, **4'-desmethoxy-1-epipodophyllotoxin glucoside**. The ability to produce this minor, naturally occurring compound by semisynthetic modification of the more abundant podophyllotoxin was a breakthrough that allowed the preparation and evaluation of a number of analogs, some of which had extraordinary activity. Two of these analogs, **etoposide** and **tenoposide**, were introduced as anticancer drugs in 1983 and 1992, respectively. These compounds act by a mechanism (**topoisomerase II inhibitors**) different from that of podophyllotoxin (**spindle poison**), illustrating that structural similarity alone is not always a reliable predictor of similar biological effect.

Paclitaxel, camptothecin, vincristine, vinblastine, and other compounds currently under development as potential anticancer drugs (i.e., the **bryostatins** isolated from marine **dinoflagellates**) were discovered through a broad-based screening program to identify, using a whole-cell inhibition assay, natural products that are active against a battery of representative cancer cell lines.

A recent and promising development is the growing body of evidence that the **retinoids**, derived from **vitamin A (retinol)**, may have potential utility in the treatment of cancer (see Chapter 66). Although several retinoids are already used clinically (i.e., **all-trans-retinoic acid [ATRA, Retin A™]** and **13-cis-retinoic acid [13-cis RA, Accutane™]** are used for the treatment of acne and the synthetic analog, **etretinate [Tegison™]** is used for the treatment of severe **psoriasis**), it has recently been recognized that these compounds may have significant potential in cancer chemotherapy. Although all these drugs may cause side effects that diminish their utility, it has been shown that the retinoids exert both therapeutic and adverse effects through activation of **retinoid receptors** (Soprano and Soprano, 1995), for which there are several subtypes. These data, when coupled with synthetic accessibility, suggest that synthetic retinoids based on the naturally occurring prototypes may be prepared that are more selective for specific receptor subtypes, thus offering the hope of separating the beneficial effects from the undesirable ones. Increasing evidence supports the potential benefit of retinoids in cancer therapy and the prevention of carcinogenesis, primarily as a result of their ability to regulate cellular growth and differentiation. **All-trans-retinoic acid**, **13-cis-retinoic acid**, **etretinate**, and **fenretinide** have undergone human clinical trials, with varying levels of response (De Smet, 1997).

## CHOLESTEROL-LOWERING AGENTS (HYPOLIPEMICS)

Some of the most exciting natural products discovered in recent years are the cholesterol-lowering agents derived from fungi (see Chapter 45). These drugs inhibit **3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase)**, an enzyme critical in the biosynthesis of choles-

terol. The first HMG-CoA reductase inhibitors were isolated from *Penicillium* sp. **Compactin**, from *P. brevicompactin*, was first reported as an antifungal agent. Following the discovery of its mechanism of action, there began a search for other naturally occurring HMG-CoA reductase inhibitors that led to the discovery of **lovastatin**, a secondary metabolite of the fungus *Aspergillus terreus*. Although lovastatin was introduced to the market in 1989, many studies were undertaken to prepare improved analogs, leading to the development of **simvastatin**, **pravastatin**, and **fluvastatin** (De Smet, 1997).

## IMMUNOMODULATORS

The immunomodulator **cyclosporin** was originally isolated from a soil fungus, *Trichoderma polysporum* (see Chapter 40). This compound was a major breakthrough for organ transplantation, because it suppressed immunological rejection of the transplanted organ. **Tacrolimus** (FK-506), a secondary metabolite of *Streptomyces tsukubaensis*, was approved in 1994 for use as an immunosuppressant in organ transplantation (De Smet, 1997).

## RECENTLY EVALUATED HERBAL PRODUCTS

The following are examples of crude herbal preparations that have caught the attention of clinical investigators in recent years.

### ALOE VERA GEL (*ALOE VERA*)

Aloe vera gel is a mucilaginous preparation obtained from the leaves of *Aloe vera* (syn. *Aloe barbadensis*) once the sap has been drained away. It is widely used in cosmetic products for its purported emollient and moisturizing effects. It is claimed to have antibacterial, antifungal, and anti-inflammatory properties and has been proposed as a potentially useful agent for radiation and thermal wounds (see Chapter 12).

### AMERICAN DWARF PALM (*SERENOA REPENS*)

Lipophilic extracts of **sabal fruit** (*Serenoa repens* syn. *Sabal seruulata*) are used in the treatment of benign **prostatic hyperplasia** (BPH) (see Chapter 55). The hexane extract of the pulp and seed contains a complex mixture of free fatty acids and their esters, small quantities of **phytosterols** (such as  $\beta$ -sitosterol), aliphatic alcohols, and **polyprenic compounds**. The efficacy of this extract was recently compared with that of the **5 $\alpha$ -reductase inhibitor finasteride** for 6 months, in a randomized, double-blind trial involving almost 1100 men with moderate BPH. Dwarf palm and finasteride reduced the International Prostate Symptom Score by 37 and 39% and increased urinary peak flow by 2.7 and 3.2 ml/sec, respectively. In contrast to finasteride, dwarf palm had little effect on prostate volume.

### CRANBERRY JUICE (*VACCINIUM* spp.)

A randomized, double-blind, placebo-controlled trial suggests that the regular intake of cranberry juice reduces the frequency of bacteriuria and pyuria in elderly women.

### EVENING PRIMROSE OIL (*OENOTHERA BIENNIS*)

Evening primrose oil is rich in the essential fatty acid **linoleic acid** and its metabolite,  **$\gamma$ -linolenic acid**. In the U.K., evening primrose oil preparations have received approval as medicines for the relief of **atopic eczema** and for the symptomatic treatment of **breast pain**.

**FEVERFEW LEAF (*TANACETUM PARTHENIUM*)**

Double-blind withdrawal of feverfew leaf from migraine sufferers who were regular users led to a significant increase in the frequency and severity of headaches (see Chapter 30). A prospective, randomized, double-blind, placebo-controlled trial subsequently found that feverfew was an effective prophylactic migraine agent. The **sesquiterpene lactone parthenolide** is considered to be an important constituent, but other constituents may also play a significant role.

**GARLIC (*ALLIUM SATIVUM*)**

Garlic has been reported to have lipid- and blood-pressure-lowering properties, as well as antiplatelet, antioxidant, and fibrinolytic effects. In animal models and human cell cultures, it has been shown to have antiatherosclerotic activity (see Chapter 50). The sulfur-containing component, **allicin**, is considered to be the principal active ingredient of garlic, but several other bioactive ingredients have also been isolated.

**GINGER ROOT (*ZINGIBER OFFICINALE*)**

Several controlled clinical trials suggest that ginger root can relieve symptoms of motion sickness by a mechanism of action that differs from that of antihistamines. The responsible constituents are believed to be **gingerols** and **shogaols**.

**GINKGO LEAF (*GINKGO BILOBA*)**

Ginkgo leaf is recommended in Germany for **cerebral insufficiency** and peripheral vascular diseases such as **intermittent claudication**. Although it may be useful to patients with mild symptoms of cerebral insufficiency, it is probably not useful in those with clear **dementia**. One of the major **terpenes** in ginkgo leaf, **ginkgolide B**, is a potent antagonist of **platelet-activating-factor** (PAF) (see Chapter 59). Because PAF plays a role in various pathological processes, including asthma, shock, ischemia, anaphylaxis, graft rejection, and renal disease, ginkgolide B (BN-52021) has been submitted in recent years to clinical evaluations in such conditions (see Chapter 36).

**HAWTHORN (*CRATAEGUS MONOGYNA* AND *C. LAEVIGATA*)**

Among the reported activities of hawthorn are positive inotropic activity, coronary vasodilatation, slowing of heart rate, and slight lowering of blood pressure.

**HORSE CHESTNUT (*AESCULUS HIPPOCASTANUM*)**

The edema-reducing effects of class II compression stockings in patients with chronic venous insufficiency have been compared with those given either a placebo or a dried horse chestnut seed extract (HSCE, providing **aescin** 50 mg twice daily) in a randomized, partially blinded, parallel study. After 12 weeks of therapy, HSCE and compression produced equivalent mean decreases in lower-leg volume (44 and 47 ml, respectively), whereas a mean increase of 10 ml was observed in the placebo group.

**IPECACUANHA (*CEPHAELIS IPECACUANHA* AND *C. ACUMINATA*)**

In the U.S., **syrup of ipecac** has long been valued as an emetic OTC agent in the treatment of poisonings, and it has been the primary form of decontamination in pediatric cases, both at home and in health-care facilities (see Chapter 55).

**ISPAGHULA HUSK (*PLANTAGO OVATO*)**

Ispaghula husk (known as **psyllium husk** or **psyllium hydrophilic mucilloid** in the U.S.) is an effective bulk-forming laxative that causes retention of fluid and an increase in fecal mass, resulting in the stimulation of peristalsis (see Chapter 12). Ispaghula husk caused small reductions in total and low-density lipoprotein cholesterol (LDL-C) levels in double-blind, placebo-controlled studies involving patients with mild to moderate hypercholesterolemia. It is best regarded as an adjunct to dietary modification rather than a primary intervention for hypercholesterolemia. A study is being conducted to determine whether the combination of ispaghula husk with a bile acid sequestrant resin at half its usual dose is as effective and better tolerated than the resin alone at its usual dose.

**KAVA-KAVA (*PIPER METHYSTICUM*)**

Several clinical studies suggest that extracts from the rhizome of kava-kava may alleviate mild symptoms of anxiety (see Chapter 65).

**MARIJUANA (*CANNABIS SATIVA*)**

Among herbs that are being reevaluated for their potential as prescription drugs is marijuana (*C. sativa*). The beneficial effects of marijuana are listed (see Chapter 18):

- Symptomatic relief in nausea and vomiting associated with cancer chemotherapy
- Alleviation of muscle spasms, tremor, ataxia, and bladder dysfunction in multiple sclerosis and after spinal cord injury
- Anticonvulsant and muscle relaxant in spastic disorders
- Reduction of intraocular pressure in glaucoma
- Appetite stimulant in the wasting syndrome of HIV infection
- Relief of phantom pain, menstrual cramps, and other types of chronic pain (see De Smet, 1997)

**ST. JOHN'S WORT (*HYPERICUM PERFORATUM*)**

According to a recent meta-analysis, St. John's wort is more effective than placebos for the treatment of mild to moderately severe depressive disorders (see Chapter 43).

**TEA TREE OIL (*MELALEUCA ALTERNIFOLIA*)**

Tea tree oil had an ameliorating effect on mild to moderate acne in a single-blind, randomized trial in which benzoyl peroxide served as comparator. It has also shown promise in **onychomycosis** in a comparative trial with **clotrimazole**. Among the antimicrobial constituents are **terpinen-4-ol**, **linalool**, and  **$\alpha$ -terpineol**.

**WHEAT BRAN (*TRITICUM SPP.*)**

There is substantial evidence that bran is useful in the treatment of simple constipation. If used in sufficient quantities, it softens stools, eliminates scybala, and prevents straining. However, a recent study has challenged its clinical merits in the management of the **irritable bowel syndrome**.

**NEW USES FOR "OLD" DRUGS**

It is important to acknowledge that as we acquire additional experience with known drugs, new uses for existing agents are often identified. For example, it has recently been shown that the combination of the antibacterial antibiotic **clindamycin** (used clinically for years for its relatively



narrow spectrum of activity against important Gram-positive bacteria and anaerobes) and the antimalarial **8-aminoquinoline primaquine** (synthesized after the quinine model) is effective in the treatment of the important **AIDS-related opportunistic infection *Pneumocystis carinii* pneumonia**. This combination therapy is currently undergoing clinical trials and demonstrates the importance of continuing to explore older, known drugs for new therapeutic applications. The original therapeutic utility of an agent may be expanded as new disease states are recognized and as experience with this agent affords more empirical observations upon which to base recommendations for such usage.

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# 6 Alternative Therapies

If you want to see what your body will look like tomorrow, look at your thoughts today.

— Navajo Proverb

## INTRODUCTION

The following are the chief alternative therapies that will be covered in this chapter:

- Acupuncture
- Energy healing
- Folk medicines
- Herbal medicines
- Homeopathy
- Massage
- Megavitamins
- Self-help group treatments (see Hammond, 1995; Lawless, 1995; Dougans, 1996; Hoffman, 1996; Thomas, 1997; Mitchell, 1997; Warriar and Gunawant, 1997; MacDonald, 1998; Liechti, 1998; and General References)

## WHY PATIENTS USE ALTERNATIVE MEDICINE

The majority of alternative medicine users appear to turn to it not so much because they feel dissatisfied with conventional medicine, but largely because they find these health-care alternatives to be more congruent with their own values, beliefs, and philosophical orientations toward health and life. Also, they are more educated and more likely to report their health status.

Herbs and related products are commonly used by patients who also seek conventional health care. All physicians, regardless of specialty or interest, care for patients who use products that are neither prescribed nor recommended.

The earliest evidence of human use of plants for healing dates to the Neanderthal period. In the 16th century, botanical gardens were created to grow medicinal plants for medical schools. Herbal medicine practice flourished until the 17th century, when more “scientific” pharmacological remedies were favored (see Thomas, 1997; Fontanarosa, 2000; and General References).

Short descriptions of alternative medicine methods follow.

## ACUPRESSURE

Acupressure involves the application of fingertip or nail pressure to acupuncture points on the body to remove blockages or pain and enhance the **flow of chi**. In Chinese medicine acupressure may be used in its own right or incorporated into acupuncture treatment (Thomas, 1997; and General References).

## ACUPUNCTURE

There are over 350 **acupoints on the meridians of the body**. Selected points are stimulated by inserting fine acupuncture needles to improve the **flow of chi or qi** in the meridians and to restore balance and healthy functioning to the internal organs of the body. Treatment points are selected on the basis of pulse and tongue diagnosis, examination, and questioning, and categorized according to their effects on specific body systems and organs. The insertion of the needles is quick and virtually painless, and often a comfortable and relaxed feeling follows (Thomas, 1997; and General References).

## AROMATHERAPY

Aromatherapy is the use of **essential oils from plants** to enhance general health and appearance. The term was coined by its originator, the French chemist **René-Maurice Gattefosse**. The following summarizes the ten most useful oils and their supposed effects (Thomas, 1997):

<b>Chamomile</b>	Calming
<b>Eucalyptus</b>	Antiseptic
<b>Geranium</b>	Mildly astringent
<b>Jasmine</b>	Antidepressant
<b>Lavender</b>	Mildly analgesic
<b>Marjoram</b>	Mildly analgesic
<b>Neroli</b>	Mildly sedative
<b>Rose</b>	Antiseptic
<b>Rosemary</b>	Mild stimulant
<b>Sandalwood</b>	Antiseptic

## AURICULAR THERAPY

Ear acupuncture is based on the idea that each part of the ear is a mirror of the body as a whole. There are, for example, **kidney meridian points on the ear**. As a result, almost any ailment can be treated with ear acupuncture. Sometimes it is used together with body acupuncture, but some practitioners use ear acupuncture on its own for diagnosis and treatment. Acupuncture points on the external ear can be used to treat disease, relieve pain, and promote anesthesia. The technique is over 1000 years old but has been further developed in both France and China in recent years. Points are located in the ear by pressing with a fine, blunt instrument to locate sensitive spots, or by using an electrical sensor to find points that have a low resistance to electricity. The point is then stimulated either electrically or with small conventional needles. The needles are kept in for about 15 min and manipulated every now and then. Alternatively, a small ring-needle or seed may be fixed to the point in the ear and retained for several days, providing continuous treatment lasting for a short period of time. These are held in place with small patches of adhesive bandage. The needles work in the same way as traditional acupuncture, but the seed operates more as a mild form of acupressure (Thomas, 1997; and General References).

## AYURVEDA

Ayurveda, meaning the “**science of life**,” is said to be the oldest and most complete medical system in the world and dates back to 5000 B.C. Its roots are in ancient Indian civilization and Hindu philosophy, and it has been an important influence on the development of all the other Eastern medical systems. The original source of Ayurveda is the **Vedas** and the texts known as the **Samhitas**, which are treatises on health care and describe medical procedures, including surgery and a form

of massage of vital energy points (similar to Chinese acupuncture). In Ayurvedic medicine, the life force is **prana**, similar to the Chinese **chi**, or **qi**. As in Chinese medicine, the functioning of the body is controlled by immaterial forces, linked to physical substances. These substances are the three basic forces or **doshas** that exist in all things:

**Pitta**, the force of heat and energy, linked with the sun, that controls digestion and all biochemical processes in the body

**Kapha**, the force of water and tides, influenced by the moon, the stabilizing influence that controls fluid metabolism in the body

**Vata**, linked to the wind, the force that controls movement and the functioning of the nervous system in the body

When balanced these three forces ensure that the body is healthy, but when they are “abnormal” or unbalanced, disease follows (Thomas, 1997; and General References).

### BIODYNAMIC MASSAGE

Developed by Norwegian therapist **Gerda Boyesen** out of the integrated form of physical and psychological therapy known as **bioenergetics**, **biodynamic massage** combines massage with exercise to release emotional tension. Participants are taught to “connect with” and experience the energy flowing through them in much the same way as they might experience an **orgasm**. Because it may have a liberating effect on the mind, as well as the body, it is known also as **dynamic psychology** (Thomas, 1997; and General References).

### BIOENERGETIC THERAPY

Bioenergetic therapies are based on the concept of the **essential involvement of the body in personal development**. They stem from the work of **Wilhelm Reich** (1897–1957) during the 1930s and 1940s, in Austria and the U.S. He was fascinated by the flow of energy through the body and wanted to find out why it became blocked and how to release it. Reich believed that **tensing our muscles** is a natural way to defend ourselves against **unendurable mental pain**, in particular the fear of **losing the love of our protectors** by displaying unacceptable emotions. Painful experience is split off from the conscious mind and kept separate by physical “**armoring**,” which also affects our breathing rhythms. Therapists are trained to read the messages of the body — which, it is said, never lies. Repressed traumas (such traumas include those that occur at birth) can be brought to awareness, released, and resolved, using a combination of physical and psychological techniques, once the central focus of the trauma has been determined. **Physical exercises, breathing exercises, and various forms of massage** may be used, usually in group therapy sessions. This liberating process can also bring back pleasurable memories of past experiences, especially childhood delights (Thomas, 1997; and General References).

### CHI KUNG MEDICINE

Although chi kung involves physical activity, its aim is to develop and conserve internal energy, and integrate body and mind. Chi kung is one of the most effective of all Eastern methods for combating stress and is also becoming highly popular as a method of enhancing and managing sexual potential. **Taoist** “secrets” of how to conserve sexual energy are now receiving serious attention as an important part of resistance to the aging process. An ancient Chinese system for the development of internal energy, **chi kung** or **qi gung** (“chee goong”) is, similar to **t’ai chi**, based on the principles of the **Taoist religion** as extended to Eastern medicine. Unlike **yoga**, chi

kung puts less emphasis on stretching movements and postures, and more on learning how to feel and move energy inside the body. Some of the basic chi kung drills involve standing still for anything from minutes to hours at a time, sensing the movement of energy in the body.

Other chi kung exercises involve gentle, rhythmic swinging or stretching movements to generate and conserve energy, but not to burn calories. The chi kung practitioner aims to avoid stress on joints and muscles and directs his or her awareness inside the body, rather than concentrating on building up what the Chinese refer to as “external” strength in the form of tight, well-developed muscles. As a result, chi kung practice develops enormous inner power in a pliable, flexible, and relaxed body. An experienced practitioner can use the therapy not only for healing but also in a preventive capacity (Thomas, 1997; and General References).

## CHINESE HERBALISM

The Chinese herbal tradition is believed to date back some 4000 years to the **Emperor Shen Nong** (or **Chi'en Nung**). He is said to have described over 300 medicinal plants and their uses in a book called the *PenT'sao*. Although versions of several ancient pharmacopoeia still exist today, the main surviving text on herbalism is the 16th-century book by the physician **Li Shih-chen** describing almost 2,000 herbs and 10,000 herbal remedies (Thomas, 1997; and General References).

## CHIROPRACTIC MEDICINE

In 1895, **Daniel David Palmer**, the founder of chiropractic medicine, treated his office janitor for deafness by realigning some small bones in his spine. Fascinated by his discovery, Palmer moved from his native Canada to Davenport, IA, where he developed the principles on which chiropractic is based. *Chiropractic* — a term that derives from two ancient Greek words meaning “manually effective” — is technically described as “**the diagnosis, treatment, and rehabilitation of conditions that affect the neuromusculoskeletal system.**” Through a series of special examinations and manipulative techniques, chiropractors can diagnose and treat numerous disorders associated with the nerves, muscles, bones, and joints of the body. The emphasis chiropractors put on the spine has led many people to believe that the therapy is useful only for treating back pain. In fact, skilled therapists can treat almost every structural problem, from headaches to ankle pain (Thomas, 1997; and General References).

## CRYSTAL AND GEM THERAPIES

More than 200 gem and mineral essences have recently been created in the belief that they will assist the healing of specific mental and emotional states. Designed to be taken orally, they are made by immersing the stones in pure water exposed to sunshine, which is said to instill the water with their “**healing vibrations.**” Healers believe that gems and crystals placed on and around their patients can focus and enhance healing energy. Placing crystals around the home is said to improve the atmosphere, absorbing negativity, but they should be washed regularly under cold running water and “**recharged**” in sunlight (Thomas, 1997; and General References).

## CUPPING THERAPY

Cupping is particularly helpful for conditions such as **rheumatism, lumbago, and stiff neck and shoulders** as it increases circulation and the mobility of affected areas. Cupping has been used in China since the 3rd century B.C. It involves lighting a match in a small rounded “cup,” made of glass, bamboo, metal or pottery, and then removing it quickly and applying the cup to the skin. The flame creates a vacuum, and the cup sticks tightly to the skin. Several cups may be applied at

any one time to a particular part of the body such as the back. The cups are left in position for 10 to 15 min while the vacuum inside the cup produces strong suction on the skin and increases the blood flow and circulation. The cup is released by pressing the skin next to the edge of the cup so that the vacuum is broken. Cupping is slightly uncomfortable but not painful (Thomas, 1997; and General References).

## DIETARY AND NUTRITIONAL THERAPIES

Diet as therapy has been practiced for centuries. The father of medicine, **Hippocrates**, wrote extensively about the therapeutic use of diet, yet until relatively recently modern medicine has largely forgotten the overwhelming role of diet, except as related to such problems as obesity and diabetes.

With the growth of nutritional science in the 20th century, particularly since World War II, specific foods have been recognized as risk factors in disease. For example, **too much fat**, and saturated animal fat in particular, is now widely recognized as a risk factor of heart disease and some cancers. Equally, too much refined food and **too little fiber** causes a range of digestive and bowel disorders, from constipation to irritable bowel syndrome — and may even be a cause of some cancers. **Too much salt** may exacerbate high blood pressure and reactions to food-trigger allergies.

Most alternative therapists believe that everybody can benefit from dietary self-help for both prevention and treatment of disease. Many therapies recommend **fasting**, perhaps drinking only fruit and vegetable juices, or eating salads or single fruits. **Fasting** is probably the oldest therapy known to humankind. Primitive people and animals instinctively stop eating when they are ill, probably because digestion takes up energy and puts extra strain on the body. The aim of fasting and dietary therapy is to rid the body of the toxins that are said to accumulate from a wrong diet, so that it can function at its optimum level.

Nutrients are the chemical components of diet and are essential to life and health. Nutrients are classed as either **macronutrients** or **micronutrients**:

- Macronutrients are **carbohydrates** (sugars and starches), **fats** (including essential fatty acids), **proteins** (including essential amino acids), and **fiber**.
- Micronutrients are **vitamins**, **minerals**, and **trace elements** that cannot be manufactured in the body, and so must be consumed daily.

If micronutrients are absent or too low, illness results. **Scurvy**, for example, is a disease resulting from **lack of vitamin C**. It was once the curse of sailors who had to make long trips to sea with no access to fresh fruit or vegetables. Once the connection between scurvy and fresh fruit had been made and the sailors were issued **lime juice** to drink, scurvy virtually disappeared.

Other factors can also increase the need for vitamins and minerals. Examples are poor digestion and absorption, smoking, and drinking. Rapid growth in childhood and **adolescence**, **pregnancy**, **lactation**, and **old age** all increase the need for nutrients. Requirements are also higher during illness, when we are under stress, when taking drugs, or when affected by environmental toxins and pollutants. It is in these situations that nutrients such as vitamins, minerals, amino acids, and essential fatty acids may be recommended and prescribed (Thomas, 1997; and General References).

## EASTERN HERBAL MEDICINE

The use of herbs once belonged partly to the realm of magic, in the healing rites performed by **shamans** (men and women of “**natural wisdom**”); and also stems from observations of how animals treat themselves by using various plants when sick or wounded. But a careful study of herbs and their properties over thousands of years has developed Eastern herbal medicine into a highly refined and complex discipline. In Chinese medicine, diet is a matter of great importance in preventing

and treating disease, and the Eastern therapist also gives instructions on how to correct the diet and lifestyle. Acupuncture may also be recommended. Western research now suggests that many of the substances that are used in Eastern medicine may contribute to the treatment of cancers and other diseases. Eastern medicinal herbs are generally used in combinations. There are approximately 300 herbal ingredients regularly used in prescriptions, and about half of these would be considered essential in any Chinese herb store. The most well known are the following:

- **Ginseng** is a well-known herbal tonic in Eastern countries, and its properties are also recognized in the West.
- **Betel nuts, Bing Lang**, are used for intestinal worms and irregular bowel movements.
- **Oyster shells** are the source for **Mu Li**, which has a sedative effect.
- The medicinal qualities of *Cinnamomum zeylanicum* as a stomachic and carminative are recognized in the West and East alike (Thomas, 1997; and General References).

### ENVIRONMENTAL THERAPIES

Air pollution is one of the worst problems caused by industries, agriculture, power stations, aerosols and other chemicals, and coal and other fires. As a result we suffer from headaches, respiratory tract infections and ailments, asthma, bronchitis, emphysema, eye problems, and eventually a profound breakdown in health manifested by various cancers. Other environmental hazards include lead from gasoline — which causes hyperactivity and birth defects — acid rain, carbon monoxide poisoning, water pollution, and radiation. Clinical ecologists treat illnesses and disorders that they believe stem from an individual's reaction to these environmental factors. They practice what is known as **environmental medicine**, and they estimate that between 10 and 30% of the population suffers from some form of ecological disease (Thomas, 1997; and General References).

### FLOWER AND TREE REMEDIES

Although flowers have played a role in healing for centuries — Australian Aborigines and Native Americans were using remedies made from flowers to ease emotional trauma and achieve peace of mind thousands of years ago — the healing power of flowers was only rediscovered in the West in the 1920s when it was revived by **Edward Bach**, who provided the following attributes:

<b>Agrimony</b>	Worry hidden by a career mask, apparently jovial but suffering
<b>Aspen</b>	Vague, unknown, haunting apprehension and premonitions
<b>Beech</b>	Intolerant, critical, fussy
<b>Centaury</b>	Kind, quiet, gentle, anxious to serve
<b>Cerato</b>	Distrust of self and intuition, easily led and misguided
<b>Cherry Plum</b>	For the thought of losing control, of doing dreaded things
<b>Chestnut Bud</b>	Failing to learn from life, repeating mistakes, lack of observation
<b>Chicory</b>	Demanding, self-pity, self-love, possessive, hurt, and tearful
<b>Clematis</b>	Dreamers, drowsy, absent-minded
<b>Crab Apple</b>	Feeling unclean, self-disgust, small things out of proportion
<b>Elm</b>	Capable people with responsibility who falter, temporarily overwhelmed
<b>Gentian</b>	Discouragement, doubt, despondency
<b>Gorse</b>	No hope, accepting the difficulty, pointless to try
<b>Heather</b>	Longing for company, talkative, excessive preoccupation with self
<b>Holly</b>	Jealousy, envy, revenge, anger, suspicion
<b>Honeysuckle</b>	Living in memories

<b>Hornbeam</b>	Feels weary and thinks cannot cope
<b>Impatiens</b>	Irritated by constraints, quick, tense, impatient
<b>Larch</b>	Expect failure, lack of confidence and will to succeed
<b>Mimulus</b>	Fright of specific, known things — animals, height, pain, etc.
<b>Mustard</b>	Gloom suddenly clouds one for no apparent reason
<b>Oak</b>	Persevering despite difficulties, strong, patient, never giving in
<b>Olive</b>	Exhausted, no more strength, need physical and mental renewal
<b>Pine</b>	Self-critical, self-reproach, assuming blame, apologetic
<b>Red Chestnut</b>	Worry for others, anticipating misfortune, projecting worry
<b>Rock Rose</b>	Feeling alarmed, intensely scared, horror, dread
<b>Rock Water</b>	Self-denial, stricture, rigidity, purist
<b>Scleranthus</b>	Cannot resolve two choices, indecision, alternating
<b>Star of Bethlehem</b>	For consolation and comfort in grief, after a fright or sudden alarm
<b>Sweet Chestnut</b>	Unendurable desolation
<b>Vervain</b>	Insistent, willful, fervent, trying too hard
<b>Vine</b>	Dominating, tyrannical, bullying, demanding obedience
<b>Walnut</b>	Protection from outside influences, for change and stages of development
<b>Water Violet</b>	Withdrawn, aloof, proud, self-reliant, quiet grief
<b>White Chestnut</b>	Unresolved, circling thoughts, constant worry
<b>Wild Oat</b>	Lack of direction, unfulfilled, drifting
<b>Wild Rose</b>	Lack of interest, resignation, no love or point in life
<b>Willow</b>	Dissatisfied, bitter, resentful, feeling life is unfair and unjust

Remedies from flowers and trees are subtle “**elixirs**” that are claimed to be able to help rekindle a feeling of mental and emotional, as well as physical, well-being. Some bring relief from unsettling moods and emotions such as anxiety, fear, guilt, and anger, and others enable people who use them to recognize and let go of deep-seated behavioral patterns that give rise to such feelings. Above all, they are claimed to be able to help people feel calm and content in times of stress. Flower and tree remedies are so safe and harmless that they are often used as self-treatment. They are not targeted at particular symptoms but at states of mind accompanying illness (Thomas, 1997; and General References).

## FOOD AND DIET THERAPY

**Naturopathy** encourages us to take responsibility for our own health by encouraging sensible diet and lifestyle management. This is a principle with which few conventional medical practitioners now argue. Diet is becoming rapidly and widely accepted as much of the basis of good health. In naturopathic terms, a good diet is whole food, comprising “**live foods**” — that is, foods that have not been processed or refined and are mostly organic. Such foods, believe naturopaths, “**fuel vitality**” and stimulate the “**vital force.**” Diets must also provide the necessary materials or “**nutrients**” on which the body relies for good health.

**Fasting** means abstaining from solid food for a specified period of time. It does not mean starving completely or going without fluids. Liquids must always be taken regularly during any fast. Neuropaths believe that fasting:

- Cleanses the system of poisons accumulated from bad eating habits, a poor environment, and suppressed or repressed emotions
- Enhances immune functioning and speeds up healing
- Gives the digestive system a well-earned and often much-needed rest



Fasting is particularly beneficial in the treatment of fevers and acute problems such as skin rashes or digestive upsets. Naturopaths also recommend fasting 1 or 2 d a month regularly as an important part of preventive health care (Thomas, 1997; and General References).

## GEOPATHIC THERAPY

The **electromagnetic field** generated around **pylons** has caused headaches, nausea, and general debility in the unfortunate people who live near or underneath them. The Earth's magnetic field generates powerful unseen energy forces that have been recognized for thousands of years. These Earth energies were probably easier to detect in the preindustrial age, and it is thought that ancient cultures sited their standing stone circles on sites where the Earth's energy could be felt particularly strongly. Not all natural energies are beneficial; for example, **granite rock strata** emit the noxious gas **radon**. Other negative energies emanate from the Earth, and artificial contributions include the local electrical fields generated by power cables. Prolonged exposure to these energies — a condition known as **geopathic stress** — contributes to illness and general debility by weakening the body's defenses against disease and potentially harmful substances in the environment (Thomas, 1997; and General References).

**Feng shui** is the ancient Chinese art of balancing energies by integrating people, buildings, and landscape to create a harmonious whole. Only when balance and harmony are achieved can the **chi**, the energy or life force of the universe, flow freely, resulting in good health, happiness, and prosperity. In Chinese culture this is taken very seriously, and alterations to existing buildings or the construction of new ones are only undertaken after consultations with a **feng shui expert**. Correcting bad feng shui is considered as much a part of the healing process as prescribing herbs or applying acupuncture or acupressure (Thomas, 1997; and General References).

## GESTALT THERAPY

Well-known **Gestalt techniques** include increasing the awareness of “**body language**” and “**negative internal messages**”; emphasizing the client's self-awareness by making him or her speak continually in the present tense and in the first person; concentrating on a part of a client's personality, perhaps even on just one emotion, and addressing it as if it were sitting by itself in the client's chair; and creating episodes and diversions that vividly demonstrate a point rather than giving verbal explanations.

**Psychodrama** is a role we all play in life. If that role is painful or frustrating, we may need to express our negative emotions in some way or to create scenarios that make us feel better. Psychodrama, which was developed in the 1920s in Austria and the U.S. by **Jacob Moreno**, provides an arena for this. The openness to self-discovery that is a feature of psychodrama derives from several factors. Once trust has been created, group dynamics encourage disclosure; acting and direction allow for safe exploration of feelings by trial and error; the rare physical freedom of moving at will across an open space promotes expansiveness. Psychodrama can be used to unlock doors to the past, to explore one person's “dark” side, to empathize with others through role exchange, and to discover and practice fresh ways of relating to others (Thomas, 1997; and General References).

## HERBAL MEDICINE

The Chinese, Japanese, Indian, and Native (North and South) American cultures all have traditional systems of **herbal medicine**. In China and Japan, the use of herbal remedies is officially promoted by a government ministry and included in national health systems. In India, herbalism is part of the ancient but still widely used system of **Ayurvedic medicine**. Native Americans use herbs in a spiritual sense, placing emphasis on their purifying and cleansing properties both physically and mentally.

Most **herbal therapists** (sometimes called **herbalists** — but not all herbalists treat clients medically) believe that the body acts in unison with the psyche (spirit) and emotions to maintain the equilibrium necessary for overall health and well-being. With this holistic approach, herbal therapists use their knowledge of plant properties to rebalance a client's life energy levels so that the body heals itself.

Generally speaking, conventional medicine takes the view that the mind and the body are separate entities. If there is illness or disease in the body, the symptoms and the affected part are treated in isolation. For example, an allergic reaction might be treated with antihistamines by a conventional doctor, whereas a therapeutic physician would look for the root of the problem, and address that. Every therapeutic herbalist acknowledges that there is a role for surgical procedures and drugs in some situations. The advances of modern medicine can complement medical herbalism, and *vice versa* (Thomas, 1997; and General References).

The following summarizes some herbs and their uses. Scientific data either verifying or denying their therapeutic efficacies do not exist:

Herbs	Used for
<b>Angelica</b>	The common cold, coughs, respiratory infections, flatulence, indigestion, loss of appetite
<b>Arnica</b>	Bruises, sprains (not for internal use)
<b>Balm of gilead</b>	Eczema, psoriasis, sore throat, laryngitis
<b>Borage</b>	Fever, inflammation, respiratory infections, stress
<b>Chamomile</b>	Anxiety, insomnia, flatulence, indigestion, inflammation, conjunctivitis, healing wounds
<b>Comfrey</b>	Bruises, burns, ulcers, healing wounds (use externally only)
<b>Dandelion</b>	Gallbladder problems, water retention, jaundice, general debility
<b>Fennel</b>	Colic, flatulence, indigestion, coughs, conjunctivitis
<b>Garlic</b>	The common cold, coughs, adenoid problems, respiratory infections, other bacterial infections, high blood pressure (hypertension), acne
<b>Hyssop</b>	The common cold, coughs, sore throat, respiratory infections, loss of appetite, bruises, anxiety
<b>Lavender</b>	Nervous exhaustion, insomnia, headache, rheumatic pain
<b>Lemon balm</b>	Flatulence, indigestion, anxiety, depression
<b>Marigold</b>	Bruises, burns, healing wounds, skin inflammation, conjunctivitis, some fungal infections, adenoid problems
<b>Meadowsweet</b>	Fever, nausea, digestive problems, constipation, urinary infections, rheumatic pain
<b>Nettle</b>	Constipation, water retention, bleeding, eczema, allergies
<b>Oregano</b>	The common cold, coughs, sore throat, headache, muscular pain, bites and stings, healing wounds
<b>Peppermint</b>	Flatulence, loss of appetite, nausea, colic, headache, menstrual problems, skin irritation
<b>Rosemary</b>	Headache, muscular pain, neuralgia, general debility, digestive problems, baldness
<b>Sage</b>	Laryngitis, inflammation, healing wounds, anxiety, depression (do not use during pregnancy)
<b>St. John's wort</b>	Burns, healing wounds, shingles, neuralgia, rheumatic pain, anxiety, tension, depression
<b>Thyme</b>	Coughs, sore throat, laryngitis, respiratory infections, infections in wounds

<b>Valerian</b>	Sedative
<b>Witch hazel</b>	Astringent
<b>Yarrow</b>	Menstrual problems
<b>Yellow dock</b>	Skin problems

## HOMEOPATHY

Homeopathy, founded by a German doctor and chemist named **Samuel Hahnemann** (1755–1843), is a holistic system that aims to help the body heal itself. It works for both acute illnesses and chronic ailments, and the prevention of illness is as crucial to its philosophy as the treatment. The name *homeopathy* comes from the Greek word *homios* meaning “like” and *pathos* meaning “suffering.” The word *homeopathy* simply means treating like with like. This means that a substance that causes symptoms of illness in a healthy person can also be used to cure similar symptoms when they result from illness (Thomas, 1997; and General References).

## HYDROTHERAPY

Hydrotherapy — water therapy — is the use of water to promote healing. It is one of the oldest, simplest, and most effective of all the natural therapies. Water treatments include taking natural spring water internally for its beneficial mineral content, and external treatments such as bathing, douches, and taking exercise in water (Thomas, 1997; and General References).

## HYPNOSIS AND HYPNOTHERAPY

Many 20th-century scientists have struggled to explain **hypnotherapy** and how it works. It is widely considered to be a useful method of encouraging healing and altering behavioral states. From the study of hypnosis has come a host of other therapies, including **biofeedback**, **autogenic training**, and **relaxation and meditation**. Many people now use self-hypnosis techniques to manage stress, pain, anxiety, and conditions such as migraine, irritable bowel syndrome, obesity, and addictions.

“**Healing**” a patient who is in a state of trance is one of the oldest therapeutic arts. Ancient cultures all around the world have revered individuals deemed to be in contact with supernatural powers and apparently able to use such contacts to cure the sick and distressed while these people were in a state resembling sleep. The supposed connection with the supernatural powers lies behind many of the prejudices and fears about hypnosis — that it is a state that enables inner connections to be made — but it has begun to be universally accepted.

The American **Friedrich Anton Mesmer** (1734–1815), the father of **mesmerism**, in the 18th century tried to harness mental energy — known at the time as “**animal magnetism**” — to effect cures. His results were variable, but he developed a ritual around his treatment that genuinely hypnotized those who came to him for help. His “**mesmerizing**” methods received scientific attention throughout the 1800s. When the Scotsman **James Braid** saw a demonstration in 1841, he began to develop his own theories and techniques. He demonstrated that a trance, for which he coined the term “**hypnosis**,” could be induced very simply, and that hypnotized subjects could not be made to act against their will. Hypnosis began to be used particularly for anesthesia during surgery (Thomas, 1997; and General References).

## IRIDOLOGY

**Iridology** was developed in the 19th century by the Hungarian **Ignatiz von Peckzely**, who as a boy noticed changes in the eye of an owl as it recovered from a broken leg. He published his theories in 1981 and, soon after, a Swedish doctor, **Nils Liliquist**, added his own observations.

But iridology did not become widely popular until **Bernard Jensen** pioneered its use in the U.S. In 1950, he published a chart that showed the location of every gland and organ reflected in each eye. According to iridologists, the iris of the eye represents a kind of map of the human glands, organs, and systems of the whole human body. Problems show up on the iris as spots, flecks, white or dark streaks, and so on. Texture and color indicate the person's general state of health. Some iridologists claim they can find tendencies toward inherited disease and possible future problems, and some even address emotional and spiritual health problems this way. Common conditions that iridologists claim to be able to diagnose include arthritis, heart disease, skin problems, and allergies (Thomas, 1997; and General References).

## JAPANESE MEDICINE

Chinese medicine was introduced to the imperial court of Japan in the 5th century A.D. by Korean physicians. Monks and traveling physicians from Korea and China introduced Chinese ideas more generally during the 5th and 6th centuries. Medical works on **acupuncture** and **moxibustion**, with detailed diagrams, were made known in Japan by the Chinese doctor **Zhi Cong** around 560 A.D., and from the early 7th century Chinese medicine began to be adopted systematically under the influence of two Buddhist monks who had spent many years in China. The Japanese adaptation of Chinese medicine is known as **kanpo**, and the main foundations of its present practice date back to the 16th and 17th centuries (Thomas, 1997; and General References).

## LIGHT THERAPY

Insufficient natural light can lead to depression, tiredness, or overeating. In the winter, especially in colder countries, the level of indoor light produces only about a tenth of the illumination of a full day of natural light. A form of “**winter blues**” that can result from this is known as **seasonal affective disorder** (SAD). It affects around 1% of the population (more women than men) but can be successfully treated with special “**full spectrum light units**” fitted in the home or office (Thomas, 1997; and General References).

## MASSAGE THERAPY

Massage is one of the oldest forms of remedial therapy which was probably first practiced in a structured way in China and Mesopotamia more than 5000 years ago. The art of massage was already well known to the physicians of ancient Greece when **Hippocrates**, the “father of medicine,” wrote in the 5th century B.C. that “**the way to health is a scented bath and an oiled massage every day.**”

## SHIATSU

Shiatsu is an ancient form of pressure-point massage, which has been practiced for centuries in Japan. It is based on the principle of applying pressure to key acupuncture points with the purpose of promoting the smooth flow of energy around the body.

## THERAPEUTIC MASSAGE

This comforting form of massage consists mostly of soothing strokes and rubbing, and is now in wide use in both conventional and unconventional medicine for the relief of pain or physical discomfort. In recent years, it has been shown to promote recovery after a heart attack and to ease the suffering of patients with some types of cancer.

## REFLEXOLOGY

This is a specialized massage for the hands and feet; it is used for both diagnosing and correcting imbalances in the body.

## SPORTS MASSAGE

This form of therapy features deep tissue massage that aims to ease stiff joints, relax tense muscles, and restore suppleness.

## BABY MASSAGE

By no means solely used on babies, baby massage relies on especially gentle strokes for promoting general health and happiness.

## BIODYNAMIC MASSAGE

This therapy combines massage with elements of physical exercise and psychological development (Thomas, 1997; and General References).

## MOXIBUSTION

Moxibustion is the application of heat to specific points on the body to treat diseases and restore the smooth **flow of chi in the meridians**. Generally, the heat is obtained by burning dried **mugwort leaves** (*Artemisia vulgaris*, known as **moxa**) either directly or indirectly on the skin. Sometimes a handful of moxa is lit in a specially designed box that is placed on the back in order to warm a larger area such as the kidneys. Moxa may also be placed on a slice of ginger or garlic, or on salt for more specific effects. **Ginger** helps promote circulation, and **garlic** has a strong antiseptic effect. Moxa is widely used for conditions such as stiff neck, cold, weak back, frozen shoulder, and fatigue and has an invigorating and warming effect (Thomas, 1997; and General References).

## MYOTHERAPY

**Janet Travell** devised “**Trigger Point Injection Therapy**” (TPIT) during the 1940s, after she published her study of muscular pain caused by trigger points. Throughout life — due to the exigencies of birth, active childhood, and the traumas, diseases, and occupational stresses of adulthood — our muscles tend to accumulate tender, irritable spots (**trigger points**). The ancient Chinese were aware of them 3000 years ago, but Western physicians devised a successful therapy to relieve trigger points only in the 20th century. In **myotherapy** a patient rests on a table; then, sustained and firm pressure is applied for about 7 sec at a time to the highly irritable spots in abnormally taut bands of muscle. Once the trigger points have been relieved and the muscles released, the client is encouraged to undertake some passive stretching exercises to retain the flexibility created during the course of the lesson (Thomas, 1997; and General References).

## NATIVE AMERICAN HERBAL MEDICINE

For modern Native Americans who live on reservations, the use of herbs and other traditional methods of healing remains vitally important and is still preferred to conventional medicine. The **Cherokee** of the Southeast recognized more than 100 types of medicinal herb. Some were used because they resembled the causative agent of the disease or because they looked like the part of the body affected. Herbs were gathered after ritual prayers and promises not to take more than was

needed. **Sage** (*Salvia officinalis*) is a sacred herb for many Native Americans (Thomas, 1997; and General References).

### NATUROPATHY (*MEDICATRIX NATURAE*)

Naturopathy is an umbrella term used in most Western countries to cover a range of therapies coming under the heading of “**natural medicine**.” Originally coined by the German pioneer **Benedict Lust**, naturopathy means, literally, “**natural treatment**,” and today its practitioners are generally those trained at specialist colleges in a range of skills that include acupuncture, herbalism, homeopathy, osteopathy, hydrotherapy, massage, nutrition, and diet (Thomas, 1997; and General References).

### OSTEOPATHY

Osteopathy was devised in 1874 by **Andrew Taylor Still** (1828–1917). His philosophy was that “**structure governs function**,” a belief that remains one of the basic principles of modern osteopathy. He claimed that tension in muscles and misaligned bones places unnecessary strain on the body as a whole. The initial strain can be caused by any number of factors, such as physical injury, or habitual poor posture, or by destructive emotions such as anxiety and fear. Adjusting the framework of the body would relieve that strain and enable all the systems to run smoothly so that the body would heal itself. Osteopathy is a manipulative therapy that works the body’s structures (the skeleton, muscles, ligaments, and connective tissue) to relieve pain, improve mobility, and restore all-round health (Thomas, 1997; and General References).

### PERSIAN MEDICINE

Traditional Persian, Arabic, or Islamic medicine became known in India, where it is widely practiced, as **Unani-Tibb**. “**Tibb**” is a Persian word meaning “medicine,” and “**Unani**” is thought to be derived from “**Ionian**” (meaning Greek) — acknowledging the influence of the early Greek healing traditions on this system of medicine. The system dates to the 7th century, when the Arab-Islamic world adopted the traditions of Europe as it expanded into areas that had been part of the Greco-Roman empires. Medical practice and theory were then dominated by the works of the Greek physician **Galen** (130–200 A.D.), who studied anatomy and made use of numerous drugs. The Muslims who invaded India in the 11th century brought their medicine with them, and the system is prominent today in India and its surrounding countries, particularly among Muslims. Most of the principles are derived from the work of the 10th-century Persian physician **Ibn Sina**, known in the West as **Avicenna**, who was a follower of Galen and considered the physical, emotional, and spiritual aspects of health and consequently developed a system of botanical medicine and dietetics for health.

**Unani-Tibb** has been influenced by **Ayurvedic medicine**, and has in turn influenced it. It is a holistic system that treats the imbalances that lead to disease and encourages the patient to adopt a balanced way of life. It incorporates the following concepts:

- **Four elements:** earth and water (heavy) and fire and air (light)
- **Nine temperatures:** one equable (balanced) and eight nonequable and relating to hot, cold, wet, and dry
- **Four humors:** as in ancient Greek medicine — blood, phlegm, yellow bile, and black bile — semigaseous vapors that maintain body fluids and balance digestion (Thomas, 1997; and General References).

## POLARITY THERAPY

Polarity therapy is based on the concept of the energy flow between the five energy centers or **chakras** in the body. Polarity therapy was developed over the course of 50 years by **Randolph Stone** (1890–1983), an Austrian-born naturopath, chiropractor, and osteopath, who also took an interest in the theories and practice of Eastern medicine and in spirituality. Polarity therapy is a holistic system of healing, based on Stone's belief that **humans are predominantly spiritual beings** whose health and happiness depend on the free flow of energy within their bodies (Thomas, 1997; and General References).

## PSYCHIC HEALING

Spiritual or psychic healing is believed to transfer healing energy by the laying of hands. Christians say it works through God or "**the Christ energy**," and spiritualists claim that the spirits of physicians heal through them. Some healers say they are helped by **angels**. Many describe themselves as channeling "cosmic" or "**universal energy**," "light," or "**bioenergy**." People may experience this energy as a hot or cool current, relieving pain and promoting well-being and relaxation. Some healers touch their clients; others work only in the energy field. Some combine healing with massage; others use crystals, color, and sound. Instant "**miracle**" cures are rare, but most people receive some benefit: from the relief of stress, depression, and pain, to the alleviation of chronic conditions. Treatment may include examining underlying emotional problems.

**Therapeutic Touch**, or TT, is a method of hands-on healing that has been taught to thousands of nurses and health-care professionals in the U.S. and 38 other countries. It was developed in the 1970s by an American nursing professor, **Dolores Krieger**, after seeing the work of Hungarian healer **Oscar Estabany**, and studying with healer **Dora Kuntz**. It became popular in the U.S. as a way of circumventing the strict laws against **psychic healing** imposed in many states. Tests have shown that nurses trained in TT effect considerable improvements in the physical and emotional states of their patients (Thomas, 1997; and General References).

## PSYCHOLOGICAL THERAPIES

Physical and mental health go hand in hand, and the many modern forms of **psychological therapy**, or "**psychotherapies**," aim to stimulate and support this process. The complex relationship between the mind and body has now been acknowledged, and there is strong evidence that many illnesses are caused and exacerbated by psychological factors. All complementary therapies promote the idea of the body as a whole, and promote the idea of treating it "holistically." Psychological influences, such as stress, worry, depression, and anxiety, have an enormous impact on health and are implicated in a number of conditions, including migraine, eczema, asthma, digestive disorders, headaches, and vision problems. Psychological therapies aim to address the areas that Western medicine has yet to reach successfully — the mind and the sense of well-being necessary to good health (Thomas, 1997; and General References).

## ANALYTICAL THERAPY

Instituted at the end of the 19th century and now comprising many variations (including **psycho-dynamic**), analytical theory regards a person's mind-set as the outcome of conflict between internal forces, and seeks answers from the unconscious. It aims to uncover and analyze the effects of **early experience** on present difficulties and to look at ways of working to resolve early blocks (Thomas, 1997; and General References).

## BEHAVIORAL THERAPY

Introduced at the beginning of the 20th century and based on learning theories, **behavioral psychology** aims to predict and control behavior in a scientific way. **Cognitive therapy**, which developed in the 1960s, is concerned with perception and belief systems: changing the way we view things can change their outcome (Thomas, 1997; and General References).

## HUMANISTIC THERAPY

This optimistic view emphasizes the **essential goodness of humans** and the belief that we all have choices. To realize our full potential we need to “get in touch with” our inner selves and true feelings, and be able to express them freely. The attitude of the therapist in conveying understanding from a position of equality is critical (Thomas, 1997; and General References).

## INTEGRATIVE THERAPY

Most therapists who work in this way have a humanistic orientation but also use elements of other therapeutic disciplines. Its ruling principle is the integration of “**mind, body, and soul**” to create a whole and aware person (Thomas, 1997; and General References).

## MEDITATION THERAPY

Meditation is a way of contacting the inner energy that powers the natural processes of healing and self-realization. Many cultures preserve some form of ritualistic technique — as seen in one or two cultures dating back thousands of years — that promotes change from the normal levels of perception and that may result in feelings of well-being. This is probably why meditation in one form or another is central to the practice of so many of the world’s religions. It has been found that meditating causes changes in heart rate and respiration, helping to reduce stress. As the process of thinking slows and the level of tension in the body drops accordingly, feelings of calm, detachment, peace, and sometimes joy begin to fill the mind and spread through the body. Meditation promotes a state of deep relaxation, as well as mental alertness and openness (Thomas, 1997; and General References).

## SOUND THERAPY

Sound therapy is a very ancient method of healing. **Tibetan monks**, for example, have used a method of “**overtone chanting**” for thousands of years to treat illness. The theory is that because everything in the universe is in a constant state of vibration, including the human body, even the smallest change in frequency can affect the internal organs. Modern sound therapists consider there is a natural resonance or “**note**” that is right for each part of the human body, and for each individual. So, by directing specific sound waves to specific areas, they can affect the frequency at which that part is vibrating and thereby restore it to balance and therefore health (Thomas, 1997; and General References).

## REFLEXOLOGY (REFLEX ZONE THERAPY)

This therapy has its roots in the practices of the healers of ancient Egypt, Greece, and possibly also of ancient China. Among the pictographs dating from around 2300 B.C. in the tomb of the Egyptian physician **Ankhmahar at Saqqara**, for example, is one that portrays two attendants working on the hands and feet of two “patients.” Reflexologists also claim that manipulation of the feet for healing purposes was common among the native peoples of both North and South America. Reflexology may be described as a specialized form of massage of the feet and — less commonly — of



the hands. It is performed to detect and correct “imbalances” in the body that may be causing ill health, but is much more than simple massage (Thomas, 1997; and General References).

### REIKI THERAPY

Treatment by a reiki practitioner is intended to promote physical, emotional, and spiritual well-being. Reiki, the Japanese word for “**universal life energy**,” is a form of healing based on tapping into the unseen flow of energy that permeates all living things. It is believed that reiki originally evolved as a branch of **Tibetan Buddhism** and that knowledge of its power and how to use it was transmitted from master to disciple. At some point in the intervening centuries, the secrets of reiki were lost. They were rediscovered in the late 19th century by a Japanese minister, **Mikao Usui**. He spent 14 years seeking the ability to heal, which he believed could be discovered through studying **Buddhism**, learning Chinese and Sanskrit to help his research. It is claimed that eventually he found the knowledge he sought in an **Indian sutra**, or sacred text. Then, after a 3-week meditation on a mountain top, he had a vision of four symbols that could be used to enable healing energy to be passed to others. The ability to channel the healing power was achieved by attunement to each of these symbols. Before he died in the 1930s, **Usui** initiated 16 others into the secret of reiki, teaching them the master attunement (Thomas, 1997; and General References).

### RELAXATION THERAPIES

Relaxation allows the mind–body complex to proceed with its own healing work, restoring internal harmony and creating afresh the conditions for optimal functioning. It is also a very pleasurable experience. In the therapeutic sense, **relaxation is the release of mental and physical tension**. Simple as that may seem, not many people can release both mental and physical tension at the same time without help or training. So a wide range of techniques have been developed to promote a profound level of relaxation and enhanced psychological integration. Some go back thousands of years; others are continually being created. All utilize the effect the mind can have on the body.

**Flotation therapy** is used more often in **psychotherapy** to lower stress response levels, thus replacing anxiety with a strong sense of well-being, enhancing creativity and awareness, improving problem-solving, and accelerating learning processes (Thomas, 1997; and General References).

### ROLFING MEDICINE

Rolfing is named after its founder, **Ida Rolf** (1896–1979), an American biochemist whose therapy was intended to integrate manipulative forms of treatment with **bioenergetics** (the study of energy in living systems). Rolf recognized that when we are well aligned, gravity can flow through us, allowing us to move easily. When the body is balanced, the mind and nervous system, and all the organs and tissues to which they relate, function more efficiently and our innate healing system can work at its optimum. A full course of rolfing involves ten treatments, lasting about an hour each. Each session features a different part of the body, but is meant to fuse that part with those that have been treated earlier, ultimately leading to complete integration (Thomas, 1997; and General References).

### SHAMANISTIC MEDICINE

**Shamanism** has been found in most tribal cultures in every continent, from Alaska to Borneo. **Witch doctors** or **sangomas** (Africa), **medicine men** (North America), **yogis** or **holy men** (India), and **witches** and **wizards** (Europe) are all shamans who follow more or less the same practices everywhere. The techniques used by a shaman to bring about a state of altered consciousness include drumming, rattling, chanting, dancing, and the taking of natural **hallucinogenic drugs**.

Drums are a feature of the northern shamanic traditions, whereas rattles are significant in South America, as are hallucinogenic plants. In Peru, shamans are known as **vegetalistas** because of their skilled use of **dangerous plants** (Thomas, 1997; and General References).

## T'AI CHI CHUAN MEDICINE

**T'ai chi chuan**, also known as **t'ai chi**, is an ancient Chinese system designed to develop **chi** within the body. **Lao Tzu** is the founder of **Taoism**. Both **t'ai chi** and **chi kung** are based on the **Taoist** principles of perfect harmony between the **yin** and **yang** energies of the body and the smooth flow of the life force known as **chi**. It can be used to rejuvenate, to heal and prevent illness and injuries, and also to lead to spiritual enlightenment (Thomas, 1997; and General References).

## THERAPEUTIC DIETS

### EXCLUSION DIET

Exclusion or elimination diets are used to detect foods suspected of causing food allergies or intolerance, or triggering attacks of illness, such as migraine. Suspected foods are avoided for about 2 weeks and then reintroduced one at a time.

### VEGETARIAN DIET

Vegetarians eat no meat, fish, or poultry, but must eat eggs and dairy products (this is called **lacto-ovo-vegetarianism**). A vegetarian diet followed correctly over a long period can reduce risk of heart disease, cancer, and other major illnesses.

### VEGAN DIET

Vegans eat no animal products. They need to take **vitamin B<sub>12</sub>** from fortified foods or supplements. A **vegan diet** provides most of the benefits of a vegetarian diet when implemented correctly.

### FOOD COMBINING DIET

Food combining (the "**Hay diet**") advises against combining starch and sugar with protein and acid fruits. At least 4 h should separate starch and protein meals. Protein, starch, and fats are eaten in small quantities, and all refined and processed foods are prohibited. This diet is said to improve arthritis and digestive problems.

### ANTI-CANDIDA DIET

Anti-*Candida* diets for the **treatment of thrush** avoid yeasts and mold — as in malted cereals, cheeses, fungi — sugar and sugary foods, and peanuts.

### LIVER DIET

In a liver diet the following foods are avoided because some alternative therapists believe they are difficult for the liver to process: meat, poultry, eggs, sugars and sugary foods, dairy produce, nuts, coffee, tea, alcohol, chocolate, and fried food.

### LOW BLOOD SUGAR DIET

A low blood sugar diet is based on three meals a day, plus small two-hourly snacks of nuts or seeds, milk, oatcakes, or whole wheat toast. Sugar and sugary foods must be avoided.

## MACROBIOTIC DIET

A macrobiotic diet classifies all foods as either yin or yang. The aim is to eat a perfect balance, taking into account the individual's different **yin/yang** needs. If the equilibrium is upset, ill health results. Food is prepared, cut, and cooked in particular ways to preserve **yin/yang characteristics**. To create balance, people living in a yang environment (hot or dry) need to become more yin (cold and wet), and vice versa. **Yin foods** grow in hot dry climates (such as the Middle East), have stronger smells, are hotter, more aromatic, and contain more water, and are therefore softer and juicier. **Yang foods** grow in cold, wet climates (such as Britain) and are drier, shorter, harder, saltier, and more sour (Thomas, 1997; and General References).

## TIBETAN MEDICINE

Tibetan medicine is practiced throughout Tibet, India, Ladakh, Nepal, and Bhutan and is now becoming more widely available through Tibetan physicians living in Western countries. Tibetan medicine is based on a unique synthesis of Indian and Chinese traditional medicine and Tibetan Buddhism, with elements of Arabic medicine. As with the Ayurvedic and Chinese systems, it is holistic and takes into account such factors as diet, lifestyle, environment, weather, attitudes, and emotions as well as symptoms of disease. The theory of meridians or energy channels is particularly highly developed. There is also a strong folk or religious tradition relating to healing, which runs parallel to the more orthodox medical tradition. Tibetan diagnosis is based on pulse-taking, urine analysis (which is exceptionally highly developed and which may stem from medieval European medicine, as introduced by the Persians), tongue diagnosis, and observations. Treatments, which aim to restore the balance of the humors, include herbal medicine, accessory therapies (massage, moxibustion, acupuncture), dietary aids, behavioral advice, religious rituals, and purification techniques (Thomas, 1997; and General References).

## TRANSCENDENTAL MEDITATION (TM)

In the late 1950s, an Indian monk named **Maharishi Mahesh Yogi** began teaching a new form of meditation that could be easily practiced by busy, modern people around the world. He called it transcendental meditation and it was based on the concept that a meditation using **mantras** of short words or phrases, repeated in the mind, could help the user subdue many thought processes and reach a deep level of consciousness. Mantras are selected on the basis of the learner's temperament and occupation. The spirit behind TM is the **Vedanta system of philosophy** that forms the basis of most modern schools of **Hinduism**. The simple technique produces a state of "**restful alertness**" that, it is considered, transcends thinking to reach the source of thought — the mind's own reservoir of energy and creative intelligence. Through this, people can find great relaxation, inner peace, enhanced vitality, and creativity. TM is ordinarily applied for 15 to 20 min twice daily.

Much of the research into the psychological and physiological effects of meditation has been carried out in relation to TM. It shows that the level of rest achieved is deeper than sleep. Another major finding is that meditation produces all the body's responses opposite to the flight-or-fight response characteristic of stress. During meditation, breathing slows, the heartbeat becomes shallower, the muscles relax, blood pressure normalizes, and there are compositional changes in blood and skin that indicate a reduction in tension.

**Siddha meditation** is another practice whose origins are in India. It utilizes both mantra and breath control to still the mind, and thus to allow a spontaneous shift in consciousness. The mantra is recited aloud and serves two purposes. Regarded as pure sound, it causes the body and mind to vibrate at a particular frequency that induces the meditative state: the energy resonates in the unconscious, and its words provide a focus to hold the mind and stop it from randomizing its energy through scattered thoughts and images (Thomas, 1997; and General References).

## TRANSPERSONAL THERAPIES

This is a spiritually oriented form of treatment that combines therapy for the individual with a concern for the whole of creation. The transpersonal dimension emerges in the drive of the individual to connect with **cosmic forces**, and in the impulse to discover an awareness of the soul. In operation, transpersonal therapies involve a wide range of functional techniques. The emphasis is on practical activities rather than verbal interpretations, and so, for example, imagery is used to explore, transform, and expand on ideas. Transpersonal therapies are holistic, aimed at balancing and fulfilling the mind, body, and soul. For this reason, a wide range of conditions may respond to therapy, particularly those that are affected by negative feelings or actions (Thomas, 1997; and General References).

## VISUALIZATION THERAPY

Visualization is the forming of meaningful images in the mind; it is usually most effective when resting comfortably with the eyes closed. This natural ability can achieve therapeutic effects in several ways, especially when undertaken in conjunction with hypnosis.

- **Relaxation:** Imaging a pleasant, relaxing place — a sunny beach, perhaps — releases body tensions.
- **Life changes:** To visualize yourself competently dealing with your problems, being successful, challenging other people, or playing a musical instrument well can overcome blocks to being assertive and achieving what you want.
- **Accessing the past:** Images of childhood may afford access to repressed memories and emotions.
- **Rewriting the past:** An event that at the time was traumatic and damaging can be reviewed, this time with a positive outcome.
- **Spiritual growth:** Once facility in visualizing is achieved, images may occur spontaneously, increasing insight into one's own condition, into the way the world works, and into higher levels of consciousness (Thomas, 1997; and General References).

## YOGA

Yoga aims to improve overall health and well-being, and through that, a number of conditions may be resolved. The full **lotus position (padmasana)** assumed by a **yogi** is excellent for meditation. It lengthens the spine, allowing one to control breathing. The mind is better able to focus and concentrate on problems or empty itself of worry. Yoga encourages relaxation. By normalizing high blood pressure, helping stave off anxiety, or dealing with stress, yoga is as effective today as it was thousands of years ago (Thomas, 1997; and General References).



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# 7 Herbal Therapeutics Then and Now

## INTRODUCTION

**Herbalists** and traditional physicians use varying terminology because they approach diseases and the medicines used to treat them differently. This is also the reason why most herbal medicine books are of little use to a physician confronted with a desperately ill patient. Many of the drugs used in modern medicine are extracted from plants. But herbalists use whole plants, whereas traditional physicians use purified ingredients derived from plants. Traditional physicians and scientists generally believe that if a plant has any medicinal value at all, it is because different components of the plant act synergistically (Cupp, 2000; and General References).

Some herbal products are very toxic. **Comfrey** may be an effective treatment for bruises and sprains, but it contains **pyrrolizidine alkaloids**, which can cause severe liver damage.

Many ancient herbs have found new uses. A few examples are listed here.

## AGNUS CASTUS

Agnus castus is used for menstrual problems resulting from corpus luteum deficiency, including premenstrual symptoms and spasmodic dysmenorrhea, for certain menopausal conditions, and for insufficient lactation.

## AGRIMONY

Agrimony is believed to possess mild astringent and diuretic properties. It is used to treat diarrhea in children, mucous colitis, grumbling appendicitis, urinary incontinence, cystitis, and as a gargle for acute sore throat and chronic nasopharyngeal catarrh.

## ALFALFA

Alfalfa is a source of vitamins A, C, E, and K, and of the minerals calcium, potassium, phosphorus, and iron. It has been used for avitaminosis A, C, E, or K, hypoprothrombinemic purpura, and debility of convalescence.

## ALOE

The use of aloe as a laxative is mentioned in Greek literature before the first century. The Greek physician **Dioscorides** wrote of its use in treating wounds, chapping, hair loss, genital ulcers, hemorrhoids, boils, mouth irritation, and inflammation. In the 7th century, aloe was used in the East for eczema and sinusitis. Today, aloe is often prescribed to heal wounds, burns, skin ulcers, frostbite, and dry skin. It is an ingredient in teas for dieters because of its laxative effect and is found in **body-cleansing** products as well (see Chapter 12).

### **ALOE VERA**

Traditionally, aloe vera is used in ointments and creams to assist the healing of wounds, burns, eczema, and psoriasis.

### **ANGELICA**

Angelica is believed to possess antispasmodic, diaphoretic, expectorant, bitter aromatic, carminative, diuretic, and local anti-inflammatory properties. It is used for respiratory catarrh, psychogenic asthma, flatulent dyspepsia, anorexia nervosa, rheumatic diseases, and peripheral vascular disease. Specifically, it has been applied as a compress for pleurisy and bronchitis, especially for bronchitis associated with vascular deficiency.

### **ANISEED**

Aniseed is stated to possess expectorant, antispasmodic, carminative, and parasiticidal properties. It is traditionally used for bronchial catarrh, pertussis, spasmodic cough, flatulent colic, topically for pediculosis and scabies, and specifically for bronchitis, tracheitis with persistent cough, and as an aromatic adjuvant to prevent colic from cathartics. It has been used as an estrogenic agent and is reputed to increase milk secretion, promote menstruation, facilitate birth, alleviate symptoms of the male climacteric, and increase libido.

### **APRICOT**

Traditionally, apricot oil is incorporated in cosmetic and perfume products such as soaps and creams.

### **ARNICA**

Arnica is believed to have topical counterirritant properties. It is used for unbroken chilblains (swelling of the hands and feet from exposure to damp cold), alopecia neurotica, and specifically for sprains and bruises. It is mainly used in homeopathic preparations and, to a lesser extent, in herbal products.

### **ARTICHOKE**

Artichoke is stated to have diuretic, choloretic, hypocholesterolemic, hypolipidemic, and hepatostimulating properties.

### **ASAFOETIDA**

Asafoetida possesses carminative, antispasmodic, and expectorant properties. It has been used for chronic bronchitis, pertussis, laryngismus stridulus, hysteria, and specifically for intestinal flatulent colic.

### **AVENS**

Avens is stated to possess antidiarrheal, antihemorrhagic, and febrifugal properties. It is used for diarrhea, catarrhal colitis, passive uterine hemorrhage, intermittent fevers, and particularly for ulcerative colitis.

### **BAYBERRY**

Bayberry has antipyretic, circulatory stimulant, emetic, and mild diaphoretic properties. It is used to treat diarrhea, colds, and, specifically, mucous colitis. An infusion can be used as a gargle for sore throat and as a douche for leucorrhea. Powdered root bark may be applied topically for the management of indolent ulcers.

### **BLACK COHOSH**

Black cohosh is said to possess antirheumatic, antitussive, sedative, and emmenagogue properties. It is used for intercostals myalgia, sciatica, whooping cough, chorea, tinnitus, dysmenorrhea, uterine colic, and specifically for muscular rheumatism and rheumatoid arthritis.

### **BLOODROOT**

Bloodroot is believed to act as an expectorant, spasmolytic, emetic, cathartic, antiseptic, cardioactive agent, topical irritant, and escharotic (scab-producing). Traditionally, it is taken for bronchitis (subacute or chronic), asthma, croup, laryngitis, pharyngitis, deficient capillary circulation, nasal polyps (as a snuff), and specifically for asthma and bronchitis with feeble peripheral circulation.

### **BLUE COHOSH**

Blue cohosh is said to possess antispasmodic, emmenagogue, uterine tonic, and antirheumatic properties. Traditionally, it has been used for amenorrhea, threatened miscarriage, false labor pains, dysmenorrhea, rheumatic pains, and specifically for conditions associated with uterine atony.

### **BLUE FLAG**

Blue flag is said to have cholagogue, laxative, diuretic, dermatological, anti-inflammatory, and antiemetic properties. It is used for skin diseases, biliousness with constipation and liver dysfunction, and cutaneous eruptions.

### **BOGBEAN**

Bogbean has bitter and diuretic characteristics. It has been used for treating rheumatism, rheumatoid arthritis, and especially muscular rheumatism associated with general asthenia.

### **BOLDO**

Boldo is stated to possess cholagogue, liver-stimulant, sedative, diuretic, mild urinary demulcent, and antiseptic properties. It has been used for gallstones, pain in the liver or gallbladder, cystitis, rheumatism, and specifically for cholethiasis with pain.

### **BONESET**

Boneset possesses diaphoretic and aperient properties. Traditionally, it has been used for influenza, acute bronchitis, nasopharyngeal catarrh, and specifically for influenza with deep aching, and congestion of the respiratory mucosa.



## BORAGE

As early as the 2nd century A.D., borage mixed with honey was used to treat sore throat for which it is still recommended by contemporary herbalists. An infusion of the leaves and stems was once used as a diuretic, diaphoretic, and emollient. Other traditional uses include relief of symptoms of rheumatism, colds, and bronchitis. It is also believed to increase breast milk production. A poultice of fresh leaves has been used to treat inflammation.

Borage is stated to possess diaphoretic, expectorant, tonic, anti-inflammatory, and galactagogue properties. Traditionally, it has been used to treat many ailments including fever, coughs, and depression, and is also reputed to act as a restorative agent on the adrenal cortex. Borage oil (**starflower oil**) is used as an alternative to evening primrose oil for **gamolenic acid** extraction.

## BROOM

Broom has cardioactive, diuretic, peripheral vasoconstrictor, and antihemorrhagic properties. It has been used for cardiac dropsy, myocardial weakness, tachycardia, profuse menstruation, and specifically for functional palpitation with lowered blood pressure. Broom is also reported to possess emetic and cathartic properties.

## BUCHU

Buchu is believed to possess urinary antiseptic and diuretic properties. It has been used for cystitis urethritis, prostatitis, and specifically to treat acute catarrhal cystitis.

## BURDOCK

Burdock is considered to have diuretic and orexigenic properties. It is used to treat cutaneous eruptions, rheumatism, cystitis, gout, anorexia nervosa, and especially eczema and psoriasis.

## BURNET

Burnet is stated to possess astringent, antihemorrhagic, styptic, and antihemorrhoidal properties. It has been used for ulcerative colitis, metorrhagia, and specifically for acute diarrhea.

## CALAMUS

Calamus has been used for centuries to treat gastrointestinal distress, including colic in children, and as a sedative. A rhizome infusion is used to treat fevers and dyspepsia, and chewing the rhizome is recommended to clear the voice, relieve dyspepsia, aid digestion, and remove tobacco odor from the breath. The powdered rhizome is used as a cooking spice, as is **calamus oil**, which is responsible for the plant's odor and taste. In the U.S., calamus was once used to flavor tooth powders, beer, bitters, and various tonics, although it is no longer used today.

Calamus acts as a carminative, spasmolytic, and diaphoretic. Traditionally, it has been prescribed for acute and chronic dyspepsia, gastritis and gastric ulcer, intestinal colic, and anorexia.

## CALENDULA

Calendula is stated to possess antispasmodic, mild diaphoretic, anti-inflammatory, antihemorrhagic, emmenagogue, vulnerary, styptic, and antiseptic properties. Traditionally, it has been used to treat gastric and duodenal ulcers, amenorrhea, dysmenorrhea and epistaxis; crural ulcers, varicose veins,

hemorrhoids, anal eczema, proctitis, lymphadenoma, and inflamed cutaneous lesions (topically); and conjunctivitis (as an eye lotion).

### CAPSICUM

Capsicum has stimulant, antispasmodic, carminative, diaphoretic, counterirritant, antiseptic, and rubefacient properties. Traditionally, it has been used for colic, flatulent dyspepsia without inflammation, chronic laryngitis (as a gargle), insufficiency of peripheral circulation, and externally for neuralgia, including rheumatic pains and unbroken chilblains.

### CASCARA

Cascara is believed to have mild purgative properties and has been used to ease constipation.

### CASCARA SAGRADA

Cascara sagrada was used as a laxative in the past and continues to be used for the same purpose today.

### CASSIA

Cassia is stated to possess carminative, antispasmodic, antiemetic, antidiarrheal, and antimicrobial properties. It has been used to treat flatulent dyspepsia, flatulent colic, diarrhea, the common cold, and especially colic or dyspepsia with flatulent distension and nausea. Cassia bark is also documented to possess astringent properties, and the oil has carminative and antiseptic characteristics.

### CAT'S CLAW

Cat's claw has long been used in South America as an anti-inflammatory, antirheumatic, and contraceptive agent. It is also traditionally used to treat gastrointestinal ulcers, tumors, gonorrhea, dysentery, various skin problems, cancers of the female genitourinary tract, and intestinal disorders. Native South Americans use cat's claw to **cleanse the kidneys** and treat bone pain. Some Europeans report that it is useful in the treatment of AIDS when used in combination with **zidovudine (AZT)**. The purported usefulness of cat's claw tea in the treatment of diverticulitis, hemorrhoids, peptic ulcer disease, colitis, parasites, and **leaky bowel syndrome** have fueled demand for the bark in the U.S.

### CELERY

Celery is stated to possess antirheumatic, sedative, mild diuretic, and urinary antiseptic properties. It has been used for arthritis, rheumatism, gout, urinary tract inflammation, and specifically for rheumatoid arthritis with mental depression.

### CENTAURY

Centaury is reputed to act as a bitter, an aromatic, and a stomachic. Traditionally, it has been used for anorexia and dyspepsia.

### CEREUS

Cereus is reputed to act as a cardiac stimulant and a partial substitute for **digitalis**, although there is no proof of its therapeutic value. It has been used in cases of **dropsy** and various cardiac afflictions.

## CHAMOMILE

Chamomile has been used medicinally since the time of ancient Rome for its purported sedative, antispasmodic, and antirheumatic effects. Today, it is used topically to treat a variety of inflammatory conditions involving the mouth, skin, respiratory tract (via inhalation), and gastrointestinal tract. It is also used internally as a gastrointestinal antispasmodic and an anti-inflammatory agent. Chamomile is believed to have sedative, hypnotic, analgesic, and immunostimulant effects.

### CHAMOMILE (GERMAN)

German chamomile is listed by the Council of Europe as a natural source of food flavoring (category N2). This category indicates that chamomile can be added to foodstuffs in small quantities, with the possible limitation of an active principle (as yet unspecified) in the final product. German chamomile is commonly used in herbal teas.

### CHAMOMILE (ROMAN)

Roman chamomile is stated to have carminative, antiemetic, antispasmodic, and sedative properties. It has been used for dyspepsia, nausea and vomiting, anorexia, vomiting during pregnancy, dysmenorrhea, and specifically for flatulent dyspepsia associated with mental stress.

## CHAPARRAL

Tea brewed from boiled leaves has been used to treat sexually transmitted diseases and intestinal cramps, and to stimulate urination. The leaves are soaked in water, producing an extract that is used as a bath for rheumatism and chickenpox. The dried powdered leaves may be used as a dusting powder for sores, and are mixed with **badger oil** to make an ointment used on burns to aid new skin formation. Today, chaparral is promoted as an anticancer agent.

Chaparral has been used in the treatment of arthritis, cancer, venereal disease, tuberculosis, bowel cramps, rheumatism, and colds.

## CINNAMON

Cinnamon is believed to have antispasmodic, carminative, orexigenic, antidiarrheal, antimicrobial, refrigerant, and anthelmintic properties. It is used for anorexia, intestinal colic, infantile diarrhea, common cold, influenza, and specifically for flatulent colic and dyspepsia with nausea. Cinnamon bark is also an astringent, and **cinnamon oil** is reported to possess carminative and antiseptic properties.

## CLIVERS

Clivers is believed to have diuretic and mild astringent properties. It is used to treat dysuria, lymphadenitis, psoriasis, and enlarged lymph nodes.

## CLOVE

Clove has been traditionally used as a carminative, antiemetic, toothache remedy, and counterirritant. **Clove oil** is believed to be a carminative, occasionally used in the treatment of flatulent colic, and is commonly used topically for symptomatic relief of toothache.

## COLA

Cola is believed to have central nervous system (CNS)-stimulant, thymoleptic, antidepressant, diuretic, cardioactive, and antidiarrheal properties. It is used to treat depressive states, melancholy, atony, exhaustion, dysentery, atonic diarrhea, anorexia, migraine, and particularly depressive states associated with general muscular weakness.

## COLTSFOOT

In addition to its usage in the treatment of respiratory ailments, coltsfoot is also used to treat diarrhea, purify the blood, stimulate metabolism, cause diuresis and swelling, and topically as a wound treatment. Today, products containing coltsfoot are promoted as antihistamines, decongestants, and expectorants.

Coltsfoot possesses expectorant, antitussive, demulcent, and anticatarrhal properties. It has been used for asthma, bronchitis, laryngitis, and pertussis.

## COMFREY

Comfrey has been used to treat respiratory problems (bronchitis, catarrh hemoptysis, pleurisy, whooping cough), gastrointestinal diseases (cholecystitis, colitis, dysentery, diarrhea, ulcers, hematemesis), metorrhagia, phlebitis, and tonsillitis. It is currently promoted for preventing kidney stones and for treating rheumatic and pulmonary disorders, and injuries such as burns and bruises.

Comfrey is stated to possess vulnerary, cell-proliferant, astringent, antihemorrhagic, and demulcent properties. It is used for colitis, gastric and duodenal ulcers, and can be applied topically for ulcers, wounds, and fractures.

## CORN SILK

Corn silk possesses diuretic and stone-reducing properties. It has been used for cystitis, urethritis, nocturnal enuresis, prostatitis, and specifically for acute or chronic inflammation of the urinary system.

## COUCHGRASS

Couchgrass is known for its diuretic properties. It has been used for cystitis, urethritis, prostatitis, benign prostatic hypertrophy, renal calculus, lithuria, and specifically for cystitis associated with irritation or inflammation of the urinary tract.

## COWSLIP

Cowslip has sedative, antispasmodic, hypnotic, mild diuretic, expectorant, and mild aperient properties. It is used to treat insomnia, nervous excitability, hysteria, and particularly anxiety states associated with restlessness and irritability.

## CRANBERRY

Cranberry has been used to prevent and treat urinary tract infections since the 19th century. Today, cranberry juice is widely used for the prevention, treatment, and symptomatic relief of urinary tract infections. Cranberry juice is also given to patients to help reduce urinary odors in incontinence. Another potential benefit of cranberry is a decrease in the rate of formation of **kidney stones**.

### DAMIANA

Damiana is believed to possess antidepressant, thymoleptic, mild purgative, stomachic, and aphrodisiac properties. It is used for depression, nervous dyspepsia, atonic constipation, coital inadequacy, and specifically for anxiety neurosis with a predominant sexual factor.

### DANDELION

Dandelion is stated to have diuretic, laxative, cholagogue, and antirheumatic properties. It has been used for cholecystitis, gallstones, jaundice, atonic dyspepsia with constipation, muscular rheumatism, oliguria, and particularly for cholecystitis and dyspepsia.

### DEVIL'S CLAW

Devil's claw is reputed to possess anti-inflammatory, antirheumatic, analgesic, sedative, and diuretic properties. It is used to treat arthritis, gout, myalgia, fibrositis, lumbago, pleurodynia, and especially rheumatic disease.

### DONG QUAI

Dong quai has been used in the treatment of dysmenorrhea, amenorrhea, metorrhagia, menopausal syndromes, anemia, abdominal pain, injuries, migraine headaches, and arthritis. It is believed to ensure healthy pregnancies and easy deliveries. In the U.S., dong quai is recommended primarily to alleviate problems associated with menstruation and menopause.

### DROSERA

Drosera is stated to possess antispasmodic, demulcent, and expectorant characteristics. It is used for treating bronchitis, asthma, pertussis, tracheitis, gastric ulceration, and specifically for asthma and chronic bronchitis with peptic ulceration or gastritis.

### ECHINACEA

Echinacea was originally utilized by Native Americans as a **blood purifier** and was used in the treatment of snake bites, infections, and malignancy. Today, echinacea is promoted primarily in oral dosage forms as an immune stimulant that helps increase resistance to colds, influenza, and other infections, although topical products for wounds and inflammatory skin conditions are also available.

Echinacea is believed to have antiseptic, antiviral, and peripheral vasodilator properties. Traditionally, it has been used for furunculosis, septicemia, nasopharyngeal catarrh, pyorrhea, tonsillitis, and specifically for boils, carbuncles, and abscesses. Scientists are currently researching its immunostimulant action.

### ELDER

Elder is known for its diaphoretic and anticatarrhal properties. Traditionally, it is used for influenza, colds, chronic nasal catarrh with deafness, and sinusitis. Elder is also believed to act as a diuretic, laxative, and local anti-inflammatory agent.

### ELECAMPANE

Elecampane is stated to possess expectorant, antitussive, diaphoretic, and bactericidal properties. Traditionally, it is used in the treatment of bronchial and tracheal catarrh, cough associated with pulmonary tuberculosis, and dry irritating cough in children. **Alantolactone** is used as an anthelmintic in the treatment of roundworm, threadworm, and whipworm infection.

### EUCALYPTUS

Eucalyptus leaves and oil are commonly used as an antiseptic, febrifuge, and expectorant.

### EUPHORBIA

Euphorbia is used to soothe respiratory disorders such as asthma, bronchitis, catarrh, and laryngeal spasm. It is also used for treating intestinal amebiasis.

### EVENING PRIMROSE

An infusion of the whole plant is reputed to have sedative and astringent properties, and it is generally used for asthmatic coughs, gastrointestinal disorders, whooping cough, and as a sedative pain killer. Externally, poultices are reputed to ease bruises and speed wound healing. Evening primrose oil (EPO) is licensed for the treatment of atopic eczema, and cyclical and noncyclical **mastalgia**. It is also used in the treatment of premenstrual syndrome, psoriasis, multiple sclerosis, hypercholesterolemia, rheumatoid arthritis, **Raynaud's phenomenon**, **Sjögren's syndrome**, **postviral fatigue syndrome**, asthma, and diabetic neuropathy.

### EYEBRIGHT

Eyebright possesses anticatarrhal, astringent, and anti-inflammatory properties. Traditionally, it has been used for nasal catarrh, sinusitis, and particularly for conjunctivitis when applied locally as an eye lotion.

### FALSE UNICORN

False unicorn is believed to act on the uterus. Traditionally, it is used for ovarian dysmenorrhea, leucorrhea, and specifically for amenorrhea. It is also reported to be useful in preventing vomiting during pregnancy and threatened miscarriage.

### FENUGREEK

Fenugreek has mucilaginous demulcent, laxative, nutritive, expectorant, and orexigenic properties, and is also used topically as an emollient and vulnerary. Traditionally, it has been used in the treatment of anorexia, dyspepsia, and gastritis, and topically for furunculosis, myalgia, lymphadenitis, gout, wounds, and leg ulcers.

### FEVERFEW

Feverfew is commonly used in the treatment of menstrual pain, asthma, arthritis, psoriasis, threatened miscarriage, toothache, opium abuse, vertigo, tinnitus, anemia, common cold, and gastrointes-

tinal disturbances. It is also used to aid in expulsion of the placenta and stillbirths, and in difficult labor. Feverfew planted around houses is known to act as an insect repellent and it is also a topical remedy for insect bites. Today, it is used in the treatment of arthritis and migraine headache.

Feverfew has traditionally been used in the treatment of migraine, tinnitus, vertigo, arthritis, fever, menstrual disorders, difficulty during labor, stomachache, toothache, and insect bites.

### **FIGWORT**

Figwort acts as a dermatological agent and a mild diuretic, and increases myocardial contraction. Traditionally, it is used for chronic skin disease, especially for eczema, psoriasis, and pruritus.

### **FRANGULA**

Frangula is believed to possess mild purgative properties and has been used traditionally for constipation.

### **FUCUS**

Fucus possesses antihypothyroid, antiobesic, and antirheumatic properties. Traditionally, it is used for lymphadenoid goiter, myxedema, obesity, arthritis, and rheumatism.

### **FUMITORY**

Fumitory has weak diuretic and laxative properties and acts as a cholagogue. Traditionally, it has been used to treat cutaneous eruptions, conjunctivitis (as an eye lotion), and chronic eczema.

### **GARLIC**

Over the centuries, garlic has been used to ward off vampires, demons, witches, and evil spirits; as an aphrodisiac to improve performance and desire; and as a cure-all for everything from athlete's foot and hemorrhoids to cancer. Today, garlic is recommended for lowering cholesterol and blood pressure, delaying atherosclerotic processes, preventing heart attack and stroke, improving circulation, and preventing cancer.

Garlic is known to possess diaphoretic, expectorant, antispasmodic, antiseptic, bacteriostatic, antiviral, hypotensive, and anthelmintic properties, and to promote leucocytosis. Traditionally, it has been used to treat chronic bronchitis, respiratory catarrh, recurrent colds, whooping cough, bronchitic asthma, and influenza.

### **GENTIAN**

Gentian is stated to possess bitter, gastric stimulant, sialagogue, and cholagogue properties. Traditionally, it is used for anorexia, atonic dyspepsia, gastrointestinal atony, and specifically for dyspepsia with anorexia.

### **GINGER**

The Chinese utilized ginger for stomachaches, diarrhea, nausea, cholera, bleeding, asthma, heart conditions, respiratory disorders, toothache, and rheumatic complaints. In China, the root and stem

are used to repel aphids and fungal spores. Today, ginger is promoted as relieving and preventing nausea caused by motion sickness and morning sickness.

Ginger has carminative, diaphoretic, and antispasmodic properties. Traditionally, it is used for colic, flatulent dyspepsia, and specifically for flatulent intestinal colic. Its role in the prevention of motion sickness is also being researched.

## GINKGO

The medicinal use of ginkgo leaves was recorded by the Chinese in *Chen Houng Pen T'sao* published in 2800 B.C., and a monograph exists in the modern Chinese pharmacopoeia. The leaves are considered to be beneficial for the heart and lungs; inhaling a decoction of leaves is used for treating asthma; and boiled leaves are used against chilblains. Standardized concentrated extracts of *G. biloba* leaves are marketed in several European countries (e.g., as **Tanakan**<sup>TM</sup> in France, and as **Tebonin**<sup>TM</sup> and **Rokan**<sup>TM</sup> in Germany). The seed is used as an antitussive and expectorant in Japan and China.

### GINKGO BILOBA

Traditional Chinese physicians used ginkgo leaves to treat **asthma** and **chilblains**. Today, *G. biloba* is used to improve both blood flow to the brain and peripheral circulation (see Chapter 36).

## GINSENG (ELEUTHEROCOCCUS)

*Eleutherococcus ginseng* is not used traditionally in the U.K., although it has been used for many years in the former Soviet Union. Similar to *Panax ginseng*, *E. ginseng* is claimed to be an adaptogen in that it increases the body's resistance to stress increases general vitality.

### GINSENG (PANAX)

Ginseng has been used in Chinese medicine for thousands of years as a stimulant, tonic, diuretic, and stomachic. Ginseng use is generally divided into two categories:

**Short-term:** to improve stamina, concentration, healing process, stress resistance, vigilance, and work efficiency in healthy individuals

**Long-term:** to improve well-being in debilitated and degenerative conditions, especially those associated with old age

## GOLDEN SEAL

Golden seal is stated to be a stimulant to involuntary muscle, and possesses stomachic, oxytocic, antihemorrhagic, and laxative properties. Traditionally, it has been used for digestive disorders, gastritis, peptic ulceration, colitis, anorexia, upper respiratory catarrh, menorrhagia, postpartum hemorrhage, dysmenorrhea, topically for eczema, pruritus, otorrhea, catarrhal deafness and tinnitus, conjunctivitis, and specifically for atonic dyspepsia with hepatic symptoms.

## GRAVEL ROOT

Gravel root possesses antilithic, diuretic, and antirheumatic properties. Traditionally, it is used for urinary calculus, cystitis, dysuria, urethritis, prostatitis, rheumatism, gout, and specifically for renal or vesicular calculi.



## GROUND IVY

Ground ivy has mild expectorant, anticatarrhal, astringent, vulnerary, diuretic, and stomachic properties. Traditionally, it has been used for bronchitis, tinnitus, diarrhea, hemorrhoids, cystitis, gastritis, and particularly for chronic bronchial catarrh.

## GUAIAECUM

Guaiacum possesses antirheumatic, anti-inflammatory, diuretic, mild laxative, and diaphoretic properties. Traditionally, it is used for subacute rheumatism, prophylaxis against gout, and specifically for chronic rheumatism and rheumatoid arthritis.

## HAWTHORN

Native Americans used hawthorn as a diuretic for kidney and bladder disorders and to treat stomachaches, stimulate appetite, and improve circulation. The flowers and berries have astringent properties and can be used to treat sore throats in the form of **haw jelly** or **haw marmalade**. Today, hawthorn is promoted for the treatment of heart failure, hypertension, arteriosclerosis, angina pectoris, **Buerger's disease**, paroxysmal tachycardia, heart valve murmurs, sore throat, skin sores, diarrhea, and abdominal distention.

Hawthorn is stated to possess cardiogenic, coronary vasodilator, and hypotensive properties. Traditionally, it is used for cardiac failure, myocardial weakness, paroxysmal tachycardia, hypertension, arteriosclerosis, and Buerger's disease.

## HOLY THISTLE

Holy thistle is believed to have bitter stomachic, antidiarrheal, antihemorrhagic, febrifuge, expectorant, antibiotic, bacteriostatic, vulnerary, and antiseptic properties. Traditionally, it has been used for anorexia, flatulent dyspepsia, bronchial catarrh, topically for gangrenous and indolent ulcers, and specifically for atonic dyspepsia and enteropathy with flatulent colic.

## HOPS

Hops have sedative, hypnotic, and topical bactericidal properties. Traditionally, they have been used for neuralgia, insomnia, excitability, **priapism**, mucous colitis, topically for crural ulcers, and particularly for restlessness associated with nervous tension headache or indigestion.

## HOREHOUND (BLACK)

Black horehound has antiemetic, sedative, and mild astringent properties. Traditionally, it is used for nausea, vomiting, nervous dyspepsia, and specifically for vomiting of central origin.

## HOREHOUND (WHITE)

White horehound is stated to have expectorant and antispasmodic properties. Traditionally, it has been used for acute or chronic bronchitis, whooping cough, and specifically for bronchitis with nonproductive cough.

## HORSE CHESTNUT

Traditionally, horse chestnut has been used for the treatment of varicose veins, hemorrhoids, phlebitis, diarrhea, fever, and enlargement of the prostate gland.

## **HORSERADISH**

Horseradish is stated to possess antiseptic, circulatory and digestive stimulant, diuretic, and vulnerary properties. Traditionally, it is used for pulmonary and urinary infection, urinary stones, edematous conditions, and externally as an application for inflamed joints or tissues.

## **HYDRANGEA**

Hydrangea is stated to possess diuretic and antilithic properties. Traditionally, it has been used for cystitis, urethritis, urinary calculi, prostatitis, enlarged prostate gland, and specifically for urinary calculi with gravel and cystitis.

## **HYDROCOTYLE**

Hydrocotyle has mild diuretic, antirheumatic, dermatological, peripheral vasodilator, and vulnerary properties. Traditionally, it is used for rheumatic conditions, cutaneous affections, and as a topical application for indolent wounds, leprosy ulcers, and cicatrization after surgery.

## **ISPAGHULA**

Ispaghula is believed to have demulcent and laxative properties. Traditionally, ispaghula has been used in the treatment of chronic constipation, dysentery, diarrhea, and cystitis. It may be applied topically as a poultice for furunculosis.

## **JAMAICA DOGWOOD**

Jamaica dogwood possesses sedative and anodyne properties. Traditionally, it is used for neuralgia, migraine, insomnia, dysmenorrhea, and specifically for insomnia due to neuralgia or nervous tension.

## **JUNIPER**

Juniper is stated to possess diuretic, antiseptic, carminative, stomachic, and antirheumatic properties. Traditionally, it has been used for cystitis, flatulence, colic, and is applied topically for rheumatic pains in joints and muscles.

## **KAVA**

Kava is sometimes used during religious ceremonies and is currently promoted for relief of anxiety and stress.

## **LADY'S SLIPPER**

Lady's slipper is believed to have sedative, mild hypnotic, antispasmodic, and thymoleptic properties. Traditionally, it has been used for insomnia, hysteria, emotional tension, anxiety states, and specifically for anxiety states with insomnia.

## **LEMON VERBENA**

Lemon verbena is reputed to possess antispasmodic, antipyretic, sedative, and stomachic properties. Traditionally, it has been used for the treatment of asthma, cold, fever, flatulence, colic, diarrhea, and indigestion.

## LICORICE

Western herbalists recognized licorice as a remedy for dropsy, as did Pliny, and asserted that the root had emollient, demulcent, expectorant, and diuretic effects. Licorice was probably introduced to Native Americans by the early English settlers and was subsequently used by medicine men to treat diabetes. In traditional Chinese medicine, licorice was considered to benefit all organs of the body. Today, licorice is employed for a variety of purposes around the world. In China, it is used to treat a variety of symptoms and diseases, including **Addison's disease**, sore throats, carbuncles, diarrhea due to "spleen deficiency," thirst due to "stomach deficiency," cough due to "dry lungs," and palpitations. Other modern uses include bronchitis and other "catarrhal conditions," gastritis, colic, arthritis, and hepatitis. Licorice contains the natural sweetener **glycyrrhizic acid** and is used to flavor soy sauce in China. It is widely used in foods as a flavoring agent and licorice root is listed by the Council of Europe as a natural source of food flavoring (category N2). This category indicates that licorice can be added to food stuffs in small quantities, with a possible limitation of an active principle (as yet unspecified) in the final product. In the U.S., licorice is listed as **GRAS** (Generally Regarded As Safe).

## LIFEROOT

Liferoot is stated to possess uterine tonic, diuretic, and mild expectorant properties. Traditionally, it has been used in the treatment of functional amenorrhea, menopausal neurosis, and leucorrhoea (as a douche).

## LIME FLOWER

Lime flower is reputed to have sedative, antispasmodic, diaphoretic, diuretic, and mild astringent properties. Traditionally, it is used for treating migraine, hysteria, arteriosclerotic hypertension, feverish colds, and specifically for raised arterial pressure associated with arteriosclerosis and nervous tension.

## LOBELIA

Lobelia is stated to possess respiratory stimulant, antiasthmatic, antispasmodic, expectorant, and emetic properties. Traditionally, it has been used for bronchitic asthma, chronic bronchitis, and specifically for spasmodic asthma with secondary bronchitis. It is also used topically for myositis and rheumatic nodules.

## MA HUANG AND THE EPHEDRA ALKALOIDS

Chinese medical practitioners in the 15th century recommended ephedra as an antipyretic and antitussive agent. Modern physicians use intravenous ephedrine for the prophylaxis and treatment of hypotension caused by spinal anesthesia, particularly during cesarean section (see Chapter 29).

## MARSHMALLOW

Marshmallow has demulcent, expectorant, emollient, diuretic, antilithic, and vulnerary properties. Traditionally, it has been used internally for the treatment of respiratory catarrh and cough, peptic ulceration, inflammation of the mouth and pharynx, enteritis, cystitis, urethritis and urinary calculus, and topically for abscesses, boils, and varicose and thrombotic ulcers.

## **MATÉ**

Maté is believed to possess CNS-stimulant, thymoleptic, diuretic, antirheumatic, and mild analgesic properties. Traditionally, it has been used for psychogenic headache and fatigue, nervous depression, rheumatic pains, and specifically for headache associated with fatigue.

## **MEADOWSWEET**

Meadowsweet is reputed to have stomachic, mild urinary antiseptic, antirheumatic, astringent, and antacid properties. Traditionally, it has been used for atonic dyspepsia with heartburn and hyperacidity, acute catarrhal cystitis, rheumatic muscle and joint pains, diarrhea in children, and specifically for the prophylaxis and treatment of peptic ulcers.

## **MISTLETOE**

Mistletoe has hypotensive, cardiac-depressant, and sedative properties. Traditionally, it is used for high blood pressure, arteriosclerosis, nervous tachycardia, hypertensive headache, chorea, and hysteria.

## **MOTHERWORT**

Motherwort is stated to possess sedative and antispasmodic properties. Traditionally, it is used for cardiac debility, simple tachycardia, effort syndrome, amenorrhea, and specifically for cardiac symptoms associated with neurosis.

## **MYRRH**

Myrrh has antimicrobial, astringent, carminative, expectorant, anticatarrhal, antiseptic, and vulnerary properties. Traditionally, it has been used for aphthous ulcers, pharyngitis, respiratory catarrh, common cold, furunculosis, wounds and abrasions, and specifically for mouth ulcers, gingivitis, and pharyngitis.

## **NETTLE**

Nettle is stated to possess antihemorrhagic and hypoglycemic properties. Traditionally, it is used for uterine hemorrhage, cutaneous eruption, infantile and psychogenic eczema, epistaxis, and specifically for nervous eczema.

## ***PANAX GINSENG***

Throughout history, the root has been used as a treatment for asthenia, atherosclerosis, blood and bleeding disorders, colitis, and relief of symptoms associated with aging, cancer, and senility. Ginseng is also widely believed to be an aphrodisiac. It is promoted as a tonic capable of invigorating the user physically, mentally, and sexually. It is also said to have antistress activity (see Chapter 60 and page 95).

## **PARSLEY**

Parsley possesses carminative, antispasmodic, diuretic, emmenagogue, expectorant, antirheumatic, and antimicrobial properties. Traditionally, it is used for flatulent dyspepsia, colic, cystitis, dysuria, bronchitic cough in elderly people, dysmenorrhea, functional amenorrhea, myalgia, and specifically for flatulent dyspepsia with intestinal colic.

### PARSLEY PIERT

Parsley piert is stated to possess diuretic and demulcent properties, and to dissolve urinary deposits. Traditionally, it has been used for kidney and bladder calculi, dysuria, strangury, edema of renal and hepatic origin, and specifically for renal calculus.

### PASSIONFLOWER

Passionflower is reputed to have sedative, hypnotic, antispasmodic, and **anodyne** properties. Traditionally, it has been used for neuralgia, generalized seizures, hysteria, nervous tachycardia, spasmodic asthma, and specifically for insomnia. Passionflower is used extensively in homoeopathy.

### PENNYROYAL

Pennyroyal has carminative, antispasmodic, diaphoretic, and emmenagogue properties, and is used topically as a refrigerant, antiseptic, and insect repellent. Traditionally, it has been used for flatulent dyspepsia, intestinal colic, common cold, delayed menstruation, and topically for cutaneous eruptions, formication, and gout.

### PILEWORT

Pilewort has astringent and demulcent properties. Traditionally, it is used for hemorrhoids, and specifically for internal or prolapsed piles with or without hemorrhage, by topical application as an ointment or a suppository.

### PLANTAIN

Plantain possesses diuretic and antihemorrhagic properties. Traditionally, it has been used for cystitis with hematuria, and specifically for hemorrhoids with bleeding and irritation.

### PLEURISY ROOT

Pleurisy root is stated to possess diaphoretic, expectorant, antispasmodic, and carminative properties. It is used for treating bronchitis, pneumonitis, influenza, and particularly pleurisy.

### POKEWEED

Pokeweed has various traditional uses, from medicinal to industrial processes. It is used as a cathartic, emetic, narcotic, and gargle. Additional medicinal uses include treatment of various skin diseases, conjunctivitis, syphilis, cancer, parasitic infestations of the scalp, chronic rheumatism, ringworm, dyspepsia, swollen glands, scabies, ulcers, edema, dysmenorrhea, mumps, and tonsillitis. It is currently popular for its antimicrobial and antineoplastic activity.

Pokeweed is stated to possess antirheumatic, anticatarrhal, mild anodyne, emetic, purgative, parasiticidal, and fungicidal properties. Traditionally, it has been used for rheumatism, respiratory catarrh, tonsillitis, laryngitis, adenitis, mastitis, mumps, skin infections (e.g., scabies, tinea, sycosis, acne), mammary abscesses, and mastitis.

### POPLAR

Poplar possesses antirheumatic, anti-inflammatory, antiseptic, astringent, **anodyne**, and cholagogue properties. Traditionally, it is used for muscular and arthrodial rheumatism, cystitis, diarrhea, anorexia

with stomach or liver disorders, the common cold, and specifically for rheumatoid arthritis. The buds of *Populus tremula* (European white poplar, aspen) and *P. nigra* (black poplar) are used as expectorant and circulatory stimulant remedies, for upper respiratory tract infections, and rheumatic conditions.

### PRICKLY ASH (NORTHERN)

Prickly ash is reputed to possess circulatory-stimulant, diaphoretic, antirheumatic, carminative, and sialagogue properties. Traditionally, it is used for cramps, intermittent claudication, Raynaud's syndrome, chronic rheumatic conditions, and specifically for peripheral circulatory insufficiency associated with rheumatic symptoms. The berries are therapeutically more active in circulatory disorders.

### PRICKLY ASH (SOUTHERN)

Southern prickly ash is stated to possess circulatory-stimulant, diaphoretic, antirheumatic, carminative, and sialagogue properties. Traditionally, it has been used for cramps, intermittent claudication, **Raynaud's syndrome**, chronic rheumatic conditions, and specifically for peripheral circulatory insufficiency associated with rheumatic symptoms. The berries are considered to be therapeutically more active in circulatory insufficiency associated with rheumatic symptoms.

### PULSATILLA

Pulsatilla possesses sedative, analgesic, antispasmodic, and bactericidal properties. Traditionally, it is used for dysmenorrhea, orchitis, ovaralgia, epididymitis, tension headache, hyperactive states, insomnia, boils, skin eruptions associated with bacterial infection, asthma and pulmonary disease, earache, and specifically for painful conditions of the male and female reproductive systems. Pulsatilla is widely used in homoeopathic preparations as well as in herbal medicine.

### QUASSIA

Quassia has bitter, orexigenic, sialagogue, gastric-stimulant, and anthelmintic properties. Traditionally, it has been used for anorexia, dyspepsia, nematode infestation (by oral or rectal administration), pediculosis (by topical application), and specifically for atonic dyspepsia with loss of appetite.

### QUEEN'S DELIGHT

Queen's delight has sialagogue, expectorant, diaphoretic, dermatological, astringent, antispasmodic, and, in large doses, cathartic properties. Traditionally, it has been used for bronchitis, laryngitis, laryngismus stridulus, cutaneous eruptions, hemorrhoids, constipation, and specifically for exudative skin eruption and irritation, lymphatic involvement, and laryngismus stridulus.

### RASPBERRY

Raspberry is stated to possess astringent and *partus praeparator* properties. Traditionally, it is used for diarrhea, pregnancy, stomatitis, tonsillitis (as a mouthwash), conjunctivitis (as an eye lotion), and specifically to facilitate parturition.

### RED CLOVER

Red clover acts as a dermatological agent and possesses mildly antispasmodic and expectorant properties. Tannins are known to have astringent properties. Traditionally, red clover has been used for chronic skin disease, whooping cough, and specifically for eczema and psoriasis.

## **RHUBARB**

Rhubarb is used traditionally as both a laxative and an antidiarrheal agent (see Chapter 57).

## **ROSEMARY**

Rosemary is known to act as a carminative, spasmolytic, thymoleptic, sedative, diuretic, and antimicrobial agent. When used topically, it exhibits rubefacient, mild analgesic and parasitocidal properties. Traditionally, rosemary is recommended for flatulent dyspepsia, headache, and topically for myalgia, sciatica, and intercostal neuralgia.

## **SAGE**

Sage possesses carminative, antispasmodic, antiseptic, astringent, and antihidrotic properties. Traditionally, it is used to treat flatulent dyspepsia, pharyngitis, uvulitis, stomatitis, gingivitis, glossitis (internally or as a gargle or mouthwash), hyperhidrosis, and galactorrhea.

## **SARSAPARILLA**

Sarsaparilla is stated to possess antirheumatic, antiseptic, and antipruritic properties. Traditionally, it has been used for psoriasis and other cutaneous conditions, chronic rheumatism, rheumatoid arthritis, as an adjunct to other treatments for leprosy, and specifically for psoriasis.

## **SASSAFRAS**

Sassafras is used for stomachache, vomiting, urinary retention, lameness, gout, dropsy, syphilis, scurvy, and jaundice. Sassafras is still popular as a spring tonic, stimulant, antispasmodic, blood purifier, and sudorific (sweat producer), and as a cure for rheumatism, skin disease, syphilis, typhus, and dropsy (congestive heart failure).

Sassafras is stated to possess carminative, diaphoretic, diuretic, dermatological, and antirheumatic properties. Traditionally, it has been used for cutaneous eruptions, gout, and rheumatic pains.

## **SAW PALMETTO**

Historically, saw palmetto has also been used to increase sperm production, breast size, and sexual vigor. Today, saw palmetto is promoted as improving prostate health and urinary flow, and as enhancing reproductive and sexual functioning.

Saw palmetto is known to have diuretic, urinary antiseptic, endocrinological, and anabolic properties. Traditionally, it is used for chronic or subacute cystitis, catarrh of the genitourinary tract, testicular atrophy, sex hormone disorders, and specifically for prostatic enlargement.

## **SENEGA**

Senega has expectorant, diaphoretic, sialagogue, and emetic properties. Traditionally, it is used for bronchitic asthma, as a gargle for pharyngitis, and specifically for chronic bronchitis.

## **SENNA**

Senna was used as a laxative in the past and continues to be used for this purpose today. Senna is stated to possess cathartic properties (the leaf more than the fruit) and has been used traditionally for treating constipation (see Chapter 12).

### SHEPHERD'S PURSE

Shepherd's purse has antihemorrhagic and urinary antiseptic properties. Traditionally, it is used for menorrhagia, hematemesis, diarrhea, and acute catarrhal cystitis.

### SKULLCAP

Once recognized as a tonic, tranquilizer, and antispasmodic, skullcap was therefore used as an ingredient in many patent medicines for "**female weakness**." It was also combined with other reputedly calming herbs, such as hops and valerian, and promoted as a sedative or anxiolytic. Other traditional uses include treatment of epilepsy, headache, insomnia, various other neurological and psychiatric disorders, hypertension, fever, rheumatism, and stress.

Skullcap is promoted commercially in the U.S. as a sedative, anxiolytic, and spasmolytic and is promoted for the treatment of premenstrual syndrome (PMS), menstrual cramps, depression, exhaustion, and muscle pain caused by stress. Other claimed uses are for headache and epilepsy.

Skullcap is known to have anticonvulsant and sedative properties. Traditionally, it has been used for epilepsy, chorea, hysteria, nervous tension states, and specifically for grand mal. In Chinese herbal medicine, the roots of *Scutellaria baicalensis* Georgi have been used traditionally as a remedy for inflammation, suppurative dermatitis, allergic diseases, hyperlipidemia, and atherosclerosis.

### SKUNK CABBAGE

Skunk cabbage is stated to possess expectorant, antispasmodic, and mild sedative properties. Traditionally, it has been used for bronchitis, whooping cough, asthma, and specifically for bronchitic asthma.

### SLIPPERY ELM

Slippery elm has demulcent, emollient, nutritive, and antitussive properties. Traditionally, it is used for inflammation or ulceration of the stomach or duodenum, convalescence, colitis, diarrhea, and locally for abscesses, boils, and ulcers (as a poultice).

### SQUILL

Squill possesses expectorant, cathartic, emetic, cardioactive, and diuretic properties. Traditionally, it has been used for chronic bronchitis, asthma with bronchitis, whooping cough, and specifically for chronic bronchitis with scanty sputum.

### ST. JOHN'S WORT

In the past, St. John's wort was used to treat neurological and psychiatric disturbances (anxiety, insomnia, bed-wetting, irritability, migraine, excitability, exhaustion, fibrosis, hysteria, neuralgia, and sciatica), gastritis, gout, hemorrhage, pulmonary disorders, and rheumatism, and has been used as a diuretic. Some forms of the herb have been used topically as an astringent and to treat blisters, burns, cuts, hemorrhoids, inflammation, insect bites, itching, redness, sunburn, and wounds. Today, St. John's wort is prescribed for the treatment of depression.



St. John's wort has sedative and astringent properties. It is used to treat excitability, neuralgia, fibrositis, sciatica, wounds and, specifically, menopausal neurosis. St. John's wort is used extensively in homoeopathic preparations as well as in herbal products (see Chapter 43).

### **STONE ROOT**

Stone root is stated to possess antilithic, litholytic, mild diaphoretic, and diuretic properties. Traditionally, it has been used for renal calculus, lithuria, and specifically for urinary calculus.

### **TANSY**

Tansy has anthelmintic, carminative, and antispasmodic properties and is known to act as a stimulant to abdominal viscera. Traditionally, it has been used for nematode infestation, topically for scabies (as a decoction) and pruritus ani (as an ointment), and specifically for roundworm or threadworm infestation in children.

### **THYME**

Thyme is reputed to possess carminative, antispasmodic, antitussive, expectorant, secretomotor, bactericidal, anthelmintic, and astringent properties. Traditionally, it is used for dyspepsia, chronic gastritis, asthma, diarrhea and enuresis in children, laryngitis, tonsillitis (as a gargle), and specifically for pertussis and bronchitis.

### **UVA-URSI**

Uva-ursi is known to have diuretic, urinary antiseptic, and astringent properties. Traditionally, it has been used for cystitis, urethritis, dysuria, pyelitis, lithuria, and specifically for acute catarrhal cystitis with dysuria and highly acidic urine.

### **VALERIAN**

Today, valerian is used for treating insomnia. It is known to have sedative, mild anodyne, hypnotic, antispasmodic, carminative, and hypotensive properties. Traditionally, it has been used for the treatment of fatigue, seizures, hysterical states, excitability, insomnia, hypochondriasis, migraine, cramp, intestinal colic, rheumatic pains, dysmenorrhea, and specifically for conditions producing nervous excitability.

### **VERVAIN**

Vervain is stated to possess sedative, thymoleptic, antispasmodic, mild diaphoretic, and galactagogue properties. Traditionally, it is used for depression, melancholia, hysteria, generalized seizures, cholecystalgia, jaundice, early stages of fever, and specifically for depression and debility of convalescence after fevers, particularly influenza (see Chapter 65).

### **WILD CARROT**

Wild carrot has diuretic, antilithic, and carminative properties. Traditionally, it is used for urinary calculus, lithuria, cystitis, gout, and specifically for urinary gravel or calculus.

## **WILD LETTUCE**

Wild lettuce has mild sedative, anodyne, and hypnotic properties. Traditionally, it has been used for insomnia, restlessness and excitability in children, pertussis, irritable cough, priapism, dysmenorrhea, nymphomania, muscular or articular pains, and specifically for irritable cough and insomnia.

## **WILLOW**

Willow is reputed to have anti-inflammatory, antirheumatic, antipyretic, antihidrotic, analgesic, antiseptic, and astringent properties. Traditionally, it is used for muscular and arthrodial rheumatism with inflammation and pain, influenza, respiratory catarrh, gouty arthritis, and other systemic connective tissue disorders characterized by inflammatory changes.

## **WITCH HAZEL**

Witch hazel has astringent, antihemorrhagic, and anti-inflammatory properties. Traditionally, it has been used for diarrhea, mucous colitis, hemorrhoids, hematemesis, hemoptysis, and externally for external hemorrhoids, bruises, and localized inflamed swellings.

## **YARROW**

Yarrow possesses diaphoretic, antipyretic, hypotensive, astringent, diuretic, and urinary antiseptic properties. Traditionally, it has been used for fevers, common colds, essential hypertension, amenorrhea, dysentery, diarrhea, and specifically for thrombotic conditions with hypertension, including cerebral and coronary thromboses.

## **YELLOW DOCK**

Yellow dock is stated to possess gentle purgative and cholagogue properties. Traditionally, it has been used for chronic skin disease, obstructive jaundice, constipation, and specifically for psoriasis with constipation.

## **YUCCA**

Yucca is used for the treatment of arthritis, diabetes, and stomach disorders. The concentrated plant juice can be used topically to soothe painful joints (see Cupp, 2000).



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# 8 Dietary Antioxidants

## INTRODUCTION

Dietary antioxidants have the following medical uses:

- Reduction of cardiovascular diseases
- Control of diabetes mellitus
- Enhancement of the efficacy of antineoplastic agents

## THE ROLE OF DIET IN CURING AND PREVENTING DISEASES

Diet is a strong factor in the control of **atherosclerosis** relating to general vascular disease, **coronary heart disease**, and **stroke**. The interrelated disorders in atherosclerosis of **hyperinsulinemia**, **hyperlipidemia**, and **hypertension** are strongly subject to dietary influence. The type of dietary protein, animal vs. plant, appears to be as important as the type of lipid, animal vs. plant, in atherosclerosis. Dietary protein type, with its differing amino acid ratios, appears to be a major secretagogue of insulin.

**Diabetes mellitus**, or Type II diabetes, is a related disease in which diet is a possible causal or at least a strong contributing factor. Diet is the basis for the control of Type II diabetes. Interestingly, people with diabetes have a high incidence of atherosclerosis.

**Renal failure** has a long history of treatment with protein-restricted diets. Dietary plant protein is a possible therapy mechanism for the treatment of chronic and acute renal failure.

Patients with **rheumatic arthritis** appear to be helped by specialized dietary approaches. A few examples of the use of vegetarian diets look very promising. Individual arthritic sensitivities or reactivities to certain foods appear to warrant more study.

**Osteoporosis** is a disease or metabolic disturbance, particularly in postmenopausal women, that indicates a need for a very high dietary calcium intake. High calcium requirements appear to be related to the very high protein intake of the modern Western diet. A decreased protein intake, as can be obtained on a total vegetarian (vegan) diet, can allow for calcium balance, in a variety of age groups, from one third to one fifth the amount of daily calcium required with a Western diet.

**Cancer** of the breast, colon, and prostate appears to have a strong dietary relationship. The incidence of cancer is significantly greater with the modern Western diet than a vegetarian or vegan diet. Increased antioxidant vitamin content, higher fiber level, higher complex carbohydrate, more unsaturated and less saturated fat, along with a variety of anticancer-like compounds in vegetables, grains, legumes, nuts, and fruits, including tomatoes, are all dietary factors that appear to reduce the risk of cancer.

## ANTIOXIDANT CAPACITY OF VEGETABLES AND FRUITS

**Reactive oxygen species** (ROS) could be important causative agents of a number of human diseases including coronary heart disease, cancer, and the degenerative processes associated with aging. It has been suggested that a high intake of fruit and vegetables, the main sources of antioxidants in the diet, could decrease the potential stress caused by ROS. The consumption of

tomato and tomato products, for example, has been inversely related to the development of some types of cancer and to plasma lipid peroxidation. **Lycopene** has been hypothesized as being responsible for most of these effects, because of its high antioxidant activity and **singlet oxygen quenching capacity**. It has been shown that tomato intake significantly increases plasma lycopene and  **$\beta$ -carotene** concentrations.

It has been suggested that the total antioxidant capacity of plasma is due to its relative concentration in antioxidant compounds and to their synergism. It is possible that molecules that are not properly chain-breaking antioxidants, such as lycopene, may nevertheless maintain other antioxidant substances in the reduced form, thus indirectly determining an increased protection against oxidative stress. Evidence for the interaction between aqueous and lipophilic antioxidants (**vitamin C** and **vitamin E**, respectively) in defending **lipoproteins** against oxidative damage has been recently suggested in a human study. Tomato contains many antioxidant substances in addition to lycopene and  **$\beta$ -carotene** that could contribute to its protective effect.

## ANTIOXIDANT ACTIVITY IN CEREAL GRAINS

The data from both experimental and epidemiological studies show that grains, vegetables, and fruits contain a large variety of substances called “plant chemicals” or “**phytochemicals**.” The term *phytochemical* refers to every naturally occurring chemical substance present in plants, especially those that are biologically active. Major phytochemicals include **phenolic acids**, **flavonoids**, and **coumarin derivatives**, as well as many other **polyphenols**. The antioxidant activities in these phytochemicals range from extremely slight to very great. The natural antioxidants may have one or more of the following roles:

- Free-radical scavengers
- Reducing agents
- Potential complexers of prooxidant metals
- Quenchers of singlet oxygen

Consequently, phytochemical dietary components may actively contribute to the control of oxidative reactions and provide protection *in vivo*. Antioxidants play an important role in preventing undesirable changes in flavor and nutritional quality of foods. Cereal grains provide significant quantities of energy, protein, and selected micronutrients to the animal and human diet. The chemical composition and bioavailability of nutrients varies between species and varieties of grains and may be affected by forms of processing as feed and food. Cereal grains are rich in phenolic acids; the total amounts may approach 500 mg/kg of edible cereals. Other phytochemicals occurring in cereals are **phytosterines**, **saponins**, and **phytoestrogens**. In cereals, flavonoids are present in small quantities. Barley contains measurable amounts of **catechins** and some di- and trimer **procyanidins**. In contrast, cereals are the major source of dietary **lignans** in human nutrition. Lignans are potent antioxidants and exert anticancer effects. They decrease the production of ROS by tumor cell types and cells of the immune system. Recent reports have described antioxidants and compounds with radical-scavenging activity present in **peabean**, **peanut**, **rice**, **buckwheat**, and **oat** (Zieliński and Kozłowska, 2000; and General References).

## ANTIOXIDANT ACTIONS OF DU-ZHONG

**Du-zhong** (*Eucommia ulmoides* Oliv.) tea is commonly used in Japan in the treatment of hypertension and is thought to be a functional health food. In Japan, statistics published by the Ministry of Health and Welfare show that billions of Japanese yen are spent on Du-zhong each year, ranking Japan at the top in the consumption of this specific health food. According to ancient records,

roasted Du-zhong cortex was recommended as a folk medicine to reinforce muscle and lung, to lower blood pressure to prevent miscarriages, to improve the tone of the liver and kidney, and also to increase longevity.

ROS, such as **superoxide** ( $O^{\cdot-}$ ) and hydrogen peroxide ( $H_2O_2$ ), have been implicated both in aging and cancer. In particular, it is now recognized that the extremely reactive **hydroxyl radical** ( $\bullet OH$ ) derived from  $O^{\cdot-}$  and  $H_2O_2$  causes **DNA strand scission** in cellular damage. While in aerobes, the generation of ROS and the level of antioxidant defense systems are approximately balanced. Once the balance is tipped, oxidative stress occurs and diseases result. This oxidative stress may be decreased partially by increasing the dietary intake of antioxidants. Therefore, much attention has been focused on the investigation of antioxidants, especially natural antioxidants, that can inhibit lipid peroxidation or protect biomolecules from damage caused by free radicals. Supplementation of antioxidants has been used successfully in some cases either to protect against physiological deterioration related to aging or to increase the average life span of some species. Natural antioxidants, especially phenolics and flavonoids, are those most often found in plants and are the most bioactive. **Phenolics** and **flavonoids** are major groups of nonessential dietary components that possess the bioactivity of an **antioxidant** together with **antimutagenic**, **anti-inflammatory**, and **anticarcinogenic** properties, and can suppress **atherosclerosis** and **cancer** as **prophylactic agents**. The bioactivity of phenolics may be related to their ability to chelate metals, inhibit **lipoygenase**, and scavenge free radicals. However, besides these beneficial effects, some phenolics can block the chain reaction of lipid peroxidation, whereas they cannot protect against oxidative damage to DNA, carbohydrates, and proteins when a transition metal ion exists.

Hsieh and Yen (2000) investigated the antioxidant effect of **water extracts of Du-zhong** (WEDZ) on oxidative damage in biomolecules such as deoxyribose, DNA, and 2'-deoxyguanosine (2'-dG) as induced by the Fenton reaction. The WEDZ used included leaves, raw cortex, and roasted cortex. All of the WEDZ inhibited the oxidation of deoxyribose induced by  $Fe^{3+}$ -EDTA/ $H_2O_2$ /ascorbic acid in a concentration-dependent manner. At a concentration of 1.14 mg/ml, the inhibitory effect of the extracts of leaves, roasted cortex, and raw cortex was 85.2, 68.0, and 49.3%, respectively. The extract of leaves inhibited the strand-breaking of DNA induced by the Fenton reaction at concentrations of 5 and 10  $\mu g/l$ . This inhibitory effect was similar to that of mannitol, whereas the extracts of raw cortex and roasted cortex had no inhibitory effect at all. WEDZ also inhibited the oxidation of 2'-dG to 8-OH-2'-dG induced by  $Fe^{3+}$ -EDTA/ $H_2O_2$ /ascorbic acid. **Gallic acid** had a pro-oxidant effect, but **trolox** and **mannitol** had an antioxidant effect. The leaf extract had a marked inhibitory effect on Fenton-reaction-induced oxidative damage in biomolecules. The extract of roasted cortex exhibited modest inhibition, whereas the extract of raw cortex had the least inhibitory effect on oxidative damage in biomolecules. This is in contrast to gallic acid in the same reaction system, whose higher reducing power and weaker chelating ability may contribute to its pro-oxidant effect. In the present study, a leaf extract Du-zhong had inhibitory effect on oxidative damage in biomolecules. Therefore, drinking **Du-zhong tea** (leaf extract) over a long period of time may have anticancer potential (Hsieh and Yen, 2000; and General References).

Oxidative stress reduces the rate of cell proliferation, and that occurring during chemotherapy may interfere with the cytotoxic effects of antineoplastic drugs, which depend on rapid proliferation of cancer cells for optimal activity. Antioxidants detoxify ROS and may enhance the anticancer effects of chemotherapy. For some supplements, activities beyond their antioxidant properties, such as inhibition of **topoisomerase II** or **protein tyrosine kinases**, may also contribute. ROS cause or contribute to certain side effects that are common to many anticancer drugs, such as gastrointestinal toxicity and muagenesis. ROS also contribute to side effects that occur only with individual agents, such as **doxorubicin-induced cardiotoxicity**, **cisplatin-induced nephrotoxicity**, and **bleomycin-induced pulmonary fibrosis**. Antioxidants can reduce or prevent many of these side effects, and for some supplements the protective effect results from activities other than their antioxidant properties. Certain side effects, however, such as alopecia and myelosuppression, are not prevented

by antioxidants, and agents that interfere with these effects may also interfere with the anticancer effects of chemotherapy (Conklin, 2000; and General References)).

Chemotherapy has long been a cornerstone of cancer therapy. Although extensive research has been done on the development of more effective and less toxic antineoplastic agents, much less attention has been paid to factors that may enhance the effectiveness of existing drugs. Nutritional factors may hold the key to enhancing the anticancer effects of chemotherapy and to reducing or preventing certain chemotherapy-induced side effects.

## OXIDATIVE STRESS AND CHEMOTHERAPEUTIC EFFECTIVENESS

Free radicals and other ROS are essential for life, because they are involved in cell signaling and are used by phagocytes for their bactericidal action. In addition to these well-controlled and necessary functions, ROS are also produced in all respiring organisms as a consequence of mitochondrial respiration, which consumes oxygen in the process of generating ATP by the coupling of electron transport and oxidative phosphorylation. Nonessential production of ROS, i.e., oxidative stress, can also be induced by exogenous factors such as drugs and environmental toxins. Oxidative stress is potentially harmful to cells, and ROS are implicated in the etiology and progression of many disease processes including cancer. However, antioxidant mechanisms that scavenge ROS, by means of low-molecular-weight antioxidant enzyme systems, protect an organism from the damaging effects of oxidative stress. Under normal conditions, these antioxidant defense systems are able to detoxify ROS and prevent damage to cellular macromolecules and organelles. Under conditions of excessive oxidative stress, however, cellular antioxidants are depleted and ROS can damage cellular components and interfere with critical cellular activities (Conklin, 2000; and General References).

## PRINCIPLE OF CANCER THERAPY

Malignant neoplastic diseases may be treated by various approaches: surgery, radiation therapy, immunotherapy, or chemotherapy, or a combination of these. The extent of a malignant disease (staging) should be ascertained to plan an effective therapeutic intervention.

## CHEMOTHERAPY

Before discussing the specific pharmacokinetics and pharmacodynamics of each class of antineoplastic agents, several fundamental concepts and therapeutic objectives will be considered first.

Because a single cancerous cell is capable of multiplying rapidly and eventually causing the host's death, one of the therapeutic objectives is to **eradicate the last neoplastic cell**. Unlike normal cells, **cancerous cells multiply ceaselessly**, and unless arrested they will kill the host. In the early phase, cancerous cells grow exponentially. However, as the tumor grows in mass, the time needed for the number of cells to double also increases. The kinetics of cell multiplication are said to follow a **gompertzian growth curve**. Tumor growth may be divided into three phases: (1) the **subclinical phase**, in which  $10 \times 10^4$  cells are present, (2) the **clinical phase**, in which  $10 \times 10^8$  cells (1-cm<sup>3</sup> nodule) are present, and (3) the fatal phase, in which the number of cancerous cells equals or exceeds  $10 \times 10^{12}$ .

Most human cancerous cells evolve from the single clone of a malignant cell. As a tumor grows, significant mutation takes place, producing cells that exhibit diversified morphological and biochemical characteristics. During the subclinical phase, the rapidly growing cell population is uniform in character and thus highly sensitive to drug treatment; this is the reason for the importance of early diagnosis and treatment. During the clinical phase, the nondividing and slowly growing

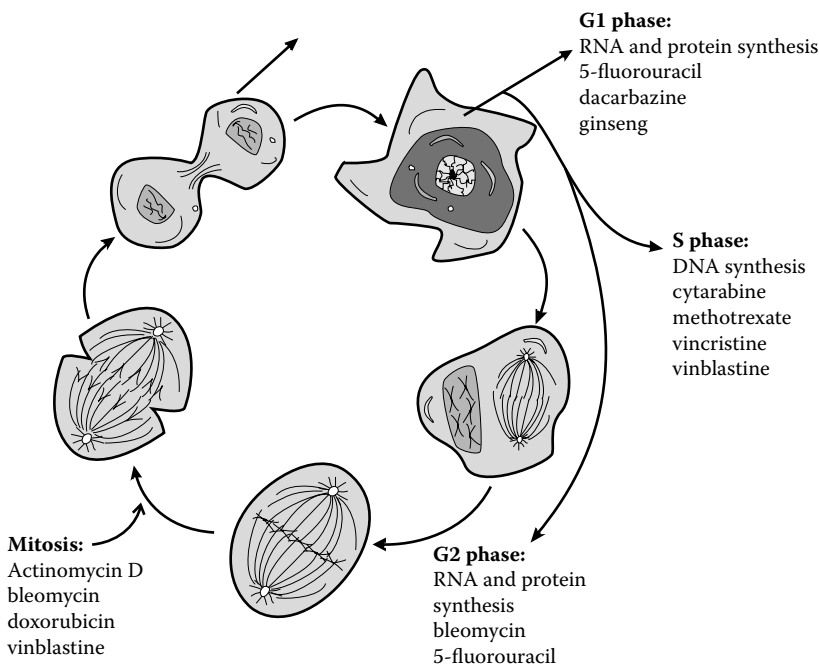
cells are nonuniform in character and less sensitive to drug treatment, thus necessitating the need for multiple-drug treatment.

**Cell destruction** with antineoplastic agents follows a **first-order kinetic**, indicating that the drugs kill a constant fraction of cells and not a constant number of cells. This concept is depicted mathematically in the following table.

Number of Treatments	Percentage Killed	Number of Tumor Cells Killed Each Treatment	Number of Surviving Tumor Cells
Start	—	—	1,000,000
1	90	900,000	100,000
2	90	90,000	10,000
3	90	9,000	1,000
4	90	900	100
5	90	90	10
6	90	9	1

**Cytotoxic drugs are not specific in their actions.** Not only do they arrest cancerous cells, but also normal cells, especially those of the rapidly proliferating tissues such as the bone marrow, lymphoid system, oral and gastrointestinal epithelium, skin and hair follicles, and germinal epithelium of the gonads. Consequently, the therapeutic regimen must be carried out using **high-dose intermittent schedules** and not a low-dose continuous approach. Succeeding doses are given as soon as the patient has recovered from the previous treatment.

Antineoplastic agents may be **teratogenic**, **carcinogenic**, or **immunosuppressant**, and they exert their lethal effects on different phases of cell cycle by being either **cell-cycle specific** or **nonspecific** (Figure 8.1).



**FIGURE 8.1** The actions of antineoplastic agents on different phases of the cell cycle.



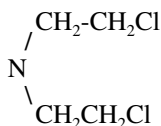
The management of cancer includes treatment with **alkylating agents** (nitrogen mustards and alkyl sulfonates), **antimetabolites** (methotrexate and purine analogs), **natural products** (vinca alkaloids and antibiotics), miscellaneous compounds (hydroxyurea, procarbazine, and *cis*-platinum), hormones (estrogens and corticosteroids), and radioactive isotopes (see Chapter 62).

## ALKYLATING AGENTS

The alkylating agents exert their antineoplastic actions by generating highly reactive **carbonium ion intermediates** that form a covalent linkage with various nucleophilic components on both proteins and **DNA**. The 7-position of the purine base **guanine** is particularly susceptible to alkylation, resulting in miscoding, depurination, or ring cleavage. **Bifunctional alkylating agents** are able to cross-link either two nucleic acid molecules or one protein and one nucleic acid molecule. Although these agents are very active from a therapeutic perspective, they are also notorious for their tendency to cause carcinogenesis and mutagenesis. Alkylating agents that have a nonspecific effect on the cell-cycle phase are the most cytotoxic to rapidly proliferating tissues (see Chapter 62).

### NITROGEN MUSTARDS

The activity of nitrogen mustards depends on the presence of a *bis*-(-2-chloroethyl) grouping:



This is present in **mechlorethamine** (Mustargen), which is used in patients with **Hodgkin's disease** and other lymphomas, usually in combination with other drugs, such as in **MOPP therapy** (**mechlorethamine**, **Oncovin** [vincristine], **procarbazine**, and **prednisone**). It may cause bone marrow depression.

### CHLORAMBUCIL

Chlorambucil (Leukeran) is the least toxic nitrogen mustard, and is used as the drug of choice in the treatment of **chronic lymphocytic leukemia**. It is absorbed orally, is slow in its onset of action, and may cause bone marrow depression.

### CYCLOPHOSPHAMIDE

Cyclophosphamide (Cytoxan and Endoxan) is used in the treatment of **Hodgkin's disease**, **lymphosarcoma**, and other lymphomas. It is employed as a secondary drug in patients with acute leukemia and in combination with **doxorubicin** in women with breast cancer. A drug combination effective in the treatment of breast cancer is **cyclophosphamide**, **methotrexate**, **fluorouracil**, and **prednisone** (CMFP). Cyclophosphamide is also an immunosuppressive agent. The toxicity of cyclophosphamide causes alopecia, bone marrow depression, nausea and vomiting, and **hemorrhagic cystitis**.

### ALKYL SULFONATE

The alkyl sulfonate busulfan (Myleran) is metabolized to an alkylating agent. Because it produces selective myelosuppression, it is used in cases of chronic myelocytic leukemia. It causes pronounced hyperuricemia stemming from the catabolism of purine.

## NITROSOUREAS

**Carmustine (BCNU)**, **lomustine (CCNU)**, and **semustine (methyl-CCNU)** generate **alkyl carbonium ions** and **isocyanate molecules** and hence are able to interact with DNA and other macromolecules. These agents, which are lipid soluble, cross the blood–brain barrier and are therefore effective in treating brain tumors. They are bone marrow depressants.

## TRIAZENES

Dacarbazine (DTIC-Dome) is metabolized to an active alkylating substance. It is used in the treatment of **malignant melanoma** and causes myelosuppression.

## ANTIMETABOLITES

Antimetabolites are structural analogs of naturally occurring compounds and function as fraudulent substances for vital biochemical reactions.

## FOLIC ACID ANALOGS

**Methotrexate** (Amethopterin) is a folic acid antagonist that binds to **dihydrofolate reductase**, thus interfering with the synthesis of the active cofactor **tetrahydrofolic acid**, which is necessary for the synthesis of **thymidylate**, **purine nucleotides**, and the amino acids serine and methionine. Methotrexate is used for the following types of cancer:

- **Acute lymphoid leukemia:** During the initial phase, vincristine and prednisone are used. Methotrexate and mercaptopurine are used for maintenance therapy. In addition, methotrexate is given intrathecally, with or without radiotherapy, to prevent meningeal leukemia.
- **Diffuse histiocytic lymphoma:** Cyclophosphamide, vincristine, methotrexate, and cytarabine (COMA).
- **Mycosis fungoides:** Methotrexate.
- **Squamous cell, large-cell anaplastic, and adenocarcinoma:** Doxorubicin and cyclophosphamide, or methotrexate.
- **Head and neck squamous cell:** *Cis*-platinum and bleomycin, or methotrexate.
- **Choriocarcinoma:** Methotrexate.

Tumor cells acquire **resistance to methotrexate** as the result of several factors:

- The deletion of a high-affinity, carrier-mediated transport system for reduced folates
- An increase in the concentration of dihydrofolate reductase
- The formation of a biochemically altered reductase with reduced affinity for methotrexate

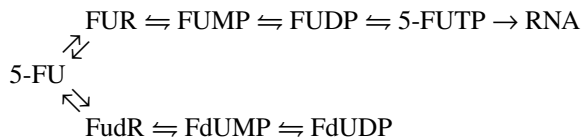
To overcome this resistance, higher doses of methotrexate need to be administered.

The effects of methotrexate may be reversed by the administration of **leucovorin**, the reduced folate. This leucovorin “rescue” prevents or reduces the toxicity of methotrexate, which is expressed as mouth lesions (stomatitis), injury to the gastrointestinal epithelium (diarrhea), leukopenia, and thrombocytopenia (see Chapter 62).

## PYRIMIDINE ANALOGS

**Fluorouracil** and **fluorodeoxyuridine** (floxuridine) inhibit pyrimidine nucleotide biosynthesis and interfere with the synthesis and actions of nucleic acids. To exert its effect, fluorouracil (5-FU)

must first be converted to nucleotide derivatives such as **5-fluorodeoxyuridylate** (5-FdUMP). Similarly, floxuridine (FUdR) is also converted to FdUMP by the following reactions:



FdUMP inhibits **thymidylate synthetase**, and this in turn inhibits the essential formation of dTTP, one of the four precursors of DNA. In addition, 5-FU is sequentially converted to 5-FUTP, which becomes incorporated into RNA, thus inhibiting its processing and functioning. Fluorouracil is used for the following types of cancer:

- **Breast carcinoma:** Cyclophosphamide, methotrexate, fluorouracil, and prednisone (CMP + P). The alternative drugs are doxorubicin and cyclophosphamide.
- **Colon carcinoma:** Fluorouracil.
- **Gastric adenocarcinoma:** Fluorouracil, doxorubicin (Adriamycin), and mitomycin (FAM), or fluorouracil and semustine.
- **Hepatocellular carcinoma:** Fluorouracil alone or in combination with lomustine.
- **Pancreatic adenocarcinoma:** Fluorouracil.

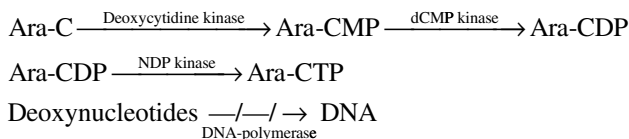
**Resistance of 5-FU** occurs as the result of one or a combination of the following factors:

- Deletion of uridine kinase
- Deletion of nucleoside phosphorylase
- Deletion of orotic acid phosphoribosyltransferase
- Increased thymidylate kinase

Because 5-FU is metabolized rapidly in the liver, it is administered intravenously and not orally. 5-FU causes myelosuppression and mucositis.

## DEOXYCYTIDINE ANALOGS

Cytosine arabinoside (Cytarabine, Cytosar, and Ara-C) is an analog of deoxycytidine, differing only in its substitution of sugar arabinose for deoxyribose. It is converted to Ara-CTP, and thereby inhibits DNA polymerase according to the following reactions:



Cytosine arabinoside is used in the treatment of **acute granulocytic leukemia**. Doxorubicin; daunorubicin and cytarabine; cytarabine and thioguanine; or cytarabine, vincristine, and prednisone are the combinations of agents employed.

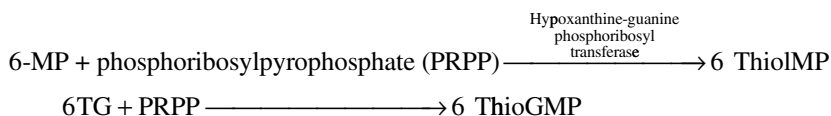
**Resistance to cytosine arabinoside** may stem from the following factors:

- The deletion of deoxycytidine kinase
- An increased intracellular pool of dCTP, a nucleotide that competes with Ara-CTP
- Increased cytidine deaminase activity, converting Ara-C to inactive Ara-U

The **toxic effects** of cytosine arabinoside are myelosuppression and injury to the gastrointestinal epithelium, which causes nausea, vomiting, and diarrhea.

## PURINE ANTIMETABOLITES

6-Mercaptopurine (6MP) and 6-thioguanine (6TG) are analogs of the purines hypoxanthine and guanine, which must be activated by nucleotide formation, according to the following scheme:



ThioIMP and ThioGMP are **feedback inhibitors** of **phosphoribosylpyrophosphate amidotransferase**, which is the first, and rate-limiting step in the synthesis of purine. In addition, these analogs inhibit the *de novo* biosynthesis of purine and block the conversion of inosinic acid to adenylic acid or guanylic acid. The triphosphate nucleotides are incorporated into DNA, and this results in delayed toxicity after several cell divisions.

**6-Mercaptopurine** is used in the treatment of acute lymphoid leukemia. Maintenance therapy makes use of both methotrexate and 6-mercaptopurine. Mercaptopurine is absorbed well from the gastrointestinal tract. It is metabolized through (1) methylation of the sulfhydryl group and subsequent oxidation, and (2) conversion to **6-thiouric acid** with the aid of **xanthine oxidase**, which is inhibited by allopurinol. Mercaptopurine may cause hyperuricemia. Its chief toxicities are hepatic damage and bone marrow depression.

**Thioguanine** is used in patients with acute granulocytic leukemia, usually in combination with cytosine arabinoside and daunorubicin.

## NATURAL PRODUCTS

### VINCA ALKALOIDS

The **vinca alkaloids** (**vinblastine**, **vincristine**, and **vindesine**), which bind to tubulin, block mitosis with metaphase arrest. Vinca alkaloids are used for the following types of cancer:

- **Acute lymphoid leukemia:** In the induction phase, vincristine is used with prednisone.
- **Acute myelomonocytic or monocytic leukemia:** Cytarabine, vincristine, and prednisone.
- **Hodgkin's disease:** Mechlorethamine, Oncovin (vincristine), procarbazine, and prednisone (MOPP).
- **Nodular lymphoma:** Cyclophosphamide, Oncovin (vincristine), and prednisone (CVP).
- **Diffuse histiocytic lymphoma:** Cyclophosphamide, Adriamycin (doxorubicin), vincristine, and prednisone (CHOP); bleomycin, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), and prednisone (BACOP); or cyclophosphamide, Oncovin (vincristine), methotrexate, and cytarabine (COMA).
- **Wilms' tumor:** Dactinomycin and vincristine.

- **Ewing's sarcoma:** Cyclophosphamide, dactinomycin, or vincristine.
- **Embryonal rhabdomyosarcoma:** Cyclophosphamide, dactinomycin, or vincristine.
- **Bronchogenic carcinoma:** Doxorubicin, cyclophosphamide, and vincristine.

The chief toxicity associated with vinblastine use is bone marrow depression. The toxicity of vincristine consists of paresthesia, neuritic pain, muscle weakness, and visual disturbances. In addition, both vinblastine and vincristine may cause alopecia.

### DACTINOMYCIN

The antibiotics that bind to DNA are nonspecific to the cell-cycle phase. Dactinomycin (actinomycin D and Cosmegen) binds to double-stranded DNA and prevents RNA synthesis by inhibiting DNA-dependent RNA polymerase. It is administered intravenously in the treatment of pediatric solid tumors such as **Wilms' tumor** and **rhabdomyosarcoma** and for gestational **choriocarcinoma**. Dactinomycin causes skin reactions, gastrointestinal injury, and delayed bone marrow depression.

### MITHRAMYCIN

The mechanism of action of mithramycin (Mithracin) is similar to that of dactinomycin. It is used in patients with advanced disseminated tumors of the testis and for the treatment of hypercalcemia associated with cancer. Mithramycin may cause gastrointestinal injury, bone marrow depression, hepatic and renal damage, and hemorrhagic tendency (see Chapter 62).

### DAUNORUBICIN AND DOXORUBICIN

Daunorubicin (Daunomycin and Cerubidine) and doxorubicin (Adriamycin) bind to and cause the intercalation of the DNA molecule, thereby inhibiting DNA template function. They also provoke DNA chain scission and chromosomal damage. Daunorubicin is useful in treating patients with acute lymphocytic or acute granulocytic leukemia. Adriamycin is useful in cases of solid tumors such as sarcoma, metastatic breast cancer, and thyroid cancer. These agents cause stomatitis, alopecia, myelosuppression, and cardiac abnormalities ranging from arrhythmias to cardiomyopathy.

### BLEOMYCIN

Bleomycin (Blenoxane) causes chain scission and fragmentation of DNA. With the exception of the skin and lungs, most tissues can enzymatically inactivate bleomycin. Bleomycin is used in the management of **squamous cell carcinoma** of the head, neck, and esophagus in combination with other drugs in patients with testicular carcinoma, and in the treatment of Hodgkin's disease and other lymphomas. Bleomycin causes stomatitis, ulceration, hyperpigmentation, erythema, and pulmonary fibrosis.

## MISCELLANEOUS ANTINEOPLASTIC AGENTS

### ASPARAGINASE

Normal cells are able to synthesize **asparagine**, but neoplastic tissues must obtain it from external sources. By metabolizing asparagine, **asparaginase** (Elspar) deprives the neoplastic tissues of asparagine, and in turn inhibits protein and nucleic acid synthesis. The resistant tumors are thought to possess higher-than-normal amounts of asparagine synthetase. Asparaginase, which is prepared from *Escherichia coli*, is used to induce remission of acute lymphocytic leukemia. Asparaginase causes malaise, anorexia, chills, fever, and hypersensitivity reactions. In general, it does not damage the bone marrow or other rapidly growing tissues as much as other antineoplastic agents do.

**HYDROXYUREA**

Hydroxyurea suppresses DNA synthesis by inhibiting ribonucleoside diphosphate reductase, which catalyzes the reduction of ribonucleotides to deoxyribonucleotides. Hydroxyurea is used in chronic cases of granulocytic leukemia that are unresponsive to **busulfan**. In addition, it is used for acute lymphoblastic leukemia. Hydroxyurea may cause bone marrow depression.

**Cis-PLATINUM**

*Cis*-platinum (cisplatin) binds to intracellular DNA, causing both interstrand and intrastrand cross-linking. It is a cell-cycle phase-nonspecific agent. *Cis*-platinum, which is ineffective orally, is used for testicular, bladder, and head and neck cancers. It precipitates nephrotoxicity, ototoxicity, and gastrointestinal injury.

**CARBOPLATIN**

Carboplatin is a promising second-generation platinum agent. Because it is less reactive, it causes less nephrotoxicity, myelosuppression, and thrombocytopenia.

**PROCARBAZINE**

Procarbazine (Matulane) inhibits DNA, RNA, and protein synthesis through an unknown mechanism. It is effective in patients with Hodgkin's disease when given in combination with mechlorethamine, vincristine, and prednisone (MOPP). Procarbazine causes neurotoxicity, bone marrow depression, and gastrointestinal injury.

**ETOPOSIDE**

Etoposide is used to combat several types of tumors, including testicular and small-cell lung cancers, lymphoma, leukemia, and Kaposi's sarcoma.

**CANCER-CHEMOTHERAPY-INDUCED EMESIS**

Nausea and vomiting are frequent side effects of radiotherapy and cancer chemotherapy. The incidence of this is relatively low for bleomycin, vincristine, and chlorambucil but is high for the other agents. Besides **prochlorperazine** and **metoclopramide (dopamine-receptor-blocking agents)**, **nabilone** (a **cannabinoid**), **batanopride**, **granisetron**, and **ondansetron** (all **serotonin-receptor-blocking agents**) have been shown to be effective in ameliorating these symptoms (see Chapter 62 and Brunton et al., 2006).

## OXIDATIVE STRESS AND INTERFERENCE WITH THE CYTOTOXIC EFFECTS OF ANTINEOPLASTIC AGENTS

The major ROS causing oxidative stress are:

**Free radicals**

Hydroxyl radical	$\text{HO}^\bullet$
Superoxide radical	$\text{O}^{2-\bullet}$
Peroxyl	$\text{ROO}^\bullet$
Alkoxy	$\text{RO}^\bullet$

**Nonradical oxygen species**

Hydrogen peroxide	$\text{H}_2\text{O}_2$
Singlet oxygen	$^1\text{O}_2$

Considerable evidence supports the contention that excessive oxidative stress, i.e., the generation of higher-than-normal amounts of ROS, interferes with the cytotoxic effects of antineoplastic agents on cancer cells. Important to this concept is how oxidative stress influences the progression of a cell through the cell cycle and at which phases of the cell-cycle antineoplastic agents are cytotoxic (see Figure 8.1).

The cell cycle consists of a presynthetic phase ( $G_1$ ), which precedes DNA synthesis, the phase of DNA synthesis (S), an interval that follows DNA synthesis ( $G_2$ ), and mitosis (M), during which the  $G_2$  cell with a double complement of DNA divides into two daughter cells. Each of these daughter cells may then immediately reenter the division cycle at  $G_1$  or pass into a nonproliferative state ( $G_0$ ) for an indefinite period of time. As the length of the cell cycle increases, the duration of the  $G_1$  phase increases, whereas the durations of the S,  $G_2$ , and M phases remain relatively constant.

**The length of the cell cycle can be influenced by many factors, one of which is oxidative stress** (Conklin, 2000). During oxidative stress, the excessive production of ROS results in lipid peroxidation. Because the rate of DNA synthesis and that of cell proliferation of cancer cells and normal cells are inversely related to the degree of lipid peroxidation, oxidative stress prolongs the  $G_1$  phase or may result in cells entering the  $G_0$  phase. This cell-cycle prolongation by lipid peroxides is also illustrated by results of *in vivo* studies that demonstrate that lipid peroxidation, induced by feeding polyunsaturated fatty acids (PUFA), slows the growth rate of human breast carcinoma implanted into **athymic nude mice**. Reversal of the inhibitory effect of oxidative stress on cell proliferation by antioxidants that prevent lipid peroxidation supports the contention that the inhibitory effect is due to lipid peroxides.

Antineoplastic agents act by blocking the synthesis of DNA precursors, damaging the integrity of DNA, or interfering with DNA replication, separation of the two double helices after replication, or the function of the mitotic spindle. Tumor cells in the nonproliferative  $G_0$  state are little affected by anticancer drugs and can reenter the division cycle after chemotherapy is completed, resulting in recurrence of disease. Even drugs that do not require ongoing DNA synthesis for activity, e.g., the alkylating agents and platinum coordination complexes, which can damage the integrity of quiescent DNA, may have little effect on  $G_0$  tumor cells, because repair mechanisms for DNA can repair damage before the cells reenter the division cycle. Tumor cells with prolonged  $G_1$  phases may likewise be resistant to the cytotoxic effects of antineoplastic agents. Because anticancer drugs are cytotoxic only when tumor cells are proliferating rapidly, this provides a mechanism whereby oxidative stress, which slows or arrests cell growth, interferes with chemotherapeutic effectiveness. It also explains why slow-growing tumors, such as lung and colon carcinoma, which are likely to have many cells in the  $G_0$  phase for prolonged periods of time, are relatively unresponsive to chemotherapy.

Cancer cells have highly evolved protective mechanisms to prevent lipid peroxidation so that rapid cell proliferation can occur. Several studies have demonstrated that lipid peroxidation is decreased significantly in tumor cells and tissues compared to that in corresponding normal cells and tissues. The primary mechanism whereby cancer cells prevent lipid peroxidation consists of a marked increase, compared to normal cells, in vitamin E relative to the peroxidizable moieties (methylene groups) of the PUFA in their biological membranes. Compared with normal cells, tumor cells also have relatively low levels of the components of the **NADPH-cytochrome P-450 electron transport chain**, which results in less favorable conditions for the initiation and propagation of lipid peroxidation. However, excessive oxidative stress may overcome even the highly evolved protective mechanisms of cancer cells, resulting in inhibition of cancer proliferation and interference with the cytotoxic activity of antineoplastic agents.

## ANTIOXIDANT EFFECTS ON ANTINEOPLASTIC ACTIVITY AND CHEMOTHERAPY-INDUCED SIDE EFFECTS

### VITAMIN E

Vitamin E resides in the lipid domain of biological membranes and plasma lipoprotein, where it prevents lipid peroxidation of PUFA. Because vitamin E is the most important antioxidant for

preventing lipid peroxidation, vitamin E adequacy may significantly impact the rate of cancer cell proliferation and the response to cancer chemotherapy. Vitamin E has been shown to effectively reverse the inhibitory effect of lipid peroxidation on cell proliferation.

Vitamin E, *in vitro*, has been shown to enhance the cytotoxic effect of several anticancer drugs, including **5-fluorouracil (5-FU)**, **doxorubicin**, **vincristine**, **dacarbazine**, **cisplatin**, and **tamoxifen**.

## VITAMIN C

Vitamin C is a versatile water-soluble antioxidant. It protects against lipid peroxidation by scavenging ROS in the aqueous phase before they can initiate lipid peroxidation.

*In vitro* studies with several tumor cell lines have shown vitamin C to enhance the cytotoxic activity of **doxorubicin**, **cisplatin**, **paclitaxel**, **dacarbazine**, **5-FU**, and **bleomycin**. Vitamin C has also been shown to increase drug accumulation and to partially reverse vincristine resistance of human nonsmall-cell lung cancer cells.

## COENZYME Q<sub>10</sub> (UBIQUINONE)

Coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) is an indispensable cofactor in the **electron transport chain of mitochondria**, functioning as an electron carrier between the enzyme complexes of the respiratory chain. CoQ<sub>10</sub> is also a lipid-soluble antioxidant that scavenges lipid radicals within biological membranes. CoQ<sub>10</sub> within mitochondria may play an important role in preventing lipid peroxidative damage of mitochondrial membranes.

A potentially important application of CoQ<sub>10</sub> supplementation during chemotherapy is for the prevention of **doxorubicin-induced cardiotoxicity**, most importantly the chronic form, which is not prevented by other dietary antioxidants. The postulated mechanism of dose-limiting chronic cardiotoxicity, a complication that occurs to a greater or lesser degree with all **anthracyclines**, involves the production of oxidizing agents through an iron-dependent process. Consistent with this hypothesis is the generation of free radicals by doxorubicin, resulting in mitochondrial lipid peroxidation within myocardial cells. However, other effects of doxorubicin on the mitochondria of cardiac myocytes may be equally or more important. These effects of doxorubicin include (1) reduction of the CoQ<sub>10</sub> content of mitochondrial membranes, (2) inhibition of mitochondrial biosynthesis of CoQ<sub>10</sub>-dependent enzymes, which interferes with the aerobic generation of ATP, and (3) inhibition of mitochondrial biosynthesis of CoQ<sub>10</sub>. These effects of doxorubicin on CoQ<sub>10</sub> biosynthesis and function may explain the acute and chronic forms of doxorubicin-induced cardiotoxicity.

Acute doxorubicin-induced cardiotoxicity, a reversible side effect, is observed soon after a single dose of doxorubicin. It can be attributed to inhibition of respiratory enzymes by doxorubicin, which may result from competition between CoQ<sub>10</sub> and doxorubicin for the enzymatic sites of the coenzyme, because both compounds contain a quinone group. Enzyme inhibition may also result from oxidation of CoQ<sub>10</sub> by doxorubicin or doxorubicin-induced ROS, thus preventing CoQ<sub>10</sub> from functioning as a cofactor for electron transport. Because the respiratory generation of ATP is essential to myocardial function, inhibition of this function by doxorubicin would interfere with the electrophysiological activity of the heart, resulting in electrocardiographic changes and reduction of ejection fraction, which are characteristic of acute doxorubicin-induced cardiotoxicity.

Chronic doxorubicin-induced cardiotoxicity, which results from repeated doses of doxorubicin, may be attributable to depletion of mitochondrial CoQ<sub>10</sub>, which disrupts electron transport and mitochondrial respiratory bioenergetics, and may ultimately lead to loss of mitochondrial integrity and necrosis of cardiac myocytes. Studies in rabbits that demonstrate that mitochondrial degeneration is the earliest and most prominent ultrastructural change associated with the chronic cardiomyopathy induced by doxorubicin support this mechanism as the primary etiology. This mechanism is also consistent with the following clinical observations: chronic doxorubicin-induced cardiotoxicity is not reversible, the associated congestive heart failure is not responsive to **digitalis**, and antioxidants such as vitamin E and vitamin C do not prevent it.



## $\beta$ -CAROTENE

$\beta$ -Carotene is one of the more than 600 **carotenoids** that are produced by microorganisms and plants.  $\beta$ -Carotene, a lipid-soluble antioxidant, occurs naturally as a mixture of *cis* and *trans* isomers. *Cis*  $\beta$ -Carotene is a more effective antioxidant than *trans*  $\beta$ -carotene.

$\beta$ -Carotene has been shown to enhance the cytotoxicity of **melphalan** and **BCNU** on human **squamous carcinoma cells** and of **cisplatin** and **dacarbazine** on **melanoma cells**. In mice with transplanted mammary carcinoma,  $\beta$ -carotene enhanced the antitumor effect of cyclophosphamide, and in mice transplanted with FsaII fibrosarcoma or SCC VII carcinoma,  $\beta$ -carotene enhanced the antitumor effect of melphalan, BCNU, doxorubicin, and etoposide.  $\beta$ -Carotene (5 to 50 mg/kg) has been shown to reduce the genotoxicity of **cyclophosphamide** in mice and of **mitomycin C**, methyl methanesulfonate, and bleomycin in cultured cells.  $\beta$ -Carotene also reduced the rate of tumor induction in animals receiving chronic low doses of cyclophosphamide.

## GLUTATHIONE (GSH) AND GLUTATHIONE ESTERS

GSH, a tripeptide of glutamic acid, cysteine, and glycine (GluCysGly), is the major water-soluble antioxidant in the cytoplasm, nuclei, and mitochondria of cells. Many of the critical antioxidant functions of GSH require GSH peroxidase, which exists in several forms. Reduction of oxidized GSH (GSH disulfide), which is produced by reactions involving GSH peroxidase, requires GSH reductase.

GSH is not transported into cells. For circulating GSH to increase intracellular GSH concentrations, it must first be hydrolyzed to Glu and CysGly, which are subsequently transported into the cell and serve as substrates for GSH synthesis. Thus, GSH administered orally or parenterally, and that produced by the liver and released into the circulation enhance tissue levels of GSH by providing a source of its constituent amino acids. In contrast, GSH monoesters, which are well absorbed after oral administration, as is GSH, are readily transported to cells and then hydrolyzed to GSH and the corresponding alcohol. Thus, higher cellular levels of GSH result from oral administration of GSH monoesters than from oral administration of comparable doses of GSH.

GSH has been investigated for its protective effect against cisplatin-induced nephrotoxicity and peripheral neuropathy. Although oxidative damage most likely contributes to these toxicities, the protective effect of GSH can be accounted for by a chemical interaction between GSH and cisplatin instead of the antioxidant properties of GSH. GSH contains a thiol (sulfhydryl, an  $-SH$  moiety) group. Thiols are strongly nucleophilic and form stable covalent compounds with electrophilic compounds, such as the platinum coordination complexes **cisplatin** and **carboplatin**. Formation of the **thiol-platinum complex** inactivates the antineoplastic agent, which blocks not only its ROS-generating activity but also its cytotoxic effects. If inactivation occurs within the circulation before uptake of the drug by tumor cells, interference with the antineoplastic activity of cisplatin or carboplatin may occur. A similar concern exists if GSH is administered with alkylating agents, which are also strong electrophiles, because thiols can compete with DNA for alkylation, resulting in inhibition of antineoplastic activity. Thus, caution should be employed when GSH or any thiol compound is administered with platinum coordination complexes or alkylating agents.

Studies in laboratory animals have shown that intravenous administration of a high dose of GSH (up to 500 mg/kg) within 30 min of cisplatin injection protects against **cisplatin-induced neurotoxicity and nephrotoxicity**. Subcutaneous injection of GSH or GSH monoisopropyl ester 2.5 h before injection of cisplatin also protected mice against nephrotoxicity and the acute lethal toxicity of cisplatin, although the GSH ester was far more effective than GSH itself. In these studies, treatment with GSH or GSH ester did not interfere with the antitumor effectiveness of cisplatin, which can be explained by the characteristics of uptake of GSH and cisplatin. GSH and cisplatin are cleared rapidly from the circulation.

## N-ACETYLCYSTEINE

**N-Acetylcysteine** (NAC) is well absorbed after oral administration and readily transported into cells, where it is deacetylated. Although NAC, a thiol compound, is a free-radical scavenger, its more important antioxidant role is providing an intracellular source of cysteine, a substrate for GSH synthesis. However, because of its **nucleophilic thiol group**, NAC (similar to GSH) can form stable covalent compounds with electrophilic alkylating agents and platinum coordination complexes, which inactivate the anticancer drugs. In this regard, NAC has been shown to block the cytotoxicity and ROS-generating capability of cisplatin *in vitro*. Thus, as with GSH, one should exercise caution when administering NAC during chemotherapy with any electrophilic antineoplastic agent.

In animal studies, NAC has been shown to prevent **hemorrhagic cystitis** that results from administration of **cyclophosphamide** or its position isomer **ifosfamide**. Hemorrhagic cystitis results from the toxic effect of **acrolein**, a metabolic product of **cyclophosphamide** or its position isomer ifosfamide. The mechanism whereby NAC prevents this toxicity may be prevention of the intracellular depletion of antioxidants, such as GSH, by acrolein. Concomitant administration of NAC with cyclophosphamide or ifosfamide does not impair antineoplastic activity, because both anticancer drugs are inactive until they are metabolized by the liver to their **phosphoramidate mustard metabolites**.

NAC (50 to 2000 mg/kg), by means of free-radical scavenging or by enhancing intracellular levels of GSH, protects mice against acute doxorubicin-induced cardiotoxicity without interfering with the antitumor activity of the drug.

## GLUTAMINE

**Glutamine** is a conditionally essential amino acid. Although it does not possess antioxidant activity, it serves as a source of glutamate for GSH synthesis, thus supporting cellular antioxidant systems. Because glutamine is a primary fuel source for the rapidly proliferating enterocytes of the gastrointestinal tract, an important role of glutamine supplementation during chemotherapy is to reduce gastrointestinal injury that results from administration of antineoplastic drugs, especially the severe mucositis that results from treatment with antimetabolites such as **5-FU** and **methotrexate**.

Glutamine has been shown to enhance the antitumor effectiveness of **methotrexate** in laboratory animals, an effect that may be attributed to the increase of the intracellular tumor concentration of methotrexate by glutamine. Oral glutamine, but not intravenous glutamine, has also been shown to reduce the bacteremia and mucosal injury associated with methotrexate-induced enterocolitis in rats. Glutamine, administered by intragastric infusion, accelerates healing of the gut mucosa in rats receiving 5-FU.

## SELENIUM

Although inorganic **selenium** does not have antioxidant properties, selenium has an important role in cellular antioxidant defenses as a necessary component of **selenoproteins**. Selenium is incorporated into **selenoproteins** as **selenocysteine**. The **glutathione (GSH) peroxidases** are the best-characterized selenoproteins, although other circulating selenoproteins also have antioxidant functions.

In laboratory animals, parenteral administration of organic and inorganic selenium (210 to 12,000 µg/kg) has been shown to protect against **cisplatin-induced nephrotoxicity**. Protection occurs without apparent inhibition of the antineoplastic activity of cisplatin, although this may be attributed to the fact that selenium administration allows for higher doses of cisplatin to be used. Additionally, selenium administration reduces cisplatin-induced myelosuppression. This raises a concern similar to that with administering cisplatin with thiol compounds, i.e., that the reduction of myelosuppression may indicate that selenium can also interfere with the antitumor activity of cisplatin. Selenium, with chemical properties similar to those of sulfur, can bind with platinum and

inactivate the antineoplastic platinum coordination complexes. Thus, caution should be used when administering selenium during chemotherapy with **cisplatin** and **carboplatin**.

Parenteral administration of 27 to 60  $\mu\text{g}/\text{kg}$  of selenium to laboratory animals has been shown to inhibit doxorubicin-induced decreases in myocardial vitamin E and GSH peroxidase levels and to reduce changes in myocardial function that are consistent with acute doxorubicin-induced cardiotoxicity. Oral supplementation of **sodium selenite** also protects against acute doxorubicin-induced cardiotoxicity in rabbits.

## GENISTEIN AND DAIDZEIN

**Soybeans** contain a number of **isoflavones**, including **genistein** and **daidzein**, which are the most extensively studied. Soybean isoflavones enhance cellular antioxidant status by scavenging ROS and by increasing the activity of antioxidant enzymes including GSH peroxidase, **GSH reductase**, and **superoxide dismutase**. Genistein has also been shown to abrogate chemical- and ligand-induced generation of ROS *in vivo* and *in vitro*, although these effects result, in part, from activities of genistein other than its antioxidant activities. In addition to its antioxidant properties, genistein has other activities that may enhance the antineoplastic effects of cancer chemotherapy. Although clinical studies are yet to be done to assess the impact of soy isoflavones on cancer chemotherapy, a substantial number of preclinical studies have been performed.

Genistein is an inhibitor of **topoisomerase I and II**. Inhibition of **topoisomerase II** by genistein has effects similar to those of doxorubicin and etoposide, i.e., enhanced **topoisomerase-II-mediated DNA cleavage**, the formation of stable **covalent protein–DNA cleavage complexes**, and cell-cycle arrest at the G2–M junction. Genistein also inhibits the binding of ATP to its binding site on the enzyme, an activity not possessed by doxorubicin or etoposide. Thus, administration of genistein during chemotherapy with either of these drugs may enhance antineoplastic activity. Enhanced antineoplastic activity may also result from inhibition of topoisomerase I by genistein, although this effect, which results in arrest of the cell cycle in the S phase, requires a higher concentration of genistein than is necessary to inhibit topoisomerase II. Genistein has been shown to induce apoptosis in a number of tumor cell lines. Although apoptosis can be explained by inhibition of topoisomerase II activity, inhibition by genistein of **protein tyrosine kinases (PTKs)** may also contribute to the process.

## QUERCETIN

Quercetin, a ubiquitous polyphenolic flavonoid, is one of the most potent natural antioxidants. In addition to its antioxidant properties, quercetin exhibits other activities that may enhance antineoplastic activity. As with genistein, clinical studies are yet to be performed to determine the impact of quercetin on cancer chemotherapy.

Quercetin inhibits topoisomerase II activity. Similar to genistein, it enhances topoisomerase-II-dependent DNA cleavage complexes. It also inhibits topoisomerase-II-catalyzed ATP hydrolysis. Because quercetin is an intercalative compound, it may enhance DNA cleavage by a mechanism similar to that of doxorubicin. Quercetin also inhibits several PTKs, with  $\text{IC}_{50}$  values that are comparable to or lower than those of genistein.

Quercetin has been shown to inhibit the growth of several human and animal cancer cell lines *in vitro*. However, the sensitivity of different cell lines varies considerably. In human breast cancer cells the  $\text{IC}_{50}$  of quercetin for inhibition of growth was 23  $\mu\text{M}$  (7  $\mu\text{g}/\text{ml}$ ), whereas in human gastric cancer cells the  $\text{IC}_{50}$  was 32 to 55  $\mu\text{M}$ . A head and neck squamous cell carcinoma line is unaffected by quercetin at  $<110 \mu\text{M}$ . Because growth inhibition of sensitive cells results from arrest of cell-cycle progression at the G<sub>1</sub>–S boundary, this effect of quercetin is likely to be independent of its inhibition of topoisomerase II.

Quercetin has been shown to enhance the cytotoxicity of several antineoplastic agents. In multidrug-resistant cancer cells, quercetin markedly enhanced the growth-inhibitory effects of doxorubicin, although it did not affect the cytotoxicity of **doxorubicin** in drug-sensitive cells. In drug-sensitive cancer cells, quercetin has been shown to enhance the antiproliferative activity of **cisplatin**, **nitrogen mustard**, **busulfan**, and **cytosine arabinoside**. Quercetin also enhances the antitumor activity of cisplatin in athymic nude mice implanted with a human large-cell lung cancer.

## CONCLUSIONS

Dietary supplementation with antioxidants may provide a safe and effective means of enhancing the response to cancer chemotherapy. **Vitamin E** may prove to be an important nutrient for enhancing antineoplastic activity because of its role in preventing lipid peroxidation, thus maintaining the rapid rate of proliferation of cancer cells. Other antioxidants may be important because of their antioxidant properties, as well as for activities such as inhibition of topoisomerase II and PTKs.

The quality of life of patients after chemotherapy may be improved by dietary supplementation with antioxidants that reduce or prevent chemotherapy-induced side effects. Although approved cytoprotectants are available, including **dexrazoxane** for **doxorubicin-induced cardiotoxicity**, **amifostine** for **cisplatin-induced nephrotoxicity**, and **mesna** for **ifosfamide-induced hemorrhagic cystitis**, these agents are not without adverse effects. For example, **dexrazoxane** can reduce the antineoplastic activity of doxorubicin. This most likely results from complex formation and inactivation of doxorubicin, which may also prevent doxorubicin from interfering with **coenzyme Q<sub>10</sub>** (CoP<sub>10</sub>) biosynthesis and function, thus explaining the cardioprotective effect of dexrazoxane. **Dexrazoxane** is also myelosuppressive and may increase the risk of secondary malignancies. **Amifostine** can induce hypotension, hypocalcemia, and nausea, and administration of mesna is associated with nausea, vomiting, and diarrhea. In contrast, certain dietary antioxidants, in doses that are without adverse effects, can ameliorate some side effects of cancer chemotherapy. In this regard, **CoQ<sub>10</sub>** may prove to be an effective means of preventing cardiotoxicity without compromising antineoplastic activity when chemotherapy employs the versatile and highly effective drug doxorubicin. However, much more work is needed to establish a clear role for the use of dietary supplements as an adjunct to cancer chemotherapy (Conklin, 2000; and General References).



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# 9 Herbal Drugs and Their High Demand in Treating Diseases

The philosophies of one age become the absurdities of the next, and the foolishness of yesterday will become the wisdom of tomorrow.

— Sir William Osler

## INTRODUCTION

Not many years ago, medical advances and innovations in the pharmaceutical industry made it seem that the use of herbal remedies in developed countries would gradually diminish to insignificant levels. It is a paradox, therefore, that at a time when there is such an unprecedented number of therapeutic drugs available for the treatment of several diseases, herbal remedies continue to be in demand among the general public (NeWall et al., 1996).

Academic medical centers are currently facing up to the challenge of incorporating so-called **alternative medicine** and **integrative medicine** into the educational programs of their scientifically based institutions. The question is no longer whether it should be done but how to do it. (Fishman, 2001; Weil, 2005).

Recent surveys show that at least half the population in the U.S. uses one of the diverse array of **complementary and alternative medicine** (CAM) practices. Virtually all these are complementary rather than alternative. These figures have grown dramatically over the past decades despite the fact that few insurance plans provide coverage for many CAM procedures. Users pay an estimated \$27 billion a year out of pocket for these services and make more visits to CAM practitioners than to primary-care physicians.

Another indication of CAM's increasing presence in the health-care system is the fact that the National Center for Complementary/Alternative Medicine at the National Institutes of Health invests more than \$50 million a year to investigate the safety and efficacy of some of these approaches. Well-known institutions such as the Memorial Sloan Kettering Cancer Center and a small but growing number of health maintenance organizations and insurance plans now also offer some CAM procedures. Big business is awakening to the growing appeal of CAM; herbal remedies, alone, have become a \$10 billion annual industry that is growing at a projected annual rate of 20 to 30%.

No single definition adequately captures the range of practices that fall under the CAM rubric. Those that define CAM as practices that are not part of mainstream medicine, or as practices used by patients to manage their own health care, or as therapies not widely taught in Western medical schools or available in most hospitals, fail to capture the complexity of this field. CAM includes health-care practices that range from the use of vitamins, herbal remedies, and massage therapies to the ancient traditions of **Ayurveda** and **Chinese medicine**, along with **chiropractic techniques**, **naturopathy** **homeopathic medicine**, **meditation**, **hypnosis**, **acupuncture**, and a host of other less well-known approaches to health and health care.

Although their usage is standard practice in much of the world, most CAM procedures have never been tested according to the rigorous scientific standards of Western, evidence-based med-

icine. Therefore, the response of medical practitioners to the growing CAM phenomenon has ranged from an outright dismissal of practices not proved safe and effective to a gradual recognition that such extensive use can no longer be ignored. Surveys suggest that at least half of practicing physicians want to know more about CAM so that they can advise and guide their patients (Fishman, 2001).

Other studies show that most CAM users are not abandoning Western medicine, but want the best of both worlds — an alternative caregiver with strong ties to the medical establishment and a physician who understands and makes appropriate referrals to CAM therapies. But this poses yet another problem for physicians, for studies also show that many CAM users do not tell their physicians what they are doing. Most practicing physicians know almost nothing about the potential benefits or risks of CAM because their training has focused almost exclusively on Western scientific medicine.

Academic health centers have started to respond to the challenge of CAM, both by introducing content into medical curricula and by considering research into some of these approaches. Perhaps they recognize that by ignoring CAM, they will fail future physicians and their patients.

## LAWS REGULATING HERBS AND DIETARY SUPPLEMENTS

### FOOD, DRUG, AND COSMETIC ACT

In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act, which served to:

- Extend control to cosmetics and therapeutic devices
- Require new drugs to be shown safe before marketing
- Institute a new system of drug regulation
- Eliminate the Sherley Amendment requirement to prove intent to defraud in drug misbranding cases
- Provide that safe tolerances be set for unavoidable poisonous substances
- Authorize standards of identity, quality, and fill-of-container for foods
- Authorize factory inspections
- Add the remedy of court injunctions to the previous penalties of seizures and prosecutions (Hoffmann and Manning, 2002; Richter, 2003; Murray, 1995; McIntyre, 1992).

The Food Additives Amendment was added in 1958, requiring manufacturers of new food additives to establish safety. **The Delaney proviso** prohibited the approval of any food additive shown to induce cancer in humans or animals, and the FDA published the first list of substances, including herbs and spices, as **Generally Recognized As Safe** (GRAS) in the Federal Register. The list contained nearly 200 substances. This list is now compiled under Title 21 of the **Code of Federal Regulations**.

### NUTRITION LABELING AND EDUCATION ACT OF 1990 (NLEA)

The Nutrition Labeling and Education Act of 1990 requires packaged foods to bear nutrition labeling and health claims that are consistent with terms defined by the Secretary of Health and Human Services (i.e., approved by the FDA). The law preempts state requirements regarding food standards, nutrition labeling, and health claims, and, for the first time, authorizes some health claims for foods. The food ingredient information panel, serving sizes, and terms such as *low fat* and *light* are standardized. The phrase “herbs, or similar nutritional substances” was added to the term *dietary supplement*.

The NLEA has been successful in raising consumer awareness and confidence about the role of nutrition in promoting health and reducing the risk of disease, and has brought structure to a

field that in the 1980s had no regulatory framework. With this success and the growing interest in health maintenance promotion and disease risk reduction, NLEA served as a springboard to the **Dietary Supplement Health and Education Act (DSHEA)** of 1994 which established the legal basis for dietary supplements to become a core element of self-care in the U.S.

### **DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994 (DSHEA)**

In 1994, DSHEA defined dietary supplements and dietary ingredients, established a new framework for ensuring safety, outlined guidelines for literature displayed where supplements are sold, provided for the use of claims and nutritional support statements, required ingredient and nutrition labeling, and granted the FDA the authority to establish good manufacturing practice regulations. The law also required formation of an executive-level Commission on Dietary Supplement Labels and an Office of Dietary Supplements within the National Institutes of Health. Enforcement authority for the FDA under the Food, Drug, and Cosmetic Act and of the Federal Trade Commission (FTC) under the Federal Trade Commission Act remained unaltered and substantial.

### **FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT (FDAMA)**

Before the Food and Drug Administration Modernization Act of 1997, companies could not use a health claim or nutrient-content claim in food labeling unless the FDA published a regulation authorizing such a claim. Two new provisions of FDAMA now permit distributors and manufacturers to use such claims if they are based on current published authoritative statements from certain federal scientific bodies, or from the National Academy of Sciences. These provisions are intended to expedite the process by which the scientific basis for such claims is established, and they place dietary supplements on an equal footing with conventional foods.

Despite popular beliefs from consumer advocates and from the media about an unregulated industry, the herb and dietary supplement industry, which includes spices, is one of the best regulated with a substantial number of laws, regulations, and proposed regulations at the federal level. According to remarks by the FDA Commissioner before the House Committee on Government Reform, March 25, 1999, "FDA has tools at its disposal to take enforcement actions against dietary supplements found to have safety, labeling, or other violations of the FD + C Act, as amended by the Dietary Supplement Health and Education Act (DSHEA) of 1994" (Soller, 2000).

Both the FDA and the FTC have displayed considerable enforcement authority, since DSHEA, to ensure that safe, beneficial, and quality dietary supplements are available for health promotion, maintenance, and disease risk reduction, as intended by Congress in the passage of DSHEA. Despite assertions to the contrary usually made by persons unfamiliar with regulatory issues, the herb and dietary supplement industries are substantially regulated; however, these regulations are significantly different from those in the pharmaceutical industry. The FDA has to prove that the herbs and spices are unsafe before they can regulate them. Spices and flavorings are used in foods and alcoholic beverages, both of which are regulated for filth, identification, decomposition, and other components; the list is then published as part of GRAS. Herbs used in pesticides are regulated, but until it can be established that herbs are foods, it will be difficult to ascertain whether they are capable of killing people.

Much of the confusion surrounding the regulation of herbal products has abated since the passage of DSHEA. No other law has ever received as much direct grassroots advocacy, with the number of supportive letters to Congress topping 2 million. Congressional intent in passing the law was to give consumers the right to make their own choices about "preventive health-care programs based on data from scientific studies of health benefits related to particular dietary supplements."

The FDA and the FTC have a long-standing agreement governing the division of responsibilities between the two agencies. With regard to dietary supplements, the FDA has the power to:



- Stop any company from selling a dietary supplement that is toxic or unsanitary
- Stop the sale of a dietary supplement that has false or unsubstantiated claims
- Take action against dietary supplements that pose “a significant unreasonable risk of illness or injury”
- Stop any company from making a claim that a product cures or treats a disease
- Stop a new dietary ingredient from being marketed if the FDA does not receive enough safety data in advance
- Require dietary supplements to meet strict manufacturing requirements (Good Manufacturing Practices), including potency, cleanliness, and stability

The FTC has the power to:

- Enforce laws outlawing “unfair or deceptive acts or practices” to ensure that consumers get accurate information about dietary supplements so they can make informed decisions about these products
- Challenge and stop advertising that is not adequately substantiated
- Investigate complaints or questionable trade practices, either informally or formally, where it has strong compulsory investigative authority, including the power to require a respondent to produce documents, give testimony, or answer written questions
- Negotiate a consent order or proceed through an FTC adjudication resulting in a cease and desist order, which can be quite broad in its scope
- Seek preliminary and permanent injunctions to stop false advertisements or other violations of the FTC Act
- Seek civil penalties for violations of trade regulation rules

Since the passage of DSHEA, both the FDA and the FTC have been active in building the regulatory framework for dietary supplements. For example, in the last four decades, the FDA has published 143 proposed and final rules in the *Federal Register* relating to dietary supplements. Between 1962 and 1981, the FDA issued 52 such publications, most related to its attempt to regulate vitamins and minerals as drug products. From December 1981 to May 1993, the FDA issued no documents pertaining to the regulation of dietary supplements; but since the passage of DSHEA in 1994, the agency has issued 91 *Federal Register* publications, a 66% increase since 1962. These proposed and final rules cover such important enforcement topics as labeling, Good Manufacturing Practices, development of a comprehensive regulatory strategy for dietary supplements, and issues relating to ingredient safety (Hoffmann and Manning, 2002).

## SCIENTISTS WHO PIONEERED HERBAL MEDICINE

In a book entitled *Plant Drugs that Changed the World*, Taylor (1965) described the discovery and use of:

- The Andean shrub that yields **cocaine**
- The Indian shrub that gave us **reserpine**
- The tropical tree yielding **strychnine**
- **Ergot**, a blessing and a scourge
- The Peruvian tree that helped control **malaria**
- The Chinese subshrub that yields **ephedrine**
- Foxglove, the only source of **digitalis**
- Belladonna alkaloid, the source of **atropine**
- Bitter aloes, one of the older **cathartics**
- The African arrow poison that became **ouabain**

- **Autumn crocus**, the remedy for gout
- **Chaulmoogra**, an ancient remedy for leprosy
- A **Mexican yam** that yields hormones

Taylor stated that the faintest whispers from the earth sometimes point to Nature's deepest secrets. Some of Nature's secrets seem so fantastic that scientists first ignored them, but later admitted that there might be something in it. Generally, these skeptics deride and categorize such rumors as "Sunday supplement science." A few of these whispers from the earth came from remote and primitive tribes and seemed so improbable that they slipped into obscurity, only to confound scientists years later. The brilliant chemists and perceptive physicians who ultimately listened to such whispers have given us a rich battery of life-saving drugs. They will probably be the first to admit that "**jungle lore may lead to medical triumph.**" Not all of Nature's secrets come from dank and sultry rain forests. Simple country people, who know nothing of chemistry or pharmacology, have ears better tuned to catch these whispers than city folks. Rustic lore often contains hidden treasures that Nature has secreted in the roots, bark, sap, leaves, flowers, fruits, and seeds of plants. Some of these are now worldwide remedies, many of them were worthless, and a few hatched a spate of fantastic quackery.

**John C. Krantz, Jr.**, Emeritus Professor of Pharmacology at the University of Maryland School of Medicine, in a book entitled *Historical Medical Classics Involving New Drugs*, while describing **William Withering** and the discovery of **digitalis**, refers to a painting entitled *Golden Sovereigns for the Secret of the Wayside Flower*. A distinguished-looking William Withering is depicted handing an "old lady" gold coins as she sits on the steps of her cottage in Shropshire surrounded by the **purple foxglove** (Krantz, 1974).

Such messages of hope have come from nearly every country. The secrets of Nature's bounty were often unlocked by people so simple that they never guessed their discoveries would someday reach the floor of the stock exchange. Centuries ago, for who knows how long, there must have been patient, watchful testing of hundreds of plants. How else to explain the final triumph?

Among these unsuspecting benefactors of mankind have been Indians from Amazonian rain forests; **arrow poisoners** from Africa and their cousins, the **ordeal poisoners**; Indians from the Andes; Greek peasants; the Jesuits of Lima; a Chinese emperor hundreds of years before the birth of Christ; a Shropshire farm woman, and scores of others.

Even our dear old grandmothers had cures made from "simples" — most of them from plants. Their reputed value has since been well explored, even remedy for "**kotekshofte**," a Persian word for a disease of unknown cause. But in spite of much fumbling, science has given us priceless remedies, many of them derived from the plant lore of people quite unaware of science. If their worth is proved, these remedies are now in the *United States Pharmacopoeia*, which is the bible of all American physicians. They have long since left the jungle, are dispensed by several doctors, and manufactured by huge pharmaceutical companies who charge more for them than many think is fair.

Such accredited remedies ought to have driven quackery out of the country. However, the belief in some magical cure still costs the public millions of dollars, because they do not know that the magic is imaginary. But who would not seek a remedy for the agony of gout, for the heart that flutters too much, for the misery of malaria, for a distraught mind, for the pain of arthritis, and a dozen other ills?

The hunt for real remedies has gone on for at least 1900 years, and perhaps longer, for we read of an Egyptian doctor in 1600 B.C. prescribing paregoric to "prevent the excessive crying of children." Today, these drugs are mostly derived from laboratories, but scientists and their primitive progenitors strive for a specific. Many real specifics are derived from plants. A recent medical dictionary defines a "specific" as "a remedy especially indicated for any particular disease."

The story of specifics and other remedies derived from plants is thus the record of centuries of trial and error. It deals with whispers from the earth that are now available in every drugstore.

For the specialist, the origin and use of these life-saving or pain-killing drugs is buried in voluminous books grouped together under the general heading of *Materia Medica*. These invaluable records are difficult for most of us to comprehend, for they are crammed with the jargon of botanists, the technicalities of pharmacologists, the lexicon of doctors, and the terrifying terminology of chemists.

But beyond such daunting complexities lies the history of our ultimate conquest of many diseases. Where these plants were found, who first used them, and how they reached us constitute the story of our emergence from what one pharmacologist called the “frailties of our existence” (Taylor, 1965). Furthermore, it is impossible to identify an individual culture throughout the world that first used herbal plants to treat specific diseases. In a book entitled *The Cherokee Herbal*, Indians are cited as using the following herbal plants to treat common maladies:

Anxiety: Catnip, celery, chamomile or yellowroot, clover, dandelion, gooseberry, heather, hops, Indian hemp or drowsy weed, jasmine, oats, periwinkle, lavender, motherwort, passionflower, skullcap, valerian, and vervain

Asthma: Anise, arrowroot, bitterweed, blackthorn, blue vervain, burdock, capsicum, coltsfoot, cotton, “co-we” (coffee), crested field fern, dandelion, evening primrose, eyebright, ferula, fireweed, foxglove, garlic, horehound, hyssop, licorice, lobelia or Indian tobacco, lungwort, ivy, maidenhair fern, mullein, rosemary, yarrow, and yellow dock

Bronchial/bronchitis: Anise, coltsfoot, elecampane, echinacea, fennel, flax, horehound, hyssop, marshmallow, mullein, peppermint, plantain, sundew, and thyme

Coughs: Anise, black cohosh, coltsfoot, comfrey, elecampane, ginseng, knotgrass, licorice, lobelia, lungwort, mullein, plantain, sage, spotted cranebill, thyme, wild cherry, and witchgrass

Colds: Anise, boneset, coltsfoot, comfrey, echinacea, elderberry, ginger, goldenseal (yellowroot), licorice, nettle, pleurisy root, slippery elm, spotted cranesbill, valerian, and willow bark or dogwood

Cold sores: Goldenseal (yellowroot), lemon balm, and licorice

Depression or “feeling low”: Lavender, oats, passionflower, and vervain

Earache: Echinacea, garlic, ginger, lemon balm, licorice, yellow dock, and yarrow

Eye soreness and irritation: Bilberry, eyebright, goldenseal (yellowroot), marigold, and rosemary

Eye: Berberine, eyebright, mullein, and yarrow

Fever: Ginseng, elderberry, feverfew, sassafras, vervain, wild ginger, willow bark, and yellow gentian

Gum soreness: Capsicum, dandelion, milk thistle, and willow

Headache: Capsicum, catnip, feverfew, ginger, passionflower, peppermint, thyme, valerian, willow bark or dogwood, and wood betony

Laryngitis: Coltsfoot, licorice, mullein, willow bark, and wild cherry

Motion sickness: Fennel, ginger, and peppermint

Mouthwash: Cloves, goldthread, oak, rosemary, spotted cranesbill, and sage

Nervousness: Hops, mistletoe, and passionflower

Respiratory complaints: Comfrey, mullein, marshmallow, and saw palmetto

Rest and calm: Anise, catnip, dill, evening primrose, fennel, melissa balm, hops, lavender, passionflower, peppermint, skullcap, St. John’s wort, and valerian

Sinus conditions: Capsicum, echinacea, goldenseal, and willow

Sore throat: Capsicum, comfrey, echinacea, ginger, goldenseal (yellowroot), licorice, marshmallow, mullein, plantain, wild cherry, and willow

Toothache: Blue flag (snake lily), clove, and garlic

**Some firmly believe in them and others do not.** The following text enumerates the consensus on herbal plants and their ancient uses. Although their usage is common, they have never been

tested by the rigorous and scientific standards of Western, evidence-based medicine. For example, **echinacea** is widely used as a herbal remedy for the common cold but efficacy studies have produced conflicting results, and there are a variety of echinacea products on the market with different phytochemical compositions. Turner et al. (2005) evaluated the effect of chemically defined extracts from *Echinacea angustifolia* roots on rhinovirus infection. The results of this study indicate that extracts of the *E. angustifolia* root, either taken alone or in combination with other medication, do not have clinically significant effects on rhinoviral infection or the clinical illness that results from it.

The following data provide information on herbal plants and their ancient and current medical uses. In citing this information, no attempt has been made to suggest dosage, and no dose–response actions have been provided. However, every attempt has been made to list plant species and their phytochemical characteristics. For example, *E. angustifolia* roots were originally used by North American Indians to treat a variety of infections and wounds. In the late 1800s, these echinacea preparations became popular as remedies for the common cold. There has been renewed interest in echinacea in the U.S. since the passage of the **Dietary Supplement Health and Education Act** in 1994 liberalized the regulation of herbal medicines. There are three species of echinacea with different phytochemical characteristics that are used for medicinal purposes. The phytochemical composition of echinacea preparations may also vary according to the part of the plant used, the method used to extract the material in the preparation, and even the geographic location and time of year that the plant is harvested (Turner et al., 2005).

Another example of this is **aloe**, one of the few medicinal plants that has been a popular cure for a long time. **Aloe latex** is used for its **laxative effect** and should not be confused with **aloe gel**, used both in cosmetics and in ointments for skin ailments. **Aloe whole leaf** is another preparation taken internally as a drink for a wide range of human diseases including **cancer, AIDS, ulcerative colitis**, and **other complaints**.

The genus *Aloe* comprises about 600 species, most of which are indigenous to South Africa (*A. ferox* Miller, *A. africana* Miller, *A. spicata* Baker); some have been introduced in Asia (*A. chinensis* Bak), the Barbados Islands in Central America (*A. barbadensis* Miller), and Europe (*A. arborescens* Miller). The genus *Aloe* includes trees (*A. ferox*), shrubs, and herbs (*A. barbadensis*); they are xerophytic plants with large, fleshy leaves having spines along the margin, and they resemble the agave or century plant (*Agave americana* Linne).

Nutrition should be given significant consideration in cancer prevention because almost a third of all cancer events can be prevented by a change in diet. Vegetables and fruit are excellent sources of cancer-preventive substances. *H. sabdariffa* L. belongs to the Malvaceae family. The calyces of *Hibiscus* have been used in traditional medicine. *Hibiscus* flowers contain **gossypetin, glucoside**, and **bibiscin**. *Hibiscus anthocyanin* and *Hibiscus protocatechuic acid* have the following effects: choleric and diuretic functions, decreasing blood pressure, reducing the viscosity of blood, and stimulating intestinal peristalsis. Thus, the dried flowers of *H. sabdariffa* are a functional natural product with a chemopreventive capacity. Chang et al. (2005) have shown that ***Hibiscus anthocyanins***' rich extract induces apoptotic cell death in human promyelocytic leukemia cells and hence has chemopreventive actions.

The following table provides a few examples of herbal plants and their ancient medical uses (Swerdlow and Johnson, 2000). Some individuals take herbal plants as medicines and others take them regularly as food products. No attempt has been made to distinguish between the two practices.

Herbal Plants	Ancient Medical Uses
<i>Achillea millefolium</i> (Yarrow, milfoil, nosebleed, woundwort, stanchweed)	The Latin name comes from the legend that Achilles cured wounds with yarrow during the Trojan War. It arrests internal and external bleeding. <b>Chamazulene</b> , found in yarrow's essential volatile oil, is an anti-inflammatory agent, an antiallergen, and an antispasmodic.

Herbal Plants	Ancient Medical Uses
<i>Aconitum napellus</i> (Aconite, monkshood, wolfsbane, soldier's cap)	Alkaloids found in the plant have analgesic and anti-inflammatory properties.
<i>Allium sativum</i> (Garlic)	Garlic has been used medicinally since the time of the ancient Egyptians (see Chapter 50).
<i>Aloe barbadensis</i> (Aloe vera)	Aloe's most important ingredients — <b>aloin</b> , <b>barbaloin</b> , and <b>aloe-emodin</b> — are responsible for its cathartic action (see Chapter 12).
<i>Ananas comosus</i> (Pineapple)	Pineapples have been used in tropical medicine for ailments ranging from constipation to jaundice.
<i>Angelica sinensis</i> (Dong quai, Chinese angelica, female ginseng)	It is used to treat many gynecological problems, namely irregular or delayed menstruation, premenstrual pains and cramps, menopausal hot flashes, and uterine bleeding.
<i>Aralia racemosa</i> (American spikenard)	Antitussive (see Chapter 47).
<i>Arnica montana</i> (Arnica, mountain daisy, mountain tobacco, leopard's bane)	The plant has been shown to be an analgesic and an anti-inflammatory, most likely due to <b>sesquiterpene lactones</b> (see Chapter 47).
<i>Artemisia absinthium</i> (Wormwood, artemisia)	Antihelminthic. One constituent of wormwood is <b>thujone</b> , which is toxic if taken in improper doses. The USFDA lists it as an unsafe herb.
<i>Aspilia mossambicensis</i> (Aspilia, wild sunflower)	Antihelmintic Aspilia is not only a powerful antiparasitic but also an effective antibiotic.
<i>Astragalus membranaceus</i> (Astragalus, Huang Qi, milk vetch)	A diuretic and an immunostimulant. It is commonly used to treat diabetes and nephritis. In the U.S., it is used to strengthen immune function after cancer chemotherapy.
<i>Atropa belladonna</i> (Belladonna, deadly nightshade, dwale)	Belladonna contains <b>tropane alkaloids</b> , <b>atropine</b> , <b>hyoscamine</b> , and <b>scopolamine</b> , all of which have sedative and antispasmodic effects (see Chapter 14).
<i>Barosma betulina</i> (Buchu)	Diuretic. <b>Fluidex</b> and <b>Odrinil</b> , two prescription drugs that relieve premenstrual bloating, both contain buchu.
<i>Bertholletia excelsa</i> (Brazil nut, creamnut)	In Brazilian folk medicine, the husks of the seedpods are administered in the form of tea to treat stomachaches.
<i>Bryonia alba</i> (White bryony, wild hops, English mandrake, wild vine, ladies' seal)	In homeopathy, it is used to treat fevers that are accompanied by dry mouth and extreme thirst.
<i>Camellia sinensis</i> (Tea, green tea, black tea)	Tea contains a large number of strong antioxidants called catechins (see Chapter 38).
<i>Camptotheca acuminata</i> (Xi shu, tree of joy, happy tree, cancer tree)	It has been used to treat leukemia. Other anticancer drugs have been modified from <i>Camptotheca acuminata</i> . <b>Topotecan</b> is used to treat ovarian and small-lung cancers. <b>Irinotecan</b> is used to treat metastatic colorectal cancer.
<i>Cannabis sativa</i> (Marijuana, cannabis, hemp, hashish)	Marijuana is the only plant known to contain the psychoactive constituent <b>tetrahydrocannabinol</b> , or THC. When smoked or eaten, marijuana relieves nausea, moderates chronic pain, increases appetite, and reduces muscle spasms (see Chapter 18).
<i>Capsicum annuum</i> (Cayenne pepper, red pepper)	Cayenne pepper's active constituent, <b>capsaicin</b> , produces a hot sensation and is used to treat pain caused by herpes, shingles, arthritis, rheumatism, and other neuralgias by desensitizing the neurons that transmit pain. Capsaicin is used to treat overactive bladders by desensitizing the neurons that trigger excess activity. Cayenne may stimulate the release of opiate-like <b>endorphins</b> and contain aspirin-like salicylates.

Herbal Plants	Ancient Medical Uses
<i>Caulophyllum thalictroides</i> (Blue cohosh, papoose root, squawroot)	It stimulates smooth muscle contraction and is used to assist the labor of childbirth. It's action is similar to that of <b>oxytocin</b> .
<i>Chondrodendron tomentosum</i> (Curare, pareira)	It contains D-tubocurarine and is given with general anesthesia to produce muscular relaxation (see Chapter 26).
<i>Cinchona pubescens</i> (Cinchona)	It is used in the treatment of malaria. Cinchona bark is also the source of quinidine, used to treat cardiac arrhythmias (see Chapter 22).
<i>Cinnamomum aromaticum</i> (Cinnamon)	Cinnamon is an ancient herbal medicine, long used to treat gastrointestinal disorders. It increases intestinal movement, heart rate, and perspiration by stimulating the vasomotor center. It improves circulation. The astringent <b>tannins</b> in cinnamon treat diarrhea; the <b>catechins</b> treat nausea. Its essential oils are considered analgesic, antifungal, and germicidal.
<i>Coleus forskohlii</i> (Coleus forkolil)	It contains <b>diterpene forskolin</b> and is used for circulatory problems such as heart failure and high blood pressure, and for respiratory problems such as bronchial asthma.
<i>Crataegus oxyacantha</i> (Hawthorn, maybush, mayhaw, whitethorn, mother-die, bread and cheese)	It is a diuretic. An extract of the flowers and leaves improves cardiac output and the contractility of the heart muscle. Flavonoids in hawthorn have been shown to increase blood flow in the heart by dilating blood vessels in coronary arteries. Hawthorn has lowered cholesterol in animal studies, probably due to its oligomeric <b>procyanidins</b> (OPC), a type of bioflavonoid similar to that found in the extracts of grape seed and grape skin.
<i>Cucurbita pepo</i> (Pumpkin, vegetable marrow)	Pumpkin seeds contain <b>cucurbitacins</b> and were listed as one of the <b>four greater cold seeds</b> in an 18th century list of medicines. Today, pumpkin is used to treat irritable bladder and prostate complaints, namely benign prostatic hyperplasia (BPH).
<i>Curcuma longa</i> (Turmeric, haldi, jiang huang)	Turmeric is highly regarded in Ayurvedic medicine, especially as a remedy for jaundice and digestive problems (see Chapter 19).
<i>Daucus carota</i> (Carrot, bird's nest, bee's nest, Queen Anne's lace)	An excellent source of beta carotene and vitamin A, reducing the risk of heart attacks.
<i>Delphinium staphisagria</i> (Delphinium, stavesacre, lousewort)	A toxic plant with anthelmintic properties.
<i>Digitalis purpurea</i> (Foxglove, fairy's glove, folk's glove)	Treatment of congestive heart failure (see Chapter 35).
<i>Dioscorea villosa</i> (Wild yam)	It contains <b>diosgenin</b> and is analgesic in nature. Wild yam is also a source of synthetic DHEA, a hormone that inhibits the production of excess fatty acids and cholesterol.
<i>Echinacea angustifolia</i> (Echinacea, coneflower, narrow-leaved purple coneflower, Rudbeckia)	Antiseptic. It has antiviral properties.
<i>Ephedra sinica</i> (Ma-huang, ephedra)	Treatment of asthma, coughs, and flu (see Chapter 29).
<i>Erythroxylum coca</i> (Coca)	It contains cocaine, a local anesthetic (see Chapter 23).
<i>Eucalyptus globulus</i> (Eucalyptus, blue gum tree)	The oil from eucalyptus leaves contains <b>eucalyptol</b> , a chemical that makes it a very powerful antiseptic.
<i>Foeniculum vulgare</i> (Fennel)	Fennel oil contains <b>anethole</b> and <b>fenchone</b> , which reduce bloating and in higher concentrations act as antispasmodics.
<i>Galega officinalis</i> (Goat's rue, French lilac)	It contains <b>Galegin</b> , which reduces blood glucose and is therefore used in diabetes mellitus.

Herbal Plants	Ancient Medical Uses
<b><i>Gelsemium sempervirens</i></b> ( <i>Yellow jessamine, yellow jasmine, false jasmine, woodbine</i> )	A sedative. Yellow jessamine root is extremely toxic.
<b><i>Ginkgo biloba</i></b> ( <i>Ginkgo, Kew tree, maidenhair tree</i> )	Extract of ginkgo leaf increases memory performance and learning capacity, deactivates toxic radicals, and improves blood flow.
<b><i>Glycine max</i></b> ( <i>Soy, soybean, soya</i> )	Soy's principal constituents, <b>isoflavones</b> , bind at estrogen receptor sites. These phytoestrogens, or plant estrogens, are used to treat menopausal symptoms, especially hot flashes, and to help prevent osteoporosis. Soy is also used to inhibit estrogen-dependent cancers, such as breast, ovarian, and prostate malignancies. The isoflavones <b>genistein</b> and <b>daidzein</b> block natural estrogen and its potentially harmful effects, but simultaneously give the benefits of increased estrogen.
<b><i>Glycyrrhiza glabra</i></b> ( <i>Licorice, sweetroot, gan cao</i> )	It contains glycyrrhizic acid, is 50 times sweeter than sugar, and can accelerate the healing of gastric ulcers. Licorice treats such respiratory ailments as bronchitis and asthma and is an ingredient in herbal cough medicines. <b>Glabridin</b> inhibits inflammation of skin.
<b><i>Guaiacum officinale</i></b> ( <i>Guaiacum, guaiac, guajacum, Lignum vitae</i> )	Bark was used in the treatment of syphilis.
<b><i>Hamamelis virginiana</i></b> ( <i>Witch hazel, Hamamelis, winterbloom, tobacco wood</i> )	Witch hazel is a rich source of tannins, which tighten skin proteins to provide increased resistance to inflammation, assist the healing of broken skin, and help repair damaged blood vessels. Witch hazel is useful for a variety of skin conditions, as well as for varicose veins, hemorrhoids, and bruises.
<b><i>Humulus lupulus</i></b> ( <i>Hop</i> )	Many of the hop's constituents, including <b>valerianic acid</b> , have a sedative effect, and it is now used to treat insomnia, restlessness, and anxiety. Its bitter principals, <b>humulon</b> and <b>lupulon</b> , are gastrointestinal stimulants used to treat indigestion and loss of appetite. These bitter acids also have antibacterial and antimicrobial properties. The hop is believed to contain chemicals that promote menstruation, and certain flavonoids have shown potential chemopreventive activity against breast and ovarian cancer.
<b><i>Hydnocarpus kurzii</i></b> ( <i>Chaulmoogra, hydnocarpus</i> )	The oil has long been used as an accepted treatment for leprosy in China and India.
<b><i>Hydrastis canadensis</i></b> ( <i>Goldenseal, Indian dye</i> )	Goldenseal contains the alkaloid <b>berberine</b> , which has antibiotic, antibacterial, and antifungal properties.
<b><i>Hypericum perforatum</i></b> ( <i>St. John's wort, Klamath weed</i> )	Antidepressant (see Chapter 27 and Chapter 43).
<b><i>Ignatia amara</i></b> ( <i>Ignatius bean, St. Ignatius bean</i> )	It is a toxic plant and has properties similar to strychnine, which is obtained from <i>Strychnos nux vomica</i> . Once recommended as a remedy for cholera, the plant is used to treat fever and acute emotional and mental afflictions such as hysteria, insomnia, and depression. In toxic doses, it causes muscle spasms, painful convulsions, and even death by asphyxiation (see Chapter 62).
<b><i>Juniperus communis</i></b> ( <i>Common juniper</i> )	A diuretic. Pregnant women should not eat juniper berries because the berries can stimulate uterine contractions.
<b><i>Laminaria digitata</i></b> ( <i>Kelp, tangleweed</i> )	It contains <b>iodine</b> and has been used to treat malfunctioning of thyroid gland.
<b><i>Larrea tridentata</i></b> ( <i>Chaparral; creosote bush, greasewood, stinkweed</i> )	Chaparral mouthwash may reduce cavities by up to 75%. Products derived from extracts of chaparral are currently marketed as treatments for several forms of herpes.
<b><i>Lavandula angustifolia</i></b> ( <i>Lavender</i> )	Lavender is used as an antifatulent and a treatment for mild stomach disorders.

Herbal Plants	Ancient Medical Uses
<i>Lentinula edodes</i> (Shiitake, Reishi)	<b>Lentinan</b> , found in shiitake mushrooms, possesses immunostimulant and antitumoral properties. Lentinan can also prevent platelet adhesion, which causes the clots responsible for coronary artery disease and strokes.
<i>Leontodon utumnales</i> (Dandelion)	Dandelion contains <b>eudesmanolides</b> , a diuretic.
<i>Ligustrum vulgare</i> (Common privet, prim)	Berries are a strong laxative, and the leaves and flowers are used to treat menstrual disorders. Studies have shown that a combination of privet and astragalus may be an immunostimulant.
<i>Linum usitatissimum</i> (Flax)	Studies using animals suggest that regular consumption of flaxseed can protect against certain types of tumors and reduce the risk of colon cancer. Flaxseed, also called <b>linseed</b> , has been shown in some studies to improve kidney function, lower LDL cholesterol levels, and increase bowel movements. A compound derived from flax is being investigated as a possible treatment for lupus.
<i>Lobelia inflata</i> (Lobelia, Indian tobacco, pukeweed, bladderpod)	Lobelia contains <b>Lobeline</b> and is used in treating asthma.
<i>Lycopodium clavatum</i> (Common club moss, running club moss, lycopodium, wolf's claw, ground pine)	The whole plant is dried, chopped, and prepared as a tea in a traditional medicine for kidney and bladder complaints.
<i>Matricaria chamomilla</i> (Genuine chamomile, common chamomile)	Chamomile contains <b>azulene</b> and is used in treating ulcers.
<i>Medicago sativa</i> (Alfalfa, lucern)	Arabs discovered the herb and named it <i>al-facl-facah</i> , or “father of all foods,” which the Spanish changed to “alfalfa.” It is rich in nutrients and minerals, including calcium, potassium, iron, magnesium, and zinc. A source of eight essential amino acids, alfalfa is used in China to treat fever, in India to treat ulcers, in Iraq and Turkey to treat arthritis, and in the U.S. in some natural therapies for cancer. It has also been employed for urinary infections, menopause, fatigue, and as an antibiotic and antiasthmatic.
<i>Mitchella repens</i> (Partridgeberry, squaw vine)	Partridgeberry is thought to contain tannins, glycosides, and <b>saponins</b> , and is generally believed to have a tonic action on the uterus and ovaries. Partridgeberry has a long history of use among Native American women. Numerous tribes used it to treat menstrual pains and cramps, to regulate menstruation and relieve heavy bleeding, and to induce childbirth and ease delivery.
<i>Monarda didyma</i> (Scarlet bergamot, Oswego tea, bee balm)	It is used to treat nausea, vomiting, and upset stomach. Bergamot contains the aromatic antiseptic <b>thymol</b> , which is widely used by dentists and modern medical practitioners. Brewed and ingested, Oswego tea treats flatulence and insomnia.
<i>Nepeta cataria</i> (Catnip, catmint)	Catnip contains <b>nepetalactone</b> , a volatile oil similar to that found in valerian root. It acts as a mild sedative to relieve migraines, menstrual cramps, tension, and anxiety. Many consider catnip effective in treating flatulence and indigestion; others regard it as a diuretic. Ozarks use catnip to treat aching teeth. A weak catnip tea is a traditional remedy to help soothe colicky babies.
<i>Nicotiana rustica</i> (Wild tobacco)	The French ambassador to Portugal, Jean Nicot, from whose name came the word <i>nicotine</i> , considered tobacco a cure for headaches and gout. Nicholas Monardes, a Spanish doctor, listed 36 illnesses that tobacco treated. Today, tobacco is linked to various forms of cancer.
<i>Oenothera biennis</i> (Evening primrose, fever plant, scabish)	Evening primrose contains <b>gamma-linolenic acid</b> (GLA), an essential fatty acid that supports the production of <b>prostaglandins</b> and thus helps maintain hormonal balance. It is approved in Britain to treat premenstrual syndrome. Native American women chewed evening primrose seeds to alleviate premenstrual and menstrual discomfort (see Chapter 59).



## Herbal Plants

***Onoclea sensibilis****(Male fern, apsidium)****Panax ginseng*** (*Ginseng, Chinese or Korean ginseng*)***Papaver somniferum****(Opium poppy)****Passiflora incarnata****(Passion flower)****Paullinia cupana*** (*Guarana, guarana*)***Petroselinum crispum****(Parsley, curly parsley)****Phoradendron flavescens****(American mistletoe, mistletoe, golden bough)****Phyllanthus niruri*** (*Phyllanthus, amla*)***Physostigma venenosum****(Calabar bean, ordeal bean)****Pilocarpus microphyllus****(Jaborandi, Arruda do mato)****Piper methysticum****(Kava, kava kava)****Podophyllum peltatum****(Mayapple, American mandrake, devil's apple, duck's foot)****Polygala senega*** (*Senega, senega root, Seneca snakeroot*)

## Ancient Medical Uses

A toxic plant containing **filicin** and **filmarone**. It is used as an antihelminthic.

Ginseng's primary constituents are **ginsenosides**, which stimulate the cardiovascular and central nervous systems to enhance physical and mental performance; **panaxans**, which lower blood sugar; and **polysaccharides**, which strengthen the immune system and help treat diabetes. Ginseng is also thought to have antioxidant, antiaging, and appetite-stimulating properties (see Chapter 37).

It possesses analgesic and antitussive properties (see Chapter 47).

Passion flowers contain **harmine** and **harmaline**, which have been used in the treatment of Parkinson's disease. Folk remedies use passion flower to treat depression and insomnia (see Chapter 65).

Guarana contains tannins and has been used to treat diarrhea. It also contains a high concentration of **caffeine**, which, in conjunction with the alkaloids **theobromine** and **theophylline**, gives guarana diuretic and stimulant properties. Guarana is used to treat fatigue, mild depression, headache, and migraine.

The most delicious Persian food, namely **Khoresh Ghaymeh Zabzee**, is made using parsley. Parsley's principal constituent, **apiol**, is effective against chills and fevers. Its secondary constituent, **myristicin**, in conjunction with apiol, gives parsley diuretic properties. It is used to treat cystitis, gout, high blood pressure, and rheumatic conditions. The medieval German herbalist **Saint Hildegard of Bingen** prescribed **parsley wine** to improve blood circulation. Parsley is rich in the bone strengthener **fluorine**, the breath freshener **chlorophyll**, and vitamins A, C, and E. Parsley root is also a strong uterine stimulant and was once employed to induce abortion.

Mistletoe contains **tyramine**, which stimulates uterine contractions. In Germany, mistletoe extract is an ingredient in many medications prescribed to regulate blood pressure.

Many species of phyllanthus have been used in **Ayurvedic medicine** for more than 2000 years. It is a traditional remedy for ailments such as jaundice, dysentery, diabetes, skin ulcers, and urinary tract infections. Phyllanthus's principal constituents — **lignans**, **alkaloids**, and **bioflavonoids** — have been found to act primarily on the liver, which confirms its traditional use in the treatment of jaundice. *Phyllanthus amarus* attracted the attention of Nobel prize winner Baruch Blumberg. He and others studied its uses in preventing hepatitis B and devised a vaccine.

Calabar bean's principal constituent is the toxic alkaloid **physostigmine**, which helps prolong the activity of acetylcholine, a neurotransmitter that stimulates gastric secretion, contracts smooth muscles, and dilates blood vessels. Chiefly employed to treat the eye, physostigmine is used to contract the pupil and drain excess fluid, which helps prevent optic nerve damage and loss of vision symptomatic of glaucoma. It is also used to reverse the central nervous system toxicity of anticholinergic drugs, such as atropine, and to stimulate the intestinal tract. Calabar bean is currently being studied for the treatment of Alzheimer's disease (see Chapter 14).

It is used in ophthalmology to contract the pupil and treat glaucoma in the early stages (see Chapter 14).

A local anesthetic and an analgesic. Kava contains two pain-relieving chemicals, **dihydrokavain** and **dihydromethysticin**, which are as effective as aspirin.

**Podophylotoxin**, a potentially lethal component of mayapple, blocks cell division and has tumor-inhibiting properties. Two drugs derived from it are approved for use in the U.S. **Etoposide** is used to treat testicular and small-cell lung cancer. **Teniposide** is employed with brain tumors and childhood leukemia (see Chapter 62).

Senega's principal constituents are **saponins**, including **senegins**. These saponins suppress coughing and their detergent activity breaks up phlegm. Senega is also thought to stimulate bronchial mucous gland secretion (see Chapter 47).

Herbal Plants	Ancient Medical Uses
<b><i>Prunella vulgaris</i></b> (Self-heal, heal-all, heart of the Earth)	It has been used to treat wounds.
<b><i>Prunus serotina</i></b> (Wild cherry, black cherry)	It contains <b>prunasin</b> , which, when broken down in the body, quells spasms in the smooth muscles that line the bronchioles. Wild cherry syrup is effective in treating coughs, bronchitis, whooping cough, and other lung problems.
<b><i>Pulsatilla vulgaris</i></b> ( <i>Pulsatilla</i> , windflower, anemone, pasqueflower, Easter flower)	<i>Pulsatilla</i> lowers arterial tension, dilates the pupils, and reduces respiration. Although there are no known hazards or side effects to the appropriate administration of extremely small therapeutic doses, <i>pulsatilla</i> is poisonous.
<b><i>Rauwolfia serpentina</i></b> (Indian snakeroot, <i>rauwolfia</i> )	Its active ingredient is <b>reserpine</b> , which lowers blood pressure and is a tranquilizer (see Chapter 56).
<b><i>Rhamnus purshiana</i></b> ( <i>Cascara sagrada</i> [sacred bark], <i>cascara buckthorn</i> )	<b>Aloe-emodin</b> , found in <i>cascara sagrada</i> , is being researched as a possible treatment for leukemia. This herb, which has had a place in the U.S. Pharmacopoeia since 1890, is one of the most popular herbal medicines in the world. It is included in many over-the-counter laxatives and is prescribed more than 2.5 million times a year. The bark must be dried for up to 1 year before it can be used officially as a laxative.
<b><i>Rosa canina</i></b> (Rose, rose hip, dog rose)	It contains many nutrients including Vitamins A, B, and K. It is used for colds, flu, and disorders of the urinary tract.
<b><i>Salix alba</i></b> (White willow, European willow)	The bark and leaves are rich in the <b>glucoside salicin</b> , an aspirin-like compound that is used in pain and fever.
<b><i>Sedum telephium</i></b> (Live-long, <i>orpine</i> , <i>stonecrop</i> )	<i>Live-long</i> has proven immunostimulant and anti-inflammatory properties because of the presence of two major polysaccharides. These polysaccharides may help inhibit tumors and increase the action of phagocytes, which effectively kill bacteria and viruses. <i>Live-long</i> is been used as a popular folk remedy for diarrhea.
<b><i>Serenoa repens</i></b> ( <i>Saw palmetto</i> )	<i>Saw palmetto</i> relieves urinary symptoms and flow measures associated with an enlarged prostate; it does not reduce the enlargement. <i>Saw palmetto</i> is chiefly employed to manage prostatic enlargement or benign prostatic hyperplasia (BPH). A hexane extract inhibits <b>5-alpha reductase</b> , the enzyme needed for the conversion of <b>testosterone</b> into <b>dihydrotestosterone</b> (DHT). <i>Saw palmetto</i> further antagonizes DHT binding at prostatic receptor sites, which increases the metabolism and excretion of DHT. It is also used to treat BPH-related inflammation (see Chapter 55).
<b><i>Silybum marianum</i></b> ( <i>Milk thistle</i> , <i>Marian thistle</i> )	<i>Milk thistle</i> is used to treat jaundice, cirrhosis, hepatitis, toxin poisoning — such as that induced by alcohol and industrial toxins — and other liver diseases. <i>Milk thistle</i> is also useful as an anti-inflammatory and a bile stimulant. It is employed in Europe to treat <i>amanita</i> mushroom poisoning. Its principal constituent, <b>silymarin</b> (actually a combination of three compounds called <b>flavonolignans</b> ), helps restructure liver cells to prevent toxins from penetrating that organ. It stimulates the regenerative ability of the liver by helping form new cells. Glutathione compounds, which are potent antioxidants and intermediates in cell metabolism, remove toxins from liver cells.
<b><i>Tanacetum parthenium</i></b> ( <i>Feverfew</i> )	<i>Parthenolide</i> , a constituent of <i>feverfew</i> , inhibits the release of certain chemicals, including the hormone <b>serotonin</b> , which is produced during a migraine attack, and certain inflammatory mediators, including the hormone <i>prostaglandin</i> , which regulates inflammation. <i>Feverfew</i> is used for prevention of migraines and headaches (see Chapter 30).
<b><i>Taxus brevifolia</i></b> ( <i>Pacific yew</i> )	The compound <b>paclitaxel</b> , from the bark of this plant, stabilizes microtubules, the part of the cell that maintains shape and aids in cell division. It combats certain cancers, most notably ovarian and breast cancer (see Chapter 62).

## Herbal Plants

***Theobroma cacao****(Cocoa, cacao, chocolate)****Thuja occidentalis****(Thuja, arborvitae, swamp cedar, white cedar)****Thymus vulgaris****(Thyme, wild thyme)****Trillium erectum****(Trillium, Beth Root, birthroot, wake-robin, stinking Benjamin)****Urtica gracilis****(Nettle, stinging nettle)****Vaccinium macrocarpon****(Cranberry)****Valeriana officinalis****(Valerian, setwell, phu, all-heal)****Veronica amygdalina****(Bitter leaf, Mujonso)****Viburnum prunifolium****(Black haw, snowball tree, king's crown, cramp bark)****Vinca rosea****(Rosy periwinkle)****Zingiber officinale****(Ginger)*

## Ancient Medical Uses

Central Americans have used cocoa for centuries to treat the pains of pregnancy and childbirth, fevers, and coughs. Cocoa's primary alkaloid, **theobromine**, has an effect similar to that of caffeine. Accordingly, theobromine and caffeine can relieve congestion during colds by opening the bronchial passages in the lungs. Theobromine also relaxes the smooth muscle in the digestive tract. In addition, cocoa contains **methylxanthines**, which have a diuretic, broncholytic, and vasodilatory effect.

It contains **Thujone**, which could be toxic. Native Americans used thuja for malaria, gout, scurvy, rheumatism, menstrual disorders, and coughs. Thuja's volatile oil acts as a stimulant, a diuretic, and an irritant. Thuja is used for respiratory tract infections and in conjunction with antibiotics in the treatment of bacterial skin infections and *Herpes simplex*.

The aromatic oil extracted from thyme leaves contains **thymol** and **carvacol**, which have preservative, antibacterial, and antifungal properties. Thyme is a bronchial antispasmodic that relaxes muscles in the respiratory tract, an effect that makes it a good treatment for bronchitis and whooping cough. Thyme also relaxes smooth muscles in the gastrointestinal tract and the uterus, making it effective as a digestive aid and reliever of menstrual cramps.

Native Americans and European settlers in North America used it to help with the labor of childbirth. Other gynecological symptoms this plant was used to relieve include menstrual problems, sore nipples, and discomforts of menopause.

The nettle is rich in vitamins A and C and in minerals, particularly iron, potassium, and silica. Modern scientific studies have focused on its diuretic action. It lowers systolic blood pressure by increasing volume, the root treats symptoms of benign prostatic hyperplasia (BPH) by increasing urine flow and reducing residual urine. Nettle herb is also used for bladder irrigation and to prevent and treat bladder and kidney stones (see Chapter 66).

Cranberry enhances the excretion of hippuric acid, a bacteria-fighting chemical. Recent studies support the speculation that eating cranberries or drinking their juice can prevent or fight urinary tract infections. Hippuric acid prevents *Escherichia coli* (*E. coli*) from adhering to the urinary tract. Cranberries also contain **arbutin**, which fights yeast infections. The berries are also used as a "**urinary deodorant**."

It is used as an hypnotic-sedative (see Chapter 65).

It contains antiparasitic, antitumoral, and antibacterial agents. Although it is used primarily to treat schistosomiasis, a disease caused by parasitic worms, bitter leaf concurrently relieves related problems such as diarrhea and malaise. In sub-Saharan Africa, bitter leaf is used to treat 25 more ailments, including fever, intestinal complaints, and malaria.

Native American women drank decoctions of Black haw bark to treat menopause and menstrual cramps, to ease pains following childbirth, and to prevent miscarriage.

Periwinkle has been shown to lower blood sugar and to act as a diuretic. The main alkaloids, **vinblastine** and **vincristine**, appear to bind to proteins in some microtubules, facilitating cancer-cell death (see Chapter 62).

In ancient India, ginger was called *vishwabhesaj*, "the universal medicine." It is commonly used to treat motion sickness and vertigo. Its primary constituents, **gingerols** and **shogaol**, soothe abdominal cramps and increase intestinal muscle contractions, and the proteolytic enzyme **zingibain** breaks down protein. Gingerols and shogaols also reduce pain and fever, suppress coughs, and have a mild sedative effect. The constituent **sesquiterone** has a specific action against the most common family of colds, rhinoviruses. Zingibain also exhibits anti-inflammatory properties, as do ginger's numerous antioxidant compounds.

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# 10 Algae

## INTRODUCTION

In herbal medicine, algae have an important role as they:

- Are used to treat roundworm disease
- Are potent neurotoxins
- Cause amnesic shellfish poisoning

The **red alga** *Digenea simplex* has been used for the treatment of **roundworm disease** for centuries. Its active principle is **kainic acid**. The related **domoic acid** is a constituent of another red alga, *Chondria armata*, used for the same purpose. These compounds, known as **kainoids**, are potent **neurotoxins** and **excitatory amino acids**. Kainoids are important tools in neurophysiological research. Domoic acids are also produced by diatoms and were responsible for the **shellfish poisonings** known as **amnesic shellfish poisonings** that occurred in Canada in 1987.

**Caulerpin** and **caulerpicin** have been described as toxic constituents of edible species of the **green algal genus** *Caulerpa*, but evidence in later studies indicates that they have no acute toxicity. Caulerpin, which has a structure related to **auxin**, promotes plant growth. **Caulerpenyne**, a toxic constituent of *Caulerpa taxifolia* and other inedible species, has been evaluated for its ecotoxicological effect in the Mediterranean regions, where *C. taxifolia* blooms explosively. Three different classes of compounds have been identified in the poisonings with species of the genus *Gracilaria*. They are **prostaglandin E<sub>2</sub>** from *G. verrucosa* in Japan, **aplysiatoxins** and related compounds from *G. coronopifolia* in Hawaii, and **polycavernosides** from *G. tsudai* in Guam (Higa and Kuniyoshi, 2000).

As a result, a large number of secondary metabolites have been described from various species of algae. Just the two best-studied groups, the **red algal genus** *Laurencia* and the brown algal family **Dictyotaceae**, account for more than 500 compounds. Many of these compounds are known to be **cytotoxic**, **ichthyotoxic**, or **antimicrobial**.

Some 400 species of seaweed are used as food, feed, medicines, fertilizers, and industrial raw materials in the world. The use of seaweed as food is perhaps more common in Asia and the Pacific regions than the rest of the world. In Japan, the majority of people take one or more kinds of seaweed in their daily diet. There are no records of poisonings with most frequently eaten seaweed such as “**kombu**” and “**wakame**” belonging to the brown algal family **Laminariaceae**, and “**nori**” to the red algal genus *Porphyra*. However, there are several recorded cases of poisonings with some other seaweed, i.e., brown algae *Nemacystus decipiens* and *Cladosiphon okamuranus*, and red algae of the genus *Gracilaria*.

Not many species of seaweed are widely known among folk remedies. A Chinese booklet, the title of which may be translated as “Medicinal Marine Organisms of the South Sea,” published in 1978 by the Ocean Research Institute of Chinese Academy of Science, lists 38 species of algae. Among them the best-known medicinal seaweed is perhaps *Digenea simplex*, an anthelmintic drug widely used in Asia over many centuries. This alga and the related *Chondria armata* are among a few species whose active ingredients have been fully identified because these active constituents, known collectively as **kainoids**, are **neurotoxins**.

## KAINIC ACID

The red alga *D. simplex* has been used as a folk remedy for the **treatment of roundworm disease (ascariasis)** in Asia for many centuries. It is described in a Japanese pharmacopoeia published in the 9th century. The disease had been quite common in postwar Japan until around 1960 because of poor sanitary conditions caused by the war devastation and also because of the then common practice of using human feces as fertilizer. After World War II, **santonin** produced from some species of **mugworts** was introduced in tablet form, but the decoction of the alga was still available. An active constituent of the alga,  **$\alpha$ -kainic acid**, has been developed into an **anthelmintic drug**. It is ten times more active than **santonin**. Later, kainic acid was found to have both **neurotoxic** and **neuroexcitatory properties**. Today, together with other **kainoid amino acids**, it is more important as a research reagent in neurophysiology than as a human medicine.

**Glutamate** and **aspartate** are found in very high concentrations in the brain, and both amino acids have extremely powerful **excitatory effects** on neurons in virtually every region of the central nervous system. Their widespread distribution tended to obscure their roles as transmitters, but there is now broad acceptance of the view that glutamate and possibly aspartate function as the principal fast (“classical”) excitatory transmitters throughout the central nervous system. Furthermore, over the past decade, multiple subtypes of receptors for excitatory amino acids have been characterized pharmacologically, based on the relative potencies of synthetic agonists and the discovery of potent and selective antagonists.

Glutamate receptors are classified functionally as ligand-gated ion channels (also called **ionotropic** receptors) or as **metabotropic** (G-protein-coupled) receptors. The metabotropic receptors couple via GTP-binding proteins to a variety of effector mechanisms, whereas the ligand-gated ion channels contain an integral cation channel that gates  $\text{Na}^+$  and, in some cases,  $\text{Ca}^{2+}$ . Metabotropic receptors are composed of a single seven-transmembrane-spanning protein, whereas ligand-gated channels are multisubunit complexes. Neither the precise number of subunits that assemble to generate a functional glutamate receptor ion channel *in vivo* nor the topography of each subunit has been established unequivocally.

The ligand-gated ion channels are further classified according to the identity of agonists that selectively activate each receptor subtype. These receptors include  **$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors**. A number of selective antagonists for these receptors are now available. In the case of NMDA receptors, noncompetitive antagonists acting at various sites on the receptor protein have been described in addition to competitive (glutamate site) antagonists. These include open-channel blockers such as **phencyclidine (PCP or angel dust)**, antagonists such as **5,7-dichlorokynurenic acid** that act at an allosteric **glycine-binding site**, and the novel antagonist **ifenprodil**, which may act as a closed-channel blocker. In addition, the activity of NMDA receptors is sensitive to pH and also can be modulated by a variety of endogenous modulators, including  $\text{Zn}^{2+}$ , some **neurosteroids**, **arachidonic acid**, **redox reagents**, and **polyamines** such as **spermine**. In some cases, the effects of endogenous modulators and of competitive and noncompetitive antagonists are selective for certain subtypes of NMDA receptors composed of particular subunit combinations. Multiple cDNAs encoding metabotropic receptors and subunits of **NMDA, AMPA, and kainate receptors** have been cloned in recent years.

The diversity of gene expression and, consequently, of the protein structure of glutamate receptors, also arises by alternative splicing and in some cases by single-base editing of mRNAs encoding the receptors or receptor subunits. Alternative splicing has been described for metabotropic receptors and for subunits of NMDA, AMPA, and kainate receptors. A remarkable form of endogenous molecular engineering occurs with some subunits of AMPA and kainate receptors in which the RNA sequence differs from the genomic sequence in a single codon of the receptor subunit and determines the extent of  $\text{Ca}^{2+}$  permeability of the receptor channel. This RNA-editing process alters the identity of a single amino acid (out of about 900 amino acids) that dictates whether or

not the receptor channel gates  $\text{Ca}^{2+}$ . The glutamate receptor genes seem to be unique families with only limited similarity to other ligand-gated channels such as the nicotinic acetylcholine receptor or, in the case of metabotropic receptors, to members of the G-protein-coupled receptor superfamily.

**AMPA and kainate receptors** mediate fast depolarization at most glutamatergic synapses in the brain and spinal cord. NMDA receptors are also involved in normal synaptic transmission, but activation of NMDA receptors is more closely associated with the induction of various forms of synaptic plasticity rather than with fast point-to-point signaling in the brain. AMPA or kainate receptors and NMDA receptors may be colocalized at many glutamatergic synapses. A well-characterized phenomenon that involves NMDA receptors is the induction of **long-term potentiation (LTP)**. LTP refers to a prolonged (hours to days) increase in the size of a postsynaptic response to a presynaptic stimulus of given strength. Activation of NMDA receptors is obligatory for the induction of one type of LTP that occurs in the hippocampus. NMDA receptors normally are blocked by  $\text{Mg}^{2+}$  at resting membrane potentials. Thus, activation of NMDA receptors requires not only binding of synaptically released glutamate but simultaneous depolarization of the postsynaptic membrane. This is achieved by activation of AMPA or kainate receptors at nearby synapses from inputs from different neurons. Thus, NMDA receptors may function as “coincidence detectors”; that is, they are activated only when there is simultaneous firing of two or more neurons. LTP has been proposed as a cellular model for some forms of learning and memory. Interestingly, NMDA receptors can also induce long-term depression (LTD, the flip side of LTP) at central nervous system synapses.

**Exposure of neurons to high concentrations of glutamate for only a few minutes can lead to neuronal cell death.** The cascade of events leads to excessive activation of NMDA receptors and influx of  $\text{Ca}^{2+}$  into the neurons. This process is thought to be similar to the neurotoxicity that occurs after ischemia or hypoglycemia in the brain, where a massive release and impaired reuptake of glutamate in the synapse leads to excess stimulation of glutamate receptors and subsequent cell death. NMDA receptor antagonists can attenuate or block neuronal cell death induced by activation of these receptors. There is considerable therapeutic potential for the use of NMDA antagonists as neuroprotectants. NMDA receptors also may be involved in the development of susceptibility to epileptic seizures and in the occurrence of seizure activity. In animal models, NMDA receptor antagonists have **anticonvulsant activity** and may find clinical use as anticonvulsants.

Because of the widespread distribution of glutamate receptors in the central nervous system, it is likely that these receptors ultimately will become the targets for diverse therapeutic interventions. It also is conceivable that abnormal expression, regulation, or function of glutamate receptors may be involved in the etiology of some neurological disorders. A role for glutamate receptors or disordered glutamatergic transmission in the etiology of chronic neurodegenerative diseases and in **schizophrenia** has been postulated. Cases of **Rasmussen’s encephalitis**, a childhood disease leading to **intractable seizures** and dementia, were found to correlate with levels of serum antibodies to a glutamate receptor subunit. Thus, an autoimmune reaction against some glutamate receptors may underlie this disease.

## DOMOIC ACIDS

Another anthelmintic folk medicine used in Japan is the red algae *Chondria armata* belonging to the same family (**Rhodomelaceae**) with *Digenea simplex*. However, its use in this purpose has only been known from **Tokunoshima**, a small island located in the northeast of **Okinawa**. Its **insecticidal property** against flies has been noted by the residents of **Yakushima**, another island farther north.

Domoic acid has been demonstrated to be responsible for the insecticidal activity of *C. armata*. It was 14 times more potent than **DDT** when administered subcutaneously into the abdomen of American cockroach.

Domoic acid had never been known to be a causative agent of seafood poisoning until 1987 when an outbreak of serious poisoning with **blue mussels** (*Mytilus edulis*) occurred in Canada.

More than 150 people were intoxicated by eating blue mussels cultured in eastern Prince Edward Island during a period from November to December 1987. The symptoms included nausea, vomiting, diarrhea, memory loss, disorientation, and coma. Three elderly patients died. In some cases, neurological symptoms such as memory loss persisted for more than 5 years. About a month after the first outbreak, Canadian scientists identified domoic acid as the causative agent by analysis of the contaminated mussels.

The term **amnesic shellfish poison** (ASP) has been coined for this new shellfish toxin. The causative organism of ASP was then identified to be the pennate diatom *Nitzschia pungens* Grunow f. multiseries Hasle, a bloom of which contaminated the cultured mussels in eastern Prince Edward Island in 1987.

In early September 1991, another outbreak of domoic acid poisoning was recorded on the other side of the American continent, Monterey Bay, CA. This time, it was not human intoxication but poisoning of **wild pelicans** and **cormorants**. The symptoms of the affected birds were unusual head movements, scratching, vomiting, the loss of righting reflex, and even death. Domoic acid was found in another species of pennate diatom, *Pseudonitzschia australis* Frenguelli, which was blooming in the bay at that time. Remnants of the diatom and high levels of domoic acid were found in the stomach contents of poisoned birds and in the viscera of local anchovies, a principal food of the birds.

### TOXICITY OF CAULERPA

Some species of the **green algal genus Caulerpa** are edible and consumed, largely as salad, in the Philippines and other tropical Pacific regions. The edible species become peppery to the taste during the rainy months in the Philippines, and other species are not eaten because of the extremely peppery taste. Chemical investigation of the toxic constituents of *Caulerpa* was initiated in the 1960s, and a compound named **caulerpicin** was reported to be responsible for the manifestation of such toxic symptoms such as a mild, anesthetizing sensation, numbness of the tongue, and cold sensation in the feet and fingers.

### TOXICITY OF GRACILARIA

The red alga *Gracilaria verrucosa* (known as “*Ogonori*”) is widely consumed as a garnish of salad or “**Sashimi**” in Japan. Other species of this genus are also eaten in wide regions of the Pacific. Some species of *Gracilaria* are important raw material for the production of **agar**. In Taiwan a species of *Gracilaria* is used as feed in the **abalone aquaculture**.

In general, *Gracilaria* species are nontoxic and seldom cause poisoning. However, there are several cases of intoxication reported from Japan, Guam, and Hawaii. Two cases in Japan involved the ingestion of *G. verrucosa* and one case, *G. chorda*. In each of these cases, one person was killed. The symptoms of the victims included nausea, vomiting, stomach pain, and diarrhea. The onsets of the poisonings were fast, often within 30 min after ingestion (Higa and Kuniyoshi, 2000).

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# 11 Alkaloids

## INTRODUCTION

An extensive number of important drugs are naturally occurring alkaloids:

- Belladonna
- Muscarine
- Oxotremorine
- Pilocarpine
- Rauwolfia
- Vinca alkaloids

One of the most common definitions states that an **alkaloid** is “a nitrogenous base of plant origin having marked physiological action.” This is quite in error because some of the alkaloids are not necessarily basic in reaction, and many of them possess little or no physiological action. All alkaloids contain one or more nitrogen atoms, which is also true of the proteins. Although it is true that most alkaloids are derived from plants, there are substances of animal origin that according to any chemical criteria certainly ought to be included with the alkaloids. Cases in point include **ephedrine** (of plant origin) and **epinephrine** (of animal origin), both of which are quite similar in chemical constitution. The best that can be said is that alkaloids are nitrogenous, usually of plant origin, frequently basic in character, and often have a definite physiological action.

In spite of the difficulty in definitely characterizing alkaloids by definition, they do have a surprising number of physical and chemical properties in common. For the most part, the alkaloids are insoluble or sparingly so in water but form salts (by metathesis or addition) that are usually freely soluble. The free alkaloids are usually soluble in ether or chloroform, or other immiscible solvents, in which, however, the alkaloidal salts are insoluble. This permits the isolation and purification of the alkaloids as well as their quantitative estimation. Most of the alkaloids are crystalline solids, although a few are either amorphous (**coniine**, **nicotine**, **sparteine**) or liquid. It is interesting to note that the liquid alkaloids have no oxygen in their molecules. Alkaloidal salts are invariably crystalline, and their crystal form and habit are often useful in their rapid microscopical identification (Sollmann, 1944).

The alkaloids, similar to other amines, form double salts with compounds of mercury, gold, platinum, and other heavy metals. These double salts are usually obtained as precipitates, and many of them are microcrystallographically characteristic. Among the common alkaloidal reagents are **Wagner's** (iodine in potassium iodide), **Mayer's** (potassium mercuric iodide), **Dragendorff's** (potassium bismuth iodide), **Hager's** (picric acid), **Marme's** (potassium cadmium iodide), **Sonnenschein's** (phosphomolybdic acid), gold chloride, mercuric chloride, tannic acid, and many others. They usually possess a bitter taste.

The alkaloids appear to have a restricted distribution in the vegetable kingdom. Such **angiosperms** as the **Apocynaceae**, **Leguminosae**, **Papaveraceae**, **Ranunculaceae**, **Rubiaceae**, **Solanaceae**, and **Fumariaceae** are outstanding for plants yielding alkaloids. The **Labiatae** and **Rosaceae** are quite free, and the **monocotyledons** and **gymnosperms** only rarely contain them. A specific alkaloid is usually confined to a specific plant family, although **caffeine** and **berberine**



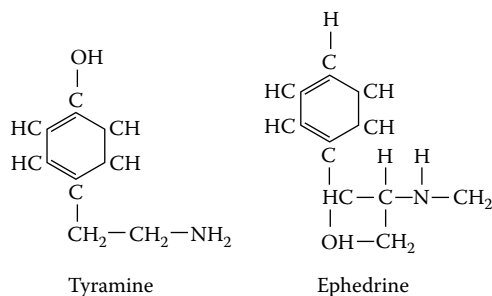


FIGURE 11.1 The structures of tyramine and ephedrine.

are exceptions to this rule. Alkaloids may occur in various plant parts: in seeds and fruits (**nuxvomica** and **black pepper**), in leaves (the **solanaceous leaves**), in rhizomes and roots (**aconite**, **corydalis**, **hydrastis**), and in barks (**cinchona**, **pomegranate**).

The names of the alkaloids are derived in various ways: (1) from the generic and specific names of the plants yielding them (**colchicine**, **belladonnine**), (2) from the name of the drug yielding them (**ergotoxine**), (3) from their physiological activity (**emetine**, **morphine**), and occasionally from the discoverer's name (**pelletierine**). Sometimes a prefix or suffix is added to the name of a principal alkaloid to designate another alkaloid from the same source (**quinine**, **quinidine**, and **hydroquinine**). By agreement, chemical rules designate that the names of all alkaloids should end in "ine."

Various schemes for the classification of alkaloids based on their constitution have been suggested. Because of the wide variation in the constitution of alkaloids, however, none of these is quite satisfactory.

**Alkaloids** usually contain one nitrogen atom, although some, such as **ergotoxine**, may contain up to five. The nitrogen may exist as a primary amine ( $R-NH_2$ ), a secondary amine such as ( $R_2NH$ ) or cyclic, a tertiary amine such as ( $R_3N$ ) or cyclic, or a quaternary ammonium hydroxide such as ( $R_4N-OH$ ) or cyclic. These forms of nitrogen linkage are basic and account for the common basic nature of the alkaloids. **Acid amides** (neutral) and **acid imides** (acid) may also be found in the alkaloids.

## CLASSIFICATION

### THE GROUP CONTAINING ALIPHATIC BASES WITH AN AROMATIC NUCLEUS

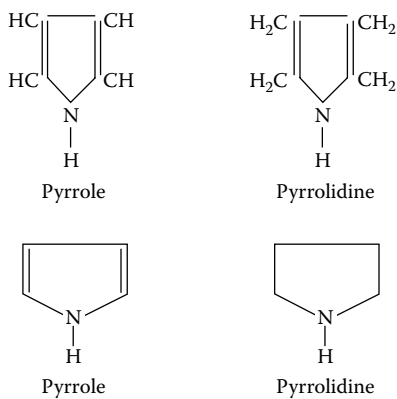
They include such compounds as **tyramine** (*p*-hydroxyphenylethylamine) from ergot, **ephedrine** from ephedra, and **colchicine** from colchicum (Figure 11.1).

### THE PYRROLIDINE GROUP

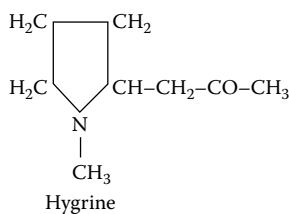
Pyrrolidine occurs free in small quantities in **tobacco** and **opium** and is related to its mother substance pyrrole (Figure 11.2). To this group belong such alkaloids as **hygrine** from *Erythroxylon coca* and **stachydrine** from *Stachys tubrifera* (Figure 11.3).

### THE PYRIDINE GROUP

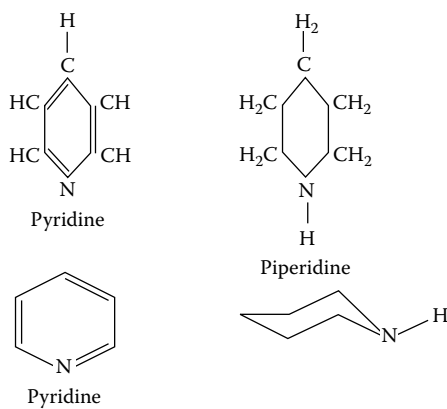
Upon reduction, the tertiary base **pyridine** is converted into the secondary base **piperidine**. These two nuclei form the basis of this group (Figure 11.4). The group is sometimes divided into four subgroups: (1) derivatives of piperidine including piperidine from **black pepper** and methysticin from **kava**, (2) derivatives of  $\alpha$ -propylpiperidine including coniine from **conium**, (3) derivatives of nicotinic acid including **arecoline** from areca, and (4) derivatives of both pyridine and pyrrolidine including **nicotine** from tobacco (Figure 11.5).



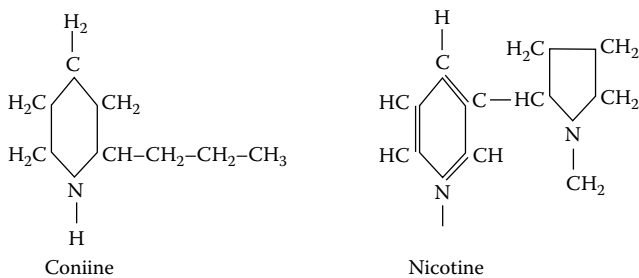
**FIGURE 11.2** The structures of pyrrole and pyrrolidine.



**FIGURE 11.3** The structure of hygrine.



**FIGURE 11.4** The structures of pyridine and piperidine.



**FIGURE 11.5** The structures of coniine and nicotine.

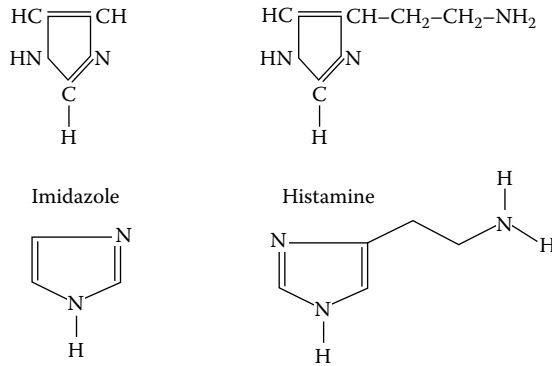


FIGURE 11.6 The structures of imidazole and histamine.

### THE GLYOXALINE GROUP

**Imidazole (glyoxaline)** is the principal nucleus in **histamine** from **ergot** and pilocarpine from **pilocarpus** (Figure 11.6).

### ALKALOIDS WITH CONDENSED PYRROLIDINE AND PIPERIDINE RINGS

**Tropane** is formed when **pyrrolidine** and **piperidine** are condensed. Closely related to tropane are tropine, the principal nucleus of the solanaceous alkaloids, **atropine**, **hyoscyamine**, **hyoscyne**, and **belladonnine**, and **ecgonine**, the nucleus of **cocaine** (Figure 11.7).

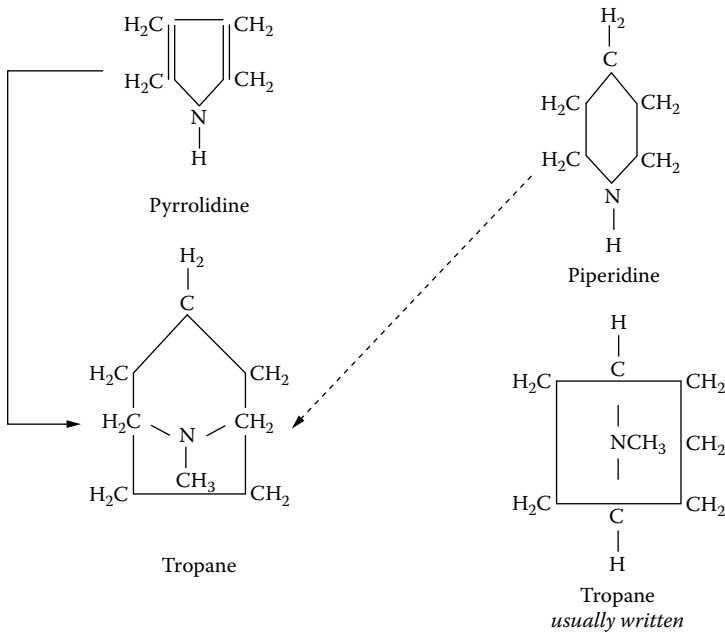


FIGURE 11.7 The structures of pyrrolidine, piperidine, and tropane.

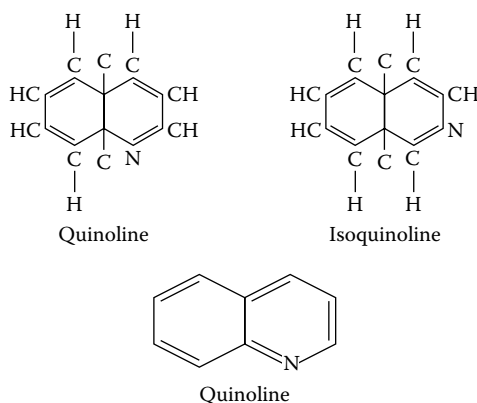


FIGURE 11.8 The structures of quinoline and isoquinoline.

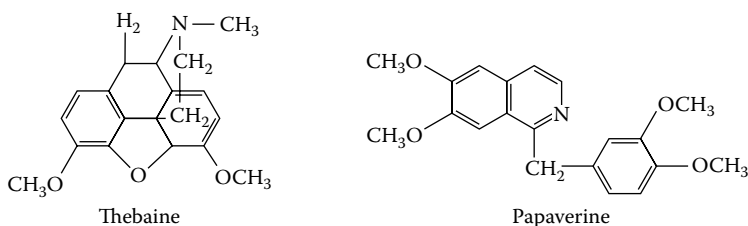


FIGURE 11.9 The structures of thebaine and papaverine.

### DERIVATIVES OF QUINOLINE

Alkaloids containing **quinoline** as the principal nucleus include **anemonine** from *Anemone thalictroides*, **galipine** from *Angostura bark* (*Galipea officinalis*), and the **cinchona** alkaloids, **quinine**, **quinidine**, **cinchonine**, and **cinchonidine** (Figure 11.8).

### DERIVATIVES OF ISOQUINOLINE

Alkaloids containing the isoquinoline nucleus may be divided into two groups: (1) **papaverine**, **narcotine**, **cotarnine**, **narcine**, and certain others of the opium group, and (2) the hydrastis group including **hydrastine**, **berberine**, and **canadine** (Figure 11.9).

### PHENANTHRENE

The opium alkaloids **morphine**, **codeine**, and **thebaine** have a phenanthrene nucleus (Figure 11.10 and Figure 11.11).

### INDOLE DERIVATIVES

Certain alkaloids upon distillation with zinc dust yield indole. It is natural, therefore, to assume that they possess an indole ring as part of their structure. **Strychnine** and **brucine** from **nux vomica** and **physostigmine** from **physostigma** belong to this group. Strychnine and brucine contain in addition a quinoline nucleus, and many authors classify them in the quinoline group. The formula for strychnine shown in Figure 11.11 is now generally accepted. Brucine is **dimethoxystrychnine**, in which the methoxy groups replace the two hydrogen atoms indicated in the formula.

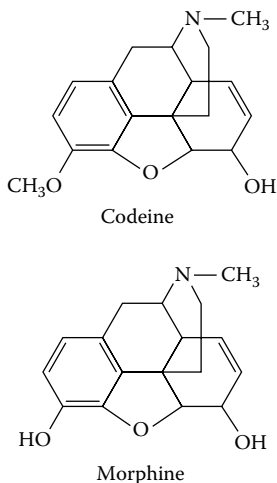


FIGURE 11.10 The structures of codeine and morphine.

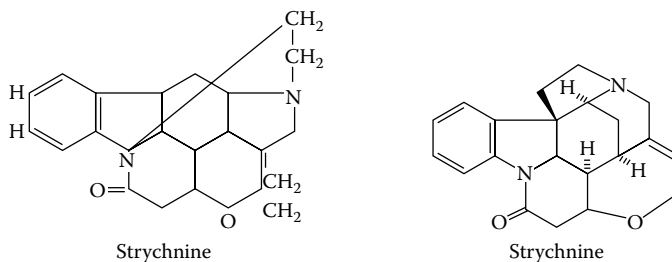


FIGURE 11.11 The structure of strychnine.

### THE PURINE BASES

The purine nucleus is constructed by a “condensation” of the pyrimidine and imidazole (glyoxaline) nuclei (Figure 11.12). **Xanthine** is 2,6-dioxypurine; **caffeine**, 1,3,7-trimethylxanthine; **theophylline**, 1,3-dimethylxanthine; and **theobromine**, 3,7-dimethylxanthine. These alkaloids are found in **coffee, tea, cacao, kola, maté, and guarana** (Figure 11.13).

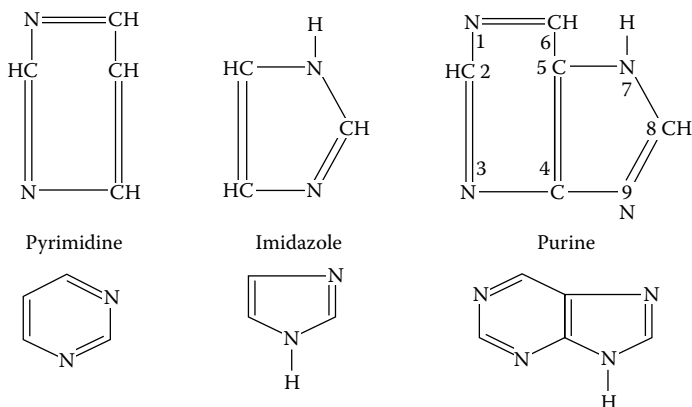


FIGURE 11.12 The structures of pyrimidine, imidazole, and purine.

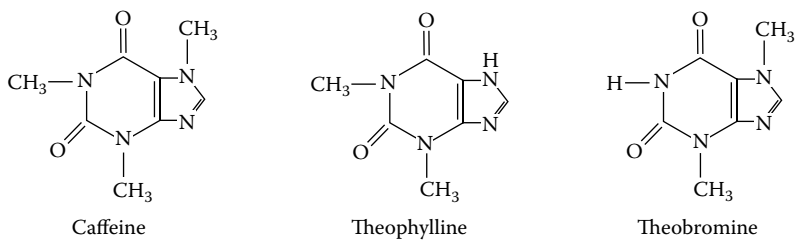


FIGURE 11.13 Pharmacology of important xanthines.

#### ALKALOIDS OF UNKNOWN CONSTITUTION

The constitution of a number of alkaloids has not as yet been definitely established. Among these are **aconitine** from **aconite**, **delphinine** from **larkspur**, **jervine** and **protojervine** from **veratrum viride**, **cevadine** from **sabadilla seed**, **lobeline** from **lobelia**, the curare alkaloids from *Chondrodendron tomentosum*, **sanguinarine** from **sanguinaria**, and many others.

As with most attempts at chemical classification, some alkaloids do not fall satisfactorily into any of the preceding groups, and others can be classified under more than one group.



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# 12 Aloe and Colon Function

## INTRODUCTION

**Aloe vera leaf** (*Aloe ferox*, *A. barbadensis*) has the following uses:

- Heals sunburn and other skin problems
- Eases constipation
- Aids treatment of ulcers
- Has antibacterial, antiviral, and antifungal activity

Almost everyone is familiar with aloe vera as a popular ingredient of skin lotion and suntan preparations. Its use for skin care and treatment goes back to ancient Mesopotamia, Egypt, and Greece.

**Aloe** is one of the few medicinal plants that have maintained their popularity for a long period of time. **Aloe latex** is used for its **laxative effect** and should be distinguished from **aloe gel**, used both in cosmetics and in ointments for skin ailments. **Aloe whole leaf** is another preparation, used as an oral medicine for a wide range of human diseases including **cancer, AIDS, ulcerative colitis**, etc.

The genus *Aloe* comprises about 600 species, most of which are indigenous to South Africa (*A. ferox* Miller, *A. africana* Miller, *A. spicata* Baker); some have been introduced in Asia (*A. chinensis* Bak), Barbados Islands in Central America (*A. barbadensis* Miller), and Europe (*A. arborescens* Miller). The genus *Aloe* includes trees (*A. ferox*), shrubs, and herbs (*A. barbadensis*); they are xerophytic plants with large, fleshy leaves, carrying spines at the margin, and they resemble the agave or century plant (*Agave americana* Linne).

The word *Aloe* in pharmacopoeias and formularies means a drug derived from the dried leaf juice. This has always created confusion because the leaves of the genus *Aloe* are the source of two products that are quite different in their chemical composition and therapeutic properties: **aloe latex** and **aloe gel**. These two products are obtained from two different specialized cells, **latex** from **pericyclic cells** and **gel** from **parenchymatous cells**. Therefore, the term *juice* must be avoided, as it could mean either the latex from the pericyclic cells or the gel after extraction from the leaf. However, to add to the confusion, there is also a preparation obtained from the whole leaf (total extract) and another obtained from the aloe wood, the so-called **lignaloe** or **aloe** of the Bible, a fragrant wood obtained from an entirely different plant that was once used as an **incense** (Capasso et al., 1998).

## ALOE PREPARATIONS

Aloe latex is prepared by cutting transversely the leaf near the base and kept in an inclined position so that the latex contained in the specialized pericyclic cells, and sometimes in the adjacent parenchyma, flows out in about 6 h. No pressure must be applied or the product will be contaminated with the mucilage present in the inner part of the leaves. The latex obtained is bitter and yellow; condensed to dryness, it becomes a shiny mass, similar to broken glass, of a yellowish green to red-black color. Slow evaporation, carried out at an inappropriate temperature, yields an opaque mass with a waxlike fracture. The taste is nauseating and bitter, and the odor sour, recalling that of **rhubarb, apple-tart, or iodoform** (Sollmann, 1944).



Aloe latex contains **anthraquinones** and is completely different from aloe gel, a colorless gelatin obtained from the central portion of the aloe leaf. The mucilaginous parenchymous tissue is excised from fresh leaves and immediately utilized for pharmaceutical preparations, or lyophilized and kept dry until use. During extraction of the gel, it is practically impossible to prevent contamination by the leaf latex as the leaves are cut. On the other hand, in intact leaves, anthraquinones may diffuse into gel from the bundle sheath cells. To reduce such contamination, the starting material must be from varieties of aloe with a reduced anthraquinone content.

Scientific research has proved in recent years that the rind and the outer leaf, normally thrown away, contain much more active therapeutic ingredients. On the other hand, the gel is sensitive to heat and light, and can quickly deteriorate at high temperature. For these reasons, the gel is now available as a cold-processed extract obtained from aloe whole leaf. The fresh whole leaf is cut into small pieces and whipped to yield a homogeneous yellowish or reddish material. The product (10% aloe leaf and 90% water), concentrated, and in some cases deprived partially of **aloins**, is bitter.

## CHEMICAL COMPOSITION OF ALOE PLANTS

The aloe plant produces **anthraquinone glycosides** (10 to 30%) such as aloins (A and B), mucilage (30%), a resinous material (16 to 63%), sugars (about 25%), mucopolysaccharides (such as **acemannan** and **betamannan**), fatty acids (cholesterol, **campesterol**,  **$\beta$ -sitosterol**), glycoproteins (alocins A and B), enzymes (including **cyclooxygenase** and **bradykinase**), together with other compounds such as **lupeol**, **salicylic acid**, urea nitrogen, **cinnamic acid**, phenol, sulfur, magnesium lactate, **prostanoids**, and fiber. The following are the chief properties of aloe:

- **Aloins** have laxative properties.
- **Alocins**, **campesterol**,  **$\beta$ -sitosterol**, and **acemannan** have anti-inflammatory properties.
- **Acemannan** has immunostimulant properties.
- **Lupeol**, **salicylic acid**, **phenol**, and **sulfur** have antiseptic properties.

## THE THERAPEUTIC USES OF ALOE

### ALOE AND CANCER

Several studies have been carried out utilizing total leaf extracts internally, which therefore combine aloe gel with aloe latex. These extracts contain, among other substances, immunostimulatory and mild anti-inflammatory mucopolysaccharides, of which acemannan is the most notable. **Mucopolysaccharides** are normally produced by the human body until puberty, after which time these substances must be introduced from outside sources. Their deficiency could produce drastic degenerative diseases. It has been shown that administration of acemannan stimulates macrophages to release **tumor necrosis factor** (TNF), **interleukin**, and **interferon**, and it is able to abrogate viral infection in both animals and humans. Aloe extract also contains **alocins** — substances that possess many biological activities, such as mitogenic activity for lymphocytes, binding of human  **$\alpha_2$ -macroglobulin**, and complement activation via the alternative pathway. Recent studies also show that **alocin A** is a promising candidate as an immunomodulator. Anti-inflammatory and immunomodulating agents are also **anthraquinones**. The presence of all these substances might be enough to explain the prophylactic, and possibly therapeutic, effect of aloe extract and its antitumor activity against leukopenia caused by exposure to cobalt-60, sarcoma-180, and Ehrlich ascites (Janeway and Travers, 1994).

Experimental studies have also reported that aloe juice has **antimetastatic activity** and aloe extract inhibits induction of **preneoplastic hepatocellular lesions**. Antitumor effects of aloe extract may also depend on the ability to augment tumor-specific immunity. These findings have encouraged cancer treatment in humans with a preparation composed of aloe (5 years old) fresh leaf 300 g,

honey 500 g, two tablespoons of gin (or vodka or whisky); the mixture can be left for 10 d in a jar, filtered, and taken (one tablespoon once or twice daily for 14 d), or mixed in a blender and then taken as above. Honey increases the palatability of the preparation and could enhance the effect of aloe because its content of **caffeic acid phenethyl ester**, a potent chemopreventive agent, is useful in combating diseases with a strong inflammatory component, i.e., various types of cancer. However, well-controlled clinical trials are insufficient to allow conclusions.

Aloe extract, used in association with **vitamin E** and **squalene**, is also able to cause regression of any tumor already formed in a mouse skin model.

### ALOE AND AIDS

Aloe extract is also considered a possible therapy for acquired immunodeficiency syndrome (AIDS), in association with an antiviral agent (**asidothymidine**).

### ALOE AND ASTHMA

There is also evidence for the efficacy of aloe extract in patients with chronic bronchial asthma. The effect of aloe extract seems to be due to formation of some **prostanoids** during dark storage of aloe extract at 4 to 30°C, for a period of 3 to 10 d.

### ALOE AND DIABETES

Hypoglycemic actions have also been referred to for aloe extract in five patients with non-insulin-dependent diabetes.

### ALOE GEL AND SKIN AILMENTS

Aloe gel is reported to contain **glycoproteins**, **polysaccharides**, and other constituents (enzymes, etc.) and is essentially used for the treatment of various skin conditions (burns, abrasions, bruises, cuts, psoriasis, herpes simplex, etc.). Therefore, it is incorporated in ointments, creams, lotions, and other preparations for external use. Several studies have shown that the activity of aloe gel varies, and that it is attributed to changes in the gel composition during growth or after harvest. On the other hand, there is general agreement that aloe gel used in a fresh state, not on storage, is more able to show anti-inflammatory properties. This variation is due in part to the instability of the active ingredients, **aloctin A** and **aloctin B**. Acemannan has been recently indicated as another important active ingredient in aloe gel. The anti-inflammatory activity of aloe gel has been postulated to be due to inhibition of **eicosanoids**. Other suggested alternative mechanisms are inhibition of histamine formation by magnesium lactate, destruction of **bradykininase**, or inhibition of **bradykinin** activity. Many pharmacologists believe that the presence of small amounts of **anthraquinones** may enhance the beneficial effect of the gel when used in the treatment of inflammation. However, the literature on the efficacy of aloe in skin ailment management is still incomplete, and further studies are required to clarify the capacity of **acemannan** to interact with **integrins**, the heterodimeric cell surface receptors. Integrins play a crucial role in inflammation, permitting inflammatory cells to leave the bloodstream and enter the damaged tissues (Capasso et al., 1998).

Aloe gel is also present in many cosmetics for its emollient properties and antiaging effects on the skin. Although aloe is considered hypoallergenic even in large doses, allergic **contact dermatitis** due to the topical application of gel preparations has been described.

### ALOE AND CONSTIPATION

Aloe latex is an active laxative. Its effect is due to **anthraquinone glycosides**, **aloin A** and **B** (formerly designated **barbaloin**). **Glycosides** are probably chemically stable in the stomach (under

conditions of pH 1 to 3), and the sugar moiety prevents their absorption in the upper part of the gastrointestinal tract. Once it has reached the large intestine, aloin is hydrolyzed by the bacterial flora to form **aloe-emodin-9-anthrone**, the active metabolite. **Hydroxyanthracene derivative** induces the secretion of fluid and electrolytes into the lumen through an inhibition of the  $\text{Na}^+ - \text{K}^+ - \text{ATPase}$  activity in the epithelial cells of the intestine, increases mucosal permeability of the endothelial cells of the colon, raises the level of cAMP in the enterocytes, and alters the motility of the large intestine by releasing endogenous substances. Taken in doses of 0.25 g, aloe causes laxation after 6 to 12 h. Excessive doses or prolonged use may cause nephritis, gastritis, vomiting, and diarrhea with elimination of mucus and blood. These side effects, occurring after chronic use or overdosage of aloe, have reduced its use as a laxative in recent years in some countries, whereas in others it is still widely used alone or in association with **choloretic** and **cholagogue** drugs in constipation (Capasso et al., 1998).

## MOVEMENTS OF THE COLON

The functions of the colon are (1) absorption of water and electrolytes from the chyme and (2) storage of fecal matter until it can be expelled. The proximal half of the colon, illustrated in Figure 12.2, is concerned principally with absorption, and the distal half with storage. Because intense movements are not required for these functions, the movements of the colon are normally sluggish. Although sluggish, the movements still have characteristics similar to those of the small intestine and can be divided into **mixing movements** and **propulsive movements**.

### MIXING MOVEMENTS: HAUSTRATIONS

In the same manner that segmentation movements occur in the small intestine, large circular constrictions also occur in the large intestine. At each of these constriction points, about 2.5 cm of the circular muscle contracts, sometimes constricting the lumen of the colon to almost complete occlusion. At the same time, the longitudinal muscle of the colon, which is aggregated into three longitudinal strips called the *tineae coli*, contracts. These combined contractions of the circular and longitudinal smooth muscle cause the unstimulated portion of the large intestine to bulge outward into baglike sacs called **haustrations**. The haustral contractions, once initiated, usually reach peak intensity in about 30 sec and then disappear during the next 60 sec. They also at times move slowly analward during their periods of contraction, especially in the cecum and ascending colon. After another few minutes, new haustral contractions occur in other areas nearby. Therefore, the fecal material in the large intestine is slowly dug into and rolled over in much the same manner that one spades the earth. In this way, all the fecal material is gradually exposed to the surface of the large intestine, and fluid is progressively absorbed until only 80 to 150 ml of the 750-ml daily load of chyme is lost in the feces.

### PROPULSIVE MOVEMENTS: "MASS MOVEMENTS"

Peristaltic waves of the type seen in the small intestine only rarely occur in other parts of the colon. Instead, most propulsion occurs by (1) the **haustral contractions** discussed previously and (2) **mass movements**.

Most of the propulsion in the cecum and ascending colon results from the slow but persistent haustral contractions, requiring as many as 8 to 15 h to move the chyme only from the ileocecal valve to the transverse colon, while the chyme itself becomes fecal in quality and also becomes a semisolid slush instead of a semifluid.

From the transverse colon to the sigmoid, mass movements take over the propulsive role. These movements usually occur only a few times each day, most abundantly for about 15 min during the first hour after eating breakfast.

A mass movement is characterized by the following sequence of events. First, a constrictive ring occurs at a distended or irritated point in the colon, usually in the transverse colon, and then rapidly thereafter the 20 cm or more of colon distal to the constriction contract almost as a unit, forcing the fecal material in this segment *en masse* down the colon. During this process, the haustrations disappear completely. The initiation of contraction is complete in about 30 sec, and relaxation then occurs during the next 2 to 3 min before another mass movement occurs. But the whole series of mass movements will usually persist for only 10 min to half an hour, and they will then return perhaps a half day or even a day later.

Mass movements can occur in any part of the colon, although most often they occur in the transverse or descending colon. When they have forced a mass of feces into the rectum, the desire for defecation is felt.

### INITIATION OF MASS MOVEMENTS BY THE GASTROCOLIC AND DUODENOCOLIC REFLEXES

The appearance of mass movements after meals is caused at least partially by gastrocolic and duodenocolic reflexes. These reflexes result from distension of the stomach and duodenum. They can take place, although with decreased intensity, when the autonomic nerves are removed; therefore, it is probable that the reflexes are basically transmitted through the **myenteric plexus**, although reflexes conducted through the autonomic nervous system probably reinforce this direct route of transmission.

It is likely that the hormone **gastrin**, which is secreted by the stomach antral mucosa in response to distension, also plays some role in this effect because gastrin has an excitatory effect on the colon and an inhibitory effect on the ileocecal valve, thus allowing rapid emptying of ileal contents into the cecum. This in turn elicits increased colonic activity.

Irritation in the colon can also initiate intense mass movements. For example, a person who has an ulcerated condition of the colon (**ulcerative colitis**) frequently has mass movements that persist almost all of the time.

Mass movements are also initiated by intense stimulation of the parasympathetic nervous system or simply by overdistension of a segment of the colon.

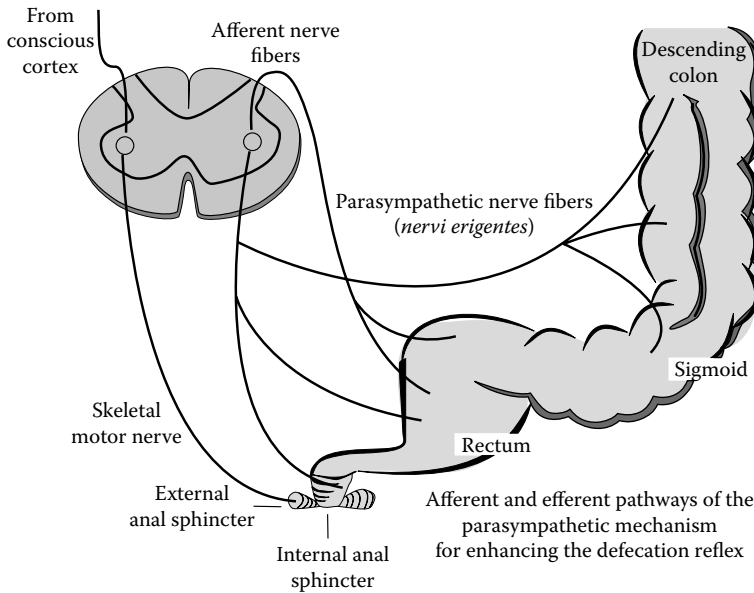
## DEFECATION

Most of the time, the rectum is empty of feces. This is partly due to the fact that a weak functional sphincter exists approximately 20 cm from the anus at the juncture between the sigmoid and the rectum. However, when a mass movement forces feces into the rectum, the desire for defecation is normally initiated, including reflex contraction of the rectum and relaxation of the anal sphincters.

Continual dribble of fecal matter through the anus is prevented by (1) tonic constriction of the **internal anal sphincter**, a circular mass of smooth muscle that lies immediately inside the anus, and (2) the **external anal sphincter**, composed of striated voluntary muscle that both surrounds the internal sphincter and also extends distal to it; the external sphincter is controlled by the somatic nervous system and therefore is under voluntary control.

### THE DEFECATION REFLEXES

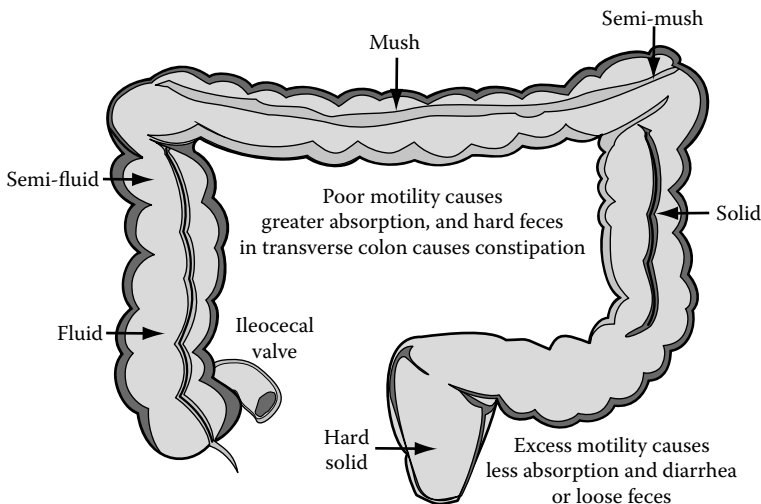
Ordinarily, defecation results from the **defecation reflexes**, which can be described as follows. When the feces enter the rectum, distension of the rectal wall initiates afferent signals that spread through the myenteric plexus to initiate peristaltic waves in the descending colon, sigmoid, and rectum, forcing feces toward the anus. As the peristaltic wave approaches the anus, the internal anal sphincter is inhibited by the usual phenomenon of **receptive relaxation**, and if the external anal sphincter is relaxed, defecation will occur. This overall effect is the **intrinsic defecation reflex** of the colon itself.



**FIGURE 12.1** The afferent and efferent pathways of the parasympathetic mechanism for enhancing the defecation reflex.

However, the intrinsic defecation reflex itself is usually weak, and to be effective in causing defecation, it must be fortified by another type of defecation reflex, a **parasympathetic defecation reflex** that involves the sacral segments of the spinal cord, as illustrated in Figure 12.1 and Figure 12.2.

When the afferent fibers in the rectum are stimulated, signals are transmitted into the spinal cord and thence, reflexly, back to the descending colon, sigmoid, rectum, and anus by way of parasympathetic nerve fibers in the **nervi erigentes**. These parasympathetic signals greatly intensify the peristaltic waves and convert the intrinsic defecation reflex from an ineffectual weak movement into a powerful process of defecation that is sometimes effective in emptying the large bowel in one movement all the way from the splenic flexure to the anus. Also, the afferent signals entering the spinal cord initiate other effects, such as taking a deep breath, closure of the glottis, and



**FIGURE 12.2** Absorptive and storage functions of the large intestine.

contraction of the abdominal muscles to force downward on the fecal contents of the colon while at the same time causing the pelvic floor to pull outward and upward on the anus to evaginate the feces downward.

However, despite the defecation reflexes, other effects are also necessary before actual defecation occurs because relaxation of the internal sphincter and forward movement of feces toward the anus normally initiates an instantaneous contraction of the external sphincter, which still temporarily prevents defecation. Except in babies and mentally challenged persons, the conscious mind then takes over voluntary control of the external sphincter and either inhibits it to allow defecation to occur or further contracts it if the moment is not socially acceptable for defecation. When the contraction is maintained, the defecation reflexes die out after a few minutes and usually will not return until an additional amount of feces enters the rectum, which may not occur until several hours thereafter.

When it becomes convenient for the person to defecate, the defecation reflexes can sometimes be excited by taking a deep breath to move the diaphragm downward and then contracting the abdominal muscles to increase the pressure in the abdomen, thus forcing fecal contents into the rectum to elicit new reflexes. Unfortunately, reflexes initiated in this way are never as effective as those that arise naturally, for which reason people who too often inhibit their natural reflexes become severely constipated.

In the newborn baby and in some persons with transected spinal cords, the defecation reflexes cause automatic emptying of the lower bowel without the normal control exercised through contraction of the external anal sphincter.

## OTHER AUTONOMIC REFLEXES AFFECTING BOWEL ACTIVITY

Aside from the duodenocolic, gastrocolic, gastroileal, enterogastric, and defecation reflexes, several other important nervous reflexes can affect the overall degree of bowel activity. These are the **intestino-intestinal reflex**, **peritoneo-intestinal reflex**, **reno-intestinal reflex**, **vesico-intestinal reflex**, and **somato-intestinal reflex**. All these reflexes are initiated by sensory signals that pass to the spinal cord and then are transmitted through the sympathetic nervous system back to the gut. And they all inhibit gastrointestinal activity. Thus, the **intestino-intestinal reflex** occurs when one part of the intestine becomes overdistended or its mucosa becomes excessively irritated; this blocks activity in other parts of the intestine, while the local distension or irritability increases activity in the localized region and moves the intestinal contents away from the distended or irritated area.

The **peritoneo-intestinal reflex** is very much like the intestino-intestinal reflex, except that it results from irritation of the peritoneum; it causes intestinal paralysis. The **reno-intestinal** and **vesico-intestinal** reflexes inhibit intestinal activity as a result of kidney or bladder irritation. Finally, the **somato-intestinal reflex** causes intestinal inhibition when the skin over the abdomen is irritatingly stimulated (Guyton, 1981).

## CONSTIPATION

### DEFINITION

Constipation is a complaint commonly seen in clinical practice. Because of the wide range of normal bowel habits, constipation is difficult to define precisely. Most persons have at least three bowel movements per week, and constipation has been commonly defined as a frequency of defecation of less than three times per week. However, stool frequency alone is not a sufficient criterion to use because many constipated patients describe a normal frequency of defecation but subjective complaints of excessive straining, hard stools, lower abdominal fullness, and a sense of incomplete evacuation. Thus, a combination of objective and subjective criteria must be used to define constipation.

## CAUSES

Pathophysiologically, constipation generally results from **disordered colonic transit** or **anorectal function** as a result of a primary motility disturbance, certain drugs, or in association with a large number of systemic diseases that affect the gastrointestinal tract. Constipation from any cause may be exacerbated by chronic illnesses that lead to physical or mental impairment and result in inactivity or physical immobility. Additional contributing factors may include a lack of fiber in the diet, generalized muscle weakness, and possibly stress and anxiety.

In the patient presenting with a recent onset of constipation, an **obstructing lesion** of the colon should be sought. In addition to a colonic neoplasm, other causes of colonic obstruction include **strictures** due to colonic ischemia, diverticular disease, or inflammatory bowel disease; foreign bodies; or **anal strictures**. Anal sphincter spasm due to painful **hemorrhoids** or **fissures** also may inhibit the desire to evacuate.

In the absence of an obstructing lesion of the colon, **disturbed colonic motility** may mimic colonic obstruction. Disruption of parasympathetic innervation to the colon as a result of injury or lesions of the lumbosacral spine or sacral nerves may produce constipation with hypomotility, colonic dilatation, decreased rectal tone and sensation, and impaired defecation. In patients with **multiple sclerosis**, constipation may be associated with neurogenic dysfunction of other organs. Similarly, constipation may be associated with **lesions of the central nervous system** caused by parkinsonism or a cerebrovascular accident. In South America, the parasitic infection **Chagas' disease** may result in constipation because of damage to myenteric plexus ganglion cells. **Hirschsprung's disease**, or **aganglionosis**, is characterized by absence of myenteric neurons in a segment of distal colon just proximal to the anal sphincter. This results in obstruction and proximal dilatation due to a segment of contracted bowel. In addition, an absent **rectosphincteric inhibitory reflex** results in the failure of the internal anal sphincter to relax following rectal distention. Most patients with Hirschsprung's disease are diagnosed by 6 months of age, but in occasional cases symptoms are mild enough that the diagnosis may be delayed into adulthood.

Drugs that may lead to constipation include those with **anticholinergic properties**, such as **antidepressants** and **antipsychotics**, **codeine** and other narcotic analgesics, **aluminum- or calcium-containing antacids**, **sucralfate**, **iron supplements**, and **calcium channel blockers**. In patients with certain endocrinopathies such as **hypothyroidism** and **diabetes mellitus**, constipation is generally mild and responsive to therapy. Rarely, life-threatening megacolon occurs in patients with **myxedema**. Constipation is common during **pregnancy**, presumably as a result of altered progesterone and estrogen levels, which decrease intestinal transit. **Collagen vascular diseases** may be associated with constipation, which may be a particularly prominent feature of **progressive systemic sclerosis**, in which delayed intestinal transit results from atrophy and fibrosis of colonic smooth muscle (Fauci et al., 1998).

## CATHARTICS

Cathartics are drugs that are employed in medicine to facilitate evacuation of the bowels. They may act by irritating the intestines or by augmenting the fluid of the feces. In the first instance, intestinal peristalsis is increased directly, and in the second instance it is increased indirectly by distention of the bowel. They are probably used more than any other class of medicinal compounds. This fact is not an index of their usefulness or value but rather a measure of the misconceptions that exist concerning their worth and the indications for their use.

The cathartics are so numerous that they require classification (see Table 12.1). This has been done in a variety of ways. The drugs may be classified according to the intensity of their action, and thus can be designated as laxatives, purgatives, and drastics, in order of increasing potency. The group can also be delineated according to the site of action, or by the interval of time before

**TABLE 12.1**  
**Classification of Cathartics**

<b>"Irritant" Cathartics</b>	<b>Bulk Cathartics</b>
Emodin cathartics	Saline cathartics
Cascara sagrada	Magnesium sulfate
Senna	Magnesium oxide
Rhubarb	Magnesium citrate
Aloe	Magnesium carbonate
Resinous cathartics	Sodium sulfate
Jalap	Sodium phosphate
Colocynth	Potassium sodium tartrate
Elaterin	Hydrophilic colloids and indigestible fiber
Podophyllum	Bran
Irritant oil cathartics	Agar
Castor oil	Tragacanth
Croton oil	Psyllium seed
Miscellaneous cathartics	Emollient cathartics
Phenolphthalein	Liquid petrolatum
Mercurous chloride	Vegetable oils

*Note:* Constipation may be defined as the passage of excessively dry stools, infrequent stools, or stools of insufficient size. Constipation is a symptom and not a disease. It may be of brief duration (e.g., when one's living habits or diet change abruptly), or it may be a life-long problem, as occurs in congenital aganglionosis of the colon (Hirschsprung's disease).

they are effective. The most useful classification, however, is that which takes into account both their mechanism of action and their chemical nature.

Cathartics act by one of three fundamental mechanisms. The so-called **irritant cathartics** are drugs that are presumed to irritate the intestinal tract and thus to increase its motor activity. This leads to a rapid propulsion of the intestinal contents and the passage of a stool that may vary in consistency from one that is formed to one that is liquid, depending on the degree of irritation. The **bulk cathartics** increase the contents of the intestinal tract and are therefore more physiological in action. They are **hydrophilic colloids**, which resist destruction in the gastrointestinal tract, or **indigestible fiber**, or inorganic salts, which are slowly absorbed from the intestinal tract and thus hold water at that site due to the osmotic pressure which they exert. The **emollient cathartics** lubricate the intestinal tract and thereby facilitate the passage of feces.

### EMODIN OR ANTHRAQUINONE CATHARTICS

Senna, rhubarb, cascara, aloes, and related drugs contain glucosidal compounds that are themselves inactive. In the alkaline intestine, they are hydrolyzed or oxidized, yielding various **oxymethyl-anthraquinones**, especially **emodin** and chrysophanic acid, which produce a cathartic effect chiefly by acting on the large intestines as **laxatives**, **aperients**, or **ecproctics**, with easier defecation of formed stools. They are often more effective when taken in divided doses (three times daily) than as a single dose. With larger doses and with the more active members, the action extends upward into the small intestines, with griping and forced evacuation of liquid stools; however, it does not readily progress to inflammation. The effects are fairly easily controlled by grading the dosage, and by repeating the smaller doses, as the action tends to be cumulative. The dosage may be reduced or omitted when the desired degree is attained. These drugs are therefore used especially in chronic



constipation, in addition to or in alternation with mineral oil. Prolonged use tends to decrease the response of the intestines, so that the effect occurs only with larger doses, which are apt to set up chronic inflammation of the mucosa. **Cascara** is the mildest of these drugs and the most easily controlled. **Senna** is the most active and generally causes griping and semiliquid stools. **Aloe** and **aloïn** are intermediate but can be pushed to drastic action, and this may result in abortion. Rhubarb catharsis is apt to be followed by constipation, which has been attributed to its **tannic acid**. **Phenolphthalein** acts similarly to cascara and aloes, but the response is variable. Its chemical structure is somewhat different.

The pure substances would be too irritant, but their action is graded by their slow liberation and by the presence of colloid extractives. The most common of these substances are **emodin** and **chrysophanic acid**. Numerous isomers of these are possible (15 for emodin alone). The special character of the different drugs is probably due to differences in these isomers, in the stability of their glucosidal combination, and to the presence of other associated substances (**tannin** in rhubarb).

Emodin is partly absorbed and is excreted into the urine and milk (laxative effects on sucklings). The drugs containing emodin color the urine yellowish-brown when it is acid, and reddish or violet when alkaline. It is advisable to warn the patient about this color change.

Other drugs that change the color of the urine act as follows. **Logwood (hematoxylon)** does not color acid urine but produces a reddish or violet color in alkaline urine. **Santonin** imparts a yellowish color to acid urine, with a yellow foam; if the urine is made alkaline, it imparts a very pronounced pink color. **Picric acid** gives reddish-brown color in both acid and alkaline urine. The various coal-tar products give a brownish-black color. **Methylene blue** imparts a green color.

### CASCARA SAGRADA

This is used chiefly in habitual constipation. It softens the stools without noticeable irritation. The susceptibility is not lost with use; on the contrary, the establishment of regular habits usually permits it to be gradually withdrawn. By its bitter taste, it acts also as a **stomachic**. It may be given as the fluid extract, 15 drops thrice daily, or in a single dose, a half teaspoonful in the evening. This causes a single soft stool in the morning. In the **aromatic fluid-extract**, which is much more pleasant, some of the bitter and cathartic principles have been destroyed by an alkali (magnesia). Twice the dose may be given.

### SENNA

The effects are more extensive and more irritant than with the other drugs of the group, so that it is better suited for acute than for chronic constipation. There is considerable griping, which may be corrected by **carminatives** or by the previous extraction of the resins with alcohol (as in the fluid extract).

### RHUBARB

This contains a considerable quantity of **tannic acid** as well as cathartic principles. The astringent action predominates with smaller doses (0.05 to 0.01 g), and these are used as astringent bitters in gastric catarrh and in diarrhea. Larger doses (1 to 5 g) are laxative with little colic. They may be employed in chronic constipation, but the astringent action makes it inferior to cascara. It may cause skin eruptions.

### ALOE

As described in previous sections, the inspissated juice of the leaves of various species of *Aloe* from the West Indies, Africa, etc., furnishes the commercial varieties of aloes, which differ somewhat in composition and action. They contain **anthraquinone** derivatives, especially **aloïns**

(10 to 16%). These are glucosides, which are probably inactive themselves, but which yield emodin and other active anthraquinone derivatives on cleavage. This cleavage occurs in the intestine; it is favored by alkalis and perhaps also by bile and by iron salts. Aloin may be used as such. Aloe is intensely bitter, so that it must be administered in pills. Very small doses may be used as a stomachic. Moderate doses are simply laxative, but tend to cause griping, and are therefore commonly combined with **belladonna** or **carminatives (myrrh, etc.)**. They do not lose their efficacy on continued use and would be suited to habitual constipation, but have no advantage over cascara. Aloes are supposed to produce considerable congestion of the pelvic organs and are therefore contraindicated in hemorrhoids, menstruation, and pregnancy. On the other hand, they may be used as **emmenagogues**. They are especially prescribed for correcting the constipative action of iron medication.

### CASTOR OIL

This consists mainly of the triglyceride of an unsaturated fatty acid, **ricinoleic acid**. The neutral fat is not active but becomes so when it is saponified in the intestine. The cathartic effect is due mainly to motor stimulation of the small intestine. The intestinal secretion is not increased, the fluid character of the stools being due to the quicker passage of the feces.

With the usual dose, 1/2 to 1 oz, the response is certain and complete, resulting in a few hours in one or two extensive semifluid stools with but slight hyperemia or irritation, there being little or no colic. It is especially suited to the treatment of acute constipation or acute diarrhea from dietetic errors, ptomaine and other poisoning, etc. It is not used continuously, because this may produce gastric disturbance. There is some pelvic congestion, so that it is avoided during menstruation and pregnancy.

### RICIN

This toxic protein is contained in **caster seeds** but does not pass into the oil. Similar **phytotoxins** occur in **croton seeds (Crotin)**; **jequirity seeds (Abrin)**; the **bark of the locust tree, Robinia pseudo-acacia (Robin)**; and in the seeds of some **leguminous plants (Phasin)**. The last is but weakly toxic. Ricin is responsible for the toxic effects on eating castor seeds; 5 or 6 of these are fatal to a child, 20 to adults, and 3 or 4 seeds may cause violent gastroenteritis with nausea, headache, persistent vomiting, colic, sometimes bloody diarrhea, thirst, emaciation, and great debility. The symptoms usually do not set in until after several days. More severe intoxications cause small frequent pulse, cold sweat, icterus, and convulsions. Death occurs in 6 to 8 d, from the convulsions or from exhaustion. The fatality rate is about 6%. This low fatality rate is due to the destruction of the poison in the alimentary canal. The treatment would be evacuant and symptomatic. Usually, 3 to 10 d are required to complete recovery.

### ABRIN

Abrin, from **jequirity beans (*Abrus precatorius*)**, resembles ricin so closely in its action that the difference was established only when it was noted that immunity against one did not constitute immunity against the other.

### CROTON OIL

This contains, besides ordinary fats, about 10% of **croton-resin**, the active component producing the local and systemic effects of the oil. It is destroyed by boiling with alkalis. Croton oil is the most violent of all cathartics, 1/2 to 1 drop producing burning in the mouth and stomach, often vomiting, and after 1/2 to 3 h, several extensive fluid evacuations, with much colic and tenesmus. It was formerly used in extreme cases of constipation, and in unconscious patients (**uremic** and

**apoplectic coma**), but it should never be employed. It may produce severe local effects on the mouth, as well as gastroenteritis. Toxic doses cause collapse. A dose of 20 drops has been fatal, but recovery is said to have followed 1/2 oz — presumably because of vomiting. The treatment would be evacuant, demulcent, opiates, and symptomatic (directed against the enteritis and collapse).

#### RESIN OF **PODOPHYLLUM**

This acts very slowly, generally only after 12 to 24 h or longer, producing several soft stools. Larger doses (20 mg, 1/3 grain, or more) act as a **hydragogue cathartic**, but it is chiefly employed in small doses (5 to 10 mg, 1/10 or 1/6 grain) as a laxative in chronic constipation, often combined with aloes or calomel; 0.3 to 0.5 g has been fatal.

**Podophyllum Resin**. U.S.P. (**Podophyllin**) is prepared from the dried rhizome and roots of *Podophyllum peltatum* (may apple, mandrake), a plant used by native peoples. An amorphous greenish-yellow powder, with a slight peculiar odor and faintly bitter taste, its active constituents are a resin and a crystalline principle, **podophyllotoxin**. The dose of the resin is 0.01 to 0.065 g, 1/6 to 1 grain. It is very irritating to mucous membranes, especially of the eyes.

Other roots and rhizomes related to this group include **Leptandra** (**Culver's root**), from *Veronica virginica*, which contains an amorphous bitter principle, not a crystalline glucoside as formerly reported. **Leptandrin** is a resinoid and pharmacologically inert but was supposed to be cholagogic without producing intestinal irritation.

#### **JALAP, SCAMMONIUM, IPOMEA**

**Jalap** is perhaps the mildest member of the group. It produces watery stools within 3 or 4 h, with little intestinal irritation and no gastric disturbance or much prostration. It has little taste and is therefore easily administered. It has been used in ascites, cerebral congestion, hypertension, and as adjuvant to anthelmintics. **Scammony** and its equivalent **Ipomea** are closely related to jalap.

#### **COLOCYNTH, ELATERIN, AND BRYONIA**

A number of plants of the cucumber family yield these drastic drugs. They are of complex composition, each containing several active principles, resinous and alkaloidal. They produce continuous watery stools, with intense irritation and hyperemia (Sollmann, 1944).

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# 13 Banisterine, Selegiline, and Parkinson's Disease

## INTRODUCTION

The following are the chief herbal treatments for Parkinson's disease:

- **Banisterine** from *Banisteria caapi* and *Nicotiana tabacum* is a monoamine oxidase inhibitor that is similar pharmacologically to selegiline (deprenyl), which is used in the treatment of Parkinson's disease.
- Plant-based drugs for Parkinson's disease include **L-dopa**, which comes from sources such as the seeds of *Mucuna pruriens* and *Vicia faba*. L-dopa is the chemical compound that has been used for Parkinson's disease for the last 30 years.
- Seeds of *Datura stramonium* have anticholinergic effects, similar to those seen with **trihexphenidyl** and **benztropine** (Ebadi and Pfeiffer, 2005).

Parkinson's disease consists of a severe reduction in the dopamine content in all components of the basal ganglia. Four separate groups of symptoms constitute the symptom complex that makes up parkinsonism. These consist of tremor at rest, akinesia or bradykinesia, rigidity, and loss of postural reflexes.

The parkinsonian tremors have been referred to as "pill-rolling," "cigarette rolling," and "to and fro" movements. These tremors are present during rest but often disappear during purposeful movement or sleep. Stress or anxiety-provoking situations aggravate the tremors and the initiation of movement becomes increasingly difficult, extremely fatiguing, and ponderously inefficient.

The akinesia or bradykinesia is characterized by a poverty of spontaneous movements and slowness in initiation of movements. Rigidity or increased muscle tone occurs in response to passive movements. The loss of normal postural reflexes is a disorder of postural fixation and equilibrium.

## THE ACTIONS OF ACETYLCHOLINE AND DOPAMINE

Neurochemically, parkinsonism is considered a **striatal dopamine-deficiency syndrome**, and the main extrapyramidal symptoms — tremor, akinesia, and rigidity — correlate positively with the degree of this deficiency. Although eight separate neurotransmitters interact in the nigro-striato-nigral loop, the basic therapeutic problem in parkinsonism has been to find suitable compounds that (1) increase the concentration of dopamine, (2) stimulate the dopamine receptor sites directly, or (3) suppress the activity at cholinergic receptor sites. These drugs fall into two main categories: those that increase dopaminergic function and those that inhibit cholinergic hyperactivity (Ebadi and Pfeiffer, 2005).

## HISTORY

Physicians in ancient India first used *Mucuna seeds* in the treatment of Parkinson's disease over 4500 years ago. The Indian medical system is called **Ayurveda**, which is the world's oldest system of medicine founded on scientific principles. It has a long history of use of herbal remedies and has documented data on mechanism of action, specific action, short-term and long-term toxic effects, drug–drug interactions, and drug–diet interactions with a long history of use in humans. As per historical evidence, **Parkinson's disease** existed in ancient India and was called **Kampavata**. This was over 4500 years ago even though the disease acquired its present name from **James Parkinson** who redescribed the disease in A.D. 1817 (see Ebadi and Pfeiffer, 2005). In the Ayurvedic system, powder of *Mucuna* is used for treating Parkinson's disease and is subjected to special processing. The English name “**cowage**” plant (*Mucuna pruriens*) is derived from Hindi nomenclature **Kiwach**. In Sanskrit, it is called **Atmagupta**. *Mucuna* is a twiner with trifoliolate leaves, purple flowers, and turgid S-shaped pods covered with hairs that cause intense itching on contact with the skin. The plant belongs to the family **Leguminosae**, which is indigenous to India and has long been used in Ayurveda since ancient times. Overdose effects of *Mucuna* were also recognized in Ayurveda. These included headache, dystonia, fatigue, tremor, syncope, and thirst. Many of these could also occur from synthetic L-dopa.

In 1929, Louis Lewin reported the use of a hallucinogenic compound prepared from the South American vine, *Banisteria caapi*, to treat Parkinson's disease (see Lewin and Schuster, 1929; Holmstedt, 1979). This psychoactive compound, named banisterine, proved to be identical to **harmine**. The first reports of the use of banisterine to treat postencephalic parkinsonism in 1929 created a stir in the popular press and banisterine was hailed as a “**magic drug.**” **Banisterine** is a reversible **monoamine oxidase inhibitor** (see Sanchez-Ramos, 1991, for a review), which in turn resulted in the discovery of **selegiline** and **rasagiline** that are now used in the treatment of Parkinson's disease (see Ebadi 1998; Ebadi et al., 2002; Ebadi et al., 2005).

## SELEGILINE

Selegiline is metabolized in the liver to (–)-**desmethylselegiline** and (–)-**methamphetamine**, which is further metabolized to **amphetamine**. Desmethylselegiline is also an irreversible inhibitor of monoamine oxidase B in human (Figure 13.1). **Rasagiline** is not metabolized to amphetamine-like derivatives. No gender- or age-related differences in the pharmacokinetics of selegiline have been reported. **Selegiline** may be used safely with **citalopram** or with **cabergoline** (Ebadi et al., 2002).

- **Selegiline** inhibits the activity of monoamine B, enhances the release of dopamine, blocks the uptake of dopamine, is a calmodulin antagonist, and enhances the level of cyclic AMP, which in turn protects dopaminergic neurons.
- **Selegiline** protects against 1-methyl-4-phenyl-1,2,3,5-tetrahydro-pyridine (MPTP)-induced neurotoxicity.
- **Selegiline** protects against neurotoxic factors present in the spinal fluid of patients with Parkinson's disease.
- **Selegiline** protects dopaminergic neurons from glutamate-induced excitotoxicity.
- **Selegiline** possesses cognition-enhancing function, rejuvenates serum insulin-like growth factor I in aging humans and enhances life expectancy.
- **Selegiline** possesses neurotrophic-like actions and rescues axotomized motoneurons independent of monoamine oxidase B (MAO-B) inhibition.
- **Selegiline** increases the striatal superoxide dismutase, protects against peroxynitrite- and nitric-oxide-induced apoptosis, and guards dopaminergic neurons from toxicity induced by glutathione depletion.

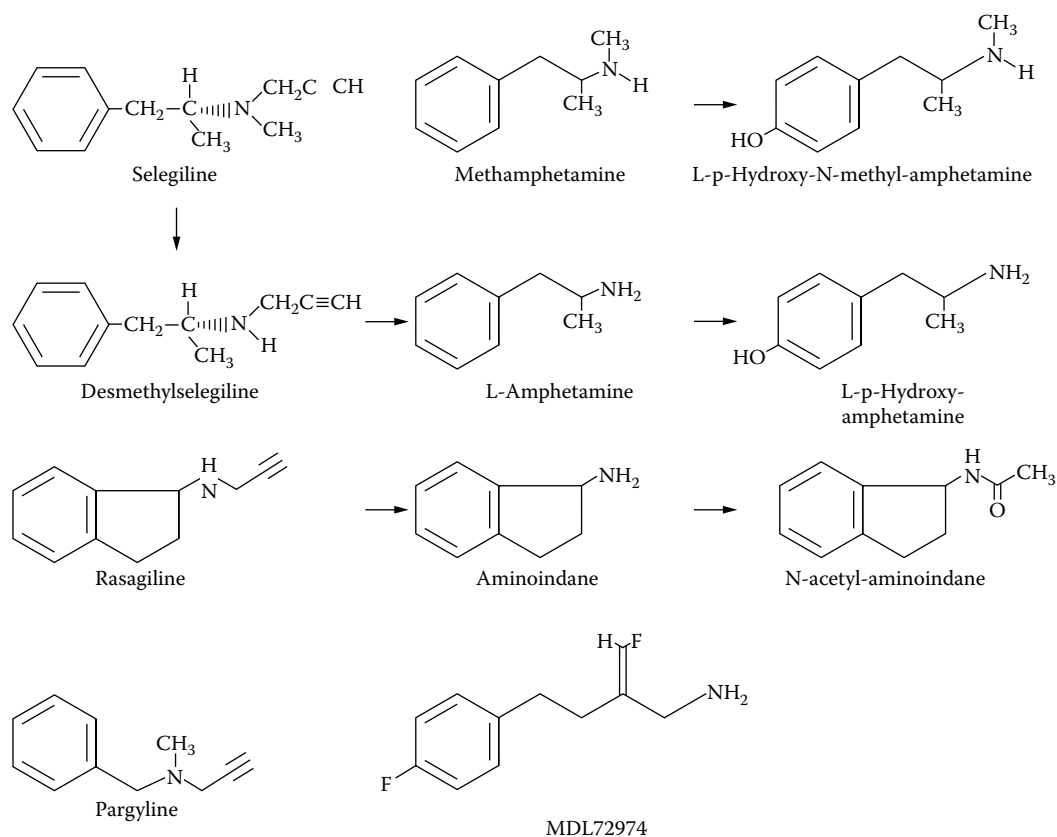


FIGURE 13.1 Metabolism of selegiline and rasagiline.

- **Selegiline** stimulates the biosynthesis of interleukin-1b and interleukin-6, is an immunoenhancing substance, possesses antiapoptotic action, and is a neuroprotectant.
- Finally, similar to banisterine, **selegiline** has been shown to be efficacious in Parkinson's disease (Ebadi et al., 2002).

### CLINICAL PHARMACOKINETICS OF SELEGILINE

The pharmacokinetic parameters of selegiline in healthy subjects have been studied. One study stated that the plasma selegiline concentration–time data are best described by a biexponential model with first-order absorption and a lag time in three volunteers, whereas a triexponential model with first-order absorption and a lag time was fitted to plasma selegiline concentration–time data in the remaining two volunteers. Selegiline in two dosage forms exhibited a lag time, the absorption was rapid, and the mean time to reach peak drug concentration ( $t_{\max}$ ) was observed between 30 and 45 min ( $t_{\max} = 36 \pm 8.2$  min) for the solution and 30 to 90 min (mean  $t_{\max} = 54 \pm 23$  min) for the tablets. The mean  $C_{\max}$  was  $2.2 \pm 1.2$   $\mu\text{g/l}$  for tablet and  $4.06 \pm 2.6$   $\mu\text{g/l}$  for solution. The apparent volume of distribution ( $V/F$ ) was  $1854 \pm 824$  l for the tablet and  $1446 \pm 1315$  l for the solution. The  $t_{1/2}$  was approximately  $1.20 \pm 0.65$  h following the administration of the 10-mg tablet. The oral clearance was  $59 \pm 44$  l/min and  $50 \pm 43$  l/min, respectively, following the administration of tablet and solution. This very high oral clearance (almost 30-fold higher than the hepatic blood flow) indicates that selegiline is extensively metabolized not only in the liver but also through extrahepatic metabolism.

No gender-related differences in the pharmacokinetics of selegiline were observed following a single oral dose of selegiline 10 mg to 6 elderly males and 6 elderly females between 60 and 85 years old.

A comparison of the pharmacokinetics of selegiline in 14 male patients (18 to 30 years of age) with 6 elderly male patients (age > 60 years) indicated that the  $C_{\max}$  and the AUC remains unaltered between the young and the elderly patients. The  $t_{1/2}$  of selegiline in the elderly patients was almost twofold longer than in the young patients (3.2 h in the elderly patients vs. 1.5 h in the young); however, because of the small sample size and high variability in  $t_{1/2}$   $\beta$ , this difference may not be a real difference and may not have any clinical impact.

Three selegiline metabolites have been detected in human plasma. Selegiline is metabolized in the liver to (–)-**desmethylselegiline** and (–)-**methamphetamine**, which is further metabolized to **amphetamine**. Furthermore, both methamphetamine and amphetamine can be metabolized into the corresponding parahydroxy derivatives, which are pharmacologically inactive after being conjugated with **glucuronic acid**. Selegiline can also be metabolized in the lung to form methamphetamine or desmethylselegiline. In the kidneys, only methamphetamine is formed, but the degree of metabolism in these tissues is minimal when compared with that in the liver (see Figure 13.1).

Desmethylselegiline is also an irreversible inhibitor of monoamine oxidase B in humans. There is evidence that the l-stereoisomers of l-amphetamine and l-methamphetamine may have some qualitatively different actions from their d-isomer counterparts, which might result in beneficial clinical effects and could complement any beneficial clinical actions of selegiline itself. Food has no effect on the pharmacokinetics of desmethylselegiline, methamphetamine, and amphetamine. At a dose of 10 mg per day, selegiline is devoid of the “**cheese effect**”; that is, it does not cause hypertension when taken with tyramine-containing foods such as cheese.

### LACK OF ADVERSE INTERACTION BETWEEN SELEGILINE AND CITALOPRAM OR BETWEEN SELEGILINE AND CABERGOLINE

The concomitant use of serotonergic antidepressive drugs with MAO inhibitors has been associated with serious adverse drug interactions manifesting as hyperexcitation of the central nervous system, known as the **serotonin syndrome**. The serotonin syndrome is caused by excessive activation of central serotonergic receptors, resulting in typical clinical symptoms that may be lethal. These symptoms include confusion, hypomania, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, and in more severe cases, elevated blood pressure, tachycardia, and hyperthermia. Several case reports indicate that the concomitant use of selegiline with the serotonin reuptake inhibitor **fluoxetine** may lead to adverse drug interactions. The risk for pharmacokinetic or pharmacodynamic interactions of concomitantly administered **selegiline** (a selective monoamine oxidase type B inhibitor) and **citalopram** (a widely used selective serotonin uptake inhibitor antidepressant) have been studied.

Two parallel groups of healthy volunteers received 20 mg of citalopram ( $n = 12$ ) or placebo ( $n = 6$ ) once daily for 10 d in a randomized, double-blind fashion, followed by concomitant selegiline, 10 mg once daily for 4 d. The safety of this drug combination was assessed by measurements of blood pressure, heart rate, body temperature, and inquiries for adverse events. Blood samples were taken for the analysis of serum concentrations of selegiline, citalopram, and their metabolites. In addition, plasma was obtained to measure prolactin, epinephrine, norepinephrine, and **3,4-dihydroxyphenolglycol (DHPG)**, the urinary excretion of norepinephrine and 5-hydroindoleacetic acid (5-HIAA), the urinary metabolite of serotonin.

After a 5-week washout, the 12 subjects who took citalopram in the first part of the study received 10 mg of selegiline once daily for 4 d to compare the pharmacokinetics of selegiline with and without concomitant citalopram. The safety analysis showed no significant differences in vital signs or the frequency of adverse events between the study groups. Plasma prolactin concentrations

were increased by 40% after 10 d of treatment with citalopram ( $p = .03$ ) and this effect was not potentiated by concomitantly administered selegiline. The comparison of plasma concentrations of norepinephrine, epinephrine, and DHPG and the amount of serotonin and 5-HIAA excreted into urine between the study groups indicated no signs of subclinical pharmacodynamic interaction between selegiline and citalopram. The relative bioavailability of selegiline was slightly reduced (by 29%;  $p = 0.008$ ) when citalopram was coadministered compared with selegiline alone. However, no indication of a pharmacokinetic interaction was found in the analysis of serum concentrations of the three main metabolites of selegiline. The pharmacokinetics of citalopram remained unaffected by concomitant selegiline. The present results indicate lack of clinically relevant pharmacodynamic or pharmacokinetic interactions between selegiline and citalopram. The interaction between cabergoline and selegiline has been studied.

As selegiline is hardly detectable in plasma, the plasma levels of its metabolites amphetamine, methamphetamine, and desmethylselegiline were used to assess the effect of cabergoline coadministration. Plasma levels of the selegiline metabolites were determined first after selegiline administration (10 mg/d) for 8 d, and then after administration of both drugs for 22 additional days (day 30). Cabergoline plasma levels were measured on day 30, and then after administration of cabergoline (1 mg/d) alone an additional 22 d. No statistical difference was found between the values of cabergoline and of the selegiline metabolites when the two drugs were given alone or in combination, indicating the absence of pharmacokinetic interaction between **cabergoline** and **selegiline**.

### DISTRIBUTION OF MONOAMINE OXIDASES A AND B mRNAs IN THE RAT BRAIN BY *IN SITU* HYBRIDIZATION

MAO-A and MAO-B are the major catabolic isoenzymes of catecholamines and serotonin in the mammalian brain. The two isoenzymes have 70% amino acid identity, identical exon-intron organization, and are encoded by two different genes that reside closely between bands Xp11.23 to Xp22.1 of the X chromosome.

MAO-B-containing structures in the nucleus accumbens, using MAO-A-deficient transgenic mice and MAO enzyme histochemistry, have been studied. Among the striatal structures, the **nucleus accumbens**, and in particular its dorsal shell, showed the strongest MAO-B activity. MAO-B-active cell bodies were embedded in a dense MAO-B-active fiber plexus. MAO-B-positive terminals formed axo-dendritic synapses that were exclusively of the asymmetric type. It is suggested that dopamine in the nucleus accumbens shell is transported into MAO-B-positive fibers where it is degraded by MAO-B.

By applying *in situ* hybridization histochemistry and by using <sup>35</sup>S-labeled **oligodeoxynucleotide probe** complementary to cloned human sequences, MAO-A and MAO-B mRNAs in the monkey brain stem have been studied. Furthermore, hybridization studies to visualize MAO-A and MAO-B mRNAs in the rat brain by using specific cDNA and oligonucleotide probes have been carried out. These studies have shown that MAO-A mRNA was present in major monoamine groups of the brain, such as the dorsal vagal complex, the C1 and A1 groups, the locus ceruleus, the raphe nuclei, substantia nigra, and the ventral tegmental area. It was also present in important brain structures of the forebrain, such as the cerebral cortex, the hippocampus, the medial habenula, the thalamus, and the hypothalamus; and of which are major projection sites of the monoamine groups of the midbrain and hind brain. Thus, MAO-A mRNA was found in serotonergic and noradrenergic cell groups as well as in dopaminergic groups. The presence of MAO-A mRNA in these groups is consistent with a role for MAO-A in oxidizing serotonin, norepinephrine, and dopamine in the rat.

In contrast to MAO-A mRNA, the distribution of MAO-B mRNA in the brain was very circumscribed. There were only three brain regions in which the amount of MAO-B mRNA exceeded the limits of detection: the **area postrema**, the **dorsal raphe**, and the **subfornical organ**. The area postrema and the subfornical organ are both circumventricular organs that contain a wide



variety of neurotransmitters, including monoamines. MAO-B expression, therefore, may play a role in the oxidation of local neurotransmitters. The area postrema and the subfornical organs also lack blood–brain barriers and are exposed to blood-borne substances; they are functionally important as detectors of humoral factors and toxic substances in the blood. It is possible that MAO-B may aid in the degradation of blood-borne factors in these circumventricular organs.

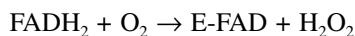
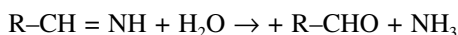
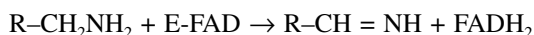
Although MAO-B mRNA was observed in the serotonergic cell group of the dorsal raphe, MAO-B was not present in the median raphe or in any major catecholaminergic cell group, such as the C1 and A1 groups, the nucleus of the solitary tract, the locus ceruleus, the substantia nigra, or the ventral tegmental area. MAO-B mRNA was also not observed in projection sites of the monoaminergic groups in the forebrain.

Although there is a considerable amount of confusion regarding the substrate specificity of MAO-A and MAO-B toward dopamine, it is widely accepted that dopamine is metabolized by both forms of the enzyme in the rat brain, and it is deaminated solely by MAO-B in the human brain. The activity of MAO-B increases with age and the age-related changes may lead to an overproduction of neurotoxic agents. The inhibition of the enzyme activity may play a preventive role against neurodegradation brain disorders.

### INHIBITION OF MONOAMINE OXIDASE B BY BANISTERINE AND SELEGILINE AND THE INITIAL RATIONALE OF USING THEM IN PARKINSON'S DISEASE

Amine oxidases catalyze the oxidation of amines, diamines, and polyamines. According to their ability to recognize one of those substrates preferentially, amine oxidases may be divided into **monoamine oxidases**, **diamine oxidases**, and **polyamine oxidases**, respectively. Several different enzymes fall into the amine oxidase class, and the classification of some of them still remains ambiguous. The term “monoamine oxidase” (flavin-containing, EC 1.4.3.4) was introduced to contrast with copper-containing amine oxidases (EC 1.4.3.6).

In the case of MAO, oxidation of the substrates is coupled to the reduction of **flavin adenine dinucleotide (FAD) cofactor**. The product of the reaction is the amine of the substrate, which hydrolyzes spontaneously to yield the corresponding aldehyde and ammonia. Reoxidation of the cofactor by molecular oxygen produces H<sub>2</sub>O<sub>2</sub>, according to the following reactions:



Flavin-containing mitochondrial MAO-A and MAO-B catalyze the oxidative deamination of neurotransmitters, such as dopamine, serotonin, and norepinephrine in the central nervous system and peripheral tissues. The enzymes share 73% sequence homology and follow the same kinetic and chemical mechanism but have different substrate and inhibitor specificities. Chemical modification experiments provide evidence that a **histidine residue** is essential for the catalysis. There is also strong evidence that two **cysteine residues** are present in the active site of MAO.

Both MAO-A and MAO-B contain a redox-active disulfide at the catalytic center. The results imply that MAO may be a novel type of **disulfide oxidoreductase** and may open the way to characterizing the catalytic and chemical mechanism of the enzyme.

When an amine is oxidized, electrons pass from the amine to the disulfide and then to the flavin. The formation in MAO of a **carboxyl–imidazole–disulfide triad**, similar to that demonstrated for **disulfide oxidoreductases**, would result in an increased positive charge on the disulfide,

**TABLE 13.1**  
**Classification of Monoamine Oxidases (MAO): Substrate Specificities and Inhibitor Sensitivities**

	Substrates for MAO-A	Substrates for MAO-B	Substrates for Both MAO-A and MAO-B
	Serotonin	Dopamine	Tyramine
	Epinephrine	2-Phenylethalamine	Inhibitors for both
	Norepinephrine	Tryptamine	MAO-A and MAO-B
	Octopamine	MPTP	
	Inhibitors for MAO-A	Inhibitors for MAO-B	
Irreversible	Clorgyline	Selegiline	Phenelzine
		Pargyline	Tranylcypromine
Reversible	Harmine		
	Harmaline		
	A-Ethyl-tryptamine		
	Quipazine		

*Note:* MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

which would facilitate electron transfer from the amine substrate. Similarities with the disulfide oxidoreductase family of enzymes, which includes **glutathione oxidoreductase**, **lipoamide dehydrogenase**, and **thioredoxin reductase**, may be useful in elucidating the mechanism. However, although there are structural analogies between the N-terminal region of MAO and the nucleotide-binding region of lipoamide dehydrogenase, the **dithiol sequence motif** common to the disulfide oxidoreductase family is not found in MAO.

MAO exists in different forms with different substrate specificities and inhibitor sensitivities (Table 13.1). These studies paved the way for utilization of selegiline in Parkinson's disease and for the discovery of a new generation of MAO inhibitors.

Placenta expresses mainly MAO-A. Platelets, lymphocytes, and chromaffin cells (Table 13.2) express mainly MAO-B. MAO-A and MAO-B are present in diversified cell population of the central nervous system (Table 13.3).

## PROTECTION OF DOPAMINERGIC NEURONS BY RASAGILINE

The success of selegiline as an adjunct to L-dopa treatment of Parkinson's disease has prompted the development of other selective inhibitors of MAO-B. The antiparkinsonian effect of selegiline is thought to comprise both symptomatic and neuroprotective components, although the extent of each of these elements in attaining clinical antiparkinsonian action is unclear. The former may depend on an increase in synaptic dopamine and **phenylethylamine** when selegiline is administered alone or together with L-dopa, and both its inhibition of MAO and the amphetamine-like properties of the molecule may play a part in achieving this effect; the latter has been demonstrated definitively only in isolated cell or intact animal experiments.

An indane derivative, AGN-1135 (*N*-propargyl-*l*-aminoindane), which produces selective inhibition of MAO-B without the amphetamine-like properties of selegiline, has been described. It has been shown that R(+)-*N*-propargyl-*l*-aminoindane (**rasagiline**) possessed nearly all of the enzyme-inhibitory activity of selegiline. Furthermore, rasagiline is not metabolized to amphetamine-like derivatives. Similar to selegiline, when given in a dose selective for inhibition of MAO-B, it did not affect striatal extracellular fluid dopamine levels, but when administered chronically (21 d), it increased striatal microdialysate dopamine without reduction in deaminated metabolites. Similar

**TABLE 13.2**  
**Tissue Distribution of MAO in Humans**

Tissues	MAO-A	MAO-B
Placenta	++(+)	±
Fibroblasts	++	+
Platelets	–	++
Lymphocytes	–	++
Erythrocytes	–	–
Brain	++	++(+)
Intestine	+++	–
Ileum	++	++
Colon	++	++
Lung	++(+)	+
Liver	+++	+++
Kidney	++(+)	++(+)
Adrenals	++(+)	++(+)
Heart	++(+)	++(+)
Pancreas	++(+)	+
Skeletal muscle	+ /+++	+ /+++
Stomach	+	+
Spleen	+	+
Tongue	++	+
Esophagus	++	+
Skin	+	+
Diaphragm	+	++
Blood vessels		
Aorta	+ /+++	+ /+++
Cerebral	+	=/–

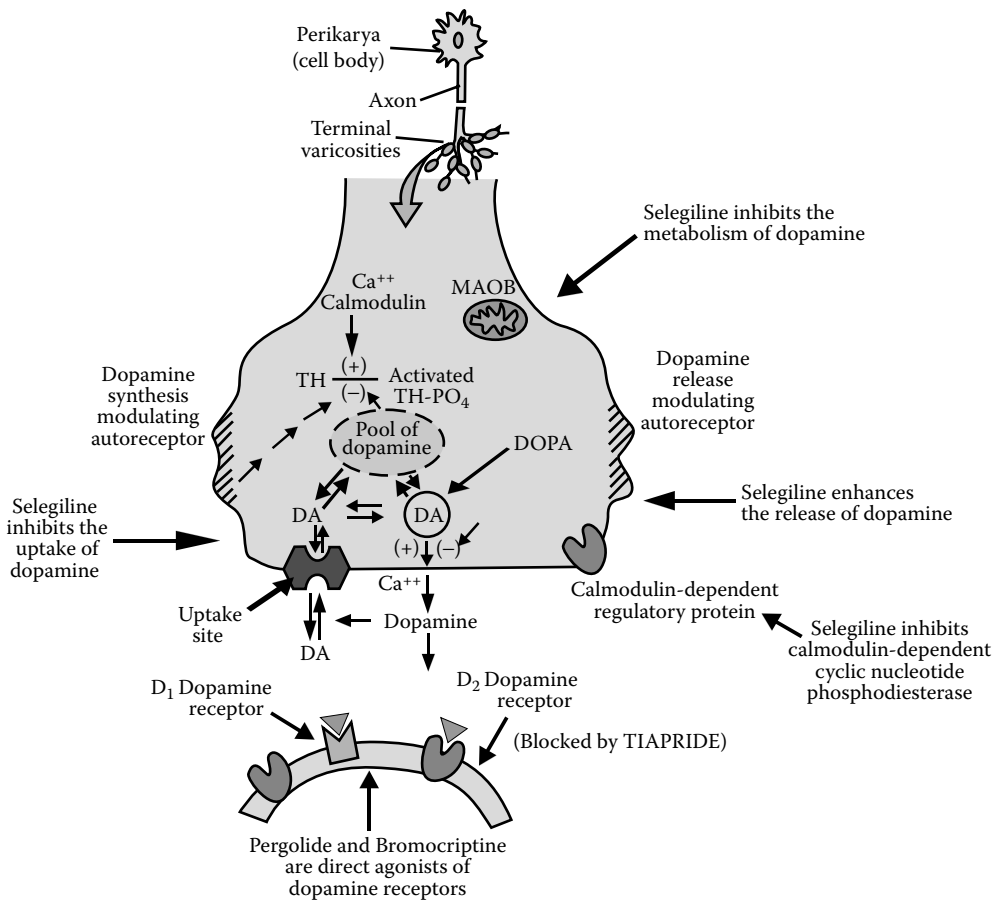
*Note:* – = no activity; ± = very low to negligible activity; + = low activity; ++ = intermediate activity; +++ = high enzyme activity.

**TABLE 13.3**  
**The Distribution of MAO Isoenzymes in the Human CNS**

Brain Areas	MAO-A	MAO-B
<b>Cortices</b>	+(+)	+(+)
Frontal Cortex	+	++(+)
Cingulate gyrus	+	++(+)
Insula cortex	+	+(+)
Temporal cortex	+	+(+)
Parietal cortex	+	+(+)
Occipital cortex	+	+(+)
Prefrontal cortex	+	+(+)
<b>Cerebellum</b>		
<b>Basal ganglia</b>		
Caudate	+(+)	++
Putamen	+	++
Globus pallidus	+	++(+)
Thalamus	+	++
<b>Limbic areas</b>		
Nucleus accumbens	+++	
Amygdala	++	++
Hippocampus	+(+)	+(+)
Dentate gyrus	++	++
Hypothalamus	+++	+++
Mammillary complex	+++	+
Interpeduncular nucleus	++	+++
Entorhinal cortex	++	++
<b>Brain stem</b>		
Locus coeruleus	+++	+(+)
Raphe nuclei	++	+++
<b>Pons</b>	++	++
<b>Medulla</b>	++	++
Substantia innominata		+++
Substantia nigra	++(+)	+++
Reticular formation	+(+)	++
<b>Others</b>		
Choroid plexus	+	+++
Nucleus rubber	++	++
White matter		+
Periaqueductal gray	++	+++
Superior colliculus		+++

*Note:* + = low activity; ++ = intermediate activity; +++ = high activity.

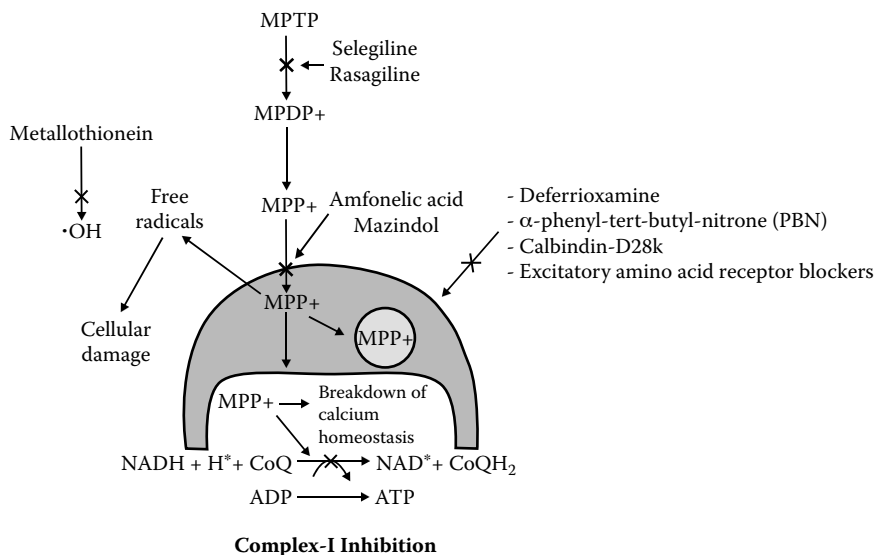
to selegiline, rasagiline ( $10^{-6}$  M) increased the percentage of **tyrosine hydroxylase-positive cells** in a primary culture of **fetal mesencephalic cells** (6 d in culture). Rasagiline, but not selegiline, also increased the number of neurons per field in this organotypic culture. The production and accumulation of neurotoxin can be blocked by drugs such as **selegiline** that inhibit the activity of MAO-B. Moreover, monkeys treated simultaneously with MPTP and selegiline do not develop Parkinson's syndrome (Figure 13.2).



**FIGURE 13.2** Selegiline inhibits the metabolism of dopamine, stimulates its release, and inhibits its uptake. In addition to possessing autoreceptors capable of modulating the release of dopamine, the corpus striatum also contains  $\gamma$ -aminobutyric acid (GABA)-producing feedback pathways, whose activation leads to the release of GABA and subsequent inhibition of dopaminergic neurons. Moreover, Ca<sup>2+</sup>-dependent release of dopamine exists that itself is attenuated. The bottom portion of the figure provides a schematic representation of a Ca<sup>2+</sup>-dependent release of dopamine, which itself is attenuated by release-modulating autoreceptors via a coupling mechanism that may involve protein carboxymethylation whose substrate may be calmodulin or a calmodulin-dependent enzyme. In addition, synthesis-modulating autoreceptors exist, which through a Ca<sup>2+</sup>-calmodulin-dependent mechanism may lead to phosphorylation of tyrosine hydroxylase (TH), producing phosphorylated tyrosine hydroxylase (TH-P04), which possesses a greater affinity for tetrahydrobiopterin cofactor and subsequently enhances the synthesis of dopa and, in turn, dopamine.

## PROTECTION AGAINST MPTP-INDUCED NEUROTOXICITY BY SELEGILINE

Endogenously produced neurotoxins have long been suspected of being involved in the pathogenesis of Parkinson's disease; however, little mechanistic evidence existed to support this concept until the neurotoxic effects of **MPTP** were found to induce a Parkinson-like syndrome. The discovery that MPTP produces a central nervous system pathology very similar to that observed with Parkinson's disease has strengthened the endogenous neurotoxin hypothesis and provided a heuristic model for investigating the pathological process of Parkinson's disease. The first stage in the mechanism of action of MPTP appears to be its deamination by MAO-B, possibly in glial cells,



**FIGURE 13.3** Oxidation of MPTP to 1-methyl-4-phenyl-2,3-dihydropyridium ion (MPDP<sup>+</sup>), and finally to MPP<sup>+</sup> generates free radicals and causes parkinsonism in humans. A deficiency of NADK Co (complex I) also causes striatal cell death. A deficiency of complex I may signify that an MPTP-like neurotoxin is generated endogenously, enhancing the vulnerability of striatum to oxidative stress reactions.

which results in the formation of 1-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>). The MPP<sup>+</sup> is then selectively accumulated in dopamine nerve terminals by way of the high-affinity dopamine reuptake system. Neurons lacking dopamine transporter remain unaffected. Once inside the nerve terminals, MPP<sup>+</sup> seems to act in a manner similar to **6-hydroxydopamine** by generating **hydrogen peroxide** and free radicals that interfere with mitochondrial respiration. MPP<sup>+</sup> is concentrated in mitochondria, where it impairs mitochondrial respiration by inhibiting **complex I** of the electron transfer complex and consequently causing death of neurons. The activity of complex I is reduced in the brains of patients with Parkinson's disease. It has been suggested that the neuromelanin present in dopaminergic neurons (by binding and storing the MPP<sup>+</sup>) acts as a storage site for MPP<sup>+</sup> or other neurotoxins. Dopaminergic cell death by MPTP (Figure 13.3) is caused by oxidative stress followed by lipid peroxidation caused by inhibition of mitochondrial enzymes participating in ATP synthesis. The production and accumulation of neurotoxin can be blocked by drugs such as **selegiline** that inhibit the activity of MAO-B. Moreover, monkeys treated simultaneously with MPTP and selegiline do not develop Parkinson's syndrome (Figure 13.3).

### PROTECTION BY SELEGILINE OF DOPAMINERGIC NEURONS IN CULTURE FROM TOXIC FACTORS

In addition to MPTP, other endogenously produced neurotoxins, namely, the monoamine-derived 1,2,3,4-**tetrahydroisoquinolines** and 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines, have been proposed as factors accelerating dopamine cell death. *N*-methylated isoquinolines were found to be oxidized by MAO, and hydroxyl radicals were found to be produced by this reaction. In addition, by incubation with the *N*-methylated isoquinolines, ATP was depleted from a dopaminergic cell model. Pretreatment of the cells with MAO inhibitors such as **selegiline** could, however, protect against ATP depletion. These results suggest that oxidation of neurotoxic isoquinolines is directly involved in the oxidative stress to induce the cell death of dopamine neurons. On the other hand, 1-methyl-1,2,3,4-tetrahydroisoquinoline and 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquino-

line were found to inhibit the activity of MAO, indicating that they may be neuroprotective agents in the brain.

The cerebrospinal fluid of patients with Parkinson's disease contains substances that inhibit the growth and function of dopaminergic neurons in culture. Moreover, selegiline, an MAO-B inhibitor (0.125 to 0.250  $\mu\text{M}$ ) enhances the number of tyrosine hydroxylase (TH)-positive neurons, augments the high-affinity uptake of dopamine, and averts the neurotoxic effects of the cerebrospinal fluid of patients with Parkinson's disease on rat mesencephalic neurons in culture.

Selegiline in protecting dopaminergic neurons from toxic factors present in the cerebrospinal fluid of patients with Parkinson's disease acts in a manner similar to those of **neurotrophic factors**, capable of partially protecting neurons against the neurotoxic effects of  $\text{MPP}^+$ . In addition to blocking the neurotoxic effects of factors present in the cerebrospinal fluid of patients with Parkinson's disease, selegiline stimulated the uptake of dopamine, enhanced the activity of TH, and increased the number of TH-positive neurons. Selegiline stimulates the uptake of [ $^3\text{H}$ ]dopamine at a lower concentration (0.125  $\mu\text{M}$ ) and inhibits it at a higher concentration (2.5  $\mu\text{M}$ ). This effect may be related to the higher level of dopamine which, in turn, causes an attenuation in carrier-mediated functions through a feedback regulatory mechanism (see Figure 13.2).

Both **selegiline** and **rasagiline** (at a concentration of 1 to 10  $\mu\text{M}$ ) increase survival of mesencephalic dopaminergic neurons that had been primed with 10% serum. Rasagiline, but not selegiline, also increases total neuronal survival. Under serum-free conditions, rasagiline, but not selegiline, retains its neuroprotective action on dopaminergic neurons; GABAergic neurons are not affected by either selegiline or rasagiline. **Chlorgyline**, an MAO-A inhibitor, does not exert any of these effects. The protective action of rasagiline on dopaminergic neurons, even under stringent serum-free conditions, is striking, and warrants a role in the treatment of Parkinson's disease.

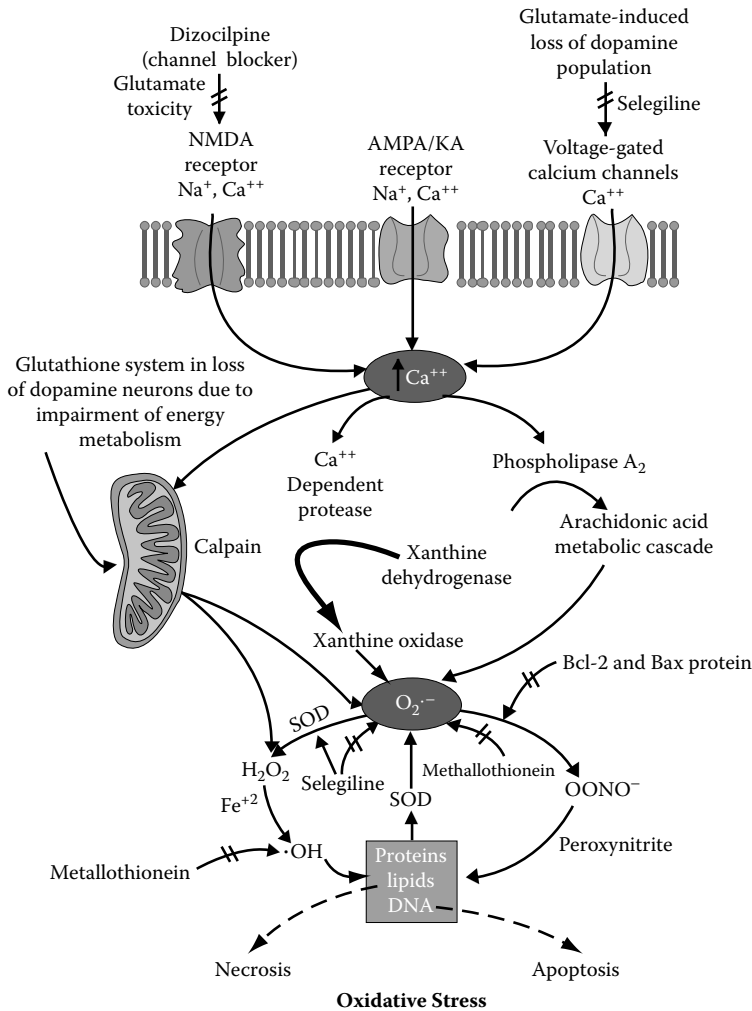
## PROTECTION BY SELEGILINE OF DOPAMINERGIC NEURONS FROM GLUTAMATE-INDUCED EXCITOTOXICITY

The excessive activity of excitatory amino acids, such as **L-glutamate** and **L-aspartate**, followed by elevation of intracellular free  $\text{Ca}^{2+}$  concentration and accumulation of free radicals has been postulated to underlie the neurodegeneration that occurs after ischemic insults and trauma. Additionally, an excitotoxic component has been shown to play an important role in the pathogenesis of chronic neurodegenerative disorders, such as **Alzheimer's disease**, **Parkinson's disease**, **amyotrophic lateral sclerosis**, and **Huntington's disease**, which are characterized by progressive loss of neuronal elements.

Activation of glutamate receptors (in particular, the NMDA type) leads to an intracellular accumulation of  $\text{Ca}^{2+}$ , which initiates a cascade of alterations resulting in the formation of free oxygen radicals. Glutamate perfusion of the striatum enhances dopamine release, a fact that also might contribute to increases in the formation of **hydroxyl radicals**. Alternatively, free-radical formation can induce a release of excitatory amino acids, as demonstrated in hippocampal slices (Figure 13.4).

There is evidence from experimental Parkinson's disease models that excessive activation of NMDA receptors might be an important factor for induction of Parkinson's disease. However, the involvement of NMDA receptors has not been shown in all parkinsonian models.

The effect of selegiline on cultured mesencephalic dopamine neurons subjected to daily changes of feeding medium, an experimental paradigm that causes neuronal death associated with activation of the N-methyl-D aspartate (NMDA) subtype of glutamate receptors, has been studied. Both selegiline (0.5 to 50  $\mu\text{M}$ ) and the **NMDA receptor blocker MK-801** (10  $\mu\text{M}$ ) protected dopamine neurons from damage caused by medium changes. The nonselective MAO inhibitor pargyline (0.5 to 50  $\mu\text{M}$ ) was not protective, indicating that protection by selegiline was not due to MAO inhibition. Selegiline (50  $\mu\text{M}$ ) also protected dopamine neurons from delayed neurotoxicity caused by exposure



**FIGURE 13.4** Growing evidence points to the involvement of free radicals in mediating nigral death in Parkinson's disease. Circumstantial evidence suggests that activation of glutamate receptors and excitotoxicity play a role in Parkinson's disease and other neurodegenerative disorders. Calcium-activated protease and phospholipase A<sub>2</sub> generate superoxide anions (O<sup>2-</sup>) and peroxynitrite (OONO<sup>-</sup>) capable of damaging proteins, lipids, and DNA, and of producing either necrosis or apoptosis. Glutathione deficiency, as seen in the substantia nigra of Parkinson's patients, causes conversion of H<sub>2</sub>O<sub>2</sub> to excess hydroxyl radicals (•OH). Selegiline (which enhances the level of superoxide dismutase), methallothionein isoforms (which scavenge •OH radicals and O<sup>2-</sup> anions), or dizocilpine (an NMDA receptor channel blocker) are postulated to avert oxidative stress in Parkinson's disease.

to NMDA. Because selegiline had no inhibitory effect on NMDA receptor binding, it is likely that selegiline protects from events occurring downstream from activation of glutamate receptors. As excitotoxic injury has been implicated in neurodegeneration, it is possible that selegiline exerts its beneficial effects in Parkinson's disease by suppressing **excitotoxic damage**.

Selegiline might exert its neuroprotection by (1) preventing free-radical formation, (2) increasing antioxidant cell defenses, (3) stimulating synthesis of growth factors, or (4) inhibiting apoptosis by interfering with the apoptotic pathways (see Figure 13.4).

Glutamate has been applied into the striatum by microdialysis, and the formation of **hydroxyl radicals** has been measured in the presence and absence of selegiline. In this study, microdialysis

probes were implanted into the striatum 1 d before measurement of levels of hydroxyl radicals. The next day, the probes were first perfused for 120 min with a modified Ringer's solution containing 5 mM salicylic acid, to obtain stable baselines. Afterward, the perfusion solution was switched to another solution that, in addition, contained 50 mM glutamate to stimulate radical formation. After 20 min,  $\alpha$ -phenyl-tert-butyl nitron (PBN, 100 mg/kg), selegiline (10 mg/kg), or saline was administered intraperitoneally. The glutamate perfusion produced marked 2- to 2.5-fold increases in 2,3-DHBA content. Treatment with PBN, a spin-trapping compound, significantly antagonized the rise of 2,3-DHBA level, indicating that PBN is a direct radical scavenger not only *in vitro* but also *in vivo*. Acute treatment with selegiline failed to reduce significantly the glutamate-induced radical formation.

**Selegiline**, in combination with the MAO-A inhibitor **chlorgyline**, inhibits the enhanced formation of hydroxyl radicals induced by the 2'-methyl analogue of MPTP. Similarly, pretreatment with selegiline administered into the striatum decreases the formation of hydroxyl radicals elicited by intrastriatal injection of MPP<sup>+</sup>. The contrasting results might be due to the different neurotoxic agents used (glutamate vs. MPP<sup>+</sup> or its derivative) or to different routes of administration of selegiline.

Under treatment with the MAO-B inhibitor selegiline, the degradation of **putrescine** might be diminished which, in turn, would suppress polyamine synthesis. Hence, the reported neuroprotective effect of selegiline might also receive a contribution from the diminished potentiation of the NMDA receptor by the polyamine-binding site. On the other hand, regarding inhibition of MAO-B, as is the case in patients with Parkinson's disease on selegiline, it is also likely that **N<sup>1</sup>-acetylated spermine** and **spermidine** will be present in the brain in increased concentrations. Therefore, it seems possible that selegiline will exert a neuroprotective effect via an antagonistic modulation of the polyamine-binding site of the NMDA receptor (see Figure 13.4).

## SELEGILINE: A CALMODULIN ANTAGONIST

The second messenger molecules Ca<sup>2+</sup> and cyclic AMP (cAMP) provide major routes for controlling cellular functions. In many instances, calcium (Ca<sup>2+</sup>) achieves its intracellular effects by binding to the receptor protein **calmodulin**. Calmodulin has the ability to associate with and modulate different proteins in a Ca<sup>2+</sup>-dependent and reversible manner. **Calmodulin-dependent cyclic nucleotide phosphodiesterase** (CaMPDE, EC 3.1.4.17) is one of the key enzymes involved in the complex interactions that occur between the cyclic-nucleotide and Ca<sup>2+</sup> second messenger systems (see Figure 13.2). CaMPDE exists in different isozymic forms, which exhibit distinct molecular and catalytic properties. The differential expression and regulation of individual phosphodiesterase (PDE) isoenzymes in different tissues relates to their function in the body.

Dopamine activates adenylate cyclase and **phospholipase C** (PLC) via a D<sub>1</sub> receptor and inhibits through a D<sub>2</sub> receptor, thereby regulating the production of intracellular second messengers, cAMP, Ca<sup>2+</sup>, and **1,2-diacylglycerol**. D<sub>1</sub> and D<sub>2</sub> receptors are decreased in the striatum of patients with dementia. There is considerable evidence to suggest that intracellular levels of cAMP have a protective role for dopaminergic neurons. Intracellular concentrations of cyclic nucleotides are regulated by **cyclic nucleotide phosphodiesterases** and CaMPDE, one of the most intensely studied and best-characterized phosphodiesterases.

The heterogeneity of dopaminergic neurons in the central nervous system may be judged by the fact that they may vary not only in terms of their projection areas but also in terms of the type of feedback pathways that they receive. Moreover, dopaminergic neurons and their receptors undergo dramatic developmental alterations that may foster a unique circumstance to produce dissimilar or opposite pathological states even with the same drugs. For example, in aged animals treated with **6-hydroxydopamine**, the loss of nigrostriatal dopamine is accommodated by a compensatory increase in the activity of the remaining neurons, whereas the **tuberinfundibular dopaminergic systems** are unable to compensate in a similar manner.



The heterogeneity of dopaminergic neurons may also be judged by the fact that the cotransmitter systems involving dopamine and peptides are varied in the central nervous system. For example, in the corpus striatum, in addition to dopamine, acetylcholine,  $\gamma$ -aminobutyric acid, serotonin, glutamate, and aspartate, one also finds peptides such as enkephalin, substance P, somatostatin, neuropeptide Y, cholecystokinin, neurotensin, and vasoactive intestinal peptide. Although many neuroleptics block dopamine receptors, they may have selective effects on the peptides and other parts of the brain. A few examples will be cited.

A high degree of coexistence of **cholecystokinin-like** and **tyrosine hydroxylase-like immunoreactivities** has been observed in the substantia nigra pars compacta. Moreover, ventral mesencephalic cholecystokinin projections encompass the full range of the well-known dopaminergic, mesolimbic, mesostriatal, and mesocortical projections. Therefore, it should not be surprising that the intrastrially injected cholecystokinin is able to stimulate dopamine-mediated transmission and to elevate the density of brain D<sub>2</sub>-dopamine receptors.

The chronic injection of **haloperidol**, but not **clozapine**, increases selectively the concentration of enkephalins in the striatum. Prolonged blockade of dopamine receptors by haloperidol causes a reduction in nigral content of substance P-like immunoreactivity, and of **substance P** and **substance K** mRNAs. Moreover, the effects of haloperidol on substance P is nonuniform in various areas of brain.

Subchronic oral administration of **lithium** causes a time-dependent increase in the substance P level in the striatum, which is prevented by coadministration of **haloperidol**. In PC12 pheochromocytoma cells, lithium dramatically increases the intracellular levels of the neuropeptide **neurotensin** and the mRNA encoding it. An extensive overlap between specific and high-affinity neurotensin binding sites and dopamine perikarya and dendrites has been shown to occur in the mesocorticolimbic and nigrostriatal projection systems. Consistent with this observation are the results of observations showing that **cocaine**, an indirect sympathomimetic agent that enhances the extrapyramidal dopaminergic activity, increases dramatically the striatal content of **neurotensin-like immunoreactivity**.

The effects of selegiline on bovine brain CaMPDE isoenzymes have been investigated. The findings indicated that selegiline inhibited brain 60-kDa isozyme; however, the inhibition for brain 63-kDa CaMPDE was observed to a lesser extent. The inhibition of brain 60-kDa CaMPDE was overcome by increasing the concentration of calmodulin, suggesting that selegiline may be a calmodulin antagonist or act specifically and reversibly on the action of calmodulin. The 60-kDa CaMPDE isozyme is predominantly expressed in brain and its inhibition can result in increased intracellular levels of cAMP. The increased intracellular levels of cAMP play a protective role for dopaminergic neurons. The cAMP may produce long-lasting physiological effects on synaptic membranes through a mechanism comprised of activation of cAMP-dependent protein kinase and consequent catalysis of phosphorylation of protein constituents of synaptic membrane. Intracellular signaling systems are complicated, but the multiple sites for pharmacological intervention may provide a basis for their mechanism of action and development of new drugs.

## INDUCTION BY SELEGILINE OF DOPAMINE RELEASE THROUGH AN ATP-SENSITIVE POTASSIUM CHANNEL

**Selegiline** is metabolized to methamphetamine (see Figure 13.1) and, by possessing amphetamine-like effects, is thought to release dopamine. By using an *in vivo* brain microdialysis technique, the chronic effects (21 d) and low doses of selegiline (0.25 mg/kg) on striatal release of dopamine have been investigated (see Figure 13.2). To determine whether amphetamine-like metabolites were responsible for the effects of selegiline, its action was compared with that of another selective propargyl MAO-B inhibitor, TVP-1012[R(+)-*N*-propargyl-*l*-aminoindan mesylate], which does not yield amphetamine-like metabolites. The action of **chlorglyline** was also studied, to compare the

effects of MAO-A and MAO-B inhibition. In addition to measuring the effects of chronic treatment with MAO inhibitors on basal dopamine release, the potassium-induced release of dopamine was also measured. The results of these studies showed that dopamine metabolism was reduced only by chlorgyline, whereas neuronal release of dopamine was enhanced by both MAO-A and MAO-B inhibitors on chronic administration. The enhanced dopamine release by chronic MAO-B inhibition does not appear to be dependent on production of amphetamine-like metabolites of the inhibitor. Possible mechanisms for the release-enhancing effect of the MAO-B inhibitors include elevation in levels of endogenous  $\beta$ -phenylethylamine, or an inhibition of dopamine reuptake, which develops only on chronic administration because selegiline has a very weak effect on amine uptake in acute experiments.

Superfusion chambers have been used to investigate the role of ATP-sensitive potassium ( $K_{ATP}$ ) channels in dopamine release elicited by the MAO inhibitor selegiline in the caudate-putamen *in vitro*. Selegiline induced increases in the extracellular concentrations of dopamine, with a maximal increase to 185% in comparison to basal outflow at 0.1 mM selegiline. **Butanedione** (0.1 mM), a specific  $K_{ATP}$  channel blocker, also significantly enhanced extracellular dopamine levels in the caudate-putamen to approximately 260%. Selegiline only led to an additional increase of dopamine outflow when added to submaximal concentrations of **butanedione** or **tolbutamide**, implying that selegiline was acting on identical sites. When the  $K_{ATP}$  channel opener **cromakalim** was added to the incubation medium, basal as well as butanedione-enhanced dopamine levels markedly decreased to about 40% when compared to baseline values. Selegiline-activated dopamine release was also antagonized by cromakalim. The selegiline effect was modulated neither by preincubation with the dopamine uptake inhibitor **nomifensine** nor by the dopamine receptor agonist **quinpirole** and the dopamine receptor antagonist **sulpiride**. These results suggest that selegiline is able to modulate  $K_{ATP}$  channels in the caudate-putamen, resulting in an enhancement of striatal dopamine release.

### NEUROTROPHIC-LIKE ACTION OF SELEGILINE: RESCUE OF AXOTOMIZED MOTORNEURONS INDEPENDENT OF MONOAMINE OXIDASE INHIBITION

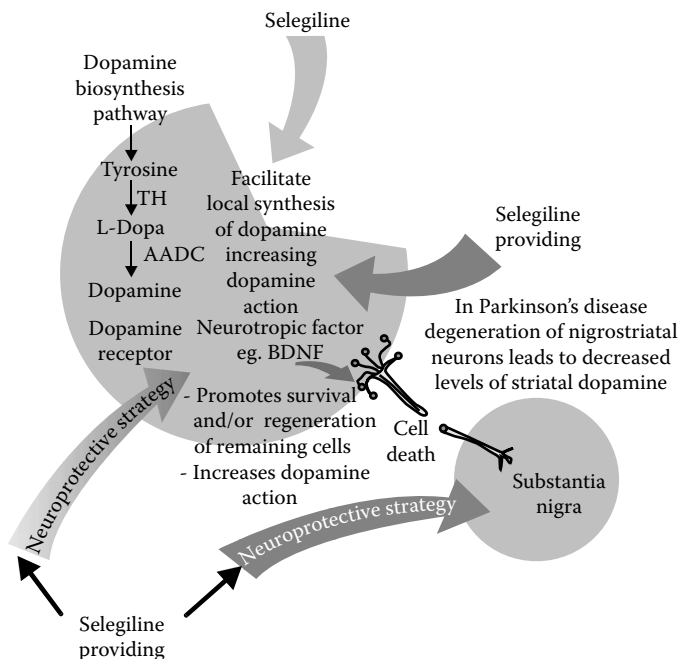
Selegiline possesses “trophic-like” action and may be of value for treating acute nervous system damage, particularly damage caused by trauma. Neuronal death is, however, difficult to establish conclusively. Immunocytochemistry for marker proteins is essential to identify specific neuronal populations, but this phenomenon suffers from the limitation that damaged nerve cells, such as motoneurons, often decrease or even halt the synthesis of some proteins such as **choline acetyltransferase**, while increasing the synthesis of cytoskeletal proteins. Hence, a loss of immunoreactive somata may indicate neuronal death or a reactive decrease in protein synthesis. Furthermore, motoneuronal somata can be premarked by the retrograde transport of an agent from their terminal areas, and the number of remaining premarked somata may be used to estimate neuronal death. The technique carries the limitation that the entire neuronal population may not be able to transport the marking substance, either due to incomplete delivery of the agent to the target tissues or due to inadequate uptake or retrograde transport by some of the neurons. If the retrograde transport of a premarker is combined with immunocytochemistry for a marker protein, it can then be used to determine if a loss of immunoreactivity has contributed to a reduction in the counts of immunoreactive somata. However, this cannot offer absolute values for neuronal death unless the entire neuronal population is shown to have transported the premarker.

The role of MAO-B and the influence of selegiline on the rescue of facial motoneurons axotomized at postnatal day 14 using the (+)- and (-)-enantiomers of selegiline [S(+)-selegiline and R(-)-selegiline] have been investigated. Motoneuronal survival was measured 21 d after unilateral facial nerve transaction. Doses of R(-)-selegiline of 0.005, 0.01, and 10.0 mg/kg/2 d increased the surviving facial motoneuron to 38, 51, and 48%, respectively. Selegiline increased motoneuronal

survival without significant inhibition of brain stem MAO-B activity. The dosage relationships for motoneuronal rescue vs. MAO-A and MAO-B inhibition and the marked difference in the stereospecificity of MAO-B inhibition vs. that of motoneuronal rescue show that the increased survival is unlikely to be dependent on the interaction of selegiline with the FAD site of MAO-A or MAO-B.

The finding that the rescue of the axotomized motoneurons appears independent of an interaction with MAO-B is in accord with work showing that selegiline was able to promote a marked increase in the survival of murine substantia nigra compacta neurons, after they had sustained otherwise lethal damage by MPTP, at dosages too low to cause any MAO inhibition. Similarly, the finding that the rescue of axotomized motoneurons occurs with doses too small to cause MAO-A inhibition is in accord with the finding that **chlorgyline**, a selective MAO-A inhibitor, did not rescue MPTP-damaged substantia nigra neurons. **Pargyline**, which inhibits both MAO-A and MAO-B and is structurally similar to selegiline, increases the survival of the axotomized immature motoneuron but is considerably less effective on an equal-molar basis. Methamphetamine and amphetamine, the major metabolites of selegiline, do not increase the survival of the motoneuron. It would seem plausible therefore that selegiline induces compensation for loss of target-derived trophic support. This does not imply that selegiline itself acts as a trophic factor but rather that it interferes with or triggers some event that supports the survival of motoneurons after the withdrawal of the trophic support. Recent research has shown that neurotrophic factors, **basic fibroblast growth factor (BFGF)**, **brain-derived neurotrophin factor (BDNF)**, and **ciliary neurotrophic factor (CNTF)**, reduce axotomy-induced death of facial or hypoglossal motoneurons in neonatal or immature rats in experiments similar to selegiline (Figure 13.5 and Table 13.4).

Neurotrophic factors of dopaminergic neurons may represent a potential neuroprotective therapy for Parkinson's disease. Apart from **nerve growth factor (NGF)**, the family of the "neurotrophins" subsumes at the present time BDNF, **neurotrophin-3 (NT-3)**, and **neurotrophin-4/5 (NT-4/5)**. However, the concept of neurotrophic factors as specific, target-derived molecules, each acting on distinct neuronal types, has to be modified because of their high degree of pleiotropism and a



**FIGURE 13.5** Selegiline enhances the release of dopamine and inhibits its metabolism. In addition, it has neurotrophic-like action capable of repairing damaged neurons.

**TABLE 13.4**  
**The Actions of Major Cytokines**

Family	Members	Major Activities and Features
Interleukins	IL-1 $\alpha$ , IL-1 $\beta$ , IL-1ra, and IL-2-IL-15	Multiple tissue and immunoregulatory activities; no similarity of activity is implied by membership of this family
Chemokines	IL-8/NAP-1, NAP-2, MIP-1 $\alpha$ and $\beta$ , MCAF/MCP-1, MGSA and RANTES	Leukocyte chemotaxis and cellular activation
Tumor necrosis factors	TNF- $\alpha$ and TNF- $\beta$	Similar to IL-1, in addition to tumor cytotoxicity
Interferons	IFN- $\alpha$ , $\beta$ , and $\gamma$	Inhibition of intracellular viral replication and cell growth regulation; IFN- $\gamma$ is primarily immunoregulatory
Colony-stimulating factors	EGF, FGF, PDGF, TGF $\alpha$ , TGF $\beta$ , and ECGF	Cell growth and differentiation
Neurotrophins	BDNF, NGF, NT-3-NT-6, and GDNF	Growth and differentiation of neurons
Neuropoietins	LIF, CNTF, OM, IL-6	Cytokines acting on the nervous system, and acting via a related receptor complex

*Note:* BDNF, brain-derived neurotrophin factor; CNTF, ciliary neurotrophic factor; EGF, epidermal growth factor; ECGF, endothelial cell growth factor; FGF, fibroblast growth factor; GDNF, glial-derived neurotrophic factor; G, M, and GM-CSF, granulocyte, macrophage, and granulocyte/macrophage colony-stimulating factors; IFN, interferon; IL, interleukin; IL-1ra, interleukin 1 receptor antagonist; MCAF, monocyte chemotactic and activating factor; MCP, monocyte chemotactic protein; MGSA, melanoma growth stimulatory activity; MIP, macrophage inflammatory protein; NGF, nerve growth factor; NT, neurotrophin; NAP, neutrophil activating protein; OM, oncostatin M; PDGF, platelet-derived growth factor; RANTES, regulated upon activation normal expressed and secreted; TGF, transforming growth factor; TNF, tumor necrosis factor.

considerable overlap in biological activities. In addition, a number of other nontarget-derived molecules exert trophic actions on certain neurons and nonneuronal cells. These factors include CNTF, **fibroblast growth factors 1 and 2** (FGF-1/FGF-2), **insulin-like growth factors 1 and 2** (IGF-1/IGF-2), **muscle-derived differentiation factor** (MDF), and members of the **transforming growth factor  $\beta$ -superfamily** such as **glial cell line-derived neurotrophic factor** (GDNF) (see Figure 13.5).

**Glial cell line-derived neurotrophic factor (GDNF)** has been purified and cloned. Furthermore, it has been identified by its promotion of survival and morphological differentiation of dopaminergic neurons with an increase of their high-affinity dopamine uptake in embryonic mid-brain cultures. In 6-hydroxydopamine (6-OHDA)-induced parkinsonism, neurochemical and behavioral improvements following intranigral administration of GDNF were demonstrated. Following hemitransection of the medial forebrain bundle, a significant protection of tyrosine hydroxylase (TH-iR) nigral neurons by GDNF was reported. Daily injections of 5  $\mu$ g GDNF for 14 d above the substantia nigra led to a survival of 84% of TH-iR nigral cells, whereas in control animals only 50% of these cells survived. In the **MPTP**-mouse model of Parkinson's disease, the protective effects of GDNF were investigated in respect to the time point of its administration. Striatal injections of GDNF (10  $\mu$ g on two consecutive days), 24 h before MPTP exposure, significantly reduced the normally observed TH-iR cell loss of 30% to about 15%. In addition, this effect was accompanied by a protection of the density of dopaminergic nerve terminals and dopamine levels in striatum as well as by increased motor behavior. When GDNF was administered 7 d after MPTP exposure, there was still some recovery of tyrosine hydroxylase immunoreactive (TH-iR) cells, increased locomotor behavior, and partial restoration of dopamine levels.

**Brain-derived neurotrophic factor (BDNF)** exhibits distinct effects on survival, morphological differentiation, neuritic growth, protection against MPP<sup>+</sup> cytotoxicity, and dopamine uptake

of fetal mesencephalic dopaminergic neurons. This neurotrophin was shown to be retrogradely transported to substantia nigra after injection into the striatum, indicating that there are functional receptors for BDNF on adult dopaminergic nigrostriatal neurons. Additionally, BDNF has been reported to prevent cell death of axotomized spinal motor neurons *in vivo*.

The effects of **metallothionein**, **neurotrophins**, and **selegiline** in providing neuroprotection in Parkinson's disease have been studied. The finding that MPTP elicits parkinsonism in humans suggests that endogenous or xenobiotic neurotoxic compounds may be involved in the etiology of Parkinson's disease. The studies have shown that the cerebrospinal fluid of newly diagnosed and drug-untreated patients with Parkinson's disease contains a low-molecular-weight substance that inhibits the growth and function of dopaminergic neurons in culture. In addition, selegiline in a dosage below the level that inhibits MAO-B, was able to protect dopaminergic neurons in culture against toxic factors present in the cerebrospinal fluid of patients with Parkinson's disease, and the said effect was mediated via elaboration of BDNF (see Figure 13.3 and Figure 13.4).

That 6-hydroxydopamine (6-OHDA) or MPTP causes parkinsonism by generating **free radicals** and that inducers of **metallothionein** isoforms avert the neurotoxicity led to the investigation of whether metallothionein isoforms were capable of scavenging free radicals. By employing **electron spin resonance spectroscopy** (ESR), the free-radical scavenging effects of metallothionein-I (MT-I) and metallothionein-II (MT-II) isoforms on four types of free radicals were examined for the first time. Solutions of 0.15 mM of MT-I and 0.3 mM of MT-II scavenged the **1,1-diphenyl-2-picrylhydrazyl radicals** completely. Further, they were able to scavenge hydroxyl radicals generated in a Fenton reaction. Moreover, MT-I scavenged almost 90% of the superoxide generated by the **hypoxanthine and xanthine oxidase system**, whereas MT-II could only scavenge 40%. By using **2,2,6,6-tetramethyl-4-piperidone** as a "spin trap" for the reactive oxygen species (containing **singlet oxygen**, superoxide, and hydroxyl radicals) generated by photosensitized oxidation of riboflavin, and by measuring the relative signal intensities of the resulting stable nitroxide adduct, **2,2,6,6-tetramethyl-4-piperidone-1-oxyl**, it was observed that MT-II could scavenge 92%, and MT-I could completely scavenge all the reactive species generated (see Figure 13.5).

The results of this investigation are interpreted to suggest that selegiline, by preventing the generation of free radicals, metallothionein isoforms; by scavenging free radicals, and neurotrophins; and by rescuing dopaminergic neurons, is capable of attenuating oxidative stress and of providing neuroprotection in Parkinson's disease.

**Epidermal growth factor (EGF)** was shown to support survival of both embryonic dopaminergic midbrain and cholinergic forebrain neurons. The trophic actions of EGF required the presence of glial cells, proposing an indirect mode of action of EGF on dopaminergic neurons. In this context, it was reported that EGF acts also on glial cells promoting their ability to proliferate and to differentiate. *In vivo* studies revealed that intraventricular administration of EGF in 5 weeks after hemitranssection of the medial forebrain bundle restores about 20% of tyrosine hydroxylase nigral neurons in comparison to vehicle-treated animals. Moreover, intraventricular infusion of EGF also accelerates recovery of striatal dopaminergic parameters, i.e., the dopamine content and tyrosine hydroxylase activity, in the MPTP-mouse model of Parkinson's disease.

**Fibroblast growth factor-2 (FGF-2)** exhibits trophic effects on central embryonic dopaminergic and GABAergic neurons in culture that appear to be mediated via glial cells. Transient increases in the amounts of FGF-2 have been described in distinct lesion paradigms of the central nervous system. The same was suggested to occur in a MPTP-induced lesion of the nigrostriatal dopaminergic system in mice. This may indicate a possible role of FGF-2 in neuronal regeneration, for example, in form of induction of synthesis of NGF or of other trophic molecules in astrocytes. In 6-OHDA-lesioned animals, intrastriatal FGF-2 infusions neither prevent striatal dopamine depletions nor diminish behavioral deficits. In the MPTP-mouse model, intrastriatal application of FGF-2 via gel foam partially attenuates the toxin-induced damage. However, this effect was only observed if FGF-2 was applied simultaneously or 3 d after the intraperitoneal MPTP injection, whereas a delay of FGF-2 administration for 7 d after MPTP injection aborted restoration of transmitters and

tyrosine hydroxylase levels. Apart from these findings, FGF-2 ameliorates rotational behavior of substantia nigra-transplanted animals with lesions of the nigrostriatal dopaminergic system.

**Muscle-derived differentiation factor (MDF)** induces tyrosine hydroxylase expression in a variety of central nervous system neurons, including those of striatum, cerebellum, and cortex. Normally, i.e., without MDF, these neurons do not express this enzyme of catecholamine synthesis. Further *in vitro* studies revealed that MDF enhances TH-mRNA 40-fold in fetal mesencephalic neurons. *In vivo* studies, employing infusion of partially isolated MDF, reported this molecule to enhance tyrosine hydroxylase activity in dopamine-depleted striata of 6-OHDA-lesioned animals. Furthermore, an increase of striatal dopamine concentrations and a partial compensation of rotational asymmetry were observed. In contrast, dopaminergic parameters were not affected by administration of MDF in control animals, suggesting that adult dopaminergic neurons may regain sensitivity toward differentiation factors after lesion.

**Transforming growth factor- $\beta$**  (TGF- $\beta$ 1,  $\beta$ 2,  $\beta$ 3) exert a survival-promoting activity on cultured dopaminergic neurons of the developing substantia nigra. In addition, TGF- $\beta$ 2 and TGF- $\beta$ 3 mRNAs were detected in developing striatum and substantia nigra. However, TGF- $\beta$ 3 did not prevent delayed degeneration of nigral dopaminergic neurons following intrastriatal 6-OHDA lesion.

The effect of chronic treatment with selegiline in an animal model of Parkinson's disease induced by unilateral knife transection of the medial forebrain bundle (MFB) in adult rats has been studied. The experimental conditions included a 3-week pretreatment with selegiline before stereotaxic transection of the MFB. Following surgery, selegiline treatment was maintained for 3 weeks. Neurochemical and immunohistochemical procedures were used to study the dopaminergic system and reactive astrocytes in the nigrostriatal system. Selegiline treatment failed to counteract the axotomy-induced degenerative changes of the nigrostriatal dopaminergic system. However, it was effective in increasing the density of reactive astrocytes in terms of glial fibrillary acidic protein (GFAP) immunoreactivity in the intact contralateral substantia nigra and also in further enhancing the axotomy-induced increase of GFAP-immunolabeled astrocytes in the lesioned substantia nigra. This selegiline-induced effect on GFAP immunoreactivity was confined to substantia nigra without effect in striatum. In addition, the investigators also found a medial-to-lateral gradient decrease in the distribution pattern of GFAP-immunolabeled astrocytes. Axotomy increased the number of reactive astrocytes in both striatal areas examined, but the preferential distribution pattern of reactive astrocytes in striatum was still evident.

### RESTORATION BY SELEGILINE OF SERUM INSULIN-LIKE GROWTH FACTOR-I IN AGED RATS

It has been reported that selegiline improves the functions of meso-limbo-cortical dopamine neurons that are known to be associated with cognitive processes. Furthermore, selegiline protects against the aging processes, increases the life span of some animals, and slows the age-related decline of performance in behavioral tests.

Selegiline is able to protect the substantia nigra in aging animals against oxidative stress, an effect that is mediated via dopaminergic neurons. Furthermore, it has been shown that moderate exposure to MPTP alters cognitive function in mice. It has also been shown that a defect in norepinephrine release may contribute to the impaired accuracy of attention in patients with severe Parkinson's disease, and dopamine may be important in maintaining rapid motor responding. The hypothalamic dopaminergic neurons have been reported to participate in the control of gonadotropin secretion and prolactin, and they also affect the secretion of thyrotropin (TSH), adrenocorticotropin, and growth hormone (GH) from the anterior pituitary. Age-related decline in bodily functions is associated with an alteration in many of the aforementioned neurohormones. For example, the concentration of dopamine in the median eminence of an older person is lower than that in a young person. A decrease of norepinephrine concentration, with some signs of neurodegeneration of serotonin (5-HT) fibers, in hypothalamus of aged animals has also been reported. All these results

support the idea that the decrease of some important hormones such as GH and TSH, which are known to be reduced in aging, could be due to the decrease in catecholamines in hypothalamic areas. Administration of drugs that increase hypothalamic catecholamine activity has been shown to inhibit or reverse many effects of physical decline due to aging.

The effects of treatment with selegiline, an MAO-B inhibitor, on plasma levels of insulin-like growth factor I (IGF-I) (as indicator of GH secretion), levels of monoamines and their metabolites, and the activity and content of tyrosine hydroxylase — the rate-limiting enzyme in the biosynthesis of catecholamines — in the hypothalamus and hypophysis of old animals have been studied. It is believed that the antiaging effects of selegiline are due to restoration of hypothalamic hormones.

**Insulin-like growth factors** (IGFs) IGF-I and IGF-II are single-chain polypeptides that have structural homology with proinsulin. IGF-I has insulin-like short-term metabolic effects and long-term effects similar to those of growth factor on cell proliferation and differentiation of various cell types. The mitogenic activity of IGF-I is mediated through binding mainly to the IGF-I receptor, also known as the type I IGF receptor, located on the cell surface. The receptor binds IGF-I and IGF-II with high affinity and insulin with low affinity. The IGF-I receptor may also form a hybrid with the insulin receptor. Animals carrying null mutations of the genes encoding IGFs or IGF receptors demonstrate embryonic and postnatal growth retardation. Distinct from other growth factors, IGFs are known to associate with specific binding proteins (IGFBPs) in plasma and tissue.

IGF-I may act as a survival factor via stimulation of the **Bcl-2 family of proteins**. Several signaling pathways such as tyrosine kinase, P13 kinase, and MAP kinase have also been suggested to mediate the **antiapoptotic effects of IGF-I** (Figure 13.6).

## PROTECTION BY SELEGILINE OF DOPAMINERGIC NEURONS FROM TOXICITY INDUCED BY GLUTATHIONE DEPLETION

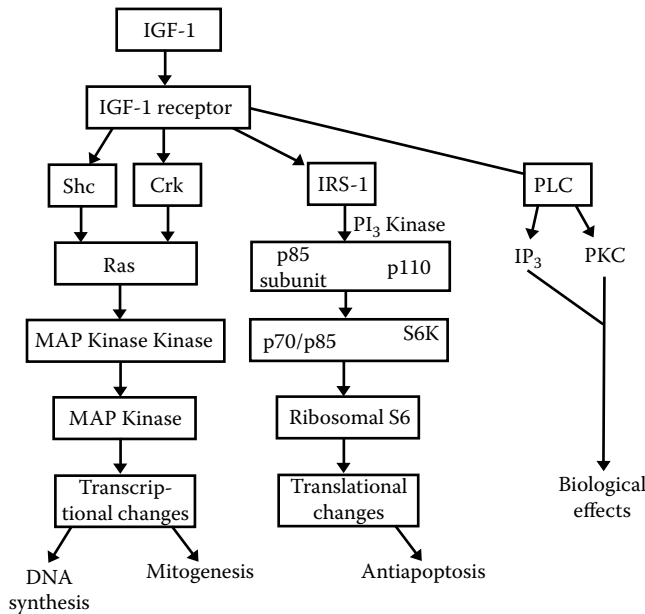
Oxygen radicals are created in the brain during oxidative stress and at other times. These oxygen radicals must be neutralized to prevent neuronal death. **Glutathione** (GSH) is one of the most important antioxidants used in detoxifying these oxygen radicals. Brain glutathione levels range from 1 to 3 mM. Astrocytes and nerve terminals have high concentrations of GSH, whereas neuronal somas have limited amounts of GSH. Therefore, it may be important for neuron cell bodies to increase the synthesis of GSH during oxidative stress to protect themselves.

GSH is synthesized by two enzymes.  **$\gamma$ -glutamyl cysteine** is formed from cysteine and glutamate by  **$\gamma$ -glutamyl synthetase**. GSH is formed from  $\gamma$ -glutamyl cysteine and glycine by glutathione synthetase. Both enzymes are found in the brain (Figure 13.7).

The turnover rates of GSH and the activity of GSH synthetase during oxidative stress induced by **butylhydroperoxide** in young and mature animals have been measured. These studies have found that defense mechanisms against oxidative stress in the brain differ with age. Young people can increase the cellular availability of GSH, whereas older people can increase GSH synthetase activity during oxidative stress. These differences make older people more susceptible to brain oxidative damage.

It has been shown that incubation with L-dopa increased the level of GSH in neurons. The pure neuronal cultures were destroyed by incubation with L-dopa, whereas the addition of ascorbic acid or superoxide dismutase protected the cells. These results show that the upregulation of cellular GSH evoked by auto-oxidizable agents is associated with significant protection of cells. Glia play an essential role in the response of mesencephalic cell cultures. An ability to upregulate GSH may serve a protective role.

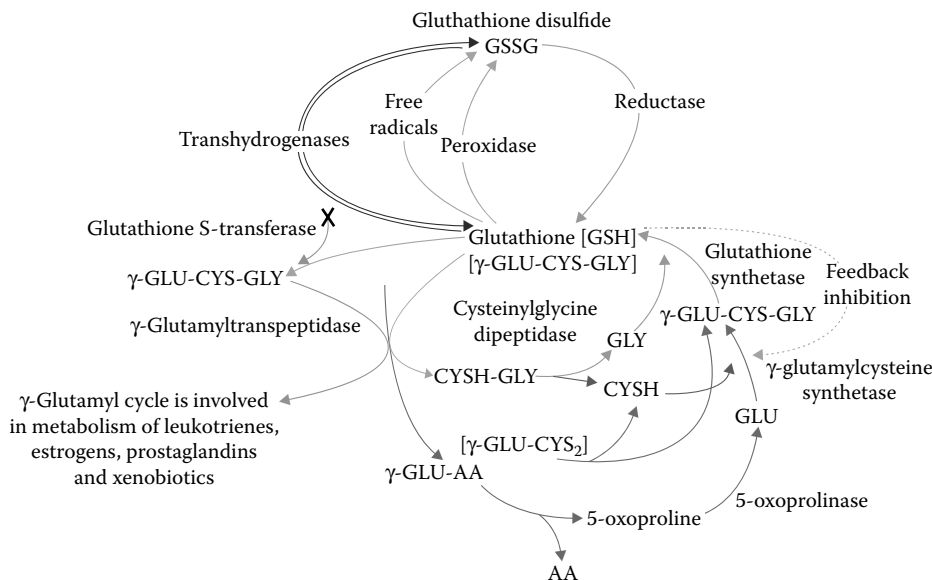
GSH protects human neuronal cells from **dopamine-induced apoptosis**. The role of GSH and other antioxidants in dopamine-induced apoptosis in cultures of the human neuronal cell line has been studied. Apoptosis, induced by 0.1 to 0.3 mM dopamine, was blocked by GSH in a dose- and time-dependent manner. This was observed by monitoring cell morphology, cell viability, and the



**FIGURE 13.6** Overview of IGF-1 signaling. IGF-1 receptors exist in a number of tissues. The IGF-1 receptor is a heterotetrameric protein with intrinsic tyrosine kinase activity. Various domains in the IGF-1 receptor share 40 to 84% amino acid sequence homology with the insulin receptor. One of the earliest steps in signal transduction by IGF-1 receptor is the phosphorylation of insulin receptor substrate (IRS). Tyrosine-phosphorylated IRS-1 and IRS-2 interacts with specific cytoplasmic proteins containing SH2 (src homology 2) domains, leading to the transduction of downstream signals. The IGF-1 signaling cascades are activated by the association of growth receptor binding protein 2-Son of Sevenless (Grb-2-SOS) with phosphorylated Crk and Shr, resulting in the activation of Ras, and the sequential activation of serine and threonine kinase Raf (A-Raf, B-Raf, and c-Raf) and MAP kinase kinase (MEK, also designated as MKK1 and MKK2). MEK is just upstream of and very specific for MAP kinases (ERK-1 and ERK-2), which it activates by phosphorylation on specific residues. MAP kinases activate a number of transcription factors, and there is evidence that they are involved in mediating IGF-1 stimulation of DNA synthesis and mitogenesis. The p85 regulatory subunit of PI3-kinase is another important SH2 domain-containing protein, the binding of which to tyrosine-phosphorylated IRS-1 activates the catalytic function of the 110-kDa subunit of PI3-kinase. PI3-kinase is essential for the transduction of metabolic growth and functional effects of IGF-1 and insulin, including stimulation of glucose transport, antilipolysis, protein and glycogen synthesis, and inhibition of apoptosis.

release of the cytosolic enzyme **lactate dehydrogenase** into the culture medium. L-cysteine and N-acetylcysteine had a similar effect in protecting against dopamine neurotoxicity, but at lower concentrations than GSH. The dopamine-induced alteration in the cell-cycle profile, detected by flow cytometry, and **intranucleosomal DNA fragmentation**, were both blocked by GSH. Treatment of cells with **buthionine sulfoximine**, an irreversible inhibitor of  $\gamma$ -glutamylcysteine synthetase, increased the neurotoxic effect of dopamine, suggesting that endogenous GSH participates in reducing dopamine neurotoxicity. The relationship between GSH and dopamine was further investigated by testing the effect of dopamine on the endogenous GSH level. Dopamine decreased GSH levels within 16 to 24 h; however, this effect was preceded by a transient increase in the level of the tripeptide within the first 0.5 to 7 h. Two other types of endogenous antioxidants, (+)- $\alpha$ -tocopherol (**vitamin E**) and ascorbic acid (**vitamin C**), were tested; vitamin E (at 1 to 100  $\mu\text{g/ml}$ ) was inactive against dopamine toxicity, whereas vitamin C had no effect at 0.05 to 0.2  $\text{mM}$ , but increased dopamine toxicity at 0.5 to 2  $\text{mM}$ . The results indicate that GSH has a selective role in protecting human neural cells from the toxic effect of dopamine. This study may contribute to a





**FIGURE 13.7** Glutathione (GSH), through  $\gamma$ -glutamyl pathway, recycles glutamate, cysteine, and glycine. GSH is synthesized by the consecutive actions of the ATP-dependent enzymes  $\gamma$ -glutamylcysteinyl synthetase and glutathione synthetase. Levels of GSH are regulated in part by feedback inhibition of  $\gamma$ -glutamylcysteinyl synthetase by GSH. In the presence of a suitable amino acid (AA) acceptor, GSH is catabolized by the action of  $\gamma$ -glutamyltranspeptidase to yield a  $\gamma$ -glutamyl amino acid ( $\gamma$ -GLU-AA) and cysteinylglycine (CYSH-GLY). The  $\gamma$ -GLU-AA is converted to free amino acid and 5-oxoproline by the action of  $\gamma$ -glutamylcyclotransferase. 5-Oxoproline is converted back to glutamate by the ATP-dependent 5-oxoprolinase reaction. The glutamate released in this process can then be reused in the synthesis of GSH, thus completing the cycle with the glutamate component of GSH. The cysteinylglycine released in the  $\gamma$ -glutamyltranspeptidase reaction is hydrolyzed by the action of a dipeptidase to glycine and cysteine, completing the cycle with the glycine and cysteine components of GSH.

better understanding of the mechanisms underlying the excessive loss of dopaminergic neurons in neurodegenerative diseases such as parkinsonism and in the aging process.

A reduction in GSH has been detected in the substantia nigra pars compacta of patients with Parkinson's disease. Furthermore, a similar reduction in GSH has been found in substantia nigra pars compacta of cases with incidental **Lewy body diseases**, who are thought to have a preclinical form of Parkinson's disease. These findings suggest that a reduction in GSH, with the ensuing oxidative stress, may be a critical factor in the pathogenesis of Parkinson's disease.

Studies have been designed to learn whether or not selegiline and its desmethyl metabolite could protect mesencephalic neurons in culture from death brought about by depletion of GSH by **L-buthionine-(S,R)-sulfoximine** (BSO). The results of these studies showed that BSO (10  $\mu$ M) caused extensive cell death after 48 h as demonstrated by disruption of cellular integrity and release of lactate dehydrogenase into the culture medium. Both selegiline and desmethyl-selegiline, at concentrations of 5 and 50  $\mu$ M, significantly protected dopaminergic neurons from toxicity without preventing the BSO-induced loss of GSH.

Protection was not associated with MAO-B inhibition in that pargyline, a potent MAO inhibitor, was ineffective; and pretreatment with pargyline did not prevent the protective effects of selegiline. Protection was not associated with inhibition of dopamine uptake by selegiline because the dopamine uptake inhibitor **mazindol** did not diminish BSO toxicity. Antioxidant ascorbic acid (200  $\mu$ M) also protected BSO-induced cell death, suggesting that oxidative events were involved. This

study demonstrates that selegiline and its desmethyl metabolite can diminish cell death associated with depletion of GSH.

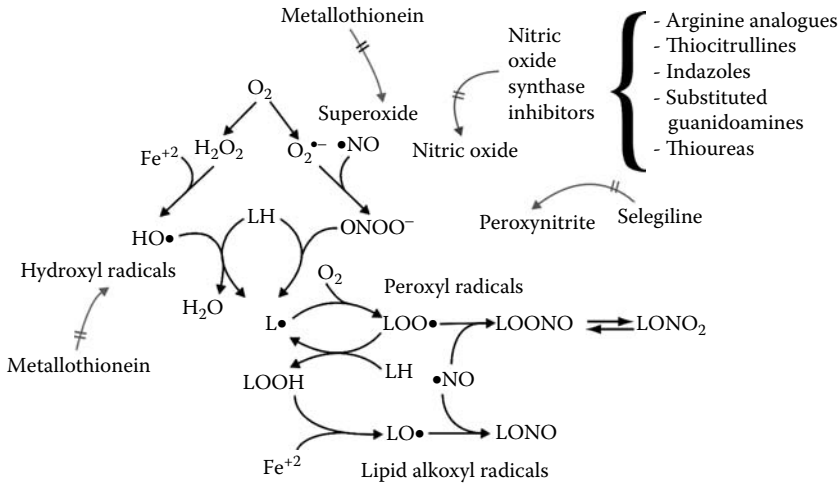
### INCREASE BY SELEGILINE OF THE STRIATAL SUPEROXIDE DISMUTASE

Reactive oxygen species are suspected of contributing to the etiology of Parkinson's disease with increasing frequency. **Superoxide dismutase (SOD: EC 1.15.1)** is a metalloenzyme system that exists in cytosolic (Cu,Zn-SOD) and mitochondrial (Mn-SOD) forms. SOD confers protection against oxidative cellular injury by conversion of superoxide radical ( $O_2^{\cdot-}$ ) to hydrogen peroxide ( $H_2O_2$ ) (see Figure 13.4). Observations of increased Cu,Zn-SOD and Mn-SOD activities in substantia nigra in Parkinson's disease are consistent with a protective effect. Elevated SOD activity in the parkinsonian brain could be an adaptive response to sustained oxidative stress induced by either defective **mitochondrial electron transport** or exposure to an MPTP-like toxicant. However, excessive SOD may produce cell injury if  $H_2O_2$  is not effectively metabolized by **catalase** and **GSH peroxidase**, because the highly reactive **hydroxyl radical ( $\cdot OH$ )** will be generated from  $H_2O_2$  by a Fenton reaction with free iron, which is abundant in substantia nigra.

Several studies have explored SOD activity in peripheral tissues of patients with Parkinson's disease as potential markers of oxidative stress, and have yielded inconsistent results. Elevations of total (combined Cu,Zn-SOD and Mn-SOD) SOD activity and GSH peroxidase activity in serum of patients with Parkinson's disease have been reported. Furthermore, elevations of immunoreactive Mn-SOD in cerebrospinal fluid of patients with Parkinson's disease but normal levels of Cu,Zn-SOD have been detected. Erythrocyte SOD activity, which is exclusively due to Cu,Zn-SOD, is unaltered in Parkinson's disease. Moreover, no differences in mean activities of total SOD, GSH peroxidase, **GSH reductase**, or catalase have been detected in either the lymphocytes, granulocytes, or cerebrospinal fluid of patients with Parkinson's disease.

The levels of Cu,Zn-SOD and Mn-SOD activities in peripheral lymphocytes of 43 newly diagnosed idiopathic Parkinson's disease cases and 62 age- and sex-matched controls free of neurodegenerative disorders have been measured. Significant excesses of both SOD forms were found among Parkinson's disease cases compared with controls; however, the excesses were found exclusively among patients treated with the Parkinson's disease MAO inhibitor selegiline (l-deprenyl). Enzyme-linked immunosorbent assays (ELISAs) confirmed that the activity excesses were due to increased protein rather than more highly reactive enzymes in lymphocytes of patients with Parkinson's disease. These findings clearly indicate the importance of selegiline on measured Cu,Zn-SOD and Mn-SOD activity in peripheral lymphocytes. Characterizing a possible therapeutic value of SOD will require longitudinal assessments of SOD in relation to the progression of Parkinson's disease.

L-selegiline induces a dose-dependent inhibition of oxygen ( $O_2$ ) consumption during ATP synthesis in the presence of complex I (pyruvate and malate) and complex II (succinate) substrates in fresh mitochondrial preparations. D-selegiline produces a similar inhibitory profile, whereas MDL 72974, a selective MAO-B inhibitor, is less effective. Administration of D-selegiline or MDL 72974 to animals results in an increase in both striatal Cu,Zn-SOD and Mn-SOD activities. This observation is consistent with previous reports in which lower L-selegiline concentrations were shown to be sufficient to induce SOD activity in the striatum. Selegiline is not a direct modulator of SOD activity and has no effects on purified SOD activity *in vitro* with concentrations as high as 4 mM. Striatal Cu,Zn-SOD and Mn-SOD activities remain elevated following L-selegiline withdrawal even though MAO-B activity had recovered by 50%. This observation suggests that the modulation of striatal SODs by L-selegiline is not readily reversible and appears to be independent, at least in part, from the inhibition of MAO-B.



**FIGURE 13.8** Nitric oxide regulates critical lipid membrane and lipoprotein oxidation events by (1) contributing to the formation of more potent secondary oxidants from  $O_2^{\cdot-}$  (i.e.,  $ONOO^-$ ), (2) catalyzing the redirection of  $O_2^{\cdot-}$  and  $H_2O_2$ -mediated cytotoxic reactions to other oxidative pathways, and (3) termination of lipid radicals to possibly less reactive secondary nitrogen-containing products. Moreover, metallothionein isoforms I and II protect against neurotoxic effects of superoxide anions and hydroxyl radicals and selegiline protects against peroxynitrite- and nitric oxide-induced apoptosis.

Several studies have shown that SOD is upregulated in animals exposed to  $O_2$  radicals. Accordingly, the mechanism by which L-selegiline modulates SOD activities within the nigrostriatal pathway and the cerebellum may represent an adaptive mechanism reacting to the endogenous formation of  $O_2$  radical. Numerous potential sources of  $O_2$  exist in the cell, including the electron transport chain and the auto-oxidation of catecholamines. Therefore, selegiline could directly modulate free-radical production by altering respiratory function within mitochondria.

L-selegiline alters the redox state of ubiquinone, suggesting that the flow of electrons is impaired in the respiratory chain. Furthermore, a decrease in **ubiquinone** levels has been observed, whereas **ubiquinol** (reduced ubiquinone) concentrations are increased in the striatum. Ubiquinol levels have been shown to augment as a result of impaired mitochondrial respiration. For example, ubiquinol concentrations were demonstrated to increase in tubular kidney cells exposed to complex IV inhibitors and in disease states with defects in respiratory chain components. These results are also consistent with the hypothesis that L-selegiline enhances  $O_2$  formation by altering the rate of electron transfer within the respiratory chain leading to increases in SOD activities in the mouse striatum.

### PROTECTION BY SELEGILINE AGAINST PEROXYNITRITE- AND NITRIC-OXIDE-INDUCED APOPTOSIS

Apoptosis is induced by various intra- and extracellular stimuli, and recently nitric oxide was reported to induce apoptosis in cultured cerebellar granule cells and cultured cortical neurons. The toxicity of nitric oxide is mainly ascribed to **peroxynitrite**, a reaction product of **nitric oxide** with **superoxide** (Figure 13.8). Cells producing an increased amount of SOD (superoxide, superoxide oxidoreductase; EC 1.15.1.1) are resistant to nitric oxide-mediated apoptosis. In contrast, superoxide levels that have been increased by downregulation of Cu,Zn-SOD lead to apoptotic cell death in PC12 cells, which required the reaction with nitric oxide to generate peroxynitrite. Peroxynitrite itself was found to induce apoptosis in PC12 cells and in cultured cortical neurons.

The pathological characteristic of Parkinson's disease is the selective degeneration of dopamine neurons in the pars compacta of the substantia nigra. The mechanism for the loss of neurons remains to be elucidated, and recently **apoptosis** has been proposed as a death process in Parkinson's disease. For example, the level of a product of the oxidative stress, 4-hydroxy-2-nonenal protein adduct, was found to increase in the nigral neurons of parkinsonian brains. **Peroxynitrite** (see Figure 13.6) has been proposed to be involved in the neuronal cell death in some neurodegenerative diseases, such as **amyotrophic lateral sclerosis**.

The induction of apoptosis by nitric oxide and peroxynitrite in human dopaminergic neuroblastoma SH-SY5Y cells and the antiapoptotic activity of selegiline have been reported. After the cells were treated with **1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine** (NOR-4), a nitric oxide donor, or **N-morpholino-sydnominine** (SIN-1), a peroxynitrite donor, DNA damage has been studied using a single-cell gel electrophoresis (comet) assay. NOR-4 and SIN-1 induce DNA damage dose dependently. **Cycloheximide** and alkaline treatment of the cells prevented the DNA damage, indicating that the damage is apoptotic in nature and depends on a signal transduction mechanism. SOD and the antioxidants reduced GSH and  $\alpha$ -tocopherol protected the cells from the DNA damage. Selegiline protected the cells from the DNA damage induced by nitric oxide or peroxynitrite almost completely. The protection by selegiline was significant even after it is washed from the cells, indicating that selegiline may activate the intracellular system against apoptosis. These results suggest that selegiline or related compounds may be neuroprotective to dopamine neurons through its antiapoptotic activity.

The neuroprotection of SH-SY54 cells from apoptosis caused by NOR-4 and SIN-1 is not related to inhibition of MAO-B, because SH-SY54 contains only MAO-A. Selegiline is able to protect dopaminergic neurons from the toxicity of MPTP and also of MPP<sup>+</sup>, an oxidized product of MPTP by MAO-B. This indicates that the neuroprotection by selegiline does not require blockage of the conversion of MPTP to MPP<sup>+</sup>.

The administration of selegiline increases the activity of SOD and catalase in the rat striatum. Selegiline reduces apoptosis in PC12 cells induced by withdrawal of serum and growth factor, and that transcription induction was required for its antiapoptotic effect. Furthermore, selegiline increases the expression of Cu,Zn-SOD, Mn-SOD, GSH peroxidase, tyrosine hydroxylase bcl-2, bcl-x, and *c-fos* and decreased that of *bax* and *c-jun*. Moreover, selegiline is able to attenuate **glutamate receptor-mediated toxicity**, which is induced by activation of neuronal nitric oxide synthase and increased nitric oxide formation (see Figure 13.4). In addition, selegiline protects cells against endogenously produced toxins. These results suggest that selegiline may be neuroprotective in general through the inhibition of "**death**" **signal transduction**, induced by endogenous and environmental factors, causing Parkinson's disease or perhaps other neurodegenerative disorders.

## ANTIAPOPTOTIC ACTIONS OF SELEGILINE IN A VARIETY OF NEURONS

Selegiline reduces neuronal death even after neurons have sustained seemingly lethal damage at concentrations too small to inhibit MAO-B and the rescuing action is related to antiapoptotic action of selegiline.

Initially, it was thought that selegiline only reduces the death of nigrostriatal dopaminergic neurons by inhibiting MAO-B and thereby blocking the conversion of MPTP to its active radical MPP<sup>+</sup>. Subsequently, it was shown that selegiline maintains dopamine levels and dopamine uptake in mesencephalic explants after MPP<sup>+</sup> treatment, thereby establishing that selegiline could reduce dopaminergic neuronal damage by a mechanism other than the blockade of the conversion of MPTP to MPP<sup>+</sup>. Selegiline was shown to reduce the death of murine dopaminergic nigrostriatal neurons even when first administered 72 h after MPTP treatment when MPTP was fully converted to MPP<sup>+</sup> and maximal striatal damage had occurred. It was then shown using the same delayed administration

that selegiline at doses of 0.01 mg/kg every 2 d induces a maximal increase in the survival of the dopaminergic nigrostriatal neurons. The 0.01 mg/kg dose was insufficient to inhibit MAO-A or MAO-B even after 20 d of administration. It has also been shown that selegiline increases the survival of dopaminergic mesencephalic neurons in culture, either after trophic withdrawal or MPP<sup>+</sup> treatment. Selegiline is also shown to reduce *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine (DSP-4) toxicity, which does not involve MAO-A or MAO-B.

Selegiline has been shown to reduce neuronal death in a variety of noncatecholaminergic neuronal types and after a variety of insults, including immature facial neurons after axotomy, adult murine facial motoneurons crush, rat CA1 hippocampal neurons after ischemia/hypoxia, and rat cerebellar Purkinje cells and granule cells with aging. Studies with axotomized immature rat facial motoneurons have shown that the maximum effectiveness of intraperitoneal (–)-selegiline for increasing the survival of the motoneurons was greater than that seen with intrathecal delivery of ciliary neurotrophic factor (CNTF), and it did not induce the cachexia caused by CNTF. Furthermore, it has been shown that a dose of selegiline insufficient to inhibit MAO-B or MAO-A induced maximum increases in the survival of the immature facial motoneuron, whereas doses of selegiline sufficient to cause 80% MAO-B inhibition did not increase motoneuron survival.

With the exception of selegiline and pargyline, most MAO-A or MAO-B inhibitors including **iproniazid**, **phenelzine**, **semicarbazide**, **tranylcypamine**, **nialamide**, MDL 72974A, RO-16-6491, **chlorgyline**, and **brofaromine** did not increase the survival of the axotomized immature motoneurons. All in all, these results show that the neuronal “rescue” action of selegiline did not involve MAO-A or MAO-B inhibition and is dependent on a structural entity shared by (–)-selegiline and pargyline but not (+)-selegiline or other structurally similar compounds such as chlorgyline.

## STIMULATION BY SELEGILINE OF BIOSYNTHESIS OF CYTOKINES INTERLEUKIN-1 $\beta$ AND INTERLEUKIN-6

**Cytokines** are a heterogenous group of polypeptide mediators that have been associated with activation of numerous functions, including the immune system and inflammatory responses. The cytokine families include, but are not limited to, **interleukins**, **chemokines**, **tumor necrosis factors**, **interferons** (INF- $\alpha$ , - $\beta$ , and - $\gamma$ ), **colony-stimulating factors**, **growth factors**, **neuroipoietins**, and **neurotrophins** (see Table 13.4).

The neurotrophins represent a family of survival and differentiation factors that exert profound effects in the central and peripheral nervous systems. The neurotrophins are currently under investigation as therapeutic agents for the treatment of neurodegenerative disorders and nerve injury either individually or in combination with other trophic factors such as ciliary neurotrophic factor (CNTF) or fibroblast growth factor (FGF).

Responsiveness of neurons to a given neurotrophin is governed by the expression of two classes of cell surface receptor. For nerve growth factor (NGF), these are p75<sup>NTR</sup> (p75) and p140<sup>trk</sup> (referred to as trk or trkA), which bind both BDNF and neurotrophin (NT)-4/5, and trkC receptor, which binds only NT-3. After binding ligand, the neurotrophin–receptor complex is internalized and retrogradely transported in the axon to the soma. Both receptors undergo ligand-induced dimerization, which activates multiple signal transduction pathways. These include the ras-dependent pathway utilized by trk to mediate neurotrophin effects such as survival and differentiation. Indeed, cellular diversity in the nervous system evolves from the concerted processes of cell proliferation, differentiation, migration, survival, and synapse formation. Neural adhesion and extracellular matrix molecules have been shown to play crucial roles in axonal migration, guidance, and grown cone targeting.

Proinflammatory cytokines, released by activated macrophages and monocytes during infection, can act on neural targets that control thermogenesis, behavior, and mood. In addition to induction of fever, cytokines induce other biological functions associated with the acute-phase response, including hypophagia and sleep. Cytokine production has been detected within the central nervous

system as a result of brain injury, following stab wound to the brain, during viral and bacterial infections (AIDS and meningitis), and in neurodegenerative processes (multiple sclerosis and Alzheimer's disease). Novel cytokine therapies, such as anticytokine antibodies or specific receptor antagonists acting on the cytokine network may provide an optimistic feature for treatment of multiple sclerosis and other diseases in which cytokines have been implicated.

An immune-mediated pathophysiology has been proposed for Parkinson's disease and Alzheimer's disease. The MAO-B inhibitor selegiline appears to slow the progression of neurological deficits in patients with Parkinson's disease and with Alzheimer's disease, but its mechanism of action is still under discussion. *In vitro* and animal trials show that the putative neuroprotective effects of selegiline may be due to reduction of oxidative stress or altered expression of a number of mRNAs and proteins in nerve and glial cells. The results of a recent animal trial suggest that selegiline might also influence the immune system because it increases the survival rate of immunosuppressed animals. Stimulation of the immune response to bacterial or viral infection and to chronic inflammatory processes, and biosynthesis of neurotrophic factors, are managed by an increased synthesis of the cytokines interleukin-1 $\beta$  (IL-1 $\beta$ ) and subsequently interleukin-6 (IL-6).

## INTERLEUKIN 1

Activated macrophages and microglia are likely cellular sources of IL-1 in the central nervous system. IL-1 $\alpha$  and  $\beta$ , both 17-kDa proteins, are the products of two distinct genes and produce many of the same effects that TNF has on glial cells. IL-1 upregulates cytokine production, includes cell surface molecules, activates nitric oxide, and stimulates proliferation. When used alone, IL-1 and TNF $\alpha$  both stimulate nitric oxide production in C6 cells. However, in human fetal astrocyte cultures, IL-1 is a better nitric oxide inducer when used in combination with IFN $\gamma$ .

IL-1 has been demonstrated to affect the production of other cytokines or growth factors. Treatment of astrocytes with IL-1 increases basic fibroblast growth factor concentrations *in vitro*. Following administration of intraventricular IL-1 $\beta$ , nerve growth factor-like immunoreactivity is evident in hippocampal astrocytes as well as in neurons. *In vitro* production of nerve growth factor by astrocytes is most evident following combined stimulation with IL-1 $\beta$  and TNF $\alpha$ . Transforming growth factor- $\beta$ -I (TGF $\beta$ 1), as measured by secreted protein and immunohistochemical presence in cells, is induced by IL-1 $\alpha$  in astrocytes and microglia. Oligodendrocytes, in response to IL-1 $\alpha$ , demonstrate increased TGF $\beta$  by immunohistochemistry, but functional TGF $\beta$ 1 protein is not significantly secreted. An IL-1 $\beta$ -stimulated human astrogloma produces increased TNF mRNA and protein concentrations. In contrast, TNF $\alpha$  is not induced or elevated after stimulating first-trimester human microglia with IL-1 $\alpha$  or rat astrocytes with IL-1 $\beta$ . When combined with IFN $\gamma$ , IL-1 $\beta$  induces astrocytes to produce TNF $\alpha$ .

Regulation of major histocompatibility complex (MHC) expression by IL-1 may be cell and species dependent. IFN $\gamma$ -induced Class Ia expression on murine astrocytes is inhibited by IL-1 $\beta$  treatment. IL-1 $\beta$  is ineffective in modulating IFN $\gamma$ -induced Class II expression on murine microglia and Class I expression on astrocytes. Additionally, Class II expression on human fetal and adult astrocytes does not appear to be modulated by IL-1.

In mixed glial cultures, IL-1 indirectly increases the proliferation of microglia, astrocytes, and oligodendrocytes but not glial precursors. The combination of IL-1 and TNF $\alpha$  leads to microglial and astrocytic *in vitro* proliferation reminiscent of microgliosis and astroglia *in vivo*. IL-1 and TNF induce astrocytes to lose their flat polygonal shape and appear as cells with long, fine processes and small compact bodies.

## INTERLEUKIN 6

Interleukin 6 (IL-6) is a protein of approximately 23 to 30 kDa with heterogeneity in size depending on differential glycosylation. It is produced by monocytes, T cells, B cells, fibroblasts, mesangial

cells, keratinocytes, and endothelial cells. IL-6 has a major role in B-cell proliferation and differentiation. In the nervous system, it is produced by endothelial cells, microglia, and astrocytes. IL-6 belongs to a family of neuropoietic and hematopoietic factors, which, though biochemically different, are structurally and functionally related. The neuropoietic family includes **cholinergic differentiation factor** (also known as **leukemia inhibitory factor**), ciliary neurotrophic factor (CNTF), and oncostatin M. The hematopoietic cytokines are IL-6, G-CSF, and myelomonocytic factor.

IL-6 induces nerve growth factor production and augments bFGF production in astrocytes. IL-6, induced *in vivo* by IL-1, may contribute to acute-phase response and fever through induction of prostaglandin E (PGE). IL-6 is present in elevated levels in several central nervous system diseases such as AIDS, multiple sclerosis, and Alzheimer's disease, of which all three pathologies may involve activated microglia and astrocytes. Interestingly, IL-6 has been shown to enhance HIV-1 expression in transfected primary rodent astrocytes but not human malignant astrocytoma cell lines.

The IL-6/LIF family members are also critical for long-term and short-term survival, but not proliferation of mature oligodendrocytes and their precursors.

The influence of selegiline on the synthesis of IL-1 $\beta$  and IL-6 in peripheral blood mononuclear cells (PBMC) from healthy blood donors cultured with or without selegiline ( $10^{-8}$ ,  $10^{-9}$ , or  $10^{-10}$  M) in a humidified atmosphere (7% CO<sub>2</sub>) has been studied. Treatment of cultured PBMC with selegiline significantly increased synthesis of both cytokines. The effect of selegiline on cytokine biosynthesis may contribute to its putative neuroprotective properties. The results of this study indicate immunomodulatory properties of selegiline. The elevated levels of IL-6 may be explained by direct stimulatory activity of selegiline. An indirect effect caused by IL-1 $\beta$  also has to be considered because IL-1 $\beta$  induces release of IL-6. The mechanism of action of selegiline on PBMC has remained unclear. Recent findings, however, demonstrate that selegiline can alter gene expression and protein synthesis in nerve and glial cells. These results suggest that immunostimulation by selegiline may be caused in a similar way, by selective action on transcription. It remains to be established whether selegiline also increases release of IL-1 $\beta$  and IL-6 from microglial cells and astrocytes in the brain.

Because of the growing evidence for a bidirectional interaction between the peripheral immune system and the brain, it has been proposed that even peripheral circulating cytokines such as IL-1 $\beta$  or IL-6 may influence regenerative and degenerative processes in the brain, acting, for example, via the organum vasculosum lamina terminalis, where the blood-brain barrier is weak. IL-1 $\beta$  stimulates the proliferation of astrocytes and the release of IL-6 and attenuates excitatory amino acid-induced neurodegeneration *in vitro*. IL-6 induces acute-phase protein synthesis and differentiation of neuronal cells and improves catecholaminergic and cholinergic cell survival.

Immune-related phenomena have been demonstrated in studies of the pathogenesis of Parkinson's and Alzheimer's diseases. Alterations in IL-1 $\beta$  and IL-6 levels in brain parenchyma, serum, and cerebrospinal fluid of patients with Parkinson's and Alzheimer's diseases have been found. A recent study showed elevated IL-1 $\beta$  and IL-6 levels in the cerebrospinal fluid of untreated patients with so-called "*de-novo*" Parkinson's and Alzheimer's diseases, which may reflect, especially in the case of Parkinson's disease, the original condition at the probable beginning of the disease. From the results of this study and evidence of the influence of IL-1 $\beta$  and IL-6 on regenerative processes in the brain, one might speculate that this cytokine status represents the regenerative potential of the brain in the fight against the neurodegenerative process.

## BANISTERINE AND SELEGILINE FOR THE TREATMENT OF PARKINSON'S DISEASE

Parkinson's disease is characterized by tremor at rest, rigidity, hypokinesia, and postural abnormality. The 4- to 6-Hz tremor of parkinsonism is characteristically most conspicuous at rest; it increases at times of emotional stress and often improves during voluntary activity. It commonly begins in

the hand or foot, where it takes the form of rhythmic flexion–extension of the fingers or of the hand or foot or of rhythmic pronation–supination of the forearm. It frequently involves the face in the area of the mouth as well. Although it may ultimately be present in all of the limbs, it is not uncommon for the tremor to be confined to one limb — or to the two limbs on one side — for months or years before it becomes more generalized.

## RIGIDITY

Rigidity, or increased tone — i.e., increased resistance to passive movement — is a characteristic clinical feature of parkinsonism. The disturbance in tone is responsible for the flexed posture of many patients with parkinsonism. The resistance is typically uniform throughout the range of movement at a particular joint and affects agonist and antagonist muscles alike — in contrast to the findings in spasticity, where the increase in tone is often greatest at the beginning of the passive movement (clasp-knife phenomenon) and more marked in some muscles than in others. In some instances, the rigidity in parkinsonism is described as *cogwheel rigidity* because of ratchetlike interruptions of passive movements that may be due in part to the presence of tremor.

## HYPOKINESIA

The most disabling feature of this disorder is hypokinesia (sometimes called bradykinesia or akinesia) — a slowness of voluntary movement and a reduction in automatic movement, such as swinging the arms while walking. The patient's face is relatively immobile (*masklike faces*), with widened palpebral fissures, infrequent blinking, with certain fixity of facial expression, and a smile that develops and fades slowly. The voice is of low volume (*hypophonia*) and tends to be poorly modulated. Fine or rapidly alternating movements are impaired, but power is not diminished if time is allowed for it to develop. The handwriting is small, tremulous, and difficult to read.

## ABNORMAL GAIT AND POSTURE

The patient generally finds it difficult to get up from bed or an easy chair and tends to adopt a flexed posture on standing. It is often difficult to start walking, so that the patient may lean farther and farther forward while walking in place before being able to advance. The gait itself is characterized by small, shuffling steps and absence of the arm swing that normally accompanies locomotion; there is generally some unsteadiness on turning, and there may be difficulty in stopping. In advanced cases, the patient tends to walk with increasing speed to prevent a fall (*festinating gait*) because of the altered center of gravity that results from the abnormal posture.

## OTHER CLINICAL FEATURES

There is often mild **blepharoclonus** (fluttering of the closed eyelids) and occasionally **blepharospasm** (involuntary closure of the eyelids). The patient may drool, perhaps because of the impairment of swallowing. There is typically no alteration in the tendon reflexes, and the plantar responses are flexor. Repetitive tapping (about twice per second) over the bridge of the nose produces a sustained blink response (*Myerson's sign*); the response is not sustained in normal subjects. Cognitive decline sometimes occurs but is usually mild.

The etiology of progressive death of dopaminergic neurons in substantia nigra of Parkinson's disease brains remains unclear. Dopamine deficiency in Parkinson's disease is commonly treated with L-dopa and **carbidopa**, a **periphera dopa decarboxylase inhibitor (Sinemet)**. Since its introduction, L-dopa has been shown to be effective in treating Parkinson's disease. However, high concentrations of L-dopa produce side effects such as psychosis, “**on-off**” effects, abnormal involuntary movements, and akinetic crisis.



By using microdialysis of substantia nigra it has been shown that L-dopa treatment produced a dose-dependent increase in output of nigral hydroxyl ( $\bullet$ OH) radicals, which could be increased further with acute inhibition of mitochondrial complex I activity. Selegiline is able to attenuate the generation of hydroxyl radicals caused by enhanced turnover in the synthesis of striatal dopamine according to the following reactions.

Unfortunately, Sinemet (L-dopa-carbidopa) does not arrest nigrostriatal degeneration or prevent the progressive disabling course of the disease. Moreover, the therapeutic effect is not sustained during long-term use. The reasons for the decline in efficacy of selegiline and increasing response fluctuations that characterize long-term L-dopa therapy are not fully understood but may reflect the inevitable progression of the disease. Other contributing factors may include deficits in storage of dopamine, changes in dopamine receptor function, competition with other amino acids, variation in gastric emptying time, and other poorly understood pharmacokinetic changes.

Irreversible MAO-B inhibitors, namely, **banisterine** and **selegiline**, are efficacious in the treatment of Parkinson's disease, and selegiline prolongs the action of L-dopa and enhances the life expectancy of patients suffering from Parkinson's disease.

Physicians have studied 54 patients who were randomly assigned to selegiline (10 mg/d) or placebo treatment groups and followed until L-dopa therapy was indicated or until the patient had been in the study for 3 years. Analysis of Kaplan–Meier survival curves for each group showed that selegiline delayed the need for L-dopa therapy; the average time until L-dopa was needed was 312.1 d for patients in the placebo group and 548.9 d for patients in the selegiline group. Disease progression, as monitored by five different assessment scales, was slowed (by 40 to 83% per year) in the selegiline group compared with placebo. Therefore, early selegiline therapy delays the requirement for antiparkinsonian medications, possibly by slowing progression of the disease.

A large multicenter trial was initiated in 1987 to examine the efficacy of selegiline (10 mg/d) and  $\alpha$ -tocopherol (2000 U/d) in delaying the onset of disability sufficiently to require no, or reduced, L-dopa therapy. The **Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP)** study involved 800 patients with early, untreated Parkinson's disease who had been randomized in  $2 \times 2$  factorial design to receive L-deprenyl (selegiline) alone, tocopherol alone, selegiline plus tocopherol, or double placebo. Of 399 patients who received active selegiline, 302 were able to function without L-dopa, compared with 225 of the 401 patients who did not receive selegiline. These striking and very significant differences favoring selegiline treatment also translated into a significant delay until patients ceased full-time employment due to emerging disability. The project concluded that the use of selegiline (10 mg/d) delayed the onset of disability associated with early, otherwise-untreated cases of Parkinson's disease.

The field of neurology seems to have more than its share of untreatable and progressive diseases. For many years, virtually all of the neurodegenerative diseases of aging (**Parkinson's disease**, **Alzheimer's disease**, and **amyotrophic lateral sclerosis**) fell into this category. Parkinson's disease became the exception with the advent of L-dopa therapy (given as carbidopa-levodopa) in the late 1960s; but similar to these other diseases, it has remained an inexorably progressive process. This is a major therapeutic problem, because progression of disease almost certainly contributes to the increasing management difficulties encountered in the later stages of the illness. Indeed, it could be argued that the management of patients with advanced Parkinson's disease represents one of the most challenging demands in the day-to-day practice of neurology.

For these reasons, the need for an alternative strategy for the treatment of Parkinson's disease has become increasingly obvious. Stated in another way, though L-dopa therapy remains a central pillar in the management of Parkinson's disease, it is not the "answer" that many had originally hoped. The advent of the dopaminergic agonists has provided another therapeutic alternative when L-dopa begins to fail, but these drugs, too, represent only a temporary station along the way to increasing disability and side effects of therapy. In this setting, it is not difficult to see why a new therapeutic strategy aimed at slowing the progress of Parkinson's disease might be warmly welcomed.

In discussing the possible utility of selegiline, physicians have concluded that selegiline deserves consideration for symptomatic use as the first measure against L-dopa-related motor fluctuations that do not respond to manipulation of the L-dopa regimen. Furthermore, a clear benefit of L-dopa with selegiline in altering the course of Parkinson's disease compared to L-dopa alone has been shown. By studying selegiline as an adjunct to L-dopa therapy in 200 patients, physicians have reported on the limitation of selegiline as a long-term antiparkinsonian adjunct to conventional L-dopa therapy. Selegiline does improve parkinsonism during the initial 6 months to 12 to 24 months of combined therapy in a third to almost half of patients with an end-of-dose type of response to long-term L-dopa therapy. But even this particular class of patients is unable to maintain such improvement by 36 months, much less by 48 months from the start of the trial. About a quarter of poor responders to L-dopa and those with random deterioration show improvement in their parkinsonian status in the first 6 months of the selegiline trial, but quickly deteriorate by 1 year.

Selegiline is able to ameliorate depression associated with Parkinson's disease. However, selegiline is not effective in parkinsonian bradyphrenia.

The efficacy of selegiline on the progression of disability in early Parkinson's disease has been studied and the following conclusions have been reached: selegiline (10 mg/d) delays the onset of disability associated with early, otherwise-untreated Parkinson's disease. It remains unclear whether these benefits derive from mechanisms that are symptomatic (dopaminergic), protective (antineurotoxic), or both.

By studying 50 *de novo* patients with Parkinson's disease, physicians have reported that selegiline was effective in decreasing the hypokinesia, whereas the rigidity was improved less by this drug. The reduction of parkinsonian symptoms developed slowly and was independent of the severity of Parkinson's disease. The maintenance of selegiline monotherapy showed a high individual variation but the average period was about 1 year.

The beneficial effects of selegiline are symptomatic in nature. Furthermore, it has been postulated that there are several mechanisms in which such a response might be achieved:

- **Banisterine** and **selegiline** could increase the concentration of dopamine in the striatal synaptic cleft by simply impeding degradation of the neurotransmitter.
- **Banisterine** and **selegiline** promote accumulation of phenylethylamine, which potentiates the action of dopamine.
- **Banisterine** and **selegiline** could enhance the release of dopamine and block its reuptake.
- **Banisterine** and **selegiline** might elicit an antidepressant action by inhibiting MAO.

The comparative effectiveness of L-dopa and carbidopa, and that of L-dopa, carbidopa, and selegiline has been studied, and the results have shown that the major usefulness of selegiline is to modify the fluctuating therapeutic response seen with L-dopa-carbidopa.

## SUMMARY AND CONCLUSIONS

**Banisterine** from *Banisteria caapi* and *Nicotiana tabacum* was the first MAO inhibitor that has shown efficacy in the treatment of Parkinson's disease. Subsequently, selegiline, a selective inhibitor of MAO-B, became one of the first adjunct therapies in clinical use. A retrospective analysis of data from long-term patients found a significant increase in survival among those treated with selegiline plus L-dopa compared with L-dopa alone. These studies, coupled with evidence that selegiline blocked parkinsonism induced by MPTP in animals, suggested that MAO-B inhibition might protect against neurodegeneration caused by an endogenously occurring neurotoxin. The findings triggered widespread interest in the potential neuroprotective effects of selegiline in humans.

Extensive data, gathered by using tissue and experimental animals, suggest that selegiline possesses a plethora of actions that may be outlined under at least three separate major categories:

1. Enhancement of dopaminergic transmission:
  - Selegiline inhibits oxidation of MPTP to MPP+.
  - Selegiline produces amphetamine-like effect, enhances release of dopamine, and blocks reuptake of dopamine.
  - Selegiline increases striatal phenylethylamine levels, enhances release of dopamine, and activates dopamine receptors.
  - Selegiline stimulates gene expression of l-amino-acid decarboxylase in PC12 cells.
2. Neuronal protection:
  - Selegiline reduces the production of oxidative radicals.
  - Selegiline upregulates SOD and catalase.
  - Selegiline suppresses nonenzymatic, iron-catalyzed autooxidation of dopamine.
3. Neuronal rescue:
  - Selegiline compensates for loss of target-derived trophic support (stereospecific).
  - Selegiline enhances glial activation.
  - Selegiline induces NT-3trikC receptor.
  - Selegiline upregulates ciliary neurotrophic factor (CNF) gene expression in astroglial cell culture.
  - Selegiline delays apoptosis in serum-deprived PC12 cells.
  - Selegiline blocks apoptosis-related fall in mitochondrial membrane potential.

Most of the aforementioned properties occur independent of the efficacy of selegiline to inhibit MAO-B. No firm clinical data exist at this time to either accept or reject the contentions that these diversified therapeutic possibilities are seen in banisterine- or selegiline-treated patients with neurological disorders.

When used as a monotherapy in the early stage of Parkinson's disease, selegiline provides a mild antiparkinsonian effect. When given concomitantly with L-dopa, it potentiates the effects of L-dopa and allows a reduction in daily L-dopa dosage. In patients with fluctuating responses, selegiline decreases their severity, particularly the "wearing off," but less so the "off-on" phenomenon.

Long-term double-blind studies have both accepted and rejected the contentions that monotherapy with selegiline is able to slow the progression of Parkinson's disease and hence delay the initiation of therapy with L-dopa. However, general agreement exists that selegiline is a relatively safe drug, because the incidences of fatigue, vertigo, constipation, insomnia, dry mouth, depression, nausea, sweating, orthostatic dizziness, involuntary movements, anxiety, and palpitation are identical to those caused by placebo.

Some of the beneficial effects attributed to high (20 to 40 mg/d) and not low (5 to 10 mg/d) doses of selegiline, such as being useful in the treatments of depression or narcolepsy, may be due to inhibition of MAO-A by selegiline altering adrenergic and serotonergic signals.

It is certain that today's selegiline and rasagiline will be replaced by even more selective and efficacious MAOs of tomorrow, possessing undisputed **neurotrophic, immunoenhancing, neuron rescuing, antiapoptotic, and neuroprotectant** properties capable of averting the deleterious effects of MPTP-like compounds produced endogenously, of protecting the striatal neurons, and of alleviating the physical disability and mental suffering of patients with Parkinson's disease (see Ebadi and Pfeiffer, 2005).

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# 14 Belladonna Alkaloids: Autonomic Drugs

## INTRODUCTION

Atropine, hyoscyamine, and hyoscine are cholinergic receptor blocking agents. Autonomic drugs have extensive clinical applications. They have the following uses:

- In the treatment of wide-angle glaucoma
- In the diagnosis of myasthenia gravis
- As gastrointestinal and urinary tract stimulants in postoperative abdominal distention and urinary retention
- As antidotes to poisoning from curare and the tricyclic antidepressants
- As preanesthetic medications
- As mydriatics
- As cycloplegics
- In peptic acid oversecretion to diminish the vagally mediated secretion of gastric juices
- In slowing gastric emptying
- In vestibular disorders
- In Parkinsonism
- In conjunction with local anesthetics
- In hypotension and shock
- In heart block to improve atrioventricular conduction and stimulate ventricular automaticity
- In bronchial asthma
- As a nasal decongestant
- In narcolepsy
- In attention deficit hyperactivity disorders
- In the diagnosis and treatment of pheochromocytoma
- In cardiac arrhythmias
- In angina pectoris
- In hypertension
- In thyrotoxicosis
- In tremor

In addition, numerous drugs such as neuroleptics and antidepressants produce side effects by modifying the function of the autonomic nervous system.

## SOLANACEAE OR NIGHTSHADE FAMILY

The plants are of varied form, most abundant in tropical regions, and the family comprises 85 genera and about 1800 species. The leaves are usually alternate; the flowers are mostly regular, except in *Hyoscyamus*; the anthers are connivent, with the pollen sacs apically or longitudinally dehiscent; and the fruits are superior berries or capsules. The plants are usually malodorous. They furnish a number of important economic products, including potato, tomato, eggplant, and tobacco, as well as a number of drugs.



**FIGURE 14.1** Belladonna (*Atropa belladonna*), from which atropine and the belladonna alkaloids are obtained.

## OCCURRENCE

The atropine series contains a number of very closely allied alkaloids of which the chief are **atropine**, **hyoscyamine**, and **hyoscine** (also called **scopolamine**). They are found in the roots and leaves of many plants of the **Solanaceae**, notably **belladonna** (*Atropa belladonna*), **henbane** (*Hyoscyamus niger*), the **thorn apple** or **jimson weed** (*Datura stramonium*), and some members of the *Duboisia* and *Scopolia* genera. These plants were used during the Middle Ages as “sorcerer’s drugs” and have been smoked, chewed, or imbibed in the form of decoctions by primitive people for the hallucinations and frenzy they produce (Figure 14.1).

## HISTORY

Galenical preparations of belladonna have been employed in medicine for many centuries and were known to the ancient Hindus. The **professional poisoners** of the Middle Ages frequently used the deadly nightshade plant to produce a type of intoxication that was often prolonged and obscure. This prompted Linné to name the shrub *Atropa belladonna*, after **Atropos**, the oldest of the Three Fates who severs the thread of life. The word *belladonna* itself is a reminder of the antiquity of the drug in that it signifies “beautiful lady,” because the women of long ago were wont to instill a decoction of the plant in their eyes to produce dilated pupils, a sign of comeliness. The resulting disturbance of vision evidently was a small price to pay for beauty. The mydriatic action of belladonna, so widely used today, was thus well understood hundreds of years before the invention of the retinoscope.

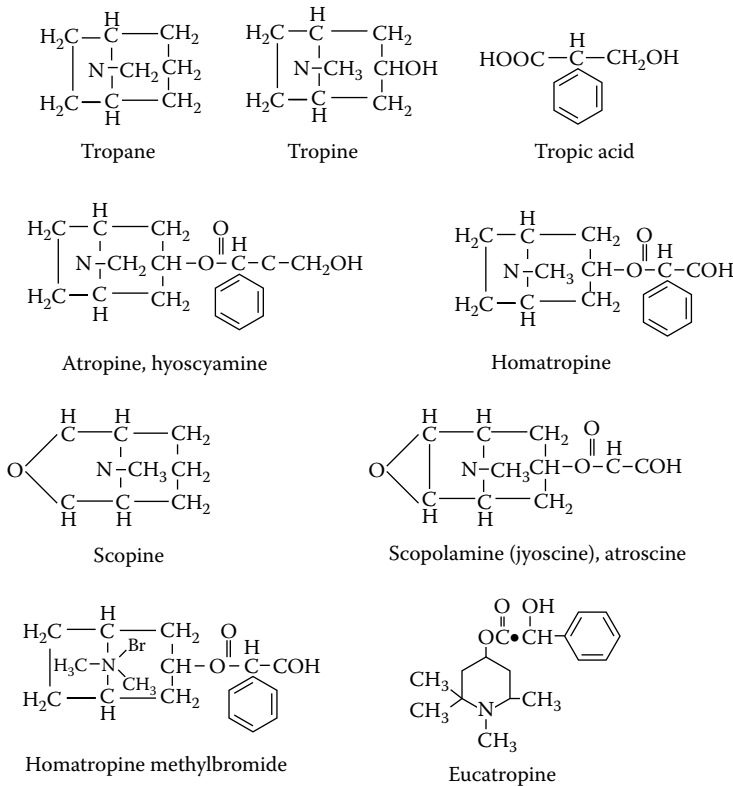


FIGURE 14.2 Structural formula of atropine and its related anticholinergic drugs.

### CHEMISTRY

The alkaloids of this group are derived from a combination of a piperidine and a pyrrolidine ring, designated as **tropane** (Figure 14.2). The 3-hydroxy derivative of **tropane** is known as **tropine** and is the basic component of atropine. When atropine is hydrolyzed, it forms **tropine** and **tropic acid** ( $\alpha$ -phenyl- $\beta$ -hydroxy-propionic acid). Atropine is the tropic acid ester of tropine. It has been prepared synthetically. Tropic acid contains an asymmetric carbon atom. The racemic compound (atropine) as obtained naturally or as synthesized may be resolved into its optically active components, *d*- and *l*-**hyoscyamine**. Atropine is racemic hyoscyamine; that is, it consists of equal parts of *l*-hyoscyamine and *d*-hyoscyamine, but as the latter is only feebly active in the body, the action of atropine is practically that of its *l*-hyoscyamine moiety. *l*-Hyoscyamine is formed in the plants, but is readily changed to atropine in the plant cells and also in the process of extraction, so that the relative proportion of the isomers in the plants and in the preparations varies. However, atropine itself does exist in small amounts in the plants, although most of it is formed from the *l*-hyoscyamine in the process of extraction.

As noted from its formula (see Figure 14.2), **scopolamine** differs from atropine chemically in having an oxygen atom attached to the end carbon atoms of the **scopine** part of the molecule. Scopolamine is levorotatory but is readily racemized to the *d,l*-form designated as **atrosine**.

A number of related compounds are also present in the **solanaceous** plants and in some *Duboisia* and *Scopolia* genera. **Apoatropine (atropamine)**, which is found in belladonna root, may also be prepared synthetically by dehydrating atropine. It is an ester of tropine and **atropic acid** ( $\alpha$ -phenylacrylic acid). **Belladonnine**, an isomer of apoatropine, is also present in belladonna root. **Norhyoscyamine (pseudohyoscyamine)**, present in *Duboisia*, *Scopolia*, and *Datura*, consists of tropic acid and **nortropine**, a tropine containing an NH group in place of NCH<sub>3</sub>.

**TABLE 14.1**  
**Drugs Obtained from Nightshade Family**

Drugs	Parts Used	Botanical Origins	Habitats
Belladonna Folium	Leaves and tops	<i>Atropa belladonna</i>	Central and Southern Europe
Belladonna Radix	Root	<i>Atropa belladonna</i>	Asia Minor and Persia
Atropina	Alkaloid	<i>Atropa belladonna</i>	Asia Minor and Persia
Stramonium	Leaves	<i>Datura stramonium</i>	Asia and Tropical America
Hyoscyamus	Leaves and tops	<i>Hyoscyamus niger</i>	Europe, Asia
Capsicum	Fruit	<i>Capsicum frutescens</i>	Tropical America
Dulcamara	Twigs and stems	<i>Solanum dulcamara</i>	Europe and Asia
Manaca	Root	<i>Brunfelsia hopeana</i>	Tropical America
Duboisia	Leaves	<i>Duboisia myoporoides</i>	Australia
Tabacum	Leaves	<i>Nicotiana tabacum</i>	Tropical America
Scopola	Rhizome	<i>Scopola carniolica</i>	Alps and Carpathian Mountains
Paprika	Fruit	<i>Capsicum annuum</i> Variety of <i>C. longum</i>	Tropical America; cultivated
Pimiento	Fruit	Variety of <i>Capsicum annuum</i>	Spain
Miré	Roots, stems, and leaves	<i>Brunfelsia, hydragaeformis</i>	South America
Solanum	Ripe fruit	<i>Solanum carolinense</i>	United States

## BOTANY OF SOLANACEAE

The members of this family are **herbs** (potato, tomato, horsenettle), **shrubs** (*Lycium* spp.), **vines** (*Solanum dulcamara*, or bittersweet), and rarely trees, as in some tropical *Datura*. Stems and leaves possess bicollateral bundles. Many of the plants, as **belladonna**, **stramonium**, **hyoscyamus**, and **scopola**, contain **mydriatic alkaloids**. Leaves are alternate, exstipulate, entire or more-or-less lobed, rarely compound; often glandular-hairy. Flowers occur in cymes or are solitary; are regular and rarely irregular (*Petunia*, *Tobacco* spp.), pentamerous, perfect, synphyllous; sepals are green (rarely petaloid), rotate to tubular, usually persistent and accrescent; petals rotate (*Solanum*) to tubular (*Atropa*) to funnel-shaped (*Tobacco*), and so are (1) open to all comers, or (2) to bees or wasps, or (3) to butterflies, moths; color is greenish-yellow, or greenish-white, to white, to pink, crimson, purple, rarely blue; stamens are five in number, epipetalous, hypogynous, along with style usually forming nectar glands. Filaments short to long, anthers dehiscent longitudinally or by apical pores; pistil bicarpellate, syncarpous, with or without nectar girdle; superior ovary, two-celled with central placentation, ovules numerous, style more or less elongate with bilobed or bifid stigma. Fruit, a capsule dehiscent longitudinally (*Tobacco*, *Stramonium*) or transversely (henbane); or a berry (potato, eggplant, tomato, red pepper) (Table 14.1).

## PHARMACOGNOSY OF BELLADONNA

The *Atropa belladonna* is a herbaceous, perennial plant, of the nat. Ord. **Solanaceae**, having dark-purple, bell-shaped flowers, and glossy, purplish-black berries about the size of cherries. It is indigenous in the mountainous districts of central and southern Europe and Asia, and is cultivated in Europe and the U.S. It contains the official alkaloid **atropine**,  $C_{17}H_{23}NO_3$ , which may be decomposed into **tropine** and **tropic acid**, also the alkaloids **belladonnine**, **hyoscyamine**, **hyoscine**, and **atropamine**, in varying quantity, all existing as malates in the plant. It also contains the usual vegetable constituents, as albumin, gums, etc., and a coloring principle named **Atrosin**. The historical titles are as follows:

- **Belladonnae Folia**, Belladonna leaves, ovate and tapering, brownish-green above, grayish-green below, with a slight odor and bitter, disagreeable taste. Stramonium leaves are more wrinkled; hyoscyamus leaves are more hairy.
- **Belladonnae Radix**, Belladonna root, occurs in cylindrical, tapering, wrinkled pieces, 1/2- to 1-in. thick, nearly odorless, taste is bitter and acrid.

Allied plants are **hyoscyamus**, **stramonium**, **duboisia**, and **scopola**, containing alkaloids that are closely allied to atropine, both chemically and physiologically.

#### PREPARATION OF THE LEAVES

- **Extractum Belladonnae Foliorum**: Extract of belladonna leaves
- **Tinctura Belladonnae Foliorum**: Tincture of belladonna leaves, 10%
- **Emplastrum Belladonnae**: Belladonna Plaster, has the above extract 30%, mixed with adhesive plaster
- **Unguentum Belladonnae**: Belladonna ointment, has the above extract 10%, diluted alcohol 5, benzoinated lard 65, and hydrous wool-fat, 20

#### PREPARATIONS OF THE ROOT

- **Fluidextractum Belladonnae Radicis**: Fluid extract of the belladonna root
- **Linimentum Belladonnae**: Belladonna liniment, has a camphor, dissolved in fluid extract of belladonna root

#### ATROPINE AND ITS DERIVATIVES

- **Atropina**: Atropine,  $C_{17}H_{23}NO_3$ , white, acicular crystals, odorless, of bitter taste and alkaline reaction; very soluble in alcohol and in chloroform, also soluble in 130 of water at 59°F. It is decomposed by prolonged contact with caustic alkalies and is resolvable into tropine and tropic acid.
- **Atropinae Sulphas**: Atropine sulfate,  $(C_{17}H_{23}NO_3)_2H_2SO_4$ , a white powder with a bitter taste and neutral reaction, soluble in 0.4 of water and 6.2 of alcohol at 59°F.
- **Oleatum Atropinae**: Oleate of atropine, a 2% solution of the alkaloid in alcohol 2, oleic acid 50, and olive oil to 100.
- **Homatropinae Hydrobromidum**: Homatropine Hydrobromide,  $C_{16}H_{21}NO_3HBr$ , is the hydrobromide of an alkaloid obtained by the condensation of tropine and **mandelic acid**. It is soluble in 6 of water, 33 of alcohol, insoluble in ether (Figure 14.3).

### BELLADONNA ALKALOIDS AND THE AUTONOMIC NERVOUS SYSTEM

The nervous and endocrine systems control an extensive number of functions in the body. The nervous system is divided into the central nervous system and the peripheral nervous system. The peripheral nervous system is further divided into the somatic nervous system (a voluntary system innervating skeletal muscles) and the autonomic nervous system (an involuntary system innervating smooth muscle, cardiac muscle, and glands).

### COMPARISON OF THE SOMATIC AND AUTONOMIC NERVOUS SYSTEMS

The somatic and autonomic nervous systems differ anatomically and physiologically (Table 14.2).

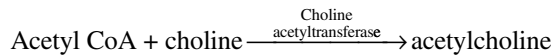




**FIGURE 14.3** The **henbane** (*Hyoscyamus niger* Linné), a member of the nightshade family, whose leaves, with or without the tops, constitute the official drug *Hyoscyamus* and are a source of the valuable medicinal alkaloids **hyoscyamine** and **scopolamine**.

### NEUROCHEMICAL BASIS OF CHOLINERGIC TRANSMISSION

Acetylcholine, an ester of choline and acetic acid, is synthesized in cholinergic neurons according to the following scheme:



The acetylcholine, in turn, is hydrolyzed by both **acetylcholinesterase** and plasma **butyrylcholinesterase**. Choline is actively transported into nerve terminals (synaptosomes) by a high-affinity uptake mechanism. Furthermore, the availability of choline regulates the synthesis of acetylcholine (Figure 14.4).

Hemicholinium blocks the transport of choline into synaptosomes, whereas botulinum toxin blocks the calcium-mediated release of acetylcholine. The released acetylcholine is hydrolyzed rapidly by acetylcholinesterase to choline and acetate.

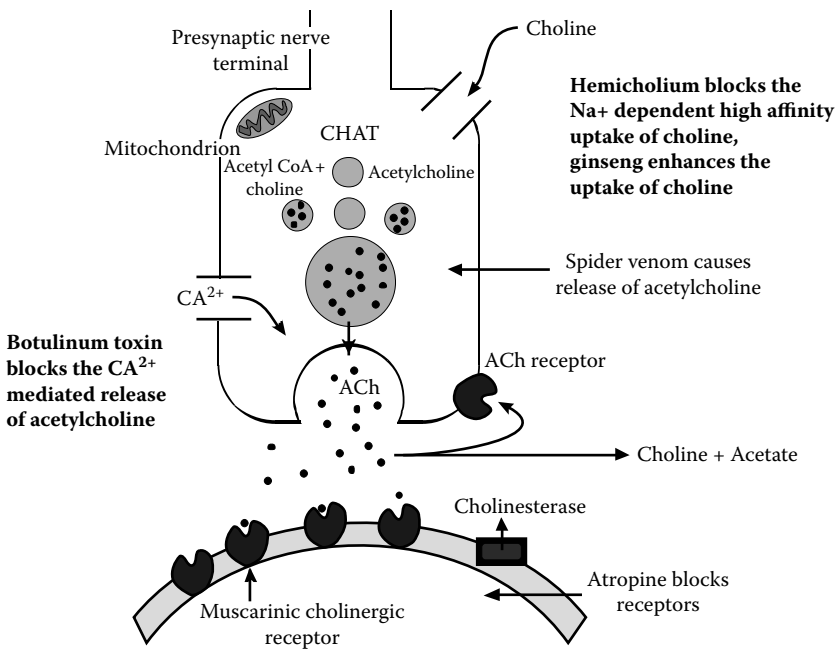
### DIVISION AND FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system consists of central connections, visceral afferent fibers, and visceral efferent fibers. The hypothalamus is where the principal integration of the entire autonomic nervous

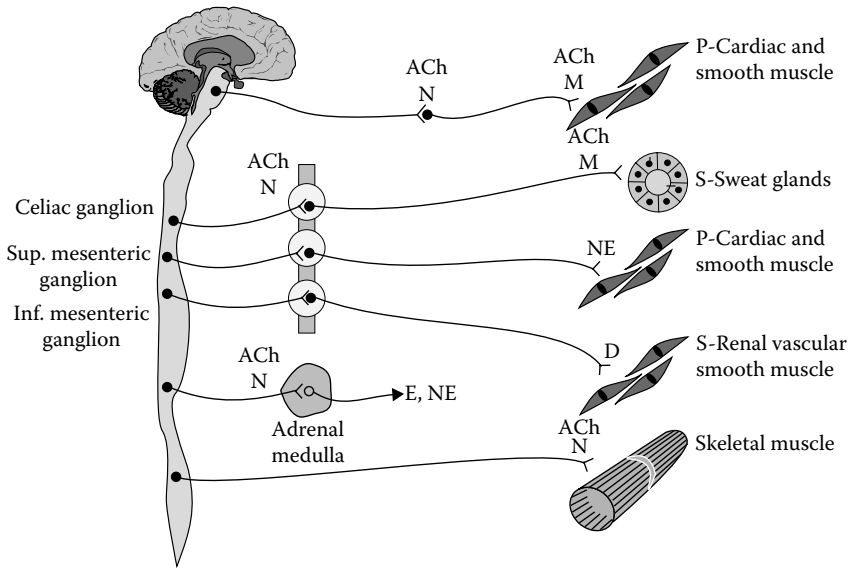
**TABLE 14.2**  
**Comparison of Somatic Nervous System and Autonomic Nervous System**

Somatic Nervous System	Autonomic Nervous System
Target tissues are skeletal muscles	Target tissues are smooth muscle, cardiac muscle, and glands
Cell bodies of somatic efferent neurons are found at all levels of the spinal cord	Cell bodies are absent in cervical, lower lumbar, and coccygeal levels of the spinal cord
The neurons have voluntary and involuntary (reflex) regulation	The neurons have involuntary regulation only
Target tissues (effectors) receive only one efferent neuron	Target tissues receive two (sympathetic and parasympathetic) efferent neurons
Only one myelinated neuron is interposed between the CNS and the effector organ	The neurons between the CNS and the organ are myelinated preganglionic fibers and unmyelinated postganglionic fibers
Acetylcholine is the transmitter	Acetylcholine and norepinephrine are the transmitters
Transmitter is necessary for skeletal muscle contraction, which is rapid	Separate transmitters are necessary for the contraction and relaxation of smooth muscles, which are slow
Denervation causes paralysis of skeletal muscle	Smooth muscle shows autoregulation
Only drugs causing skeletal muscle relaxation are used for clinical purposes	Both stimulants and depressants of smooth muscles are used for clinical purposes

*Note:* The autonomic nervous system (ANS) regulates the functions of internal viscera such as the heart, blood vessels, digestive organs, and reproductive organs.



**FIGURE 14.4** The metabolism and actions of acetylcholine (ACh). CoA = coenzyme A; CHAT = choline acetylase.



**FIGURE 14.5** The autonomic nervous system innervates smooth muscle, cardiac muscles, and gland. ACh = acetylcholine; N = nicotinic cholinergic receptors; M = muscarinic cholinergic receptors; S = sympathetic chain; P = parasympathetic chain; E = epinephrine; D = dopamine; NE = norepinephrine; Sup. = superior; Inf. = inferior.

system takes place, and it is involved in the regulation of blood pressure, body temperature, water balance, metabolism of carbohydrates and lipids, sleep, emotion, and sexual reflexes. To a lesser extent, the medulla oblongata, limbic system, and cerebral cortex also integrate, coordinate, and adjust the functions of the autonomic nervous system (Figure 14.5).

Most blood vessels, the sweat glands, and the spleen are innervated only by one division of the autonomic nervous system. In the salivary glands, the two divisions of the autonomic nervous system supplement one another. In the bladder, bronchi, gastrointestinal tract, heart, pupil, and sex organs, the two divisions of the autonomic nervous system have opposing effects (see Figure 14.5).

## CLASSIFICATION OF CHOLINERGIC RECEPTORS

**Acetylcholine receptors** are classified as either **muscarinic cholinergic receptors** or **nicotinic cholinergic receptors**. The alkaloid **muscarine** mimics the effects produced by stimulation of the parasympathetic system. These effects are postganglionic and are exerted on exocrine glands, cardiac muscle, and smooth muscle. The alkaloid **nicotine** mimics the actions of acetylcholine, which include stimulation of all autonomic ganglia, stimulation of the adrenal medulla, and contraction of skeletal muscle.

**Dimethylphenylpiperazinium** stimulates the autonomic ganglia, **tetraethylammonium** and **hexamethonium** block the autonomic ganglia, **phenyltrimethylammonium** stimulates skeletal motor muscle end plates, **decamethonium** produces neuromuscular blockade, and ***d*-tubocurarine** blocks both the autonomic ganglia and the motor fiber end plates.

Among the agents cited, only *d*-tubocurarine is useful as a drug (skeletal muscle relaxant); the rest are useful only as research tools. Cholinesterase, found in liver and plasma, can hydrolyze other esters such as **succinylcholine** (a skeletal muscle relaxant). Cholinergic peripheral receptors are located on (1) postganglionic parasympathetic fibers, (2) postganglionic sympathetic fibers, (3) all autonomic ganglia, and (4) skeletal end plates.

**TABLE 14.3**  
**The Pharmacological Actions of Atropine**

Doses (mg)	Effects
0.5	Slight cardiac slowing; some dryness of mouth; inhibition of sweating
1.0	Definite dryness of mouth; thirst; acceleration of heart, sometimes preceded by slowing; mild dilatation of pupil
2.0	Rapid heart rate; palpitation; marked dryness of mouth; dilated pupils; some blurring of near vision
5.0	All the preceding symptoms are more marked; difficulty in speaking and swallowing; restlessness and fatigue; headache; dry, hot skin; difficulty in micturition; reduced intestinal peristalsis
10.0 and more	Preceding symptoms are more marked; pulse rapid and weak; iris practically obliterated; vision very blurred; skin flushed, hot, dry, and scarlet; ataxia, restlessness, and excitement; hallucinations and delirium; coma

*Note:* The best-known antimuscarinic or anticholinergic drugs are the belladonna alkaloids. The major drugs in this class are atropine, hyoscyamine, and scopolamine. A number of plants belonging to the potato family (*Solanaceae*) contain similar alkaloids. *Atropa belladonna* (deadly nightshade), *Hyoscyamus niger* (henbane), *Datura stramonium* (jimsonweed or thorn apple), and several species of *Scopolia* also contain belladonna alkaloids.

## CHOLINERGIC RECEPTOR BLOCKING AGENTS

Atropine and scopolamine, which are obtained from belladonna alkaloids, as well as other synthetic anticholinergic drugs, inhibit the actions of acetylcholine and **cholinomimetic drugs** at muscarinic receptors in smooth muscles, heart, and exocrine glands. In addition to these peripheral effects, anticholinergic drugs, by blocking the acetylcholine receptor sites in the central nervous system, have pronounced effects such as restlessness, irritability, excitement, and hallucinations. Scopolamine, on the other hand, depresses the central nervous system and, in therapeutic doses, produces fatigue, hypnosis, and amnesia. Therefore, it is used extensively in numerous medications, often in combination with antihistamines.

## DOSE-DEPENDENT EFFECTS OF ATROPINE

The pharmacological effects of atropine in general are dose dependent (Table 14.3). It produces mydriasis (blockade of the iris sphincter muscle), cycloplegia (blockade of the ciliary muscle), and cardiovascular effects characterized by transient bradycardia (central vagal stimulation) and tachycardia (vagal blockade at the sinoatrial node). Lacking any significant effects on circulation, atropine is often used as a preanesthetic medication to depress bronchial secretion and prevent pronounced bradycardia during abdominal surgical procedures. In still larger doses, it depresses the tone and motility of the gastrointestinal tract, the tone of the urinary bladder, and gastric secretion. Therefore, the effective doses for use in acid-pepsin diseases are preceded by numerous side effects.

Atropine is absorbed orally and crosses the placental barrier, whereupon it causes fetal tachycardia. Atropine has been used to examine the functional integrity of the placenta.

## THE HISTORICAL USES OF BELLADONNA ALKALOIDS

**Belladonna** was one of the most valuable agents in the materia medica, ranking high in its efficacy and its wide range of usefulness. It was employed to **relieve pain, relax spasm, stimulate the circulation, decrease secretion, and check local inflammation**. Atropine was used for the same purposes, as well as to antagonize the effects of certain poisons, to dilate the pupils, and to paralyze

the accommodation of the eye. These agents were administered in **rheumatic torticollis, lead colic, spasmodic colic, spasmodic dysmenorrhea, laryngismus stridulus, whooping cough, asthma, constipation, irritability of the bladder**, and many other **spasmodic affections**.

## THE MODERN USES OF SYNTHETIC MUSCARINIC RECEPTOR ANTAGONISTS

The various applications of synthetic muscarinic receptor antagonists are listed in the following text.

### Ophthalmology

Homatropine: Produces **mydriasis** and **cycloplegia**

Eucatropine: Produces only mydriasis (Figure 14.6)

### Preoperative Uses

Atropine: To prevent excess salivation and bradycardia

Scopolamine: In obstetrics, to produce sedation and amnesia

### Cardiology

Atropine:

- To reduce severe bradycardia in **hyperactive carotid sinus reflex**
- Diagnostically in **Wolff–Parkinson–White syndrome** to restore the PRS complex to normal duration

### Gastroenterology

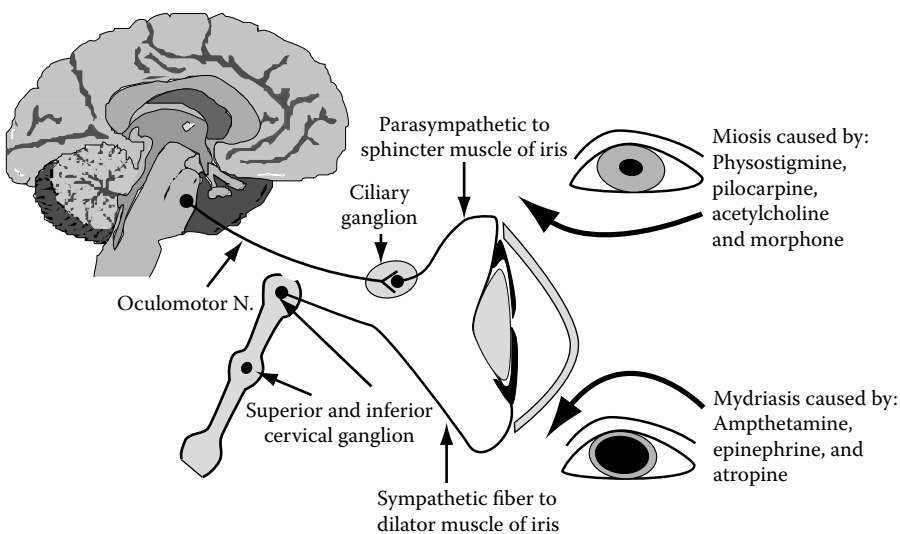
**Propantheline, oxyphenonium, pirenzepine:**

- To diminish vagally mediated secretion of gastric juices and slow gastric emptying in peptic ulcer
- To reduce diarrhea associated with dysenteries and diverticulitis
- To reduce excess salivation associated with heavy metal poisoning or parkinsonism

### Neurology

**Trihexyphenidyl, benztropine:** In parkinsonism and drug-induced pseudoparkinsonism

Scopolamine: In vestibular disorders such as motion sickness



**FIGURE 14.6** Miosis and mydriasis caused by autonomic drugs. N = nerve.

**Methantheline** and **propantheline** are synthetic derivatives that, besides their antimuscarinic effects, are ganglionic blocking agents and block the skeletal neuromuscular junction. Propantheline and **oxyphenonium** reduce gastric secretion, whereas **pirenzepine**, in addition to reducing gastric secretion, also reduces gastric motility.

## CONTRAINDICATIONS TO ANTICHOLINERGIC AGENTS

Conditions that are contraindications to the use of atropine and related drugs are **glaucoma** and **prostatic hypertrophy**, in which cases they cause urinary retention.

**Atropine toxicity** is characterized by dry mouth, burning sensation in the mouth, rapid pulse, mydriasis, blurred vision, photophobia, dry and flushed skin, restlessness, and excitement.

**Physostigmine**, given intravenously, counteracts both the peripheral and central side effects of atropine and other anticholinergic drugs such as **thioridazine** (neuroleptic), **imipramine** (antidepressant), and **benztropine** (antiparkinsonian medication).

## HYOSCYAMINE

Hyoscyamine, which, as already noted, is the *l*-isomer of racemic atropine, exerts the same action as the latter but is approximately twice as potent. It is, however, rarely obtainable in pure form, as it is almost always mixed with atropine, into which it changes when kept in solution. The action of atropine, as has been stated, is compounded by that of natural or levorotary hyoscyamine with that of its dextrorotary isomer. The latter does not exist free in nature and possesses little or no parasympatholytic action.

## SCOPOLAMINE

Scopolamine (also called) hyoscine resembles atropine closely in its peripheral action, except that it passes off more quickly. Following the administration of therapeutic doses, the pulse remains unaltered in rate or may be slower, owing to the hypnotic action. Applied to the conjunctiva it produces mydriasis and loss of accommodation more quickly than atropine, but for a much shorter time. The effects on the central nervous system present the greatest divergencies from those described for atropine, for the characteristic stimulation is absent in the great majority of cases. As a general rule, scopolamine produces a marked sensation of fatigue. In drowsiness, the patient moves about less and speaks less, and a condition in no way dissimilar to natural sleep follows. In many cases, however, a short stage of excitement with giddiness, uncertain movements, and difficult and indistinct speech precedes sleep, and occasionally symptoms exactly resembling those produced by atropine follow the administration of scopolamine, especially if large doses are employed. Sleep generally lasts from 5 to 8 h, and the patient may then remain quiet for several hours longer. As a general rule, after small doses, no confusion results on awakening, but dryness of the throat and thirst are often present. Larger doses do not cause deeper sleep but give rise to delirium and excitement resembling those following atropine administration. Rarely, collapse has been observed after scopolamine. The respiratory center does not seem to be stimulated as by atropine, the respiration generally becoming slower from the beginning.

In lower mammals, scopolamine reduces the excitability of the motor areas as tested by electric shocks, and the reflex excitability in the frog is not increased as by atropine. Scopolamine appears to be excreted or destroyed in the tissues much more rapidly than atropine, for its effects last a shorter time.

The action of scopolamine, then, seems to correspond with that of atropine, except that the central nervous system is here depressed, while the action on the peripheral structures is of shorter duration. It depresses the brain in very small quantities; 0.5 mg is generally sufficient to induce

quiet. The therapeutic dose is well below the fatal dose, but medicinal doses occasionally produce toxic symptoms, apparently a form of idiosyncrasy. A certain degree of tolerance is produced after repeated use, so that the dose has to be increased after a week or two.

Scopolamine is much less reliable as a hypnotic than morphine or the members of the chloral hydrate group. It is most effective when sleep is prevented by motor excitement, and the sleep seems to arise from the relief of this condition and not from depression of the consciousness.

Scopolamine is levorotary to polarized light; the racemic form, **atropine**, which is often present in commercial scopolamine, acts only half as strongly on the peripheral organs, because in it the levorotary is mixed with the dextrorotary isomer, which is almost inactive. The cerebral action is equal, however, in the two forms.

## SYNTHETIC AND SEMISYNTHETIC SUBSTITUTES FOR BELLADONNA ALKALOIDS

### QUATERNARY AMMONIUM MUSCARINIC RECEPTOR ANTAGONISTS

There are several differences in the pharmacological properties of the quaternary muscarinic receptor antagonists as compared to the belladonna alkaloids described earlier. Compounds with a quaternary ammonium structure are poorly and unreliable absorbed after oral administration. Penetration of the conjunctiva also is poor, so that most quaternary ammonium compounds are of little value in ophthalmology. Central effects are generally lacking, because these agents do not readily cross the blood–brain barrier. The quaternary ammonium compounds usually have a somewhat more prolonged action than the belladonna alkaloids; little is known of the fate and excretion of most of these agents. Because the ratio of ganglionic blocking (nicotinic) to muscarinic-blocking activity is greater for quaternary ammonium compounds than for tertiary amines, side effects attributable to ganglionic blockade, such as impotence and postural hypotension, can occur. Poisoning with quaternary ammonium muscarinic receptor antagonists also may cause a curariform neuromuscular block, leading to respiratory paralysis.

There is a clinical impression that the quaternary ammonium compounds have a relatively greater effect on gastrointestinal activity and that the doses necessary to treat gastrointestinal disorders are, consequently, somewhat more readily tolerated than are other agents of this type; this effect has been attributed to the additional element of ganglionic block. Nevertheless, most of these drugs, similar to atropine, generally control gastric secretion or gastrointestinal motility only at doses that also cause significant side effects due to muscarinic blockade at other sites.

### IPRATROPIUM

**Ipratropium bromide** (Atrovent) is a quaternary ammonium compound formed by the introduction of an isopropyl group to the N atom of atropine. A similar agent, **oxitropium bromide**, also is available in Europe; it is a quaternary ammonium derivative of scopolamine, formed by the introduction of an ethyl group. The most recently developed and bronchoselective member of this family is **tiotropium bromide**, which has a longer duration of action and currently is in clinical trial. Ipratropium bromide produces effects similar to those of atropine when each agent is administered parenterally. These include bronchodilatation, tachycardia, and inhibition of salivary secretion. Although somewhat more potent than atropine in these actions, ipratropium lacks appreciable effect on the central nervous system and has greater inhibitory effects on ganglionic transmission, similar to other quaternary ammonium muscarinic receptor antagonists. One unexpected and therapeutically important property of ipratropium is the relative lack of effect on mucociliary clearance, in contrast to the inhibitory effect of atropine; this difference is evident upon either local or parenteral administration and remains unexplained. Hence, the use of ipratropium in patients with

airway disease avoids the increased accumulation of lower airway secretions and the antagonism of  $\beta$ -adrenergic agonist-induced enhancement of mucociliary clearance encountered with atropine.

When solutions are inhaled, the actions of ipratropium are confined almost exclusively to the mouth and airways. Even when administered in amounts many times the recommended dosage, little or no change occurs in heart rate, blood pressure, bladder function, intraocular pressure, or pupillary diameter. This selectivity results from the very inefficient absorption of the drug from the lungs or the gastrointestinal tract. The degree of bronchodilatation produced by ipratropium is thought to reflect the level of parasympathetic tone, supplemented by reflex activation of cholinergic pathways brought about by various stimuli. In normal individuals, the inhalation of ipratropium can provide virtually complete protection against the bronchoconstriction produced by the subsequent inhalation of such substances as sulfur dioxide, ozone, nebulized citric acid, or cigarette smoke. However, patients with asthma or with demonstrable bronchial hyperresponsiveness are less well protected. Although ipratropium causes a marked reduction in sensitivity to **methacholine** in asthmatic subjects, more modest inhibition of responses to challenge with **histamine**, **bradykinin**, or **prostaglandin F<sub>2 $\alpha$</sub>**  is achieved, and little protection is provided against the bronchoconstriction induced by serotonin (5-HT) or the **leukotrienes**. The principal clinical use of ipratropium is in the treatment of chronic obstructive pulmonary disease; it is less effective in most patients with asthma.

### METHOSCOLAMINE

**Methoscopolamine bromide** (Pamine) is a quaternary ammonium derivative of scopolamine and therefore lacks the central actions of scopolamine. It is less potent than atropine and is poorly absorbed; however, its action is more prolonged, the usual oral dose (2.5 mg) acting for 6 to 8 h. Its use has been limited chiefly to gastrointestinal diseases.

### HOMATROPINE METHYLBROMIDE

**Homatropine methylbromide** is the quaternary derivative of homatropine. It is less potent than atropine in antimuscarinic activity, but it is four times more potent as a ganglionic blocking agent. It is available in some combination products intended for relief of gastrointestinal spasm.

### METHANTHELIN

**Methantheline bromide** (Banthine) differs from atropine in having a particularly high ratio of ganglionic blocking activity to antimuscarinic activity. High doses may cause impotence, an effect rarely produced by purely antimuscarinic drugs and indicative of ganglionic block. Toxic doses may paralyze respiration by neuromuscular block. Restlessness, euphoria, fatigue, or, very rarely, acute psychotic episodes may be seen in some patients despite the relatively poor penetration of the drug into the central nervous system. The duration of methantheline action is slightly more prolonged than that of atropine, the effects of a therapeutic dose (50 to 100 mg) lasting 6 h. An additional toxic manifestation unrelated to the blocking actions is the occasional appearance of skin rashes, including exfoliative dermatitis.

### PROPANTHELIN

**Propanteline bromide** (Pro-banthine) resembles methantheline chemically (isopropyl groups replace the ethyl substituents on the quaternary N atom). Its pharmacological properties are also similar to those of methantheline, but it is two to five times more potent. It is one of the more widely used of the synthetic muscarinic receptor antagonists. Very high doses block the skeletal neuromuscular junction. The usual clinical dose (15 mg) acts for about 6 h.



## OTHER COMPOUNDS

Other drugs in this category include **anisotropine methylbromide** (Valpin), **clidinium bromide** (**Quarzan**; also in combination with chlordiazepoxide as **Librax** and others), **glycopyrrolate** (Robinul; also used parenterally in conjunction with anesthetics), **isopropamide iodide** (Darbid), **mepenzolate bromide** (Cantil), **tridihexethyl chloride** (Pathilon), and **hexocyclium methylsulfate** (Tral).

## TERTIARY-AMINE MUSCARINIC RECEPTOR ANTAGONISTS

Some of these agents are particularly useful in ophthalmology; included in this category are **homatropine hydrobromide** (Isopto homatropine) (a semisynthetic derivative of atropine); **cyclopentolate hydrochloride** (Cyclogyl), and **tropicamide** (Mydracyl). These agents are preferred to atropine or scopolamine because of their shorter duration of action.

Tertiary-amine muscarinic receptor antagonists gain access to the central nervous system and are therefore the anticholinergic drugs used to treat parkinsonism and the extrapyramidal side effects of antipsychotic drugs. Specific agents used primarily for these conditions include **benztropine mesylate** (Cogentin) and **trihexyphenidyl hydrochloride** (Artane, others).

Tertiary amines used for their antispasmodic properties are **dicyclomine hydrochloride** (Bentyl, others), **oxyphencylimine hydrochloride** (daricon), **flavoxate hydrochloride** (Uripas), and **oxybutynin chloride** (Ditropan). The latter two are indicated specifically for urological disorders. These agents appear to exert some nonspecific direct relaxant effect on smooth muscle. In therapeutic doses they decrease spasm of the gastrointestinal tract, biliary tract, ureter, and uterus; characteristic atropine-like effects on the salivary glands and the eye also are seen with oxybutynin.

**Pirenzepine** is a tricyclic drug, similar in structure to imipramine. Pirenzepine has selectivity for  $M_1$ -, relative to  $M_2$ -, and  $M_3$ -muscarinic receptors. **Telenzepine** is an analog of pirenzepine that has higher potency and similar selectivity for  $M_1$ -muscarinic receptors. Both drugs are used in the treatment of peptic ulcer. At therapeutic doses, the incidence of dry mouth and blurred vision is relatively low with pirenzepine. Central effects are not seen because of the low lipid solubility of the drug and its limited penetration into the central nervous system. Some studies also have shown pirenzepine and telenzepine to be of therapeutic value in **chronic obstructive bronchitis**, presumably as a result of blockade of **vagally mediated bronchoconstriction**. In both the gastrointestinal tract and airway, the site of  $M_1$  receptor antagonism is believed to be on receptors in ganglia.

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# 15 Blueberry (*Vaccinium*)

The following are the chief uses of blueberry:

- Antioxidant (similar to pomegranate, the richest source of all fruits)
- Anti-inflammatory effect
- Cardiovascular protectant
- Fights urinary tract infection
- Enhances memory
- Improves vision
- Fights cancer

The blueberry of the genus *Vaccinium* is a native American species. In fact, the blueberry is one of the few fruits native to North America. Many different names have been given to the numerous varieties of *Vaccinium* that produce edible fruits, such as blueberry, bilberry, cowberry, cranberry, crowberry, farkleberry, lingonberry, partridgeberry, huckleberry (not the true huckleberry, which is *Gaylussacia*), whortleberry, and sparkleberry, to mention a few.

All blueberries belong to the genus *Vaccinium*. The family includes the Highbush (*V. corymbosum* and *V. ashei*) and the Native American “wild” low bush (*V. augustifolium*). All blueberries originated in the wild. Highbush blueberries represent 57% of total North American blueberry production.

For centuries, blueberries were gathered from the forests and the bogs by Native Americans and consumed fresh and also preserved. The Northeast Native American tribes revered blueberries, and much folklore developed around them. The blossom end of each berry, the calyx, forms the shape of a perfect five-pointed star; the elders of the tribe would tell of how the **Great Spirit** sent “**star berries**” to relieve the children’s hunger during a famine. Parts of the blueberry plant were also used as medicine. A tea made from the leaves of the plant was thought to be good for the blood. Blueberry juice was used to treat coughs. The juice also made an excellent dye for baskets and cloth. In food preparation, dried blueberries were added to stews, soups, and meats. The dried berries were also crushed into a powder and rubbed into meat for flavor. Blueberries were also used for medicinal purposes along with the leaves and roots. A beef jerky called **Sautauthig**, was made with dried blueberries and meat and was consumed year round.

Blueberries contain **flavonoids** (see Chapter 31), which include the following items.

Subclass	Flavonoid
<b>Anthocyanidins</b>	Cyanidin
	Delphinidin
	Malvidin
	Peonidin
	Petunidin
<b>Flavan-3-ols</b>	(–)-Epicatechin
<b>Flavonols</b>	Myricetin
	Quercetin

Flavonoids possess varied biological properties including antioxidative, antimicrobial, and potential anticarcinogenic, and cardioprotective effects. Blueberries contain **Proanthocyanidin**. The free-radical scavenging properties of proanthocyanidins, including their potential for risk reduction of cardiovascular diseases, cancer, blood clotting, and protection against urinary tract infection, have been under investigation by scientists. Also referred to as “**condensed tannins**,” proanthocyanidins polymers of flavan-3-ols impart an astringent flavor to foods. The following is a listing of the proanthocyanidin content of raw blueberries.

#### Proanthocyanidin

Monomers  
Dimers  
Trimers  
4-6mers  
7-10mers  
Polymers

In addition, blueberries contain the following minerals: calcium, copper, iron, magnesium, manganese, phosphorus, potassium, selenium, sodium, and zinc; and the following vitamins: vitamin C, thiamin, riboflavin, niacin, pantothenic acid, vitamin B<sub>6</sub>, folate, vitamin A, and vitamin E. The dye that is released from the blueberries’ skin may well be the most valuable nutrient the fruit has to offer. The pigments in blueberries and also in red crops such as cherries, plums, and red cabbage are powerful antioxidants. They have been determined to be a much-heralded chemical warrior against heart disease and also cancer. Blueberries actually have the highest antioxidant capacity because of their large anthocyanin concentration. Nutritional antioxidants such as **polyphenols** found in blueberry are able to reverse age-related declines in memory seen in Alzheimer’s disease; hence, blueberry has been called **brainberry**.

Blueberries contain **condensed tannins** that help prevent urinary tract infections. Blueberries contain **Anthocyanin** (which is responsible for its deep blue color), which is a **flavonoid**, a plant antioxidant (see Chapter 8 and Chapter 31). Flavonoids such as anthocyanin found in blueberries have a different chemical structure compared to other common antioxidants such as **vitamin C**, which makes them three to four times more potent. Antioxidants neutralize the effects of “**free radicals**,” which are unstable molecules that can attack human cells and damage their DNA.

The antioxidants fight heart disease and cancer and are primarily located in the blue pigment in the berry. Blueberries are not only a powerful antioxidant but also have been proved to preserve vision. Blueberry extract, high in compounds called **anthocyanosides**, has been found in clinical studies to **slow down vision loss**. Wild blueberries, similar to their European cousins, bilberries, have very high concentrations of anthocyanin, a natural compound linked with many health benefits, including reducing eyestrain and improving night vision. The anti-inflammatory properties of blueberries appear to boost the protective proteins in the brain and help cells repair damage that can lead to a host of aging-related diseases and conditions. Fruits and vegetables have been shown to contain high levels of antioxidant compounds, which provide protection against harmful free radicals and have been suggested to lower the incidence and mortality rates of cancer and heart disease in addition to a number of other health benefits. Blueberries belong to the category of **superfoods**. The remaining foods in this group are beans, broccoli, honey, oats, oranges, pumpkin, spinach, soy, tea (green or black), tomatoes, walnuts, wheatgerm, and yogurt.

**Apple** lowers cholesterol and risk for cancer. Has mild antibacterial, antiviral, and anti-inflammatory estrogenic activity. It is high in fiber, helps avoid constipation, and suppresses appetite.

**Asparagus** is a super source of the antioxidant **glutathione**, which lowers cancer risk (see Chapter 13).

- Avocado** benefits circulation, lowers cholesterol, and dilates blood vessels. Its main fat, **monounsaturated oleic acid** (also concentrated in olive oil), acts as an antioxidant to block artery-destroying toxicity of bad-type-LDL cholesterol. It is one of the richest sources of **glutathione**, a powerful antioxidant shown to block 30 different carcinogens and to block proliferation of the AIDS virus (see Chapter 13).
- Banana and plantain** soothe the stomach. They are good for dyspepsia (upset stomach), strengthen the stomach lining against acid and ulcers, and have antibiotic activity.
- Barley** reduces cholesterol, has antiviral and anticancer activity, and contains potent antioxidants, including **tocotrienols**.
- Beans** are legumes, and include navy, black, kidney, pinto, soy beans, and lentils. They are a potent medicine in lowering cholesterol.
- Beets** are richer than spinach in iron and other minerals. The greens are helpful in cases of anemia, tuberculosis, constipation, poor appetite, obesity, tumors, gout, and pimples and are helpful in the elimination of irritating drug poisons. Beets are one of the best foods to relieve constipation and they are also good for obesity.
- Bell pepper** is rich in antioxidant vitamin C. It helps to fight off colds, asthma, bronchitis, respiratory infections, cataracts, macular degeneration, angina, atherosclerosis, and cancer.
- Berry fruits** have been shown to contain high levels of antioxidant compounds such as **carotenoids**, vitamins, phenols, flavonoids, dietary glutathione, and endogenous metabolites.
- Broccoli** are abundant in antioxidants, including **quercetin**, **glutathione**, **beta carotene**, **indoles**, **vitamin C**, **lutein**, **glucarate**, and **sulforaphane**. They exhibit extremely high cancer-fighting activity, particularly against lung, colon, and breast cancers. Similar to other cruciferous vegetables, they speed up removal of estrogen from the body, helping suppress breast cancer. They are rich in cholesterol-reducing fiber and, have antiviral, antiulcer activity. They are a super source of **chromium**, which helps regulate insulin and blood sugar. Cooking and processing destroy some of the antioxidants and antiestrogenic agents, such as indoles and glutathione.
- Brussels sprouts** are in the Cruciferous family and have some of the same properties as broccoli and cabbage (see Bomser et al., 1996; Brown et al., 1998; Cao et al., 1999; Colantuoni et al., 1991; Cunio et al., 1993; Ehlenfeldt et al., 2001; Hakkinen et al., 1999; Head et al., 2001; Howard et al., 2003; Lietti et al., 1976; Logan et al., 2001; Morazzoni et al., 1996; Moyer et al., 2002; Muth et al., 2000; Prior et al., 1998; Prior et al., 2001; Sellappan et al., 2002; Skrede et al., 2000; Wang et al., 2000; Wu et al., 2004; Zheng et al., 2003).



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# 16 Botulinum Toxin

## INTRODUCTION

This chapter deals with **botulinum toxin type A (BOTOX)** in the treatment of **strabismus**, **blepharospasm**, and related disorders. **Botulinum toxin type A (BOTOX)** has been used to treat strabismus, blepharospasm, Meige's syndrome, and spasmodic torticollis. By preventing acetylcholine release at the neuromuscular junction, botulinum toxin A usually causes a temporary paralysis of the locally injected muscles. The variability in duration of paralysis may be related to the rate of developing antibodies to the toxin, upregulation of nicotinic cholinergic postsynaptic receptors, and aberrant regeneration of motor nerve fibers at the neuromuscular junction. Complications related to this toxin include double vision (**diplopia**) and lid droop (**ptosis**).

## BOTULINUM TOXIN TYPE A (OCULINUM)

Botulinum, a neurotoxin with muscle relaxant properties, is used in the treatment of strabismus.

## BOTULISM ANTITOXIN, TRIVALENT (ABE) EQUINE

Botulism antitoxin, which binds and neutralizes toxin, is used in the treatment of botulism.

## USES OF BOTULINUM TOXIN INJECTION IN MEDICINE TODAY

**Botulinum neurotoxin** is produced by the anaerobic bacterium **Clostridium botulinum**. It is the most poisonous substance known. Very small amounts of botulinum toxin can lead to botulism, a descending paralysis with prominent bulbar symptoms and often affecting the autonomic nervous system (see Chapter 14). Botulism can occur in two ways. It can result from infection with bacterial spores that produce and release the toxin in the body, as in **enteric infectious botulism**, in which the bacteria grow in the intestine, and in **wound botulism**, in which the wound becomes infected. Alternatively, botulism occurs after ingestion of the toxin (**food-borne botulism**). The following are the main features of the clinical use of botulinum toxin:

- Botulinum toxin inhibits release of **acetylcholine** (Ach) at the neuromuscular junction and in cholinergic sympathetic and parasympathetic neurons.
- Local injections of toxin weaken overactive muscles and control hypersecretion of glands supplied by cholinergic neurons.
- Botulinum toxin injections have an established role in some disorders of ocular motility.
- Botulinum toxin is the treatment of choice for **focal dystonias** such as **torticollis** and **writer's cramp** and for **hemifacial spasm**, and may complement the management of **spasticity**.
- Local injections have also been shown to be beneficial in many other conditions including **achalasia**, **chronic anal fissure**, and **hyperhidrosis**.
- Treatment is usually well tolerated, the main side effect being weakness in adjacent muscles (Münchau and Bhatia, 2000).

Serotype A is the only one commercially available for clinical use, although experience is emerging with serotypes B, C, and F. Two preparations exist: **Dysport**, which is most widely used in the U.K., and **Botox**, which is used in the U.S. and elsewhere.

Strains of *C. botulinum* produce seven antigenetically distinct neurotoxins designated as serotypes A through G. All seven serotypes have a similar structure and molecular weight, consisting of a heavy (H) chain and a light (L) chain joined by a disulfide bond. They all interfere with neural transmission by blocking the release of ACh (see Chapter 14), which is the principal neurotransmitter at the neuromuscular junction.

After synaptic transmission is blocked by botulinum toxin, the muscles become clinically weak and atrophic. The affected nerve terminals do not degenerate, but the blockage of neurotransmitter release is irreversible. Function can be recovered by the sprouting of nerve terminals and formation of new synaptic contacts; this usually takes 2 to 3 months.

Estimates of the ACh content of synaptic vesicles range from 1000 to over 50,000 molecules per vesicle, and it has been calculated that a single motor-nerve terminal contains 300,000 or more vesicles. In addition, an uncertain but possibly significant amount of ACh is present in the extraventricular cytoplasm. The release of ACh and other neurotransmitters by exocytosis through the presynaptic membrane is inhibited by toxins from *Clostridium*. Some of the most potent toxins known are produced by this microbe. Clostridial toxins inhibit **synaptobrevin** and related proteins in the nerve terminals. Specificity of these toxins for particular nerves is due to the larger subunit of the toxin heterodimer, which binds to surface proteins on the nerve prior to internalization. Internalization, in turn, enables the small subunit to proteolyze synaptobrevin or other target proteins. Botulinum toxin A binds to cholinergic motor nerve terminals, giving rise to flaccid paralysis. **Tetanus toxin**, also from *Clostridium*, selectively binds to and enters spinal neurons, where it blocks **glycine** release and causes spastic paralysis. Once internalized, the larger subunit functions as a selective Zn<sup>2+</sup>-dependent protease and hydrolyzes the target protein. The toxin from **black widow spider venoms** ( $\alpha$ -**latrotoxin**) promotes massive vesicle release, presumably by binding to the neurexins on the neuronal membrane (see Figure 14.4, Chapter 14).

## RATIONALE FOR TREATMENT WITH BOTULINUM NEUROTOXIN

Botulinum toxin induces weakness of striated muscles by inhibiting transmission of motor neurons at the neuromuscular junction. This has led to its use in conditions with muscular overactivity, such as **dystonia**. Transmission is also inhibited at  $\gamma$  neurons in muscle spindles, which may alter **reflex overactivity**.

The toxin also inhibits release of ACh in all parasympathetic and cholinergic postganglionic sympathetic neurons. This has fueled interest in its use as a treatment for overactive smooth muscles (for example, in **achalasia**) or abnormal activity of glands (for example, **hyperhidrosis**). Over the past 15 years, botulinum toxin has been shown to be useful in many conditions, especially strabismus and various movement disorders (Table 16.1).

Encouraging clinical reports have generated an abundance of ideas for other uses. Following are examples of overactive muscle conditions and other disorders for which treatment with botulinum toxin A has been tried (Münchau and Bhatia, 2000).

### OPHTHALMIC DISORDERS

- Disorders of ocular motility (nystagmus and oscillopsia)
- Thyroid disease (upper eyelid retraction, glabellar furrowing)
- Therapeutic ptosis for corneal protection

**TABLE 16.1**  
**Disorders Caused by Overactivity of Muscles for Which Treatment with Botulinum Toxin A Is Established**

**Ophthalmological Disorders**

Concomitant misalignment

Primary or secondary esotropia or exotropia

Nonconcomitant misalignment

Paralytic strabismus (III, IV, VI nerve palsy, internuclear ophthalmoplegia, skew deviation)

Duane's syndrome

Restrictive or myogenic strabismus

**Movement Disorders**

Idiopathic focal dystonias

Craniocervical (torticollis and isolated head tremor, blepharospasm, oromandibular dystonia, lingual dystonia, laryngeal dystonia)

Other focal dystonias (writer's cramp, occupational cramps such as musician's cramp)

Tardive dystonia

Hemifacial spasm/postfacial nerve palsy synkinesis

*Note:* Many drugs and toxins block neuromuscular transmission by other mechanisms, such as interference with the synthesis or release of acetylcholine, but most of these agents are not employed clinically for this purpose. One exception is **botulinus toxin**, which has been administered locally into muscles of the orbit in the management of **blepharospasm** and **strabismus**. This treatment produces a long-lasting interruption of neuromuscular transmission and reduction of spasmodic ocular movements. Another exception is **dantrolene**, which blocks release of  $Ca^{2+}$  from the sarcoplasmic reticulum and is used in the treatment of **malignant hyperthermia**.

**MOVEMENT DISORDERS**

- Secondary dystonia
- Tic disorders (simple tics, **Tourette's syndrome**, dystonic tics)
- Tremor (essential, primary writing, palatal, cerebellar)
- Painful spinal myoclonus
- Parkinson's disease (freezing of gait, off-period dystonia, severe constipation)
- Cephalic tetanus, **stiff man syndrome**, neuromyotonia
- Muscle stiffness, cramps, spasms

**SPASTICITY**

- Multiple sclerosis
- Stroke
- Traumatic brain injury
- Cerebral palsy
- Spinal cord injury

**NEUROMUSCULAR DISORDERS**

- Myokymia
- Neurogenic tibialis anterior hypertrophy with myalgia
- Benign cramp-fasciculation syndrome



**PAIN**

- Headache (tension type, migraine, cervicogenic)
- Backache (neck, lower back)
- Myofascial pain
- Tennis elbow

**EAR, NOSE, AND THROAT DISORDERS**

- Oromandibular disorders (**bruxism**, Masseter hypertrophy, temporomandibular joint dysfunction)
- Pharyngeal disorders (cricopharyngeal dysphagia, closure of larynx in chronic aspiration)
- Laryngeal disorders (vocal fold granuloma, ventricular dysphonia, mutational dysphonia)
- Stuttering with glottal blocks

**DISORDERS OF PELVIC FLOOR**

- Anismus
- Vaginismus
- Anal fissures
- Detrusor-sphincter dyssynergia
- Cosmetic applications

**OVERACTIVITY OF SMOOTH MUSCLES**

- Esophageal disorders (achalasia, diffuse esophageal spasm, esophageal diverticulosis)
- Sustained sphincter of Oddi hypertension
- Gastric pyloric spasms

**HYPERSECRETION OF GLANDS SUPPLIED BY CHOLINERGIC SYMPATHETIC OR PARASYMPATHETIC NEURONS**

- Ptyalism
- Increased tearing
- Hyperhidrosis (axillary, palmar, gustatory)
- Intrinsic rhinitis (see Münchau and Bhatia, 2000)

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# 17 Brussels Sprouts

## INTRODUCTION

Cancer prevention by naturally occurring substances in the diet is an area of great scientific interest. Fruits and vegetables such as brussels sprouts, cabbage, leeks, citrus, herbs and spices, and food ingredients such as antioxidant vitamins, flavonoids, glucosinolates, and organo-sulfur compounds may have antimutagenic or anticarcinogenic potential (see Chang et al., 2005).

## EFFECTS OF BRUSSELS SPROUTS ON OXIDATIVE DNA DAMAGE

The hypothesis that certain components of plant foods are protective against cancers at many sites has gained interest in the past two decades and is supported in many studies. A large number of potentially anticarcinogenic agents have been suggested in fruits and vegetables so far, e.g., fiber, vitamins C and E, **carotenoids**, **flavonoids**, **phenols**, **phytoestrogens**, **diallylsulfides**, **limonene**, and hydrolysis products of **glucosinolates**. The mechanisms by which these agents may act include dilution and binding of carcinogens in the digestive tract (fiber), antioxidant effects, inhibition of **nitrosamine formation**, inhibition of activation of promutagens/procarcinogens, induction of detoxification enzymes, alteration of hormone metabolism, and others.

One group of vegetables that has been widely regarded as potentially cancer protective are vegetables of the Cruciferae family. **Cruciferous vegetables** are the major source of glucosinolates in the diet, which distinguishes them from other vegetables. **Brassica vegetables**, including all cabbage-like vegetables, belong to a genus of the family Cruciferae and contribute most to our intake of glucosinolates.

In the 1960s interest emerged in the possibility that certain aromatic and indolic glucosinolate hydrolysis products might influence carcinogenesis. In *in vivo* experiments animals were fed glucosinolate hydrolysis products together with a carcinogen, and it was found that fewer animals developed tumors in comparison to control animals not receiving the products. From that time on, many studies have been carried out to examine the possible anticarcinogenic effect of *Brassica* vegetables and glucosinolate hydrolysis products.

Direct proof regarding whether antimutagenic or anticarcinogenic effects also occur in humans under normal dietary conditions can only be obtained from studies with humans. Indeed, epidemiological studies indicate that consumption of fruits and vegetables is inversely associated with the risk of cancer. In particular, **brassica vegetables** such as **cabbage**, **brussels sprouts**, and **broccoli** have been attributed with beneficial health effects in humans.

Oxidative DNA damage is considered an important mechanism underlying many cancers. Therefore, by reducing the amount of oxidative DNA damage, one could reduce the risk of developing cancer. The DNA adduct most abundantly formed by reactive oxygen species is **8-oxo-7,9-dihydro-2'-deoxyguanosine** (8-oxodG). *In vivo* this mutagenic lesion induced in DNA is repaired by excision. The resulting product, 8-oxodG, is excreted unchanged and independently of diet into the urine. Thus, the rate of this excretion serves as a biomarker of the integrated rate of oxidative DNA damage in the whole body.

Verhagen et al. (1997) investigated the effect of consumption of brussels sprouts on the excretion of 8-oxodG into human urine. Ten nonsmoking volunteers (five males and five females) were

randomly assigned to two groups. Five volunteers started on a diet of 300 g of **glucosinolate-free vegetables**, whereas the other five consumed 300 g of brussels sprouts per day. After 1 week, the dietary regimes were reversed. Levels of 8-oxodG in 24-h urine samples were measured by high-performance liquid chromatography. In four of five males a reduction in 8-oxodG was found, whereas in the fifth male the 8-oxodG excretion was high in the control period and was even much higher in the sprouts period. In females, no effect of consumption of brussels sprouts on excretion of 8-oxodG was found. These findings support the results of epidemiological studies that consumption of brassica vegetables may diminish cancer risk.

Brussels sprouts has putative antimutagenic and anticarcinogenic properties in humans by induction of **glutathione-S-transferase** and by decreasing the rate of **oxidative DNA damage**. These findings lend further support to the notion that brassica vegetables have health-promoting effects under normal dietary conditions and apparently without side effects. In general, the beneficial effects of fruits and vegetables have been related to their content of antioxidant vitamins, such as **vitamins C** and  **$\beta$ -carotene**, as well as other antioxidants. However, brassica vegetables differ in particular from other vegetables by the presence of **glucosinolates**. Apparently, the specific reducing effect of brussels sprouts on oxidative DNA damage may seem to be attributable to one or more of these **phytochemicals**. In addition to an induction of the detoxification enzyme **glutathione-S-transferase**, the protection against oxidative DNA damage possibly is a second mechanism underlying cancer prevention by **phytochemicals** in brassica vegetables. The urinary excretion of 8-oxodG as a biomarker for integrated oxidative DNA damage in the body allows for determination of dose–effect relationships with vegetable intake and identification of the preventive principles of fruits and vegetables, such as brussels sprouts.

The **indolyisothiocyanates** liberated from myrosinase catalyzed breakdown of, for example, **glucobrassicin** and **neoglucobrassicin**, are highly unstable and ultimately condense to products such as **indole-3-carbazole**, which are potent inducers of **cytochrome P-450 enzymes**, particularly CYP1A1 and CYP1A2 in the liver and intestine. However, in cell cultures responsive to CYP1A1 inducers, indole-3-carbazole increased 8-oxoGua formation along with the enzyme activity.

Cooked brussels sprouts — in particular an extract from these vegetables — decrease the spontaneous rate of oxidative DNA damage as shown by reduced 8-oxodG excretion. Moreover, the extract prevented **2-nitropropaine** (2-NP)-induced 8-oxodG formation, as shown by the reduced urinary excretion of 8-oxodG and the lowering of the induced nuclear levels of 8-oxodG in liver, kidney, and bone marrow. In contrast, raw brussels sprouts, noncruciferous vegetables, or isolated intact or myrosinase-degraded indolyl glucosinolates had no effect. This indicates that cooked brussels sprouts contain bioactive substances with a potential for reducing the physiological as well as oxidative stress-induced oxidative DNA modification. Remarkably, this applies to the overall DNA modification measured by urinary 8-oxodG excretion and the organ-specific changes measured by the nuclear DNA level of oxidized guanine.

In a previous study in humans, cooked brussels sprouts decreased 8-oxodG excretion, whereas noncruciferous vegetables had no effect. The data by Verhagen et al. (1997) and Deng et al. (1998) confirm and extend this observation indicating that the protective effect may be specific for cruciferous vegetables that are characterized by their content of glucosinolates. This large family of compounds and their transformation products have various potent pharmacological and toxicological effects, among which some could be responsible for the beneficial effect on oxidative DNA damage. Moreover, cooking was essential for the protective effect. Antioxidants, including **vitamin E**, **ellagic acid**, and **tea extracts** (see Chapter 38), have been shown to protect the liver from 8-oxoG induction by 2-NP, although other signs of hepatotoxicity were unaffected.

The brassica vegetables are rich in **glucosinolates**, which are hydrolyzed by **myrosinase** contained in the plants and liberated by processing and storage. Many of the resulting **isothiocyanate** breakdown products have potent pharmacological and toxicological effects. The indolyl derivatives are unstable and their further breakdown and condensation products are potent inducers of **cytochrome P-450 (CYP) enzymes**, particularly the CYP1A subfamily, and some phase II

enzymes. Other resulting **isothiocyanates** with aryl, alkyl, and/or sulfinyl side chains, such as **sulforaphane** isolated from broccoli, are potent inducers of particular phase II enzymes and may inhibit **chemical carcinogenesis**.

A specific cancer-preventive mechanism of cruciferous vegetables could be related to reduction of oxidative DNA damage, particularly guanine oxidation, which is the most abundant and mutagenic oxidative modification known. Similarly, **green tea** (see Chapter 38) and its extracts can reduce oxidative DNA damage, measured by 8-oxodG formation, induced by the **hepatocarcinogen 2-NP**. Indeed, in an intervention study in humans, 300 g of brussels sprouts as compared to noncruciferous vegetables reduced the urine excretion of 8-oxodG, a repair product of guanine oxidation and biomarker of the rate of oxidative DNA damage. The effects of cruciferous vegetables on the rate of DNA damage induced by oxidative stress and the levels of 8-oxodG in the relevant organs or surrogate tissue have not been investigated (Deng et al., 1998).



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# 18 Cannabis

## INTRODUCTION

The following are the key medical uses of **cannabis**:

- **Cannabis**, also called **marijuana**, whether ingested or smoked, has a long history of reportedly safe and effective use in the treatment and prophylaxis of migraine.
- It has a mild but definite analgesic effect in its own right.
- It seems to affect nociceptive processes in the brain, and may interact with serotonergic and other pathways implicated in migraine.
- It is an effective antiemetic, which is a useful property in migraine treatment.
- Even when abused, cannabis has mild addiction potential, and seems to be safe in moderate doses, particularly under the supervision of a physician.
- Its primary problem as a medicine lies in its possible pulmonary effects, which seem to be minimal in occasional and intermittent use.
- When inhaled, it is rapidly active, obviates the need for gastrointestinal absorption (impaired markedly in migraine), and may be titrated to the medical requirement of the patient for symptomatic relief.
- **Cannabis**, delivered by **pyrolysis**, in the form of a marijuana cigarette, or “joint,” has the hypothetical potential for quick and effective parenteral treatment of acute migraine.

There can be no doubt that a plant that has been in partnership with humans since the beginnings of agricultural efforts, that has served humans in so many ways, and that, under the searchlight of modern chemical study, has yielded many new and interesting compounds, will continue to be a part of our economy. It would be a luxury we could ill afford if we allowed uninformed prejudice to deter scientists from learning as much as possible about this ancient and mysterious plant (Alger, 2002; Baker et al., 2003; Stella, 2004).

## THE PSYCHOACTIVE EFFECTS OF CANNABIS

The hemp plant, *Cannabis sativa* (Figure 18.1), when cultivated in warm climates, develops products that affect the central nervous system, and has been used as an intoxicant in Asiatic countries and Africa from time immemorial, under the names of **hashish**, **bhang**, **ganja**, **charas**, or **churrus**. Some of the preparations are smoked either alone or mixed with tobacco; others form an intoxicating drink, and in others the plant is mixed with sugar or honey and taken as a confection.

Marijuana is the flowering tops and leaves of the hemp plant known as *C. sativa* (**grass**, **pot**, **weed**, **Mary Jane**). The dried leaves are most commonly smoked as cigarettes (**joint**, **reefer**, **doobie**, **number**) or in a pipe. The drug may be ingested orally in a prepared food (brownies) or beverage, but onset is slow (45 to 60 minutes) and absorption incomplete. Although all parts of the male and female plant contain psychoactive substances, the highest concentrations are found in the flowering tops of the female plant. The dried resinous exudate of the tops is called **hashish**. More than 60 cannabinoids have been isolated from marijuana. The euphoric and psychoactive effects may be due to a combination of several of them. However, **THC** is the agent believed to



**FIGURE 18.1** A marijuana leaf (*Cannabis sativa*) used in the preparation of marijuana cigarettes.

produce most of the characteristic effects. Hundreds of other compounds are produced by pyrolysis when marijuana is smoked and may be important in the long-term toxic effects of chronic use.

Another form of the drug, “**hashoil**,” is extracted from the plant with organic solvents and may contain a concentration of up to 50 to 60% THC. However, much of the “pure THC” or hashoil that is found on the street is often **phenyleclidine (PCP)**. The major effects of marijuana are seen in the central nervous system and range from a mild relaxation and sedation to euphoria. Intoxication with marijuana is known as **being stoned** or **high**. Users commonly describe an increased sense of well-being, giddiness, alteration of time and space perception, and subjective enhancement in senses of touch, taste, smell, and sound. Users experience unusual hunger and craving for food referred to as the **munchies**. Some users claim that the drug increases their creativity and awareness of their surroundings. Many of the subjective effects appear to depend on the expectations of the user and the circumstances under which the drug is used. Other physiological effects are a mild increase in heart rate, dry mouth and throat, dryness of the eyelids, and conjunctival reddening. Performance of simple motor tasks and reaction times are unimpaired in small doses but are significantly affected by doses equivalent to one or two cigarettes. Driving performance is clearly impaired for 4 to 8 h, well beyond the time that the user thinks the subjective effects of the drug have worn off. Impairment produced by marijuana is additive to that of alcohol if the two are used concurrently. The effects of smoking marijuana occur rapidly within 5 to 10 min, may last 2 to 3 h, depending on the dose, and are occasionally followed by a period of drowsiness.

Relative to opiates, cocaine, depressants, and hallucinogens, emergency treatment of marijuana intoxication is rare. Occasionally, a first-time user may experience a syndrome known as a **panic attack**, consisting of anxiety, disorientation, and paranoid feelings. Previous users of the milder forms of marijuana may also experience this reaction if exposed to more potent forms of cannabis THC. Treatment for this reaction is primarily reassuring and talking down the fear and panic. Placing the person in quiet surroundings and avoiding stimulants are also beneficial. Panic attacks

seldom last more than 2 to 3 h and may be relieved by small doses of **benzodiazepines** if “**talk-down therapy**” is not fully effective. Individuals with combative or aggressive behavior may have been using a product known as “**super weed,**” which is laced with PCP.

Tolerance to the effects of marijuana clearly exist even though chronic users have described a “**reversed tolerance**” and claim that smaller doses of the drug are necessary to produce the desired effects. This effect is probably related to the manner of use and the expectations of the user. Chronic, high-dose cannabis users may experience an abstinence or **withdrawal syndrome** on abrupt discontinuation of use. Signs and symptoms include irritability, restlessness, nervousness, weight loss, insomnia, and rapid eye movement (REM) rebound. Onset of this syndrome is several hours after the last dose, and it lasts 4 to 5 d. Because withdrawal is not life-threatening, treatment involves little more than supportive therapy with short-term, low doses of benzodiazepines.

In addition to the slowed psychomotor response while under the influence of the drug, there is a decrease in **short-term memory** that is reversible on discontinuing the drug. Several reported physiological effects produce concern. The respiratory effects of long-term marijuana use produce chronic cough, laryngitis, bronchitis, and pathological changes similar to those in chronic tobacco smokers. Chronic smoking of one marijuana cigarette daily will decrease vital lung capacity equal to that seen after chronic smoking of one pack of tobacco cigarettes daily. In addition, the smoke from a marijuana cigarette contains high concentrations of several key carcinogenic agents found in tobacco smoke. Another concern is the possibility of **pulmonary fibrosis** from smoking marijuana that has been sprayed with **paraquat**, other herbicides, or other insecticides. However, the latest reports indicate that smoking destroys paraquat by pyrolysis.

Other effects of marijuana are decreased **testosterone** concentrations and a **reversible decreased spermatogenesis** in males. Females experience decreased **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)** concentrations in the normal ovulatory cycle. Although THC crosses the placenta, there are no reports in humans of teratogenic effects directly attributable to marijuana alone. However, avoiding any unnecessary drug during pregnancy is advisable. Children born to mothers who were chronic marijuana smokers during pregnancy may be at increased risk for learning disabilities such as **attention-deficit disorders**. *Salmonella* and *Aspergillus* **contaminants** have been reported to produce infections.

Chronic use of marijuana has been implicated in producing psychological changes and production of what has been called an “**amotivational syndrome,**” characterized by diminished drive, ambition, and motivation; loss of effectiveness; impairment of judgment, concentration, memory, and communication skills; and inability to set goals or manage stress. Cessation may lead to gradual improvement over several weeks but may require months. It is difficult to determine whether these effects were present prior to and not caused by marijuana use, but they are observed very commonly. Several studies have implicated marijuana in structural brain damage, but much controversy exists about these. Seizures have occurred in some epileptics.

There has been much recent information on the dangers of passive tobacco smoke. Concern could also be expressed over potential problems of **passive marijuana smoke**, although intoxication is rarely reported from passive inhalation of marijuana. However, there are numerous reports of cannabis metabolites detected in the urine of the passive inhaler. THC metabolites may be present in the urine up to 2 months after heavy chronic use.

Marijuana is considered, along with alcohol and tobacco products, as one of the major “**gateway drugs.**” Although this does not imply that users of marijuana will all progress to more dangerous drugs (e.g., **cocaine**), use of one or more of these commonly available agents is part of the history of most drug abusers.

## MARIJUANA IN HISTORY

**Cannabis (Indian hemp, American hemp** [listed in the U.S.P. from 1873 to 1942]) consists of the dried flowering tops of the pistillate plants of *Cannabis sativa* Linné. The plant is an annual



herb indigenous to central and western Asia, and is cultivated in India and other tropical and temperate regions for the fiber and seed. *Cannabis* is the ancient Greek name for hemp.

Cannabis was used in China and India, spreading slowly through Persia to the Arabs, and it probably was introduced into European and American materia medica about the time of Napoleon.

The amount of resin found in the pistillate flowering tops of *C. sativa* markedly decreases as the plants are grown in more temperate climates. Thus, Indian cannabis yields 20% or more of resin; Mexican cannabis, 15% or less; Kentucky hemp, 8% or less; and Wisconsin hemp, 6% or less. The active principles are found in the resin in about the same, or even smaller, ratios as those indicated earlier. The hemp leaves contain a small amount of the resin.

Indian cannabis is prepared rather carefully from the pistillate flowerheads only, with relatively few leaves, but Mexican and American cannabis consist of the whole upper portion of the stalk of the pistillate plant. Indian cannabis may have an activity about ten times greater than that of poor-quality American cannabis.

The *U.S. Pharmacopoeia* recognized *Cannabis Americana* in a separate monograph in the 1870 and the 1880 revisions; then the monograph was deleted because of the poor quality of the drug. During World War I (1914–1918) the importation of Indian cannabis ceased, and as a war measure, American cannabis was permitted in the cannabis monograph in the U.S.P. of 1916. It remained in the monograph until the drug was deleted in 1942.

The pleasurable sensations induced in humans by the controlled use of cannabis are obtained from inhaling the smoke of burning cannabis, more promptly and with less drug, than by oral dosage. Some decades ago unscrupulous persons began the importation into the U.S. of rather crude Mexican cannabis (marijuana) cigarettes for sale at high prices. As the demand for these cigarettes increased and the habit of smoking them spread even to schoolchildren, federal and state narcotics agents started a campaign to stamp out their sale. The importation of Indian cannabis was prohibited, and even large areas of growing American hemp were destroyed. This campaign has been successful; however, the official substitution of a poor-quality drug for the high-quality Indian cannabis, along with the marijuana campaign, has cost the materia medica a valuable drug, for the medicinal use of cannabis in the U.S. has been discontinued. The therapeutic potential of marijuana as an analgesic, antimigraine medication, and antiemetic is being rediscovered.

### BOTANICAL PROPERTIES OF *CANNABIS INDICA* OR INDIAN CANNABIS (INDIAN HEMP)

Hemp is an annual plant, 4 to 8 ft or more in height, with an erect, branching, angular stem. The leaves are alternate or opposite, on long, lax footstalks, roughish, and digitate, with linear-lanceolate, serrated segments. The stipules are subulate. The flowers are axillary; the male hemp in long, branched, drooping racemes; the female hemp in erect, simple spikes. The stamens are five, with long pendulous anthers; the pistils two, with long, filiform, glandular stigmas. The fruit is ovate and one-seeded. The whole plant is covered with a fine pubescence, scarcely visible to the naked eye, and somewhat viscid to the touch. The hemp plant of India, from which the drug is derived, has been considered by some as a distinct species, and named *C. indica*; but the most observant botanists, upon comparing it with our cultivated plant, have been unable to discover any specific difference. It is now, therefore, regarded merely as a variety, and is distinguished by the epithet *indica*.

The seeds have been used in medicine. They are about 1/8 in. long, roundish-ovate, somewhat compressed, of a shining ash-gray color, and of a disagreeable, oily, sweetish taste. They yield by expression about 20% of a fixed oil, which has a drying property, and is used in the arts. They contain also uncrystallizable sugar and albumen, and when rubbed with water form an emulsion, which may be used advantageously in inflammations of the mucous membranes, although without narcotic properties. The seeds are much used as food for birds, as they are fond of them. They are generally believed to be in no degree poisonous.

In India, Iran, and other parts of the East, hemp has long been habitually employed as an intoxicating agent. The parts used are the tops of the plant, and a resinous product obtained from them. *Ganja* or *gunjah* is at the top of cultivated female plants, cut while unfertilized directly after flowering, and formed into bundles from 2 to 4 ft long by 3 in. in diameter. The utmost care is taken to prevent fertilization, it being affirmed that a single male plant will spoil a whole field. When hemp is cultivated in India for its fiber or seed, male and female plants are grown together.

The name *bhang* is given to a mixture of the larger leaves and capsules, without the stems, of wild plants, male and female. There is on the surface of the plant a resinous exudation, which gives it a clammy feel. Men clothed in leather run through the hemp fields, brushing forcibly against the plants, and thus separating the resin, which is subsequently scraped from their dress and formed into balls. These balls and also masses formed out of resin mechanically separated from **gunjah bundles** are called *charas*. In these different states of preparation, the hemp is smoked similar to tobacco, with which it is said to be frequently mixed. *Momea* or *mimea* is a hemp preparation said to be made in Tibet with human fat. An infusion or decoction of the plant is also sometimes used as an “**exhilarating drink**.”

**Fresh hemp** has a peculiar narcotic odor, which is said to be capable of producing vertigo, headache, and a species of intoxication. It is much less in the dried tops, which have a feeble bitter taste. *Charas* is pure when of a blackish-gray, blackish-green, or dirty olive color, with a fragrant and narcotic odor and a slightly warm, bitterish, and acrid taste. The Indian hemp is officially described as branching, compressed, brittle, about 5 cm or more long, with a few digitate leaves, having linear-lanceolate leaflets, and numerous sheathing, pointed bracts, each containing two small, pistillate flowers, sometimes with the nearly ripe fruit, the whole more or less agglutinated with a resinous exudation.

## MARIJUANA-INDUCED INEBRIATION

The effects of marijuana in humans are identical for oral administration (about 2 grains of the solid extract) and for smoking. The inebriation sets in rather abruptly, after a latent period of about an hour, in which there may be temporary digestive phenomena, anorexia, dryness, or burning thirst. The phenomena differ in kind as well as in degree according to the individual personality and disposition, the surroundings, and the mental preparation. The **emotional sphere** develops euphoria, expansiveness, gaiety, and less commonly, anxiety. Waves of exaltation sweep over the consciousness and may alternate precipitously with fear and terror. The individual is likely to be quarrelsome and violent if crossed. In the subjective sphere, a feeling of unreality is among the first effects, with a consciousness of double personality. Objects and sensations appear exaggerated in size and in degree, the limbs lengthened, the head swollen, the body alternately light and heavy, time enormously lengthened. **Motor excitement** and restlessness vary in different persons; tremors of the tongue and fingers, and muscular rigidity may occur. The **pupils** become widely dilated and barely react to light. The eyes appear glazed, the conjunctiva congested, and the lids reddened. The pulse is generally rapid, with marked palpitation. **Mental confusion** may deepen to visual illusions and hallucinations. The imagery is apt to become terrifying in the dark. **Aphrodisiac desire**, rather than impulse, occurs in some and not in others. The **after effects** are generally light. The exaltation is succeeded by irritability and somnolence, and after some hours by sleep, from which the subject awakens hungry and thirsty, with a clear recollection of the episodes. **Toxic doses** cause vertigo and collapse, with soft arrhythmic pulse, and blood concentration sometimes to 50%. Serious poisoning is rare because the margin between the effective and fatal dose is wide; the intravenous fatal dose for dogs is a hundred times the narcotic dose.

Addiction to cannabis is usually casual, because psychopathic individuals tend to drop it for a more potent narcotic. It generally takes the form of an occasional hedonistic indulgence, whose chief danger lies in the introduction to more serious addictions. No relation to criminal offenses, sexual or other, has been established. Physical consequences are no more significant than with

tobacco. Digestive disturbances and marasmus are not prominent. Conjunctival congestion is common. There is apparently no material tolerance, either in humans or in animals, nor are there withdrawal symptoms, except in extreme cases. Insanity is a rare sequel, and in these the cannabis is probably only a provocative agent that unveils the latent psychopathy. **Psychopathic individuals** react to cannabis as do normal individuals, but usually become more self-absorbed and less communicative, in contrast to their response to cocaine and amylal (Sollmann, 1944).

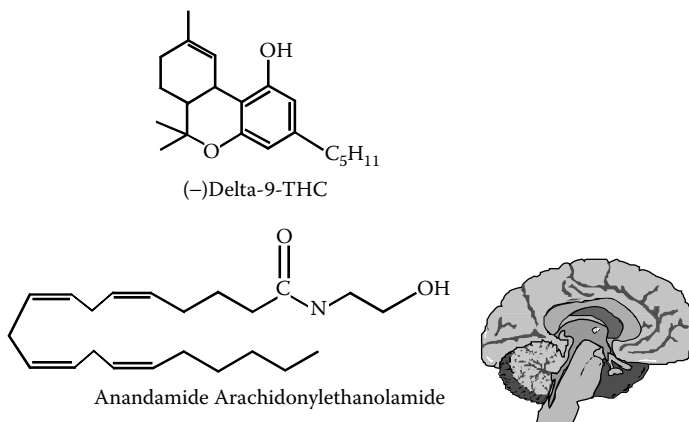
In summary, subjective effects of smoking marijuana usually include elation and a tendency to be amused easily. Occasionally, there may be feelings of depersonalization with detachment from reality, but overt behavior is usually limited to giggling, singing, and dancing. The conjunctiva are reddened and the upper lids become ptotic, giving an appearance of sleepiness. Appetite is enhanced. In susceptible individuals, toxic psychoses may occur with acute mania and convulsions. No great degree of tolerance to the drug develops, and no abstinence syndrome follows its withdrawal.

Death from acute poisoning is extremely rare, and recovery has occurred after enormous doses. It has been observed in the East that the continued abuse of hashish sometimes leads to mania and dementia.

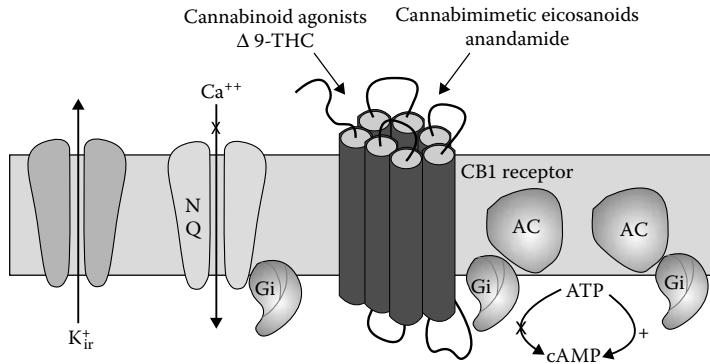
### CANNABINOID RECEPTOR SUBTYPES

$\Delta^9$ -Tetrahydrocannabinol ( $\Delta^9$ -THC) is considered to be the predominant compound in preparations of *C. sativa* (marijuana, hashish, bhang) that is responsible for the central nervous system effects in humans. The recognized central nervous system responses to these preparations include alterations in cognition and memory, euphoria, and sedation. Potential therapeutic applications of **cannabis** preparations that are of either historical or contemporary interest include analgesia, attenuation of the nausea and vomiting of cancer chemotherapy, appetite stimulation, decreased intestinal motility of diarrhea, decreased bronchial constriction of asthma, decreased intraocular pressure of glaucoma, antirheumatic and antipyretic actions, and treatment of convulsant disorders. These effects have been reviewed recently (Howlett, 1995).

Two subtypes of **cannabinoid receptors**, CB<sub>1</sub> and CB<sub>2</sub>, have been described to date, although future investigations may elucidate other receptors. Actions of cannabimimetic agents via CB<sub>1</sub> receptors in brain are mediated by G<sub>I/O</sub> to inhibit adenylate cyclase and Ca<sup>2+</sup> channels. Little is known about signal transduction mechanisms utilized by CB<sub>2</sub> receptors. Three classes of agonist ligands regulate cannabinoid receptors: **cannabinoid**, **aminoalkylindole**, and **eicosanoid derivatives**. Cannabinoid receptors produce analgesia and modify cognition, memory, locomotor activity, and endocrine functions in mammals (Figure 18.2 and Figure 18.3).



**FIGURE 18.2** Chemical structures of  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) derived from marijuana, and the endogenous cannabimimetic eicosanoid, anandamide (arachidonylethanolamide), identified in the human brain.



**FIGURE 18.3**  $\Delta^9$ -THC and anandamide bind to the CB<sub>1</sub> cannabinoid receptor and stimulate receptor coupling to heterotrimeric guanine nucleotide binding proteins Gi and Gs and subsequent activation or inhibition of signal transduction effectors. The receptor is a single subunit polypeptide that spans the plasma membrane seven times. The CB<sub>1</sub> receptor couples to the inhibition of adenylate cyclase and Q-type voltage-dependent calcium channels through Gi, and to the stimulation of adenylate cyclase through Gs. CB<sub>1</sub>-receptor-mediated stimulation of inwardly rectifying potassium channels may be a consequence of cAMP formation and independent of G protein coupling.

### CANNABINOID RECEPTOR (CB<sub>1</sub>)

The first identified cannabinoid receptor subtype, CB<sub>1</sub>, was cloned and demonstrated to have an amino acid sequence consistent with a tertiary structure typical of the seven transmembrane-spanning proteins that are coupled to G proteins. In addition to being found in the central nervous system, mRNA for CB<sub>1</sub> has also been identified in testes. The central nervous system responses to cannabinoid compounds are believed to be mediated exclusively by CB<sub>1</sub>, inasmuch as CB<sub>2</sub> transcripts could not be found in brain tissue by either Northern analysis or *in situ* hybridization studies. CB<sub>1</sub> transduces signals in response to central-nervous-system-active constituents of *C. sativa* as well as synthetic bicyclic and tricyclic cannabinoid analogs, **aminoalkylindole**, and **eicosanoid cannabimimetic compounds**. CB<sub>1</sub> is coupled to G<sub>i</sub> to inhibit adenylate cyclase activity and to a pertussis-sensitive G protein to regulate Ca<sup>2+</sup> currents.

### CANNABINOID RECEPTOR (CB<sub>2</sub>)

The second cannabinoid-binding seven-transmembrane-spanning receptor, CB<sub>2</sub>, exhibits 68% identity to CB<sub>1</sub> within the helical regions, and 44% identity throughout the total protein. The CB<sub>2</sub> clone was derived from a **human promyelocytic leukemia cell** HL60 cDNA library. The rat or human CB<sub>2</sub> clones were able to hybridize with mRNA in undifferentiated HL60 cells and in HL60 cells that had been differentiated into granulocytes or macrophages. Probes also hybridized with a splenic macrophage/monocyte preparation but not to splenic T cells. Northern blots detected CB<sub>2</sub> mRNA from spleen, but not from mature blood neutrophils, thymus, liver, brain, lung, or kidney, indicating that the distribution is distinct from that of CB<sub>1</sub>. Probes derived from CB<sub>1</sub> have identified a signal in splenocytes and mononucleocytes after reverse transcription–polymerase chain reaction amplification. At present it is unclear which are the cell types that express CB<sub>1</sub> or CB<sub>2</sub>. The relative abundance of each subtype within immune or other tissues is also known.

## CANNABINOID RECEPTORS AND THEIR ENDOGENOUS AGONIST, ANANDAMIDE

Analogous to the discovery of endogenous opiates, isolation of cannabinoid receptors provided the appropriate tool to isolate an endogenous **cannabimimetic eicosanoid, anandamide**, from porcine

**TABLE 18.1**  
**Evidence for an Interaction between the Cannabinoid–Anandamide System and Other Neuroreceptor Systems**

$\Delta^9$ -Tetrahydrocannabinol (THC) and anandamide enhance  $\gamma$ -aminobutyric acid (GABA)ergic neurotransmission

The cannabinoid receptor gene is under the negative control of dopamine receptor-mediated events

THC regulates substance P and enkephalin messenger RNA (mRNA) levels in the caudate putamen

Dizocilpine (MK-801; a noncompetitive antagonist of *N*-methyl-D-aspartate receptors) ameliorates THC-induced catalepsy  
 The mRNA for the cannabinoid receptor in the caudate putamen of adrenalectomized rats is 50% higher than that in control animals

Anandamide and THC significantly increase serum levels of corticotrophin (ACTH) and corticosterone in a dose-dependent manner

*Note:* The cannabis plant has been cultivated for centuries both for the production of hemp fiber and for its presumed medicinal and psychoactive properties. The smoke from burning cannabis contains many chemicals, including 61 different cannabinoids that have been identified. One of these,  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), produces most of the characteristic pharmacological effects of smoked marijuana.

brain. Recent studies indicate that **anandamide** is a member of a family of fatty acid ethanolamides that may represent a novel class of lipid neurotransmitters (see Figure 18.2 and Figure 18.3; Axelrod and Felder, 1998).

The cannabinoid–anandamide system interacts with several neuroreceptor systems (Table 18.1).

## CENTRAL NERVOUS SYSTEM CANNABINOID RECEPTORS

*Cannabis sativa* was one of the first plants to be used by humans to treat a wide range of medical conditions. In the early 19th century, O’Shaughnessy demonstrated that many of the therapeutic claims for cannabis that had arisen as a result of its use in Indian medicine (such as treatment of cramps, convulsions in children, migraine, neuralgia, and tetanus) were well founded. His reports made “**Indian hemp**” an accepted therapeutic agent, first in England and later in other European countries and North America. Indeed, Reynolds, a noted English physician, stated that “Indian hemp when pure and administered carefully is one of the most valuable medicines we possess” (Mechoulam et al., 1994).

Around the turn of the century, the medical use of cannabis declined because reproducible clinical effects could not be obtained. At that time, the active constituent in cannabis had not been isolated in pure form. Instead, plant extracts were generally used and these were known to deteriorate rapidly, thus accounting for the nonreproducible effects.

Work on the medicinal use of cannabis restarted when the major, and essentially only, psychoactive constituent of cannabis, **THC** (see Figure 18.2), was isolated in pure form. The structure of THC was elucidated in 1964. Simple synthetic routes became available and the pharmacological activity of numerous cannabinoids was examined in animals and humans.

A long list of potential therapeutic effects was recorded for THC, including **analgesic, bronchodilatory, antiemetic, anticonvulsant, and anti-inflammatory action, reduction of intraocular pressure, and alleviation of some neurological conditions** (such as seizure disorders, spasticity associated with spinal cord injuries, and multiple sclerosis) (Mechoulam et al., 1994).

## THERAPEUTIC POTENTIAL OF CANNABINOID LIGANDS

### MOVEMENT DISORDERS

Autoradiographic localization of brain cannabinoid receptors using a labeled probe has revealed a unique distribution. Binding is most dense in the outflow nuclei of the basal ganglia, in the substantia nigra pars reticulata, the globus pallidus, the hippocampus, and cerebellum.

The high levels recorded in the basal ganglia and cerebellum, regions that coordinate motor functions, strongly suggest that the **cannabinoid–anandamide system** is involved in this activity. This is supported by the wide spectrum of neurological effects of cannabis or THC in laboratory animals (impaired coordination and balance, decreased muscle tone and reflexes, and, at higher doses, tremor, myoclonic jerks, muscle spasms, and convulsions). In humans, uncoordinated movements, muscle weakness, and tremulousness are frequently observed after cannabis use.

At present, there is no approved medical use for cannabis in patients with neurological disorders. However, it is illegally used for **spasticity** and ataxia in patients with **multiple sclerosis** and **spinal cord injury**, and for the treatment of **trigeminal nerve pain** and, to a lesser extent, **attention deficit hyperactivity disorder**. Individuals with spinal cord injury have reported a reduction in spasticity after cannabis use.

## MULTIPLE SCLEROSIS

The effect of THC in patients with multiple sclerosis has been investigated in a placebo-controlled, double-blind, crossover trial involving nine patients who were orally administered placebo or THC 5 to 10 mg/d. Clinical and electromyographic measurements indicated a significant reduction in spasticity, with negligible adverse effects. In another trial, patients with multiple sclerosis reported subjective improvement of tremor and sense of well-being. Smoking cannabis was reported to result in symptomatic improvement, as judged by clinical rating, electromyographic investigation of leg flexor reflexes, and recording of hand action tremor, in a single patient with multiple sclerosis.

The ability of THC to suppress the effects of **experimental autoimmune encephalomyelitis (EAE)**, the laboratory model of multiple sclerosis, has been investigated in Lewis rats and guinea pigs. All animals treated with placebo developed severe clinical EAE 10 to 12 d postinjection of myelin and more than 98% died. THC-treated animals had either no clinical signs or mild signs with delayed onset, with survival greater than 95%. Examination of central nervous system tissues revealed a marked reduction of inflammation in the THC-treated animals. Multiple sclerosis is considered to be an autoimmune disease. Because the cannabinoid CB<sub>2</sub> receptor has been found in the spleen (an organ involved in the immune system), it is possible that the effect of THC on multiple sclerosis is mediated through both CB<sub>1</sub> and CB<sub>2</sub> receptors.

## HUNTINGTON'S CHOREA

A major effect of **Huntington's chorea** is the loss of neostriatal neurons, accompanied by the loss of dopamine D<sub>1</sub> receptors. A group of investigators has found that this loss of neurons also causes a 97.5% reduction of CB<sub>1</sub> receptors in the substantia nigra pars reticulata. On the basis of these data, the authors have suggested a role for cannabinoids in the control of movement in, and possibly in the therapeutics or symptomatology of, **hyperkinetic** and **dystonic disorders**, such as Huntington's disease, as well as in the treatment of Parkinson's disease.

## NEUROPROTECTION

Cannabinoids may also cause effects via mechanisms distinct from the cannabinoid receptor pathways. The most extensively investigated compound is (+)-HU 211, a synthetic cannabinoid with a stereochemistry opposite to that present in the naturally occurring compounds. It does not produce THC-type effects in animals and shows insignificant binding to the CB<sub>1</sub> receptor. However, HU 211 blocks **N-methyl-D-aspartate (NMDA) receptors** and calcium uptake through the NMDA-receptor-ion channel in primary cell cultures. HU 211 is a potent blocker of NMDA-induced tremor, seizures, and lethality in mice. It may therefore prove useful as a nonpsychoactive drug that protects against NMDA-receptor-mediated neurotoxicity. This is supported by the potent attenuation of NMDA-receptor-mediated neurotoxicity in cell cultures by HU 211.

Cerebroprotective effects of HU 211 have been demonstrated after experimental closed head trauma in rats. The drug is very effective in improving recovery of motor function. The drug was given 1 or 2 h after the trauma, and the clinical status was evaluated 24 and 48 h later. The percentage of rats able to perform a beam-walking task increased significantly. The drug was also effective in reducing by more than fourfold, the blood–brain barrier breakdown that is observed during head trauma. It also attenuates cerebral edema.

## CANNABIS FOR MIGRAINE

Cannabis, or marijuana, has been used for centuries for both symptomatic and prophylactic treatment of **migraine**. It was highly esteemed as a headache remedy by the most prominent physicians of the age between 1874 and 1942, remaining part of the Western pharmacopoeia for this indication even into the mid-20th century. Current ethnobotanical and anecdotal references continue to refer to its efficacy for this malady, and biochemical studies of THC and anandamide have provided a scientific basis for such treatment (Russo, 1998).

## ANTIEMETIC EFFECTS OF CANNABIS

### THE PHYSIOLOGY OF VOMITING

The physiological purpose of nausea is to discourage food intake, and vomiting is meant to expel food or other toxic substances present in the upper part of the gastrointestinal tract. Protracted vomiting may not only cause electrolyte imbalance, dehydration, or a malnutrition syndrome, but may also lead to mucosal laceration and upper gastrointestinal hemorrhage (**Mallory–Weiss syndrome**).

Nausea and vomiting may occur when the stomach is overly irritated, stimulated, or distended (from overeating). In addition, nausea and vomiting may occur when the **chemoreceptor trigger zone for emesis** or the vomiting center, or both, are directly stimulated.

Pharmacological agents such as aspirin and L-dopa may cause vomiting by directly irritating the stomach. Agents such as aminophylline, isoniazid, reserpine, anti-inflammatory steroids, and caffeine may also elicit vomiting in susceptible individuals by causing the release of hydrochloric acid. This drug-induced emesis may be avoided by having patients take the drugs with meals. Antiemetics are not effective in rectifying these conditions and their use is not justified.

### THE CENTRAL CONTROL OF VOMITING

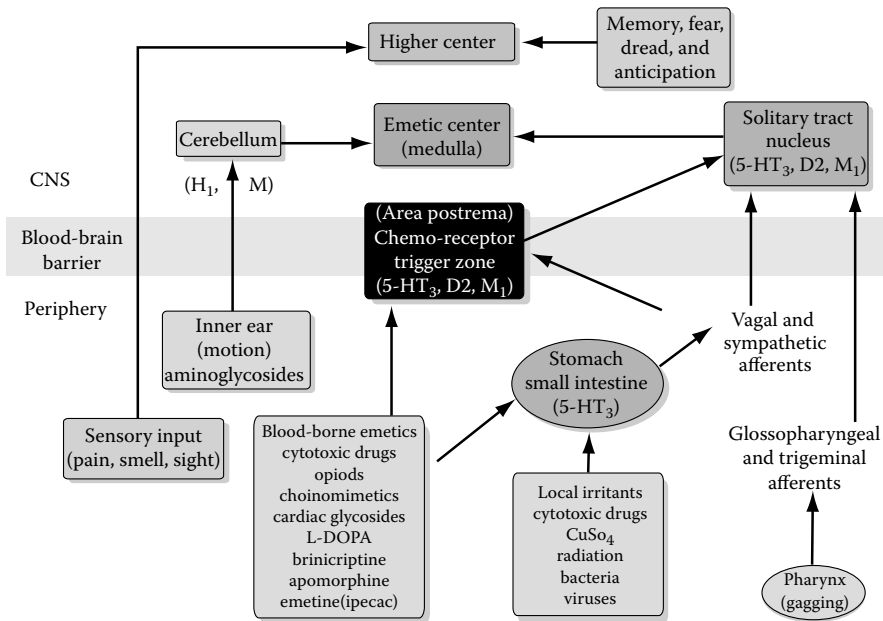
In addition to agents that stimulate or irritate the stomach, many other factors may be responsible for inducing emesis centrally. The central control of vomiting is vested in two areas:

1. The **vomiting center**, which is located in the lateral reticular formation in the midst of a group of cells governing such activities as salivation and respiration
2. The **chemoreceptor trigger zone**, which is a narrow strip along the floor of the fourth ventricle located close to the vomiting center

The functions of these two areas are distinct but interdependent.

The vomiting center is activated by impulses that originate from the gastrointestinal tract and other peripheral structures. In addition, there are unidentified tracts that extend from the cerebral cortex to the vomiting center, such that emotional trauma and unpleasant olfactory and visual stimuli may cause nausea and vomiting.

Stimulation of the vestibular apparatus that responds to movements of the head, neck, and eye muscles may also cause nausea and vomiting by stimulating the vomiting center. On the other hand, circulating chemicals, toxins, viruses, and ions may provoke nausea and vomiting by first stimulating the chemoreceptor zone for emesis, which in turn stimulates the vomiting center (Figure 18.4).



**FIGURE 18.4** Pharmacologist's view of emetic stimuli. Myriad signaling pathways lead from the periphery to the emetic center. Stimulants of these pathways are noted in *italics*. These pathways involve specific neurotransmitters and their receptors (**bold** text). Receptors are shown for: dopamine, D; acetylcholine (muscarinic), M; histamine, H; and 5-hydroxytryptamine, 5-HT. Some of these receptor types also may mediate signaling in the emetic center. This knowledge offers a rationale for current antiemetic therapy.

## DRUGS TO CONTROL THE VOMITING CAUSED BY CANCER THERAPY

Several currently available antiemetic drugs can prevent vomiting caused by cancer chemotherapy. Anticancer drugs that cause vomiting are listed in Table 18.2.

### ONDANSETRON

Ondansetron antagonizes the action of serotonin at receptors in the upper gastrointestinal tract and in the chemoreceptor trigger zone of the central nervous system. Given intravenously (IV), it prevents vomiting completely for 24 h in 40% of patients treated with high doses (>100 mg/m<sup>2</sup>) of **cisplatin** and in 70 to 80% of patients treated with 50 to 100 mg/m<sup>2</sup> of cisplatin or a combination of **cyclophosphamide** and **doxorubicin**.

Ondansetron is also available in an oral formulation, which can be used for mildly or moderately emetogenic chemotherapy. In one double-blind trial in 318 patients taking combinations of cyclophosphamide with methotrexate and/or doxorubicin, oral ondansetron 1, 4, or 8 mg t.i.d. for 3 d was completely effective in preventing emesis in 57, 65, and 66% of patients, respectively, compared to 19% who did not vomit with placebo.

Ondansetron generally does not cause severe toxicity. Headache and constipation are the most frequent **adverse effects**. Light-headedness, dizziness, and transient increases in serum aminotransferase activity can occur. Extrapyramidal effects have occurred rarely, and anaphylactoid reactions have been reported.

### DEXAMETHASONE

How **corticosteroids** prevent vomiting is unclear, but many studies have confirmed the effectiveness of a single dose of dexamethasone against a variety of anticancer agents. A randomized trial found



**TABLE 18.2**  
**Vomiting with Anticancer Drugs**

Severe	Moderate	Mild
Cisplatin (Platinol)	Carboplatin (Paraplatin)	Bleomycin (Blenoxane)
Cyclophosphamide (Cytosan, others) — high dose	Garmustine (BiCNU)	Chlorambucil (Leukeran)
Cytarabine (Cytosar-U, others) — high dose	Cyclophosphamide (Cytosan)	Cytarabine (Cytosar-U)
Dacarbazine (DTIC-Dome, others)	Dactinomycin (Cosmegen)	Etoposide (VePesid)
Mechlorethamine (Mustargen)	Daunorubicin (Cerubidine)	Fluorouracil (Adrucil, others)
Streptozocin (Zanosar, others)	Doxorubicin (Adriamycin, others)	Hydroxyurea (Hydrea)
	Idarubicin (Idamycin)	Melphalan (Alkeran)
	Ifosfamide (Ifex)	Methotrexate (Folex, others)
	Lomustine (CeeNU)	Paclitaxel (Taxol)
	Mitomycin (Mutamycin)	Plicamycin (Mithracin)
	Mitoxantrone (Novantrone)	Thioguanine
	Pentostatin (Nipent)	Vinblastine (Velban, others)
	Procarbazine (Matulane)	Vincristine (Oncovin, others)

*Note:* Antineoplastics are often given in combination. Dose, route, and schedule of administration also affect the incidence and intensity of nausea and vomiting.

low doses of dexamethasone (Decadron, and others) alone equivalent to low doses of ondansetron alone for control of acute emesis in patients receiving moderately emetogenic chemotherapy that included cyclophosphamide and/or doxorubicin. A double-blind crossover trial found that IV ondansetron given with dexamethasone to patients treated with cisplatin ( $\geq 50$  mg/m<sup>2</sup>) prevented vomiting for 24 h in 81 (91%) of 89 patients, compared to 57 (64%) who did not vomit with ondansetron alone.

Short courses of dexamethasone generally cause no **adverse effects**, although rapid injection can cause intense genital or perineal pain. Mild insomnia and epigastric discomfort can occur.

### METOCLOPRAMIDE

Metoclopramide (Reglan, and others) is both a serotonin- and dopamine-receptor antagonist. Given alone, it is less effective than IV ondansetron. Given concurrently with dexamethasone and either the antianxiety agent lorazepam (Ativan, and others) or the antihistamine **diphenhydramine** (Benadryl, and others), it can control emesis due to high-dose cisplatin (120 mg/m<sup>2</sup>) in older adults. One study in older patients, however, found metoclopramide, dexamethasone, and diphenhydramine less effective than IV ondansetron combined with dexamethasone in patients taking  $\geq 50$  mg/m<sup>2</sup>

of cisplatin. Another double-blind study found metoclopramide combined with dexamethasone at least as effective as oral ondansetron in women receiving cyclophosphamide-containing regimens.

**Metoclopramide can cause adverse effects such as sedation, akathisia** (motor restlessness), involuntary movements, diarrhea, and dizziness. The extrapyramidal reactions, which are more common in patients  $\leq 30$  years old, can be relieved by intravenous or oral **diphenhydramine** or **benztropine** (Cogentin).

## PHENOTHIAZINES

Prochlorperazine (Compazine, and others) can be effective for prevention of vomiting due to cancer chemotherapy, but is generally less so than dexamethasone or metoclopramide. Phenothiazines can cause orthostatic hypotension, sedation, dystonic reactions, and akathisia.

## Cannabinoids

Dronabinol ( $\Delta^9$ -**tetrahydrocannabinol**; THC; **Marinol**) is FDA approved for treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetics. With mildly or moderately emetogenic chemotherapy, it is more effective than placebo and equivalent or superior to oral prochlorperazine. Dry mouth, sedation, orthostatic hypotension, ataxia, dizziness, and dysphoria occur frequently, particularly in middle-aged and older patients.

## Benzodiazepines

**Lorazepam** (Ativan, and others) is used as an adjunct to antiemetic regimens, particularly in patients with anticipatory vomiting. **Alprazolam** (Xanax) has also been used as an adjunct. Benzodiazepines can cause somnolence and amnesia lasting for several hours, which may be beneficial.

## ANTICIPATORY NAUSEA AND VOMITING

If chemotherapy-associated nausea and vomiting are not well controlled, some patients develop nausea and vomiting in anticipation of their next chemotherapy treatment. This conditioned response, once it occurs, is often difficult to treat. Adequate early antiemetic treatment, particularly with regimens that include a benzodiazepine, may prevent this reaction.

## DELAYED EMESIS

Even after an effective regimen for prophylaxis, nausea or vomiting can begin again or persist 24 h or more after chemotherapy, particularly with cisplatin. Concurrent use of oral dexamethasone (8 mg twice daily for 2 d, then 4 mg twice daily for 2 d) and oral metoclopramide (0.5 mg/kg four times daily for 4 d) has been effective for this condition. Ondansetron alone has not been effective for treatment of delayed emesis following high doses of cisplatin.

## MULTIPLE-DAY CISPLATIN CHEMOTHERAPY

Many chemotherapeutic regimens include cisplatin for 4 or 5 d. Concurrent intravenous ondansetron and dexamethasone in two studies prevented emesis in 58 and 66% of patients for the entire 5-d period (see Table 18.3).

## SUMMARY

Intravenous ondansetron combined with dexamethasone, with or without lorazepam, is the most effective treatment available for prevention of severe vomiting due to cancer chemotherapy and

**TABLE 18.3**  
**Dosage and Cost of Antiemetic Drugs**

Drug	Dosage <sup>a</sup>	Cost <sup>b</sup>
Ondansetron — Zofran	0.15 mg/kg IV q2–4h × 3 or 32 mg IV once <sup>c</sup>	\$207.50 <sup>d</sup>
	8mg PO tid <sup>e</sup>	53.50
Dexamethasone	20mg IV once	
Generic — average price		3.65
Decadron		27.89
Metoclopramide	1–3 mg/kg IV q2h × 2–6	
Generic — average price		30.60
Reglan		36.32
Prochlorperazine	10mg IV q4–6h × 4	
Generic — average price		10.60
Compazine		25.44
Dronabinol — Marinol	10mg PO q3–4h × 4	47.84
Lorazepam — Ativan	1–2 mg IV once	6.01

<sup>a</sup> Beginning 1/2 h before chemotherapy.

<sup>b</sup> Cost to the pharmacist for the lowest recommended dosage for a 70-kg patient, according to average wholesale price.

<sup>c</sup> Based on cost of a 20-ml vial containing 40 mg.

<sup>d</sup> An 8-mg IV dose may be equally effective in some patients.

<sup>e</sup> Four mg t.i.d. may be effective in some patients.

causes little toxicity. Metoclopramide is less effective than ondansetron and can cause extrapyramidal effects, but it is much less expensive and, used together with dexamethasone and lorazepam, is often effective, particularly for older patients and those taking less emetogenic drugs.

## CANNABIS FOR DYSKINESIA

Archeological records chronicle the ancient association of man with the plant genus *Cannabis*, of the plant family Cannabaceae. The use of cannabis fibers for the production of hemp has been dated to 4000 B.C. using carbon-14 methods. Seeds and pollen of the plant have been found in tombs, their leaves painted on funerary urns. The plant has been so well cultivated that a wild variant no longer exists.

Sir William Brooke O'Shaughnessy introduced Indian hemp to the West in 1839. William Brooke O'Shaughnessy entered the service of the East India Company in 1833 as assistant surgeon. He studied the botany and chemistry of herbs used in oriental medicine and incorporated some into his edition of the *Bengal Pharmacopoeia* published in 1842. One of these herbs was cannabis, or Indian hemp. His medical treatise recommended an extract from the plant for patients with rabies, cholera, tetanus, and infantile convulsions. Until the end of the 19th century prominent physicians of Europe and North America advocated cannabis extracts for the prevention and symptomatic treatment of migraine headache.

Between 1874 and 1942 it was highly esteemed as a headache remedy by most prominent physicians of the age. Although the American Medical Association vigorously opposed the action, cannabis became essentially illegal in 1937. Whether or not the plant became a scapegoat for a perceived social problem, research funding was curtailed. In 1941, preparations of cannabis were dropped from the United States Pharmacopoeia (USP) and the National Formulary. Yet a year later, the *Journal of the American Medical Association* advocated that oral preparations of cannabis be prescribed for the relief of menstrual migraine.

Pharmacologists from outside the U.S. may be more willing to see the merits of the age-old remedy. Two researchers from the Institute of Pharmacology at the Academy of Sciences in the Czech Republic of Prague contended 5 years ago:

Cannabinoids might alleviate some parkinsonian symptoms by their remarkable receptor-mediated modulatory action in the basal ganglia output nuclei. Moreover, it was recently observed that some cannabinoids are potent antioxidants that can protect neurons from death even without cannabinoid receptor activation. It seems that cannabinoids could delay or even stop progressive degeneration of brain dopaminergic systems, a process for which there is presently no prevention.

In the 1990s, researchers discovered the psychoactive principle in cannabis attached to two specific membrane receptor sites within the brain and body to produce drug effects. Why the body should harbor receptors for a substance not an integral part of the human organism was soon answered. Identified also were two “endogenous ligands” or endocannabinoids, called *anandamide* and 2-arachidonoylglycerol, in addition to enzymes for their creation and inactivation, and the signaling system upon which they operate. The endocannabinoids are compounds with the same psychoactive effects as cannabis and attach at the same cellular sites. The term *endocannabinoid* is used for the body-produced substance because cannabis attaches to its unique cellular sites.

Similar to opioids, the cannabinoid system appears to be intricately involved in normal physiology, specifically in the control of movement, formation of memories, and appetite control. Basic research has discovered that members of this family of compounds have the capacity to protect threatened neurons, thereby slowing neurodegenerative processes that ultimately lead to physical disability. As the function of the physiological role of endocannabinoids becomes clearer, it appears the system may be involved in the pathology of several neurological diseases, specifically multiple sclerosis, spasticity, and pain. In 1999 the German journal, *Forschende Komplementärmedizin und Klassische Naturheilkunde* (Research in Complementary and Classical Natural Medicine) commented:

Despite the lack of controlled studies, there is evidence that cannabinoids are of therapeutic value in the treatment of tics in Tourette syndrome, the reduction of levodopa-induced dyskinesia in Parkinson’s disease, and some forms of tremor and dystonia.

Parkinson’s disease (PD) is a chronic neurodegenerative illness characterized by dopaminergic neuronal loss in the basal ganglia. However, several other neurotransmitters — serotonin, gamma-amino-butyric acid (GABA), and glutamate — are involved in the symptoms of PD and each individual response to levodopa treatment. Scientists have speculated about the close proximity between cannabinoid and dopamine receptors lying within the basal ganglia. The wide receptor distribution within the striatum provides the framework for interactions of endogenous cannabinoids, such as anandamide and arachidonoylglycerol, with the dopaminergic nigrostriatal pathway (which degrades in PD). They see a potential role for endocannabinoids (created by the body) in the control of voluntary movement in PD. The feedback channels, or signaling systems used by cannabinoid receptors and their endogenous ligands are mostly inhibitory, suggesting a role for cannabinoids as therapeutic agents in CNS disease where inhibition of neurotransmitter release would be beneficial. The main function of the endocannabinoid system is to regulate synaptic transmission in excitatory and inhibitory pathways in the brain. In PD when the neurotransmitter dopamine becomes scarce, neurons normally activated no longer fire. The balance between dopamine and acetylcholine becomes skewed. Excessive excitatory output triggered by undampened acetylcholine results in the slowness and rigidity seen in PD. Evidence suggests cannabinoids may prove useful in PD by inhibiting the excitotoxic (the property of exciting, then poisoning cells) neurotransmitter glutamate and counteracting oxidative damage to the surviving dopaminergic neurons.

In 2004 a group of French researchers published their work evaluating the effects of three drugs or antagonists known to act upon specific receptors, one of which was the cannabinoid receptor. The exploratory study measured severity of motor symptoms and dyskinesias in 24 patients after treatment with the antagonist and a single dose of levodopa. The drugs were tolerated well, though they did not improve motor skills.

A group of British investigators concluded in 2004 that cannabis “does not have a therapeutic role in the treatment of dyskinesia in patients with PD.” Their study had two phases. Phase one involved 4 weeks of increasing doses of cannabis to assess its safety and tolerability in 6 PD patients with levodopa-induced dyskinesia. In phase two 19 PD patients were randomly assigned to receive either oral cannabis extract followed by the placebo, or the placebo followed by the oral extract. Treatment phases lasted 4 weeks with 2 weeks between the “washout phase.” Changes in items 32 through 34 of the Unified Parkinson’s Disease Rating Scale (UPDRS) assessing dyskinesia were the primary outcome measure determining therapeutic effect of the cannabis extract. Secondary outcome measures comprised more than a half a dozen evaluations ranging from analysis of movement frequency during a computerized graphic tablet-drawing task, to sleep scores and patient diaries. All failed to suggest a beneficial treatment effect on dyskinesia. Patients reported they did not feel better using the cannabis extract, nor did they find it helpful.

## CONCLUSION

There may yet be promise in the search for a therapeutic agent in cannabis. However, any positive advantage the plant may harbor will have to counter the taboo image it has been given in our society (Baker et al., 2003).

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# 19 Capsicum, Rosemary, and Turmeric

Several spices possess antioxidative properties — a **turmeric extract (curcuminoid)**, a **hexane extract of rosemary**, and the  **$\alpha$ -tocopherol-supplemented capsicum pigment** exhibit their antioxidative effects *in vivo* by dietary supplementation. Turmeric extract has demonstrated the ability to reduce liver triacylglycerol deposition as well as cholesterol.

Many spices have been extensively used as natural food additives for flavoring, seasoning, coloring, and antiseptic properties. Several spices are known to exhibit antioxidative activities. In recent years, the antioxidative property of food constituents has been seriously noted by medical and nutritional experts, because the reactive-oxygen-species-mediated oxidation of biological molecules has been proposed to induce a variety of pathological events such as atherogenesis, carcinogenesis, and even aging.

Although many *in vitro* studies on the antioxidative property of food constituents have been reported, little is known about the biological functions of dietary antioxidants *in vivo*, except for several well-known antioxidants such as **tocopherols**,  **$\beta$ -carotene**, and **ascorbic acid**. Because the bioavailability of food constituents is limited by their digestibility and metabolic fate, an oral administration trial of a dietary antioxidant is favored to evaluate its biological function.

Asai et al. (1999) examined extracts of **turmeric (*Curcuma longa* L.)**, **rosemary (*Rosmarinus officinalis* L.)**, and **capsicum** (red pepper, *Capsicum annum* L.) as antioxidative food supplements. These spices contain types of antioxidants different from each other. The rhizome of **turmeric** has been used as a traditional remedy for treating sprains and inflammation in several Asian countries. **Curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin)**, the phenolic yellowish pigments of turmeric, have been suggested to have antioxidative, anticarcinogenic, anti-inflammatory, and hypocholesterolemic activities. Several **phenolic diterpenes** isolated from rosemary have been reported to prevent lipid peroxidation in bulk, emulsified, liposomal, and microsomal systems. The main constituents of capsicum pigment are **hydroxylated carotenoids (xanthophylls)**. Both hydroxylated and nonhydroxylated carotenoids are expected to act as potential membrane antioxidants because of their reactivity with **singlet molecular oxygen** and **peroxyl radicals**.

Asai et al. (1999) determined that **phospholipid hydroperoxides (PLOOH)** are key products for oxidative injury in membranous phospholipid layers in the plasma, red blood cells (RBC), and liver of mice. The formation and accumulation of PLOOH have been confirmed in several cellular disorders, various diseases, and in aging. A lower PLOOH level was found in RBC of the spice-extract-fed mice (65 to 74% of the nonsupplemented control mice). The liver lipid peroxidizability induced with  $\text{Fe}^{2+}$ /ascorbic acid was effectively suppressed in mice by dietary supplementation with the turmeric and capsicum extracts. Although no difference in the plasma lipids was observed, the liver triacylglycerol concentration of the turmeric-extract-fed mice was markedly reduced to half of the level in the control mice. These findings suggest that these spice extracts could act antioxidatively *in vivo* by food supplementation, and that the turmeric extract has the ability to prevent the deposition of triacylglycerols in the liver.

Liu and Ng (2000) studied the antioxidative and superoxide- and hydroxyl-radical-scavenging activities and pro-oxidant effect of 12 selected medicinal herbs. The aqueous extracts of *Coplis*

*chinensis*, *Paeonia suffruticosa*, *Prunella vulgaris*, and *Senecio scandens* exhibited the highest potency in inhibiting erythrocyte hemolysis and lipid peroxidation in rat kidney and brain homogenates. The aforementioned four herbs also demonstrated strong superoxide- and hydroxyl-radical-scavenging activity.

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# 20 Carotenoids

## INTRODUCTION

Carotenoids reduce:

- Risk of prostate cancer
- Breast cancer
- Head and neck cancers
- Cardiovascular diseases
- Age-related macular degeneration

Carotenoids, a class of yellow to deep-red pigments present in many commonly eaten **fruits** and **vegetables**, have been hypothesized to play a role in the prevention of chronic diseases such as cancer and heart disease. Most research to date has focused on the relationship between  $\beta$ -carotene and lung cancer. Lung cancer is one of the most common cancers in the U.S., and  $\beta$ -carotene was initially the most thoroughly studied carotenoid because of its role as a **vitamin A precursor** (Cooper et al., 1999).

Vitamin A is an essential nutrient for humans and other vertebrates. Dietary sources of vitamin A are provided either by **retinol esters**, which are present in foods of animal origin and are hydrolyzed in the intestine to form **retinol**, or by **plant carotenoids**. More than 600 carotenoids have been identified in nature, of which 50 to 60 possess provitamin A properties and ~10 have nutritional relevance (De Flora et al., 1999).

**Provitamin A carotenoids** may be converted by central cleavage through a **15,15-dioxygenase** present in the intestinal mucosa to yield one or two molecules of **retinaldehyde (retinal)**, which is then reduced by an **aldehyde reductase** to **retinol**. **Retinoic acid** may be formed by eccentric cleavage of such carotenoids as  $\beta$ -carotene. A central feature of vitamin A physiology is the strong mechanism of homeostatic control of the circulating concentrations of retinol in blood across a broad range of intake of preformed vitamin A and provitamin A. Circulating retinol concentrations remain fairly constant until liver reserves fall to very low levels. This is in contrast to concentrations of carotenoids in blood, which are mainly determined by the levels of carotenoids in the diet.

The **antigenotoxic** and **anticarcinogenic** effects of carotenoids or vitamin A have been studied extensively. The bulk of available data support the view that carotenoids and vitamin A do not induce genotoxic effects per se. Even in the absence of any genotoxic agent, these nutrients appear, on the contrary, to display some mechanisms that play protective roles in tumor promotion and progression, such as inhibition of ***N*-myc gene expression** resulting in antiproliferative effects, upregulation of **cell-to-cell communication**, an increase in ***connexin 43* gene expression**, a decrease in the “spontaneous” **cell transformation frequency**, and induction of **differentiation *in vitro***. A large number of studies investigated the modulation by carotenoids and vitamin A of genotoxic and related effects produced by 69 genotoxicants, including biological agents, physical agents, chemical compounds, and complex mixtures. In spite of some discrepant data, the general trend was that both carotenoids and vitamin A are poorly effective in acting as **nucleophiles**, nor do they appear to interfere substantially with the induction or repair of DNA damage produced by direct-acting agents. In contrast, vitamin A and carotenoids, irrespective of their provitamin A role,



in most studies inhibited those genotoxicants that require metabolic activation to **electrophilic derivatives** in either bacterial or mammalian cells. Coupled with biochemical data, the distinctive patterns observed with genotoxic agents belonging to different chemical classes suggest a complex modulation of both phase I and phase II enzymes involved in the metabolism of **xenobiotics**. Furthermore, carotenoids and vitamin A shared other protective mechanisms, such as scavenging of **genotoxic oxygen species**, modulation of signal transduction pathways, inhibition of cell transformation induced by physical and chemical agents, and facilitation of intercellular communication inhibited by genotoxic compounds. Therefore, carotenoids and vitamin A appear to work via multiple mechanisms, which would support a potential protective role in cancer initiation and in the pathogenesis of other mutation-related diseases. These conclusions are consistent with the recognized cancer-preventive activity of these nutrients in certain animal models and with the evidence provided by observational epidemiological studies, which suggested cancer-protective effects at many sites as related to their dietary intake or plasma levels (De Flora et al., 1999).

### PROSTATE CANCER

Prostate cancer is the most common cancer in U.S. males, and there is evidence that **dietary fat, soy proteins, vitamin E, and selenium** affect risk for this disease. Furthermore, it has been shown that consumption of **lycopene** and lycopene-containing foods (tomato and tomato paste) is associated with reduced risk of prostate cancer.

### BREAST CANCER

Breast cancer is the most common form of cancer among women in developed countries. Approximately one in eight U.S. women will be diagnosed with breast cancer at some point in her life. A number of dietary factors have been investigated for their role in breast cancer etiology, including caloric intake, dietary fat, protein, fiber, vitamins A, C, and E, carotenoids, and fruits and vegetables. Higher  $\beta$ -carotene consumption has been reported to be associated with a lower risk of breast cancer in some epidemiological studies; however, the evidence is insufficient to reach a firm conclusion.

### CANCER OF THE HEAD AND NECK

Cancers of the head and neck include cancers of the oral cavity, pharynx, and larynx. In the U.S., approximately 42,000 of these squamous cell cancers are diagnosed each year. Worldwide, head and neck cancers are the sixth most common cancers. Tobacco and alcohol use are the most significant risk factors for development of head and neck cancers. Epidemiological and experimental data have suggested that **retinoids** and **carotenoids** may have chemopreventive activity causing regression of **oral leukoplakia**, a premalignant lesion, thus preventing its progression to oral cancer.

### CARDIOVASCULAR DISEASE

Research on carotenoids and cardiovascular disease (CVD) stems from the discovery that the etiology of this disease involves oxidative processes that may be slowed by exogenous antioxidants. One of the best understood processes contributing to development of CVD is the oxidation of **low-density lipoprotein (LDL)**. When LDL becomes oxidized, it is readily taken up by **foam cells** in the vascular endothelium where it contributes to the development of **atherosclerotic lesion**. Enhancement of the oxidative stability of LDL may also prevent other oxidative steps involved in clinical expression of coronary disease (e.g., **myocardial infarction**) and possibly steps not related to LDL oxidation. There is optimism about the potential role of  $\beta$ -carotene in prevention of CVD

because  $\beta$ -carotene is carried on LDL and has the capacity to trap **peroxyl radicals** and quench **singlet oxygen** *in vitro*.

### AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is the leading cause of legal blindness in people over the age of 65 in the U.S. This disease is characterized by degenerative changes in the central region of the retina, the macula, which eventually lead to loss of central detail vision. The cause of AMD is unknown; however, age, smoking, and genetics are risk factors. In addition, many medical, lifestyle, and environmental factors have also been associated positively or negatively with risk of AMD.

The role of carotenoids in the pathogenesis of AMD has gained considerable attention because the macula contains the carotenoids **lutein** and **zeaxanthin** in concentrations high enough to give it a yellow color. It has been hypothesized that these carotenoids reduce the risk of AMD by preventing damage to the retina by absorbing high-energy blue light or by antioxidant activity. The retina is a highly oxidizing environment because of light exposure, a high rate of photoreceptor catabolism and oxidative metabolism, and a high content of polyunsaturated fatty acids. Risk factors for atherosclerosis have also been associated with increased risk of AMD in some studies. Atherosclerotic disease of the retina could play a role in AMD by limiting the flow of blood, oxygen, and nutrients to and from the area. If carotenoids inhibited the atherosclerotic process, this could provide another mechanism for preventing AMD. At the present time, no significant association seems to exist between intake or serum concentrations of carotenoids and risk of AMD (Cooper et al., 1999).



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# 21 Chocolate

**Chocolate has antioxidant properties for low-density lipoproteins and hence could prevent heart disease.** Foods and beverages derived from cocoa beans have been consumed by humans since 460 A.D. Cocoa pods from the cocoa tree (*Theobroma cacao*) are harvested and the beans removed and fermented. Dried and roasted beans contain about 300 chemicals including **caffeine**, **theobromine**, and **phenethylamine**. Chocolate liquor is prepared by finely grinding the nib of the cocoa bean and is the basis for all chocolate products. Cocoa powder is made by removing part of the cocoa butter from the liquor. **Bittersweet chocolate**, sometimes called **dark chocolate**, contains between 15 and 60% chocolate liquor, the remainder being **cocoa butter**, sugar, and other additives. **Milk chocolate** is the predominant form of chocolate consumed in the U.S. and typically contains 10 to 12% **chocolate liquor**.

The appeal of chocolate is universal, but the pleasures of eating chocolate products may perhaps be tempered by their fat and sugar content. However, in a series of human feeding studies it has been shown that the high proportion of **stearic acid** in the cocoa butter of chocolate does not adversely affect plasma lipids. Two recent reports of antioxidant activity have increased interest in the health aspects of chocolate: an *in vitro* low-density lipoprotein (LDL) oxidation study and a short-term *in vivo* study. **Epicatechin**, the major monomeric polyphenol antioxidant in chocolate, and an extract of chocolate liquor were both found to stimulate **cellular immune response** *in vitro*.

**Polyphenol** consumption as **flavonoids** has been shown to decrease the risk of heart disease in a cross-cultural epidemiological study. Most recently, an epidemiological study found that Harvard male graduates who ate a “moderate” amount of chocolate and other candy had a 36% lower risk of death compared with non-candy eaters. The authors speculate that it is the antioxidants present in the chocolate that provide a health benefit.

Vinson et al. (1999) investigated in detail the antioxidant properties of polyphenols in cocoa and two types of chocolate using an *in vitro* model of heart disease. These authors found that **epicatechin** and **catechin** were found in all of the six samples analyzed by high-performance liquid chromatography (HPLC). These two monomeric polyphenols were minor components of the chocolates, ranging from 1.97 to 2.76 mol% of the phenols in the milk chocolate, from 2.98 to 5.48 mol% in the dark chocolate, and from 5.45 to 6.11 mol% in the cocoa powder. Assuming a 35% content of fat and moisture, the concentrations of the catechins are 15 to 16 mg/100 g in milk chocolate, 48 to 137 mg/100 g in dark chocolate, and 296 to 327 mg/100 g in cocoa powder. A recent HPLC analysis of single samples of European chocolate found 16 mg/100 g in milk chocolate and 54 mg/100 g in dark chocolate. Another report found 300 mg/100 g in cocoa powder, which also agrees well with these results. The total concentration of the two catechins in chocolate correlates well with the total polyphenols as measured by the Folin method, with a Pearson correlation coefficient of 0.9326,  $p < 0.01$ .

The quality of the phenol antioxidants was assessed by Vinson et al. (1999) using the IC<sub>50</sub> for LDL + VLDL (very low density lipoprotein) oxidation, with smaller values indicating a higher quality. Quality of the antioxidants was due to free-radical scavenging activity and not chelation as the concentration of polyphenols for 50% inhibition was  $< 1 \mu\text{M}$  and cupric ion  $25 \mu\text{M}$  in the oxidation medium. There was less percent variation within the groups for this parameter than for the total polyphenol content. The quality order was dark chocolate  $>$  cocoa  $>$  milk chocolate. The dark chocolate and cocoa were significantly different from the milk chocolate ( $p < 0.05$ ), but not

from each other. There was no correlation between the quantity of phenolic antioxidants in the chocolate and the quality as measured by  $IC_{50}$ ,  $p > 0.05$ . There was also no correlation between the amount of **epicatechin** and **catechin** in the chocolates and the  $IC_{50}$ . **Theobromine** and **caffeine**, two major ingredients in chocolate, were neither pro-oxidants nor antioxidants.

Some interesting comparisons can be made between the antioxidant properties of chocolate and other foods and beverages. The average total polyphenol content of dry, defatted chocolate was 133.9  $\mu\text{mol/g}$ . The foods with the highest dry weight total phenols were **beet**, 53.4  $\mu\text{mol/g}$ , **apple** 6.4  $\mu\text{mol/g}$ , and **black tea** 12.0  $\text{mol/ml}$ . Chocolate has a higher polyphenol content than the 23 vegetables and the several fruits and beverages studied. The  $IC_{50}$  average for chocolate products is 0.33  $\mu\text{M}$  and is superior to the average for vegetables, 0.69  $\mu\text{M}$ . The **phenol antioxidant index** (PAOXI) for chocolate averaged  $378 \times 10^3$ , whereas the highest vegetable, asparagus, was  $144 \times 10^3$  and the highest commonly consumed beverage black tea,  $31.5 \times 10^3$ .

An important antioxidant parameter with respect to head disease is the **lipoprotein-bound antioxidant activity**. The value for epicatechin, a polyphenol component of chocolate, was 63% greater than the control average, and increase in lag time for the three representative chocolate products was 41%. All beverages, such as wine and tea, that had this antioxidant activity were also found to produce an increase in lag time after ingestion.

Thus, chocolates contain both a high quantity and a high quality of phenol antioxidants. When expressed as catechin equivalents on a fresh-weight basis, the average chocolate contains 28.7  $\text{mg/g}$ , assuming a 35% content of fat and moisture. A serving (40 g of chocolate is the reference amount commonly consumed per eating occasion) of milk chocolate, the most popular type of chocolate, provides 394 mg of polyphenol antioxidants and a serving of dark chocolate 951 mg. For comparison, the average black tea contains 943  $\text{mg}/240\text{-ml}$  serving and red wine 431  $\text{mg}/240\text{ ml}$ . The average hot cocoa mix made according to instructions provides 45 mg of polyphenols in a 240-ml serving. Using 5 g of the average cocoa powder (35% fat and moisture), a homemade serving of hot cocoa has 211 mg of polyphenols as catechin. Therefore, polyphenols from chocolate may provide additional antioxidant protection for LDL and thus be beneficial for preventing heart disease (Vinson et al., 1999).

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# 22 Cinchona Tree

## INTRODUCTION

The medicinal use of **quinine**, an antimalarial agent, dates back over 350 years. Quinine is the chief alkaloid of **cinchona**, the bark of the South American **cinchona tree**, otherwise known as **Peruvian bark**, **Jesuit's bark**, or **Cardinal's bark**. In 1633, an Augustinian monk named **Calancha of Lima, Peru**, first wrote that a powder of cinchona "given as a beverage, cures the fevers and tertians." By 1640, cinchona was used to treat fevers in Europe, a fact first mentioned in the European medical literature in 1643. The Jesuit fathers were the main importers and distributors of cinchona in Europe, hence the name Jesuit's bark. Cinchona also was called Cardinal's bark because it was sponsored in Rome by the eminent philosopher, **Cardinal de Lugo**.

## CINCHONA: A PERUVIAN BARK

The cinchona tree belongs to the **Rubiaceae** family and is a native of the eastern slope of the Andes but has been largely planted in India, Sri Lanka, Indonesia, and Myanmar, with the result of improving the quinine-yielding value of many species by cultivation. There are two official species:

1. **Cinchona**, the dried bark of *Cinchona ledgeriana*, *C. calisaya*, *C. officinalis*, and of hybrids of these and of other species of Cinchona, yielding, when assayed by a prescribed process, not less than 5% of total alkaloids.
2. *Cinchona rubra*, **red cinchona**, is the bark of *C. succirubra* or of its hybrids, containing not less than 5% of cinchona alkaloids. From it is prepared the compound tincture of cinchona.

## VARIETIES OF CINCHONA

The principal varieties of the tribe Cinchoneae, the barks of which are found in commerce and are used by manufacturers of the alkaloids, are *Cinchona calisaya*, *C. flava*, **yellow bark**, from Peru, Bolivia, and India; *C. succirubra* (Figure 22.1), **red bark**, from Ecuador, Indonesia, and Sri Lanka; *C. condaminea*, **pale bark**, from Ecuador and Peru; *C. pitayensis*, **pitaya bark**, from New Granada; and *C. micrantha*, **gray bark**, from Peru and Bolivia. Altogether, there are some 31 species acknowledged by botanists, and the list is constantly increasing, from the tendency of different trees to hybridize. Moreover, several trees formerly acknowledged as cinchonas are now placed in the **genus Cascarilla**, but their barks are to be found on the market. Cuprea bark is from trees of the **genus Remijia**, growing in Colombia; it contains quinone and a peculiar alkaloid, **cinchonamine**, but no cinchonidine (Potter, 1910).

## COMPOSITION OF CINCHONA

Cinchona bark contains 21 natural alkaloids (3 of which are official), 8 artificial alkaloids, 2 simple acids, 2 tannic acids, a resinoid, and a coloring matter, with characteristics as follows:



FIGURE 22.1 *Cinchona succirubra*.

- **Quinine**,  $C_{20}H_{24}N_2O_2$ , a strong base, fluorescent, the most valuable of all the alkaloids; heated with glycerin to  $374^\circ F$ , it is converted into the isomeric base, **quinicine**.
- **Quinidine**,  $C_{20}H_{24}N_2O_2$ , isomeric with quinine, fluorescent, probably the most powerful as an antiperiodic, but existing in very small quantity.
- **Cinchonine**,  $C_{19}H_{22}N_2O$ , the least active of the official three, having about half the therapeutic power of quinine. Not fluorescent.
- **Cinchonidine**,  $C_{19}H_{22}N_2O$ , isomeric with cinchonine, not fluorescent, one of the most powerful of the alkaloids. (The other alkaloids are of no interest medicinally.)

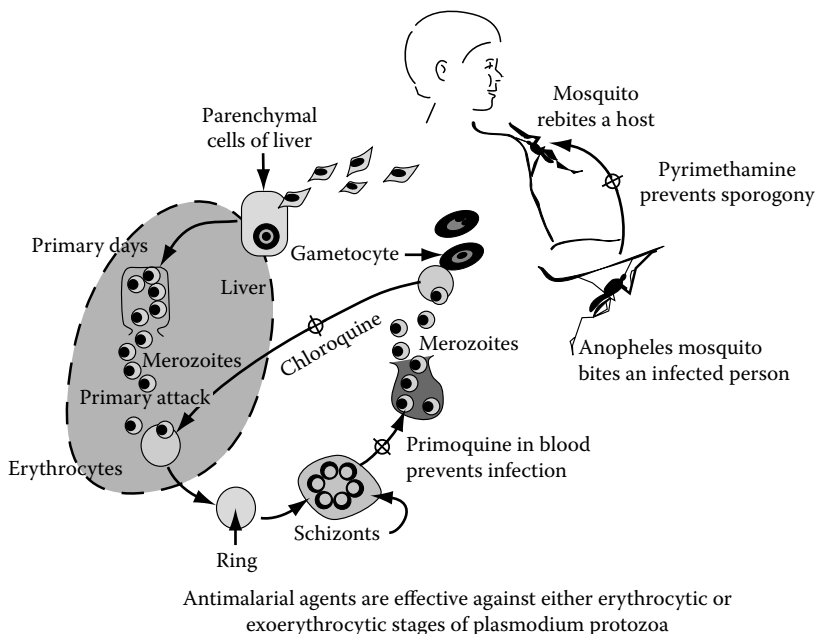
- **Kinic and kinovic acids** are combined in the bark with the alkaloids. The former is used to make a kinate of quinine, and the latter occurs in the nonofficial pharmacy as **Kinovate of Lime**, an ingredient in **Deloude's Extract**, which is used in Europe and India for dysentery.
- **Kino-tannic and kinovo-tannic acids** give to bark its peculiar and powerful astringent qualities. They have not been fully studied.
- **Kinovin** is a bitter, amorphous resinoid, which is resolvable into **kinovic acid** and sugar. It is soluble in alcohol, but not in water.
- **Cinchona red** is a reddish-brown, insipid, inodorous substance.

## QUININE FOR TREATMENT OF MALARIA

The causative organisms of malaria are protozoa of the genus *Plasmodium*, with four species known to infect humans only:

- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium malariae*
- *Plasmodium ovale*

The major antimalarial agents are the **4-aminoquinoline derivative** (e.g., **chloroquine**), **8-aminoquinoline derivative** (e.g., **primaquine**), **follic acid antagonist** (e.g., **pyrimethamine**), and alkaloid (e.g., **quinine**). These antimalarial agents can be classified according to their effectiveness in interfering with various stages of parasitization. These are the primary tissue schizonticides. An agent such as primaquine destroys the primary tissue schizonts in the liver soon after infection has taken place (Figure 22.2).



**FIGURE 22.2** The actions of quinine, chloroquine, and primaquine.



## BLOOD SCHIZONTICIDES

Agents such as **quinine**, **quinacrine**, **amodiaquine**, and **chloroquine** suppress the symptoms of malaria by destroying the schizonts and merozoites in the erythrocytes.

- **Gametocides.** Agents such as primaquine, by destroying the gametocytes in the blood, prevent infection caused by bites of the Anopheles mosquito.
- **Sporonticides.** Agents such as **chlorguanide** and **pyrimethamine** help to eradicate the disease by preventing sporogony and multiplication of the aforementioned parasites.
- **Secondary tissue schizonticides.** Agents such as primaquine destroy exoerythrocytic tissue schizonts such as those developing in the liver.

## QUININE SULFATE: A CLASSIC DRUG

**Quinine sulfate**, the classic drug, the salt of an alkaloid obtained from cinchona bark, has been superseded by newer drugs in most parts of the world. It is only a fairly good suppressant, even in toxic dosage, and is so rapidly eliminated that it must be given at very frequent intervals to maintain its effects. When used to check an established attack, it achieves the control of **parasitemia** in 96 h that chloroquine accomplishes in little more than 72 h, and its effects on fever and most other symptoms also lag (Figure 22.3).

Absorption from the upper intestinal tract is rapid and reliable, and less than 10% is excreted as such in the urine; excretion begins in about 15 min, reaches its maximum in 4 h, gradually declines, and is complete in 24 h. The other 90% or more of the drug is rapidly destroyed in liver, kidneys, and muscles, some of it being oxidized to the **carbostyryl derivative** that is only about one third as active as quinine in experimental infections. Quinine does not accumulate in the body even though taken daily for a long period. Full action is obtainable with a plasma concentration of 5 mg/l, but frequent administration is required to maintain this level. Adult dosage of quinine sulfate (or bisulfate, which is more soluble) in tablets or capsules is usually 1 g (15 grains) three times daily (preferably some time before the taking of food) for 2 d, followed by 0.6 g (10 grains) at the same intervals for an additional 5 d. However, in Holland and Indonesia it has been customary to use only 1.5 g (22 grains) daily dosage in *P. falciparum*, and 1 g (15 grains) in *P. vivax* cases, which probably at least partially accounts for the greater satisfaction with the drug in those regions. Good results are claimed as with higher dosage, and there must certainly be a lower incidence of disturbing reactions. On the higher dosage scale used in this part of the world, infants under 1 year are given 30 mg (1/2 grain) three times daily; 1 year, 60 mg (1 grain); 2 years, 120 mg (2 grains); 3 and 4 years, 200 mg (3 grains); 5 and 6 years, 250 mg (4 grains); 7 and 8 years, 300 mg (5 grains), etc. In serious *P. falciparum* cases, a continuous intravenous drip has been employed in some tropical countries, delivering 30 to 40 drops/min of a solution containing 0.5 to 0.6 g (7 1/2 to 10 grains) per 1000 ml, with the aim of administering 2 g (30 grains) in 24 h.

Quinine in the usual dosage frequently makes the patient uncomfortable because one or more of the following symptoms of **cinchonism** appear: nervousness, headache, giddiness, palpitation, tremors, nausea, and disturbances of sight and hearing. Some people also experience allergic reactions such as skin rashes, pseudoasthmatic and anginal phenomena, and hemorrhagic disturbances (the action of vitamin K is apparently antagonized). **Quinine blindness**, which is usually a reflection of retinal spasm, is probably an allergic reaction in the beginning.

All the new synthetic antimalarials may apparently be administered safely to the pregnant woman, but it is a firmly entrenched clinical impression that quinine in full dosage is contraindicated in the mother and may cause serious visual and oral disturbances in the infant. **Black-water fever**, a little-understood hemolytic syndrome sometimes complicating *P. falciparum* cases, has been associated with quinine administration in a high proportion of instances. If quinine is injected

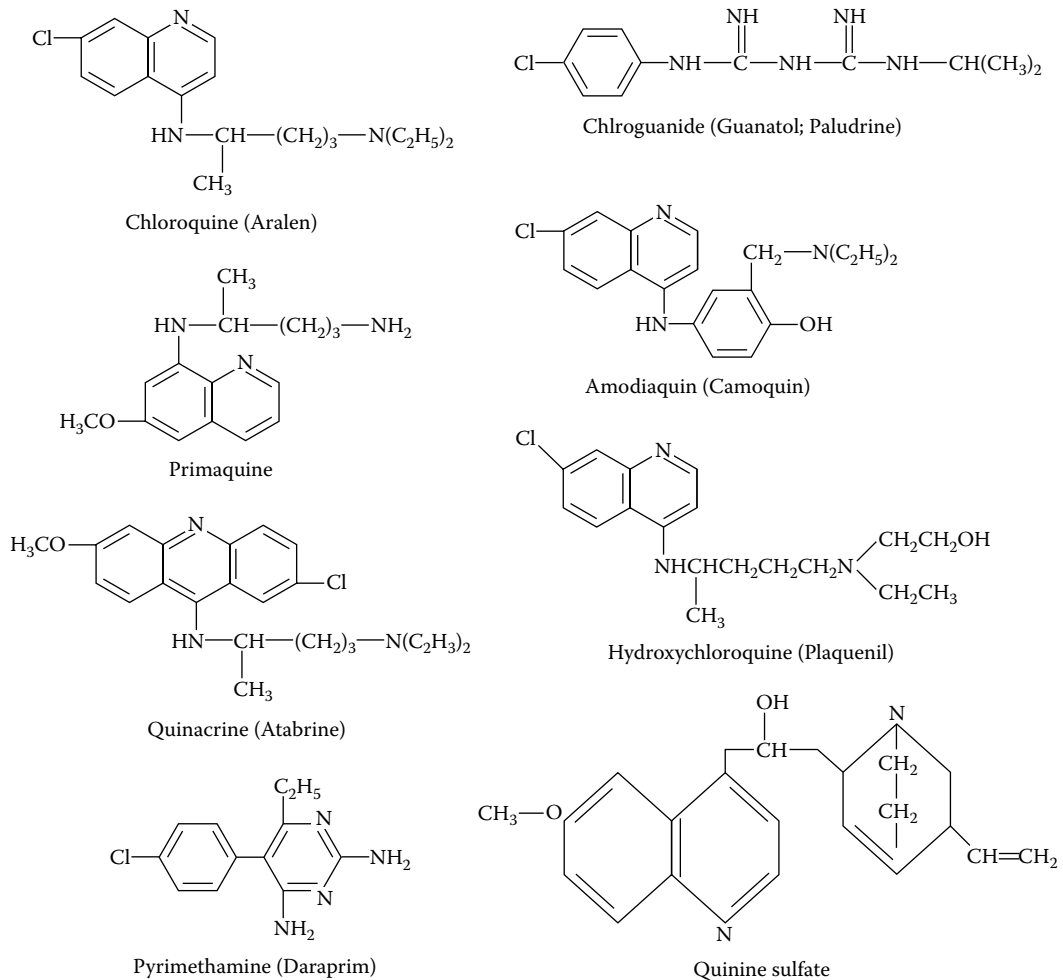


FIGURE 22.3 The structure of quinine and other antimalarial agents.

rapidly intravenously, it causes severe hypotension that is probably compounded of myocardial depressant and peripheral vasodilator actions, with the possible addition of a flocculent “nitritoid” type of occurrence.

Quinine has certain minor pharmacological actions quite distinct from its antimalarial role: analgesic (in prohibitively high dosage), striated muscle relaxant, and antipyretic. Other uses of quinine are as a sclerosing agent, a bowel evacuant, and in dermatological practice.

The structures of the newer antimalarial agents are given in Figure 22.3 and their pharmacological properties are outlined in Table 22.1.

Other pharmacological agents are sometimes used in combination with the antimalarial agents for greater effect. These include:

- **Sulfonamides** — Sulfadoxine or sulfadiazine is used with pyrimethamine.
- **Sulfones** — Dapsone (DDS) is used in place of or in addition to the sulfonamides and pyrimethamine.
- **Acridines** — Quinacrine (Atabrine) has an action similar to that of chloroquine.
- **Biguanides** — Clorguanide (Proguanil and Paludrine) has suppressive as well as prophylactic actions.

**TABLE 22.1**  
**Pharmacological Properties of Antimalarial Agents**

Antimalarial Drug	Properties
<b>Chloroquine</b> (Aralen) <b>Amodiaquine</b> (Camoquin, as an alternate drug)	Chloroquine destroys schizonts in erythrocytes by interfering with DNA synthesis. The phosphate salts are active orally, whereas the hydrochloride salt is used for intravenous purposes. It accumulates in normal and parasitized erythrocytes. Overdosage has caused reversible corneal damage and permanent retinal damage. In toxic doses, chloroquine causes visual disturbances, hyperexcitability, convulsions, and heart block. It is an antimalarial of choice in all cases except chloroquine-resistant <i>Plasmodium falciparum</i> . In addition, it has a certain degree of effectiveness in amebiasis and in the late stages of rheumatoid arthritis.
<b>Primaquine</b>	Primaquine attacks plasmodia in the exoerythrocytic stages. It is effective for preventing relapse and as a prophylactic measure when staying in an infested area. Primaquine may cause hemolytic anemia, especially in patients who are deficient in glucose 6-phosphate dehydrogenase.
<b>Quinine</b>	Quinine is a naturally occurring alkaloid obtained from Cinchona bark, with a mechanism of action similar to that of chloroquine. Quinine is very useful in treating chloroquine-resistant <i>Plasmodium falciparum</i> . In toxic doses, it may cause cinchonism characterized by tinnitus, headache, nausea, and visual disturbances.
<b>Pyrimethamine</b> (Daraprim)	Pyrimethamine is a folic acid antagonist (antifol) with pharmacological actions similar to chlorguanide, methotrexate, and trimethoprim. Pyrimethamine may be used in combination with sulfadoxine for suppression and sulfadiazine for treatment of chloroquine-resistant <i>Plasmodium falciparum</i> .

*Note:* The main objective in the clinical management of patients suffering from an acute malaria attack is the prompt elimination of the parasite form responsible for the symptoms, that is, the asexual erythrocytic form. Drugs that are particularly effective in this regard are called *schizontocidal* or *suppressive* agents. They include such compounds as amodiaquine, chloroguanide, chloroquine, hydroxychloroquine, pyrimethamine, quinine, and tetracycline.

## OTHER ACTIONS OF QUININE

The bark of the cinchona tree (Peruvian or Jesuit's bark or Cardinal's bark) has a very selective effect on malaria, so that a single adequate dose suppresses the plasmodia in the blood. This action is due chiefly to the alkaloid **quinine**, but is shared more or less by other cinchona alkaloids, **quinidine**, **cinchonine**, **cinchonidine**, etc., and by most of the numerous chemical derivatives of quinine and also by certain benzene derivatives, notably **atabrine** and **plasmaquine**, and to a minor degree by several other drugs. It is especially toxic to ameboid cells, and relatively nontoxic to higher organisms. Quinine is a fairly effective antipyretic, increasing heat loss by hydremia and by dilatation of the skin vessels. It is useful as an analgetic in colds; and in the form of **quinine-urea hydrochloride** as a local anesthetic. Through its bitterness, it acts as a **stomachic tonic**. It may stimulate the uterus. Full doses produce "**cinchonism**," characterized especially by auditory and visual disturbances, which may assume grave proportions with excessive doses. These also cause renal irritation. Very large quantities have sometimes been consumed without serious poisoning, chiefly because the absorption of the drug is limited. Hypersusceptibility and other idiosyncrasies are quite common. Cinchona also contains considerable **tannic acid**.

## COLLOIDS AND SURFACE PHENOMENA

Quinine, like **saponin** and proteins, tends to concentrate at the surface of solutions, to form rather rigid films. These interfere with the condensation of other substances at the surface, and therefore

hinder catalytic phenomena, inorganic as well as organic. This may explain the decreased metabolism. The surface action is also shown by arrest of "**Brownian movement**," and there is a tendency to precipitate colloidal solutions, such as the proteins. Quinine may therefore produce **anaphylactoid phenomena**. The quinine film presumably diminishes the permeability of the cell, and would thereby lead to a narcotic action, such as is seen on local application to nerves and muscles. Quinine tends to arrest cell movements, for example, of the white blood cells, infusoria, cilia, spermatozoa, etc., presumably through the rigidity of its film. All these render quinine a "**general protoplasmic poison**," toxic to all kinds of cells. However, its toxicity to vertebrates is relatively low, probably because it is largely bound and deposited in insoluble and harmless form.

### LOCAL ACTIONS

Quinine produces some local irritation and anesthesia. When given hypodermically, it occasions severe pain, and may lead to abscess formation. When given by the stomach, large doses cause gastralgia, nausea, vomiting, and diarrhea. It also retards the absorption of salts and probably of food. Its excretion through the kidneys may give rise, with large doses, to albuminuria and hemoglobinuria. The hemoglobinuria of severe malaria (**black-water fever**) may be partly due to increased sensitiveness to quinine.

### ULCERS

The sulfate has been used as antiseptic, styptic, and stimulant dusting powder on ulcers.

### SUNBURN PROPHYLAXIS

Quinine sulfate is protective through its fluorescence, which scatters the actinic rays.

### QUININE AS ANESTHETIC

Quinine and its derivatives, when brought in contact with sensory nerves, produce local anesthesia. This is used clinically in the form of the more soluble and less irritant double salts, especially quinine urea hydrochloride. The anesthesia is more lasting than with other local anesthetics; it may persist for several days. This is indeed due to necrosis of the axis cylinders and sheaths, with subsequent regeneration. However, the concentrations above 0.25% sometimes produce considerable irritation, edema, and fibrous indurations and above 1% there may be sloughing. Its employment has therefore greatly diminished, although some clinicians consider these fears as exaggerated.

### ANTISEPTIC ACTION

Bacteria and yeasts are killed by quinine but require a higher concentration (2 to 8:1000) than do the protozoa. The efficiency is not materially hindered by serum or pus.

### EFFECT ON DIGESTION

Small doses of quinine (0.05 g, 1 grain), taken before meals, act as a stomachic and tonic; but they are probably inferior to other bitters. Larger doses diminish gastric secretion.

### ANTIPYRETIC ACTION

The suppression of malarial fever by quinine is etiological. However, quinine also reduces other febrile temperatures to normal, analogous to the other antipyretic drugs, i.e., by adjustment of the temperature-regulating centers, primarily through increased heat loss, assisted somewhat by diminished heat production.

### **USE OF QUININE IN COLDS, HEADACHES, AND NEURALGIAS**

Like other antipyretics, quinine has an analgetic effect in these conditions. It is used in doses of 0.05 to 0.2 g, 1 to 3 grains.

### **SKELETAL MUSCLE**

Quinine, quinidine, cinchonine, and cinchonidine have similar actions. Dilute solutions cause direct depression with prolonged refractory phase. Concentrated solutions produce rigor.

### **CINCHONISM**

The larger therapeutic doses of quinine produce headache, ringing in the ears, and disturbed vision, a complex of symptoms grouped under the name of cinchonism. These are probably due to a selective action on the vessels of the eye and ear, which can also be demonstrated experimentally on animals. Toxic doses produce photophobia, deafness, and blindness, at first partial, later complete. These are probably partly central. Similar phenomena occur with salicylates and related drugs, as indeed also with fever itself, and with "colds." Cinchonism is more easily produced in some individuals than in others. It is said that the minor symptoms may be somewhat diminished by bromides. Hyperthyroid patients generally have marked tolerance for quinine, and absence of cinchonism has some diagnostic significance. With very high doses of quinine, the symptoms of cinchonism are accompanied by difficulty of speech, confusion of ideas and somnolence, followed by loss of consciousness, alternating with delirium, coma, and at times convulsions. The treatment is by evacuation and is symptomatic.

### **SKIN ERUPTIONS AND IDIOSYNCRASY**

Scarlatinal or urticarial rashes are not rare after therapeutic doses of quinine, and susceptible individuals may develop dangerous edemas of the mucous membranes and serious collapse (Sollmann, 1944).

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# 23 Coca

## INTRODUCTION

The leaves of *Erythroxylon coca*, the divine plant of the Incas, contain a local anesthetic and a psychostimulant. Erythroxylaceae is a very small family, represented by two genera, the more important of which is **Erythroxylon**. They are mostly tropical shrubs with entire leaves and 5-merous flowers, and the fruit is a 1-seeded, reddish drupe resembling that of dogwood. The anatomy of the plants of this family closely resembles that of the *Linaceae*. Of special interest is the development of *papillae* on the dorsal surface of the leaves. This is found in most species of *Erythroxylon*.

## COCA

Coca. Cocaina. Cocaine, *Erythroxylon coca*, Lamarck and other species are sources. An alkaloid is obtained from the leaves.

### Habitat

In Peru, Bolivia, and Ecuador, on the eastern slopes of the Andes, as well as in Colombia, Brazil, India, Sri Lanka, and the Indonesian island of Java are regions where coca is cultivated.

### Synonym

*Erythroxylon*, Spadic, Coca leaves, Cuca, Hayo, Ipado, Coca Folia; Fr. Feuilles de Coca; Ger. Kokablätter; Cocain, Methyl-benzoyl-ecgonine; Br. Cocaina; Fr. Cocaine; Ger. Cocainum, and Kokaina are some of the names by which the substances is known.

### Er-y-throx'y-lon L.

See etymology of Erythroxylaceae, discussed previously.

### Co'ca

The name *co'ca* (Spanish) is derived from the native name, meaning tree or plant, par excellence.

## HISTORY

Coca leaves were highly valued by the natives long before the Spanish conquest, the tree being known as "**The Divine Plant of the Incas**." Monardes published an extensive article on the drug in 1569. The natives chew the leaf, either as such or mixed with lime, and are thus able to travel great distances, often with heavy loads, without experiencing fatigue and without any but the most meager food rations. Cocaine was first isolated in 1860, but until 1884 coca was considered as but an inferior substitute for tea. In that year **Koller** discovered its local anesthetic properties.

## PLANT

The plants are shrubs or small trees that attain a height of about 2 m; they are indigenous to Peru (*E. truxillense*) and Bolivia (*E. coca*) and are cultivated not only in these countries but also in Indonesia (*E. truxillense*), and to some extent in Sri Lanka. Erythroxyton is from two Greek words meaning red and wood, alluding to the color of the plants; *coca* is the Spanish name for the tree; and *truxillense* is from Truxillo, a coastal city in northern Peru.

Huanuco coca leaves are oval, obovate, or elliptical, 3 to 7 cm in length, 2 to 3 cm in breadth (Figure 23.1), with an acute, slightly mucronate apex, an acute base, and an entire, somewhat revolute margin. The upper surface is dark green, glabrous, and the undersurface is yellowish green, with numerous minute papillae that distinctly undulate. A parallel line about 4 mm from the midrib on either side and extending from the base to the summit is often noted. The texture is somewhat coriaceous, the odor distinct, and the taste bitter, producing a sensation of numbness.

**Truxillo coca leaves** are usually more broken, a little larger, and the curved line on either side of the midrib is usually wanting.

**Javanese coca leaves** resemble *Truxillo coca* and are employed for the manufacture of cocaine in Holland.



FIGURE 23.1 *Erythroxyton coca*.

## COMMERCIAL PROPERTIES

Coca, although not introduced into England until 1870, was used in South America prior to the Spanish conquest, 1569, by the aborigines, who extolled it as a God-given plant that satisfied hunger, strengthened the weak, and banished man's misfortunes. However, the invaders, intolerant of such homage, forbade its use and cultivation until they observed that it enabled the conquered to perform better work and service. Previous to 1884, the alleged properties were thought legendary and imaginative, and coca was considered simply a mild stimulant like tea. Then, in 1884, **Koller** proclaimed its local anesthetic power (see Culbreth, 1927).

Species differ when wild and under cultivation, and after collection soon degenerate and show marked changes in leaf characteristics. Cocoa is cultivated extensively in the Andes on terraced plantations, *cocales*, cleared from the forests on the warm declivities, thriving best in a moist atmosphere amid scattered trees, but not deep shade which, as well as low elevation, develops bitterness; consequently, any variation in this or in the prescribed soil, exposure, and curing may affect quality. Propagation is similar to peach, yielding leaves the second year and continuing for 50 years thereafter. Leaves when bright green above and yellow-green below are picked carefully to avoid breaking or injuring young leaf-buds that form the next crop; the leaves are removed in baskets, spread on unroofed floors, and dried quickly for a few hours in the sun: if dried too rapidly, they lose odor and green color; if too slowly, they acquire a disagreeable odor and taste. After remaining 2 to 3 days in the coca house, in loose piles, they are exposed again for a short time to the sun, to drive off developed sweat and then compressed into bales (*cestos*), 25 to 50 lb (11.6 to 23.3 kg) or, better, packed in tin-lined boxes that prevent likely deterioration in shipping through fermentative decomposition. Irrespective of the care in drying and storing, impairment begins at once, and the cocaine decreases materially, especially in dampness; the leaves should be discarded after a few months. Although in some localities collection is almost continuous, there are at least two to three yearly harvests; the September harvest is the best and the April harvest next, each yielding when dried 60 to 80 lb (27 to 37 kg) per acre. The annual production is about 80,000,000 lb (37,383,177 kg), exported largely from Huanuco, Lima, Truxillo, etc.

There are two varieties:

1. *Huanuco* (*Cuzco-E. Coca*, short-styled), named after cities of southern Peru, has best aroma, most cocaine, and less isatropyl-cocaine; grown mostly in Bolivia and southern Peru, thriving and yielding maximum product at 1050 to 1800 *M* (3500 to 6000°), in 18° south, and inferior grades at lower elevations.
2. The true Bolivian (*E. bolivia'num*, long-styled) is prized most highly.

These two distinct varieties or, perhaps, species of *Erythroxylon coca*, one the Bolivian form and the other the Peruvian, are distinguished by much larger fruits in the Bolivian variety and much larger leaves in the Peruvian. The Bolivian drug is the more highly esteemed in Peru. The coca, which grows wild in various parts of South America, is cultivated not only in its native country, but also in India, Sri Lanka, and Indonesia. The coca plant, which is propagated from seed in nurseries, begins to yield in 18 months, and continues productive for half a century. The leaves, when mature, are carefully picked by hand so as to avoid breaking them or injuring the young buds, are slowly dried in the sun, and are then packed in bags (*cestos*) holding from 25 to 150 lb each. They were in general use among the natives of Peru at the time of the conquest (Wood and Bache, 1894).

## BOTANICAL PROPERTIES

The leaves resemble in size and shape those of tea; they are oval-oblong, pointed, 2 in. or more in length by somewhat over an inch in their greatest breadth, and furnished with short delicate



footstalks. However, unlike tea-leaves, they are not dentate and are distinguished from most other leaves by a slightly curved line on each side of the midrib, running from the base to the apex. These lines are not ribs but curves, which have been produced by the peculiar folding of the leaf in the bud. Good specimens are perfectly flat, of a fine green color; brown leaves should always be rejected as inferior. They have an agreeable odor resembling that of tea, and a peculiar taste which, in decoction, becomes bitter and astringent. Leaves vary between ovate, lanceolate, and obovate—oblong, and are from 2 to 5 or 7 cm in length; they are short-petiolate, entire, rather obtuse or emarginate at the apex, slightly reticulate on both sides, with a prominent midrib, and on each side, a curved line runs from base to apex; their odor is slight and tealike; taste is somewhat aromatic and bitter. When chewed, it temporarily numbs the lips and tongue (Culbreth, 1927).

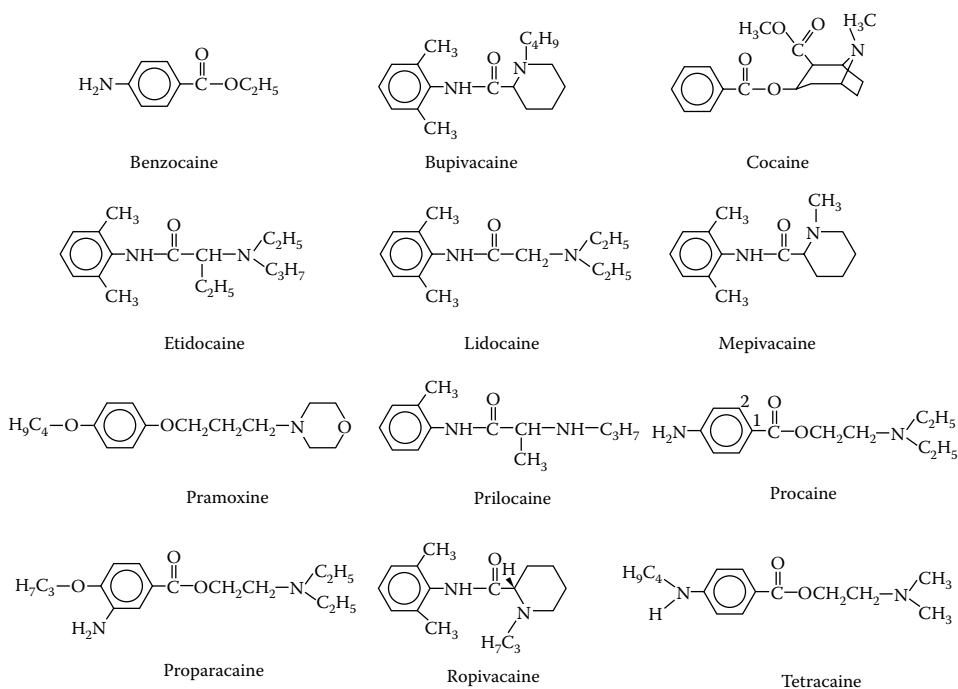
### CHEMICAL COMPOSITION

In 1853, it was demonstrated that coca leaves contained **tannic acid** and a peculiar bitter principle, resin, **tannin**, an aromatic principle, extractive, **chlorophyll**, a substance analogous to **theine**, and **salts of lime**. In 1855, the crystalline alkaloid **erythroxyline** was discovered in coca leaves, which was called **cocaine**. The earlier methods for isolating cocaine were as follows:

1. The leaves are exhausted with 85% alcohol and acidulated with 2% of sulfuric acid; the tincture is treated with milk of lime and filtered; the filtrate is neutralized with sulfuric acid, and the alcohol distilled off. The syrupy residue is treated with water to separate resin and then precipitated by sodium carbonate. The deposited matter is exhausted by ether, and the ethereal solution, after most of the ether has been distilled, is allowed to evaporate spontaneously. The cocaine is thus obtained in colorless crystals, mixed with a yellowish-brown matter of a disagreeable odor, which is separated by washing with cold alcohol.
2. Coarsely ground coca leaves are re-percolated with an aqueous 5% solution of sulfuric acid, and a very dense, slightly acid percolate is obtained, which is thoroughly agitated with pure coal oil and an excess of sodium carbonate. The liberated alkaloid is retained by the coal oil and is nearly free from coloring matter. The oily solution is then agitated with acidulated water and again precipitated by sodium carbonate in the presence of ether. The ethereal solution of cocaine is treated with diluted hydrochloric acid fractionally, and the nearly colorless solutions of cocaine hydrochlorate are cautiously evaporated in shallow porcelain pans almost to dryness. The product is in the form of a white, crystalline, granular powder and is a nearly pure anhydrous salt.
3. Pure cocaine is in colorless, transparent prisms, inodorous, of a bitter taste, soluble in 704 parts of cold water, more soluble in alcohol, and freely so in ether. The solution has an alkaline reaction and a bitter taste, leaving a peculiar numbness on the tongue. The alkaloid melts at 97.7°C (208°F) and on cooling congeals into a transparent mass, which gradually becomes crystalline. Heated above this point, it changes color and is decomposed. It is inflammable, burning with a bright flame and leaving charcoal. With the acids it forms soluble and crystallizable salts, which are more bitter than the alkaloid itself. The formula is  $C_{17}H_{21}NO_4$ .

### COCAINE AS A LOCAL ANESTHETIC

When applied locally to nerve tissue in appropriate concentrations, local anesthetics (Figure 23.2) reversibly block the action potentials responsible for nerve conduction. They act on any part of the nervous system and on every type of nerve fiber. Thus, a local anesthetic in contact with a nerve trunk can cause both sensory and motor paralysis in the area innervated. The necessary practical advantage of the local anesthetics is that their action is reversible at clinically relevant concentra-



**FIGURE 23.2** Structural formulas of selected local anesthetics.

tions; their use is followed by complete recovery in nerve function with no evidence of damage to nerve fibers or cells.

## GENERAL PHARMACOLOGY OF LOCAL ANESTHESIA

When a local anesthetic is injected near a nerve, it blocks the flow of electrons along the axons and eliminates the pain without loss of consciousness. These effects are reversible. When administering a local anesthetic, one must remember that the larger the diameter of the nerve fiber, the more anesthetic is needed to produce anesthesia.

All local anesthetics contain a **lipophilic group**, an **amino derivative**, and an **intermediate chain** (Figure 23.3). The intermediate chain may be either an ester, as seen in compounds such as **cocaine**, **procaine** (Novocain), and **tetracaine** (Pontocaine), or an **amide**, as seen in compounds such as **lidocaine** (Xylocaine), **mepivacaine** (Carbocaine), **bupivacaine** (Marcaine), and **dibucaine** (Nupercaine). **Cross-sensitivity** occurs among drugs in the same group (e.g., cocaine, procaine, and tetracaine), but not between compounds containing ester and amide linkages.

Local anesthetics are unstable and insoluble in **basic solution**. If a local anesthetic lacks an amine, it is insoluble in water and is only used topically.

### VASCULAR SUPPLY AT THE SITE OF INJECTION

Epinephrine is used in combination with a local anesthetic to reduce its uptake, prolong its duration of action, produce a bloodless field of operation, and protect against systemic effects (Figure 23.4). Local anesthetic solutions containing epinephrine should not be used in areas supplied by end arteries such as in the digits, ear, nose, and penis, because of the threat of ischemia and subsequent gangrene. Furthermore, under no circumstances should anesthetic solutions containing epinephrine be used intravenously in patients with cardiac arrhythmias. In general, solutions designed for multiple doses should not be used for **spinal or epidural anesthesia**.

Amides	Potency	Duration of Action
Lidocaine	4	Medium
Medpicacaine	2	Medium
Prilocaine	3	Medium
Bupicacaine	16	Long
Etidocaine	16	Long
Esters		
Cocaine	2	Medium
Procaine	1	Short
Tetracaine	16	Long

FIGURE 23.3 Duration of action of various local anesthetics.

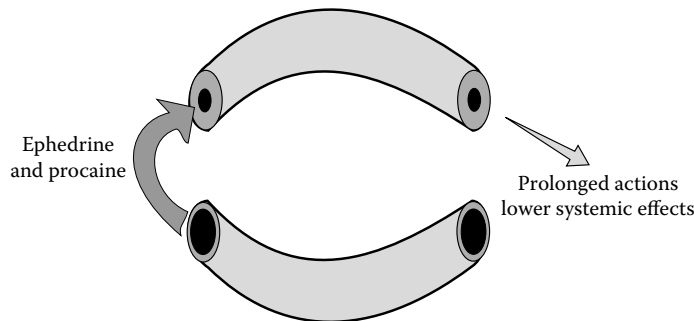


FIGURE 23.4 Epinephrine prolongs the duration of action of local anesthetics.

## SYSTEMIC REACTIONS

### CARDIOVASCULAR EFFECTS

Local anesthetics block the sodium channels, are cardiac depressants, and bring about a ventricular conduction defect and block that may progress to cardiac and ventilatory arrest if toxic doses are given. In addition, these agents produce arteriolar dilation. Circulatory failure may be treated with vasopressors such as **ephedrine**, **metaraminol** (Aramine), or **mephentermine** (Wyamine). Artificial respiration and cardiac massage may also become necessary. Among the local anesthetics, only cocaine blocks the uptake of norepinephrine, causes vasoconstriction, and may precipitate cardiac arrhythmias.

### CENTRAL NERVOUS SYSTEM EFFECTS

An overdose of local anesthetics can produce dose-dependent central nervous system (CNS) side effects such as insomnia, visual and auditory disturbances, nystagmus, shivering, tonic-clonic convulsions, and finally fatal CNS depression. The initial CNS excitation and convulsions may be brought under control by **diazepam** or **thiopental**.

### ALLERGIC REACTIONS

The **ester-containing local anesthetics** become metabolized to ***p*-aminobenzoic acid derivatives**, which have a potential for causing hypersensitivity reactions. Allergic reactions to amide are

extremely rare. In general, patients who have shown hypersensitivity reactions to ester compounds are treated with amide compounds. If a patient proves sensitive to both ester and amide compounds, then the hypersensitivity reaction is treated with certain antihistaminics such as diphenhydramine, which also possesses local anesthetic properties.

### EFFECT OF COCAINE

Cocaine, which blocks the uptake of catecholamines, produces dose-dependent effects, initially causing euphoria, vasoconstriction, and tachycardia, and in toxic doses, convulsions, myocardial depression, ventricular fibrillation, medullary depression, and death. Cocaine is able to block nerve conduction and currently is used only for topical anesthesia.

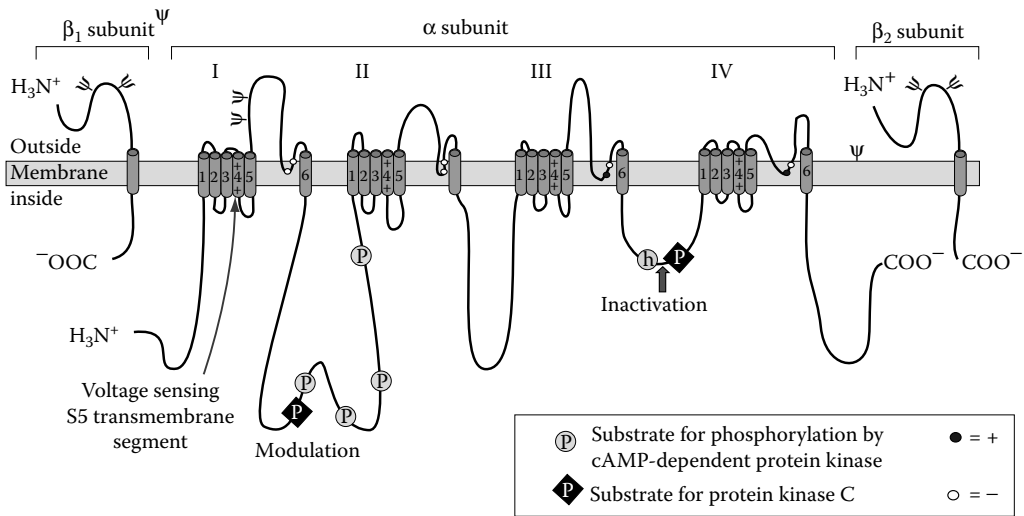
### MECHANISM OF LOCAL ANESTHETIC ACTION OF COCAINE

Cocaine and other local anesthetics prevent the generation and the conduction of the nerve impulse. Their primary site of action is the cell membrane. Local anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to  $\text{Na}^+$  that normally is produced by a slight depolarization of the membrane. This action of local anesthetics is due to their direct interaction with **voltage-gated  $\text{Na}^+$  channels**. As the anesthetic action progressively develops in a nerve, the threshold for electrical excitability gradually increases, the rate of rise of the action potential declines, impulse conduction slows, and the safety factor for conduction decreases; these factors decrease the probability of propagation of the action potential, and nerve conduction fails (Figure 23.5).

### DETAILED PHARMACOLOGY OF COCAINE AS A LOCAL ANESTHETIC

Many substances of widely different chemical structure abolish the excitability of nerve fibers on local application in concentrations that do not cause permanent injury and that may not affect other tissues. Sensory nerve fibers are most susceptible, so that these agents produce a selective sensory paralysis, which is utilized especially to suppress the pain of surgical operation. This property was first discovered in **cocaine**, but because of its toxicity and addiction liability, it has been largely displaced by synthetic chemicals. The oldest of these, **procaine** (novocaine), is still the most widely used. Its relatively low toxicity renders it especially useful for injections, but it is not readily absorbed from intact mucous membranes and is therefore not very effective for them. Many of its chemical derivatives are also used. They differ in penetration, toxicity, irritation, and local injury as well as in duration of action and potency. Absolute potency is not so important for practical use as is its balance with the other qualities. If cocaine is absorbed in sufficient quantity, it produces complex systemic actions, involving stimulation and paralysis of various parts of the CNS. These are mainly of toxicological and scientific interest. Its continued use leads to the formation of a habit, resembling **morphinism**. This is not the case with the other local anesthetics.

Direct contact with cocaine or procaine paralyzes all forms of nervous tissue, without preceding stimulation. The susceptibility of the various nerve fibers presents marked and characteristic quantitative differences. Sensory fibers are especially easily attacked and, by using appropriate dilutions, the paralysis is as complete as if the nerve fibers had been severed with a knife. If the drug is washed away, or absorbed, the nerve recovers its functions promptly and completely (but very strong solutions of cocaine may produce neuritis and permanent paralysis). Because these effects are strictly local, it follows that the anesthetic agent must be applied in such a way that an effective concentration reaches the nerve supply of the part which it is desired to affect. This may be accomplished by painting a solution on mucous membranes (from which cocaine is very readily absorbed); or by injecting it into or under the skin (**infiltration and subcutaneous anesthesia**), or



**FIGURE 23.5** Structure and function of voltage-gated  $\text{Na}^+$  channels. A two-dimensional representation of the  $\alpha$  (center),  $\beta_1$  (left), and  $\beta_2$  (right) subunits of the voltage-gated  $\text{Na}^+$  channel from mammalian brain. The polypeptide chains are represented by continuous lines with length approximately proportional to the actual length of each segment of the channel protein. Cylinders represent regions of transmembrane,  $\alpha$  helices.  $\Psi$  indicates sites of demonstrated *N*-linked glycosylation. Note the repeated structure of the four homologous domains (I through IV) of the  $\alpha$  subunit. **Voltage Sensing:** The S4 transmembrane segments in each homologous domain of the  $\alpha$  subunit serve as voltage sensors. (+) represents the positively charged amino acid residues at every third position within these segments. Electrical field (negative inside) exerts a force on these charged amino acid residues, pulling them toward the intracellular side of the membrane. **Pore:** The S5 and S6 transmembrane segments and the short membrane-associated loops between them (segments SS1 and SS2) form the walls of the pore in the center of an approximately symmetrical square array of the four homologous domains. The amino acid residues indicated by circles in segment SS2 are critical for determining the conductance and ion selectivity of the  $\text{Na}^+$  channel and its ability to bind the extracellular pore-blocking toxins tetrodotoxin and saxitoxin. **Inactivation:** The short intracellular loop connecting homologous domains III and IV serves as the inactivation gate of the  $\text{Na}^+$  channel. It presumably folds into the intracellular mouth of the pore and occludes it within a few milliseconds after the channel opens. Three hydrophobic residues (isoleucine-phenylalanine-methionine, IFM) at the position marked *h* appear to serve as an inactivation particle, entering the intracellular mouth of the pore and binding to an inactivation gate receptor there. **Modulation:** The gating of the  $\text{Na}^+$  channel can be modulated by protein phosphorylation. Phosphorylation of the inactivation gate between homologous domains III and IV by protein kinase C slows inactivation. Phosphorylation of sites in the intracellular loop between homologous domains I and II by either protein kinase C or cyclic AMP-dependent protein kinase (p) reduces  $\text{Na}^+$  channel activation.

around or into the trunk (**peri- or intraneural anesthesia**), or around the spinal nerve roots (**subdural or spinal anesthesia**). The intact skin is practically impermeable even to cocaine, although it penetrates slightly if the skin has been macerated.

### SELECTIVE ACTION ON MOTOR AND SENSORY FIBER

When a 1/2 to 2% solution of cocaine is injected into a mixed nerve or into the subdural canal, the selective action is very marked, so that there is complete anesthesia, without motor impairment. If the contact is prolonged, by stopping the circulation, or if stronger solutions are employed, the motor fibers become paralyzed, so that the difference is merely quantitative. A similar difference in the susceptibility of motor and sensory structures exists also for the alcohol group, **aconitine**, **phenol**, **hydrocyanic acid**, and for pressure, and even for the centrally acting narcotics, ether, etc. It is therefore a characteristic of nervous tissue rather than of cocaine. It is now generally

accepted that the selective action in peripheral nerves is due chiefly if not entirely to differences in the size of the myelinated nerve fibers, for it follows this order closely, the smallest fibers being blocked first, the largest last. The selective action may therefore depend on penetration of the axis cylinder fibrillae.

### PERIPHERAL PARALYSIS OF SPECIAL SENSE NERVES

Cocaine and other local anesthetics abolish not only the sensation of pain, but other special sensations, if they are suitably applied. Here also there is some selection. In the skin, they paralyze first the vasoconstrictor reaction, then progressively the sensations of cold, warmth, touch, tickling, pressure, pain, and "joint sense." In the nose, they abolish the olfactory sense. On the tongue, they destroy the taste for bitter substances but have less effect on sweet and sour taste and none on salty taste. When cocaine is applied to the appropriate nerves, it is found that the **centrifugal vagus fibers** are paralyzed before the centripetal, vasoconstrictor fibers before vasodilator, bronchial constrictors before the dilators, etc. (Sollmann, 1944).

### SITE OF ACTION

All local anesthetics including cocaine paralyze the nerve fibers anywhere in their course, wherever they are brought into contact with them. When applied to mucous membranes or hypodermically, they select the portions peripheral to the main trunks, the thinner sheath of the terminal fibrils facilitating its penetration. It is therefore unnecessary to assume selective action on the histological sensory endings.

The **oxygen consumption** of nerve is decreased by cocaine, procaine, and urethane, approximately in the ratio of their anesthetic concentrations.

### COMBINATION OF ANESTHETICS

The efficiency of mixtures of the local anesthetics corresponds to more or less complete summations, generally without a potentiation. Thus, if solutions of different anesthetics are diluted until they are "just effective" — then a mixture of any two of these solutions will also be "just effective" — no more and no less.

### POTASSIUM SYNERGISM

Potassium salts may considerably potentiate other anesthetics. However, this seems to hold mainly for motor fibers and not for sensory. A 1% potassium chloride solution could be used with some advantage in place of sodium chloride for making up isotonic anesthetic solutions.

### ALKALINIZATION

The addition of sodium bicarbonate increases the potency of the local anesthetics two to four times for direct application or injection into nerve trunks and probably for subdural injection and on application to mucous surfaces. This is due to the easier penetration of the free anesthetic bases, as compared with their salts. For these purposes, the usual solutions of the anesthetic salts may be mixed with an equal volume of 0.5% sodium bicarbonate solution, without loss of efficiency, and with a saving of one half of the anesthetic, and correspondingly smaller danger of accidents. The mixtures, however, do not keep well, and must be made just before use. Alkalinization or buffering has *no advantage for hypodermic or intradermic injections*, because these do not require much penetration. Procaine base dissolved by the aid of carbon dioxide is also more potent than the hydrochloride when applied to the cornea, but not for intramuscular injection.

The **effects of temperature on local anesthesia** of frog's nerve differ for various types of anesthetics; **cocaine**, **salicylamide**, and **monacetine** are more effective on cooled nerves, whereas

alcohol and chloral are more effective on heated nerves. This is probably connected with differences in solubility and the "partition coefficient."

### OTHER SYNERGISMS

Additions of 1/10 to 2 1/2% of urea to dilute procaine solutions increase materially their potency, to ten times, on direct application to nerve trunks, presumably by favoring penetration. The effect is not due to alkalization. The action of local anesthetics is reported to be increased by intravenous injection of **methylene blue**, by the local application of **caffeine** or **theophylline**, by morphine, and by the antipyretic analgesics. Cocaine anesthesia is said to be ineffective in tissue impregnated with **oxalic acid**. Inflamed tissues are less susceptible to local anesthesia, probably because of their difficult penetration.

### EPINEPHRINE ANESTHETIC COMBINATIONS

The anesthetic effect of cocaine injections is greatly improved by the addition of epinephrine (about 1:50,000). The duration of the anesthesia is prolonged for over an hour. The effective concentration can therefore be considerably lowered, and the danger of poisoning greatly reduced. These results are due to the vasoconstriction, which practically arrests absorption into the circulation. On the other hand, the nervousness induced by epinephrine in hypersensitive individuals may make them more susceptible to cocaine collapse. The greatest field for the epinephrine combination is in connection with operations involving bleeding. It is useless on the intact cornea. Epinephrine is similarly efficient with procaine and most other local anesthetics. Its effect is not as pronounced with **stovaine** and is practically absent with **tropacocaine** because H% of this destroys the vasoconstriction effect of epinephrine. **β-eucaine** also counteracts epinephrine.

Epinephrine is not directly anesthetic either alone or in combination with cocaine for it does not increase the anesthetic effect when the circulation has previously been arrested. It also does not lower the threshold concentration in wheals, although the duration of the anesthesia is greater for a given concentration.

### LOCAL VASCULAR ACTION

Cocaine produces vasoconstriction (blanching) probably by sensitizing to sympathetic stimulation. This action is lacking in the other local anesthetics. Procaine has practically no vascular effect; **alypin**, **eucaine**, and **stovaine** cause some dilatation. Cocaine decreases capillary hemorrhage; **procaine**, **apothesine**, and other synthetic anesthetics tend rather to increase bleeding.

### PRACTICAL APPLICATION OF LOCAL ANESTHETICS

This involves considerable art, which must be learned in the clinic. It falls into two divisions: (1) surface application to the mucous membranes, especially of the eye, nose, throat, and urethra; and (2) injections about nerves, in different parts of their course and distribution, from their spinal roots to their ultimate fibrils. The advantages and disadvantages in comparison with general anesthesia and the selection of the local anesthetic agent also depend on clinical discrimination. Nervous, fearful, and excitable patients often suffer severely from apprehension, which also disposes toward accidents. They may be at least somewhat quieted by sedatives, morphine (0.015 g hypodermically) half an hour before the operation, or by barbiturates. The latter also tend to prevent convulsions.

The onset of the action depends on the penetration into the nerve fibers, and the duration on the sojourn of the drug. In general, the sensation becomes blunter in a few minutes but the anesthesia does not reach its maximum for 10 to 20 min and lasts 10 to 30 min, after a single application. The duration depends more on the concentration than on the total amount of the agent, so that it is more economical to use small quantities in high concentration, repeating if necessary.

## LOCAL ISCHEMIA

As the anesthetic agent is absorbed and thus removed from the site of application, its local action ceases, and its systemic and toxic effects start. Because most of these drugs, especially cocaine, are rapidly destroyed in the body, the systemic toxicity increases with the rapidity of absorption. It is therefore desirable and often necessary to delay the absorption. This may be done by restricting the local circulation. Cocaine itself tends to do this by producing a local vasoconstriction, an action that is not shared by its substitutes. This vasoconstriction should be reinforced by the addition of epinephrine. More dilute solution may thus be used, and the anesthetic effect is much more prolonged. With intracutaneous infiltration, the pressure and edema also result in ischemia. In suitable situations, the circulation may be slowed by bandages, or arrested by temporarily clamping the arterial blood supply.

## SURFACE ANESTHESIA

Anesthesia from intact surfaces requires that the drug must be absorbable. This excludes the intact skin. **Cocaine**, **butyn**, **metycaine**, and **diothane** are readily absorbed from mucous membranes, and are therefore efficient but also correspondingly toxic. Procaine and **apothesine** are relatively inabsorbable and therefore less applicable. **Alypin** and  $\beta$ -**eucaïne** are intermediate, but the order of absorbability varies for different mucosae.

## OPHTHALMIC ANESTHESIA

Cocaine, 4% or butyn, 2% is applied to the conjunctiva for deep penetration as in cataract operations; **phenacaine (holocaine)**, 2% or **butyn**, 2% for surface action (foreign bodies), etc. Toxic manifestations are rare and slight because only small quantities are used. For infiltration, 2% procaine is advised. Several of the anesthetic agents produce some conjunctival irritation, smarting, and congestion. Cocaine blanches the conjunctiva, but cloudiness and even ulcers of the cornea sometimes follow its application; they are partly explainable by the drying and by the irritation of dust and other foreign matters that are not perceived on account of the anesthesia, and by the abolition of the winking reflex. The protoplasmic toxicity may play a part in their production.

## ACTIONS OF COCAINE ON THE EYE

When cocaine is applied to the conjunctiva, it produces local anesthesia (which may not extend to the iris), local anemia (which extends to the iris but not to the retina), and submaximal dilatation of the pupil by peripheral sympathetic stimulation. Mydriasis occurs also on systemic administration. The accommodation is impaired, but the light reflex is preserved; there is some **exophthalmos**. The intraocular pressure is usually lowered, but may be increased. The mydriasis and its associated phenomena are not produced by most of the cocaine substitutes.

## INSOLUBLE ANESTHETICS FOR OPEN WOUNDS AND ULCERS

The soluble anesthetics are absorbed too rapidly to be of material use in persistent pain. The limited and slow solubility of some of the free synthetic bases renders them more adapted to these conditions. However, their practical usefulness is not great. They are employed for painful wounds, ulcers, etc., of the skin and accessible mucous membranes, for example, after dental operations. **Ethyl aminobenzoate (anesthesine)** may be applied diluted with 5 to 20 parts of talcum or boric acid, or lozenges of 0.01 to 0.02 g, but it has been reported that it delays the healing of x-ray burns and increases their depth and extent. Insoluble anesthetics have also been used against the pain of gastric ulcer or cancer and other gastralgiias, but their efficiency is doubtful. Anesthesine, **cycloform**, **orthoform**, and **propaesin** are about equally effective through intact mucous membranes. They are practically nonirritant and nontoxic.



## CONDUCTION AND INFILTRATION ANESTHESIA

This consists in the injection of the local anesthetic into or around the nerve trunk or in the area of its distribution, so as to block off sensory impulses from the operative field. Because fatal effects may arise from the absorption of the anesthetic, the smallest amount of the least-toxic agent that is effective should be employed, under conditions that minimize absorption. Procaine with the addition of epinephrine (1:100,000) is generally preferred. A well-planned technique is important. It is not necessary to flood the entire field of operation, as in the earliest methods, nor even to infiltrate the whole line of incision, as in "infiltration anesthesia." It is now aimed at confining the anesthetic mainly to the nerves, by placing it where the nerves chiefly run or injecting it into the nerves themselves.

## SPASTIC RIGIDITY OF SKELETAL MUSCLES

The local injection of 0.1 to 2% procaine or other anesthetics blocks the **centripetal proprioceptive impulses** and thereby relaxes muscular tonus, normal and abnormal, such as **spasmodic torticollis**. It effects almost instantaneous relief of the pain, stiffness, malposition, and incapacity of **fibrositis**, **lumbago**, and acute sprains and fractures. The site of greatest tenderness may be infiltrated with 10 to 30 cc of 1 or 2% procaine hydrochloride. Injected systemically, it relaxes traumatic tetanus and removes decerebrate rigidity, so that spontaneous movements of the limbs and of the respiration return. Its curare action may also be concerned in this effect. It relaxes parkinsonian, but not myotonic, rigidity.

## SPINAL ANESTHESIA

Spinal anesthesia is really nerve-root anesthesia, produced by lumbar or sacral subdural injection of procaine or other local anesthetics, which anesthetizes the sensory nerve roots at their emergence from the spinal cord and abolishes sensation in their entire peripheral distribution, beginning in 2 to 10 min, and lasting 1/2 to 2 h. There is little if any interference with motor functions, and consciousness is of course preserved. The anesthesia extends to the level of the nerve roots reached by the anesthetic, with the aim of confining it to the lower half of the body. If it extends to the fourth ventricle, it paralyzes respiration. Alarming symptoms and fatalities from this cause are not infrequent. Other side actions are a drop in blood pressure, severe headache that may sometimes last for days or weeks, and cord injury. Bronchial pneumonia and atelectasis are fairly common. The technique requires some practice, is disagreeable to the patient, and the anesthesia is not always completely successful. Spinal anesthesia causes more psychic shock than general anesthesia but usually less somatic disturbance. It is especially useful in pulmonary disease, arteriosclerosis, bladder and rectal operations, impending uremia, and in patients with diabetes. It is more difficult and more dangerous for operations above the costal margin. If the respiration stops, artificial respiration is the most effective treatment. **Strychnine** and caffeine have little or no value. Epinephrine or ephedrine is injected if the blood pressure falls.

## SYMPATHETIC STIMULATION

The phenomena of systemic cocaine poisoning are largely those of sympathetic stimulation but not as consistently as with epinephrine. The sympathetic stimulation is mainly central (midbrain) but partly peripheral. The chief manifestations of sympathetic stimulation are (1) sensitization to epinephrine (but antagonization to ephedrine) by peripheral action, (2) mydriasis and slight exophthalmos by central and peripheral action, and (3) cardiac acceleration (chiefly central). Other sympathetic symptoms are constriction of the blood vessels, erection of hair, and relaxation of the intestines. High concentrations of cocaine paralyze all smooth muscles. Procaine also produces

sympathetic stimulation on systemic administration, dilating the pupils, augmenting the heart, inhibiting the intestines, increasing the pressor action of tyramine.

### CIRCULATION

The effects of cocaine on the general circulation are partly central, and partly peripheral. They vary according to the dose, and are also influenced by individual susceptibility. **The systemic actions of cocaine** are rather variable and complex, depending largely on the dose.

### CEREBRAL STIMULATION

The first systemic effects of cocaine consist in physical stimulation somewhat resembling caffeine. This differs considerably in degree and in kind with individuals and may be manifested as alertness, loquacity, elation, wakefulness, excitement (sometimes markedly sexual), or anxiety and flutter. The stimulation is greatest in excitable individuals and may interfere seriously with operations. Patients should be forewarned of the anxiety complex.

### INCOORDINATION, NARCOSIS, AND CONVULSIONS

The stage of stimulation may be very short or even absent. With somewhat larger doses, it is usually succeeded by depression, first of the coordinating functions. The movements lose their purposive type and become choreic. This is followed by general narcosis and then by epileptiform convulsions, located chiefly in the midbrain. If the paralysis is rapid, the convulsive stage may not appear.

The **respiration** is at first accelerated. During the spasms, it is irregular. The volume then diminishes. It may assume the Cheyne–Stokes type. Respiratory paralysis is the usual cause of death. This is also the first center to fail when the cocaine is applied locally to the fourth ventricle.

### EMESIS

The vomiting that frequently occurs in cocaine poisoning is perhaps due to the medullary stimulation, but its mechanism has not been fully investigated.

### TEMPERATURE

Cocaine produces hyperpyrexia in mammals, due to increased heat production, by the motor excitement and rise of basal metabolic rate, reinforced by the convulsions. It probably acts directly on the midbrain temperature centers. Cocaine lowers the temperature of birds. Procaine lowers the temperature of mammals by increasing heat loss. It is antagonized by **thyroxin** and by **dinitrophenol**.

## EXAMPLES OF CURRENTLY USED LOCAL ANESTHETICS

### PROCAINE

Procaine, which has a  $pK_a$  of 8.9, is highly ionized at physiological pH and has a short duration of action. Because it causes vasodilation, a vasoconstricting substance is added to the procaine solution to delay systemic absorption. Procaine may prolong the effect of **succinylcholine** because both drugs are metabolized by the same enzyme. **Cholinesterase inhibitors** alter metabolism of procaine.

### CHLOROPROCAINE

Chloroprocaine has an onset of action of 6 to 12 min and its pharmacological properties resemble those of procaine.

### TETRACAINE

Tetracaine, which is metabolized slowly by **pseudocholinesterase**, has a relatively long duration of action.

### LIDOCAINE

Lidocaine is effective in producing analgesia when administered by infiltration, or by nerve, epidural, caudal, and spinal block. In addition, it is effective when applied topically, with an onset of action of 5 min and a duration of action of 15 to 30 min. Lidocaine (1.5 µg/ml) is the agent of choice for the acute suppression of most ventricular arrhythmias.

### MEPIVACAINE

Mepivacaine, which is ineffective topically, is used for infiltration plus nerve, epidural, and caudal block. Its potency and speed of action are similar to those of lidocaine.

### PRILOCAINE

Prilocaine, which is equal in potency to lidocaine, has a longer duration of action. It is metabolized to *o-toluidine*, which in toxic doses may cause **methemoglobinemia**.

### BUPIVACAINE

Bupivacaine, which is more potent than lidocaine, has a prolonged duration of action.

### ETIDOCAINE

Etidocaine is a long-acting derivative of lidocaine but is far more potent. It is effective for infiltration anesthesia, peripheral nerve block, and epidural and caudal blockade.

## CLINICAL USES OF LOCAL ANESTHETICS

Local anesthesia is the loss of sensation in a body part without the loss of consciousness or the impairment of central control of vital functions. It offers two major advantages. The first is that the physiological perturbations associated with general anesthesia are avoided; the second is that neurophysiological responses to pain and stress can be modified beneficially.

### INFILTRATION ANESTHESIA

Infiltration anesthesia is the injection of local anesthetic directly into tissue without taking into consideration the course of cutaneous nerves. Infiltration anesthesia can be so superficial as to include only the skin. It also can include deeper structures such as intra-abdominal organs when these too are infiltrated. The advantage of infiltration anesthesia and other regional anesthetic techniques is that it is possible to provide satisfactory anesthesia without disruption of normal bodily functions.

### FIELD BLOCK ANESTHESIA

Field block anesthesia is produced by subcutaneous injection of a solution of local anesthetic such that the region distal to the injection is anesthetized.

## NERVE BLOCK ANESTHESIA

Injection of a solution of a local anesthetic into or about individual peripheral nerves or nerve plexuses produces even greater areas of anesthesia than do the techniques described previously. Blockade of mixed peripheral nerves and nerve plexuses also usually anesthetizes somatic motor nerves, producing skeletal muscle relaxation, which is useful for some surgical procedures.

## INTRAVENOUS REGIONAL ANESTHESIA (BIER'S BLOCK)

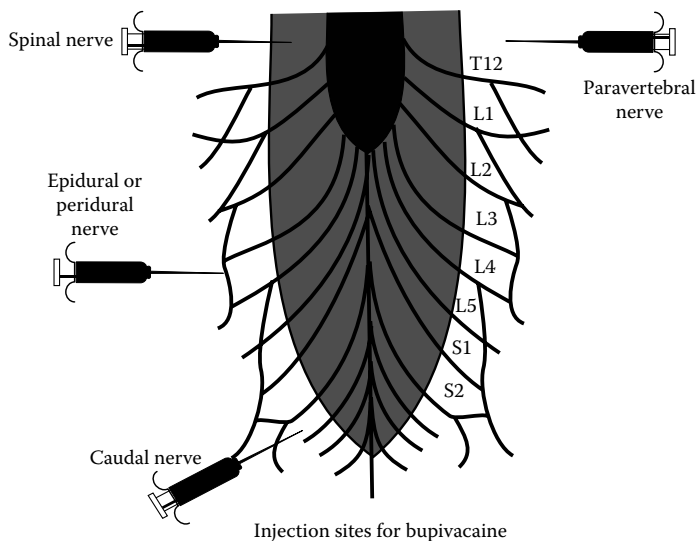
This technique relies on using the vasculature to bring the local anesthetic solution to the nerve trunks and endings. In this technique, an extremity is exsanguinated with an Esmarch (elastic) bandage, and a proximally located tourniquet is inflated to 100 to 150 mm Hg above the systolic blood pressure. The Esmarch bandage is removed, and the local anesthetic is injected into a previously cannulated vein. Typically, complete anesthesia of the limb ensues within 5 to 10 min.

## SPINAL ANESTHESIA

Anesthesia of the lower extremities and abdomen may be induced by the introduction of anesthetic drugs into the **subarachnoid space** (Figure 23.6). The drug most often used for this purpose is **bupivacaine**. The latency period plus the duration of the maximal cephalad level for both **plain and hyperbaric bupivacaine** lasts from 10 to 60 min. A bupivacaine solution is made hyperbaric by the addition of 5 to 8% glucose. The distribution of bupivacaine in the cerebrospinal fluid (CSF) is affected by gravity and is therefore influenced by the patient's position. With a dose of 15 mg of plain 0.5% bupivacaine, a half-life of about 3 h is achieved. The addition of epinephrine to bupivacaine prolongs the duration of block.

The advantages of spinal anesthesia are the ease of administration, rapid onset of anesthesia, and good muscular relaxation, plus it allows patients to remain awake.

The disadvantages of spinal anesthesia are hypotension (**ephedrine** and **methoxamine** may prevent this), nausea and vomiting (avoided by thiopental), respiratory depression (treated by artificial respiration), and postoperative headache (treated by increasing the CSF pressure).



**FIGURE 23.6** Administration of anesthetics into subarachnoid space. T<sub>12</sub> = 12th thoracic nerves; L<sub>1</sub>, L<sub>2</sub>, L<sub>3</sub>, L<sub>4</sub>, L<sub>5</sub> = first, second, third, fourth, and fifth lumbar nerves; S<sub>1</sub>, S<sub>2</sub> = first and second sacral nerves.

## EPIDURAL ANESTHESIA

Epidural anesthesia is administered by injecting local anesthetic into the epidural space (the space bounded by the ligamentum flavum) posteriorly, the spinal periosteum laterally, and dura anteriorly. Epidural anesthesia can be performed in the sacral hiatus (caudal anesthesia) or in the lumbar, thoracic, or cervical regions of the spine.

## EPIDURAL AND INTRATHECAL OPIATE ANALGESIA

Small quantities of opiate injected intrathecally or epidurally produce segmental analgesia. This observation led to the clinical use of spinal and epidural opiates during surgical procedures and for the relief of postoperative and chronic pain. As with local anesthesia, analgesia is confined to sensory nerves that enter the spinal cord dorsal horn in the vicinity of the injection. Presynaptic opioid receptors inhibit the release of **substance P** and other neurotransmitters from primary afferents, whereas postsynaptic opioid receptors decrease the activity of certain dorsal horn neurons in the spinothalamic tracts.

## SAFE AND TOXIC DOSAGE OF LOCAL ANESTHETICS

**Acute poisoning by local anesthetics** is fairly common, especially with cocaine, and is apt to be fatal. Some accidents are due to excessive doses through mistakes or faults of technique, but the susceptibility varies greatly owing to differences of absorption and of destruction, and to varying response to the actions. Fright plays a considerable part.

Probably all commonly used local anesthetics have produced fatal accidents. These depend not only upon the absolute dose, but also on the rate of absorption, on idiosyncrasy, and on other conditions. The Local Anesthetic Committee of the American Medical Association has made recommendations that should minimize the accidents. The following are the most important. Procaine appears the safest of the more widely used local anesthetics and may be employed for subcutaneous and submucosal injections, but the concentration should not exceed 1%. Cocaine and butyn should not be injected under the skin or mucous membranes but restricted to surface application. The total quantity of cocaine should not exceed 0.06 to 0.1 g (1 to 1 1/2 grains). The patient should be recumbent if the operation permits. With nervous patients, it is advisable to inject morphine 15 min before the local anesthetic and to delay the start of the operation until 20 min after the injection of the local anesthetic. Urethral injections are especially dangerous, and should be avoided if there is trauma or stricture.

Strict attention should be given to prevent the confusion of procaine and cocaine. The solutions should be kept in different kinds of bottles. Cocaine solution may be distinguished by tinting with sodium fluorescein, 1 mg/g of cocaine. This would also show the concentration of the solution.

The **treatment of poisoning by local anesthetics** should begin with prevention and the selection, dosage, and technique of the administration; gross errors and carelessness have caused many deaths. The previous administration of a sedative, especially of the barbituric series, diminishes the risk by suppressing the convulsions and their interference with respiration, so that animals survive one and a half to four times the ordinary fatal dose of cocaine or procaine if administered hypodermically.

Clinically, 0.2 g of phenobarbital or 0.6 g of sodium barbital may be administered an hour before operation. Barbiturates do not prevent the direct circulatory collapse and depression of respiration that occur on intravenous injection of procaine, and are useless or harmful for either prophylaxis or treatment if the anesthetic agent is rapidly absorbed. However, if the symptoms develop slowly, the suppression of the convulsions is at least helpful.

If an overdose of the local anesthetic has been taken by mouth, evacuation and chemical antidotes are indicated. If the anesthetic was injected, absorption should be blocked by ligation, if possible. Whatever delays death is likely to save the life in view of the rapid destruction of these drugs. If

the symptoms have developed, the head should be lowered, the convulsions arrested by intravenous injection of **sodium pentobarbital** or amytal, and artificial respiration instituted if necessary, with cardiac massage if the circulation fails. The use of epinephrine or morphine is not advised.

### DESTRUCTION OF COCAINE *IN VITRO*: STERILIZATION

Long-continued boiling decomposes cocaine into **benzoyl-ecgonine** and methyl alcohol. It was therefore believed that solutions could not be sterilized by boiling. However, the decomposition on boiling half an hour is in fact insignificant; even longer boiling only decreases the activity, because the decomposition products are merely inactive and not toxic. Any decomposition on boiling is probably due to alkalinity from the glass.

### COCAINE, A "NERVE STIMULANT"

As a nerve stimulant, coca leaves have been used immemorially by the Peruvian and Bolivian natives. In 1853, it was stated (Wood and Bache, 1894):

Coca leaves produce a gently excitant effect, with an indisposition to sleep, in these respects resembling tea and coffee; also that it will support the strength for a considerable time in the absence of food, but does not supply the place of nutriment, and probably in this respect also acts like the two substances referred to. The Indians, while chewing it, mixed with some alkaline substance, as the ashes of certain plants, or lime, pass whole days in traveling or working without food. It is, however, clearly proved that these leaves do not take the place of nutriment, but simply put off the sense of fatigue and hunger, the Indian making up at his evening meal for the day's abstinence. It is probable that they prevent hunger simply by their local benumbing influence upon the nerves of the stomach. Their moderate habitual use does not seem to be injurious, but the habit is said readily to grow upon the person, and finally the inveterate excessive coca-chewer can be recognized by his uncertain step, general apathy, sunken eyes surrounded by deep purple aureoles, trembling lips, green and crusted teeth, and excessively fetid breath, with peculiar blackness about the corners of the mouth. An incurable insomnia is apt to be developed, emaciation becomes extreme, dropsy appears, and even death results in a condition of general marasmus. When coca is taken in a single large dose it produces a condition of peculiar physical beatitude and calm, followed by a sensation of excessive power, which is affirmed to be accompanied by a real increase of physical ability.

In one case, where 900 grains of coca leaf were used by a physician named Mantegazza, the following symptoms appeared:

The ingestion of coca leaf caused great increase in the number of heart-beats, and a condition of intoxication resembling that produced by hasheesh. He was possessed by a feeling of intense joyousness, while a succession of visions and phantasmagoria, most brilliant in form and color, trooped rapidly before his eyes. He then passed into a condition of delirious excitement, which was succeeded by a deep sleep lasting three hours. (Culbreth, 1927)

Coca leaf can cause poisoning; in mild cases, the ordinary symptoms have been great restlessness and nervous excitement, but no sense of beatitude, rather a condition of fear and terror. With this state come usually distinctly accelerated pulse, increased frequency of respiration, and perhaps muscular twitching or even mild convulsions. In the more severe cases of poisoning, the symptoms vary; sometimes there have been nausea, vomiting, rapid almost imperceptible pulse, great perspiration, collapse with or without loss of consciousness; in other cases, the pulse has been slow and feeble, and sometimes pronounced cyanosis with slow or almost arrested respiration has been the most alarming manifestation. The pupils are usually dilated but are reported in some cases as "contracted." After very large doses, convulsions usually occur; they are often violent and epileptiform, and in many cases **opisthotonos** has been pronounced. Consciousness is usually lost, but

sometimes it merges into a mania with hallucinations and delusions; the mania may become violent and even homicidal. Poisoning has followed both the internal administration and the local uses of the alkaloid. The occasional overeffects of small doses are quite remarkable; thus, four drops of a 2% solution in the eye produced in an old woman intoxication that persisted 4 d; eight drops of a 10% solution in the eye of a girl of 12 years caused violent poisoning; and even one drop of a 1% solution in the eye of a child 14 years old is said to have been followed by violent symptoms. A number of cases are on record in which one grain of the alkaloid given hypodermically has caused very severe fainting. Death is reported in several cases from the local use of the remedy, and 12 drops of a 4% solution given hypodermically to a girl of 11 caused death in 40 sec. On the other hand, large doses have been recovered: 22 grains by the mouth, 10 grains hypodermically, 5 grains hypodermically, and 6 grains hypodermically.

### COCAINE ADDICTION

The elation and euphoria that cocaine induces in susceptible individuals tend to render it a “**habit drug**,” but it is more apt to be used for occasional “**jags**,” by criminals, rather than daily, as is morphine. The treatment is therefore easier and more likely to be successful. However, it may be used continuously as it was by the South American natives; in India, it is combined with the chewing of **betel leaf**. Cocaine inebriation is active and sociable, in contrast to the dreamy state induced by morphine. It may also induce a more or less maniacal condition, in which the individual becomes dangerous to others. The immediate effects include the phenomena of sympathetic stimulation, resembling hyperthyroidism: tachycardia, polypnea, mydriasis, exophthalmos, and fine tremors. Some individuals, especially women, react with marked erotic excitement. The stimulation is succeeded by depression, tremors, pallor, and sunken and unsteady eyes.

The chronic effects show rapid emaciation and severe psychic disturbances, insomnia, hallucinations, apathy, melancholia, and suicidal mania. The pupils are inconstant. Acne is common. It is claimed that considerable tolerance is acquired, so that the daily hypodermic consumption may reach 2.5 g or even 10 g. Morphine addicts are relatively tolerant to cocaine. Sudden withdrawal leads to abstinence symptoms similar to morphine. With cocaine snuffing, where smaller amounts are used in intermittent debauches, the chronic effects such as the craving and the abstinence symptoms are proportionately less marked. Such patients develop atrophic rhinitis, with characteristic ulceration of the nasal fossae — also present in people who snuff heroin.

### USES OF COCAINE IN THE 18TH CENTURY

In the treatment of melancholia, hysteria, epilepsy, spinal paralysis, insanity, diabetes, headache, typhoid state, opium habit, uterine inertia, vomiting of pregnancy, gastric irritability, cholera morbus, spermatorrhea, debility, poisoning by chloral hydrate, opium, or bromides cocaine was used. It was applied locally, to burns, painful ulcers, fissures of anus, hay fever, sore throat, laryngitis, hemorrhoids, bronchitis, coryza, and in surgical operations. It is effective hypodermically in fingers, toes, and small tumors (for amputation); for spinal anesthesia, cocaine is not as safe as novocaine, stovaine, or eucaine; no more than 3/4 g (0.045 g) should be applied at a time.

### COCAINE: A PSYCHOSTIMULANT

Not all users of cocaine become addicts. A key factor is the widespread availability of relatively inexpensive cocaine in the alkaloidal (free base, “**crack**”) form suitable for smoking and the hydrochloride powder form suitable for nasal or intravenous use. Drug abuse in males occurs about twice as frequently as in females. However, smoked cocaine use is particularly common in young women of childbearing age, who may use cocaine in this manner as commonly as do males.

The half-life of cocaine in plasma is about 50 min, but inhalant (crack) users typically desire more cocaine after 10 to 30 min. Intranasal and intravenous uses also result in a high of shorter

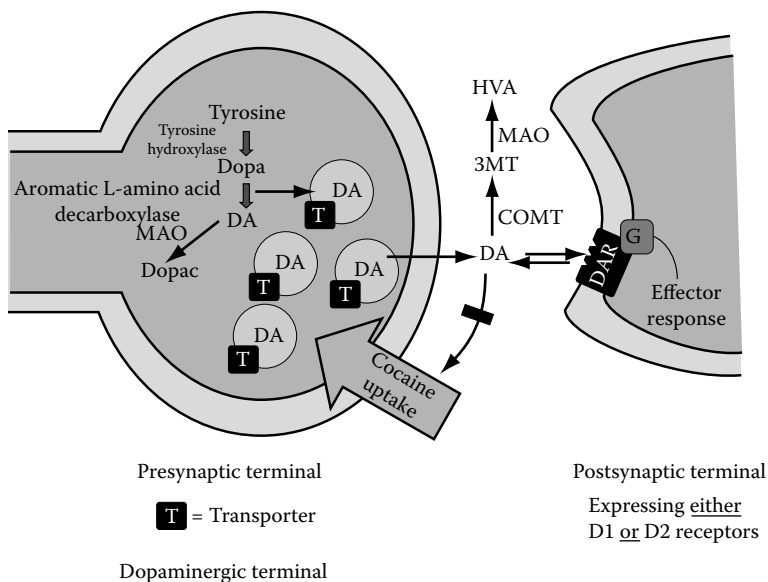
duration than would be predicted by plasma cocaine levels, suggesting that a declining plasma concentration is associated with termination of the high and resumption of cocaine seeking. This theory is supported by positron emission tomography (PET) imaging studies using  $C^{11}$ -labeled cocaine, which show that the time course of subjective euphoria parallels the uptake and displacement of the drug in the corpus striatum.

### COCAINE BLOCKS DOPAMINE TRANSPORTER

The reinforcing effects of cocaine and cocaine analogues correlate best with their effectiveness in blocking the **dopamine transporter**, which leads to increased dopaminergic stimulation at critical brain sites. However, cocaine also blocks both norepinephrine (NE) and serotonin (5-HT) reuptake, and chronic use of cocaine produces changes in these neurotransmitter systems as measured by reductions in the neurotransmitter metabolites MHPG (**3-methoxy-4 hydroxyphenethyleneglycol**) and 5-HIAA (**5-hydroxyindoleacetic acid**).

### BIOSYNTHESIS OF DOPAMINE

Dopamine, a catecholamine, is synthesized in the terminals of dopaminergic neurons from tyrosine, which is transported across the blood-brain barrier by an active process (Figure 23.7). The rate-limiting step in the synthesis of dopamine is the conversion of l-tyrosine to l-dihydroxy-phenylalanine (l-dopa), catalyzed by the enzyme tyrosine hydroxylase, which is present within catecholaminergic neurons.



**FIGURE 23.7** Dopamine (DA) is synthesized within neuronal terminals from the precursor tyrosine by the sequential actions of the enzymes tyrosine hydroxylase, producing the intermediary L-dihydroxyphenylalanine (Dopa), and aromatic L-amino acid decarboxylase. In the terminal, dopamine is transported into storage vesicles by a transporter protein (T) associated with the vesicular membrane. Release, triggered by depolarization and entry of  $Ca^{2+}$ , allows dopamine to act on postsynaptic dopamine receptors (DAR). Several distinct types of dopamine receptors are present in the brain, and the differential actions of dopamine on postsynaptic targets bearing different types of dopamine receptors have important implications for the function of neural circuits. The actions of dopamine are terminated by the sequential actions of the enzymes catechol-O-methyl-transferase (COMT) and monoamine oxidase (MAO), or by reuptake of dopamine into the terminal.



The major route for cocaine metabolism involves hydrolysis of each of its two ester groups. **Benzoyllecgonine**, produced upon loss of the methyl group, represents the major urinary metabolite and can be found in the urine for 2 to 5 d after a binge. As a result, benzoyllecgonine tests are useful for detecting cocaine use; heavy users have been found to have detectable amounts of the metabolite in urine for up to 10 d following a binge.

Cocaine frequently is used in combination with other drugs such as heroin or alcohol. An important metabolic interaction occurs when cocaine and alcohol are taken concurrently. Some cocaine is transesterified to **cocaethylene**, which is equipotent to cocaine in blocking dopamine reuptake. Other risks of cocaine use, beyond the potential for addiction, involve cardiac arrhythmias, myocardial ischemia, myocarditis, aortic dissection, cerebral vasoconstriction, and seizures. Death from trauma also is associated with cocaine use. Pregnant cocaine users may experience premature labor and **abruptio placentae**. Reports of developmental abnormalities in infants born to cocaine-using women are confounded by prematurity, multiple drug exposure, and poor pre- and postnatal care. Cocaine has been reported to produce a prolonged and intense orgasm if taken prior to intercourse, and its use is associated with often compulsive and promiscuous sexual activity. Long-term cocaine use, however, often results in reduced sexual drive; complaints of sexual problems are common among cocaine users presenting for treatment. Psychiatric disorders including anxiety, depression, and psychosis are common in cocaine users who request treatment. Although some of these psychiatric disorders undoubtedly existed prior to the stimulant use, many develop during the course of the drug abuse.

Experienced users require more cocaine over time to obtain euphoria. Since cocaine typically is used intermittently, even heavy users go through frequent periods of withdrawal or “**crash**.” The symptoms of withdrawal are seen in users admitted to the hospital.

## COCAINE WITHDRAWAL SYMPTOMS AND SIGNS

The chief symptoms include:

- Dysphoria, depression
- Sleepiness, fatigue
- Cocaine craving
- Bradycardia

## PHARMACOLOGICAL INTERVENTIONS

Because cocaine withdrawal is generally mild, treatment of withdrawal symptoms generally is not required. The major problem in treatment is not stopping cocaine, but helping the patient to resist the urge to restart compulsive cocaine use. Rehabilitation programs involving individual and group psychotherapy based on the principles of Alcoholics Anonymous and behavioral treatments based on reinforcing cocaine-free urine tests result in significant improvement in the majority of cocaine users. Nonetheless, there is great interest in finding a medication that can aid in the rehabilitation of cocaine addicts.

**Desipramine** is a tricyclic antidepressant that has been tested in several double-blind trials among cocaine addicts. Like cocaine, desipramine inhibits monoamine neurotransmitter reuptake, but its principal effects are on norepinephrine reuptake. It was hypothesized that desipramine could relieve some of the withdrawal symptoms of cocaine dependence and reduce the desire for cocaine during the vulnerable period following cessation of cocaine. This drug showed efficacy early in the epidemic in a group of patients who were primarily white collar intranasal cocaine users. The majority of subsequent studies of desipramine-using, more severely ill cocaine addicts have been negative.

Several other classes of medications have been tried in this disorder. Examples are: **amantadine**, a dopaminergic drug that has been reported to aid in detoxification, **fluoxetine**, a selective serotonin reuptake antagonist that has been reported to reduce cocaine use, and **buprenorphine**, a partial opioid agonist that has been found to reduce cocaine self-administration in monkeys. Thus far, all of the studies of medications to help prevent relapse to cocaine dependence have revealed modest benefits at best. Reports of success in uncontrolled trials have not been replicated in carefully controlled, double-blind studies. At present, there is general agreement that no medication is yet available that can be used reliably in the treatment of cocaine addiction.



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# 24 Colchicine and Gout

## INTRODUCTION

Colchicine (*Colchicum autumnale*) is useful in the following:

- Acute attacks of gout
- Familial Mediterranean fever
- Amyloidosis
- Psoriasis
- Behcet's syndrome

The focus of this chapter is on effects on gout.

## HISTORY

Colchicine is an alkaloid found in the corm and seeds of *Colchicum autumnale* (also called **autumn crocus** or **meadow saffron**), a plant so named because it grew in Colchis in Asia Minor (Figure 24.1). It is a bulbous liliaceous plant that blooms during the fall in the wet meadows of central and southern Europe. Although the poisonous action of colchicum was known to **Dioscorides**, preparations of the plant were first recommended for pain of articular origin by **Alexander of Tralles** in the 6th century A.D. Colchicum was known to Byzantine physicians as hermodactyl (**finger of Hermes**); it was also called *articulorum* (**soul of the joints**). Colchicum was introduced for the therapy of acute gout by **Baron Anton Von Storck** in 1763, and its specificity for this syndrome soon resulted in its incorporation in a number of “**gout mixtures**” popularized by charlatans. **Benjamin Franklin**, himself a sufferer from gout, is reputed to have introduced colchicum therapy in the U.S. The alkaloid colchicine was isolated from **colchicum** in 1820 by Pelletier and Caventou (Goodman and Gilman, 1955).

## GOUT AND HYPERURICEMIA

Gout is a hyperuricemic state (> 6 mg/dl) that is effectively diagnosed through the detection of **monosodium urate crystals** in the synovial fluid of the involved joint. Conditions causing hyperuricemia include the excessive synthesis of uric acid, the excessive synthesis of purine-precursor to uric acid, a high dietary intake of purine (shellfish, organ meat, anchovies, and wild game), diminished renal excretion of uric acid, and tissue destruction following injury or therapeutic irradiation.

Numerous agents, when used in therapeutic doses, can also cause hyperuricemia. This includes an analgesic dose of aspirin, thiazide diuretics, nicotinic acid, chronic consumption of alcohol, and antineoplastic agents.

If left untreated, the hyperuricemic state may precipitate an acute attack of gout, which first appears in metatarsal phalangeal joints. Ultimately, tophaceous deposits form in the joints and soft tissues such as the kidneys. The hyperuricemic state may be corrected either by inhibiting the synthesis of uric acid by **allopurinol** or by enhancing the elimination of uric acid by uricosuric agents.

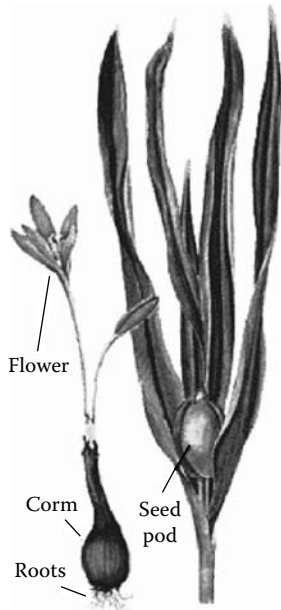


FIGURE 24.1 *Colchicum autumnale*.

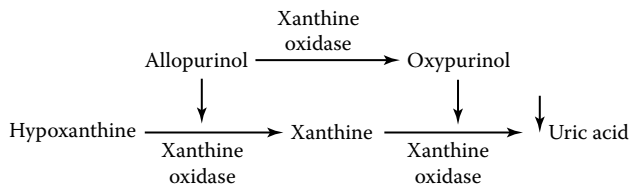


FIGURE 24.2 Allopurinol reduces the pool of uric acid.

## ALLOPURINOL

Allopurinol (Zyloprim) reduces the synthesis of uric acid by inhibiting the activity of xanthine oxidase, according to the scheme shown in Figure 24.2. The reduction in the uric acid pool occurs slowly. Because **xanthine** and **hypoxanthine** are more soluble than uric acid, they are easily excreted.

Allopurinol is used not only in treating the hyperuricemia associated with gout, but also in the secondary hyperuricemia associated with the use of antineoplastic agents. However, allopurinol may interfere with the metabolism of antineoplastic agents such as **azathioprine** and **6-mercaptopurine**.

## URICOSURIC AGENTS

The most commonly used uricosuric agents are **probenecid** (Benemid) and **sulfinpyrazone** (Anturane). In low doses, these agents block tubular secretion, but at higher doses, they also block the tubular resorption of uric acid. Because the solubility of uric acid is increased in alkaline urine, the administration of sodium bicarbonate may at times be advantageous for offsetting this condition. In addition, probenecid and sulfinpyrazone inhibit the excretion of agents such as aspirin, penicillin, ampicillin, and indomethacin. Although probenecid and sulfinpyrazone may be coadministered, neither should be given with aspirin, as their uricosuric effects will then be nullified.

## TREATMENT WITH COLCHICINE FOR GOUT

Colchicine (an alkaloid obtained from meadow saffron or autumn crocus) may be used both diagnostically to ascertain the presence of gout and prophylactically to prevent its further occurrence. Usually, 0.5-mg oral doses of colchicine are given hourly until either the therapeutic effects appear or the side effects develop. In addition to colchicine, phenylbutazone, indomethacin, adrenocorticotrophic hormone (ACTH), and steroidal anti-inflammatory agents may be used to treat the acute attack of gout.

### PHARMACOLOGICAL PROPERTIES

The anti-inflammatory effect of colchicine in acute gouty arthritis is relatively selective for this disorder. Colchicine is only occasionally effective in other types of arthritis; it is not an analgesic and does not provide relief of other types of pain.

Colchicine is an **antimitotic agent** and is widely employed as an experimental tool in the study of cell division and function.

### EFFECT IN GOUT

Colchicine does not influence the renal excretion of uric acid or its concentration in blood. By virtue of its ability to bind to tubulin, colchicine interferes with the function of the mitotic spindles and causes depolymerization and disappearance of the fibrillar microtubules in granulocytes and other motile cells. This action is apparently the basis for the beneficial effect of colchicine, namely, the inhibition of the migration of granulocytes into the inflamed area and a decreased metabolic and phagocytic activity of granulocytes. This reduces the release of lactic acid and proinflammatory enzymes that occurs during phagocytosis and breaks the cycle that leads to the inflammatory response.

Neutrophils exposed to urate crystals ingest them and produce a glycoprotein, which may be the causative agent of **acute gouty arthritis**. Injected into joints, this substance produces a profound arthritis that is histologically indistinguishable from that caused by direct injection of urate crystals. Colchicine appears to prevent the elaboration by leukocytes of this glycoprotein.

### EFFECT ON CELL DIVISION

Colchicine can arrest plant and animal cell division *in vitro* and *in vivo*. Mitosis is arrested in metaphase because of failure of spindle formation. Cells with the highest rates of division are affected earliest. High concentrations may completely prevent cells from entering mitosis, and they often die. The action also is characteristic of the vinca alkaloids (**vincristine** and **vinblastine**), **podophyllotoxin**, and **griseofulvin**.

### OTHER EFFECTS

Colchicine inhibits the release of histamine-containing granules from mast cells, the secretion of **insulin** from  $\beta$ -cells of pancreatic islets, and the movement of **melanin** granules in melanophores. Although it is questionable whether these effects occur at clinically achieved concentrations of colchicine, all these processes may involve the translocation of granules by the microtubular system.

Colchicine also exhibits a variety of other pharmacological effects. It lowers body temperature, increases the sensitivity to central depressants, depresses the respiratory center, enhances the response to sympathomimetic agents, constricts blood vessels, and induces hypertension by central vasomotor stimulation. It enhances gastrointestinal activity by neurogenic stimulation but depresses it by a direct effect, and alters neuromuscular function.

## PHARMACOKINETICS AND METABOLISM

Colchicine is rapidly absorbed after oral administration, and peak concentrations occur in plasma by 0.5 to 2 h. Large amounts of the drug and metabolites enter the intestinal tract in the bile and intestinal secretions, and this fact, together with the rapid turnover of intestinal epithelium, probably explains the prominence of intestinal manifestations in colchicine poisoning. The kidney, liver, and spleen also contain high concentrations of colchicine, but it is apparently largely excluded from heart, skeletal muscle, and brain. The drug can be detected in leukocytes and in the urine for at least 9 d after a single intravenous dose.

Colchicine is metabolized to a mixture of compounds *in vitro*. Most of the drug is excreted in the feces; however, in normal individuals, 10 to 20% of the drug is excreted in the urine. In patients with liver disease, hepatic uptake and elimination are reduced and a greater fraction of the drug is excreted in the urine.

## TOXIC EFFECTS

The most common side effects reflect the action of colchicine on the rapidly proliferating epithelial cells in the gastrointestinal tract, especially in the jejunum. Nausea, vomiting, diarrhea, and abdominal pain are the most common and earliest untoward effects of colchicine overdosage. To avoid more serious toxicity, administration of the drug should be discontinued as soon as these symptoms occur. There is a latent period of several hours or more between the administration of the drug and the onset of symptoms. This interval is not altered by dosage or route of administration. For this reason, and because of individual variation, adverse effects may be unavoidable during an initial course of medication with colchicine. However, because patients often remain relatively consistent in their response to a given dose of the drug, toxicity can be reduced or avoided during subsequent courses of therapy by reducing the dose. The drug is equally effective when given intravenously; the onset of the therapeutic effect may be faster, and the gastrointestinal side effects may be almost completely avoided.

In acute poisoning with colchicine, there is hemorrhagic gastroenteritis, extensive vascular damage, nephrotoxicity, muscular depression, and an ascending paralysis of the central nervous system.

Colchicine produces a temporary leukopenia that is soon replaced by a leukocytosis, sometimes because of a striking increase in the number of basophilic granulocytes. The site of action is apparently directly on the bone marrow. Myopathy and neuropathy also have been noted with colchicine treatment, especially in patients with decreased renal function. Long-term administration of colchicine entails some risk of agranulocytosis, aplastic anemia, myopathy, and alopecia; azoospermia has also been described.

## THERAPEUTIC USES

Colchicine provides dramatic relief from acute attacks of gout. The effect is sufficiently selective that the drug has been used for diagnostic purposes, but the test is not infallible. Colchicine also has an established role in preventing and aborting acute attacks of gout. However, its toxicity and the availability of alternative agents that are less toxic have substantially lessened its usefulness.

## ACUTE ATTACKS

When colchicine is given promptly within the first few hours of an attack, fewer than 5% of patients fail to obtain relief. Pain, swelling, and redness abate within 12 h and are completely gone in 48 to 72 h. Although for many years colchicine was administered orally, current practice is to administer the drug intravenously. Although a number of regimens have been used, a single dose of 2 mg, diluted in 10 to 20 ml of 0.9% sodium chloride solution, usually is adequate; a total dose of 4 mg

should not be exceeded. To avoid cumulative toxicity, treatment with colchicine should not be repeated within 7 d.

Great care should be exercised in prescribing colchicine for elderly patients, and for those with cardiac, renal, hepatic, or gastrointestinal disease. In these patients and in those who do not tolerate or respond to colchicine, indomethacin or another nonsteroidal anti-inflammatory agents (NSAID) is preferred.

### PROPHYLACTIC USES

For patients with chronic gout, colchicine has established value as a prophylactic agent, especially when there is frequent recurrence of attacks. Prophylactic medication also is indicated upon initiation of long-term medication with allopurinol or the uricosuric agents, because acute attacks often increase in frequency during the early months of such therapy.

The prophylactic dose of colchicine depends on the frequency and severity of prior attacks. As small an oral dose as 0.5 mg two to four times a week may suffice; as much as 1.8 mg per day may be required by some patients. Colchicine should be taken in larger abortive doses immediately upon the first twinge of articular pain or the appearance of any prodrome of an acute attack. Before and after surgery in patients with gout, colchicine should be given for 3 d (0.5 or 0.6 mg, thrice a day); this greatly reduces the very high incidence of acute attacks of gouty arthritis precipitated by operative procedures.

### OTHER USES OF COLCHICINE

Daily administration of colchicine is useful for the prevention of attacks of **familial Mediterranean fever (familial paroxysmal polyserositis)** and for prevention and treatment of **amyloidosis** in such patients. Colchicine appears to benefit patients with primary **biliary cirrhosis** in terms of improvement of liver function tests and perhaps of survival. Colchicine also has been employed to treat a variety of skin disorders, including **psoriasis** and **Behcet's syndrome**.





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# 25 Compositae

## INTRODUCTION

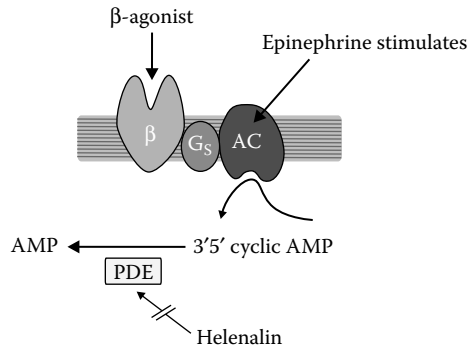
Compositae (Mexican Asteraceae) possess numerous properties and exhibit numerous actions, which include but are not limited to:

- Antimigraine efficacy
- Antiulcer efficacy
- Anti-inflammatory property
- Antitumor action
- Antiepileptic property
- Antihelminthic property
- Antiseptic action
- Antitussive property
- Antidiabetic action
- Cardiotonic property
- Diuretic action
- Diaphoretic
- Analgesic action

There are 380 genera with 3000 species recognized in the **Asteraceae** in Mexico. The most important source of knowledge about indigenous plant use in historical Mexico is the **Florentine Codex** compiled by the Franciscan monk **Fray Bernardino de Sahagun**. Also important are the work of the Spanish physician **Francisco Hernandez** and an herbal guide written in Nahuatl by the Aztec healer **Martin de la Cruz** from Tezcoco, which was translated into Latin by **Juan Badiano** and sent to the King of Spain, Philip II, in 1552 (see Heinrich et al., 1998).

## SESQUITERPENE LACTONES

Sesquiterpene lactones (SQLs), one of the major classes of chemical compounds reported from the Asteraceae, are a large and diverse group of biologically active plant constituents that have been reported from ten families of flowering plants; however, the greatest number are derived from the Asteraceae, with over 3000 reported structures. Some of the important medicinal plants from this family, such as *Arnica montana*, *Artemisia annua*, and *Tanacetum parthenium*, contain SQLs as the active constituents. SQLs are commonly present in large quantities (> 2% dry weight of leaves); these SQLs are usually comparatively nontoxic but have an intensely bitter taste that presumably deters herbivores. A few SQLs are highly toxic (e.g., **repin** and **helenalin**), but many have anti-inflammatory activity and relax smooth muscle *in vitro*. SQLs have antitumor activity (e.g., **Parthenin**), antiulcer activity (e.g., *Artemisia douglasiana*), and cardiotonic activity (e.g., *Helienium autumnale*) as they are ionotropic in nature. Helenalin inhibits the activity of phosphodiesterase, increases the concentration of cyclic adenosine monophosphate, causes Ca<sup>2+</sup> influx, and subsequently enhances the contractility of myocardium (Figure 25.1).



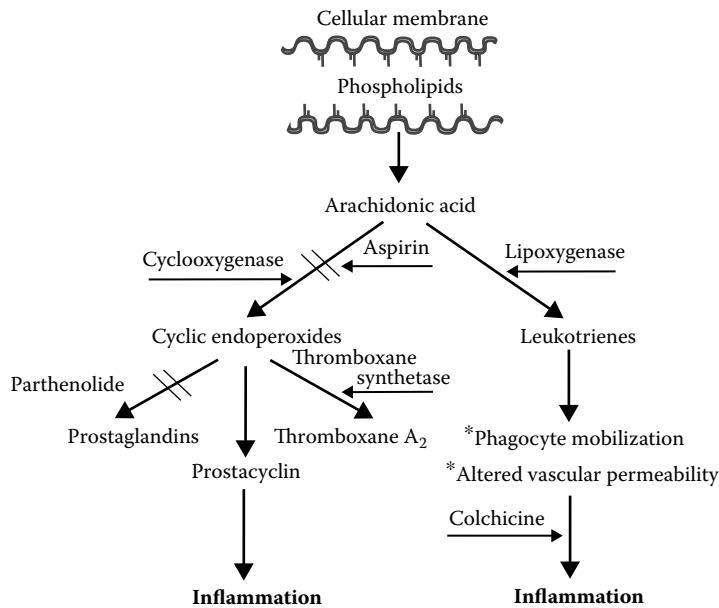
**FIGURE 25.1** Amrinone exerts positive inotropic and vasodilating actions. AMP = adenosine monophosphate, AC = adenylate cyclase, PDE = phosphodiesterase,  $G_s$  = stimulatory guanine nucleotide-binding regulatory protein.

## SESQUITERPENE-INDUCED NEUROTOXICITY

Ingesting a large amount of *Centaurea repens*, a member of Asteraceae containing a copious amount of sesquiterpene by horses causes “**chewing disease**.” Neuropathological examination of the brain from an intoxicated horse revealed bilateral necrosis of the anterior globus pallidus and zona reticulata of the substantia nigra.

### TANACETUM PARTHENIUM (FEVERFEW)

Feverfew is widely consumed in England as a remedy for arthritis and migraine. Feverfew contains **parthenolide**, which is a member of sesquiterpene. Parthenolide inhibits the activity of **prostaglandin synthetase**. It also inhibits **platelet aggregation** and alter **serotonin release** (Figure 25.2).



**FIGURE 25.2** Sites of action of aspirin, colchicine, and parthenolide.

Compositae behave as aspirin, which has an anti-inflammatory action as well as antirheumatic and antiarthritic effects, and may therefore be used in the treatment of rheumatic fever. However, aspirin cannot alter the cardiac lesion and other visceral effects of the disease. Aspirin is extremely effective in managing rheumatoid arthritis and allied diseases involving the joints, such as **ankylosing spondylitis** and **osteoarthritis**. It is thought that aspirin and indomethacin exert their anti-inflammatory effects by inhibiting prostaglandin synthesis through the inhibition of **cyclooxygenase**. The presynthesized prostaglandins are released during a tissue injury that fosters inflammation and pain. Furthermore, aspirin reduces the formation of prostaglandin in the platelets and leukocytes, which is responsible for the reported hematological effects associated with aspirin (see Figure 25.2).

**Parthenolide** may have a similar mechanism of action as seen following administration of **sumatriptan**, which is an effective analgesic and antimigraine drug. Sumatriptan has a selective agonist for serotonin receptor subtype, causing vasoconstriction of cranial arteries.

The introduction of **sumatriptan** in the therapy of migraine led to significant progress in preclinical and clinical research on migraine. At the scientific level, the selective pharmacological effects of sumatriptan at **serotonin** (5-HT<sub>1</sub>) receptors have led to new insights into the pathophysiology of migraine. At the clinical level, sumatriptan is an effective acute antimigraine agent. Its ability to decrease, rather than exacerbate, nausea and vomiting in migraine appears to be an important advance in the treatment of the condition.

The significance of one or more 5-HT<sub>1</sub> receptors in migraine pathophysiology relates to the observation that both 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors serve as *autoreceptors*, presynaptic receptors that modulate neurotransmitter release from neuronal terminals. Conceivably, 5-HT<sub>1</sub> agonists may block the release of proinflammatory neurotransmitters at the level of the nerve terminal in the perivascular space. It has been shown that antimigraine drugs such as **ergotamine**, **dihydroergotamine**, and **sumatriptan** are able to block the development of **neurogenic plasma extravasation** in dura mater that follows depolarization of perivascular axons following **capsaicin** injection or unilateral electrical stimulation of the trigeminal nerve. The ability of potent 5-HT<sub>1</sub> agonists such as sumatriptan, or maybe parthenolide, to inhibit endogenous transmitter release in the perivascular space could account for their efficacy in the acute treatment of migraine.

## OTHER ASTERACEAE GROUPS

The therapeutic efficacies of other members of the Asteraceae containing SQLs are summarized in the following text.

### ACHILLEA

The genus *Achillea* is distributed in temperate regions of the Northern Hemisphere, especially in Europe and Asia. *Achillea millefolium* is a species frequently used in Europe and America alike. Many species of this genus are rich in essential oil, SQLs, and flavonoids. It is used internally as an **antitussive agent** and externally as an **analgesic**.

**Cirsiliol**, a flavone isolated from the species *Achillea fragrantissima*, causes a concentration-dependent relaxation of isolated ileum, interferes with calcium channels, and thus inhibits Ca<sup>2+</sup> influx from the extracellular compartment. Its therapeutic efficacy is not known.

### ARTEMISIA

The genus *Artemisia* contains more than 200 species that have been reported from many parts of the world and has been selected for remedies by cultures throughout the world because of its medicinal properties. The reported active constituents of the genus include all types of the common natural products of the Asteraceae: SQLs, polyacetylenes, flavonoids, essential oils (monoterpenes),

**diterpenes, triterpenes, and coumarins.** Their therapeutic efficacies are not known. A brief discussion on some of the species follows:

- *Artemisia abrotanum*: Four flavonols isolated from *A. abrotanum* reportedly possess spasmolytic activity. These flavonols show a dose-dependent relaxing effect on the **carbacholine**-induced contraction of trachea. Its therapeutic efficacy is not known.
- *Artemisia herba-alba*: It is widely used for the treatment of diabetes mellitus.
- *Artemisia verlotorum*: Water-alcoholic extract showed a protective effect against experimental convulsions elicited by various agents, as well as analgesic and hypothermic actions. *Artemisia verlotorum* is used as an anticonvulsant and analgesic.
- *Artemisia monosperma*: The relaxant effects of **7-O-methylesteriodictyol**, a flavone isolated from the aerial parts of *A. monosperma*, on smooth muscle contraction has been studied. The inhibition of contraction induced by known therapeutic agents such as acetylcholine and **oxytocin** are consistent with the use of this plant in the treatment of certain gastrointestinal disorders.
- *Artemisia tridentata*: *Artemisia tridentata* is frequently used as an **anthelmintic, antiseptic**, and analgesic. Many of the compounds identified in this species have notable pharmacological activities, particularly the monoterpenes, SQLs, coumarins, and flavonoids.

## BACCHARIS

*Baccharis* is a large, strictly American genus with approximately 350 species. Only a few are important medicinal plants, and their uses seem to be rather diverse. Some of the principal medicinal species are discussed in the following text:

- *Baccharis conferta*: In the region of Vera Cruz, Mexico, *B. conferta* is used to treat stomachaches.
- *Baccharis glutinosa*: **Axixtlacotl** was used as a diuretic, against fevers, as a diaphoretic, and to remove blotches from the face. Tea made from the leaves is taken to lose weight and as a contraceptive. The tea is also used to stop blood loss after giving birth. The leaves, heated over coals, are placed on the head as a remedy for headache or on a sore area of the body.
- *Baccharis salicifolia*: The green leaves/leafy branches of *B. salicifolia* are applied externally as a remedy for inflammation, diarrhea, and dysentery.
- *Baccharis saathroides*: A tea made by boiling the twigs of *B. saathroides* is taken as a remedy for colds. The same tea is rubbed on sore muscles for relief.
- *Baccharis serraefolia*: *Baccharis serraefolia* is a popular form of treatment for various gastrointestinal illnesses.
- *Baccharis multiflora*, *Baccharis* spp.: An infusion prepared from the leaves of *B. multiflora*, *Baccharis* spp. is said to be effective against catarrhs and was used for urinary problems in 19th century Mexico. Two unidentified species of this genus — **quappatli** and **malinalli** — are listed in the **Florentine Codex** as treatments for blotched face (applied internally) and for worms in the eyes and crab lice in the eyelids (especially applied externally), respectively.
- *Baccharis trinervis*: *Baccharis trinervis* is used by the Huastec in the treatment of high fever, edema, sores, and muscle cramps. It is also applied in the case of dizziness and lack of blood. The Huastec regard it as effective if one feels sleepy and if there is insufficient milk production. In Veracruz, a preparation made from the leaves is used for the treatment of typhoid fever.
- *Baccharis vaccinooides*. *Baccharis vaccinooides* is one of the most popular remedies from Chiapas for gastrointestinal disorders.

## ELEPHANTOPUS

This tropical genus is particularly well known because one species, *Elephantopus scaber*, is now a widely distributed, invasive herb in many countries. There are approximately one dozen species of these herbaceous perennials in North and South America.

The levels of *Elephantopus spicatus* [syn.: *Pseudelephantopus spicatus* C.F. Baker, **Vernoniaeae**] are used for the treatment of cough and headache. Applied topically, they are employed as an antipyretic, for the treatment of erysipelas, skin infections, and measles. A preparation made from the roots is taken as a remedy for colic; the whole plant helps against diarrhea. It is one of the most popular cough remedies of middle America.

## HELENIUM

This American genus has yielded several ornamental plants (e.g., *Helenium autumnale*), but is also known for its toxic effects on herbivores. *Helenium* genus comprises about 40 species of annual and perennial herbs. *Helenium mexicanum* is taken orally if a person is very sick or to treat a stomachache, faint heartbeat, throbbing temples, quivering nerves, fever, or pus in the genital organ. *Helenium quadridentatum* is used for treatment of fever, catarrh, and testicular inflammations and as a diuretic and insecticide.

## MONTANOA

Most Asteraceae are herbs or little shrubs. The trees of the genus *Montanoa* (**tree daisy**) therefore stand out as very unusual plants. They also are very showy during the flowering season. But the genus also includes one of the most important medicinal plants of Mexico, *Montanoa tomentosa*.

## PACKERA

The whole plant *Packera candissima* is used as a tea for kidney ailments, as a general medicine, and to cure sores, ulcers, and vaginal ailments. Similar uses are reported for *P. bellidifolia*.

## PARTHENIUM

*Parthenium* is a small genus of approximately 16 species of shrubs, herbaceous perennials, and annuals. A well-known species of this genus is **guayule** (*P. argentatum*), which is considered an alternative source of rubber and was an emergency rubber during World War II. All species of this genus, especially *P. hysterophorus*, are known to cause severe contact dermatitis. *Parthenium hysterophorus* is used medicinally by many indigenous and mestizo groups of Mexico as a remedy for malaria, for neuralgia, and as a vermifuge.

## TITHONIA

*Tithonia* is a small genus of fewer than ten species. The Mexican and Central American genus *Tithonia* has yielded some ornamental plants (e.g., *T. rotundifolia*), and at least one species, *T. diversifolia*, is now a pantropically distributed bad weed. It is used to treat malaria (see Heinrich et al., 1998).



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# 26 Curare and Neuromuscular Blockade

## INTRODUCTION

Curare is an arrow poison used by the native people of South America. It causes muscular relaxation and is used in anesthesiology.

Curare (Woorara) is a vegetable extract obtained from various members of the **Strychnos** family, as well as from *Paullinia curare* and other plants. In South America, it is known by the names **Caroval** and **Vao**. Its active principle is the very poisonous alkaloid *curarine*,  $C_{18}H_{35}N$ .

## CURARE

Curare was first brought to the attention of Queen Elizabeth of England by **Sir Walter Raleigh**. The remarkable ability of the drug to induce paralysis of the muscles led to its early use by **Claude Bernard**, **Kölliker**, **Langley**, and subsequent physiologists to study the mechanism of neuromuscular activity. However, the uncertain supplies of the drug, its variability, and the effects of its contaminants prevented its therapeutic application.

Curare is obtained from various members of the **menisperm** or **moonseed** family, particularly from the vines of *Chondodendron tomentosum* and other members of the *Chondodendron* genus as well as from various species of *Strychnos* (Figure 26.1).

The earliest available preparations, made as infusions and concentrated to a syrup by the native people, were designated as **calabash** (gourd), **tubo-** (bamboo), or **pot** (clay pot) curare depending upon the containers in which the drug was packaged. Curare is obtained from the upper regions of the Amazon river, the Orinoco basin, and the eastern slopes of the Ecuadorian plateau. The term *curare* is derived from the Indian name (**woorari**, **urari**) for poison (Grollman, 1962).

**Curare** or **South American arrow poison** varies in composition among Indian tribes. However, the bark of one or more species of *Strychnos* apparently is always used in its preparation. *Strychnos castelnaei* Weddell, *S. toxifera* Bentham, *S. Crevauxii* G. Planchon, and *Chondodendron tomentosum* Ruiz Pavon are commonly employed.

The young bark is scraped off the plants, mixed with other items, boiled in water, and strained, or extracted by crude percolation with water, then evaporated to a paste over the fire or in the sun. The imported article is a brownish or black shiny resinoid, a very bitter mass, readily soluble in cold water and in dilute alcohol.

The drug contains several alkaloids; **curarine** and **protocurarine** give the typical effects. Curine is devoid of muscle-nerve action, but first stimulates, then depresses the heart action. Curare has a definite paralyzing action on voluntary muscle-nerve endings. Hypodermic injection of a suitable dose causes a total loss of motion, first of the voluntary, then of the respiratory muscles, and death results from respiratory failure. Therapeutically, the drug is a powerful antispasmodic, used in the convulsions of strychnine poisoning and of tetanus, as an adjunct to shock therapy in neuropsychiatry, and to promote muscular relaxation in surgical anesthesia. It is an important laboratory item for paralyzing the skeletal muscles of test animals.





**FIGURE 26.1** Left, *Chondodendron tomentosum* from which curare is derived; right, the Amazonian rain forest, the habitat of the plant.

### SKELETAL MUSCLE RELAXANTS

Neuromuscular blocking agents may be used to diagnose myasthenia gravis, facilitate endotracheal intubation, relieve laryngeal spasm, provide relaxation during brief diagnostic and surgical procedures, prevent bone fracture in electroconvulsive therapy, produce apnea and controlled ventilation during thoracic surgery and neurosurgery, reduce muscular spasticity in neurological diseases (multiple sclerosis, cerebral palsy, or tetanus), and reduce the muscular spasm and pain resulting from sprains, arthritis, myositis, and fibrositis. Skeletal muscle relaxants can be classified into four categories:

#### 1. Depolarizing agents

Succinylcholine chloride (Anectine, Quelicin, Suxcert, Sucostrin)

#### 2. Nondepolarizing or competitive-blocking agents

Tubocurarine chloride (Tubarine)

Pancuronium (Pavulon)

Metocurine

Alcuronium

Fazadinium

Atracurium

Vecuronium

Pipecuronium

Doxacurium

Mivacurium

#### 3. Direct-acting relaxants

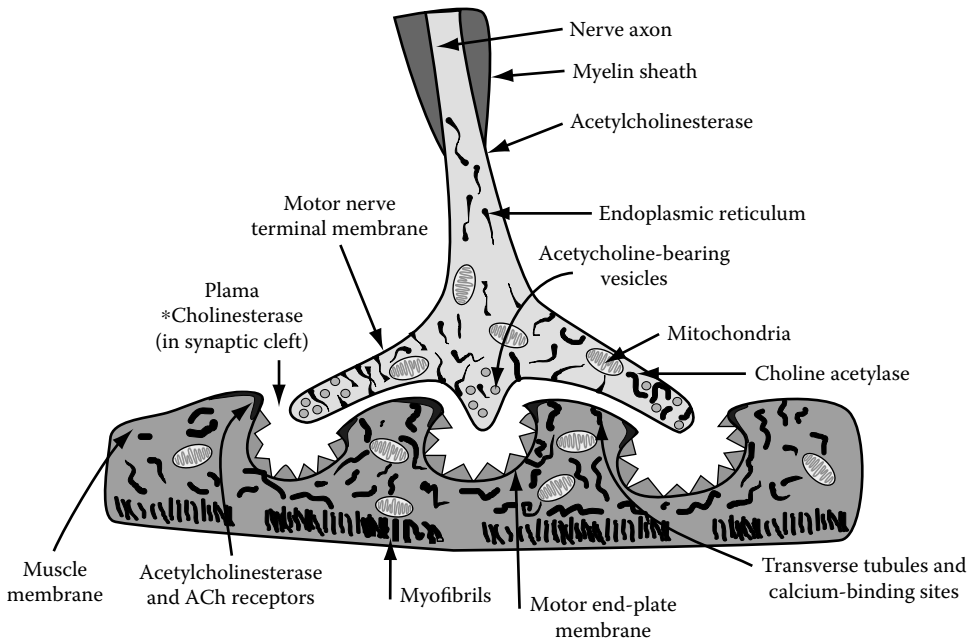
Dantrolene sodium (Dantrium)

#### 4. Centrally acting muscle relaxants

Chlordiazepoxide (Librium)

Diazepam (Valium)

Baclofen (Lioresal)



**FIGURE 26.2** Botulinum poisoning causes progressive parasympathetic and motor paralysis. The toxin exerts its effects by inhibiting the release of acetylcholine.

### THE NEUROMUSCULAR JUNCTION

The neuromuscular junction consists of a motor nerve terminal and skeletal muscle motor end plate, separated by a synaptic cleft that is filled with extracellular fluid (Figure 26.2).

### NICOTINIC CHOLINERGIC RECEPTORS

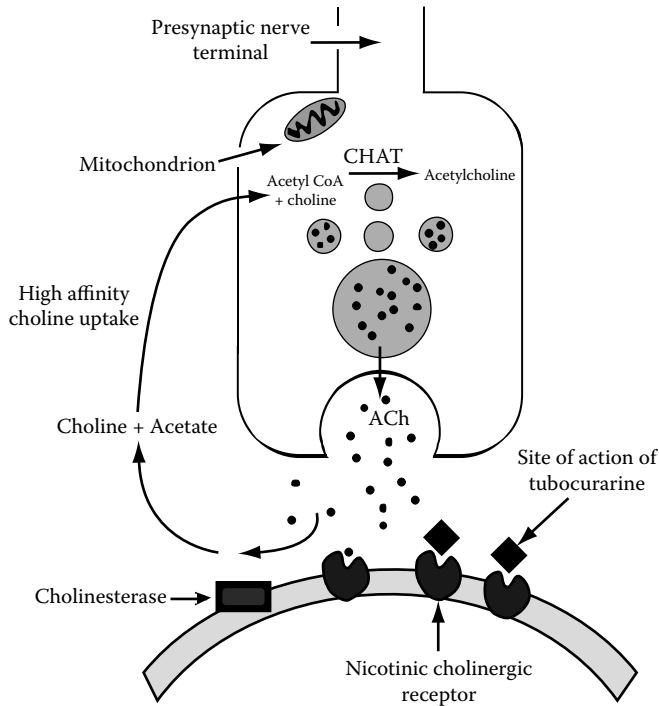
Acetylcholine and agents acting at the autonomic ganglia or the neuromuscular junctions interact with nicotinic cholinergic receptors to initiate the end plate potential in muscle or an excitatory postsynaptic potential in nerve. The nicotinic receptor in skeletal muscle is a pentamer composed of four distinct subunits.

### MECHANISM OF ACTION OF NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular agents are classified as either depolarizing agents (e.g., succinylcholine) or nondepolarizing agents (e.g., tubocurarine). Succinylcholine has dual modes of action in that it possesses two phases of blocking action: depolarization and desensitization.

#### Phase I: Blockade (Depolarization)

Succinylcholine, similar to acetylcholine, interacts with the cholinergic receptors at the end plate region of the muscle, resulting in depolarization of the chemically excitable membrane. This, in turn, creates local action potentials, spreading them to and depolarizing the adjacent excitable membranes, finally culminating in a muscle contraction, or fasciculation, which is an uncoordinated muscle contraction. However, unlike acetylcholine, succinylcholine is not metabolized by acetylcholinesterase, and hence causes persistent depolarization of the end plate. The continuous presence of succinylcholine leads to inexcitability of the membrane adjacent to the end plate, resulting in



**FIGURE 26.3** Tubocurarine competes with acetylcholine (ACh) at cholinergic receptor. CHAT = choline acetylase, CoA = coenzyme A.

neuromuscular blockade, which is not reversed by the administration of cholinesterase inhibitors. In fact, agents such as **neostigmine** may even prolong neuromuscular blockade.

### Phase II: Blockade (Desensitization)

In time and as the result of repeated administration of succinylcholine, depolarization no longer promotes the formation of the neuromuscular blockade (desensitization). The blockade is then changed in character and becomes antagonized by neostigmine through the operation of an ill-defined mechanism that is very distinct from competitive blockade.

Agents such as tubocurarine and pancuronium compete with acetylcholine for the cholinergic receptors at the end plate (Figure 26.3). They combine with the receptors but do not activate them. Competitive or nondepolarizing agents are antagonized by neostigmine. Nondepolarizing muscle relaxants can also be classified according to their duration of action, as shown in Table 26.1.

Dantrolene, a hydantoin derivative, reduces the contraction of skeletal muscle, acting directly on the muscle and not at the neuromuscular junction. It is thought to reduce the amount of calcium released and hence prevent excitation–contraction coupling (Figure 26.4). Its usefulness in the treatment of anesthetic-induced malignant hyperthermia may be due to its calcium-related uncoupling actions.

**Chlordiazepoxide** and **diazepam** augment presynaptic inhibition by enhancing the release of  $\gamma$ -aminobutyric acid, an inhibitory transmitter (Figure 26.5). **Baclofen** interferes with the release of excitatory transmitters.

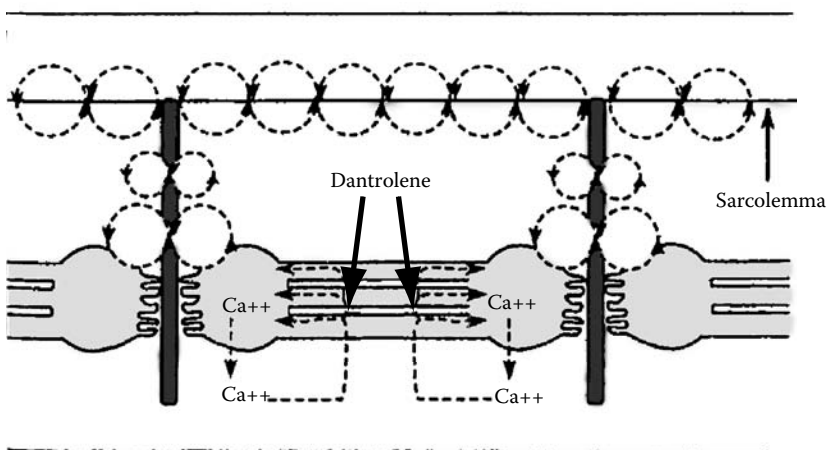
### SEQUENCE AND ONSET OF NEUROMUSCULAR BLOCKADE

Neuromuscular blockade takes place in the following sequence: rapidly contracting muscles (eye, fingers, and toes) followed by slowly contracting muscles (diaphragm, limbs, and trunk). The onset

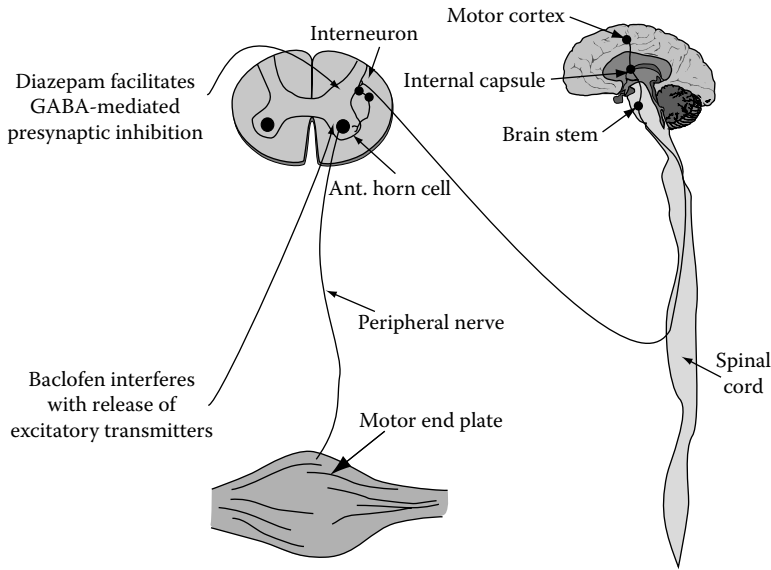
**TABLE 26.1**  
**Duration of Action of Neuromuscular Blocking Agents**

Neuromuscular Blocking Agent	Duration of Action (min)	Potency Relative to Tubocurarine
Atracurium	20–30	1.5
Doxacurium	> 30	6
Metocurine	> 30	4
Mivacurium	10–20	4
Pancuronium	> 30	6
Pipecuronium	> 30	6
Tubocurarine	> 30	1
Vecuronium	20–30	6

*Note:* Several drugs have as their major action the interruption or mimicry of transmission of the nerve impulse at the neuromuscular junction of skeletal muscle or autonomic ganglia. These agents can be classified together, because they interact with a common family of receptors; these receptors are called *nicotinic cholinergic*, because they are stimulated by both the natural transmitter acetylcholine (ACh) and the alkaloid nicotine. Distinct subtypes of nicotinic receptors exist at the neuromuscular junction and the ganglia, and the pharmacological agents that act at these receptors discriminate between them. Neuromuscular blocking agents are distinguished by whether or not they cause depolarization of the motor end plate and, for this reason, are classified either as *competitive (stabilizing)* agents, of which curare is the classical example, or as depolarizing agents, such as succinylcholine. The depolarizing and competitive agents are used widely to achieve muscle relaxation during anesthesia. Ganglionic agents usually act by stimulating or blocking nicotinic receptors on the postganglionic neuron.



**FIGURE 26.4** Dantrolene reduces the release of calcium.



**FIGURE 26.5** Diazepam facilitates GABAergic transmission. GABA =  $\gamma$ -aminobutyric acid.

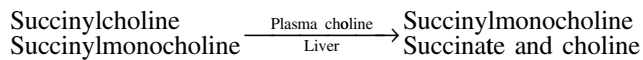
phase and duration of action of succinylcholine are 1 and 5 min, respectively. The onset phase and duration of action of tubocurarine are 5 and 20 min, respectively.

## FACTORS AFFECTING NEUROMUSCULAR BLOCKADE

### Drug Interactions

Antibiotics such as neomycin, streptomycin, kanamycin, gentamycin, polymyxin A, polymyxin B, colistin, lincomycin, and tetracycline have all been implicated as augmenting the action of the nondepolarizing agents.

Substances that inhibit plasma cholinesterase prolong the response of succinylcholine. Succinylcholine is metabolized according to the following scheme:



Because cholinesterase is synthesized in the liver, the duration of action of succinylcholine is elevated in the presence of liver disease. Cholinesterase inhibitors dramatically increase the duration of action of succinylcholine. In patients with atypical cholinesterase, the intensity and duration of the effects of succinylcholine are enhanced.

Antiarrhythmic agents such as **quinidine**, **propranolol**, and **propranolol** have all been shown to augment *d*-tubocurarine-induced blockade. Quinidine has also been reported to unmask or worsen the symptoms of **myasthenia gravis** and to cause postoperative respiratory depression after the use of muscle relaxants.

Diuretics such as thiazides, **ethacrynic acid**, and **furosemide** intensify the effects of nonpolarizing muscle relaxants, possibly because of a diuresis-induced reduction in the volume of distribution and an associated electrolyte imbalance, such as hypokalemia.

The local anesthetics **procaine** and **lidocaine** enhance the neuromuscular block produced by nondepolarizing and depolarizing muscle relaxants.

**Phenytoin** has been shown to interfere with neuromuscular transmission, and the drug has been reported to exacerbate myasthenia gravis. **Lithium** augments the effects of both depolarizing and nondepolarizing muscle relaxants and also reportedly unmasks myasthenia gravis.

**Chlorpromazine** has been shown to potentiate nondepolarizing relaxants. The administration of steroids may lead to a transient worsening of symptoms in patients with myasthenia gravis, but the mechanism by which they interfere with neuromuscular transmission is unknown. The antagonism of **pancuronium-induced blockade** by hydrocortisone has also been reported. **d-Penicillamine**, which is used in the treatment of **Wilson's disease**, may cause a myasthenia-gravis-like syndrome. These patients have elevated serum levels of antibody to acetylcholine receptors, suggesting that an immunological mechanism is involved in this drug-induced syndrome. **Azathioprine** antagonizes nondepolarizing neuromuscular blockade, possibly by inhibiting phosphodiesterase.

Calcium ions play an important role in the presynaptic release of acetylcholine, and prolonged neuromuscular blockade has been reported after calcium antagonist administration during anesthesia that includes concurrent nondepolarizing neuromuscular blockade. **Ketamine** potentiates neuromuscular blockade produced by tubocurarine and **atracurium**, but not that produced by pancuronium or succinylcholine.

All of the inhalational anesthetic agents augment both the degree and duration of the neuromuscular blockade induced by the nondepolarizing muscle relaxants.

## Electrolytes

The generation of action potentials by muscle and nerve results from changes in the conductance of their membranes to sodium and potassium, and normal neuromuscular function depends on the maintenance of the correct ratio between intracellular and extracellular ionic concentrations.

An acute decrease in the extracellular potassium concentration tends to elevate the end plate transmembrane potential, causing hyperpolarization and an increased resistance to depolarization, together with a greater sensitivity to the nondepolarizing muscle relaxants. Conversely, an increased extracellular potassium concentration lowers the resting end plate transmembrane potential and thereby partially depolarizes the membrane, which should augment the effects of the depolarizing agents and oppose the action of the nondepolarizing drugs. Diuretic-induced chronic hypokalemia reduces the pancuronium requirements for neuromuscular blockade and thus more neostigmine is required to achieve antagonism.

The release of acetylcholine from the motor nerve terminal is also affected by calcium and magnesium ion concentrations, which have opposing effects. Calcium increases the quantal release of acetylcholine from the nerve terminal, decreases the sensitivity of the postjunctional membrane to transmitter, and enhances the excitation–contraction coupling mechanisms of muscle. In contrast, magnesium decreases acetylcholine release and reduces the sensitivity of the postjunctional membrane to acetylcholine. Consequently, the action of the nondepolarizing muscle relaxants can be accentuated by low calcium and high magnesium levels. In addition, magnesium augments the block produced by depolarizing relaxants. Therefore, the dose of a muscle relaxant should be reduced in patients who have toxemia associated with pregnancy and are undergoing **magnesium replacement therapy**.

## Acid–Base Balance

Respiratory acidosis enhances *d*-tubocurarine- and pancuronium-induced neuromuscular block and opposes reversal by neostigmine.

## Hypothermia

Hypothermia prolongs the neuromuscular blockade produced by *d*-tubocurarine and pancuronium.

## Disease States

The plasma concentrations of d-tubocurarine and pancuronium are increased in patients with impaired liver functions because liver disease interferes with the metabolism of pancuronium.

## Age

Neonates are more sensitive to nondepolarizing muscle relaxants, and the response of the small infant to some extent resembles that of an adult patient with myasthenia gravis.

## SIDE EFFECTS OF NEUROMUSCULAR BLOCKING AGENTS

### Cardiovascular Effects

Although the main site of action of the neuromuscular blocking agents is the nicotinic receptor of striated muscle, they may act at other cholinergic receptor sites throughout the body, such as the nicotinic receptors in the autonomic ganglia and the muscarinic receptors in the heart.

Succinylcholine may cause tachycardia, cardiac arrhythmias, and hypertension, which is brought about by stimulation of the sympathetic ganglia. It may also provoke bradycardia, caused by stimulation of muscarinic receptor sites in the sinus node of the heart. This effect is more pronounced following a second dose of succinylcholine. The bradycardia may be blocked by thiopental, atropine, and ganglionic blocking agents.

### Ocular and Muscular Effects

Succinylcholine increases intraocular pressure transiently. It can also cause muscle pain, which may be due to fasciculation and uncoordinated muscle contraction. The prior administration of a competitive blocking agent may prevent both fasciculation and pain.

Patients with **myotonia congenita** and **myotonia dystrophica** respond differently to succinylcholine, in that their muscles are contracted rather than relaxed.

## Histamine Release

**Tubocurarine**, **metocurine**, and **succinylcholine** have all been shown to elicit histamine release in humans. However, histamine release is less common with **pancuronium** and **alcuronium**. **Vecuronium** does not cause histamine release.

## ERYTHRINA ALKALOIDS

The beanlike seeds of the trees and shrubs of the genus *Erythrina*, a member of the legume family, contain substances that possess curare-like activity. The plants are widely distributed in the tropical and subtropical areas of the American continent, Asia, Africa, and Australia, but apparently they are not used by the natives in the preparation of arrow poisons. Of 105 known species, the seeds from more than 50 have been tested, and all were found to contain alkaloids with curariform properties. *Erythroidine*, from *E. americana*, was the first crystalline alkaloid of the group to be isolated. It consists of at least two isomeric alkaloids,  $\alpha$  and  $\beta$ -**erythroidine**; both are dextrorotatory. Most experimental and clinical study has centered on the  $\beta$  form because it is more readily obtainable in pure state.  $\beta$ -Erythroidine is a tertiary nitrogenous base. Several hydrogenated derivatives of  $\beta$ -erythroidine have been prepared; of these, **dihydro- $\beta$ -erythroidine** has been studied most carefully and subjected to clinical trial. Conversion of  $\beta$ -erythroidine into the quaternary metho salt ( **$\beta$ -erythroidine methiodide**) does not enhance, but rather almost entirely, abolishes its curariform activity; this constitutes a notable exception to the rule that conversion of many alkaloids into quaternary metho salts results in the appearance of curare-like action.

The pharmacological properties of  $\beta$ -erythroidine and its dihydro derivative are very similar to those of *d*-tubocurarine and therefore need not be described in any detail. The two compounds differ from curare in three important respects, namely, less potent paralytic action on neuromuscular junctions, briefer duration of paralysis, and oral efficacy. Indeed, gastrointestinal absorption of the alkaloids is so rapid and complete that the difference between effective oral and subcutaneous doses is rather small. Dihydro- $\beta$ -erythroidine is longer acting than  $\beta$ -erythroidine and about six times as active. Similar to curare,  $\beta$ -erythroidine and its dihydro derivative are antagonized at the neuromyal junction by anticholinesterases such as **neostigmine**.

### METHONIUM COMPOUNDS

In the search for synthetic agents capable of blocking neuromuscular and autonomic ganglionic transmission, that is, for substances blocking the nicotinic effects of acetylcholine, thousands of interesting compounds have been made and scores of new chemical series explored. One of the most fruitful discoveries was that of the British investigators who introduced the **polymethylene bis-trimethylammonium** series, referred to herein by the generic term *methonium compounds*, a name approved by the British Pharmacopoeia Commission. Not only has the methonium series revealed an entirely new field of investigation for structure–activity relationship and provided valuable laboratory tools for autonomic pharmacology, but it has also yielded at least three clinically useful drugs, one causing neuromuscular blockade in skeletal muscle (**decamethonium**) and two causing blockade in autonomic ganglia (**pentamethonium** and **hexamethonium**) (Goodman and Gilman, 1955).





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# 27 Daffodil and Alzheimer's Disease

When daffodils begin to peer,  
With heigh! The doxy over the dale,  
Why, then comes in the sweet o' the year.

— **Autolykus**, *The Winter's Tale*, iv., 3

## INTRODUCTION

In Greek mythology, *Narcissus* was a beautiful youth who was loved by the goddess **Echo**. He was so beautiful that he could love no one but himself after seeing his reflection in a pool. He became so focused on his beauty that the gods felt pity for him and turned him into a **daffodil**, which has thus become known as *Narcissus*. It is said that the scent is so strong that it was used by **Pluto**, the god of the underworld to lure the beautiful **Proserpine** to hell and by the gods in their coronas to adorn their brows. Finally, the Greeks have used the flower to ward off the Furies and Pluto and to subdue the dark spirits.

## HISTORY AND GENERAL EFFECTS

Since ancient times, it has been known that daffodil bulbs exert toxic effects upon ingestion. Even the name of the daffodil genus, *Narcissus*, implies that daffodils have physiological effects. The word *Narcissus* is derived from the Greek term *narkao*, “to benumb,” because of the narcotic properties attributed to the daffodil bulb. Similarly, the narcotic effects of the daffodil inspired **Socrates** to proclaim the daffodil as “**chaplet of the infernal gods.**” Daffodil bulbs contain powerful emetics; the flowers themselves are slightly poisonous (Figure 27.1).

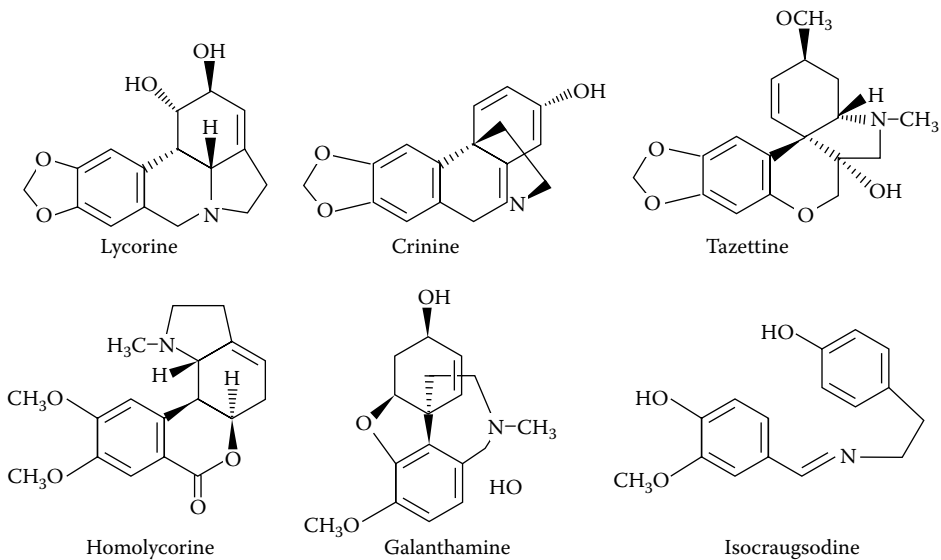
Ancient uses of daffodil components included systemic administration for “hysterical affections,” emesis, dysentery, chronic bronchial congestion, ague, and spasms. In addition, a plaster made of the roots was applied topically to dissolve hard swellings. An extract of the bulbs was also applied to open wounds, presumably as a crude anti-inflammatory agent, although wound treatment with **Narcissus** bulb extract could produce “staggering, numbness of the whole nervous system, and paralysis of the heart.”

## COMPOUNDS FOUND IN DAFFODILS

Many compounds are found in daffodil bulbs: **lycorine, narcitine, pseudolycorine, suisemine, tazettine, galanthamine, narzettine, nartazine, haemanthanmine, homolycorine, fiancine, hippastrine pluviine, galanthine, panceratine, narcissidine** (Figure 27.2). Galanthamine is used in mood disorders and in Alzheimer's disease.



**FIGURE 27.1** *Narcissus Pseudo-Narcissus*. Daffodil. Narcisse des prés Porillon, Fr. Gelbe Narcisse, G. (Nat. ord. Amaryllidaceae). Both the bulb and the bright yellow flowers of this common garden plant have been used in medicine. The flowers have a feeble peculiar odor, and both have a bitter mucilaginous taste. They are an uncertain emetic. It is probable that the flowers of the wild European plant are more powerful than those of the cultivated.



**FIGURE 27.2** Structures of some drugs found in daffodils.

### LYCORINE (FORMERLY NARCISSINE)

Although narcissine was isolated as early as 1578, much of the initial information that exists concerning narcissine dates to the early 1900s. In 1910 narcissine was purified from both resting bulbs and flowering bulbs, at a yield of 0.2 and 0.1%, respectively. In the same year, it was demonstrated that narcissine was a very stable alkaloid, not easily decomposed. Other scientists from this era noted that cats treated with narcissine were inflicted with vomiting, salivation, and purgation. In 1920, it was demonstrated that narcissine is the same compound as the alkaloid lycorine previously isolated from *Lycoris radiata*, and the name narcissine was dropped. Lycorine is an **isoquinolone (phenanthridine derivative)** alkaloid of molecular weight 287.32; its structure is shown in Figure 27.2. Although further details on the pharmacokinetics and pharmacological effects of lycorine are not available, the results of treating cats with lycorine suggest that it has **cholinomimetic effects**.

### GALANTHAMINE

A second compound isolated from daffodils, more extensively characterized than lycorine, is **galanthamine** (or **galantamine**) (see Figure 27.2). It has been suggested that galanthamine was the active compound in the potion that protected Odysseus from poisoning in **Homer's *Odyssey***. Known effects of galanthamine include antinociceptive effects and cholinomimetic effects. Current clinical trials are assessing the use of galanthamine in **Alzheimer's disease**, which is a neurodegenerative disease, not a mood disorder. However, successful treatment of the mood disorder mania with galanthamine has also been reported.

### Chemistry of Galanthamine

Galanthamine is a phenanthrene-derivative alkaloid of molecular weight 368.43; its structure is shown in Figure 27.2. Galanthamine can be purified from the bulbs of different strains of *Narcissus*; the quantity recovered per 100 mg of dried bulb ranges from 3.9 to 78.7 mg depending on the specific daffodil cultivar used.

### Pharmacological Mechanisms of Galanthamine Activity

Galanthamine is a long-lasting reversible **acetylcholinesterase (AChE) inhibitor**; as it is a tertiary amine, it rapidly crosses the blood–brain barrier and has effects on the central nervous system. Galanthamine is relatively selective for AChE over **butyrylcholinesterase**, with  $IC_{50}$  values of  $0.35 \times 10^{-7}$  for erythrocyte AChE and  $18.6 \times 10^{-7}$  for plasma butyrylcholinesterase. The inhibition of AChE by galanthamine results in slower degradation of **acetylcholine (ACh)** and thus generates longer responses to endogenous ACh.

Galanthamine also increases the frequency of opening of **nicotinic receptor channels** and potentiates agonist-activated receptors. This activity suggests that galanthamine can modulate the activity of nicotinic currents. Galanthamine binds to an allosteric site on the  $\alpha$ -subunits of nicotinic ACh receptors. This result might be related to the ability of galanthamine to increase responses to the nonhydrolyzable **carbachol**, as theoretically, galanthamine cannot increase the duration of response to a nondegradable cholinomimetic.

Analysis of the cholinergic effects of galanthamine in a mouse model suggests that galanthamine does not affect **choline acetyltransferase**, the choline carrier, or agonist binding to the active site of either muscarinic or nicotinic ACh receptors.

### Pharmacokinetics of Galanthamine

Single doses of 10 mg are tolerated by humans without any unwanted side effects. Maximal plasma concentrations are reached 2 h after either oral or subcutaneous ingestion. Elimination half-life is

5.3 (standard deviation 4.2) h. Both oral and subcutaneous application show similar drug absorption parameters. Galanthamine shows first-order pharmacokinetics and good oral bioavailability (estimates range from 65 to 100%). Galanthamine is absorbed in all segments of the gastrointestinal tract, including the stomach, duodenum, colon, and rectum (16%, 54 to 85%, 43%, 76%). Studies in mice suggest that galanthamine accumulates in the kidney, liver, and parenchymous tissues such as the brain (drug levels were tenfold, fivefold, and twofold increased over plasma levels).

Galanthamine is metabolized in the liver; small amounts of the active metabolites **epigalanthamine** and **galanthaminone** can be measured in the plasma. These metabolites are 130-fold less potent than galanthamine. Negligible quantities of these two metabolites can also be detected in urine. Galanthamine is cleared from the body by excretion in the kidneys; renal clearance has been estimated at 0.084 l/kg/h.

In one study, 65% inhibition of AChE was observed within 2 min of bolus injection of 10-mg galanthamine; enzyme activity returned to baseline within 24 h. The median maximal value of AChE inhibition in this study was 53%. Studies have also undertaken to analyze the effects of galanthamine on AChE inhibition in human brain tissue.  $IC_{50}$  values for galanthamine for AChE inhibition in postmortem human frontal cortex and hippocampus were  $3.2 \times 10^{-6} M$  and  $2.8 \times 10^{-6} M$ , respectively. Interestingly, the  $IC_{50}$  was tenfold higher for galanthamine treatment of human erythrocytes. In a mouse model of Alzheimer's disease (lesion of the **nucleus basalis magnocellularis**), the  $IC_{50}$  for AChE inhibition was  $4.1 \times 10^{-7} M$ .

### Use of Galanthamine to Treat Depression

The potential role of galanthamine in depression is complicated — manic and depressive symptoms are thought to be mediated by hyperadrenergic and hypercholinergic stimuli, respectively. In this model, a cholinomimetic is appropriate for restoring the adrenergic/cholinergic balance in mania. However, galanthamine also has antinociceptive (analgesic) effects; perhaps these effects inspired the ancients to promote daffodil use in depression.

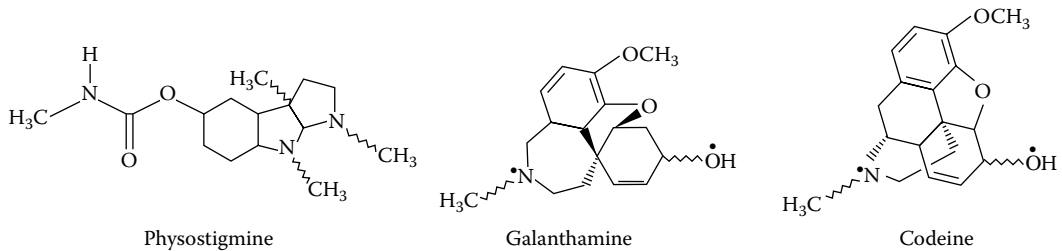
One published case report using galanthamine hydrobromide to treat mania appeared in the *Lancet* in 1991. A 74-year-old woman was admitted to the hospital with lithium-resistant manic depression. Within 2 h of treatment with 10 mg galanthamine hydrobromide, she exhibited considerable reduction in manic symptoms. As cessation of galanthamine therapy led to a relapse in her manic symptoms, she was maintained on galanthamine hydrobromide, 10 mg three times a day as a long-term therapy (Snorrason and Stefansson, 1991). Interestingly, galanthamine is useful in the cholinergic REM test, which is used to diagnose depression on the basis of REM onset.

### Specific Studies Showing Antinociceptive Effects of Galanthamine

Galanthamine has antinociceptive effects. This may partially be explained by the similarity in the structure of galanthamine to the structure of codeine (Figure 27.3). In the rat hot plate test, the antinociceptive effect could be partially blocked by **naloxone**, suggesting that galanthamine may have opioid-like activity. Galanthamine also provided analgesia in the mouse acetic acid writhing test, similar to that induced by morphine. In a separate study, intrathecal administration of galanthamine was shown to inhibit bradykinin-induced bioelectric activity in the rat spinal ventrolateral tracts.

### Summary

In summary, although bulbs of the *Narcissus* genus contain many alkaloid compounds, the most-studied alkaloid component of daffodils is galanthamine. Galanthamine is a long-lasting AChE inhibitor, which also affects the nicotinic ACh receptor directly by binding an allosteric site. Galanthamine has cholinomimetic as well as antinociceptive effects. Because of its cholinomimetic



**FIGURE 27.3** Chemical structures of physostigmine, galanthamine, and codeine.

properties, galanthamine is used in clinical trials to treat Alzheimer's disease. In addition, galanthamine has been used successfully to treat mania.

## THE TREATMENT OF COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE

Alzheimer's disease is characterized by a progressive dementia of insidious onset leading to a gradual deterioration of intellectual abilities, neuropsychological deficits, and personality changes. The disease process eventually results in **anomia**, **agnosia**, and **apraxia**, and a **complete loss of memory and learning abilities**. The disease is occasionally accompanied by sleep disturbances, agitation, anxiety, depressive states, or psychosis. In the final stages of the disease some patients are mute, unable to stand or walk, bedridden, and incontinent.

Generally, but not invariably, postmortem macroscopic examination of the brain reveals **cerebral atrophy** with narrowed convolutions, widened sulci, and enlarged lateral and third ventricles. On microscopic examination brain specimens from patients with a clinical diagnosis of Alzheimer's disease are characterized by widely spread cortical **senile plaques**, **neurofibrillary tangles**, and **granulovascular degeneration**.

Histochemically, Alzheimer's disease is associated with multiple deficits in various neurotransmitters or their associated markers such as **acetylcholine**, **noradrenaline**, **somatostatin**, and **others**.

## THERAPEUTIC OBJECTIVES IN ALZHEIMER'S DISEASE

Although the disease is accompanied by various psychiatric noncognitive symptoms, the progressive deterioration represents the core phenomenon of Alzheimer's disease and the major target of current therapeutic efforts. As in any other disease characterized by progressive deterioration, the therapeutic intent can vary from wanting to alleviate some symptoms of the disease to slowing or arresting the deterioration, or if possible, reversing the damage completely. The neurotransmitter-based approaches described in the following text offer modest palliation by augmenting deficient neurotransmission. Recent advances in the understanding of the biology of Alzheimer's disease may permit the development of strategies aimed at retarding or halting the progression of the illness. These strategies based on various pathophysiological models of the illness attempt to interfere with putative pathogenetic mechanisms involved, such as **glutamate's neurotoxicity**, **free-radical production**, **central nervous system (CNS) inflammation**, **amyloid production**, and **aluminum accumulation**. However, regenerative treatments however, aimed at restoring incurred damage are not yet in sight.

## THE CHOLINERGIC HYPOTHESIS OF ALZHEIMER'S DISEASE AND CHOLINERGIC ENHANCEMENT STRATEGIES

The cholinergic hypothesis of Alzheimer's disease postulates that

- There is significant cerebral cholinergic neurotransmission deficit.
- This deficit causes some of the cognitive disturbances observed in the patient with Alzheimer's disease.
- Enhancing cholinergic neurotransmission will produce some amelioration in cognitive function in this population (see Figure 27.4).

Several lines of evidence support this hypothesis. Centrally active anticholinergic drugs have been shown to induce dose-related cognitive deficits in humans whereas cholinergic neurotransmission has been shown to be specifically involved in memory and learning. The hypothesis is further supported by studies demonstrating that chemical, surgical, or pharmacological lesions to cerebral cholinergic systems impair learning and memory in animals and that cholinomimetic agents can reverse lesion-induced behavioral disturbances. Finally, brains of patients with Alzheimer's disease exhibit consistent cholinergic cell loss in the **septum** and **nucleus basalis of Meynert (NBM)**, a decrease in the cholinergic markers choline-acetyl transferase (CAT) and acetylcholinesterase (AChE), and a correlation between these neurochemical changes and the degree of cognitive impairment in Alzheimer's disease.

Analogous to the dopaminergic treatment approach used in Parkinson's disease, therapeutic trials in Alzheimer's disease have been aimed at augmenting cerebral cholinergic neurotransmission. The various cholinomimetic agents that have been assessed in Alzheimer's disease can be classified according to their particular cholinomimetic mechanism of action into (1) AChE inhibitors, (2) cholinergic agonists, (3) acetylcholine (ACh) precursors, (4) ACh-releasing agents, and (5) agents with various other cholinomimetic effects.

## ACETYLCHOLINESTERASE INHIBITORS

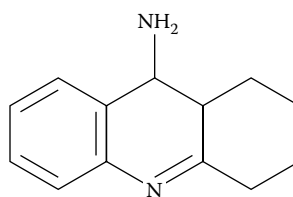
### TETRAHYDROAMINOACRIDINE

1,2,3,4-Tetrahydro-9-acridinamine (THA), known as **tacrine**, is a synthetic aminoacridine, which was initially synthesized more than 40 years ago. Tacrine and physostigmine are the two AChE inhibitors that have been most extensively evaluated in the treatment of Alzheimer's disease. Tacrine was the first drug ever to be approved by the FDA (available as of 1993) for the treatment of cognitive impairment in Alzheimer's disease in the U.S. (Figure 27.4).

### Pharmacology

**Cholinesterase Inhibition:** Tacrine is thought to be a noncompetitive reversible inhibitor of AChE. The drug has been shown to be a more potent inhibitor of **butyrylcholinesterase** than of AChE. The AChE inhibitory activity of Tacrine is thought to be mediated by its binding to a hydrophobic area close to the active site.

**Effects on Choline Metabolism:** THA has been reported to increase ACh brain levels.



Tacrine  
Molecular structure of THA

FIGURE 27.4 Molecular structure of THA.

**Effects on Cholinergic Receptors:** THA has been shown to bind to muscarinic and nicotinic receptor sites.

**Inhibition of Monoamine Oxidase (MAO):** The enzymatic activity of monoamine oxidases of type A (MAO-A) and type B (MAO-B) have been shown to be reduced by THA. MAO-A seems to be inhibited to a larger degree than MAO-B. At therapeutic concentrations, THA is believed to produce a significant decrease in MAO activity leading to an enhanced monoaminergic activity. Given that some cognitive deficits in Alzheimer's disease are believed to be due to a monoaminergic deficit, this monoaminergic enhancement might also contribute to the therapeutic effect of THA in the illness.

**Monoamine Release and Uptake:** Tacrine has been shown to induce monoamine release and to inhibit monoamine uptake, leading to an increase in several monoamine neurotransmitters including dopamine, serotonin, and norepinephrine.

### Pharmacokinetics

Cognex®, the THA brand currently available on the U.S. market, is rapidly absorbed and reaches maximal plasma concentration 2 hours after oral administration.

### Clinical Applications

Cognex is available in 10, 20, 30, and 40 mg capsules. It is recommended that treatment should be started with 10 mg orally four times a day (po qid) for 6 weeks. Additional dosage increments of 10 mg po qid up to a maximum of 160 mg po/day should be initiated every 6 weeks. Weekly transaminase monitoring should be performed for the first 18 weeks of treatment and for at least 6 weeks after each dosage increment. Thereafter, checks at 3-month intervals are recommended.

### Side Effects

Reversible liver toxicity was common in THA-treated patients.

### Drug-Drug Interactions

*Cimetidine* was found to increase the concentration and rate of absorption of THA by 50%. THA administration may double the elimination half-life and plasma concentrations of theophylline.

### Overdosage

THA overdosage can result in a **cholinergic crisis** with severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, convulsions, etc. Progressive muscle weakness may result in death from asphyxiation. Treatment with anticholinergics (such as intravenous atropine sulfate) and general supportive treatment are recommended.

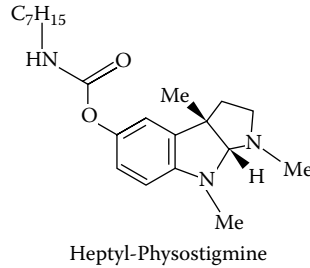
### Physostigmine and Its Derivatives

**Physostigmine** (PHS) is a natural alkaloid, first isolated in 1864 (Figure 27.5). **Heptylphysostigmine** was well tolerated in healthy volunteers and up to 48-mg tid in patients with Alzheimer's disease. Unfortunately, heptylphysostigmine trials in humans have been abandoned because of **neutropenia** observed with this agent.

### Limitations of AChE-Inhibitor Therapy in Alzheimer's Disease

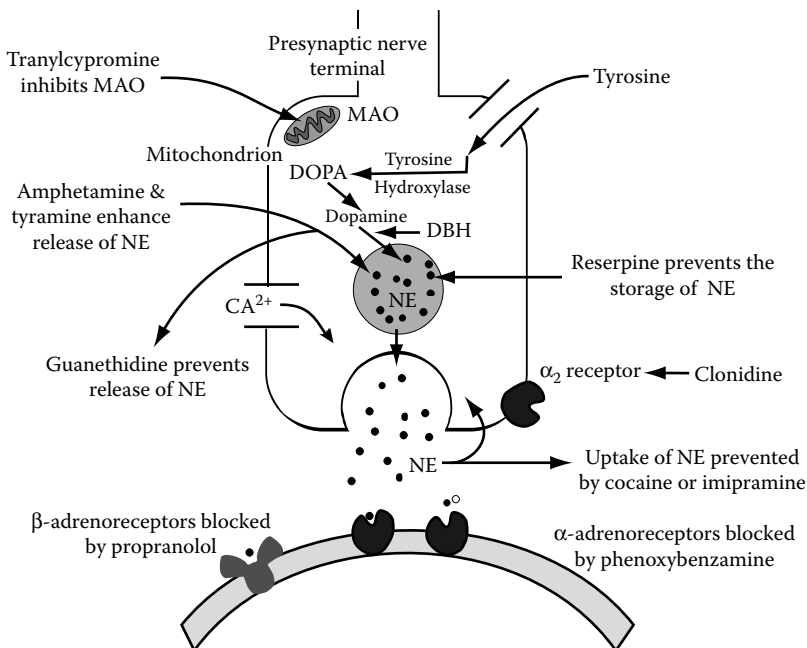
Adverse effects of AChE inhibitors are due to the enhancement of peripheral cholinergic tonus and are primarily gastrointestinal (nausea, vomiting, abdominal cramping, and diarrhea) but may include





**FIGURE 27.5** Molecular structure of heptyl-physostigmine.

**diaphoresis** and light-headedness. However, some nausea is undoubtedly of central origin and could be related to the rate of rise of the drug in plasma. **Bradycardia** and **hypotension** are anticipated risks, but appear infrequently. Depression and agitation have also been encountered. Individual susceptibility to such side effects varies widely. Considering the inverted U-shape form of the dose–response curve to cholinergic enhancement in Alzheimer’s disease, AChE inhibitor levels that are too high or too low may easily be outside the therapeutic window. Nonoptimal levels may easily occur with fluctuations in drug levels due to uncertain CNS availability of the drug. Under such circumstances, fixed-dose treatment studies can be of limited benefit. Thus, studies should include individual titrations and confirmation of CNS availability using biological markers such as AChE activity in cerebrospinal fluid (CSF) or endocrinological parameters. Ultimately, some patients might present with such a severe degree of presynaptic cholinergic cell loss that any degree of AChE inhibition would fail to induce a clinically significant enhancement of the cholinergic transmission (Figure 27.6). Overall, it appears that short-term administration of AChE inhibitors can induce a mild to moderate improvement of memory in Alzheimer’s disease, and that long-term AChE treatment should be evaluated for additional benefits.



**FIGURE 27.6** The synthesis and actions of norepinephrine. MAO = monamine oxidase; NE = norepinephrine; DBH = dopamine α-hydroxylase.

## CHOLINERGIC AGONISTS

Bethanechol, arecoline, oxotremorine, and **nicotine** have been tried and had no beneficial effect on memory.

## ACETYLCHOLINE PRECURSORS

**Phosphatidylserine**, **L- $\alpha$ -glyceryl-phosphorylcholine**, and **cytidine diphosphate choline** have shown positive effects.

## ACETYLCHOLINE-RELEASING AGENT

**4-Aminopyridine** or **linopirdine** provides some improvement.

## NONCHOLINERGIC NEUROTRANSMITTER REPLACEMENT STRATEGIES

In addition to the cholinergic deficit, Alzheimer's disease has also been shown to be characterized by marked deficits in the monoamine neurotransmitters **norepinephrine** and **serotonin**, as well as in **glutamate** and some neuropeptide neurotransmitters (Figure 27.6).

### MONOAMINERGIC DRUGS

L-deprenyl (**selegiline**), a monoamine oxidase B inhibitor, **clonidine** and **guanfacine**,  $\alpha_2$ -adreno-receptor agonists, and **levodopa** (L-dopa) have been reported to improve cognitive function in some subjects. **Zimeldine**, **citalopram**, and **alaproclate** — selective serotonin uptake blockers — have no beneficial effects.

### NEUROPEPTIDES

**Adrenocorticotrophic hormone** (ACTH), **vasopressin** (VP), **somatostatin**, and **cholecystokinin** (CCK8) look promising.

### DRUGS AFFECTING GLUTAMATE RECEPTOR SITES

**Milacemide** and **D-cycloserine** look promising.

### NOOTROPICS

**Piracetam** and derivatives, such as **pramiracetam**, **oxiracetam**, **aniracetam**, or **acetyl-L-carnitine**, showed no significant improvement.

### ANTIOXIDANTS

Several studies have demonstrated increased free-radical production in aging in general and in Alzheimer's disease in particular. Increased **superoxide dismutase**-derived hydrogen peroxide fluxes, metal ions, and damaged mitochondria can contribute to cell damage mediated by free radicals. Free-radical production in Alzheimer's disease may also be caused by amyloid  $\beta$ -protein and glutamate. These findings suggest that antioxidants could have beneficial effects in Alzheimer's disease by interfering with free-radical production and preventing consequent cell injury. **L-deprenyl** is thought to possess antioxidant properties and is believed to have neuroprotective effects in Alzheimer's disease as well as in Parkinson's disease by acting as scavenger of free radicals.

**Vitamin E** and **idebenone** are also potential antioxidant treatments for Alzheimer's disease as they prevent cell death caused by glutamate and amyloid  $\beta$ -protein. Clinical trials with L-deprenyl and vitamin E are currently evaluating their ability to slow the progression of Alzheimer's disease.

### DEFERRIOXAMINE: AN IRON-CHELATING AGENT

Several findings suggest an association between aluminum and Alzheimer's disease. Epidemiological studies have reported an association between the **aluminum** concentration in drinking water and the occurrence of Alzheimer's disease. In addition, aluminum administration has been shown to be neurotoxic to the cholinergic system. These findings have led clinical trials with **desferrioxamine mesylate** in Alzheimer's disease, which has a particularly high affinity for aluminum and has been used to treat iron and aluminum overload. In a 2-year-long double-blind controlled trial, desferrioxamine administered intramuscularly was compared to placebo. Patients who received desferrioxamine treatment showed less decline in daily living skills when compared to the placebo group. The therapeutic effects observed with this agent may not necessarily be due to its chelating action because it has been shown to inhibit **free-radical formation** and **inflammation** as well. The required intramuscular administration and toxic side effects of this compound, however, might limit its clinical utility. Replication studies are necessary to confirm the efficacy of this approach.

### NERVE GROWTH FACTOR

Another conceivable therapeutic approach for Alzheimer's disease could be based on the administration of **neurotrophic factors**. **Nerve growth factor** (NGF) is a 118 amino acid polypeptide with no blood-brain barrier penetrance. Other substances with neurotrophic activity such as **epidermal growth factor**, **brain-derived neurotrophic factor**, **gangliosides**, and the  **$\beta$ 1-28 peptide** of the b-amyloid protein might also have a therapeutic potential. Intracerebroventricular (ICV) administration of NGF has been shown to partially reverse lesion-induced deficits of cortical AChE and choline acetyltransferase (CHAT) activities to promote survival of septal cholinergic neurons after fimbrial transection in adult rats and to reverse behavioral deterioration in rats with such lesions.

### ANTI-INFLAMMATORY AGENTS

The involvement of the immune system and inflammation in the pathophysiology of Alzheimer's disease has been suggested by several findings, such as the presence of inflammation markers in the brain and the colocalization of some acute-phase and complement proteins in senile plaques. Furthermore, increased numbers of **reactive glia** and **microglia** (believed to be related to macrophages) have been observed. **Activated T lymphocytes**, a **hallmark of the cell-mediated response** observed in chronic inflammatory states, have also been observed in postmortem studies of Alzheimer's disease cases. The use of anti-inflammatory agents in the treatment of Alzheimer's disease is further supported by the low prevalence of Alzheimer's disease found in patients with rheumatoid arthritis and in elderly patients with leprosy. These findings could potentially be explained by the long-standing exposure of these patients to chronic anti-inflammatory therapy. Furthermore, preliminary observations suggest that **steroids** and **nonsteroidal anti-inflammatory agents (NSAIDs)** such as **indomethacin** and aspirin may have protective effects against Alzheimer's disease. In a recent 6-month-long double-blind placebo-controlled study in Alzheimer's disease, indomethacin 100 to 150 mg/po/d was found to improve cognitive function and potentially delay further deterioration. These results are promising; however, the toxicity of indomethacin might limit its use.

**Corticosteroids** offer a logical anti-inflammatory therapy for Alzheimer's disease as these agents are widely used and efficacious for several inflammatory diseases in the CNS, including **lupus cerebritis** and **multiple sclerosis**. Unfortunately, the systemic toxicity of steroids limits the use of high doses or long-term treatments with these agents. Animal studies suggest that prolonged exposure to high doses of glucocorticoids is toxic to hippocampal neurons. Low-dose steroid therapy

may be the safest strategy because this dose is well tolerated and effective in patients with rheumatoid arthritis.

*Colchicine* is another possible candidate for the treatment of Alzheimer's disease. This drug effectively treats **familial Mediterranean fever**, a condition in which recurrent inflammation and **renal amyloidosis** occur. Although the amyloid constituents in familial Mediterranean fever and Alzheimer's disease differ, both illnesses involve chronic inflammation, elevated acute-phase proteins, and abnormal processing of a precursor protein leading to deposition of insoluble amyloid fragments. These similarities suggest the potential therapeutic efficacy of colchicine for patients with Alzheimer's disease.

*Hydroxychloroquine* is historically an antimalarial agent that has been adopted as a safe and effective second-line agent for the treatment of *rheumatoid arthritis* and *lupus erythematosus*. The efficacy of hydroxychloroquine is thought to be related to its effects on the immune response and lysosomal functioning. This agent suppresses cytokine and acute-phase reactant levels in these illnesses. Hydroxychloroquine also interferes with lysosomal enzymatic activity by increasing the pH in these organelles and by stabilizing lysosomal membranes. The safe clinical profile of hydroxychloroquine as a chronic treatment for rheumatoid arthritis supports it as a possible candidate for the treatment of Alzheimer's disease.



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# 28 Eggplant

Flowers of eggplant are similar to those of potato and tomato.

All three plants are solanaceous species. An **eggplant**, **aubergine**, or **brinjal** is either of two species of nightshade, *Solanum melongena* and *S. esculentum*, bearing large pendulous purple or white fruit. Although **aubergine** is the English name given to this fruit, it is often invoked to describe other objects with a dark plum color. This name comes from the French aubergine, derived from Catalan **algerinia**, Arabic **al-bAdhinjAn**, Persian **Badimjan**, the eggplant. The word **melongena** is from the Sanskrit **vatinganah**, which has produced a number of names for this plant in various languages: brinjal, badingan, melongena, melanzana, berenjena, alberginia, aubergine, brown-jolly, and mad-apple.

Eggplant stew (**Khoresht Badimjan**) served with saffron rice is a national food of Iran and is served at formal banquets. Other favorites throughout the world are:

- **Caviar d'aubergine** (French Provencal cuisine)
- **Escalivada** (Catalan cuisine)
- **Moussaka** (Greek cuisine)
- **Mutabal** (Lebanese cuisine)
- **Salat de vinete** (Romanian cuisine)

Eggplant is very low in saturated fat, cholesterol, and sodium; is a good source of vitamin C, vitamin K, thiamin, niacin, vitamin B<sub>6</sub>, and pantothenic acid; is an excellent source of manganese, potassium, magnesium, phosphorus, and copper; and is a good source of folate. Eggplant contains an **anthocyanin** phytonutrient called **nasunin**, which is a potent antioxidant (see Chapter 8). In addition, it is an excellent source of numerous phenolic compounds such as **chlorogenic acid**, which is one of the most potent free-radical scavengers found in plant tissues. Benefits attributed to chlorogenic acid include antimutagenic (anticancer), antimicrobial, anti-LDL, and antiviral activities. Nasunin is also an iron chelator. Excess iron generates free radicals and causes cellular damage (see Chapter 8). Eggplant contains **oxalates**, which may interfere with absorption of **calcium**, hence calcium supplementation is recommended. Eggplant contains **solanine**, a calcium inhibitor, hence individuals with arthritis should avoid fruit of the night shade family, including eggplant (see Noda et al., 1998 and 2000; Sakamura et al., 1963; Wantanabe et al., 1996).



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# 29 Ephedrine (Ma Huang): A Decongestant and Vasopressor

## THE ACTIONS OF EPHEDRINE

*Ephedrine sulfate*, *Kondon's Nasal*, *Pretz-D*, or *Vicks Vatronol* is classified as a decongestant and vasopressor.

Ephedrine stimulates both  $\alpha$ - and  $\beta$ -receptors, causing increased heart rate, unchanged or augmented stroke volume, enhanced cardiac output, and increased blood pressure. It causes relaxation of smooth muscle of bronchi and gastrointestinal tract, stimulation of cerebral cortex, and pupil dilation.

Ephedrine, given im/iv/sc, is indicated for the treatment of acute hypotensive states, treatment of Adams–Stokes syndrome with complete heart block, stimulation of the central nervous system (CNS) to combat **narcolepsy** and depressive states, treatment of acute bronchospasm, treatment of enuresis, and treatment of **myasthenia gravis**. When given in nasal form, ephedrine is used in the treatment of nasal congestion, promotion of nasal or sinus drainage, or relief of **eustachian tube congestion**.

The contraindications to ephedrine are angle-closure glaucoma, patients anesthetized with cyclopropane or halothane, cases in which vasopressor drugs are contraindicated (e.g., thyrotoxicosis, diabetes mellitus, hypertension during pregnancy), or treatment with monoamine oxidase (MAO) inhibitor therapy.

Ephedrine may negate the antihypertensive effects of *guanethidine* and may potentiate the pressor effects of MAO inhibitors causing hypertensive crisis and intracranial hemorrhage.

## HISTORY

Ephedrine is an alkaloid occurring in various plants belonging to the genus *Ephedra*, a gymnosperm related to pines and firs. The genus is indigenous to the temperate and subtropical latitudes of Europe, Asia, and America, and grows especially in northern and western China, northern India, and Spain. In the U.S., ephedra plants grow along the Rocky Mountains but most of the naturally occurring types in this country do not yield the ephedrine alkaloid. The stems of the plant contain up to about 1% of the alkaloid and its isomers. The content increases through the spring and summer and becomes maximal just before the frosts; the old Chinese custom of collecting the plant for medicinal use in the autumn is thus vindicated.

The Chinese herb containing ephedrine and called *ma huang* (yellow astringent) has been employed empirically by native physicians for over 5000 years. The **Emperor Shen Nung** (2760 B.C.) is supposed to have tasted ma huang, as well as all other drugs in the pharmacopeia, and placed it in the “medium class.” The Chinese Dispensatory (*Pentsao Kang Mu*) written in 1569 by **Shih-Cheng Li** mentions that the drug is valuable as an antipyretic, diaphoretic, circulatory stimulant, and sedative for cough. Ephedrine came to be an ingredient of several favorite native



prescriptions. The plant was also widely employed in Russia for many centuries, particularly for respiratory disorders and rheumatism. The Native Americans and Spaniards of the southwestern U.S. used ephedrine plants for various medicinal purposes, especially venereal diseases.

An active principle was first isolated from ma huang by Yamanashi in 1885. In 1887, Nagai obtained the alkaloid in pure form and named it **ephedrine**. Pharmacological investigation by Japanese workers indicated that the drug was toxic, but large doses were used in the study. However, its mydriatic properties were noted by Miura (1887), and as early as 1888, Takahashi and Miura concluded that the drug caused dilatation of the pupil through stimulation of the sympathetic nerves (see Sollmann, 1944). Ephedrine then enjoyed a passing vogue as a mydriatic, several years before the isolation of epinephrine. Japanese scientists continued their investigations of the alkaloid, observed its sympathomimetic properties, and employed it in the treatment of asthma.

Interest in ephedrine in Western medicine was created by the classical investigations of Chen and Schmidt, which began in 1923 as a result of a Chinese druggist's assurance that ma huang was really a potent drug. These workers reported the cardiovascular effects of the alkaloid, its similarity to epinephrine, and its absorption from the intestinal tract. Numerous clinical and experimental studies soon followed, and the use of ephedrine spread so rapidly that several tons of the alkaloid are now consumed yearly. Synthetic ephedrine (racemic) was first prepared in 1927 and marketed under the name *Ephetonin* (Goodman and Gilman, 1955).

## EPHEDRA

**Ephedra** or **ma huang** is the entire plant, or the portion (above the ground) of *Ephedra sinica* grown in China. In Chinese characters “**ma**” means astringent and “**huang**” means yellow, probably referring to the taste and color of the drug. It has been used as a medicine in China for more than 5000 years. Its use in modern medicine began with the recent discovery of the valuable properties of ephedrine. The plant is found near the seacoast in southern China and the drug is exported from Canton.

The plant is a low, dioecious, practically leafless shrub, 60 to 90 cm high. The stem, green in color, is slender, erect, small ribbed and channeled, 1.5 mm in diameter, and usually terminates in a sharp point. Nodes are 4 to 6 cm apart, at which the leaves appear as whitish triangular scarious sheaths. Small blossoms appear in the summer.

Various species of *Ephedra* grow in different parts of the world. It is believed that the Chinese species contain the official levorotatory ephedrine, whereas the same species and other varieties from Europe yield only dextrorotatory **pseudoephedrine**. East Indian species range from rich to none. Ephedrine exists in the seed of another, totally unrelated Indian plant, *Sida cordifolia*, which was also used in folk medicine. Ma huang also contains another alkaloid, *ephedine*, which lowers blood pressure and has other complex actions.

## EPHEDRINE

This **alkaloid** was first isolated from *Ephedra equisetina*, a plant (ma huang) that has been used as medicine by the Chinese since antiquity. Most of the present supply is probably synthetic. Its chemical structure is closely related to **epinephrine** and **tyramine**, and differs from epinephrine chiefly by the absence of the two phenolic hydroxyls. Its effects on the circulation, intestines, bronchi, iris, etc., are superficially similar to those of epinephrine. It requires that larger doses be given but they are more lasting, due probably to ephedrine's much greater stability and resistance to oxidation. The effects can be produced by oral administration. Unlike epinephrine, it is not sensitized by **cocaine** or by denervation. From this, it has been argued that its point of attack is not sympathomimetic but muscular. It also stimulates the CNS. A number of isomers with similar actions are known. Ephedrine is used therapeutically in hay fever and asthma, in which it is less

effective than epinephrine, but more convenient; as a mydriatic with minimal effect on intraocular tension; and as a stimulant to respiration, especially against barbiturate poisoning in conjunction with **metrazol** or **picrotoxin** (Sollmann, 1944).

**Ephedrine** is an alkaloid obtained from *E. equisetina*, *E. sinica*, and other species of *Ephedra*, or produced synthetically.

Ephedrine occurs in white, rosette, or needle crystals, or as an unctuous mass. It is soluble in water, alcohol, chloroform, ether, and in liquid petrolatum, the latter solution being turbid if the ephedrine is not dry. Ephedrine melts between 34 and 40°C, depending upon the amount of water it contains; it contains not more than 0.1% of ash; its solutions are alkaline to litmus; it readily forms salts with acids; and it responds to the usual tests for alkaloids. Ephedrine excites the sympathetic nervous system, depressing smooth and cardiac muscle action, and produces effects similar to those of epinephrine. It produces a rather long-lasting rise of blood pressure and mydriasis and diminishes hyperemia. The alkaloid may be used in 0.5 to 2% oil spray.

**Ephedrine hydrochloride** ( $C_{10}H_{15}ON \cdot HCl$ ), when dried over sulfuric acid for 24 h, contains not less than 80% and not more than 82.5% of anhydrous ephedrine,  $C_{10}H_{15}ON$ .

**Ephedrine sulfate** ( $C_{10}H_{15}ON$ )<sub>2</sub>H<sub>2</sub>SO<sub>4</sub>, when dried over sulfuric acid for 24 h, contains not less than 75.5% and not more than 77.3% of anhydrous ephedrine  $C_{10}H_{15}ON$ .

Both of these salts are readily soluble in water and in hot alcohol, but not in ether. They have the same pharmacological properties as ephedrine and are used orally in an average dose of 0.25 g. They are also used, in aqueous solution, intramuscularly and intravenously.

## PHARMACOLOGICAL PROPERTIES OF EPHEDRINE

The change from the phenolic structure of epinephrine to the phenyl structure of ephedrine results in a marked difference in action. Unlike epinephrine, ephedrine is effective orally, has a prolonged action, exhibits tachyphylaxis, and is a potent corticomedullary stimulant. The oral effectiveness and prolonged action of ephedrine are apparently due to the presence of the methyl group on the a carbon atom, a configuration that renders the molecule refractory to deamination by the amine oxidase of the liver.

At first, ephedrine was assumed to have a mechanism of action similar to that of epinephrine, acting through the same receptive mechanism. Later, as it was found that not all the effects of epinephrine could be duplicated by ephedrine, it was conjectured that some of its effects were due to direct excitation of smooth muscle.

## EFFECT ON ORGAN SYSTEMS

### CARDIOVASCULAR

In experimental animals the effect of ephedrine administered intravenously is similar to that of epinephrine. The arterial pressure — systolic, diastolic, and mean pressure — rises and vagal slowing occurs. Compared with epinephrine, the pressor response to ephedrine occurs somewhat more slowly and lasts about ten times longer. Furthermore, it requires more ephedrine than epinephrine to obtain an equivalent pressor response. How much more depends on the species tested, type and degree of anesthesia, dose level, and individual variability of the test animal. It is, therefore, almost impossible to give a definite figure for the relative potency of ephedrine and epinephrine. It is commonly accepted that it requires about 250 times more ephedrine than epinephrine to achieve equipressor responses.

If a second dose of ephedrine is administered too soon, its pressor response proves weaker than that of the first dose. This phenomenon, known as *tachyphylaxis*, occurs with many adrenergic agents and is related to the duration of action of the drugs. The longer acting the adrenergic agent, the more marked the tachyphylaxis.

The shorter the time interval between doses, the smaller the pressor response to each subsequent dose. Tachyphylaxis probably represents a dynamic blockade of the adrenergic receptors. Ephedrine, for example, activates the receptor, and this activation persists until the drug is completely eliminated. Before the drug is eliminated, however, the arterial pressure returns toward the control level because of compensatory cardiovascular changes, involving only an apparent loss of activity rather than a real one. When another dose is then administered, it acts on receptors still activated so that the pressor response obtained is less than expected.

The pressor response to ephedrine is due in part to peripheral constriction and in part to myocardial stimulation. Vasoconstriction can be demonstrated by intra-arterial injection, but compared to epinephrine, ephedrine is only about one thousandth as active. This would imply that the cardiac effect is predominant in increasing the arterial pressure. This, however, is difficult to demonstrate. In perfused hearts, ephedrine produces only minor stimulation and cardiac depression appears if the drug is repeated.

In humans, ephedrine increases the arterial pressure both by peripheral vasoconstriction and by cardiac stimulation. The heart rate is usually increased, as is the pulse pressure, both suggesting an increased cardiac output. The cardiovascular response to ephedrine is, however, quite variable. In some cases the arterial pressure is not elevated; in others bradycardia occurs at the height of the pressure rise. The peripheral resistance has been reported as increasing, decreasing, or remaining unchanged. However, the hypotension that commonly occurs during surgery under spinal anesthesia is practically always prevented by ephedrine. The vasoconstrictive action of ephedrine is demonstrated by the decongestive effect of solutions applied topically to the mucous membranes of the nose. Similar to epinephrine, ephedrine often produces a secondary congestive response.

In summary, based on the cardiovascular responses that can be observed, it can be stated that ephedrine activates the same adrenergic receptors as does epinephrine but is less potent and has a longer duration of action.

## BRONCHI

The smooth muscle of the bronchial tree is relaxed by ephedrine. Compared with epinephrine, the action of ephedrine is slow in onset, becoming complete only an hour or more after administration. Ephedrine prevents **histamine-induced bronchoconstriction** in patients with asthma.

## EYE

Ephedrine produces mydriasis when applied locally to the conjunctiva, as well as upon systemic absorption. In humans, there is a striking disparity between the mydriatic effects of ephedrine in Caucasians and in Chinese or blacks. It is most active in the first, less active in the second, and almost completely inactive in the last. The reason for this differential effect on irides of different color has not yet been completely explained.

## OTHER SMOOTH MUSCLE

In general, ephedrine produces the same effects on smooth muscle as epinephrine. Inhibition of the intact gastrointestinal musculature and contraction of the splenic capsule and of pilomotor muscles are produced. Ephedrine has the same myometrial and urinary bladder actions as does epinephrine.

## GLANDS

The effects of ephedrine are similar to those of epinephrine. However, ephedrine is much less potent, and with routes of administration other than intravenous, the glandular responses do not always occur. Ephedrine does produce hyperglycemia and eosinopenia.

## CENTRAL NERVOUS SYSTEM

All the adrenergic agents possessing the unsubstituted phenyl ring and the methyl group on the  $\alpha$  carbon atom are corticomedullary stimulants. Depending on the dose, this stimulant action in humans results in feelings of anxiety, tremor, insomnia and mental alertness, and increased respiration. When ephedrine is used for its adrenergic effects, the central stimulation produced by it may be considered as an undesirable side action. When it is used as a central stimulant, the adrenergic effect becomes the side action.

At one time, ephedrine was advocated as a useful central stimulant in **narcolepsy** and depressant poisoning. Although it still can be used if necessary, other agents such as **amphetamine** and **methamphetamine** are more often used today.

## SKELETAL MUSCLE

Although it has long been known that ephedrine occasionally influences the muscular weakness of **myasthenia gravis** favorably, the exact mechanism of this action is unknown.

## ROUTES OF ADMINISTRATION

Ephedrine can be administered by almost any route. Most frequently, it is given orally. It is also injected subcutaneously, intramuscularly, or intravenously. For local action, as in the eye or on the nasal mucosa, ephedrine solutions are applied directly by drops, on a tampon, or as a spray.

## ABSORPTION, FATE, AND EXCRETION

Ephedrine is readily and completely absorbed after oral or parenteral administration. As it is less active than epinephrine, it does not produce enough local vasoconstriction to hinder absorption after subcutaneous or intramuscular injection. As has been indicated, ephedrine is resistant to amine oxidase, but it is deaminated to some extent in the liver, probably by the **ascorbic-dehydroascorbic acid system**. Conjugation also occurs. In addition, up to 40% of the ephedrine administered may be excreted unchanged in the urine. Inactivation and excretion are so slow that the action of ephedrine may persist for several hours.

**Urinary acidifiers** may increase elimination of ephedrine, and **urinary alkalizers** may decrease the elimination of ephedrine. Ephedrine is chemically incompatible with sodium bicarbonate and the two should not be used together.

## THERAPEUTIC USES OF EPHEDRINE

### BRONCHIAL ASTHMA

In this condition, ephedrine is used primarily as a chronic medication for mild or only moderately acute cases, especially in children. In severe asthma, the response to ephedrine is usually poor. Compared with epinephrine, ephedrine is less reliable, is slower in action and longer in duration, and probably more often produces undesirable side effects. The average dose is 25 to 50 mg, orally, repeated three or four times a day. Resistance often develops; it may often be controlled by discontinuing the drug for a few days. In many patients, ephedrine produces anxiety, nervousness, and insomnia, so a barbiturate is often administered at the same time. Capsules containing either 15 mg of **amobarbital**, 25 mg of **pentobarbital sodium**, or 30 mg of **phenobarbital** in addition to 25 mg of ephedrine sulfate have been used in the past.

## ALLERGIC DISORDERS

One of the principal uses of ephedrine and other adrenergic activators is to relieve nasal congestion when applied locally to the mucous membrane. This decongestive effect, brought about by vasoconstriction, is used in acute coryza, vasomotor rhinitis, acute sinusitis, hay fever, and other allergic reactions. To be most useful, a decongestive agent should have the following characteristics:

- It should have a prompt, reliable action.
- A secondary or “rebound” congestion should not occur.
- Side effects due to systemic absorption should be minimal.
- Tachyphylaxis should not occur.
- The solution or preparation applied should not in itself be irritative or harmful to cilia.
- The duration of action should be fairly long so that frequent application does not become necessary.

Ephedrine rates as a fairly good decongestive; its principal disadvantages are that secondary congestion often occurs, tachyphylaxis is common, and symptoms of central stimulation usually appear. Ephedrine is used in concentrations ranging from 0.5 to 3% in aqueous or oily solution. The oil solutions should probably not be used, especially in children, because of the danger of producing lipoid pneumonia. Ephedrine administered orally very often produces a satisfactory decongestive effect. In many cases of allergy, this route should be used. Added to cough mixtures, ephedrine acts as an adjuvant to the expectorants by controlling edema in the respiratory tract.

## SPINAL ANESTHESIA

Hypotension frequently occurs during surgery under spinal anesthesia. Ephedrine has long been used to prevent or abate this possibly undesirable phenomenon. The skin and subcutaneous area over the spinal puncture site are usually anesthetized with procaine solution as a preliminary step. Adding 50 mg of ephedrine sulfate to this solution, and injecting it partly at the puncture site and partly into the interspinous muscles or ligaments, serves as a convenient way to administer the pressor agent. Some anesthesiologists add this amount of ephedrine sulfate to the anesthetic–spinal fluid mixture. The purpose here is to prolong the anesthesia as aforementioned for epinephrine. The usual dose of ephedrine employed to treat, rather than prevent, the hypotension is 50 mg intramuscularly or 15 mg intravenously. The central stimulant action of ephedrine, which may be objectionable, is controlled by adequate preanesthetic sedation or the concomitant use of a short-acting barbiturate.

## HEART BLOCK

In complete heart block with Stokes–Adams syncope, ephedrine may prove of value in a manner similar to epinephrine. In the attempt to increase ventricular rate and prevent ventricular asystole, an initial dose of about 8 mg of ephedrine sulfate orally may be tried. Later, the dosage may be increased to 25 mg three or four times daily. Syncope due to ventricular tachycardia can also be prevented in some cases with ephedrine.

## MYDRIASIS

Many of the adrenergic agents produce a transient, incomplete mydriasis when applied to the eye. **Cycloplegia** does not occur. Ephedrine sulfate in a 3% concentration has been used for this purpose. As has been indicated, the effect is most positive in Caucasians with light-colored irides. Ephedrine is not considered to be a good mydriatic, as it is none too reliable and its solutions are quite irritating to the cornea. **Phenylephrine** should probably be the adrenergic mydriatic of choice.

## ENURESIS

Medical treatment of this condition consists of either diminishing cholinergic activation of the bladder by means of atropine-like drugs, or increasing adrenergic control by means of drugs such as ephedrine. For the latter, ephedrine sulfate in fairly large doses, 60 to 120 mg given orally at bedtime, can be tried. As ephedrine does tend to prevent micturition, however, urinary retention may occur in any patient being treated with this drug. This usually occurs in elderly male patients and may in some cases be considered a definite contraindication.

## MYASTHENIA GRAVIS

This serious condition is usually treated with **neostigmine**. Before the value of this drug had been discovered, ephedrine was the only drug available that in any measure would benefit this disease. How it works is not known. Its action may be related to the observation that in certain nerve–muscle preparations, epinephrine exhibits an anticholinergic effect. Compared to neostigmine, ephedrine is much less effective and should not be considered the drug of choice. Small doses of 8 to 25 mg several times a day should be used, as large doses may aggravate the disease.

## MISCELLANEOUS ACTIONS OF EPHEDRINE

The effect of ephedrine on secretions is not prominent. Sweating occurs after ephedrine in humans but is not demonstrable in animals. Secretions of the gastrointestinal tract are usually inhibited. Ephedrine decreases the output of pancreatic juice, and the suggestion has been made that the drug may be serviceable in the management of patients with pancreatic fistula. The metabolic effects of ephedrine are generally similar to those of epinephrine. Thus, the drug causes hyperglycemia, but the action is neither as prominent nor as constant as after epinephrine; indeed, in animals, ephedrine has been shown to block epinephrine hyperglycemia. The metabolic rate is increased in humans, but the response is not marked. Changes observed in the formed elements of the blood after administration of ephedrine are generally similar to those noted after epinephrine and are mainly the result of contraction of the spleen and other blood depots.

Ephedrine exerts interesting but as yet inadequately explained actions on skeletal muscle. Isolated skeletal muscle is contracted by ephedrine; this indicates that the observed effect is independent of actions of the drug on the vascular system or CNS. Numerous investigations have established the ability of ephedrine, epinephrine, and related substances to improve neuromuscular transmission depressed by curare, and to enhance the tension response of both normal and denervated fatigued skeletal muscle. **Tyramine** was twice as effective and **dihydroxyphenylethylamine** 20 times as active as ephedrine in this respect, and the influence on skeletal muscle far outlasted the vasopressor action. In myasthenia gravis, ephedrine produces a real but modest increase in motor power. It will be recalled that epinephrine may potentiate the effects of acetylcholine, anticholinesterases, and cholinergic nerve impulses in skeletal muscle; ephedrine intensifies these effects of epinephrine. The exact mechanism by which ephedrine influences skeletal muscle contraction remains unknown. The effect of ephedrine on autonomic ganglia has been studied, and it has been shown that doses larger than those affecting peripheral autonomic receptor cells cause depression of ganglionic transmission.

The relative potency of ephedrine with other sympathomimetic agents is shown in Table 29.1.

## SIGNS AND SYMPTOMS OF EPHEDRINE TOXICITY

Toxic doses of ephedrine may cause the following:

- Convulsions
- Nausea

- Vomiting
- Chills
- Cyanosis
- Irritability
- Nervousness
- Fever
- Suicidal behavior
- Tachycardia
- Dilated pupils
- Blurred vision
- Opisthotonos
- Spasms
- Pulmonary edema
- Gasping respirations
- Coma
- Respiratory failure
- Personality changes

**TABLE 29.1**  
**Relative Potency and Duration of Pressor Activity of Epinephrine Congeners**

						Activity of Epinephrine = 1.0	
	CH	CH	NH	Pressor Activity	Duration of Pressor Action		
$\beta$ -Phenylethylamine	H	H	H	H	0.005–0.0125	3–4	
Tyramine	OH	H	H	H	0.01–0.05	2	
Synephrine	OH	H	OH	H	CH <sub>3</sub>	0.01–0.04	4
Phenylephrine	H	OH	OH	H	CH <sub>3</sub>	0.2	2
Levarterenol	OH	OH	OH	H	H	1.5	2
Epinephrine	OH	OH	OH	H	CH <sub>3</sub>	1.0	1.0
Amphetamine	H	H	H	CH <sub>3</sub>	H	0.002–0.01	5–10
Phenylpropanolamine	H	H	OH	CH <sub>3</sub>	H	0.003–0.017	7
Ephedrine	H	H	OH	CH <sub>3</sub>	CH <sub>3</sub>	0.005–0.01	7–10
Paredrinol	OH	H	H	CH <sub>3</sub>	CH <sub>3</sub>	0.033	10

*Note:* The *adrenomimetic drugs* mimic the effects of adrenergic sympathetic nerve stimulation on sympathetic effectors. Thus, these drugs are also referred to as *sympathomimetic agents*. The adrenergic transmitter norepinephrine and the adrenal medullary hormone epinephrine also are included under this broad heading. The adrenomimetic drugs are an important group of therapeutic agents, which may be used to maintain blood pressure or to relieve a life-threatening attack of acute bronchial asthma. These drugs are also present in many over-the-counter preparations, in which advantage is taken of their ability to constrict mucosal blood vessels and thus relieve nasal congestion.

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# 30 Ergot, Its Alkaloids, and Headache

## INTRODUCTION

Ergot alkaloids:

- Cause abortion
- Are used to treat headache
- Are psychotherapeutic agents as ergoloid mesylate

## ERGOT AND THE ERGOT ALKALOIDS

### SOURCE

Ergot (*Claviceps purpurea*) is a fungus that grows on rye and other grains. The parasitic nature of ergot was not appreciated until the 19th century; before that time it was considered to be just diseased rye. The parasite is especially prevalent during moist, warm weather and can be found in the grain fields of North America and Europe.

The spores of ergot are carried by insects or the wind to the ovaries of young rye, where they germinate into hyphal filaments. The filaments secrete an enzyme that enables the fungus to penetrate the basal portions of the ovary. The decomposition product resulting from this enzymatic action is a yellow mucoid material called honeydew, which at one time was erroneously thought to be the active substance of ergot. The **honeydew** attracts insects, and in this way the fungus is further disseminated. As the hyphal filaments penetrate deep into the ovary of the rye, a dense tissue forms. This tissue gradually consumes the entire substance of the grain and hardens into a purple, curved body called the sclerotium. This **sclerotium** is the commercial source of ergot. It is either picked by hand or separated from the grain by a special threshing process (Figure 30.1).

### CONSTITUENTS OF ERGOT

Ergot has been termed a “veritable treasure house of pharmacological constituents.” The substances isolated from ergot have been divided into two main groups. In the first group are those products peculiar to ergot and not obtainable from any other source. The second group consists of a large number of compounds that can be isolated from ergot but are also obtainable elsewhere. The important members of the first group are the ergot alkaloids. In addition, there are certain pigments peculiar to ergot but without pharmacological significance. The second group consists of a heterogeneous collection of compounds including inorganic constituents, carbohydrates, glycerides, sterols, acids, amino acids, amines, and quaternary ammonium bases. The amines and bases are of pharmacological importance. Ergot contains amines that result from the decarboxylation of six amino acids: leucine, tyrosine, histidine, lysine, arginine, and ornithine. Bacteria are capable of causing the decarboxylation of amino acids, and it is thought that similarly fungi may account for





**FIGURE 30.1** Ergot. Head of rye with ergot growing in it.

the presence of amines in ergot. At least three amines are of pharmacological importance — histamine, tyramine, and isoamylamine. The pharmacologically active quaternary ammonium bases found in ergot are choline and acetylcholine.

## HISTORY

The contamination of an edible grain by a poisonous, parasitic fungus spread death and destruction for centuries. As early as 600 B.C., an Assyrian tablet alluded to a “**noxious pustule in the ear of grain,**” and in one of the sacred books of the Parsees (400 to 300 B.C.) the following pertinent passage occurs: “Among the evil things created by Angro Maynes are noxious grasses that cause pregnant women to drop the womb and die in childbed.” It was fortunate for the ancient Greeks that they objected to the “**black malodorous product of Thrace and Macedonia,**” and therefore did not eat rye. Rye was also comparatively unknown to the early Romans for it was not introduced into southwestern Europe until after the beginning of the Christian era. Consequently, there is no undisputed reference to ergot poisoning in the early Greek and Roman literature.

It was not until the Middle Ages that written descriptions of ergot poisoning first appeared, although it is probable that the disease was prevalent long before this time. Strange epidemics were described in which the characteristic symptom was gangrene of the feet, legs, hands, and arms. In severe cases, the tissue became dry and black and the mummified limbs separated off without loss of blood. Limbs were said to be consumed by the “**Holy Fire**” and blackened like charcoal. Mention was also made of agonizing burning sensations in the extremities. The disease was called Holy Fire or “**St. Anthony’s fire,**” the latter name in honor of the saint at whose shrine relief was said to be obtained. The relief that followed migration to the shrine of St. Anthony was probably real, for the sufferers received a diet free of contaminated grain during their sojourn at the shrine. The symptoms of ergot poisoning were not restricted to the limbs. Indeed, a frequent complication of ergot poisoning was abortion. A convulsive type of ergotism was also known. There still is no clear explanation of why, in certain instances, ergotism affected the central nervous system. It has been suggested that the convulsive form of ergotism occurred in persons with vitamin deficiency.

It was not until 1670 that ergot was proved to be the cause of the destructive epidemics that, for centuries, had raged uncontrolled. Today, knowledge of the etiology of ergot poisoning makes its prevention quite simple. Yet, outbreaks of ergot poisoning have occurred in the present century: in Russia in 1926, in Ireland in 1929, and in France in 1953. A fungus growing on corn and causing “**corn smut**” (*Ustilago maydis*) is analogous to that found on rye and has been the cause of small outbreaks of maize poisoning, especially in the northern Mediterranean countries. The condition is known as *ustilaginitis* and closely resembles **ergotism**.

Ergot was known as an obstetrical herb before it was identified as the source of St. Anthony's fire and was mentioned as causing "*pain in the womb*." It was used by midwives long before it was recognized by the medical profession (Goodman and Gilman, 1955).

## CHEMISTRY

All the ergot alkaloids can be considered to be derivatives of the tetracyclic compound **6-methyl-ergoline**. The naturally occurring alkaloids contain a substituent in the configuration at position 8 and a double bond in ring D. The natural alkaloids of therapeutic interest are amide derivatives of *d-lysergic acid*; these compounds contain a double bond between C-9 and C-10 and thus belong to the family of **9-ergolene compounds**. Many alkaloids, containing either a methyl or a hydroxymethyl group at position 8, are present in ergot in small quantities. These have been called *clavine alkaloids* and consist principally of both **9-ergolenes** (e.g., **lysergol**) and **8-ergolenes** (e.g., *elymoclavine*, the **8-ergolene isomer of lysergol**). A crystalline, pharmacologically active preparation first isolated from ergot was called *ergotoxine*. It is now known to be a mixture of four alkaloids: *ergocomine*, *ergocristine*,  $\alpha$ -*ergocryptine*, and  $\beta$ -*ergocryptine*. The first pure ergot alkaloid, *ergotamine*, was obtained from lysergic acid. The discovery of the "water-soluble uterotonic principle of ergot" was subsequently determined to be ergonovine (also designated *ergometrine*) (Peroutka, 1996). A classification of the natural alkaloids of ergot and their dextrorotatory isomers follows.

	Natural Alkaloids	Dextrorotatory	Formula
A. Ergotamine group	Ergotamine	Ergotaminine	$C_{33}H_{35}O_5N_5$
	Ergosine	Ergosinine	$C_{30}H_{37}O_5N_5$
B. Ergotoxine group	Ergocritine	Ergocristinine	$C_{35}H_{39}O_5N_5$
	Ergocryptine	Ergocryptinine	$C_{32}H_{41}O_5N_5$
	Ergocornine	Ergocorninine	$C_{31}H_{39}O_5N_5$
C. Ergobasine group	Ergonovine	Ergonovinine	$C_{19}H_{23}O_2N_3$
	(Ergobasine, ergometrine)	(Ergobasinine, ergometrinine)	

## THE EFFICACY OF ERGOTAMINE IN HEADACHE

The following drugs are used in migraine and cluster headache treatment:

### 1. Migraine

#### a. Abortive therapy

- Acetaminophen
- Aspirin
- Ergotamine preparations
- NSAIDs (nonsteroidal anti-inflammatory agents)
- Midrin
- Sumatriptan
- Others (chlorpromazine, prochlorperazine, metoclopramide)

#### b. Prophylactic therapy

- Antidepressants
- Aspirin
- $\beta$ -Blockers
- Calcium-channel blockers
- **Ergotamine preparations**
- Methysergide
- NSAIDs
- Others (cyproheptadine, clonidine, anticonvulsants, steroids, calcitonin)

2. Cluster headaches
  - a. Abortive therapy
    - **Ergotamine preparations**
    - Local anesthetic agents
    - Oxygen
    - Sumatriptan
  - b. Prophylactic therapy
    - Calcium-channel blockers
    - Corticosteroids
    - **Ergotamine preparations**
    - Lithium
    - Methysergide
    - Others (capsaicin, leuprolide)

## INTRODUCTION

Headache, one of the most common symptoms, can be precipitated by a great variety of stimuli: emotional stress; fatigue; sensitivity to certain foods and beverages, including alcohol; medications, and acute illness. There may be no apparent underlying cause. In some individuals, headaches occur frequently but irregularly; however, they are usually acute and short-lived and can be relieved by over-the-counter preparations containing aspirin, acetaminophen, or ibuprofen. This type of headache is usually not debilitating and consulting a physician is not necessary.

In contrast, chronic recurrent headache, for which patients most often consult physicians, is associated with various medical, neurological, or psychogenic disorders. Appropriate therapy depends on an accurate diagnosis of the type of headache.

The Headache Classification Committee of the International Headache Society (1988) has developed diagnostic criteria for classification of headache disorders, cranial neuralgias, and facial pain; the criteria include painful and nonpainful disorders of the entire head and are based on the diagnosis rather than on the underlying pain mechanisms.

A major type of headache that must be considered in differential diagnosis is that caused by underlying disease: intracranial disturbances (e.g., vascular anomalies, infections, tumors, trauma); diseases involving the head and neck but not the brain (e.g., cervical osteoarthritis; disorders of eye, ear, nose, sinuses, and throat; cranial neuralgias); and systemic diseases (e.g., sudden and severe hypertension, hyperthyroidism). These headaches usually can be relieved by specific therapy for the underlying disorder (e.g., surgical correction of tumors, antibiotics for infections, antiarthritic drugs for osteoarthritis).

Considerations in the management of recurrent migraine cluster, or tension-type headache include the following (Table 30.1): most headaches are dull, deeply located, and painful. Superimposed on such nondescript pain may be other types of pain that have greater diagnostic value. It is useful to identify all types of pain that have been experienced by the patient, regardless of their frequency or intensity. A throbbing quality and tight muscles about the head, neck, and shoulder girdle are common nonspecific accompaniments of headache. It was formerly believed that tight "hat-band" headaches indicated stress, anxiety, or depression, but investigations have not supported this view. Jabbing, brief, sharp cephalic pain, often occurring multifocally (ice-pick-like pain), is the signature of a benign disorder.

In conclusion, it has been found that:

1. No single therapy is effective in all patients with the same type of headache, which serves to underscore the uncertainty about the pathophysiology of these disorders and the

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**TABLE 30.1**  
**Classification of Headaches**

- I. Primary headache disorders
    - A. Muscle contraction headaches
    - B. Vascular headaches
      - 1. Migraine
        - a. Classic migraine
        - b. Common migraine
        - c. Complicated migraine
      - 2. Cluster
        - a. Episodic
        - b. Chronic
          - i. Primary
          - ii. Secondary
        - c. Chronic paroxysmal hemicrania
  - II. Psychogenic headache disorders
  - III. Secondary headache disorders
- 

variability among individuals. Therefore, drug therapy must be individualized, and trials of different therapies and drugs may be required to establish an effective regimen.

2. In addition to treatment, some patients should receive prophylactic therapy; these individuals should be monitored closely and adjustments made in choice of therapy or dosage when necessary.
3. Many patients with chronic headaches have received drugs that may cause drug dependence (e.g., barbiturates, antianxiety agents, ergotamine, narcotics, analgesic and caffeine mixtures), and their withdrawal along with instructions regarding their proper use is necessary.

This last consideration may be a primary obstacles in the long-term relief of headache.

## CLASSIFICATION OF HEADACHES

Headaches are classified into three major categories: primary, psychogenic, and secondary (Table 30.1). This section focuses on the characteristics, pathophysiology, management, and prevention of only **migraine headache**.

## PRECIPITATING FACTORS OF HEADACHE SYMPTOMS

Many factors are known to precipitate attacks of headache (Table 30.2). Stress, anxiety, excitement, depression, fatigue, anger, exertion, hunger, loss of sleep, and poor diet are identified as the most common precipitating factors of nonorganic headaches. Patients may experience headaches precipitated by particularly stressful events, or by sudden relaxation after a period of stress (i.e., during weekends or the first few days of a holiday). Other factors include being subjected to environmental extremes (high altitudes, high humidity, rapid changes in the weather, temperature extremes), slight trauma to the head, and ingestion of vasoactive substances, including some types of beer, grain alcohol, red wines, or certain foods (e.g., those high in tyramine content, those using preservatives or flavor-enhancing substances such as nitrites or monosodium glutamate, chocolate, hard cheeses, and citrus fruits). Cigarette smoking precipitates cluster attacks in some patients. Many drugs may precipitate headaches.

**TABLE 30.2**  
**Precipitating Factors of Headache Symptoms**

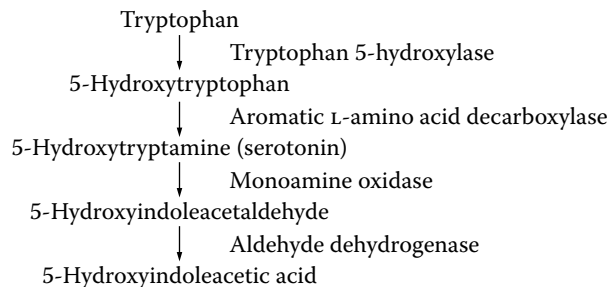
Physiological factors: stress, nervous tension, anxiety  
 Physical exertion, fatigue  
 Alcohol  
 Hormonal changes  
 Environmental: temperature extremes of rapid changes, glare  
 Foods containing: nitrites, glutamates, tyramine  
 Drugs: nitroglycerine, hydralazine, oral contraceptives, reserpine, theophylline, digitalis, estrogens, ergotamine, corticosteroids, or caffeine withdrawal

*Note:* Pain is most commonly due to tissue injury resulting in stimulation of peripheral nociceptors in an intact nervous system, as in the pain of scalded skin or appendicitis. Pain can also result from damage to or anomalous activation of pain-sensitive pathways of the peripheral or central nervous system. Headache may originate from either mechanism. The following cranial structures are sensitive to mechanical stimulation: the scalp and aponeurotica, middle meningeal artery, dural sinuses, flax cerebri, and the proximal segments of the large pial arteries. The ventricular ependyma, choroid plexus, pial veins, and much of the brain parenchyma are pain insensitive. Electrical stimulation of the midbrain in the region of the dorsal raphe has resulted in migraine-like headaches. Thus, whereas most of the brain is insensitive to electrode probing, a site in the midbrain represents a possible source of headache generation.

## MIGRAINE: THE INVOLVEMENT OF SEROTONIN AND THE EFFECTIVENESS OF SUMATRIPTAN IN MIGRAINE HEADACHE

### METABOLISM OF SEROTONIN

5-Hydroxytryptamine (serotonin, 5HT) is metabolized according to the following scheme:



### ACTIONS OF SEROTONIN

- Serotonin is involved in the neural network that regulates intestinal mobility.
- Serotonin is released by platelets (also ADP) during aggregation.
- Serotonin causes vasoconstriction by stimulating 5HT<sub>2</sub> receptors, and this effect is blocked by **ketanserine**.
- Serotonin causes vasodilation by stimulating 5HT<sub>1</sub> receptors.
- Serotonin causes positive inotropic and chronotropic effects by interacting with both 5HT<sub>1</sub> and 5HT<sub>3</sub> receptors.

- Serotonin increases the motility of the stomach as well as small and large intestines.
- Serotonin causes uterine contractions.
- Serotonin causes bronchial contractions.

### SEROTONERGIC ABNORMALITIES

Serotonin (5-hydroxytryptamine; 5HT) is a biogenic amine neurotransmitter that has been implicated in the pathogenesis of migraine. Biochemical studies have documented abnormalities of serotonergic systems in migraine. For example, plasma and platelet levels of 5HT have been reported to vary during different phases of the migraine attack. At the same time, increased amounts of 5HT and its metabolites are excreted in the urine during most headache attacks. The observation that migraine may be precipitated by drugs that cause release of this biogenic amine from tissue stores, such as **reserpine** and **fenfluramine**, also supports a role for 5HT in the disorder.

### OTHER HYPOTHESES

Many theories have been proposed to explain migraine pathogenesis. Alterations in neurotransmitter systems (e.g., glutamate, nitric oxide, opioids), anatomical structures (e.g., the raphe system, vasculature), and the autonomic nervous system may be either primary or secondary factors in the evolution of a migraine attack.

### SEROTONIN RECEPTORS AND THEIR SUBTYPES

Extensive ligand-binding studies and molecular biologic examination of membrane preparations have revealed that there are many types of serotonin receptors, including 5HT<sub>1A</sub>, 5HT<sub>1B</sub>, 5HT<sub>1C</sub>, 5HT<sub>1D</sub>, 5HT<sub>2</sub>, 5HT<sub>3</sub>, and 5HT<sub>4</sub>.

### SEROTONIN RECEPTOR ANTAGONISTS

Serotonin receptor antagonists include:

**Ketaserine**, a 5HT<sub>2</sub> and alpha<sub>1</sub>-adrenergic receptor antagonist, lowers blood pressure.

**Methysergide**, a 5HT<sub>1C</sub> antagonist, has been used for the prophylactic treatment of migraine and other vascular headache, including **Horton's syndrome**.

**Cyproheptadine**, a serotonin and histamine receptor- and muscarinic cholinergic receptor-blocking agent, has been used in the treatment of **postgastrectomy dumping syndrome** and the intestinal hypermotility seen with carcinoid.

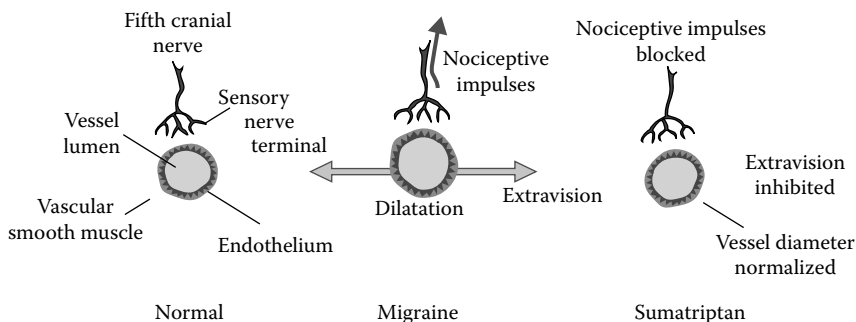
**Sumatriptan**, antagonist of the 5HT<sub>1</sub>-like receptor, is highly effective in the treatment of migraine.

**Ondansetron**, **granisetron**, **topisetron**, and **batanopride** are antagonists of the 5HT<sub>3</sub> receptor, and are considered effective in controlling cancer-chemotherapy-induced emesis.

**Clozapine**, an effective antipsychotic agent (neuroleptics) with little or no extrapyramidal side effects, blocks the 5HT<sub>2</sub> receptor.

### CLINICAL EFFICACY OF SUMATRIPTAN

When administered during the headache phase of migraine attack, sumatriptan has a rapid effect on all the symptoms: headache, nausea, vomiting, photophobia, and phonophobia. This effect applies to both migraine attacks preceded by an aura (classic migraine) and those without an aura (common migraine). Similar but identical effects have been reported for **naratriptan**, **rizatriptan**, and **zolmitriptan** (Brunton et al., 2006).



**FIGURE 30.2** Summary of the vascular effects of sumatriptan. A schematic representation of the action of the sumatriptan in migraine therapy is shown. Vasoconstriction leads to reduced extravasation, blockage of sterile inflammatory response, and diminished head pain.

### SIDE EFFECTS OF SUMATRIPTAN

The acute side effects of sumatriptan are generally minor and transient and seldom lead to serious complications. Following subcutaneous administration, short-lasting pain and redness at the injection site are the most frequently reported adverse symptoms. Other adverse effects reported include a tingling feeling in the chest and limbs, hot flashes, nausea and vomiting, dizziness, and painfulness in the limbs, fatigue, drowsiness, and painfully stiff neck. It should be noted, however, that some of these symptoms are part of the recovery phase of a migraine attack and may reflect migraine relief rather than a direct drug-related effect. Some patients may experience a frightening feeling of severe pressure on the chest that mimics cardiac ischemia.

### MECHANISMS OF ANTIMIGRAINE ACTION OF SUMATRIPTAN

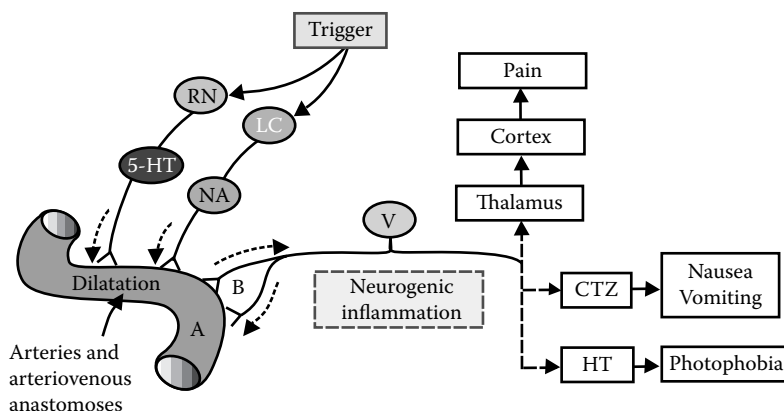
The pathology of unilateral migraine is based on the anatomy of the trigeminal nerve. Cranial blood vessels, including the large cerebral arteries and vessels in the dura mater, are innervated by a dense perivascular network of sensory nerves. Vasodilation of these vessels may cause profound headache, mediated by nociceptive impulse transmission via the **trigeminal (fifth cranial) nerve**. As a result, vasoactive neuropeptides, such as **substance P** and calcitonin-gene-related peptide, are released, causing increased vascular permeability in the meninges and leading to protein extravasation. Sumatriptan stimulates vascular 5HT receptors that constrict the affected vessels and block the inflammatory response, reducing extravasation, and consequently relieving pain (Figure 30.2 and Figure 30.3).

## PREVENTION AND TREATMENT OF MIGRAINE

The most important drugs for the prevention of migraine are the  $\beta$ -adrenergic blocking agents (Table 30.3). Their value in chronic daily headache and mixed forms is also recognized. Nadolol (Corgard) and propranolol (Inderal) are the most widely administered and tested agents, but others may be of similar value.

### METHYSERGIDE

The use of methysergide (Sansert), the oldest of the migraine prophylactic agents, is marred by a history of adverse consequences, but most authorities believe that selective and carefully monitored usage is both appropriate and necessary in difficult-to-manage cases. The drug is given as 2 mg three to four times a day in equally divided dosages. Treatment should be continued for no more than 6 months (Figure 30.4).



**FIGURE 30.3** Putative sites of action of sumatriptan. Changes in the activity of raphe nuclei (RN), with their 5HT-containing neurons, and the locus coeruleus (LC) with its noradrenaline-containing (NA) efferents, might induce dilatation of arteries and arteriovenous anastomoses in cephalic (dural and scalp) circulation. This, in turn, may stimulate perivascular sensory afferents of the fifth cranial nerve (V) to cause headache and possibly nausea, vomiting, and photophobia through putative neurons to the chemoreceptor trigger zone (CTZ) and hypothalamus (HT). In addition, neurogenic inflammation through retrograde release of vasoactive neuropeptides and local ischemia caused by arteriovenous shunting may accentuate pain sensation. Sumatriptan appears to abort migraine attacks by constricting the dilated cephalic vessels. (A) Sumatriptan may also have inhibitory influence at the perivascular nerve terminals (B) and CTZ, outside the blood–brain barrier.

**TABLE 30.3**  
**Summary Pharmacology of  $\beta$ -Adrenergic Receptor-Blocking Agents**

Drug Name	ISA	$\beta$ -1 Selectivity	$\alpha$ -Blocking Activity	Lipophilicity	Bioavailability, <sup>a</sup> %
Propranolol	–	–	–	+++	30
Timolol	–	–	–	++	75
Metoprolol	–	+	–	++	45
Nadolol	–	–	–	–	30
Atenolol	–	+	–	+	55
Acebutolol	±	+	–	+	40
Labetolol	–	–	+	++	30
Pindolol	+++	–	–	+	100
Penbutolol	±	–	–	+	100

<sup>a</sup> The adrenergic blocking agents, presumably because of their structural similarity to the adrenergic agonists, also have an affinity for the adrenoreceptors. The antagonists, however, have only limited or no capacity to activate the receptors; that is, they have little or negligible intrinsic activity. The blocking drugs compete with the adrenomimetic substances for access to the receptors. Thus, these agents reduce the effects produced by both sympathetic nerve stimulation and by exogenously administered adrenomimetics. This action forms the basis for their therapeutic and investigational use.



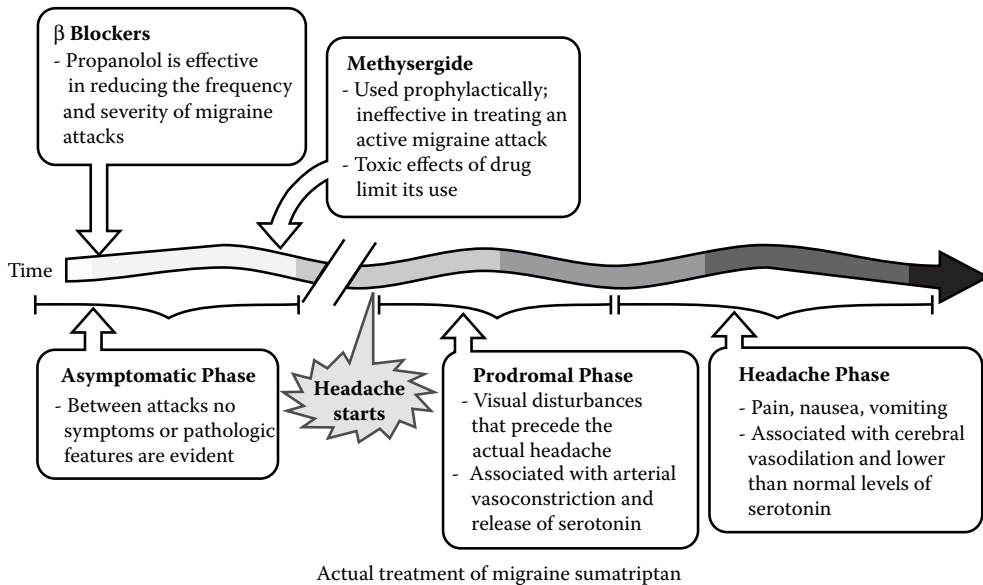


FIGURE 30.4 Drugs useful in the treatment and prophylaxis of migraine headaches.

## CALCIUM AND CALCIUM-CHANNEL BLOCKERS

### CALCIUM ANTAGONISTS

Of the available calcium antagonists — **verapamil** (Isoptin, Calan), **diltiazem** (Cardizem), and **nifedipine** (Procardia) — verapamil and diltiazem seem to be most effective in the treatment of headache. Calcium antagonists do not appear to be as effective as the  $\beta$ -blockers for prophylaxis of migraine but may be very effective in certain instances. They are agents of choice in patients who cannot take  $\beta$ -adrenergic blockers, such as patients with asthma. Verapamil is given in a dose range of 40 to 160 mg, two to three times per day; diltiazem is administered in a dose range of 30 to 90 mg, two to three times per day. Many patients to whom nifedipine is administered report increased headache, at least initially, although successful results are occasionally evident.

### OTHER PREVENTATIVE AGENTS

**Clonidine hydrochloride** (Catapres), **carbamazepine** (Tegretol), and **methylphenidate** (Ritalin) are occasionally useful in intractable cases of migraine. **Cyproheptadine** (Periactin) may be effective in adults with migraine; it is of considerable importance in the treatment of childhood migraine, and many consider it to be the drug of first choice. Dosages range from 4 to 3 mg, three to four times a day, in adults and 4 mg, two to three times a day, in children.

## CRANIAL NEURALGIAS

A variety of drugs with antiepileptic, antispastic, or antidepressant activity are used to manage cranial neuralgias. These compounds are usually more useful than agents with general analgesic properties.

### TRIGEMINAL AND GLOSSOPHARYNGEAL NEURALGIAS

**Trigeminal neuralgia**, an episodic facial pain syndrome, occurs most often in elderly patients. Unilateral paroxysms of severe shooting pain in one or more divisions of the trigeminal nerve are

followed by a period of relief and then by another paroxysm of severe pain. This pain is characteristically triggered by tactile stimuli on the face and by using the jaws or the mouth (e.g., chewing, talking, brushing teeth).

**Carbamazepine** (Epilex, Tegretol) is the drug of choice but if attacks are not controlled completely by carbamazepine or the patient cannot tolerate this agent, the addition of **baclofen** (Lioresal) has been effective. **Phenytoin** (Dilantin) also may be administered when results are suboptimal with carbamazepine. Both drugs may be given alone, with carbamazepine, or with each other, but phenytoin is less effective than baclofen.

A recent limited but controlled study indicated that **pimozide** (Orap) was more effective than carbamazepine. However, the potential for severe extrapyramidal adverse effects with pimozide is considerable, and it is not a drug of choice.

**Clonazepam** (Klonopin), a benzodiazepine anticonvulsant, has been useful in a limited number of patients, but controlled studies comparing this drug with carbamazepine and baclofen have never been performed.

**Glossopharyngeal neuralgia** is much less common than trigeminal neuralgia and is characterized by similar paroxysms of lancinating pain in the pharynx, tonsils, and ear. Pain is often triggered by swallowing. It may be accompanied by syncope that is thought to be due to vagal activity and usually is responsive to atropine. Carbamazepine is the drug of choice, but the other agents employed in trigeminal neuralgia may be substituted or used concomitantly. If pain persists, **cocainization of the pharynx** may provide temporary relief. When glossopharyngeal neuralgia is refractory to drug therapy, **microvascular decompression of the glossopharyngeal nerve** or surgical section of the ninth and tenth cranial nerve roots is recommended.

### ERGOLOID MESYLATES (DIHYDROGENATED ERGOT ALKALOIDS; DIHYDROERGOTOXINE)

Ergoloid is a psychotherapeutic agent that is indicated in the treatment of age-related decline in mental capacity, primary progressive dementia, Alzheimer's dementia, multi-infarct dementia, and senile onset. Ergoloid is thought to increase cerebral blood flow.



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# 31 Flavonoids

## INTRODUCTION

The flavonoids are found in fruits, vegetables, nuts, seeds, herbs, spices, stems, flowers, as well as in tea and red wine. They are prominent components of citrus fruits. Flavonoids are effective in:

- Chronic inflammation
- Allergic diseases
- Coronary artery disease
- Breast cancer

The flavonoids protect cells against oxidative stress.

**Flavonoids** may have existed in nature for over 1 billion years and thus have interacted with evolving organisms over the eons. Clearly, the flavonoids have some important functions in nature, because they have survived in vascular plants throughout evolution. The very long association of plant flavonoids with various animal species and other organisms throughout evolution may account for the extraordinary range of biochemical and pharmacological activities of these chemicals in mammalian and other biological systems. Unique examples are:

- The inhibition of gamete membrane fusion in sea urchins caused by **quercetin** during egg fertilization
- Modulation of mammalian sperm motility by quercetin
- Influence on sexual differentiation

Over 4000 structurally unique flavonoids have been identified in plant sources (Middleton et al., 2000; Table 31.1). They are primarily recognized as the pigments responsible for the autumnal burst of hues and the many shades of yellow, orange, and red in flowers and food.

Flavonoids, low-molecular-weight substances found in all vascular plants, are **phenylbenzopyrones (phenylchromones)** with an assortment of structures based on a common three-ring nucleus. They are usually subdivided according to their substituents into **flavanols, anthocyanidins, flavones, flavanones, and chalcones**.

On average, the daily U.S. diet was estimated to contain approximately 1 g of mixed flavonoids expressed as glycosides. The flavonoid consumed most was **quercetin**, and the richest sources of flavonoids consumed in general were **tea** (48% of total), **onions**, and **apples**.

The amount consumed could be considerably higher in the Mediterranean diet, which is rich in olive oil, citrus fruits, and greens. These quantities could provide pharmacologically significant concentrations in body fluids and tissues. Nevertheless, flavonoid dietary intake far exceeds that of **vitamin E**, a monophenolic antioxidant, and that of  **$\beta$ -carotene** on a milligram per day basis. From this we can conclude that

- The flavonoids have long been recognized to possess anti-inflammatory, antioxidant, antiallergic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic activities.

**TABLE 31.1**  
**Some Examples of Subclasses of Naturally**  
**Occurring Flavonoids**

Classes	Flavonoids
Flavan-3-ols	(+)-Catechin
Anthocyanidins	Cyanidin
	Pelargonidin
Flavones	Apigenin
	Diosmin
	Luteolin
Flavonones	Naringenin
	Naringin
	Hesperetin
	Hesperedin
Chalcones	Phloretin
	Phloridzin
Flavan-3-ols	Quercetin
	Kaempferol
	Myricetin
	Fisetin
	Morin

*Note:* Flavonoids are among the most widely distributed natural product compounds in plants with over 2000 different compounds reported, occurring both in the free state and as glycosides. Their chemical structures are based upon a C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub> carbon skeleton with a chroman ring bearing a second aromatic ring in position 2, 3, or 4. The major general structural categories are flavones, flavanones, flavonols, anthocyanidins, and isoflavones. In some cases, the six-membered heterocyclic ring is replaced by a five-membered ring (aurones) or exists in an open-chain isomeric form (chalcones). In addition to glycosylated derivatives, methylated, acylated, prenylated, or sulfated derivatives also occur. A variety of flavonoids have been assigned different roles in nature as antimicrobial compounds, stress metabolites, or signaling molecules.

- The flavonoids are typical phenolic compounds and therefore act as potent metal chelators and free-radical scavengers.
- The flavonoids are potent chain-breaking antioxidants.

## THE PHARMACODYNAMICS OF FLAVONOIDS

### PROTEIN KINASE C INHIBITION

**Protein kinase C (PKC)**, the ubiquitous, largely Ca<sup>2+</sup>- and phospholipid-dependent, multifunctional serine- and threonine-phosphorylating enzyme, is involved in a wide range of cellular activities, including tumor promotion, mitogenesis, secretory processes, inflammatory cell function, and T-lymphocyte function. PKC has been shown to be inhibited *in vitro* by certain flavonoids. It has been demonstrated that **quercetin** inhibited the phosphorylating activity of the Rous sarcoma virus, transforming gene product both *in vitro* and *in vivo*. In addition, quercetin was competitive toward the nucleotide substrates ATP and GTP. Mitogen-activated protein (MAP) kinase in human epider-

mal carcinoma cells was strongly inhibited by quercetin (30  $\mu\text{M}$ ). **Fisetin**, **quercetin**, and **luteolin** are the most active flavonoid inhibitors of protein kinase C.

### PHOSPHOLIPASE A<sub>2</sub> INHIBITION

Phospholipase A<sub>2</sub> (PLA<sub>2</sub>), an enzyme involved in many cell activation processes, catalyzes the hydrolysis of phospholipids esterified at the second carbon in the glycerol backbone. Arachidonic acid is commonly esterified in this position, and the action of PLA<sub>2</sub> releases arachidonic acid for subsequent metabolism via the **cyclooxygenase** (CO) and **lipooxygenase** (LO) pathways. PLA<sub>2</sub> is likely an important intra- and extracellular mediator of inflammation. **Quercetin** was found to be an effective inhibitor of PLA<sub>2</sub> from human leukocytes. **Quercetagenin**, **kaempferol-3-O-galactoside**, and **scutellarein** inhibited human recombinant synovial PAL<sub>2</sub> with IC<sub>50</sub> values ranging from 12.2 to 17.6  $\mu\text{M}$ .

### NA<sup>+</sup>- AND K<sup>+</sup>-ATPASE INHIBITION

Flavonoids can affect the function of plasma membrane transport Na<sup>+</sup>- and K<sup>+</sup>-ATPase, mitochondrial ATPase, and Ca<sup>2+</sup>-ATPase. The Mg<sup>2+</sup>-ectoATPase of human leukocytes is inhibited by **quercetin**, which acts as a competitor of ATP binding to the enzyme. The sarcoplasmic reticulum Ca<sup>2+</sup>-ATPase of muscle is effectively inhibited by several flavonoids that were also active inhibitors of antigen-induced mast cell histamine release.

### LIPOXYGENASE AND CYCLOOXYGENASE INHIBITION

Arachidonic acid released from membrane phospholipids or other sources is metabolized by the LO pathway to the smooth muscle contractile and vasoactive leukotrienes (LT), LTC<sub>4</sub>, and LTD<sub>4</sub>, as well as to the potent chemoattractant LTB<sub>4</sub>. These molecules are intimately involved in inflammation, asthma, and allergy, as well as in other multiple physiological and pathological processes. For example, **cirsiliol** (3',4',5-trihydroxy-6,7-dimethoxyflavone) proved to be a potent inhibitor of 5-LO (IC<sub>50</sub>, 0.1  $\mu\text{M}$ ) derived from basophilic leukemia cells and peritoneal polymorphonuclear leukocytes.

### CYCLIC NUCLEOTIDE PHOSPHODIESTERASE INHIBITION

The cyclic nucleotides cAMP and cGMP mediate many biological processes through their ability to stimulate cyclic-nucleotide-dependent protein kinases, which in turn phosphorylate cellular protein substrates and evoke specific responses. cAMP and cGMP are formed from ATP and GTP by the catalytic activity of adenylate and guanylate cyclases stimulated by various agonists. Their activity is terminated by the cyclic nucleotide phosphodiesterases (PDEs). The cyclic nucleotides are involved in regulation of many cellular processes, such as cell division, smooth muscle contractility, secretory functions, immunological processes, and platelet aggregation, to name a few. Flavonoid inhibition of PDEs from many cellular sources has been described. The minimal structural requirements for PDE inhibitor activity include a **flavone**, **flavonol**, or **flavylium** skeleton.

### REVERSE TRANSCRIPTASE INHIBITION

Selected naturally occurring flavonoids have been shown to inhibit three reverse transcriptases (RT) (avian myeloblastosis RT, Rous-associated virus-2 RT, and Moloney murine leukemia virus, or MMLV, RT) when poly(rA)oligo(dT) 12–18 or rabbit globin mRNA was used as a template. **Amentoflavone**, **scutellarein**, and **quercetin** were the most active compounds, and their effect was concentration dependent. The enzymes exhibited differential sensitivity to the inhibitory effects of the flavonoids. These flavonoids also inhibited rabbit globin mRNA-directed MMLV RT-catalyzed

DNA synthesis. **Amentoflavone** and **scutellarein** inhibited ongoing new DNA synthesis catalyzed by Rous-associated virus-2 RT.

### HIV-1 PROTEINASE INHIBITION

This enzyme is a necessary component for the processing and replication of HIV-1. It has been suggested that certain flavones may be potential nonpeptidic inhibitors of the enzyme. **Gardenin A**, **myricetin**, **morin**, **quercetin**, and **fisetin** exhibited activity with  $IC_{50}$  values in the 10- to 50-*M* range. Lineweaver–Burk analysis indicated competitive inhibition for fisetin and quercetin. Yet another enzyme involved in HIV replication could be inhibited by quercetin, namely, **integrase**. This inhibition required at least one ortho pair of phenolic hydroxyl groups and at least one or two additional hydroxyl groups.

### ORNITHINE DECARBOXYLASE INHIBITION

Ornithine decarboxylase catalyzes the transformation of ornithine to the polycationic bases, **putresine**, **spermine**, and **spermidine**. These compounds exert regulatory effects on cell growth. It has been shown that quercetin (10 to 30  $\mu\text{mol}/\text{mouse}$ ) markedly suppressed the stimulatory effect of the transporters associated with antigen processing (TPA) on ornithine decarboxylase (ODC) activity and on skin tumor formation in mice initiated with **dimethylbenzanthracene**. Such inhibition may be related to the activation of the catalytic site, which is under nonconventional regulation by small molecules. Also, the synthetic flavonoid **flavone acetic acid** was shown to inhibit the activity of ODC in stimulated human peripheral blood lymphocytes and human colonic lamina propria lymphocytes.

### TOPOISOMERASE INHIBITION

DNA topoisomerases are enzymes that introduce transient breaks in linear DNA sequences. They participate in several genetically related processes, including replication, transcription, recombination, integration, and transposition. DNA topoisomerase II is an important cellular target for several antineoplastic DNA intercalators and nonintercalators. Flavonoids have different effects on these enzymes. It has been shown that **genistein** inhibits mammalian DNA topoisomerase II as well as **protein tyrosine kinase**. Two flavones, **fisetin** and **quercetin**, also showed the same activity. Genistein selectively suppressed the growth of the ras-transformed NIH 3T3 cells, but not the normal NIH 3T3 cells, and inhibited topoisomerase II-catalyzed ATP hydrolysis. In contrast, **baicalein**, **quercetin**, **quercetagenin**, and **myricetin**, known inhibitors of RT, unwound DNA and appeared to promote mammalian DNA topoisomerase-mediated site-specific DNA cleavage.

### XANTHINE OXIDASE INHIBITION

**Xanthine oxidase** catalyzes the formation of urate and superoxide anion from xanthine. Quercetin and baicalein inhibit both xanthine oxidase and xanthine dehydrogenase. The level of xanthine oxidase is high in patients with hepatitis and brain tumor and select flavonoids might be useful in treating this disorder.

### AROMATASE INHIBITION

The conversion of **androstenedione** to **estrone** is catalyzed by aromatase. Inhibition of aromatase (human estrogen synthetase) by several naturally occurring flavonoids, including **quercetin**, **chrysin**, and **apigenin**, has been described. The synthetic **flavone 7,8-benzoflavone** was most active. Aromatization of androstenedione was affected by several flavonoids, of which **7-hydroxyflavone** and **7,4-dihydroxyflavone** were the most potent.

Inhibition by 7-hydroxyflavone was competitive with respect to the substrate androstenedione. Flavonoids of the 5,7-dihydroxyflavone series could bind to the active site human cytochrome P-450 aromatase with affinity. The flavonoid **kaempferol** inhibited aromatase enzyme activity competitively in a human Glyoxalase cell culture system. Such results suggest that diets rich in these compounds could contribute to the control of estrogen-dependent conditions, such as breast cancer.

#### ALDOSE REDUCTASE INHIBITION

Lens aldose reductase has been implicated in the pathogenesis of cataracts in diabetic and galactosemic animals. The enzyme catalyzes the reduction of glucose and galactose to their polyols, which accumulate in large quantities in the lens and ultimately lead to mature lens opacities. Several key bioflavones have activity against this enzyme. Oral administration of **quercitrin** decreased the accumulation of sobital in the lens. Therefore, the accumulation of lens opacities could be partially abrogated by certain flavonoids. In a study of 30 flavones, 4 isoflavones, and 13 coumarins, many potent inhibitors were found, but **5,7,3',4'-tetrahydroxy-3,6-dimethoxyflavone** and **6,3',4'-trihydroxy-5,7,8-trimethoxyflavone** were especially active.

#### FAD-CONTAINING MONOAMINE OXIDASE INHIBITION

Flavones, coumarins (neoflavonoids), and other oxygen-containing compounds were found to inhibit monoamine oxidases A and B in a reversible and time-independent manner.

#### CARBONYL REDUCTASE INHIBITION (ALDO-KETO-REDUCTASE FAMILY OF ENZYMES)

Carbonyl reduction is a metabolic pathway widely distributed in nature. Many endogenous substances, such as prostaglandins, biogenic amines, and steroids, together with xenobiotic chemicals of several varieties, are transformed to the corresponding alcohols before further metabolism and elimination. Carbonyl reduction in several continuous cell lines was investigated using metyrapone as a substrate ketone. Quercitrin was reported to inhibit carbonyl reductase.

#### HYALURONIDASE INHIBITION

Hyaluronidases, which depolymerize **hyaluronic acid** to **oligosaccharides** by breaking glucosaminidic bonds, have been referred to as a "**spreading factor**," and are possibly involved in tumor cell invasiveness. The most effective flavonoids are **kaempferol** and **silybin**.

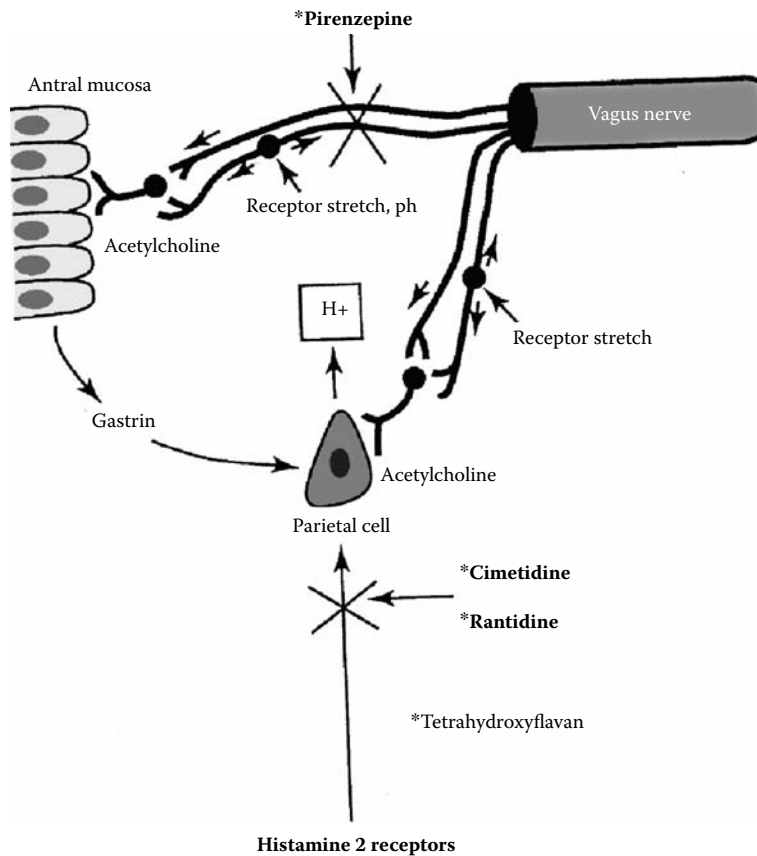
#### HISTIDINE DECARBOXYLASE AND DOPA DECARBOXYLASE INHIBITION

It has been shown that histidine decarboxylase is inhibited by flavonoids such as **quercetin** and **(+)-catechin**, whereas the flavonoid glycosides were inactive. Histamine stimulates gastric acid secretion, making the reported inhibition of histamine-induced gastric secretion by the synthetic flavone-6-carboxylic acid of interest (Figure 31.1). It has been shown that the flavan derivative **3-methoxy-5,7,3',4'-tetrahydroxyflavan**, a compound that appears to be a specific histidine decarboxylase inhibitor, is as effective as **cimetidine** in reducing gastric acid secretion. This flavan also reduced gastric tissue histamine content. **Naringenin**, the aglycone of **naringin**, is a weak inhibitor of **histidine decarboxylase** and also exhibits some gastric antiulcer activity. **Orobol** and **3',4',5,7-tetrahydroxy-8-methoxy isoflavone** obtained from culture filtrates of fungi and streptomycetes were effective inhibitors of **DOPA decarboxylase**, and **orobol** had a significant hypotensive effect in spontaneously hypertensive animals.

#### ALDEHYDE AND ALCOHOL DEHYDROGENASE INHIBITION

An extract of *Radix puerariae*, a herb long used in traditional Chinese medicine for alcohol addiction and intoxication, suppresses the free-choice ethanol intake of ethanol. The isoflavonoids





**FIGURE 31.1** Flavonoids inhibit and decrease gastric secretion.

**daidzein** (4,7-dihydroxy-isoflavone) and **daidzin** (7-glucoside of daidzein) isolated from the extract were shown to account for this effect by inhibiting human alcohol dehydrogenase. Daidzin and daidzein, at doses that suppressed ethanol intake, exhibited no effect on overall acetaldehyde and ethanol metabolism in hamsters, although they inhibited human mitochondrial aldehyde dehydrogenase and  $\gamma$ - $\gamma$  alcohol dehydrogenase *in vitro*. These observations clearly distinguish the actions of these isoflavones from those of the classic, broadly acting inhibitors of aldehyde dehydrogenase and of class I alcohol dehydrogenase enzymes. Consequently, daidzin and daidzein represent a new class of compounds offering the possibility as safe and effective therapeutic agents for alcohol abuse.

### RNA AND DNA POLYMERASE INHIBITION

Studies have shown that **quercetin**, **kaempferol**, and **fisetin** inhibited transcription with RNA polymerase II in permeabilized normal human fibroblasts (WI-38 cells); **flavone** and **chrysin** exhibited weak activity. Addition of quercetin to an ongoing transcription reaction arrested it promptly, suggesting that quercetin was inhibiting the elongation step. The effects of several flavonoids (**quercetin**, **quercetagetin**, **myricetin**, and **baicalein**) exhibited complex interactions with DNA and RNA polymerases, depending on the particular flavonoid and the enzyme species.

### HUMAN DNA LIGASE I INHIBITION

Several natural products have been tested to determine their ability to disrupt the function of human DNA ligase I, which catalyzes the covalent joining of single-stranded breaks in double-stranded

DNA. Interestingly, a flavonoxanthone glucoside, **swertifrancheside** (isolated from *Swerua franchetiana*), inhibited enzyme function with an  $IC_{50}$  value of 11  $\mu M$ .

### SIALIDASE INHIBITION

**Sialidase (neuraminidase)** catalyzes the hydrolysis of sialic acid residues from sialoglyco conjugates and may have an effect on biological functions such as antigen presentation and receptor function. Mouse liver sialidase was noncompetitively inhibited by **isoscutellarein-8-O-glucuronide** ( $IC_{50}$ , 40  $\mu M$ ), whereas influenza virus sialidase was only weakly inhibited. **Flavanone** and **chalcone** structures showed no activity against the liver enzyme. In studies of influenza sialidase, the effect of other flavonoids derived from *Scutellana baicalensis*, the compound **5,7,4'-Trihydroxy-8-methoxyflavone** proved to be moderately active among the 103 tested. Because binding of influenza virus to target cells takes place via sialic acid residues in the viral envelope glycoprotein, it is of interest that **5,7,4'-trihydroxy-8-methoxyflavone** also inhibited infection by influenza virus.

## ANTIOXIDANT PROPERTIES OF FLAVONOIDS

Flavonoids are a family of antioxidants found in fruits and vegetables as well as in popular beverages such as red wine and tea. Although the physiological benefits of flavonoids have been largely attributed to their antioxidant properties in plasma, flavonoids may also protect cells from various insults. Nerve cell death from oxidative stress has been implicated in a variety of pathologies, including stroke, trauma, and diseases such as Alzheimer's disease and Parkinson's disease.

To determine the potential protective mechanisms of flavonoids in cell death, Ishige et al. (2001) used the mouse hippocampal cell line HT-22, a model system for oxidative stress. In this system, exogenous glutamate inhibits cystine uptake and depletes intracellular glutathione (GSH), leading to the accumulation of reactive oxygen (ROS) and an increase in  $Ca^{2+}$  influx, which ultimately causes neuronal death. Many, but not all, flavonoids protect HT-22 cells and primary neurons from glutamate toxicity as well as from five other oxidative injuries. Three structural requirements of flavonoids for protection from glutamate are the hydroxylated C3, an unsaturated C ring, and hydrophobicity. These authors also found three distinct mechanisms of protection, which include increasing intracellular GSH, directly lowering levels of ROS, and preventing the influx of  $Ca^{2+}$  despite high levels of ROS. These data show that the mechanism of protection from oxidative insults by flavonoids is highly specific for each compound.

## MUTAGENICITY AND GENOTOXICITY OF EXCESSIVE FLAVONOID INTAKE

Plant **flavonoids** are **diphenylpropane derivatives** that exert a wide range of biochemical and pharmacological effects. Their antioxidant properties, cytostatic effects in tumorigenesis, and ability to inhibit a broad spectrum of enzymes, such as protein kinase C, tyrosine protein kinase, and topoisomerase II, have led researchers to regard these compounds as potential **anticarcinogens** and **cardioprotective** agents. These findings have contributed to the dramatic increase in the consumption and use of dietary supplements containing high concentrations of plant flavonoids by some health-conscious individuals. Marketing strategies by manufacturers of flavonoid concentrates and herbal remedies advertise, and often exaggerate, their nontoxic therapeutic effects, most of which are not substantiated by regulated clinical trials. Furthermore, manufacturers' recommended doses of these products might far exceed the flavonoid dose one could attain from a typical vegetarian diet. This, coupled with the common misconception that if a little of something is good then more is better, may result in individuals ingesting extremely high levels of these compounds (Skibola and Smith, 2000).

Despite the apparently beneficial health effects of flavonoids, several studies indicate their mutagenicity and genotoxicity in mammalian systems. This may be due to their activity as pro-

oxidants in generating free radicals that damage DNA or their inhibition of DNA-associated enzymes such as topoisomerase. Unrepaired or misrepaired oxidative DNA damage can result in DNA strand breaks and mutations that may lead to irreversible preneoplastic lesions. Furthermore, high intakes of these compounds may potentiate other deleterious effects due to their diverse pharmacological properties, which may alter drug and amino acid metabolism, modulate the activity of environmental genotoxicants, and alter the activity of other key metabolizing enzymes. Although there is ample evidence that a flavonoid-rich diet may promote good health and provide protection from age-related diseases, there remains uncertainty regarding the conditions and the levels of flavonoid intake necessary to pose a potential health hazard.

### CHARACTERISTICS AND CONTENT OF FLAVONOIDS IN COMMON FOODS

Flavonoids are widespread in nature, occurring in all plant families, and are found in considerable quantities in fruits, vegetables, grains, cola, tea, coffee, cocoa, beer, and red wine. In the U.S., the daily dietary intake of mixed flavonoids is estimated to be in the range of 500 to 1000 mg, but can be as high as several grams in those supplementing their diets with flavonoids or flavonoid-containing herbal preparations such as **ginkgo biloba**, **Pycnogenol 227**, or **grape seed extract**. Assuming that absorption from the gastrointestinal tract is effective, such intakes could provide pharmacologically active concentrations in body fluids and tissues.

Among the major groups of flavonoids in the human diet are the flavonols, proanthocyanidins (which include the catechins), isoflavonoids, flavones, and flavanones. The closely related lignans (resorcylic acid lactones) have similar properties as flavonoids, and are therefore included here for completeness. Quercetin, a flavonol, is the most predominant flavonoid in the human diet and estimates of human consumption are in the range of 4 to 68 mg/day. Among these studies, the Japanese population had the highest levels of flavonol intake, which was mainly attributed to their green tea consumption.

Biological activities ascribed to quercetin include its antiviral, anti-inflammatory, antiproliferative, and antimicrobial properties. Quercetin is found in high concentrations in commonly consumed foods such as onions, apples, kale, red wine, and green and black teas, and other foods shown in the following table.

Flavonoid	Common Sources
Quercetin	Onion
	Apple
	Kale
	Red wine
	Green/black teas
Genistein/diadzein	Tofu
	Soy milk
	Soy milk formula
Coumestrol	Alfalfa sprouts
	Clover sprouts
Secoisolariciresinol	Flaxseed
	Flaxmeal
Apigenin/luteolin	Millet (fonio)
Naringin	Grapefruit juice

**Genistein** has been considered the primary anticancer constituent in soy, based on putative *in vitro* activities that include its ability to inhibit topoisomerase I and II activity, inhibit protein tyrosine phosphorylation, induce differentiation of cancer cell lines, and act as an estrogen agonist.

**Coumestans**, such as **coumestrol**, are found in high concentrations in alfalfa and clover and have been recognized, along with **formononetin**, as the cause of infertility in grazing herbivores. Whereas coumestrol acts as an estrogen mimic directly, formononetin has to be metabolized to the estrogenically active compounds **diadzein**, **equol**, or **O-demethylangolensein**.

**Lignans** are present in many fruits, vegetables, tea beverages, and cereal grains such as flaxseed. **Flaxseed** is one of the richest sources of **phytoestrogens**. It contains very high concentrations of the lignan 2,3-bis(3-methoxy-4-hydroxybenzyl)butane-1,4-diol (**secoisolariciresinol**), which is a precursor to the primary mammalian lignans **enterolactone** and **enterodiols**. **Lignans** are known for their antioxidant activity, and have recently been associated with a reduction in hypercholesterolemic atherosclerosis in animal-feeding studies.

Unlike the phytoestrogens mentioned earlier, flavones do not possess estrogenic activity. However, the flavones **apigenin** and **luteolin** act as potent inhibitors of **aromatase** and **17 $\beta$ -hydroxysteroid oxidoreductase**, enzymes involved in estrogen metabolism. Studies have also demonstrated these flavones and several **glycosylflavones** are potent **goitrogens**, particularly in association with **millet consumption**.

### SAFE FLAVONOID INTAKE

Recent epidemiological studies indicate that the intake of flavonoids is associated with a reduced risk of coronary heart disease, stroke, diabetes, and cancer, including cancers of the breast, prostate, lung, colon, and stomach, and is associated with increased consumption of fruits, vegetables, and soy products (see Anila and Vijayalakshmi, 2000). Populations at lowest risk are Asians and vegetarians. Based on the average daily intake of flavonols (68 mg) and isoflavones (20 to 240 mg) in Asian populations, dietary exposures at these doses are not likely to cause adverse health effects. To date, no human data on the long-term effects of high-dose supplementation are available. The level of flavonoids required to induce mutations and cytotoxicity may not be physiologically achievable through dietary sources. However, the use of supplements, particularly antioxidant formulas and herbal mixtures that are commonly recommended in terms of gram rather than milligram doses, could result in exposure to potentially toxic levels. For example, typical manufacturers' recommended doses of quercetin supplements range between 500 and 1000 mg/day, which is 10 to 20 times what can be consumed in a typical vegetarian diet. This suggests that unregulated, commercially available flavonoid-containing supplements may have biologic activity that can adversely affect human health.

A significant number of studies provide evidence that the biologic activities of flavonoids may play a dual role in mutagenesis and carcinogenesis. They can act as antimutagens/promutagens and antioxidants/pro-oxidants, which is largely dependent on the levels consumed as well as the physiological conditions in the body. Exposure to increased levels of flavonoids, whether through the diet or by supplementation, may potentially overwhelm the system, leading to the formation of ROS, and ultimately DNA damage. Furthermore, these effects may be enhanced in fetal development (during which there is rapid cell growth), which may increase sensitivity to phytochemical exposure. Indeed, little is actually known about the toxicology of excess flavonoid intake, and beneficial attributes are commonly overemphasized (see Skibola and Smith, 2000).



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# 32 Flaxseed

The seeds of the flax plant have a hard outer coating. Unless they are ground or thoroughly chewed, they pass through the body undigested. Also, the raw seeds do contain small amounts of **cyanogenic glucoside**, which can be toxic if consumed in large quantities. Cooking seems to break down the toxic components.

- Flax seed is used primarily for constipation (see also Chapter 12 and Chapter 47).
- Flax seed contains **alpha-linolenic acid** and hence is cardioprotective (see Chapter 8).
- Flax seed contains **gluten** (a protein in wheat, rye, and barley), so it can be eaten by people with **celiac disease**, or **gluten intolerance**.
- Flax seed contains **lignans** and hence is an antioxidant (see Chapter 8).

Lignans have antiviral, antibacterial, antifungal, and anticancer properties. Flax seeds have the richest source of lignans, 100 more than the next best source, wheat bran. The majority of lignans is found in the seed, giving it an advantage over flax oil. Flax seed also contains **lecithin**, which emulsifies fat and cholesterol. These little seeds improve digestion, help stabilize blood glucose levels, fight tumor formation, and enhance cardiovascular health. Lignans are **phytoestrogen**, where in the digestive tract become converted into estrogen-like substances called **enterodiols** and **enterolactone**, which are thought to have antitumor effects. Consumption of flaxseed alters estrogen metabolism in ways that may indicate a protective effect against breast cancer.

The cultivation of flaxseed reaches back to the remotest periods of history. Both the seeds as well as the cloth woven from this plant fabric have been found in **ancient Egyptian tombs**. In fact, the first linen mentioned in the Bible has been proven by historians and archaeologists to have been spun from flax. Later on, **Hippocrates** stated that flaxseed was used for the relief of abdominal pains in some of his writings. For 8000 years flaxseed has been used as a source for sustaining energy.

- Flax seed contains both **soluble and insoluble fibers**. About one-third of the fiber in flax seed is soluble, soluble fiber can aid in lowering cholesterol and regulating blood sugar levels.
- Ground flax seed is rich in protein, B vitamins, vitamin E, beta-carotene, calcium, potassium, magnesium, manganese, and zinc.

**Flaxseed oil** or **linseed oil** is the best source of **omega-3-fatty acid**, which has efficacy against breast, lung, and prostate cancers. A gram of flaxseed has twice as much omega-3 fatty acid as a gram of fish oil. Although the **alpha-linolenic acid** found in flaxseed oil is not identical to the omega-3 fatty acids found in fish, the body does convert alpha-linolenic acid from flaxseed oil into the same type of omega-3 fatty acids found in fish oil in a somewhat slow and inefficient process. In addition to its omega-3 fatty acid content, the seed of the flax plant contains significant amounts of soluble fiber, mainly in the form of **mucilage gum**. Similar to the fiber found in oat bran and pectin, mucilage gum may aid in lowering blood levels of cholesterol. In addition to protecting against cancer, omega-3 fatty acids offer important protection against heart disease. Omega-3 fatty acids can lower high cholesterol and high blood pressure, reduce elevated blood triglyceride levels, and prevent blood clots. Omega-3 fatty acid lowers the blood level of **homocysteine**, a major risk

factor for heart disease. Linseed contains 30 to 40% fixed oil (including 36 to 50% **linolenic acid** and 23 to 24% linolenic acid), 6% **mucilage**, 25% protein, and small amounts of **linamarin** (a cyanogenic glycoside) that suppresses bronchoconstriction.

Flaxseed and oil have anti-inflammatory effects and are beneficial in **gastritis**. High amounts of flaxseed and flaxseed oil can reduce blood clotting and promote bleeding, and may interact with drugs that have a similar effect, such as aspirin (see Chapter 59). In rare instances, some individuals may have an allergic reaction to flaxseed. Twelve percent of flax seeds is mucilage, which makes it a gentle, nonirritating, natural laxative. Flax mucilage is perfect for those who have a sensitive stomach, acting as a buffer for excess stomach acids, soothing ulcers or irritable bowel disorders. Flax expands 20 times in volume and should be taken with a generous amount of water (see Chapter 12; Thompson et al., 1997; Prasad, 1997; Cunnane et al., 1993 and 1995).

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# 33 Folate in Fruit

## INTRODUCTION

Both **vitamin B<sub>12</sub>** and **folate** are essential for the synthesis of DNA, and this process is impaired in patients with megaloblastic anemia. In the absence of adequate DNA synthesis, cells cannot divide but continue to grow.

There exists an inverse association between folate and cardiovascular disease. **Folate deficiency** may result from:

- Nutritional deficiency
- Malabsorption syndrome
- Reduced folate-binding protein
- Folate antagonists (e.g., methotrexate)
- Drugs reducing the level of folate (anticonvulsants and pyrimethamine)
- Agents blocking purine synthesis (e.g., mercaptopurine, thioguanine) or pyrimidine synthesis (5-fluorouracil)
- Hemolytic diseases (accelerated hematopoiesis)
- Proliferative diseases and other conditions

Folate is administered orally and should not be used in the treatment of pernicious anemia (see Paul et al., 2004).

## FUNCTIONS OF VITAMIN B<sub>12</sub>

Vitamin B<sub>12</sub> is a biologically active corrinoid, a group of cobalt-containing compounds with macrocyclic pyrrol rings. Vitamin B<sub>12</sub> functions as a cofactor for two enzymes, methionine synthase and L-methylmalonyl coenzyme A (CoA) mutase. Methionine synthase requires methylcobalamin for the methyl transfer from methyltetrahydrofolate to homocysteine to form methionine tetrahydrofolate. L-methylmalonyl-CoA mutase requires adenosylcobalamin to convert L-methylmalonyl-CoA to succinyl-CoA in an isomerization reaction. An inadequate supply of vitamin B<sub>12</sub> results in neuropathy, megaloblastic anemia, and gastrointestinal symptoms (Baik and Russell, 1999).

## BIOAVAILABILITY OF VITAMIN B<sub>12</sub>

Vitamin B<sub>12</sub> is available in pure form for oral administration or in combination with other vitamins and minerals for oral or parenteral administration. The choice of a preparation always must be made with recognition of the cause of the deficiency. Although oral preparations may be used to supplement deficient diets, they are of relatively little value in the treatment of patients with deficiency of intrinsic factor or ileal disease. Even though small amounts of vitamin B<sub>12</sub> may be absorbed by simple diffusion, the oral route of administration cannot be relied upon for effective therapy in the patient with a marked deficiency of vitamin B<sub>12</sub> and abnormal hematopoiesis or neurological deficits. Therefore, the preparation of choice for treatment of a vitamin B<sub>12</sub>-deficiency state is cyanocobalamin, and it should be administered by intramuscular or deep subcutaneous injection.



In healthy adults, the percentage of vitamin B<sub>12</sub> absorbed from eggs is 24 to 36%; from trout, 25 to 47%; and from chicken, mutton, and liver, 60, 65, and 9%, respectively. The bioavailability of vitamin B<sub>12</sub> from liver is low because its content of vitamin B<sub>12</sub> is high.

### **FOOD SOURCES OF VITAMIN B<sub>12</sub> FOR ELDERLY PEOPLE**

Animal-origin food is the only natural food source of vitamin B<sub>12</sub>. Plant foods do not provide it unless the plant is exposed to vitamin B<sub>12</sub>-producing bacteria, contaminated with vitamin B<sub>12</sub>-containing substances (soil, insect parts, etc.), or fortified with vitamin B<sub>12</sub> (e.g., fortified ready-to-eat breakfast cereals). Foods high in vitamin B<sub>12</sub> are dairy products, meat, liver, fish, eggs, and shellfish. Because atrophic gastritis with decreased acid pepsin production is prevalent among elderly people, absorption of food-bound vitamin B<sub>12</sub> is lower for older rather than younger, healthier people. Milk is the most important source of vitamin B<sub>12</sub> for lactovegetarians because it contains 0.4 µg/100 ml (0.9 µg/cup).

### **FACTORS CONTRIBUTING TO DECLINING VITAMIN B<sub>12</sub> STATUS WITH AGING**

Pernicious anemia associated with gastric atrophy is the most common cause of clinically apparent vitamin B<sub>12</sub> deficiency in North American and European populations.

### **PREVALENCE OF VITAMIN B<sub>12</sub> DEFICIENCY IN ELDERLY PEOPLE**

Serum vitamin B<sub>12</sub> levels decrease with age, and serum methylmalonic acid concentrations increase with age. These findings reflect a decline in vitamin B<sub>12</sub> status in elderly people.

## **EFFECTS OF DEFICIENCY**

### **NEUROLOGICAL EFFECTS OF DEFICIENCY**

In the past, neurological complications were thought to occur at a later stage of vitamin B<sub>12</sub> deficiency than hematological changes, but recent reports indicate that neurological changes can occur in the absence of any hematological abnormalities.

### **HEMATOLOGICAL EFFECTS OF DEFICIENCY**

Megaloblastic anemia is a classical symptom of vitamin B<sub>12</sub> deficiency. However, recent studies have demonstrated that subjects with vitamin B<sub>12</sub> deficiency often lack anemia and macrocytosis, and that there is a dissociation between the neurological and hematological manifestations.

### **GASTROINTESTINAL EFFECTS OF DEFICIENCY**

Gastrointestinal signs and symptoms of vitamin B<sub>12</sub> deficiency occur in 26% of cases. These include sore tongue, stomatitis, mucosal ulceration, appetite loss, flatulence, and constipation or diarrhea. Appetite loss, excess gas, and diarrhea are probably related to the underlying gastric disorder (i.e., gastric atrophy) in pernicious anemia. Gastrointestinal symptoms may occur in the absence of symptomatic anemia or macrocytosis.

### **INDICATORS OF HEMATOLOGICAL STATUS**

Hematological indices are the simplest way to diagnose megaloblastic anemia, a typical symptom of vitamin B<sub>12</sub> deficiency.

## REPLACEMENT THERAPY

In pernicious anemia, vitamin B<sub>12</sub> should be given as intramuscular injection or high-dose oral supplements. Intramuscular injections of 100 to 1000 µg of cyanocobalamin for 5 d and 100 to 1000 µg of cyanocobalamin each month thereafter is a sufficient protocol for treating pernicious anemia (see Baik and Russell, 1999).

## FUNCTION OF FOLIC ACID IN GESTATION

More than 30 years ago, it was suggested that maternal intake of certain vitamins during pregnancy affected the incidence of serious fetal malformations. Subsequent research has revealed that folate (folic acid), a B vitamin, plays a crucial role in the development of the central nervous system during the early weeks of gestation, which is generally before the pregnancy is confirmed. In a significant number of embryos, an inadequate supply of folate at this time leads to a failure of the primitive neural tube to close and differentiate normally and results in neural tube birth defects (NTD). Numerous studies have confirmed the importance of an adequate intake of folate during the weeks just before and after conception. Overall, the data predict that if women consume multivitamin supplements containing folic acid during the periconceptual period, the number of children born with serious malformations (such as spina bifida and anenphaly) could be reduced by half. Although programs to increase dietary folate intake of potential mothers may be effective in reducing NTD, the only proven and practical preventive measure currently available is to take oral multivitamin supplements containing folic acid. Multivitamin supplementation has also been associated with reduced incidence of other congenital malformations (see Butterworth, 1996).

## FUNCTION IN CARDIOVASCULAR DISEASE

The **atherosclerotic lesions** develop in a complex, chronic process. The first detectable lesion is the so-called “fatty streak,” an aggregation of lipid-laden macrophage foam cells. The next stage of development is the formation of plaques consisting of a core of lipid and necrotic cell debris covered by a layer of connective tissue and smooth muscle cells. These plaques hinder arterial blood flow and may precipitate clinical events by plaque rupture and thrombus formation. Platelets from the thrombi, activated macrophages, and smooth muscle cells release growth factors and cytokines resulting in an inflammatory–fibroproliferative response that leads to the advanced lesions of atherosclerosis.

Evidence that a diet rich in fruits and vegetables may protect against coronary heart disease is accumulating. It is unclear exactly which substances in fruits and vegetables are responsible for the observed inverse association with cardiovascular disease. The inverse association may be attributed to **folate**, **antioxidant vitamins**, or other constituents such as **fiber**, **potassium**, **flavonoids**, or other **phytochemicals**. The protective effect of folate may be attributed to its role as a cosubstrate in **homocysteine metabolism** (Eichholzer et al., 2001).

## ANTIOXIDANT VITAMINS

Fruits and vegetables are rich sources of antioxidant vitamins. Oxidation of low-density lipoproteins (LDL) by free radicals facilitates the uptake of LDL by macrophages to form the cholesterol-laden **foam cells** involved in the development of atherosclerotic lesions. Oxidative processes may also play a role in lesion maturation and the precipitation of clinical events. The antioxidant vitamins **α-tocopherol** and **β-carotene** are both carried within LDL particles. **Vitamin E** prevents the oxidation of unsaturated fatty acids to peroxides, and β-carotene has singlet oxygen scavenging ability. **Vitamin C** may regenerate vitamin E and scavenge free radicals in the cytoplasm. Vitamin E may also have an additional role in that it may inhibit the proliferation of smooth muscle cells and reduce the adhesiveness of platelets to collagen.

The observed associations between folate, antioxidant vitamins, and cardiovascular disease may be confounded by other substances in fruits and vegetables, as the following examples of studies show: **Flavonoids** (see Chapter 31) are naturally occurring, water-soluble antioxidants found widely distributed in **vegetables, fruits, tea, and wine**. There is an inverse relationship between flavonoids and decreased risk of coronary heart disease. **Lycopene**, the key antioxidant in **tomatoes**, shows an inverse association with myocardial infarctions. There is an inverse association between folate and cardiovascular disease.

## VITAMIN B<sub>12</sub>, FOLIC ACID, AND THE TREATMENT OF MEGALOBLASTIC ANEMIAS

As described in previous sections, vitamin B<sub>12</sub> and folic acid are dietary essentials. A deficiency of either vitamin results in defective synthesis of DNA in any cell in which chromosomal replication and division occur. Because tissues with the greatest rate of cell turnover show the most dramatic changes, the hematopoietic system is especially sensitive to deficiencies of these vitamins. An early sign of deficiency is a megaloblastic anemia. Abnormal macrocytic red blood cells are produced, and the patient becomes severely anemic. Recognition of this pattern of abnormal hematopoiesis more than 100 years ago permitted the initial diagnostic classification of such patients as having “**pernicious anemia**” and spurred investigations that subsequently led to the discovery of **vitamin B<sub>12</sub>** and **folic acid**. Even today, the characteristic abnormality in red blood cell morphology is important for diagnosis and as a therapeutic guide following administration of the vitamins.

### RELATIONSHIPS BETWEEN VITAMIN B<sub>12</sub> AND FOLIC ACID

Intracellular vitamin B<sub>12</sub> is maintained as two active coenzymes: **methylcobalamin** and **deoxyadenosylcobalamin**. Deoxyadenosylcobalamin (deoxyadenosyl B<sub>12</sub>) is a cofactor for the mitochondrial mutase enzyme that catalyzes the isomerization of **L-methylmalonyl-CoA** to **succinyl CoA**, an important reaction in both carbohydrate and lipid metabolism. This reaction has no direct relationship to the metabolic pathways that involve folate. By contrast, methylcobalamin (CH<sub>3</sub>B<sub>12</sub>) supports the methionine synthetase reaction, which is essential for normal metabolism of folate. Methyl groups contributed by methyltetrahydrofolate (CH<sub>3</sub>H<sub>4</sub>PteGlu<sub>1</sub>) are used to form methylcobalamin, which then acts as a methyl group donor for the conversion of **homocysteine** to **methionine**. This folate–cobalamin interaction is pivotal for normal synthesis of purines and pyrimidines and, therefore, of DNA. The methionine synthetase reaction is largely responsible for the control of the recycling of folate cofactors; the maintenance of intracellular concentrations of **folylpolyglutamates**; and, through the synthesis of methionine and its product, **S-adenosyl-methionine**, the maintenance of a number of methylation reactions.

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# 34 Food–Drug Interactions

Poison and medicines are oftentimes the same substances given with different intents.

— Peter Mere Latham (1789–1875)

## INTRODUCTION

**Grapefruit juice** carries the American Heart Association’s healthy “heart-check” food mark and contains compounds that may both reduce **atherosclerotic plaque formation** and inhibit **cancer cell proliferation**. However, unlike other citrus fruit juice, **grapefruit juice interacts with a variety of drugs, elevating their serum concentration** (see Izzo, 2004; Butterweck et al., 2004; Chan, 2005). This is particularly worrying because juice and medications are commonly consumed together at breakfast. This drug–food interaction seems to occur through inhibition by grapefruit juice of one of the intestinal cytochrome P-450 (CYP) enzyme systems, **cytochrome P-450 3A4 (CYP3A4)**. This enzyme system in the liver is well known for its involvement in drug–drug interactions. Most notably, **terfenadine**, **mibefradil**, and **cisapride** have been withdrawn from the U.S. market in recent years, in part because of deaths due to drug–drug interactions involving the hepatic CYP3A4 (Kane and Lipsky, 2000).

## BIOTRANSFORMATION

Biotransformation may be defined as the enzyme-catalyzed alteration of drugs by the living organism. Although few drugs are eliminated unchanged, urinary excretion is an ineffective means of terminating the action of most drugs or poisons in the body. In fact, the urinary excretion of a highly lipid-soluble substance such as **pentobarbital** would be so slow that it would take the body a century to rid itself of the effect of a single dose of the agent. Therefore, mammalian and other terrestrial animals have developed systems that allow the conversion of most lipid-soluble substances to water-soluble ones, so that they may be easily excreted by the kidney. In general, biotransformation may be divided into two forms of metabolism: hepatic and nonhepatic.

## HEPATIC DRUG METABOLISM

The major portion of biotransformation is carried out in the liver by **cytochrome P-450 (P-450)**, which is a collective term for a group of related enzymes or isoenzymes that are responsible for the oxidation of numerous drugs; endogenous substances such as fatty acids, prostaglandins, steroids, and ketones; and carcinogens such as **polycyclic aromatic hydrocarbons**, **nitrosamines**, **hydrazines**, and **arylamines**.

## NONHEPATIC METABOLISM

### PLASMA

One of the drugs that is metabolized in the blood is **succinylcholine**, a muscle relaxant that is hydrolyzed by the **pseudocholinesterase** of liver and plasma to succinylmonocholine. The short

duration of action of succinylcholine (5 min) is due to its rapid hydrolysis in plasma. Patients with atypical cholinesterase who cannot metabolize succinylcholine suffer pronounced apnea. **Procaine**, a local anesthetic, is also hydrolyzed by pseudocholinesterase.

## LUNG

The lung is involved in both the activation and inactivation of numerous physiological and pharmacological substances. For example, **angiotensin I** is converted to **angiotensin II** in the lung.

## INTESTINAL EPITHELIUM

The intestinal epithelium is capable of removing numerous agents.

## MOLECULAR BIOLOGY OF MULTIPLE ISOENZYMES OF P-450

In recent years, an extensive number of complementary DNAs for the P-450 genes for humans have been isolated and sequenced. Genes that encode proteins that are less than 36% similar in their amino acid sequence belong to different families. Currently, eight different families have been identified in humans, each designated by a Roman numeral. The drug metabolizing P-450s belongs to families I, II, III, and IV. P-450s that are 70% or more similar are encoded by genes in the same subfamily. Finally, the individual gene is designated by an Arabic numeral.

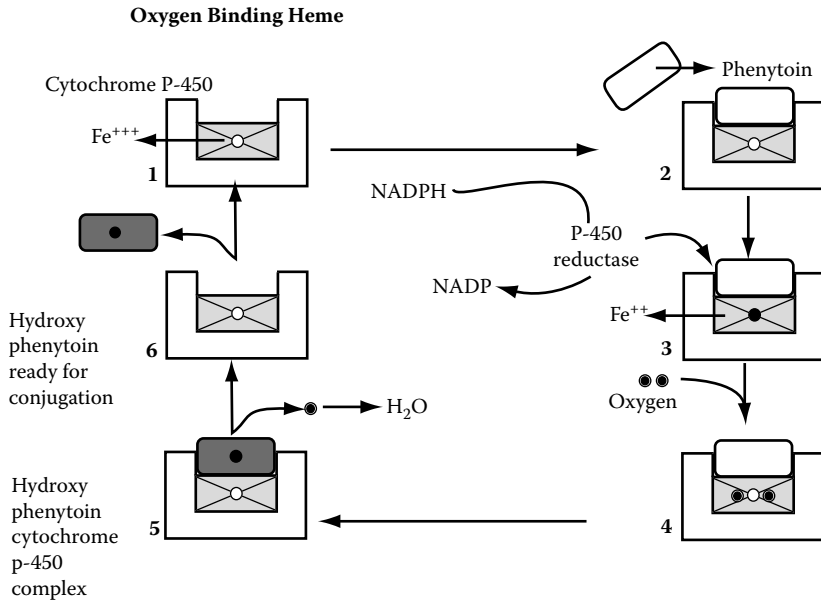
During Phase I, most drugs are inactivated pharmacologically; some remain unaltered and some become more active and toxic. For example, **phenytoin** in the liver is first hydroxylated to **hydroxy-phenytoin** (Phase I) and is then conjugated with glucuronic acid (Phase II) and excreted by the kidney as **phenytoin glucuronide conjugate**. During Phase I, besides introducing a polar group such as an -OH group, a potential polar group may also be unmasked from the drug to be metabolized. For example, compound R-OCH<sub>3</sub> is converted to compound R-OH by demethylation. **Codeine** becomes demethylated to **morphine**. The free or unmasked polar group is then conjugated with glucuronate, sulfate, glycine, or acetate. With the exception of **morphine 6-glucuronide**, almost all conjugates lack pharmacological activity.

## SCHEME OF THE MIXED-FUNCTION OXIDATION REACTION PATHWAY

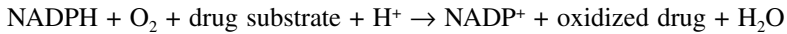
The hepatic endoplasmic reticulum possesses oxidative enzymes called mixed-function oxidases or monooxygenase with a specific requirement for both molecular oxygen and a reduced concentration of **nicotinamide adenine dinucleotide phosphate** (NADPH). P-450 is essential in the mixed-function oxidase system (Figure 34.1). The primary electron donor is NADPH, whereas the electron transfer involves P-450, a **flavoprotein**. The presence of a heat-stable fraction is necessary for the operation of the system.

A drug substrate to be metabolized binds to **oxidized P-450**, which in turn is reduced by **P-450 reductase**. The drug-reduced P-450 complex then combines with molecular oxygen. A second electron and two hydrogen ions are acquired from the donor system, and the subsequent products are oxidized drug and water, with regeneration of the oxidized P-450. This process is summarized as follows:

1.  $\text{NADPH} + \text{oxidized cytochrome P-450} + \text{H}^+ \rightarrow \text{reduced P-450} + \text{NADP}^+$
2.  $\text{Reduced cytochrome P-450} + \text{O}_2 \rightarrow \text{“active oxygen complex”}$
3.  $\text{“Active oxygen complex”} + \text{drug substrate} \rightarrow \text{oxidized drug} + \text{oxidized cytochrome P-450} + \text{H}_2\text{O}$



**FIGURE 34.1** A simplified scheme for the mechanism of action of cytochrome P-450. NADP = nicotinamide adenine dinucleotide phosphate; NADPH = the reduced form of NADP.



The overall scheme for the mechanism of action of P-450 is shown in Figure 34.1.

### CONSEQUENCE OF BIOTRANSFORMATION REACTIONS

The process of biotransformation usually inactivates or detoxifies, or both, the administered drugs or ingested poisons, but other reactions may also take place.

#### PRECURSOR ACTIVATION

Occasionally, an inactive precursor such as **levodopa** is converted to an active metabolite such as **dopamine**.

#### METABOLIC ACTIVATION OF DRUGS

An active drug is often converted to another pharmacologically active substance. The following table lists a few examples of this.

Drug	Action	Active Metabolite
Mephobarbital	is demethylated to	Phenobarbital
Primidone	is oxidized to	Phenobarbital
Imipramine	is demethylated to	Desmethylimipramine
Prednisone	is reduced to	Prednisolone

#### CONVERSION TO METABOLITES WITH DISSIMILAR ACTIONS

In certain instances, the body converts a drug to several active metabolites possessing dissimilar pharmacological properties. For example, **phenylbutazone** undergoes aromatic hydroxylation to

produce a metabolite that has sodium-retaining and antirheumatic activities, and also undergoes alkyl chain oxidation to produce a metabolite with a strong uricosuric property. Thus, phenylbutazone has both **uricosuric** and **antirheumatic effects**.

### CONVERSION TO MORE ACTIVE PRODUCTS

The conversions of **cyclophosphamide** to **aldophosphamide** and **prednisone** to **prednisolone** are examples of active compounds that are converted to more active substances.

### LETHAL SYNTHESIS

The metabolism of drugs and agents does not always lead to detoxification; occasionally, the metabolites are toxicologically more potent. Some examples of this are **sulfamethazine**, which is metabolized to **N<sub>4</sub>-acetylsulfamethazine**, and **aminopyrine**, with **4-aminoantipyrine** as its metabolite.

## DRUG METABOLITE KINETICS

In most cases, drugs are converted to metabolites, which, in the more polar and water-soluble forms, are readily excreted. Often, the concentration of a metabolite far exceeds the concentration of the drug. For example, orally administered **propranolol** is rapidly converted to **4-hydroxypropranolol**, which has a concentration that is severalfold higher than that of propranolol. Sometimes the metabolites are able to inhibit the further metabolism of the parent drug. For example, **phenytoin** becomes metabolized to **hydroxyphenytoin**. When administered in higher-than-recommended individual doses, hydroxyphenytoin inhibits the hydroxylase system that metabolizes phenytoin, increasing its concentration in free form and its potential to produce toxicity.

The **enterohepatic circulation** may sometimes prolong the half-life of a drug. A drug that is absorbed from the gastrointestinal tract, excreted in the bile, and resorbed from the intestine is said to have undergone enterohepatic cycling. Drugs are delivered to the liver by both the portal vein and hepatic artery and returned to the rest of the body by the hepatic vein. The difference between the concentration of a drug transported to and removed from the liver accounts for the amount of drug metabolized or excreted, or both, in the bile. For example, if the liver has conjugated a drug containing glucuronic acid to its metabolite, the conjugated product may appear in the bile and finally be excreted in the small intestine. However, in the intestine, the  $\beta$ -glucuronidase originating from the resident flora may hydrolyze the glucuronide-drug conjugate back to the parent drug, thus allowing the parent drug to be resorbed. The continuous enterohepatic cycling will therefore increase the half-life of this agent in the body.

## FACTORS THAT MODIFY THE METABOLISM OF DRUGS

Many environmental factors and pathophysiological conditions inhibit or stimulate the activity of drug-metabolizing enzymes and hence may alter the outcome of a therapeutic regimen. **Pharmacogenetics**, the immaturity of drug-metabolizing enzyme systems, and drug-drug interactions are a few of the factors that have been shown to alter drug metabolism.

### PHARMACOGENETICS

Pharmacogenetics represents the study of the **hereditary variation in the handling of drugs**. Pharmacogenetic abnormalities may be entirely innocuous, until the affected individual is challenged with particular drugs. The hyposensitivity and resistance of certain individuals to **coumarin** anticoagulants and the hypersensitivity of patients with **Down's syndrome** to atropine most

probably stem from abnormalities in their respective receptor sites. **Acatalsia** and the decrease in the activities of **pseudocholinesterase**, **acetylase**, and **glucose 6-phosphate dehydrogenase** are a few examples of enzymatic deficiencies that can lead to adverse reactions that range from mild to very severe.

### LIVER DISEASE

The liver is the principal metabolic organ, and hepatic disease or dysfunction may impair drug elimination. Any alteration in the serum albumin or bilirubin levels and in the prothrombin time indicates impaired liver function. Similarly, skin bruising and bleeding tendency indicate decreased production of clotting factors by the liver.

### THE INFLUENCE OF AGE

Drug metabolism is very deficient — qualitatively and quantitatively — in newborns. For example, chloramphenicol, when used injudiciously, may cause **gray syndrome**. The mechanism of chloramphenicol toxicity is apparently the failure in the newborn to conjugate **chloramphenicol** with glucuronic acid, because of inadequate activity of hepatic **glucaronyl transferase**. This, in combination with inadequate renal excretion of the drug in the newborn, results in a higher-than-expected plasma level of chloramphenicol. Therefore, a newborn should receive doses of chloramphenicol not greater than 25 to 50 mg/kg of body weight.

Elderly people are also prone to toxicity from numerous drugs, including cardiac glycosides. A dose of **digitoxin**, which may be totally therapeutic and innocuous at the age of 60, may produce severe toxicity and even death at the age of 70. The abilities of the liver to metabolize drugs and of the kidney to excrete drug metabolites decline with age.

### ENZYME INDUCTION AND INHIBITION

The activities of microsomal drug-metabolizing enzymes in humans can be enhanced by altering the levels of endogenous hormones such as androgens, estrogens, progestational steroids, glucocorticoids, anabolic steroids, norepinephrine, insulin, and thyroxine. This effect can also be elicited by the administration of exogenous substances such as drugs, food preservatives, insecticides, herbicides, and polycyclic aromatic hydrocarbons. This increase in the activities of drug-metabolizing enzymes appears to stem from an elevated rate of synthesis of the enzyme protein; hence, it is truly an enzyme-induction phenomenon.

Liver microsomal enzyme inducers that are lipid soluble at the physiological pH can be classified into two general groups. Some, such as phenobarbital, tend to stimulate all enzymes; others, such as **3-methylcholanthrene**, tend to be selective. The administration of phenobarbital increases the amounts of **NADPH-cytochrome C reductase** and P-450, and the rate of P-450 reduction. In contrast, the administration of 3-methylcholanthrene increases the amount of P-450, but neither the activity of NADPH-cytochrome C reductase nor the rate of P-450 reduction.

## CLINICAL IMPLICATIONS OF ENZYME INDUCTION AND INHIBITION

Patients are often given several drugs at the same time. The possibility that one drug may accelerate or inhibit the metabolism of another drug should always be kept in mind. When this phenomenon occurs, the removal of an enzyme inducer could be hazardous. The following examples reveal the consequence of enzyme induction. Phenylbutazone is an analgesic, antipyretic, uricosuric, and anti-inflammatory agent. Among its side effects are activation of peptic ulcer and gastrointestinal hemorrhage. If a dog is given large amounts of phenylbutazone, side effects such as vomiting and



diarrhea with bloody stool ensue. However, if phenylbutazone treatment is continued for several days, these side effects disappear. In this case, phenylbutazone “induces” its own hydroxylation, which results in a lower plasma level of the drug and, ultimately, the absence of the side effects. Long-term treatment with phenylbutazone and many other drugs should be expected to result in decreased effectiveness and toxicity.

Patients who are on anticoagulant therapy may suffer severe hemorrhage several days after discharge from the hospital. Often, these patients are sedated with barbiturates during their hospitalization which tend to stimulate the enzymes that metabolize dicumarol. The abrupt withdrawal of barbiturates after discharge tends to revert the activity of the drug-metabolizing enzymes to their prebarbiturate stage, which raises the free circulating level of the anticoagulant and results in hemorrhage. Obviously, treatment with phenobarbital should prompt altering the maintenance dosage of anticoagulants.

### GRAPEFRUIT JUICE ACTION ON INTESTINAL CYTOCHROME P-450 (CYP) ENZYMES

The effects of some CYP3A4 inhibitors wane with repeated administration, as they cause induction of CYP3A4 through upregulation of CYP3A messenger RNA and protein over time. However, this is not the case with grapefruit juice. Recurrent ingestion of grapefruit juice leads to a selective decrease of both CYP3A4 and CYP3A5 protein expression in enterocytes, resulting in increased drug bioavailability. Messenger RNA expression is not reduced, which suggests that this decrease in activity is not transcriptionally mediated. The mechanism of the decrease in CYP3A4 protein most likely reflects either accelerated protein degradation or reduced messenger RNA translation. It would be reasonable to suppose that one or more components of grapefruit juice cause a rapid intracellular degradation of the intestinal CYP3A4 enzyme through irreversible “suicide” inhibition. This would explain the rapid and sustained onset of inhibition by grapefruit juice. A 47% reduction in intestinal CYP3A4 concentration occurs within 4 h of the ingestion of grapefruit juice, and grapefruit juice maintains a bioavailability-enhancing effect for up to 24 h (see Kane and Lipsky, 2000).

Grapefruit juice also inhibits the CYP1A2 enzyme system *in vitro* but not *in vivo*. This is consistent with the understanding that the effect of grapefruit juice occurs at the level of the intestinal wall where levels of CYP2A expression are low. These CYP2A substrates studied with grapefruit juice have included **caffeine**, **theophylline**, and **coumarin** (Table 34.1).

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**TABLE 34.1**  
**Medications with which Grapefruit Juice Should Not Be Consumed without Supervision**

**Calcium Channel Blockers**

Felodipine  
Nimodipine  
Nisoldipine  
Nitrendipine  
Pranidipine

**Immunosuppressants**

Cyclosporine  
Tacrolimus

*Continued.*

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**TABLE 34.1 (Continued)**  
**Medications with which Grapefruit Juice Should**  
**Not Be Consumed without Supervision**

**HMG-CoA Reductase Inhibitors\***

Atorvastatin

Cerivastatin

Lovastatin

Simvastatin

**Antihistamines**

Ebastine

Terfenadine

**Psychiatric Medications**

Buspirone

Carbamazepine

Diazepam

Midazolam

Triazolam

**Prokinetics**

Cisapride

**Others**

Methadone

Sildenafil

\* HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.

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# 35 Foxglove, Cardiac Glycosides, and Congestive Heart Failure

## DIGITALIS

One of the most important additions to our therapeutic resources occurred at the end of the 18th century with the demonstration of the efficiency of digitalis in certain cases of **dropsy**. The drug had been used for different purposes long before, but its specific action was proved by **William Withering**, “**the flower of English physicians**” (Figure 35.1) as he was referred to at his death bed. Withering (1741–1799) was born in Wellington, England. He studied medicine in Edinburgh and graduated in 1766 with a paper titled “Malignant Putrid Sore Throat.” He then worked for some years in Stafford as a physician at the infirmary for the poor. From 1775, he lived in Birmingham, attached to the staff of the general hospital. He was also much appreciated as a consultant. In 1786, he moved to Edgbaston outside Birmingham.

Cardiac glycosides have been used from time immemorial principally because of their toxic effects. **Strophanthus**, for example, is mentioned in the **Ebers Papyrus** (1500 B.C.) and was used by the ancient Egyptians to treat many illnesses. In 1785, Withering first introduced the use of digitalis in his classic monograph, *An Account of the Foxglove and Some of Its Medical Uses: with Practical Remarks on Dropsy and Other Diseases*. He was led to this discovery on investigating the remarkable cures effected by an old woman in the treatment of dropsy. Withering found that the beneficial effects were due to the presence of digitalis among the many herbs that the “old woman of Shropshire” used in her treatment.

Because of the lack of information regarding the mechanism of action of digitalis, and its toxic effects when used indiscriminately, the drug gradually fell into disrepute until **MacKenzie** reestablished the correctness of Withering’s research in 1905. Subsequent physiological studies elucidated the mechanism of its action in human disease. Many of the active principles derived from the digitalis bodies have been isolated and made available in pure form for clinical use, in addition to the galenical preparations of crude drugs (see Grollman, 1962).

## THE DIGITALIS SERIES

The digitalis series embraces a considerable number of substances that are characterized by their action on the heart. They are widely distributed in the vegetable kingdom in very different botanical families and have long been used for various purposes in civilized countries. Some of them were employed as remedies by the laity long before their virtues were recognized by the medical profession, and others have been used as **arrow poisons** and **ordeal poisons** by the natives of different parts of Africa and the Eastern Archipelago.

The most important plants containing bodies belonging to this group that are used therapeutically are *Digitalis purpurea* (**purple foxglove**), *D. lanata*, *Strophanthus hispidus* and *S. kombè*, *A. ouabia*, *A. venenata*, and *Scilla maritima* (**squills**). Others that are now used are *Helleborus niger* (**Christmas rose**), *Convallaria majalis* (**lily of the valley**), *Apocynum cannabinum* (**Canadian hemp**), *Adonis vernalis* (**pheasant’s eye**), *Erythrophlaeum* (**sassy or Casca bark**), *Thevetia*

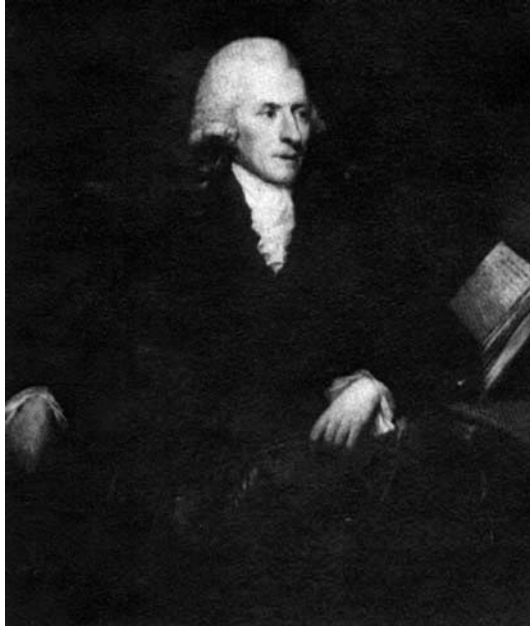


FIGURE 35.1 William Withering.

(yellow oleander), *Cheiranthus* (wallflower), *Periploca graca* (silk vine), and *Coronilla* (axseed). Other plants resemble digitalis in their effects. Moreover, these bodies are not confined to the vegetable kingdom, but have also been isolated from various species of toads (Figure 35.2).

## CHEMISTRY

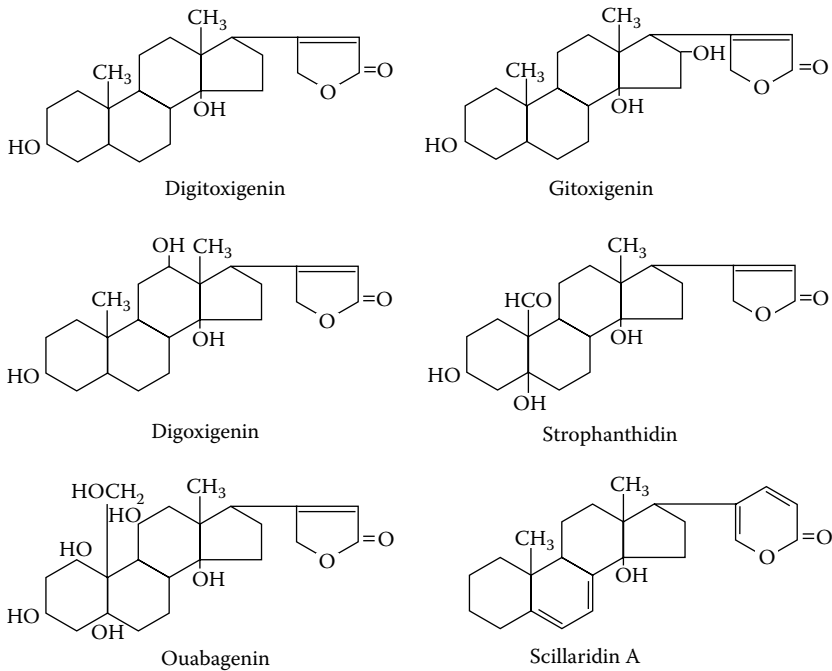
The distribution of cardiac glycosides in the plant varies in different species. **Digitalis** is obtained from the leaves and seeds; **strophanthus**, from the seeds; **squill**, from the bulbs; *Convallaria*, from the flowers; and **ouabaio**, from the wood and bark. In addition, there are saponin bodies that do not show the typical digitalis effect on the heart but which are extracted along with the glycosides, which possess the cardiac actions.

The digitalis molecules are present in the plant in the form of **glycosides**, which are readily altered by enzymatic processes. Purpurea may be separated by physical methods into two fractions that are designated as **purpurea glycosides A and B**, whereas from *Digitalis lanata* three glycosides designated as **lanatosides A, B, and C** can be obtained, and these are called **acetyldigitoxin, acetylgitoxin, and acetyldigoxin**, respectively. The acetyl derivatives when hydrolyzed with mild alkali, or their corresponding deacetyllanatosides when hydrolyzed enzymatically, split off an acetyl group or glucose, respectively, to give the simple derived glycosides **digitoxin, gitoxin, and digoxin**. Digitoxin and gitoxin can also be obtained from *Digitalis purpurea*; digoxin is a specific glycoside of *Digitalis lanata*.

By splitting off the molecule of glucose, purpurea glycoside A is converted to digitoxin, which consists of a steroid nucleus attached to three molecules of **digitoxose**. Purpurea glycoside B may be hydrolyzed in the same way to give one molecule each of glucose and gitoxin. The digitalis bodies can then be hydrolyzed further to form steroidal compounds designated as “**aglycones**” or “**genins**” and sugars, which can sometimes possess unusual characteristics. Many of the aglycones are very closely related chemically and possess the same number of carbon atoms. The structures of several typical members of this group are given in Figure 35.3. They are steroid compounds possessing the **pentanoperhydro-phenanthrene nucleus** with a four or five carbon lactone ring



**FIGURE 35.2** Foxglove (*Digitalis purpurea*) in bloom. Note the thimble (finger)-shaped flowers from which it derives its name and the leaves from which medicinal digitalis is derived.



**FIGURE 35.3** Structural formulas of the aglycones of the cardiac glycosides.

attached at the C-17 atom. The hydroxyl group at C-3 is attached to one or more sugar molecules to give the glycoside. The differences between the various aglycones are mainly due to the number, arrangement, and function of the oxygen atoms present in the molecule. Thus, **digoxigenin** differs from **digitoxigenin** in having an –OH group at C-14. **Strophanthidin** possesses, in addition to the tertiary hydroxyl group at C-14, a second tertiary hydroxyl group at C-5. The importance of these aglycones and recent interest in them stem from the fact that it is in this portion of the glycosidal molecule that the characteristic cardiac action resides.

The sugar portion of the cardiac glycosides, though inert, by its union with the aglycone gives the special character to the molecule that affects its absorption and transport in the organism and so influences its specific affinity for cardiac muscle. Many of the sugars, e.g., **digitoxose**, **cymarose**, **sarmentose**, and **digitulose**, have so far been found to occur naturally only in the cardiac glycosides. Several synthetic glycosides have also been prepared from glucose and the naturally occurring genins. The  $\beta$ -glycosides prepared in this manner are in some cases more potent than the naturally occurring drugs, but have not been applied clinically.

The other members of this series also consist of glycosides that undergo reactions comparable to those already described. Thus, when hydrolyzed, the principal glycosides of strophanthus (cymarin,  $C_{30}H_{44}O_9$ ) are split into its aglycone, strophanthidin (and a sugar, cymarose). The other glycosides of strophanthus consist of cymarin in combination with one or more molecules of glucose.

From *Strophanthus gratus* a crystalline glycoside, **ouabain**, has been obtained. It was so named because it was first isolated from the root and bark of the **Ouabaio tree**, which is the source of an arrow poison used by the Somalis of East Africa. Because of its well-defined physical characteristics and crystalline structure, ouabain,  $C_{29}H_{44}O_{12}$ , served for a time as a standard in the U.S. for the assay of the digitalis group of drugs.

The close relationship of the various glycosides of the digitalis series to each other is especially well depicted when the aglycones into which they are hydrolyzed are arranged in a series, as follows:

<b>Strophanthidin</b>	$C_{23}H_{32}O_6$	<b>Digoxigenin</b>	$C_{23}H_{34}O_5$
<b>Digitoxigenin</b>	$C_{23}H_{34}O_4$	<b>Periplogenin</b>	$C_{23}H_{34}O_5$
<b>Gitoxigenin</b>	$C_{23}H_{34}O_5$	<b>Ouabagenin</b>	$C_{23}H_{34}O_8$

## CARDIAC GLYCOSIDES IN THE TREATMENT OF CONGESTIVE HEART FAILURE

The most important and common drugs in the treatment of congestive heart failure are the cardiac glycosides, which may occur naturally in the body.

When the heart can no longer pump an adequate supply of blood to meet the metabolic needs of the tissues or in relation to venous return, cardiac failure may ensue. The causes of cardiac failure are complex, but stem from **mechanical abnormalities** (e.g., pericardial tamponade), **myocardial failure** (e.g., cardiomyopathy and inflammation), and **arrhythmias**. In high-output failure, the cardiac output, which may be normal or even higher than normal, is not sufficient to meet the metabolic requirement of the body. Cardiac failure may predispose a patient to **congestive heart failure**, which is a state of circulatory congestion. **Toxic injury**, caused by agents such as **doxorubicin**, the alkaloid **emetine** in ipecac syrup, **cocaine**, or **ethyl alcohol**, is another way by which the functional integrity of the heart may also be compromised.

A **compensatory mechanism** is initiated in the event of **congestive heart failure**. This consists of:

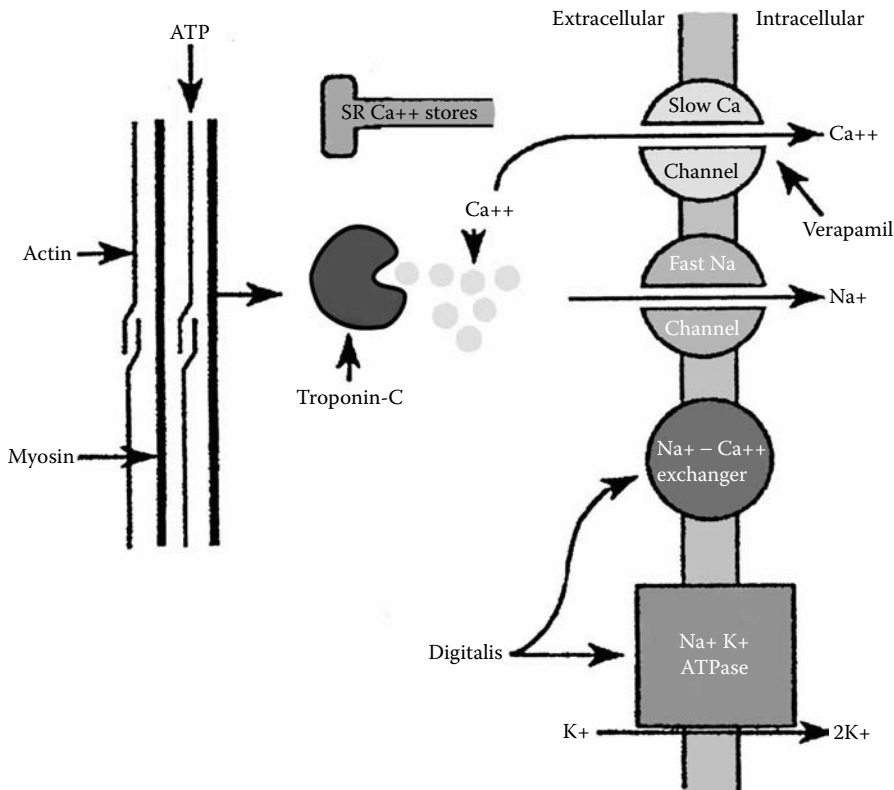
- Cardiac dilatation and hypertrophy — taking advantage of the Frank–Starling relationship to utilize more contractile elements.
- Sympathetic stimulation — increasing the heart rate to maintain contractility and cardiac output.

- Increasing oxygen consumption through the arterial-venous oxygen difference — increasing extraction of oxygen from limited blood flow.
- Production of aldosterone — increasing sodium and fluid retention, which may not be advantageous to the organism.

Agents with **positive inotropic actions** that may be used in the management of congestive heart failure include the **cardiac glycosides** (e.g., **digoxin** and **digitoxin**), **dopaminergic analogs** (e.g., **dobutamine**), **phosphodiesterase inhibitors** (e.g., **amrinone** and **milrinone**), **angiotensin antagonists** (e.g., **captopril**, **enalapril**, and **lisinopril**), and **vasodilators** (**nitrates** and **hydralazine**).

### BIOCHEMICAL BASIS OF MYOCARDIAL CONTRACTION

The myocardium develops force by forming **cross bridges** between **actin** and **myosin myofilaments**. By using the energy contained in adenosine triphosphate (ATP), myosin and actin are engaged and cardiac muscle shortens. The contraction of the myocardial cell is initiated by **membrane depolarization** with the rapid influx of **sodium** through the fast sodium channels. The myofilament interaction is regulated by **troponin**, which contains three subunits — **troponin-C**, **troponin-I**, and **troponin-T**. Troponin-C has a specific site for **calcium**. The subsequent activation of contractile protein is brought about by the influx of extracellular calcium through the slow calcium channels and the subsequent release of calcium from the sarcoplasmic reticulum.  $\text{Na}^+\text{-K}^+\text{-ATPase}$ , sarcolemmal  $\text{Ca}^{2+}\text{-ATPase}$ , and the sodium–calcium exchanger play important roles in maintaining the steady-state intracellular level of calcium, sodium, and potassium (Figure 35.4).



**FIGURE 35.4** The action of **verapamil** on myocardial contraction. ATP = adenosine triphosphate; SR = sarcoplasmic reticulum.











Action site	Action characteristic	Action site	Action characteristic
	Cardiac output increased		Blood pressure unchanged
	Heart rate decreased		Aldosterone production reversed
	Heart size decreased		Sodium retention blocked
	Cardiac efficiency increased		Diuresis occurs

FIGURE 35.5 Actions of digitalis in congestive heart failure.

### THE POSITIVE INOTROPIC ACTION OF CARDIAC GLYCOSIDES

Cardiac glycosides (**digitalis**) potentiate the coupling of electrical excitation with mechanical contraction, and provoke a more forceful contraction by augmenting the myoplasmic concentration of calcium. It is thought that digitalis inhibits sodium–calcium exchanges by inhibiting  $\text{Na}^+\text{-K}^+\text{-ATPase}$ . This results in an enhanced intracellular concentration of sodium, which in turn leads to a greater sodium influx that then elicits stronger systolic contraction.

### THE MODES OF ACTION OF CARDIAC GLYCOSIDES

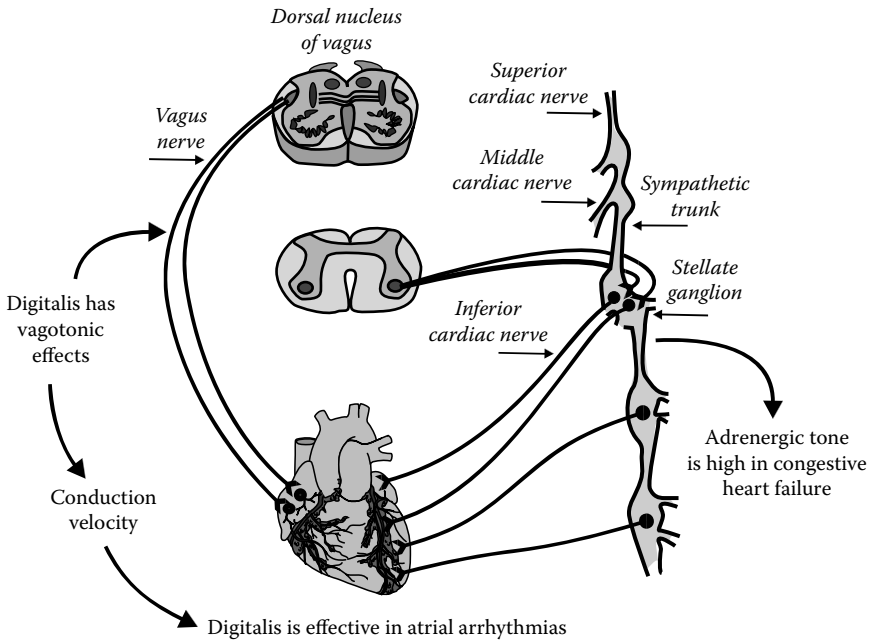
The cardiac glycosides increase **cardiac output** through their positive inotropic effect. They slow **heart rate** by relieving the sympathetic tone and through their vagotonic effects. They reduce the heart size by relieving the Frank–Starling relationship. They increase **cardiac efficiency** by increasing cardiac output and decreasing oxygen consumption (decreased heart size and rate).

**Blood pressure** remains unchanged following the administration of cardiac glycosides. In **congestive heart failure**, the cardiac output is reduced but the total peripheral resistance is increased, and these effects are reversed by cardiac glycosides.

Cardiac glycosides bring about diuresis by increasing both cardiac output and renal blood flow; the latter in turn reverses the **renal compensatory mechanism** activated in congestive heart failure. Consequently, the production of **aldosterone** is reduced, sodium retention is reversed, and the excretion of edematous fluid is enhanced (Figure 35.5).

### ELECTROPHYSIOLOGICAL EFFECTS OF CARDIAC GLYCOSIDES

Cardiac glycosides have a **vagotonic effect** and may decrease impulse formation in the sinoatrial node. Although **automaticity** is not directly influenced by digitalis, **conduction velocity** is decreased. This effect of digitalis on the atrioventricular node is more prominent in the context of congestive heart failure, in which the vagal tone is low and the adrenergic tone is high. Digitalis shortens the refractory period, in part because of enhanced intracellular calcium levels, decreasing membrane resistance, and increasing membrane potassium conductance, which lead to shortening of the action potential and contribute to shortening of atrial and ventricular refractoriness. The electrophysiological properties of digitalis make it a useful compound in the treatment of **atrial**



**FIGURE 35.6** The vagotonic effects of digitalis are useful in treating atrial arrhythmias.

**arrhythmias** (for its vagotonic effect), **atrial flutter** (for its depressant effect on atrioventricular conduction), and **atrial fibrillation** (also for its vagotonic effect) (Figure 35.6).

## DIGITALIS TOXICITY

The toxic effects of digitalis are frequent and may be fatal. Toxicity may result from **overdosage**, **decreased metabolism and excretion**, and **hypokalemia** stemming from the use of thiazide diuretics, diarrhea, and vomiting. Digitalis toxicity has several manifestations:

- Any arrhythmia occurring *de novo*
- Renal insufficiency
- Electrolyte disturbances
- Visual symptoms
- Headache
- Psychotic symptoms
- Pulmonary disease
- Anorexia

Digitalis toxicity should also be closely observed in **elderly** patients and those who have had a **recent myocardial infarction**, as these conditions predispose to toxic reactions.

### SYMPTOMS OF DIGITALIS TOXICITY

#### Cardiac Effects

The most commonly reported cardiac signs of toxicity are **dysrhythmias**, such as **ventricular ectopic depolarization**, **second- and third-degree heart block**, **junctional tachycardia**, **atrial tachycardia with block**, **ventricular tachycardia**, **sinoatrial block**, and **sinus arrest**.

## Gastrointestinal Effects

Anorexia is observed as a gastrointestinal complication of cardiac glycoside use and is followed by nausea and vomiting.

## Visual Effects

The most common visual side effects are blurring, dimness of vision, flickering or flashing lights, color vision (yellow, green, red, and white), **cycloplegia**, and **diplopia**.

## Neuropsychiatric Symptoms

A few of the neuropsychiatric symptoms that have been reported in conjunction with cardiac glycoside use are agitation, apathy, aphasia, ataxia, belligerence, changes in effect or personality, confusion, delirium, delusions, depression, disorientation, dizziness, drowsiness, euphoria, excitement, fatigue, hallucinations, headache, insomnia, irritability, mania, muscle pain, nervousness, neuralgias, nightmares, paresthesias, vertigo, violence, and weakness.

## TREATMENT OF DIGITALIS TOXICITY

### General Treatment

Once digitalis toxicity is diagnosed, digitalis and diuretic use should be discontinued. Furthermore, the patient should be monitored closely for any alteration in the pharmacokinetic profile of the cardiac glycoside being used.

### Specific Treatment

Treatment with **potassium** and magnesium may be indicated. Potassium is recommended for patients with digitalis-induced ectopic beat or tachycardia, provided the patient is not hyperkalemic, uremic, or oliguric. It is the preferred drug if the patient is hypokalemic.

To manage digitalis-induced arrhythmia, **lidocaine**, with its quick onset and short duration of action, is the drug of choice. Because lidocaine is metabolized, it should be used cautiously in patients with liver disease. **Phenytoin** may be used if potassium or lidocaine prove ineffective. **Propranolol** is effective in treating ventricular tachycardia. **Atropine** is effective if digitalis-induced conduction delay is at the atrioventricular node and is mediated via the vagus. Calcium channel-blocking agents, such as **verapamil**, are effective if the arrhythmia is due to reentry, increased diastolic depolarization in the Purkinje fibers, or **oscillatory after-potential**. In addition to these drugs, a temporary pacemaker may be indicated.

The following interventions are contraindicated: **Quinidine** should not be used because it displaces digoxin from binding sites, and **bretylum** should not be used because it releases norepinephrine. **Carotid sinus stimulation** should be discouraged because it may precipitate ventricular fibrillation.

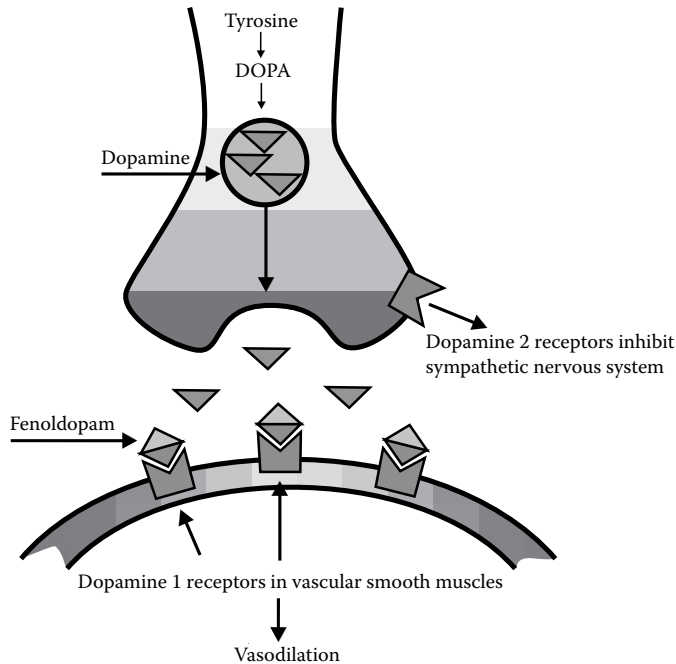
### Antidigoxin Antibodies

The antidigoxin or the **antidigoxin antibodies (Digibind)** have been used to control digitalis intoxication. The antibody mobilizes depot digoxin and is excreted by the kidney as an antibody–digoxin complex.

## DRUGS ACTING ON PERIPHERAL DOPAMINE RECEPTORS

### DOPAMINE RECEPTORS

Peripheral dopaminergic receptor agents are useful in the treatment of congestive heart failure (Figure 35.7). Two distinct subtypes of dopamine receptors have been identified. The **dopamine<sub>2</sub> (DA<sub>2</sub>)**



**FIGURE 35.7** Fenoldopam, which causes vasodilation, is useful in congestive heart failure.

receptors are located at various sites within the sympathetic nervous system, and their activation results in inhibition of the sympathetic nervous system. In contrast, activation of the postsynaptic dopamine<sub>1</sub> (DA<sub>1</sub>) receptors, which are located on vascular smooth muscles, causes vasodilation in the renal, mesentery, cerebral, and coronary vascular beds. Thus, the pharmacological response to activation of the DA<sub>2</sub> and DA<sub>1</sub> receptors is hypotension, bradycardia, diuresis, and naturesis.

**Dopamine** stimulates dopamine,  $\alpha$ -, and  $\beta$ -adrenergic receptors. The use of dopamine in congestive heart failure is limited because it causes nausea and vomiting, becomes inactive when given orally, increases afterload ( $\alpha$ -adrenergic receptor-mediated peripheral vasoconstriction), and enhances oxygen demand on the left ventricle.

**Dobutamine**, which is available only for parenteral administration, stimulates  $\beta$ <sub>1</sub>-adrenergic receptors, producing a strong inotropic effect.

**Ibopamine**, which is active orally, is capable of eliciting peripheral and renal vasodilation, positive vasodilation, and a positive inotropic action. Ibopamine is converted to **epinine**, which is the active drug.

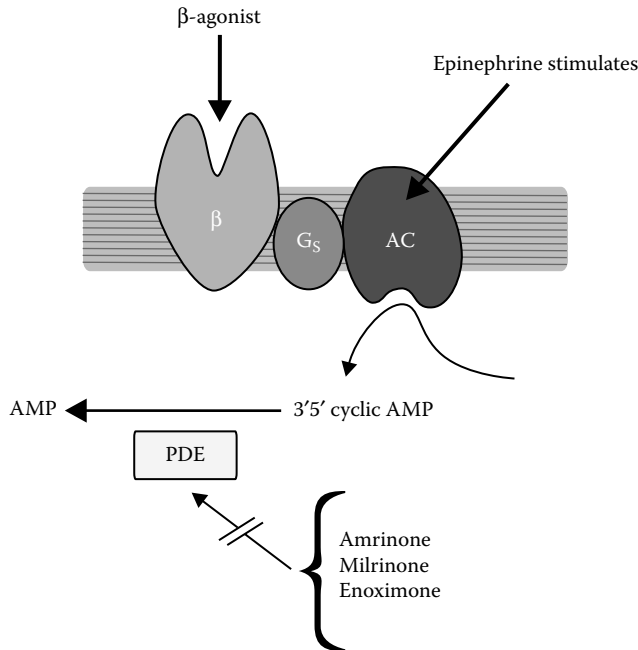
**Fenoldopam** is an orally active DA<sub>1</sub>-receptor agonist. It is more potent than dopamine in causing renal vasodilation without having adrenergic, cholinergic, or histaminergic properties.

## DRUGS INHIBITING PHOSPHODIESTERASE

**Amrinone**, **milrinone**, and **enoximone** differ from aminophylline in that they exhibit a certain degree of selectivity for peak III phosphodiesterase, which is found predominantly in myocardial and vascular tissues. These agents exert both **positive inotropic** and **direct vasodilating actions** (Figure 35.8).

## VASODILATORS AND ANGIOTENSIN ANTAGONISTS

**Nitrates** and **hydralazine** have been used in patients with congestive heart failure. An **angiotensin-converting enzyme** inhibitor such as **lisinopril** increases the left ventricular ejection fraction in



**FIGURE 35.8** Amrinone exerts positive inotropic and vasodilating actions. AMP = adenosine monophosphate; AC = adenylate cyclase; PDE = phosphodiesterase;  $G_s$  = stimulatory guanine nucleotide-binding regulatory protein.

patients with congestive heart failure, and the effectiveness of the drug is not diminished in the presence of impaired renal function.

In addition, a **vasodilator** in combination with an angiotensin-converting enzyme inhibitor has been used in congestive heart failure. The vasodilators may be classified as **venodilators**, **arterial dilators**, or **balanced-type vasodilators**.

The rationale for vasodilation in the management of congestive heart failure is based on the increased arteriolar vasotone that occurs. This initiates a vicious circle in which cardiac function is further depressed by an increase in afterload and in resistance to ejection (Figure 35.9).

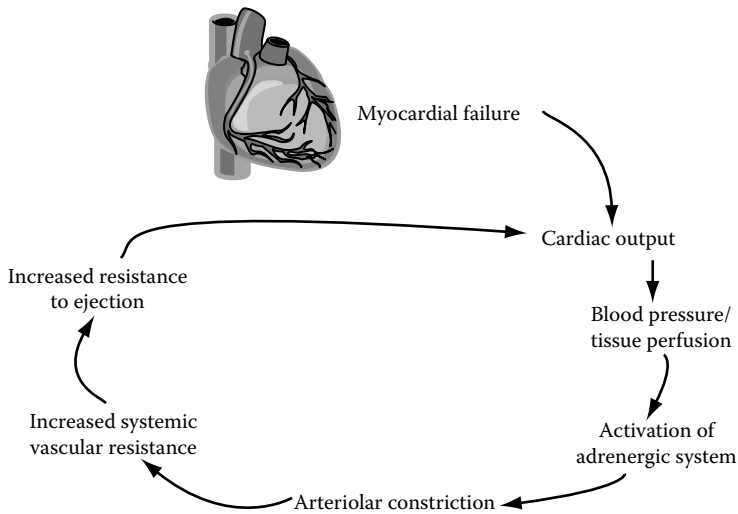
### RECEPTOR-DEPENDENT VASODILATION

Vascular tone is regulated by the cytosolic **calcium** level, the interaction of calcium and **calmodulin** with myosin light-chain kinase, and subsequent myosin light-chain phosphorylation, which promotes the interaction of myosin with actin and finally leads to contraction.

Receptor-dependent vasodilation may also take place in a more indirect manner through the presynaptic modulation of the release of neurotransmitters, such as **norepinephrine** and **acetylcholine**. In addition to its effects on postsynaptic receptors, norepinephrine stimulates the presynaptic  $\alpha_2$ -receptor, thereby inhibiting further transmitter release. Moreover, the activation of other presynaptic receptors such as the muscarinic cholinergic, dopaminergic, purinergic, serotonergic, and histaminergic receptors leads to diminished norepinephrine release and subsequent vasodilation.

### ENDOTHELIUM-DEPENDENT VS. INDEPENDENT VASODILATORS

A number of vasodilators, such as acetylcholine, bradykinin, adenine nucleosides, thrombin, histamine, and serotonin, require an **intact vascular endothelium** to exert their effects. For example, stimulation of endothelial cholinergic receptors causes the release of **endothelium-derived relaxing**



**FIGURE 35.9** Neurohumoral activation during myocardial failure.

**factors** (EDRF), which may involve **arachidonic acid formation** and compartmentalization via the lipoxygenase pathway. EDRF, which is identical to **nitric oxide**, activates guanylate cyclase and enhances the formation of **cyclic guanosine monophosphate** (cyclic GMP) in smooth muscle. **Tetranic acid** (a vasoconstrictor), **thromboxane A<sub>2</sub>** (a vasoconstrictor), and **prostacyclin** (a vasodilator) are formed through the lipoxygenase pathway.

The vasodilating properties of **captopril** or **hydralazine** (antihypertensive agents) are mediated by the formation of EDRF or prostaglandin, or both. On the other hand, the vasodilating properties of **nitroprusside** (an antihypertensive agent) result directly from the formation of cyclic GMP.



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# 36 *Ginkgo biloba*

## INTRODUCTION

*Ginkgo biloba* has the following pharmacodynamic effects:

- It is an antioxidant
- It causes vasoregulation
- It inhibits platelet aggregation
- It reduces brain edema
- It enhances functional recovery following ischemia (see Christen and Maixent, 2002)

***Ginkgo biloba* extract** enhances, accelerates, and prolongs the activation of microglia and astrocytosis at the site of brain injury. Extract of *Ginkgo biloba* (EGb 761) is a complex mixture of different compounds, containing about 25% **flavonoidic substances** such as **kaempferol**, **quecetine**, **isorhamnetine**, and **proanthocyanidines**, **terpenes heterosides** (**ginkgolides** and **bilobalides**), and some organic acids. Systemic administration of *Ginkgo biloba* extract has been shown to enhance functional recovery after a variety of lesions in locations in the rat brain. There are many possible mechanisms proposed for its protective effects, including its **anti-ischemic–antiedemic action**, **free-radical scavenging activity**, **neurotransmitter activity**, and **neurotrophin gene expression**. In addition, *Ginkgo biloba* extract could manifest its beneficial effects through modification of the injury-induced proliferation, labeling, and staining of glia.

When tissue damage occurs, astrocytes and microglia are the first cells to be activated. Until recently, the role of astrocytes in the injured brain was believed to be limited to scar tissue formation, separating dying from healthy tissue. Microglial cells were thought to be confined to a primarily phagocytic function, i.e., removing tissue debris after trauma. Now, it is widely recognized that astrocytes and microglia play a more pivotal role in the recovery process by reestablishing homeostasis, synthesizing and releasing neuroactive substances, and triggering an orchestrated immune reaction within the brain itself. These events are called *glial activation*. Furthermore, activated astrocytes can enhance **axonal sprouting** and **reactive synaptogenesis** — events that are known to correlate well with behavioral recovery. Under appropriate conditions, glial cells can intervene in neuronal signal transduction by absorbing or releasing neurotransmitter molecules such as glutamate and aspartate. Although the activation of both glial populations occurs after trauma, the reported time delays between the appearance of microglial and astroglial cells led to the assumption that microglia respond first and, then, they in turn trigger the increased metabolic and biological activity of astrocytes (see Dietrich et al., 2000).

## GINKGO BILOBA EXTRACT AND INHIBITION OF MONOAMINE OXIDASE A AND B IN LIVING HUMAN BRAIN

Extracts of *Ginkgo biloba* contain dozens of chemical compounds including **flavonoids** and **terpene lactones**, which are considered to be the active compounds. Although the pharmacological actions of these compounds are not yet known, a number of studies suggest that *Ginkgo biloba* has the following pharmacodynamic effects:



- Vasoregulation
- Platelet-activating factor antagonism
- Neurotransmitter regulation
- Antioxidant properties

The increasing use of alternative and complementary medicines presents many challenges, including the need for careful clinical trials to demonstrate efficacy, the need to understand mechanisms of action, and an awareness of potential adverse interactions between alternative medicines and conventional drugs. The extract of *Ginkgo biloba*, EGb 761, is a popular alternative medicine. Its main use has been for treating symptoms of **cerebral insufficiency**. In a double-blind, placebo-controlled trial, EGb 761 was reported to stabilize and improve cognitive function in patients suffering with **dementia**. There is evidence that some of its effects stem from its antioxidant properties, which may confer neuroprotective effects. This is supported by *in vitro* studies showing that EGb 761 reduces lipid peroxidation. In addition, it has been recently reported that EGb 761 is neuroprotective in a dose-dependent fashion against MPTP-induced neurotoxicity (see Chapter 13) and evidence was presented suggesting that the inhibitory effect of EGb 761 on brain monoamine oxidase (MAO) may be involved in the neuroprotective effect.

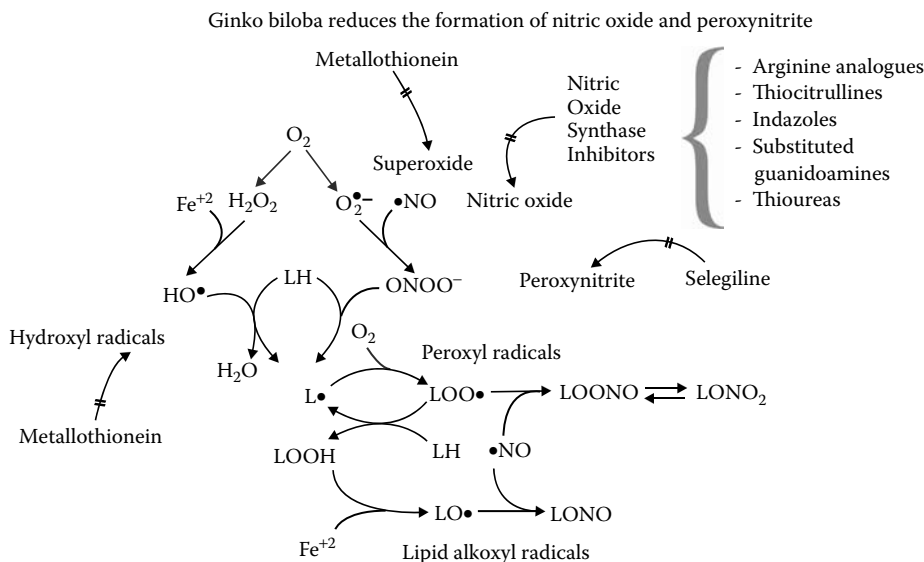
Fowler et al. (2000) used positron emission tomography (PET) to measure the effects of *Ginkgo biloba* on human brain MAO-A and MAO-B in ten subjects treated for 1 month with 120 mg/d of the *Ginkgo biloba* extract EGb 761, using [<sup>11</sup>C]clorgyline and [<sup>11</sup>C]-deprenyl-D<sub>2</sub> to measure MAO A and B, respectively. A three-compartment model was used to calculate the plasma-to-brain transfer constant  $K_1$ , which is related to blood flow and  $\lambda k_3$ , a model term that is a function of the concentration of catalytically active MAO molecules. *Ginkgo biloba* administration did not produce significant changes in brain MAO-A or MAO-B suggesting that mechanisms other than MAO inhibition need to be considered as mediating some of its central nervous system (CNS) effects.

### GINKGO BILOBA AND NITRIC OXIDE

The *Ginkgo biloba* extract (EGb 761) protects and rescues hippocampal cells against **nitric-oxide-induced toxicity** (Bastianetto et al., 2000). An excess of the free-radical nitric oxide (NO) is viewed as a deleterious factor involved in various CNS disorders. Numerous studies have shown that the ***Ginkgo biloba* extract EGb 761 is a NO scavenger with neuroprotective properties**. The effects of different constituents of *Ginkgo biloba* extracts, i.e., **flavonoids** and **terpenoids**, against toxicity induced by NO generators on cells of the **hippocampus**, a brain area particularly susceptible to neurodegenerative damage, have been studied.

Exposure of rat primary mixed hippocampal cell cultures to either **sodium nitroprusside** (SNP; 100  $\mu$ M) or **3-morpholinopyridone** resulted in both a decrease in cell survival and an increase in free-radical accumulation. These SNP-induced events were blocked by either EGb 761 (10 to 100  $\mu$ g/ml) or its flavonoid fraction CP 205 (25  $\mu$ g/ml), as well as by inhibitors of protein kinase C (PKC; **chelerythrine**) and l-type calcium channels (**nitrendipine**). In contrast, the terpenoid constituents of EGb 761, known as **bilobalide** and **ginkgolide B**, as well as inhibitors of **phospholipases A** [**3-[4-octadecyl]benzoyl]acrylic acid (OBAA)**] and C (**U-73122**), failed to display any significant effects. Moreover, EGb 761 (50  $\mu$ g/ml), CP 205 (25  $\mu$ g/ml), and **chelerythrine** were also able to rescue hippocampal cells preexposed to SNP (up to 1 mM). Finally, EGb 761 (100 g/ml) was shown to block the activation of PKC induced by SNP (100  $\mu$ M). These data suggest that the protective and rescuing abilities of EGb 761 are not only attributable to the antioxidant properties of its flavonoid constituents but also by their ability to inhibit NO-stimulated PKC activity (Figure 36.1).

NO is a neuronal messenger molecule whose overproduction can initiate neurotoxic events under pathological conditions. NO production has clearly been linked to neurodegeneration in animal models of ischemia and *in vitro* cultured cells. The final cellular pathways that lead from



**FIGURE 36.1** Nitric oxide regulates critical lipid membrane and lipoprotein oxidation events by (1) contributing to the formation of more potent secondary oxidants from  $O_2^{\bullet-}$  (i.e.,  $ONOO^-$ ), (2) catalyzing the redirection of  $O_2^{\bullet-}$  and  $H_2O_2$ -mediated cytotoxic reactions to other oxidative pathways, and (3) termination of lipid radicals to possibly less reactive secondary nitrogen-containing products. Moreover, metallothionein isoforms I and II protect against neurotoxic effects of superoxide anions, hydroxyl radicals, and peroxynitrite radicals. *Ginkgo biloba* reduces the formation of nitric oxide and peroxynitrite.

the generation of NO to neuronal death include the formation of the potent oxidant **peroxynitrite**, the release of intracellular  $Ca^{2+}$ , and the activation of PKC and **phospholipase C**. NO also mediates the neurotoxic effects of glutamate that are implicated in hypoxic/ischemic brain injury and possibly in Alzheimer's disease.

The *Ginkgo biloba* extract EGb 761 is a standardized mixture of active substances, including 24% **flavonoid glycosides** and 6% **terpenoids**, obtained from green leaves of the *G. biloba* tree. EGb 761 is a polyvalent agent capable of scavenging free radicals such as NO, reducing  $Ca^{2+}$ -stimulated intracellular events, and modulating intracellular signal transduction events, including those involving phospholipases A and C and PKC. All of these signal transduction molecules are likely to be involved in brain ischemia and neurodegenerative diseases.

It is interesting that *in vivo* experiments have revealed that a treatment with EGb 761 inhibits ischemia-induced activation of total PKC activity in rat and decreases, partly via the inhibition of phospholipase C, the accumulation of hippocampal lipid-derived second messengers in rats subjected to electroconvulsive shock. In addition, systemic administration of **bilobalide**, one of the terpenoid constituents of EGb 761, protects hippocampal slices against hypoxia-induced phospholipid breakdown, presumably owing to an inhibition of phospholipase A. Moreover, **ginkgolide B**, another terpenoid constituent, has been reported to display an antagonistic activity against platelet-activating factor, a potent phospholipid derivative that is produced during cerebral ischemia through **calcium-activated phospholipase A<sub>2</sub>**. Such intracellular changes may contribute to the neuroprotective effects of EGb 761 in animal models of focal and global cerebral ischemia, retinal damage induced by ischemia, and in hypoxia. Clinical trials support the potential therapeutic usefulness of EGb 761 in the treatment of **cerebral insufficiency** and mild **cognitive impairments** in elderly patients, as well as in Alzheimer's disease and vascular dementia.

The precise mechanisms underlying the neuroprotective effects of EGb 761, particularly with respect to ischemia, have yet to be clearly established, but they have been reported to be associated with either its terpenoid or its flavonoid fractions. The present evidence indicates that EGb 761,

acting principally through its flavonoid constituents, is able to protect and rescue hippocampal neuronal cells against NO-induced toxicity. This is consistent with earlier data reporting protective effects of EGb 761 in animal models of cerebral ischemia, in *in vitro* models of oxidative stress-induced toxicity and, more recently, in a model of  $\beta$ -amyloid-induced toxicity. This is of particular interest given that ischemic neurodegeneration is associated with a loss of hippocampal neurons and that this event is likely the result of an increased production of NO (see Figure 36.1).

The production of **superoxide anions** is one of the major factors involved in NO toxicity because superoxide anions can react with NO to form the highly toxic free-radical peroxynitrite. A pivotal role for superoxide anions in NO-related insults is emphasized by results showing that transgenic mice overexpressing superoxide dismutase (SOD) are resistant to brain ischemia. Superoxide can protect against SNP-induced toxicity. Thus, the superoxide-scavenging properties of EGb 761 are likely to explain, at least in part, its ability to block cell death and the increase in reactive oxygen species accumulation induced by the two NO donors used here, SNP and SIN-1.

EGb 761 might also directly scavenge peroxynitrites and inhibit **lipid peroxidation** because it has been reported both to block the cytotoxicity induced by peroxynitrites and inhibit **cyclosporine-A-induced peroxidation**. This hypothesis is supported by the finding that the purported anti-ischemic agent **esbelen** completely protected and rescued hippocampal cells against SNP-induced toxicity. In contrast, the hydroxyl radical scavenging properties of EGb 761 do not seem able to account for its protective effects because catalase failed to display any neuroprotective properties in this model.

Aside from decreases in reactive oxygen species accumulation and inhibition of PKC (whose levels are increased in the hippocampal CA1 region during cerebral ischemia), it has also been shown that *Ginkgo biloba* blocks the toxic effects of NO, which is linked to neuroprotection during global ischemia. In this respect, EGb 761 shares with the PKC inhibitor **chelerythrine chloride**, but not with phospholipase C (U-73122) or A<sub>2</sub> (OBAA) inhibitors, the ability to block the toxic effects of SNP. These results are consistent with previous studies and suggest that the protective effects of EGb 761, together with its antioxidant properties, may be related to its inhibitory actions on PKC. The fact that EGb 761 was able to block SNP-induced toxicity suggests that the blockade of L-type voltage-dependent calcium influx maybe an early event that may inactivate PKC.

The rescuing effect of EGb 761 against NO-induced toxicity suggests that it can also inhibit active, but reversible, molecular pathways that are induced by NO and that lead to cell death. Among those, PKC is certainly a strong candidate because chelerythrine chloride mediated both the neuroprotective and neurorescuing effects of EGb 761 against NO-induced toxicity. In contrast, inhibitors of phospholipase C (U-73122) and A<sub>2</sub> (OBAA) failed to mimic the actions of EGb 761, indicating that EGb 761 regulates PKC through phospholipase A<sub>2</sub> and C independent mechanisms (Calapai et al., 2000; Bastianetto et al., 2000).

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# 37 Ginseng and Cholinergic Transmission

## INTRODUCTION

Ginseng contains 20 different **ginsenosids**, which belong to a family of steroids named **steroidal saponins**. They have been named **ginsenoside saponins**, **triterpenoid saponins**, or **dammarane derivatives** under previous classifications. Ginsenosides possess the four *trans*-ring rigid steroid skeleton, with a modified side chain at C-20. The classical steroid hormones have a truncated side chain (**progesterone**, **cortisol**, and **aldosterone**) or no side chain (**estradiol** and **testosterone**).

Ginsenosides belong to a family of steroids and share their structural characteristics. They can traverse cell membranes freely similar to steroids. Moreover, their presence has been demonstrated within cells, particularly the nucleus. Steroid hormone action, steroids that bind nuclear receptors, are thought to affect primarily the transcription of mRNA and subsequent protein synthesis. Intracellular steroid-binding proteins present possible attractive targets for ginsenosides.

Ginseng has the following effects:

- It enhances memory
- It protects neurons against ischemic damage
- It exhibits antineoplastic actions
- It possesses immunomodulating actions

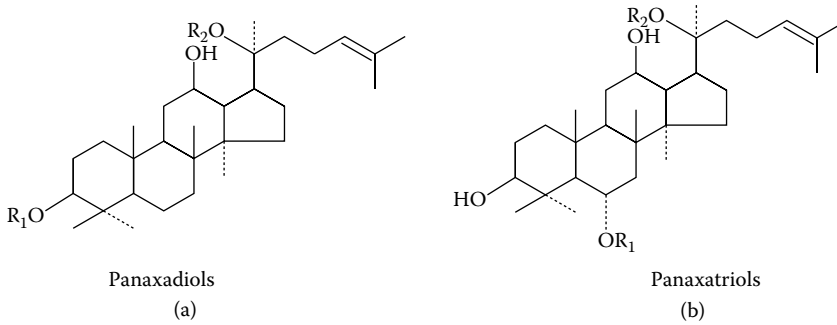
**Ginseng** is a highly valued herb in the Far East and has gained popularity in the West during the last few decades. There is extensive literature on the beneficial effects of ginseng and its constituents. The major active components of **ginsenosides** are a diverse group of **steroidal saponins** (Attele et al., 1999).

The **ginseng root** has been used for over 2000 years in the belief that it **is a panacea and promotes longevity**. Recently, there has been renewed interest in investigating ginseng pharmacology using biochemical and molecular biological techniques. Pharmacological effects of ginseng have been demonstrated in the central nervous system (CNS) and in cardiovascular, endocrine, and immune systems. In addition, ginseng and its constituents have been ascribed antineoplastic, antistress, and antioxidant activity. It is an herb with many active components, and there is evidence from numerous studies that ginseng does have beneficial effects.

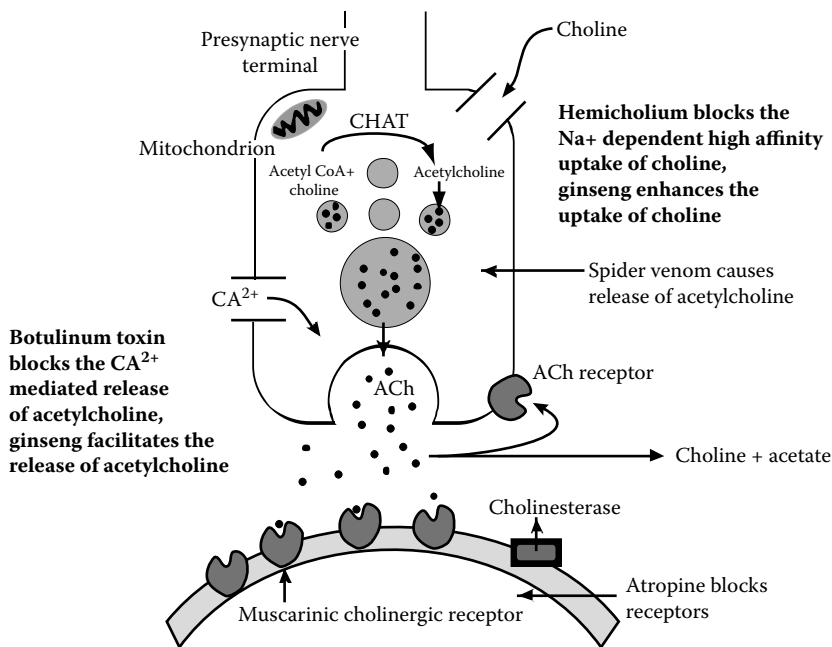
Ginseng has three species:

- *Panax ginseng* (Asian ginseng)
- *Panax quinquefolius* (American ginseng)
- *Panax japonicus* (Japanese ginseng)

Active constituents found in most ginseng species include **ginsenosides**, **polysaccharides**, **peptides**, **polyacetylenic alcohols**, and **fatty acids**. There is a wide variation (2 to 20%) in the ginsenoside content of different species of ginseng. Moreover, pharmacological differences within a single species cultivated in two different locations have been reported. For example, the potency



**FIGURE 37.1** Structures of ginsenosides based on chemical structure; there are two major groups: (A) panaxadiols and (B) panaxatriols.



**FIGURE 37.2** The metabolism and actions of acetylcholine (ACh). CoA = coenzyme A; CHAT = choline acetylase.

of extracts from *P. quinquefolius*, cultivated in the U.S., for modulating neuronal activity is significantly higher than for the same species cultivated in China (Figure 37.1). Most pharmacological actions of ginseng are attributed to ginsenosides. More than 20 ginsenosides have been isolated, and novel structures continue to be reported, particularly from *P. quinquefolius* and *P. japonicus*.

Ginseng prevents **scopolamine**-induced memory impairment (Figure 37.2) by increasing the uptake of **choline** and facilitating the release of **acetylcholine**.

## CHOLINERGIC TRANSMISSION

### DIVISION AND FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM

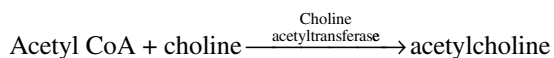
The autonomic nervous system consists of central connections, visceral afferent fibers, and visceral efferent fibers. The hypothalamus is where the principal integration of the entire autonomic nervous

system takes place and it is involved in the regulation of blood pressure, body temperature, water balance, metabolism of carbohydrates and lipids, sleep, emotion, and sexual reflexes. To a lesser extent, the medulla oblongata, limbic system, and cerebral cortex also integrate, coordinate, and adjust the functions of the autonomic nervous system.

Most blood vessels, the sweat glands, and the spleen are innervated only by one division of the autonomic nervous system. In the salivary glands, the two divisions of the autonomic nervous system supplement one another. In the bladder, bronchi, gastrointestinal tract, heart, pupils, and sex organs, the two divisions of the autonomic nervous system have opposing effects.

## NEUROCHEMICAL BASIS OF CHOLINERGIC TRANSMISSION

Acetylcholine, an ester of choline and acetic acid, is synthesized in cholinergic neurons according to the following scheme:



The acetylcholine, in turn, is hydrolyzed by both **acetylcholinesterase** and plasma **butyrylcholinesterase**. Choline is actively transported into nerve terminals (synaptosomes) by a high-affinity uptake mechanism. Furthermore, the availability of choline regulates the synthesis of acetylcholine (see Figure 37.2).

**Hemicholinium** blocks the transport of choline into synaptosomes, whereas botulinum toxin blocks the calcium-mediated release of acetylcholine. The released acetylcholine is hydrolyzed rapidly by acetylcholinesterase to choline and acetate. **Ginseng enhances the uptake of choline and facilitates the release of acetylcholine.**

## CLASSIFICATION OF CHOLINERGIC RECEPTORS

Acetylcholine receptors are classified as either muscarinic or nicotinic. The alkaloid **muscarine** mimics the effects produced by stimulation of the parasympathetic system. These effects are postganglionic and are exerted on exocrine glands, cardiac muscle, and smooth muscle. The alkaloid nicotine mimics the actions of acetylcholine, which include stimulation of all autonomic ganglia, stimulation of the adrenal medulla, and contraction of skeletal muscle.

**Dimethylphenylpiperazinium** stimulates the autonomic ganglia, **tetraethylammonium** and **hexamethonium** block the autonomic ganglia, **phenyltrimethylammonium** stimulates skeletal motor muscle end plates, **decamethonium** produces neuromuscular blockade, and **d-tubocurarine** blocks both the autonomic ganglia and the motor fiber end plates.

Among the agents cited, only *d*-tubocurarine is useful as a drug (skeletal muscle relaxant); the rest are useful only as research tools. Cholinesterase, found in liver and plasma, can hydrolyze other esters such as **succinylcholine** (a skeletal muscle relaxant). Cholinergic peripheral receptors are located on (1) postganglionic parasympathetic fibers, (2) postganglionic sympathetic fibers, (3) all autonomic ganglia, and (4) skeletal end plates.

In addition, cholinergic receptors are distributed extensively in the CNS and participate in diversified functions such as audition, vision, learning and memory, ingestive behaviors (thirst and hunger), thermoregulation, locomotor activity, diurnal rhythms, sleep, and sexual activity. Changes in cholinergic neurons have been observed in neurological syndromes such as catalepsy, stereotypy, and tremor and in psychiatric disorders such as schizophrenia. Furthermore, cholinergic neurons have been implicated in addiction to opiates and alcohol, and in physiological dependence and withdrawal syndromes. The role of acetylcholine in schizophrenia has been extensively studied. For example, anticholinergic drugs such as **atropine**, **benztropine**, and **trihexyphenidyl** result in an acute exacerbation of schizophrenic psychosis; they may also provoke toxic psychosis in

nonpsychotic patients, similar to paranoid schizophrenia. On the other hand, **cholinomimetic agents** such as **physostigmine** ameliorate schizophrenic symptoms.

### CHOLINERGIC (CHOLINOMIMETIC) RECEPTOR AGONISTS

**Methacholine, carbachol, and bethanechol** are all agents that mimic the effects of stimulation of cholinergic nerves.

The two currently used derivatives of acetylcholine are bethanechol (urecholine chloride) and carbachol (miostat). Unlike acetylcholine, both agents are resistant to hydrolysis by cholinesterase. Both agents are muscarinic agonists. The nicotinic action of carbachol is greater than that of acetylcholine, whereas bethanechol is devoid of nicotinic action. The cardiovascular actions of acetylcholine are vasodilation and negative chronotropic and inotropic effects. The cardiovascular effects of methacholine are more pronounced than those of acetylcholine, which in turn are greater than those of carbachol or bethanechol. The gastrointestinal effects (increase in tone, amplitude of contractions, and peristalsis) of bethanechol and carbachol are equal but greater than those of acetylcholine. The effects of carbachol and bethanechol on the urinary tract (consisting of ureteral peristalsis, contraction of the detrusor muscle of the urinary bladder, and an increase in voluntary voiding pressure) are equivalent and exceed those produced by acetylcholine.

The miotic effects of carbachol and bethanechol are greater than those of acetylcholine. Atropine is able to antagonize all cholinergic (muscarinic) effects produced by acetylcholine, methacholine, carbachol, and bethanechol. However, this antagonism is least evident with carbachol.

Bethanechol is of value in the management of postoperative abdominal distention, gastric atony or stasis, and urinary retention. Carbachol (0.25 to 3.00%) may be used for the long-term therapy of noncongestive **wide-angle glaucoma**.

Pilocarpine is a naturally occurring (active ingredient of poisonous mushrooms, *Amanita muscaria*) cholinomimetic agent possessing both muscarinic and nicotinic properties (stimulates autonomic ganglia). This agent causes miosis, reduces intraocular pressure, and is used in the treatment of wide-angle glaucoma. In addition, it may be applied topically in the eye in the form of a drug reservoir (**Ocusert**).

### ANTICHOLINESTERASE AGENTS

Anticholinesterases are drugs that inhibit or inactivate acetylcholinesterase, causing the accumulation of acetylcholine at the cholinergic receptors.

#### Structure of Acetylcholinesterase

The active site of acetylcholinesterase consists of an anionic site, which interacts with the quaternary group on the choline moiety of acetylcholine, and an esteratic site, which interacts with and hydrolyzes the ester grouping of acetylcholine. A serine hydroxyl group at the esteratic site becomes acetylated and is subsequently regenerated by interaction with water. The inhibition of acetylcholinesterase by drugs such as **physostigmine, neostigmine, or edrophonium** produces effects similar to those seen with the prolonged stimulation of cholinergic fibers. Anticholinesterases are classified as reversible and irreversible inhibitors.

### CLASSIFICATION OF CHOLINESTERASE INHIBITORS

The reversible inhibitors, which have a short to moderate duration of action, fall into two categories. Type one, exemplified by edrophonium, forms an ionic bond at the anionic site and a weak hydrogen bond at the esteratic site of acetylcholinesterase. Type two, exemplified by neostigmine, forms an ionic bond at the anionic site and a hydrolyzable covalent bond at the esteratic site. The irreversible inhibitors, exemplified by organophosphorus compounds (**diisopropyl fluorophosphate, parathion,**

**malathion**, and **diazinon**), have long durations of action and form a covalent bond with acetylcholinesterase, which is hydrolyzed very slowly and negligibly, but the inhibition may be overcome by cholinesterase activators such as pralidoxime.

Cholinesterase inhibitors may also be classified according to agents that possess tertiary nitrogens (e.g., **physostigmine** and most organophosphorus compounds) and those that contain quaternary nitrogens (e.g., **neostigmine**, **pyridostigmine**, and some organophosphorus compounds such as **echothiophate**). The following table summarizes the comparative properties of these agents.

Property	Physostigmine	Neostigmine
Oral absorption	Good	Poor
Passing across blood–brain barrier	Well	No
Stimulating nicotinic receptors (skeletal muscle)	Yes	Yes
Used to combat the CNS toxicity of numerous anticholinergic drugs	Yes	No

**Physostigmine (eserine sulfate)** causes miosis and spasm of accommodation; it also lowers intraocular pressure and hence can be used in the treatment of wide-angle glaucoma. As it is lipid soluble, it penetrates into the brain rapidly, raises the acetylcholine concentration and, in toxic amounts, may cause cholinergic CNS toxicity, which is characterized by restlessness, insomnia, tremors, confusion, ataxia, convulsions, respiratory depression, and circulatory collapse. These effects are reversed by **atropine**.

**Neostigmine**, which is unable to penetrate the blood–brain barrier, does not cause CNS toxicity. However, it may produce a dose-dependent and full range of muscarinic effects, characterized by miosis, blurring of vision, lacrimation, salivation, sweating, increased bronchial secretion, bronchoconstriction, bradycardia, hypotension, and urinary incontinence. Atropine is able to oppose these muscarinic effects. In addition, neostigmine, which has both a direct action as well as an indirect action that is mediated by acetylcholine on end-plate nicotinic receptors, may produce muscular fasciculation, muscular cramps, weakness, and even paralysis. These effects are not countered by atropine. Furthermore, neostigmine enhances gastric contraction and secretion. Neostigmine itself is metabolized by plasma acetylcholinesterase.

The therapeutic uses of neostigmine include the treatment of atony of the urinary bladder and postoperative abdominal distention. In addition, it antagonizes the action of **d-tubocurarine** and curariform drugs. Edrophonium, neostigmine, or pyridostigmine may be used to diagnose **myasthenia gravis**. Because edrophonium has the shortest duration of action, it is most often used for this purpose.

#### ANTIDOTE TO IRREVERSIBLE CHOLINESTERASE INHIBITORS

The irreversible cholinesterase inhibitors, such as DFP (**isofluorophate**), are used only for local application in the treatment of wide-angle glaucoma. Their pharmacological effects, which are similar to those produced by physostigmine, are intense and of long duration. As organophosphorus insecticides, they are of paramount importance in cases of accidental poisoning and suicidal and homicidal attempts. They produce a cholinergic crisis that must be treated by (1) decontaminating the patient, (2) supporting respiration, (3) blocking the muscarinic effects by atropine, and (4) reactivating the inhibited cholinesterase by treatment with **pralidoxime**.

#### CHOLINERGIC RECEPTOR BLOCKING AGENTS

Atropine and scopolamine, which are obtained from **belladonna alkaloids**, as well as other synthetic anticholinergic drugs, inhibit the actions of acetylcholine and cholinomimetic drugs at muscarinic receptors in smooth muscles, heart, and exocrine glands. In addition to these peripheral



effects, anticholinergic drugs, by blocking the acetylcholine receptor sites in the CNS, have pronounced CNS effects such as restlessness, irritability, excitement, and hallucinations. **Scopolamine**, on the other hand, depresses the CNS and, in therapeutic doses, produces fatigue, hypnosis, and amnesia. Therefore, it is used extensively in numerous medications, often in combination with antihistamines.

### DOSE-DEPENDENT EFFECTS OF ATROPINE

The pharmacological effects of atropine in general are dose dependent. For example, in small doses, atropine depresses sweating, elevates body temperature, decreases salivary and bronchial secretions, and relaxes bronchial smooth muscles. In somewhat larger doses (1 to 3 mg), it produces **mydriasis** (blockade of the iris sphincter muscle), **cycloplegia** (blockade of the ciliary muscle), and cardiovascular effects characterized by transient bradycardia (central vagal stimulation) and tachycardia (vagal blockade at the sinoatrial node). Lacking any significant effects on circulation, atropine is often used as a preanesthetic medication to depress bronchial secretion and prevent pronounced bradycardia during abdominal surgical procedures. In still larger doses, it depresses the tone and motility of the gastrointestinal tract, the tone of the urinary bladder, and gastric secretion. Therefore, the effective doses for use in acid-pepsin diseases are preceded by numerous side effects.

Atropine is absorbed orally and crosses the placental barrier, whereupon it causes fetal tachycardia. Atropine has been used to examine the functional integrity of the placenta. Atropine toxicity is characterized by dry mouth, burning sensation in the mouth, rapid pulse, mydriasis, blurred vision, photophobia, dry and flushed skin, restlessness, and excitement.

Physostigmine, given intravenously, counteracts both the peripheral and central side effects of atropine and other anticholinergic drugs such as **thioridazine** (neuroleptic), **imipramine** (antidepressant), and **benztropine** (antiparkinsonian medication).

### SYNTHETIC MUSCARINIC RECEPTOR ANTAGONISTS

The following are the various applications of synthetic muscarinic receptor antagonists.

#### Ophthalmology

- Homatropine: Produces mydriasis and cycloplegia
- Eucatropine: Produces only mydriasis

#### Preoperative Uses

- Atropine: Prevents excess salivation and bradycardia
- Scopolamine: Produces sedation and amnesia in obstetrics

#### Cardiology

- Atropine  
To reduce severe bradycardia in hyperactive carotid sinus reflex  
Diagnostically in Wolff–Parkinson–White syndrome, to restore the PRS complex to normal duration

#### Gastroenterology

- Propantheline, oxyphenonium, pirenzepine  
To diminish vagally mediated secretion of gastric juices and slow gastric emptying in peptic ulcer

To reduce diarrhea associated with dysenteries and diverticulitis

To reduce excess salivation associated with heavy metal poisoning or parkinsonism

## Neurology

- Trihexyphenidyl, benztropine: In parkinsonism and drug-induced pseudoparkinsonism
- Scopolamine: In vestibular disorders such as motion sickness

**Methantheline** and **propantheline** are synthetic derivatives that, in addition to their antimuscarinic effects, are ganglionic blocking agents and block the skeletal neuromuscular junction. Propantheline and **oxyphenonium** reduce gastric secretion and **pirenzepine**, in addition to reducing gastric secretion, also reduces gastric motility.

## CONTRAINDICATION TO ANTICHOLINERGIC AGENTS

Conditions that are contraindications to the use of atropine and related drugs are glaucoma and prostatic hypertrophy, in which they cause urinary retention.

## OTHER CNS ACTIONS OF GINSENG

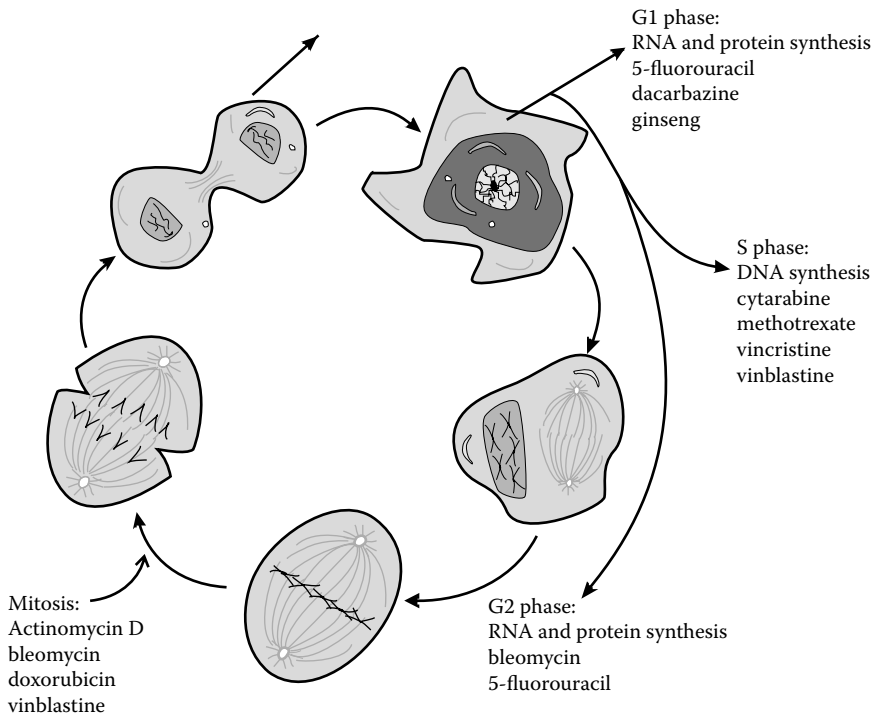
The following are the other CNS actions of ginseng.

- Ginseng protects **hippocampal neurons** from **ischemic damage**.
- Ginseng inhibits the uptake of **GABA, glutamate, norepinephrine, dopamine, and serotonin**.
- *Panax quinquefolius* extracts are agonists at **GABA A** receptors.
- Ginseng prolongs the **hexobarbital** sleeping time.
- **Ginseng** inhibits **calcium channels** on primary sensory neurons.

## ANTINEOPLASTIC AND IMMUNOMODULATORY EFFECTS OF GINSENG

The following are the antineoplastic and immunomodulatory effects of ginseng:

- **Ginseng** extracts exert antineoplastic effects and have cytotoxic properties and growth inhibitory properties *in vivo*.
- **Ginseng** arrests cell-cycle progression at the G1 stage and inhibits **cyclin-dependent kinase** activity (Figure 37.3).
- Ginseng enhances and activates both **polymerase** and **exonuclease activities of DNA polymerase  $\delta$** .
- **Ginseng** possesses some immunomodulatory properties, primarily associated with NK cell activity. Ginsenoside was shown to increase both humoral and **cell-mediated immune responses** (see Attele et al., 1999).



**FIGURE 37.3** The actions of antineoplastic agents on different phases of the cell cycle.

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# 38 Green, White, and Black Teas

## INTRODUCTION

Tea has the following properties:

- Antioxidant
- Antineoplastic agent
- Dental anticariogenic

Approximately 78% of the 2.5 million metric tons of tea leaves produced worldwide was used for the preparation of black tea, which is mainly consumed in Western nations, and about 20% was used for the preparation of green tea, which is mainly consumed in Asian countries and in some parts of North Africa. Green tea mainly contains polyphenols such as **flavanols (catechins)**, **flavanols**, **flavandiols**, and **phenolic acids**. These polyphenols account for about 25 to 30% of the solids in water extracts of green tea leaves. The major green tea catechins are **(-)-epigallocatechin-3-gallate (EGCG)**, **(-)-epigallocatechin (EGC)**, **(-)-epicatechin-3-gallate (ECG)**, **(-)-epicatechin (EC)**, and **(+)-catechin**. In the manufacture of black tea, the polyphenols in tea leaves undergo polyphenol oxidase-catalyzed oxidative polymerization, which leads to the formation of **bisflavanols**, **theaflavins**, **thearubigins**, and other oligomers in a process commonly known as *tea fermentation*. Theaflavins (about 1 to 2% of the solids in water extracts of black tea leaves) include **theaflavin**, **theaflavin-3-gallate**, **theaflavin-3'-gallate**, and **theaflavin-3,3'-digallate**, and these substances contribute to the characteristic color and taste of black tea. A substantial portion of the solids in water extracts of black tea leaves represents **thearubigens**, which are even more extensively oxidized and polymerized than the aflavins. The thearubigens have a wide range of molecular weights and are poorly characterized. Thus, it has been assumed that there are significant differences in antioxidant properties between green and black teas (see Hogg and Chakravarthy, 2004).

## ANTIOXIDANT PROPERTIES

Wei et al. (1999) compared the effects of different extractable fractions of green and black teas on scavenging hydrogen peroxide  $H_2O_2$ , and ultraviolet (UV)-irradiation-induced formation of **8-hydroxy 2'-deoxyguanosine (8-OHdG)** *in vitro*. Green and black teas were extracted by serial chloroform, ethyl acetate, and *n*-butanol, and divided into four subfractions designated as GT1 to GT4 for green tea and BT1 to BT4 for black tea, respectively. The total extracts from green and black teas exhibited a potent scavenging capacity of exogenous  $H_2O_2$  in a dose-dependent manner. It appeared that the total extracts from black tea scavenging  $H_2O_2$  were more potent than those from green tea. When tested individually, the potency of scavenging  $H_2O_2$  by green tea subtractions was  $GT2 > GT3 > GT1 > GT4$ , whereas the order of efficacy for black tea was  $BT > 2 > BT3 > BT4 > BT1$ . In addition, they demonstrated that total fractions of green and black teas substantially inhibited induction of 8-OHdG in calf thymus by all three portions of UV spectrum (UVA, B, and C). Consistent with the capacity of scavenging  $H_2O_2$ , the subfractions from black tea showed a greater inhibition of UV-induced 8-OHdG than those from green tea. At low concentrations, the order of potency of quenching of 8-OHdG by green tea subfractions was  $GT2 > GT3 > GT4 >$

GT1 and the efficacy of all subfractions became similar at high concentrations. All subfractions of the black tea except BT1 strongly inhibited UV-induced 8-OHdG and the order of potency was BT2 > BT3 > BT4 > BT1. Addition of EGCG, an ingredient of green tea extract, to low concentrations of green and black tea extracts substantially enhanced the scavenging of H<sub>2</sub>O<sub>2</sub> and quenching of 8-OHdG, suggesting the important role of EGCG in the antioxidant activities of tea extracts. The potent scavenging of oxygen species and blocking of UV-induced oxidative DNA damage may, at least in part, explain the mechanisms by which green teas inhibit **photocarcinogenesis**.

In recent years, evidence has been accumulated showing that tea has anticancer properties. Although the epidemiological data are lacking, the experimental studies have consistently demonstrated that drinking of tea, either black or green, substantially inhibited carcinogen- or UV-irradiation-induced animal tumors including skin, lung, stomach, colon, and breast cancer. In spite of exciting results in animal studies, the mechanisms of the anticarcinogenic action of tea have remained largely unclear. Some studies have attributed the inhibitory effects of green or black tea on UV-induced carcinogenesis to the antioxidant and free-radical scavenging activities of the teas, as numerous antioxidants, such as **ascorbic acid**, **α-tocopherol**, **β-carotene**, **selenium**, **butylated hydroxytoluene**, and a mixture of dietary antioxidants, have been reported to inhibit UV-induced skin carcinogenesis. Several **polyphenolic substances** in green and black teas have been shown to have antioxidant activities.

Oral administration of black or green tea was reported to have a similar inhibitory effect on **N-nitrosomethyl-benzylamine-induced esophageal tumorigenesis**, and oral administration of decaffeinated black or green tea was reported to have a similar strong inhibitory effect on **4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis**, as well as UV-induced skin carcinogenesis in mice. **(-)-Epigallocatechin-3-gallate** is considered a potent antioxidant and major anticarcinogenic component in tea. It has been hypothesized that blockage of UV-induced oxidative DNA damage may be the mechanisms by which tea inhibits UV-induced skin tumorigenesis. Several investigators reported that drinking of green tea significantly inhibited the formation of carcinogen-induced elevation of 8-OHdG in lung, liver, pancreas, and colon, and thereby reduced the toxicity and carcinogenicity in those organs.

In summary, aqueous extracts from green and black teas have potent antioxidant activities and exceptional quenching capacity of UV-induced oxidative DNA damage. These effects could be, at least in part, the mechanisms of action by which green and black teas counteract carcinogenic processes (Wei et al., 1999).

## THE EFFICACY OF TEA IN ATTENUATING SKIN CANCER

It is estimated that 1.2 million new cases of **skin cancer** occur each year in the U.S., and the majority of these are believed to result from heavy **exposure to UV light** from the sun. Although most of these skin cancers are curable **squamous cell carcinomas** and **basal cell carcinomas**, deaths do occur from these cancers and from more fatal sunlight-related **malignant melanomas**. In the past two decades, the skin cancers (both nonmelanoma and melanoma) have been increasing alarmingly. Thus, elucidation of etiologies of skin cancers and development of preventive strategy have been greatly advocated.

Tea is widely used as a beverage in Asian countries, including China, Japan, and India. Although **green tea** is also used in North America and Europe, **black tea** is a more popular beverage in the Western countries.

The topical application of cation of **EGCG**, a major **polyphenolic catechin** in green tea, inhibited **teleocindin-induced tumor promotion** in the skin of mice previously initiated with **7,12-dimethylbenz[a]anthracene**. In subsequent studies, it was found that oral administration of EGCG or tea fractions inhibited the carcinogen-induced tumors of various organs in animals, including the duodenum, stomach, lung, esophagus, and colon. Topical application of a green tea polyphenol fraction to CD-1 mice inhibited the tumor-initiating activities of **benzo[a]pyrene** and **7,12-dime-**

**thylbenz[a]anthracene** and the tumor-promoting activity of **tissue plasminogen activator** (TPA). The oral administration of a green tea polyphenol fraction or an aqueous extract of green and black teas to SKH-1 mice as their sole source of drinking fluid was shown to inhibit UVB-induced skin tumorigenesis. Tumors from animals treated with UVB together with green tea were much smaller in volume as compared to UVB-treated positive controls. In addition, green and black teas were found to inhibit the growth of established skin papillomas in mice.

## ANTICARIOGENIC EFFECTS OF TEA

### PATHOGENESIS OF DENTAL CARIES

Dental caries is a very common chronic disease, arising from interplay among oral flora, the teeth, and dietary factors. The major etiological players are thought to be the two a-hemolytic “mutans group” streptococci, *Streptococcus mutans* and *S. sobrinus*, although several other types of bacteria (notably **lactobacilli** and **actinomyces**) may also be involved. The nature of the condition does not readily lend itself to conventional antibacterial therapy (i.e., the use of an antibiotic active against the causal agent), and prevention is largely directed toward the individual host — e.g., diet, mechanical factors — and the public health measure of fluoridation of drinking water.

The pathogenesis of dental caries may involve three distinct processes: (1) adherence of the bacteria to the tooth, (2) formation of glycocalyx due to synthesis of a sticky glucan by the action of the bacterial enzyme **glucosyl transferase** on sucrose, and (3) accumulation of **biobilm** (plaque), within which there is continuing acid production by constituent bacteria (including **streptococci** and **lactobacilli**) able to metabolize carbohydrates at low pH values. This acid demineralizes an enamel.

The second and third of these steps depend on a supply of appropriate carbohydrate substrates, most favorably sucrose, in the mouth. The latter can become available either directly (sugar ingested in food or drink) or be derived from dietary starch by the action of bacterial or salivary amylases, or both. Of particular relevance in this context is the trapping of carbohydrates as or on food particles remaining in the mouth for considerable periods.

### POTENTIAL ANTICARIOGENIC ACTIONS OF TEA

Various components in green and black tea, the beverages made by infusing appropriately processed dried leaves of *Camellia sinensis*, notably simple catechins, have properties *in vitro* that suggest an anticariogenic activity. These include a direct bactericidal effect against *S. mutans* and *S. sobrinus*, prevention of bacterial adherence to teeth, inhibition of **glucosyl transferase**, thus limiting the biosynthesis of sticky glucan, and inhibition of human and bacterial **amylases**. Studies in animal models show that these *in vitro* effects can translate into caries prevention. A limited number of clinical trials in humans suggest that regular tea drinking may reduce the incidence and severity of caries. If substantiated, this could offer a very economical public health intervention (see Hamilton-Miller, 2001).

### BENEFITS OF WHITE TEA

White tea originated from the **Fujian province of China**. They go through very little processing and are therefore not oxidized in any of the ways that other teas are. The leaves are picked while the buds are still closed and covered by fine white hair. Once that is done they are dried in the sun. Because of the lack of processing, it is as close to its natural state as it can be. Its antioxidant content is very high, surpassing even that of green tea. These health benefits have made it one of the most sought-after teas. It can be more expensive than green tea because of the small time gap available for picking. It also consists of two leaves and a bud available for picking only when the time is right. The primary regions of white tea production are China and Japan; however, Darjeeling in India also produces some excellent white tea.

White tea is produced in a manner different from all other teas. The leaves come from special varietal bushes and are not processed but are dried in the sun. Only special leaves are selected; the ideal is two leaves wrapped around a new shoot. After drying the leaves are again selected and sorted by hand.

White tea is especially potent in that it has three times as much antioxidant polyphenols as green or black tea and has been shown to be 100% more effective in mopping up free radicals that cause skin to sag. Some of the world's top cosmetic companies are becoming very interested in white tea for skin creams, and the result is that high-grade white tea is becoming even more rare than before.

Researchers at Oregon State University's Linus Pauling Institute in Corvallis have discovered that white tea has even more **epigallocatechin gallate** than green tea has. Tea infused from the leaves of the **Camellia sinensis plant** is the world's most popular beverage after water. The darker the tea, the more processing it has undergone and, the more the processing, the more antioxidants are lost.

The antimutagenic activity of white tea was studied by Santana-Rios et al. (2001), who reported that four varieties of white tea, which represent the least processed form of tea, were shown to have marked antimutagenic activity in the *Salmonella* assay, particularly in the presence of S9. The most active of these teas, Exotica China white tea, was significantly more effective than Premium green tea (Dragonwell special grade) against 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) and four other heterocyclic amine mutagens, namely 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 2-amino-3,4,8-trimethyl-3*H*-imidazo[4,5-f]quinoxaline (4,8-DiMeIQx), 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), and 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-2). Mechanism studies were performed using rat liver S9 in assays for methoxyresorufin *O*-demethylase (MROD), a marker for the enzyme cytochrome P4501A2 that activates heterocyclic amines, as well as *Salmonella* assays with the direct-acting mutagen 2-hydroxyamino-3-methylimidazo[4,5-f]quinoline (*N*-hydroxy-IQ). White tea at low concentrations in the assay inhibited MROD activity and attenuated the mutagenic activity of *N*-hydroxy-IQ in the absence of S9. Nine of the major constituents found in green tea were also detected in white tea, including high levels of epigallocatechin-3-gallate (EGCG) and several other polyphenols. When these major constituents were mixed to produce "artificial" teas, according to their relative levels in white and green teas, the complete tea exhibited higher antimutagenic potency compared with the corresponding artificial tea. The results suggest that the greater inhibitory potency of white vs. green tea in the *Salmonella* assay might be related to the relative levels of the nine major constituents, perhaps acting synergistically with other (minor) constituents, to inhibit mutagen activation as well as scavenging the reactive intermediates.

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# 39 Herbal Plants and Tuberculosis

## ANTITUBERCULOSIS EFFICACY OF NATURAL PRODUCTS

The plants with the highest antimycobacterial activity include:

- *Allium sativum*
- *Borrichia frutescens*
- *Ferula communis*
- *Heracleum maximum*
- *Karwinskia humboldtiana*
- *Leucas vokensii*
- *Moneses uniflora*
- *Oplopanax horridus*
- *Salvia multicaulis*
- *Strobilanthus cusia*

Plant species from a wide range of families have been shown to have significant *in vitro* antimycobacterial activities, and a number of active plant-derived compounds belonging to various chemical classes have been isolated.

The infectious killer disease, **tuberculosis** (TB), is the leading cause of death worldwide from a single human pathogen, claiming more adult lives than diseases such as **acquired immunodeficiency syndrome** (AIDS), **malaria**, **diarrhea**, **leprosy**, and all other tropical diseases combined. The organism usually responsible, the **tubercle bacillus**, *Mycobacterium tuberculosis* (MT), was discovered by Robert Koch in 1882. However, *M. bovis*, which infects cattle, may also infect humans, and *M. africanum* is a cause of TB in West Africa. Furthermore, a number of normally nonpathogenic mycobacteria, especially *M. avium*, *M. intracellulare*, and *M. scrofulaceum*, cause opportunistic infectious disease in patients with AIDS. Pulmonary TB, the most common type of the disease, is usually acquired by inhalation of the bacillus from an infectious patient and causes irreversible lung destruction (Newton et al., 2000).

About one-third of the world population is currently infected with *M. tuberculosis*; 10% of those infected will develop clinical disease, particularly those who also have the human immunodeficiency virus (HIV) infection. With the discovery of effective antimycobacterial agents (including **ethambutol**, **isoniazid**, **pyrazinamide**, **rifampicin**, and **streptomycin**) and a reduction in poverty, there was a drastic decline in the number of TB cases, especially in developed nations. However, since the late 1980s, the number of cases of TB throughout the world has been increasing rapidly partly because of the emergence of multidrug-resistant *M. tuberculosis*. Thus, the TB problem requires urgent attention. Short-course anti-TB regimens initially using at least three first-line drugs (including **isoniazid**, **rifampicin**, and **pyrazinamide**) are effective. The major problems faced in tuberculosis control are poor infrastructures for diagnosis and drug supply and failure of patients to complete their course of drugs. This is usually due to poor supervision and medical care and, as a result, drug resistance develops. Second-line drugs (e.g., **capreomycin**, **kanamycin**, **cycloserine**, and **ethionamide**), which are often more toxic, have to be used in this case. Furthermore, drugs with broader ranges of activity are also required to target emerging pathogens, such as those



**TABLE 39.1**  
**Select Pharmacological Properties of Drugs Most Often Used in Treating Tuberculosis**

Drug	Properties
Isoniazid	Isoniazid is bactericidal for growing tubercle bacilli, is absorbed orally, and is metabolized by acetylation. It is a structural analogue of pyridoxine and may cause pyridoxine deficiency, peripheral neuritis and, in toxic doses, pyridoxine-responsive convulsions. Its mechanism of action is not known.
Streptomycin	Streptomycin is given intramuscularly. It exerts its effects only on extracellular tubercle bacilli. When combined with other drugs, it delays the emergence of streptomycin-resistant mutants. It is ototoxic and may cause deafness.
Rifampin	Rifampin is absorbed from the gastrointestinal tract and excreted mainly into bile. It binds to DNA-dependent RNA polymerase and inhibits RNA synthesis. In higher than therapeutic doses, rifampin may cause a flulike syndrome and thrombocytopenia.
Ethambutol	Ethambutol suppresses the growth of isoniazid- and streptomycin-resistant tubercle bacilli. The most important but not common side effects are optic neuritis, decreased visual acuity, and inability to perceive the color green.

*Note:* The treatment of mycobacterial infections has become an even more important and challenging problem because of the emergence of multiple-drug-resistant organisms and because of the acquired immunodeficiency syndrome (AIDS) pandemic, which has been associated with a marked increase in tuberculosis and infection caused by the *M. avium* complex. Because the microorganisms grow slowly and the diseases often are chronic, patient compliance, drug toxicity, and the development of microbial resistance present special therapeutic problems.

of the *M. avium* complex. Hence, there is a great need to search for and develop new, affordable, anti-TB agents.

A number of plant extracts and compounds have potent antimycobacterial properties. Examples of the species that appear to be among the most active include *Allium sativum*, *Borrichia frutescens*, *Ferula communis*, *Heracleum maximum*, *Karwinskia humboldtiana*, *Leucas volkensii*, *Moneses uniflora*, *Oplopanax horridus*, *Salvia multicaulis*, and *Strobilanthus cusia*. (Newton et al., 2000).

## MYCOBACTERIAL DISEASES

### TUBERCULOSIS

Tuberculosis is a necrotizing infection caused by *Mycobacterium tuberculosis* that primarily affects the lungs, but can also involve the kidneys, bones, lymph nodes, and meninges. Treatment takes two forms: chemoprophylaxis and active treatment. The recommended drug for chemoprophylaxis is isoniazid (300 mg/d for 1 year). In cases of active tuberculosis, the primary drugs are isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide. Secondary drugs consist of *p*-aminosalicylic acid, ethionamide, viomycin, kanamycin, capreomycin, and cycloserine. The drug combination is determined by the stage of the disease.

During the initial phase, isoniazid is always used in combination with one other drug — rifampin, streptomycin, or ethambutol. In advanced or cavitary pulmonary tuberculosis, often three drugs are used — isoniazid, rifampin, and streptomycin or ethambutol. The pharmacological properties of the most often used drugs are summarized in Table 39.1.

### LEPROSY

Leprosy (**Hansen's disease**) is a chronic granulomatous disease that attacks superficial tissues such as the skin, nasal mucosa, and peripheral nerves. There are two types of leprosy, lepromatous and tuberculoid. The **sulfones**, which are derivatives of **4,4'-diaminodiphenylsulfone**, are bacteriostatic.

**Dapsone** (DDS) and **sulfoxone sodium** are the most useful and effective agents currently available. They should be given in low doses initially, and then the dosage gradually increased until a full dose of 300 to 400 mg/week is reached. During this period, the patient must be monitored carefully. With adequate precautions and appropriate doses, sulfones may be used safely for years. Nevertheless, side effects such as anorexia, nervousness, insomnia, blurred vision, paresthesia, and peripheral neuropathy do occur. Hemolysis is common, especially in patients with **glucose 6-phosphate dehydrogenase deficiency**. A fatal exacerbation of **lepromatous leprosy** and an infectious mononucleosis-like syndrome occur rarely. **Clofazimine** (Lamprene) may be effective in patients who show resistance to the sulfones and may also dramatically reduce an exacerbation of leprosy. Red discoloration of the skin and eosinophilic enteritis have occurred following clofazimine therapy.

## OTHER DISEASES

Not all mycobacterial infections are caused by *M. tuberculosis* or *M. leprae*. These atypical mycobacteria require treatment with secondary medications as well as other chemotherapeutic agents. For example, *M. marinum* causes skin granulomas, and effective drugs in the treatment of infection are **rifampin** or **minocycline**. *Mycobacterium fortuitum* causes skin ulcers and the medications recommended for treatment are **ethambutol**, **cycloserine**, and **rifampin** in combination with **amikacin**.

## ANTIMICROBIAL ACTIVITY OF PLANTS

Screening plant extracts for antimycobacterial activity is usually carried out using mycobacteria cultured in various types of broth- and agar-based media. *Mycobacterium tuberculosis* has the disadvantages of being slow growing such that tests take several weeks and containment facilities are needed because it is a dangerous pathogen. Many investigators have therefore used nonpathogenic species of mycobacteria such as *M. avium*, *M. intracellulare*, and *M. kansasii*, which are slow growing similar to *M. tuberculosis*, and other species including *M. chelonae*, *M. fortuitum*, and *M. smegmatis*, which are faster growing, allowing tests to be completed in a few days (see Table 39.2 and Newton et al., 2000 for a few examples).

**TABLE 39.2**  
**Antimicrobial Activities of Natural Plants**

Plants	Origin	Part Used	Active Constituents/Comments
(Ranunculaceae) <i>Adhatoda Vasica</i> (Acanthaceae)	India	Leaf	<b>Bromhexine</b> <b>Ambroxol</b> (semisynthetic derivatives of alkaloid vasicine)
<i>Allium sativum</i> (Liliaceae)	—	Bulb	<b>Garlic</b> has been used in traditional Chinese and Egyptian medicine for many centuries; positive controls included <b>isoniazid</b> , <b>streptomycin</b> , <b>ethambutol</b> , <b>rifampicin</b>
<i>Alnus rubra</i> Bong. (Betulaceae)	Br C	Bark	<b>Isoniazid</b> was used as positive control
<i>Amyris elemifera</i> L. (Rutaceae)	—	—	<b>Taxalin</b> (Oxazole)
<i>Antirrhinum majus</i> (Scrophulariaceae)	—	—	Active
<i>Balsoamorhiza sagittata</i>	Br C	Root	Active
<i>Borrichia frutescens</i> L. (Asteraceae)	U.S.	Flower	Active
<i>Chrysoma pauciflosculosa</i> Michx. (Asteraceae)	U.S.	Root	Active
<i>Chrysanthum sinense</i> Sab. (Asteraceae)	China	—	Active

*Continued.*

**TABLE 39.2 (Continued)**  
**Antimicrobial Activities of Natural Plants**

Plants	Origin	Part Used	Active Constituents/Comments
<i>Ferula communis</i> (Umbelliferae)	Saudi Arabia	Rhizome	Active
<i>Lavandula angustifolia</i> Mill. (lavender) (Labiatae)	France	Flower	Active
<i>Leucas volkensii</i> Gurke (Labiatae)	Kenya	Aerial	Active
<i>Mammea Americana</i> (Guttiferaceae)	Puerto Rico	Leaf	Active
<i>Melia volkensii</i> Gurke (Meliaceae)	Kenya	Seeds	Active
<i>Piper cubeba</i> (Piperaceae)	Indonesia	—	Active
<i>Propolis</i>	Chile	Resin	Active
<i>Solanum sodomaeum</i> L. (Solanaceae)	Libya	Berry	Active

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# 40 Herbal Products for the Chemotherapy of Human Immunodeficiency Virus Infection

## INTRODUCTION

The **acquired immune deficiency syndrome** (AIDS) was first recognized in the U.S. in the summer of 1981 when the Centers for Disease Control and Prevention (CDC) reported the unexplained occurrence of *Pneumocystis carinii* pneumonia in five previously healthy homosexual men in Los Angeles and of **Kaposi's sarcoma** in 26 previously healthy homosexual men in New York and Los Angeles. Within months, the disease became recognized in male and female injection drug users (IDUs) and, soon thereafter, in **recipients of blood transfusions** and in **hemophiliacs**.

In 1983, human immunodeficiency virus (HIV) was isolated from a patient with **lymphadenopathy**, and by 1984 it was demonstrated clearly to be the causative agent of AIDS. The virus, which belongs to the **lentivirus subfamily** of the large family of **retroviruses** (Retroviridae), was formerly called *lymphadenopathy associated virus* (LAV), *human T-lymphotropic virus* (HTLV) *type III*, and *AIDS-associated retrovirus* (ARV).

At the present time, there are at least 14 compounds that have been formally approved for the treatment of **human immunodeficiency virus (HIV) infections**. There are six **nucleoside reverse transcriptase inhibitors** (NRTIs) that, after their intracellular conversion to the 5'-triphosphate form, are able to interfere as competitive inhibitors of the normal substrates (dNTPs). These are **zidovudine** (AZT), **didanosine** (ddI), **zalcitabine** (ddC), **stavudine** (d4T), **lamivudine** (3TC), and **abacavir** (ABC). There are three **nonnucleoside reverse transcriptase inhibitors** (NNRTIs) — **nevirapine**, **delavirdine**, and **efavirenz** — that, as such, directly interact with the reverse transcriptase at a nonsubstrate binding, allosteric site. There are five **HIV protease inhibitors** (PIs: **saquinavir**, **ritonavir**, **indinavir**, **nelfinavir**, and **amprenavir**) that block the cleavage of precursor to mature HIV proteins, thus impairing the infectivity of the virus particles produced in the presence of these inhibitors.

A number of products exist that are targeted at any of the successive events implicated in the replicative cycle of HIV: **virus entry**, **viral adsorption**, **virus–cell fusion**, **reverse (RNA → DNA) transcription**, **proviral DNA integration**, **viral (DNA → RNA) transcription** (transactivation), **viral (mRNA → protein) translation**, **virus release**, **viral assembly**, **budding**, and **maturation** (see Fauci et al., 1998; De Clercq, 2000).

## HERBAL PRODUCTS USED IN HIV THERAPY

The following are the herbal products used for chemotherapy of HIV infection:

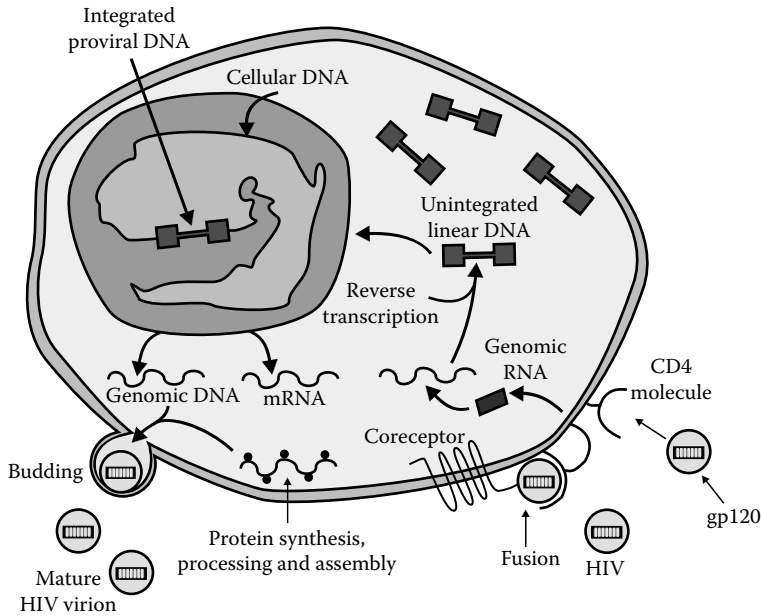
- **Blue-green algae:** **Cyanovirin-N**, an 11-kDA protein from *Cyanobacterium* (blue-green algae) irreversibly inactivates HIV and also aborts cell-to-cell fusion and transmission of HIV, due to its high-affinity interaction with gp120.
- **Seaweed:** Various sulfated polysaccharides extracted from seaweed (i.e., *Nothogenia fastigiata*, *Aghardhiella tenera*) inhibit the virus adsorption process.
- **Ingenol derivatives:** Ingenol derivatives may inhibit virus absorption at least in part through downregulation of CD4 molecules on the host cells.
- **Flavonoids:** Inhibition of virus adsorption by flavonoids such as (–) **epicatechin** and its 3-*O*-gallate has been attributed to an irreversible interaction with gp120 (although these compounds are also known as *reverse transcriptase inhibitors*).
- **Licorice root:** For the triterpene **glycyrrhizin** (extracted from the licorice root *Glycyrrhiza radix*) the mode of anti-HIV action may be attributed at least in part to interference with virus–cell binding.
- **Lectins:** The mannose-specific plant lectins from *Galanthus*, *Hippeastrum*, *Narcissus*, *Epipactis helleborine*, and *Listera ovata*, and the *N*-acetylglucosamine-specific lectin from *Urtica dioica* would primarily be targeted at the virus–cell fusion process.
- **Streptomyces spp:** The **siamycins**, **siamycin I** (BMY-29304), **siamycin II** (RP71955, BMY 29303), and NP-06 (FR901742), which are tricyclic 21-amino acid peptides have been isolated from *Streptomyces* spp.
- **Horseshoe crabs:** The **betulinic acid derivative** RPR 103611, and the peptides **tachyplesin** and **polyphemusin**, which are highly abundant in hemocyte debris of the horseshoe crabs *Tachyplesus tridentatus* and *Limulus polyphemus*.
- **Tropical rainforest tree and Malaysian tree:** A number of natural products have been reported to interact with reverse transcriptase, i.e., **baicalin**, **avarol**, **avarone**, **psychotrine**, **phloroglucinol derivatives** and, in particular, **calanolides** (from the tropical rainforest tree, *Calophyllum lanigerum*) and **inophyllums** (from the Malaysian tree, *Calophyllum inophyllum*).
- **Marine products:** The natural marine substance **illimaquinone** would be targeted at the RNase H function of the reverse transcriptase.
- **Tumeric:** **Curcumin** (**diferuloylmethane**, from tumeric, the roots/rhizomes of *Curcuma* spp).
- **Fungal products:** **Dicaffeoylquinic** and **dicaffeoyltaric acid**, **L-chicoric acid**, and a number of fungal metabolites (**equisetin**, **phomasetin**, **oteromycin**, and **integric acid**) have all been proposed as HIV-1 **integrase inhibitors** (see De Clercq, 2000).

## ETIOLOGICAL AGENT

The etiological agent of AIDS is HIV, which belongs to the family of human **retroviruses** and the subfamily of **lentiviruses**. Nononcogenic lentiviruses cause disease in other animal species, including sheep, horses, goats, cattle, cats, and monkeys. The four recognized human retroviruses belong to two distinct groups: the **human T lymphotropic viruses**, HTLV-I and HTLV-II, which are transforming retroviruses; and the **human immunodeficiency viruses**, HIV-1 and HIV-2, which are cytopathic viruses. The most common cause of HIV disease throughout the world, and certainly in the U.S., is HIV-1.

## LIFE CYCLE OF HIV

HIV is an RNA virus whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme **reverse transcriptase**. The life cycle of HIV begins with the high-affinity binding of the gp120 protein via a portion of its V1 region near the N terminus to its receptor on the host cell surface, the **CD4 molecule** (Figure 40.1).



**FIGURE 40.1** The life cycle of HIV.

The CD4 molecule is a **55-kDa protein** found predominantly on a subset of **T lymphocytes** that are responsible for helper or inducer function in the immune system. It is also expressed on the surface of monocytes/macrophages and dendritic/Langerhans cells. It has recently been demonstrated that the coreceptor that must be present together with the CD4 molecule for fusion and entry of T-cell-tropic strains of HIV-1 is a molecule termed **CXCR4**, whereas the coreceptor for macrophage-tropic strains of HIV-1 is the  **$\alpha$ -chemokine receptor CCR5**. Both receptors belong to the family of seven-transmembrane-domain G-protein-coupled cellular receptors. Following binding, fusion with the host cell membrane occurs via the gp41 molecule, and the HIV genomic RNA is uncoated and internalized into the target cell. The **reverse transcriptase enzyme**, which is contained in the infecting virion, then catalyzes the reverse transcription of the genomic RNA into double-stranded DNA. The DNA translocates to the nucleus, in which it is integrated randomly into the host cell chromosomes through the action of another virally encoded enzyme, **integrase**. This provirus may remain transcriptionally inactive (latent), or it may manifest varying levels of gene expression, up to active production of virus.

Cellular activation plays an important role in the life cycle of HIV and is critical to the pathogenesis of HIV disease. Following initial binding and internalization of virions into the target cell, incompletely reverse-transcribed DNA intermediates are labile in quiescent cells and will not integrate efficiently into the host cell genome unless cellular activation occurs shortly after infection. Furthermore, activation of the host cell is required for the initiation of transcription of the integrated proviral DNA into either genomic RNA or mRNA. In this regard, activation of HIV expression from the latent state depends on the interaction of a number of cellular and viral factors. Following transcription, HIV mRNA is translated into proteins that undergo modification through **glycosylation, myristylation, phosphorylation, and cleavage**. The viral core is formed by the assembly of HIV proteins, enzymes, and genomic RNA at the plasma membrane of the cells. Budding of the progeny virion occurs through the host cell membrane, where the core acquires its external envelope. Each point in the life cycle of HIV is a real or potential target for therapeutic intervention. Thus far, the reverse transcriptase and protease enzymes have proved to be susceptible to pharmacological disruption (Fauci et al., 1998).

## IMMUNOPHARMACOLOGY

The immune system defends the body against invading organisms, foreign antigens, and host cells that have become neoplastic. In addition, the immune system is an active participant in autoimmune diseases, hypersensitivity reactions, and transplant tissue rejections.

The ability of the immune system to discriminate between foreign molecules and antigenic sites of foreign cells, normal endogenous molecules, and cells of the host results in elimination of most diseases before an overt pathological condition is established. Moreover, after an infection or neoplasm becomes established and chemotherapy initiated, drugs kill only a fraction of the invading organisms or neoplastic cells, and a functional immune system is needed to eradicate the remaining organisms or cells. This ability to recognize foreign antigens allows destruction and removal of invading organisms by various effector mechanisms of the immune system. However, in autoimmune diseases, inappropriate immune responses against host cells (**self-antigens**) may occur. In addition, an overt response to an antigen may result in tissue-damage reactions known as **hypersensitivity responses**.

## IMMUNE SYSTEM COMPONENTS

The cells of the immune system are formed from **pluripotent stem cells** produced in the bone marrow. These stem cells undergo a sequence of cellular differentiations to form B lymphocytes, T lymphocytes, erythrocytes, polymorphonuclear leukocytes, monocytes, macrophages, and mast cells.

Lymphocytes are one of the primary cell types involved in the immune response. There are two general types of lymphocytes, B and T. Both are derived from bone marrow lymphoid stem cells, but T cells go through an additional maturation process in the thymus. Although the morphology of T cells and B cells is similar, the functions of these two types are distinct. After antigen exposure, B cells develop into **antibody-producing plasma cells**, whereas T cells are divided into functional subtypes that possess distinct cell surface antigens.

The other major participant in the immune response is the **bone-marrow-derived macrophage**. When circulating, it is referred to as a monocyte; however, when it migrates into the extravascular spaces, it is known as a macrophage. In comparison to unactivated lymphocytes, macrophages are larger and possess a greater cytoplasmic-to-nuclear ratio. The macrophage contains lysosomes filled with various catabolic enzymes. The macrophage membrane possesses digestive enzymes and receptors for binding complement components and the constant or Fc region of antibodies (**immunoglobulins**). The size and cytoplasmic contents are determined by the activation state. The primary functions of macrophages are **phagocytosis**, **antigen presentation**, and **cytokine production**. Phagocytic macrophages are distributed throughout many tissues and collectively are called the **reticuloendothelial system**. The generation of superoxide free radicals and digestive enzymes allows the macrophage to destroy other phagocytized organisms or molecules. This phagocytic process is also important in altering and cleaving large antigen molecules before presentation to T lymphocytes (**antigen processing**). The targets of anti-HIV therapy are shown in Table 40.1.

### Cells That Constitute the Reticuloendothelial Systems

Tissues	Cell Types
Liver	Kupffer cells
Brain	Microglial cells
Spleen	Macrophages
Lymph node	Macrophages
Lung	Aveolar macrophages

**TABLE 40.1**  
**The Targets and Compounds for Anti-HIV Therapy**

<b>Targets (within the HIV Replicative Cycle)</b>	<b>Compounds (Interacting with the Identified Target)</b>
Virus particles, infectivity, entry	Cyanovirin-N (Hypericin) Sulfated polysaccharides Ingenol derivatives
Virus adsorption	Flavonoids Glycyrrhizin (Mannose-specific plant lectins)
Virus-cell fusion	Mannose-specific plant lectins Siamycins Betulinic acids Polyphemusins
Reverse transcription	Baicalin Avarol, avarone, psychotrine, phloroglucinol derivatives Calanolides, Inophylliums Illimaquinone (Flavonoids)
Integration	Curcumin, dicaffeoylquinic acid, L-chicoric acid Equisetin (Hypericin) (Cyclosporins)
Transcription, transactivation	Flavonoids Melittin EM2487
Translation	Trichosantin, MAP30, GAP31, DAP30, DAP32
Assembly, secondary viral spread	Bellenamine Hypericin, pseudohyperion (Cyclosporins)

*Note:* AIDS is caused by HIV, which impairs both cellular and humoral immune functions, and this results in increased susceptibility to opportunistic infection and certain malignancies. The medical aspects of HIV infection include AIDS-related complex (weight loss, chronic diarrhea, fever, thrush, herpes zoster, fatigue), opportunistic infections and cancer, end-stage renal disease, blindness (cytomegalovirus), HIV encephalopathy, and dementia. The psychological aspects of HIV infection include major depression, regression, and suicidal impulses, delirium, substance abuse, antisocial personality, and bereavement.

## CYANOVIRIN-N

Cyanovirin-N is an 11-kDa protein that has been isolated from the **cyanobacterium (blue-green algae) *Nostoc ellipsosporum***. At low nanomolar concentrations, cyanovirin-N irreversibly inactivates both laboratory strains and primary isolates of HIV-1 and HIV-2. In addition, cyanovirin-N aborts cell-to-cell fusion and transmission of HIV-1 infection. The antiviral activity of cyanovirin-N has been attributed to a tight binding of the compound to the viral envelope glycoprotein gp120, which must result in reduced infectivity of the virus as well as reduced capacity of virus-infected cells to fuse with uninfected cells.



## SULFATED POLYSACCHARIDES

**Sulfated polysaccharides**, such as **dextran sulfate**, **pentosan polysulfate**, and **heparin**, as well as sulfated polysaccharides extracted from **sea algae**, have long been recognized as effective anti-HIV agents. The sulfated galactan from the **red seaweed *Aghardhiella tenera*** inhibits HIV-1 and HIV-2 infection at a concentration that is tenfold higher than the  $IC_{50}$  (50% inhibitory concentration) required for a dextran sulfate to inhibit these viruses ( $IC_{50}$ : 0.5 and 0.05  $\mu\text{g/ml}$  for HIV-1 and HIV-2, respectively). The **sulfated xylomannan** from the **red seaweed *Nothogenia fastigiata*** is only weakly active against HIV-1 and HIV-2 ( $IC_{50}$ :  $\sim 10$   $\mu\text{g/ml}$ ), but much more so against other enveloped viruses, such as herpes **simplex virus (HSV)**, **human cytomegalovirus (HCMV)**, **respiratory syncytial virus (RSV)**, and **influenza A virus** ( $IC_{50}$ : 0.2  $\mu\text{g/ml}$  for the last). Antivirally active polysaccharides have also been isolated from the **marine brown alga *Fucus vesiculosus***. The sulfated polysaccharides extracted from the marine *Pseudomonas* and the marine plant ***Dinoflagellata*** inhibit HIV-1 and HIV-2 infection at a similar level ( $IC_{50}$ :  $\sim 1$   $\mu\text{g/ml}$ ) as dextran sulfate and, again, inhibit other enveloped viruses (HSV-1, influenza A and B virus, RSV, and measles virus).

Sulfated polysaccharides are notorious for their anticoagulant properties but, apparently, the anti-HIV activity of sulfated polysaccharides can be dissociated from their antithrombin activity. They invariably show activity against various enveloped viruses other than HIV, particularly HSV, HCMV, influenza A, RSV, and **vesicular stomatitis virus (VSV)**. They block the binding (adsorption) of these viruses to the cells, which, in the case of HIV, is due to a direct interaction of the sulfated polysaccharides with the V3 loop of the viral envelope gp120. As a consequence, the sulfated polysaccharides also block **syncytium formation** (fusion) between HIV-infected cells (expressing the **gp120 glycoprotein** on their surface) and uninfected cells (expressing the **CD4 receptor** for gp120). All retro- and myxoviruses that are sensitive to the sulfated polysaccharides share a tripeptide segment (Phe-Leu-Gly), which may be involved either directly or indirectly in the inhibitory effects of the compounds on virus–cell binding and fusion.

Sulfated polysaccharides are very poorly absorbed following oral administration, and efficacy upon parenteral administration has not been demonstrated. Their greatest potential may well reside in their topical application, i.e., as a gel formulation in the prevention of **sexual HIV**, and HSV, transmission.

## INGENOL DERIVATIVES

Ingenol derivatives extracted from **kansui**, the **dried roots of *Euphorbia kansui***, have various biological activities, including anti-HIV activity, due to inhibition of virus adsorption to the host cells. Among the ingenol derivatives, **13-hydroxyingenol-3-(2,3-dimethylbutanoate)-13-dodecanoate (RD4-2138)** proved to be exquisitely potent ( $IC_{50}$ : 0.07 nM) against HIV-1 (IIIB strain) in MT-4 cells and selective (50% cytotoxic concentration, or  $CC_{50}$ : 8.7  $\mu\text{M}$ ). The mechanism of anti-HIV action of RD4-2138 could be attributed at least in part to downregulation of the CD4 receptor for gp120, thus accounting for the inhibitory activity of this class of compounds on virus adsorption.

Although ingenol derivatives are highly potent inhibitors of HIV-1 replication in acutely infected cells, it was recently shown that some ingenol derivatives enhance HIV-1 replication in chronically infected cells, whether or not through activation of the nuclear factor  $\kappa\text{B}$  (NF- $\kappa\text{B}$ ) and protein kinase C (PKC).

## FLAVONOIDS

Of a series of flavonoids that were evaluated for their anti-HIV potential, (–)-**epicatechin** and (–)-**epicatechin-3-O-gallate** (from *Detarium microcarpum*) were found to block HIV infection through an irreversible interaction with the glycoprotein gp120:  $IC_{50}$  for HIV replication in C8166 cells: 2 and 1  $\mu\text{g/ml}$ , respectively, as compared to a  $CC_{50}$  of  $>100$   $\mu\text{g/ml}$ . (–)-Epicatechin gallate and

(-)-epigallocatechin gallate, two components from the **tea plant *Camelliasinensis***, were previously described as inhibitors of reverse transcriptase and cellular RNA and DNA polymerases. They may thus be able to interact at multiple targets of the HIV replicative cycle.

The flavonoid **crysin** and **benzothiophenes** have been shown to inhibit **casein kinase II (CKII)**, a cellular protein that may regulate HIV-1 transcription by phosphorylating (other) cellular proteins involved in the HIV-1 transcription transactivation process. This mechanism of action is independent of the **nuclear factor  $\kappa$ B-driven transcription pathway**. Thus, flavonoids interfere with HIV-1 transcription and hence prevent HIV expression in latently infected cells. Their specificity and usefulness as HIV transcription inhibitors remain to be assessed.

## GLYCYRRHIZIN

Glycyrrhizin, from **licorice root (*Glycyrrhiza radix*)**, has been known for some time as an antiviral agent; its  $IC_{50}$  for HIV-1(III<sub>B</sub>) in MT-4 cells is 0.15 mM. The mechanism of action of glycyrrhizin may at least partially be attributed to an interference with virus–cell binding, although the site of interaction of glycyrrhizin (at the envelope glycoprotein) has not been further characterized.

## MANNOSE-SPECIFIC PLANT LECTINS

A number of **mannose-specific agglutinines (lectins)** from *Galanthus nivalis*, Hippeastrum hybrid, *Narcissus pseudonarcissus*, *Listera ovata*, *Cymbidium hybrid*, *Epipactis helleborine*, and the ***N-acetylglucosamine-specific*** lectin from *Urtica dioica* have been found to inhibit HIV-1 and HIV-2 infection at similar concentrations as dextran sulfate ( $IC_{50}$ : 0.2 to 0.6  $\mu$ g/ml), or even lower ( $IC_{50}$ : 0.04 to 0.08  $\mu$ g/ml). Akin to sulfated polysaccharides, the plant lectins also exhibit activity against various enveloped viruses other than HIV, i.e., HSV-1, HSV-2, CMV, RSV, and influenza virus. Plant lectins would primarily interfere with the virus–cell fusion process. Their precise mode of action remains to be resolved.

## SIAMYCINS

Three varieties of siamycin, from *Streptomyces*, have been described: **siamycin II** (RP 71955, BMY 29303), NP-06 (FR 901724), and **siamycin I** (BMY-29304). They differ from one another only at position 4 (Val or Ile) or 17 (Val or Ile), which should not make much of a difference in terms of conformational or functional properties. The siamycins have been found to inhibit HIV infection *in vitro*; they exert a strong inhibitory effect on syncytium formation whereas only weakly inhibiting virus–cell binding. The most likely target for the mode of action of siamycins is the HIV envelope glycoprotein gp41. In fact, 33% sequence identity was observed between siamycin II and residues 608 to 628 of gp41 (amino acid numbering for the gp160 precursor). This sequence is part of the **ectodomain of gp41** (residues 527 to 655). Siamycins can be assumed to interfere with the **fusogenic activity of gp41**. They may do so by various mechanisms: for example, through direct binding to the hydrophobic gp41 fusion domain, through inhibition of the anchoring of gp41 in the cellular plasma membrane, or through induction of conformational alterations in gp41. The exact mechanism of action of siamycins remains to be resolved and so are their clinical potential and pharmacokinetics.

## BETULINIC ACIDS

**Betulinic acid** and **platanic acid** are **triterpenoids** isolated from *Syzygium claviflorum*. They exhibit inhibitory activity against HIV-1 replication in H9 lymphocyte cells at an  $IC_{50}$  of 1.4 and 6.5  $\mu$ M, respectively (selectivity index: 9.3 and 14, respectively). Hydrogenation of betulinic acid

yielded **dihydrobetulinic acid**, which showed an  $IC_{50}$  of 0.9  $\mu$ M and a selectivity index of 14. Introduction of a **3,3-dimethylsuccinyl group** at the C3 hydroxyl group of betulinic acid and dihydrobetulinic acid significantly increased the anti-HIV activity of betulinic acid and dihydrobetulinic acid ( $IC_{50}$ : < 0.35 nM; selectivity index > 20,000 and > 14,000, respectively). This is a remarkably high potency and selectivity, which leaves one wondering about the mechanism underlying the anti-HIV activity of 3-O-(3',3'-dimethylsuccinyl)betulinic acid and dihydrobetulinic acid.

The betulinic acid derivative RPR 103611 blocks HIV infection at an  $IC_{50}$  of about 10 nM, through inhibition of a postbinding, envelope-dependent step involved in the fusion of the virus with the cell membrane. The target for the anti-HIV action of RPR 103611 is the HIV-1 glycoprotein gp41. HIV resistance to RPR 103611 is associated with amino acid substitutions in positions 22 (Arg  $\rightarrow$  Ala) and 84 (Ile  $\rightarrow$  Ser) of gp41. RPR 103611 has so far remained the only small-molecular-weight, nonpeptidic agent blocking HIV-1 entry by affecting gp41. It can be considered an attractive lead compound for the design and development of HIV-cell fusion inhibitors.

### POLYPHEMUSINS

The polypeptides **tachyplexins** and **polyphemusins** are highly abundant in hemocyte debris of the **horseshoe crabs** *Tachypleus tridentatus* and *Limulus polyphemus*. An analogue of one of these polypeptides, T22 or [Tyr-5,12,Lys-7]polyphemusin II, a synthetic peptide that consists of 18 amino acid residues was found to inhibit HIV infection at an  $IC_{50}$  of 8 ng/ml ( $CC_{50}$ : 54  $\mu$ g/ml). A postbinding process, probably corresponding to virus-cell fusion, has been suggested as the target for the anti-HIV action of T22. Structure-activity relationship studies have pointed to the importance of the arginine residues in the anti-HIV activity of T22 and, in further studies, the compound was shown to act as a specific antagonist of CXCR4, the coreceptor used by T-tropic (X4) HIV-1 strains to enter the cells. This antagonism toward the CXCR4 coreceptor can be attributed to the polycationic (polyargininic) character of T22. New T22 derivatives with lower cytotoxicity have been synthesized and, one of these T22 derivatives, T134, was shown to block HIV-1 infection with a higher selectivity index (33,889 as compared with 645) than T22.

### BAICALIN

**Baicalin monohydrate** (TJN-151) is a flavonoid (**5,6,7-trihydroxyflavone-7-O-b-D-glucopyranoside uronic acid monohydrate**), from *Scutellariae radix*, that has been reported to inhibit HIV-1 replication in peripheral blood mononuclear cells (PBMC) at an  $IC_{50}$  of 0.5  $\mu$ g/ml. Baicalin also inhibits **HIV-1 reverse transcriptase**, but not human **DNA polymerases  $\alpha$  and  $\gamma$**  (DNA polymerase  $\beta$  being slightly inhibited), such that it was tempting to attribute the anti-HIV-1 effect of baicalin, even partly, to inhibition of HIV-1 reverse transcriptase. No inhibition of virus adsorption was noted, which contrasts to the anti-HIV activity of other flavonoids that have been claimed to inhibit HIV adsorption through an (irreversible) interaction with the glycoprotein gp120.

### AVAROL, AVARONE, PSYCHOTRINE, AND PHLOROGLUCINOL DERIVATIVES (i.e., MALLOTOJAPONIN)

Avarol and avarone derivatives (from the **Red Sea sponge** *Dysidea cinerea*), the alkaloids **psychotrine** and **O-methylpsychotrine** (from **ipecacac**, the dried rhizome and root of *Cephaelis ipecacuanha*), and phloroglucinol derivatives such as **mallotojaponin**, from the pericarps of *Mallotus japonicus*, have all been reported to inhibit the reverse transcriptase activity of HIV-1, noncompetitively with respect to the natural substrate (dNTP). In neither case was the anti-HIV-1 activity determined in cell culture, so it is not clear whether any of these compounds is really an effective

inhibitor of HIV replication, and, if so, whether they inhibit HIV replication through an inhibitory effect on HIV-1 reverse transcriptase.

## CALANOLIDES AND INOPHYLLUMS

The calanolides and inophyllums represent novel HIV-inhibitory coumarin derivatives, isolated from the **tropical rainforest tree, *Calophyllum lanigerum***, and the **Malaysian tree, *Calophyllum inophyllum***, respectively. Both compounds were found to inhibit HIV-1 replication at an IC<sub>50</sub> of approximately 0.1 and 1  $\mu$ M. These compounds can be considered NNRTIs, as they are primarily active against HIV-1 reverse transcriptase, but differ from the classical (synthetic) NNRTIs in their HIV sensitivity/resistance profile. Several structural analogs of (+)-calanolide A have been prepared. Two isomers of **calanolide A**, **(-)-calanolide B (costatolide)** and **(-)-dihydrocalanolide B (dihydrocostatolide)**, possess antiviral properties similar to those of calanolide A. The calanolide analogs exhibit tenfold enhanced antiviral activity against drug-resistant viruses that bear one of the most prevalent NNRTI-resistance reverse transcriptase mutations (Y181C); in turn, the calanolide analogs lead to the selection of drug-resistant virus strains carrying the T1391, L1001, Y188H, or L187F mutations in their reverse transcriptase. The calanolide isomers represent a novel and distinct subgroup of the NNRTI family; they should be further evaluated for their therapeutic potential in combination with other anti-HIV agents.

## ILLIMAQUINONE

Illimaquinone, such as **avarone** and **avarol** isolated from a Red Sea sponge, i.e., *Smenospongia*, has been reported to inhibit the **RNase H activity** associated with the HIV-1 reverse transcriptase at a concentration of 5 to 10  $\mu$ g/ml, whereas it was not active against the **RNA-dependent DNA polymerase (RDDP)** and **DNA-dependent DNA polymerase (DDDP)** activities of the enzyme at a concentration of 50  $\mu$ g/ml.

## CURCUMIN, CURCUMIN ANALOGS, DICAFFEYOYLQUINIC ACID, AND L-CHICORIC ACID

**Curcumin** corresponds to the yellow pigment in **turmeric (*Curcuma longa*)** that is widely used as a spice, food coloring (**curry**), and preservative. Curcumin has been reported to inhibit **HIV-1 integrase** at an IC<sub>50</sub> (for strand transfer) of 40  $\mu$ M. **Dicaffeoylquinic acids** inhibit HIV-1 integrase at submicromolar concentrations: molecular modeling of these ligands with the core catalytic domain of integrase indicate that the most potent inhibitors fill a groove within the catalytic site and interact with the integrase in an energetically favorable fashion. The **dicaffeoylquinic acids** and **L-chicoric acid** were reported to inhibit HIV-1 integrase at concentrations ranging from 0.06 to 0.66  $\mu$ g/ml and HIV-1 replication in cell cultures at 1 to 4  $\mu$ g/ml. Within the HIV-1 integrase different activities can be discerned, i.e., 3'-end processing and strand transfer; curcumin analogs such as **dicaffeolymethane** and **rosmarinic acid** inhibit both activities of integrase with IC<sub>50</sub> values below 10  $\mu$ M.

In follow-up studies, dicaffeoylquinic acids (DCQAs) and dicaffeoyltartaric acids (DCTAs) were found to inhibit HIV-1 integrase at concentrations between 0.15 and 0.84  $\mu$ M, and HIV replication at concentrations between 2 and 12  $\mu$ M; no inhibition of gp120 binding to CD4 was noted at concentrations up to 80  $\mu$ M. Similarly, no inhibition of reverse transcription or RNase H was noted, and it was concluded that the DCQAs and DCTAs act as specific integrase inhibitors and that their activity against integrase is consistent with their observed anti-HIV activity in cell cultures. That the integrase would be an "excellent" target for combination chemotherapy of HIV

infection was further ascertained by combination experiments in which l-chicoric acid, the putative integrase inhibitor, was combined with a protease inhibitor (AG1350) and zidovudine.

## EQUISETIN

The screening of natural product extracts has recently yielded a few more HIV integrase inhibitors: equisetin, from the fungus *Fusarium heterosporum*, the enantiomeric homologue of equisetin from Phoma species, and two additional analogues, a novel decalin derivative, **integric acid**, and **oteromycin**. Equisetin inhibits 3'-end processing and strand transfer at an  $IC_{50}$  of approximately 10  $\mu M$ . Equisetin and related compounds also inhibit disintegration catalyzed by either full-length enzyme or the truncated integrase core domain (amino acids 50 to 212). These compounds also inhibit strand transfer reactions catalyzed by stable complexes assembled *in vitro* and integration reactions catalyzed by preintegration complexes isolated from HIV-1-infected cells, but whether these fungal metabolites also inhibit HIV-1 replication within the cells, whether or not due to inhibition of integration, remains to be determined.

## MELITTIN

**Melittin**, a 26-amino acid **amphipathic  $\alpha$ -helical peptide** that occurs in bee venom, has recently been found capable of suppressing HIV-1 gene expression. Melittin inhibits HIV-1 infection in both acutely and persistently infected t-lymphoma (KE37/1) and fibroblastoid ( $LC_5$ ) cells at an  $IC_{50}$  of 0.5 to 1.5  $\mu M$ ; this effect is apparently mediated by a direct suppressive action on the HIV long terminal repeat (LTR). Antimicrobial peptides such as **melittin (honeybees)**, **cecropin (moths)**, and **magainin (frogs)** may thus inhibit cell-associated HIV-1 production at the transcription level.

## TRICHOSANTIN, MAP30, GAP31, DAP31, AND DAP32

A series of proteins, i.e.,  **$\alpha$ -trichosanthin** (a-TCS) isolated from the **root tubers of *Trichosanthes kirilowii***, MAP30 isolated from the seeds and fruits of the **bitter melon *Momordica charantia***, GAP31 from **Euphorbiaceae himalaya seeds (*Gelonium multiflorum*)**, and DAP30 and DAP32 from **carnation leaves (*Dianthus caryophyllus*)**, have been described to inhibit HIV infection, allegedly, at noncytotoxic concentrations. These compounds (also referred to as RIPs for "**ribo-some-inactivating proteins**") are known to abrogate eukaryotic protein synthesis through inactivation of the ribosomes. RIPs inactivate ribosomes by cleaving the adenine *N*-glycosidic bond at position 4324 of 28S rRNA. In addition to this RNA *N*-glycosidase activity, RIPs, such as MAP30, also act as **DNA glycosylase/apurinic (ap)lyases**, thus explaining the apparent ability of MAP to inhibit HIV-1 integrase and irreversibly relax supercoiled DNA.

## BELLENAMINE

**Bellenamine, (R)-3,6-diamino-N-(aminomethyl)hexanamide** is a (very) small-molecular-weight (MW: 174) antibiotic produced by *Streptomyces nashvillensis*. It has only weak antibacterial activity but inhibits HIV-1 infection at an  $IC_{50}$  of 0.62  $\mu g/ml$  (3.6  $\mu M$ ). With a  $CC_{50}$  of > 2 mg/ml (11.5 mM), the selectivity index of bellenamine can be estimated at well above 2000. Similarl to the well-established glycosylation inhibitors **castanospermine** and **1-deoxynojirimycin**, bellenamine inhibits the secondary spread of HIV, although, unlike the glycosylation inhibitors, bellenamine had no apparent inhibitory effect on the glycosylation process. Therefore, its antiviral mechanism remains to be elucidated.

### HYPERICIN AND PSEUDOHYPERICIN

The aromatic polycyclic diones hypericin and pseudohypericin, which are present in plants of the family *Hypericum* (**St. John's wort**), have been accredited with anti-HIV activity for more than a decade. They possess the capacity to inactivate HIV virions directly as well as to interfere with their assembly or processing. Hypericin has received continued interest as a potential therapeutic agent and was more recently found to interact with preintegration complexes (PICs) and thus affect the **proviral DNA integration process** (De Clercq, 2000).



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# 41 Honey: The Nectar of Life

Nature, to be commanded, must be obeyed.

**Francis Bacon**

Honey is the flower transformed, the landscape distilled. From the rich chestnut-blossom honey of Italy to the pale gold eucalyptus and acacia honeys of the rugged California coast, every variety of honey is redolent of a distinct place.

**Stephanie Rosenbaum**

The methodical waltz of the honeybee... from flower to flower he dances, producing a treasure disguised in a near heavenly sweetness. This dance holds within it a secret. The secrets he keeps few discover. There is more to his beautiful concoction than he reveals. His golden secret hidden in plain view, all over the world. He gathers his ingredients with care. The bee suckles nectar from flowers and trees. He then carefully blends it with select pollens creating a mixture so unique and powerful in its ability to heal that modern medicine has yet to discover its equal. As its golden threads drip from the hive, man watches the sunlight reflect back at him from the sugars nestled within this viscous treasure. Does man realize as the grasps the brittle comb that he holds in his hand nature's gift of healing?

**Cynthia Hagen**

## INTRODUCTION

Honey has long been touted as an all-purpose panacea, able to soothe sore throats, nourish convalescents, prevent infections, and give instant energy. In the days before widespread refrigeration, honey's antibacterial properties made it indispensable, both as a preservative and an infection fighter. In the ancient world, a general killed in battle far from home would be submerged in a coffin filled with honey. Sealed, the coffin could then be transported back for burial without fear of putrefaction along the way. **St. Ambrose**, bishop of Milan from 347 to 397, was established as the patron saint of beekeepers.

In Jewish communities, honey had become an important component of festive occasions. **Rosh Hashanah**, the Jewish New Year, was celebrated with apples dipped in honey, symbolizing a wish for a sweet year to come. Round loaves of **challah** (a braided yeast bread enriched with eggs) were spread with honey, and the meal ended with slices of spiced honey cake and honey-sweetened fruit compotes. On the first day of a boy's enrollment in **chadar**, or religious school, letters from the **Talmud** (the collection of Jewish laws and traditions) would be written in honey on a slate and licked off by the new boys so as to make their learning sweet (Rosenbaum, 2002).

## WONDER OF HONEY

Although many people recognize the nutritional properties of honey, not many realize that there is much more to honey than meets the eye. One of nature's oldest medicines, scientists are discovering that honey has unique healing powers.



Honey is not only just a natural sugar substitute, but also certain strains of honey can actually help to heal wounds and kill bacteria. Honey has been used to prevent and cure illness for centuries. The Chinese used it to neutralize toxins and relieve pain, treat stomach ulcers, high blood pressure, and constipation. It is also perfect for dabbing onto burns and wounds to help heal the tissue.

Not all honeys are equal in their goodness. New Zealand **Manuka honey** is one of the best, as it is harvested from native **tea trees**, a natural antibacterial agent in itself.

## CURATIVE PROPERTIES OF HONEY

Honey gathered from different flowers and from different parts of the world has different efficacies in treating different maladies unique to that region. Only a few of these remedies will be mentioned here:

- Honey has potent antioxidant actions.
- It enhances memory.
- It heals wounds and burns.
- It is effective in peptic ulcer.
- It is effective in the treatment of gastroenteritis.
- It is effective in treating inflammatory bowel disease.
- It is effective in preventing carcinogenesis.
- It is effective in treating herpes simplex lesions.
- It is effective in the treatment of bullous keropathy.

## COMMON KINDS OF HONEY

It has long been known that honey differs not only in color, aroma, and flavor, but also in chemical, biological, and curative properties. The chemical composition of honey depends in a certain measure on the plants from which they are collected and even on the soil on which the plants grow:

- **Alfalfa** (*Medicago sativa* L.) **honey** is collected from the lilac or purple blossoms of cultivated alfalfa.
- **Angelica** (*Archangelica officinalis* Hoffm.) **honey** is collected from the flowers of angelica or archangel, which is widespread in the Soviet Union. This honey has a pleasant aroma and flavor.
- **Apple** (*Pyrus malus* L.) **honey** is pale yellow with an exceptionally pleasant aroma and a delicate sweetness.
- **Asclepias** (*Asclepias syriaca* L.–*A. cornuti* Des.) **honey** is produced from the fragrant nectar of this valuable honey plant.
- **Barberry** (*Berberis vulgaris* L.) **honey** is golden yellow with a pleasant aroma and delicate sweet flavor.
- **Bashkir** (*Ufa*) **linden honey** is colorless and granulates into a white coarse-grained mass.
- **Bilberry** (*Vaccinium myrtillus* L.) **honey** is reddish and possesses an excellent aroma and pleasant flavor.
- **Blackberry** (*Rubus caesius* L.) **honey** is water-white and has a pleasant flavor.
- **Black locust** (*Robinia pseudoacacia* L.) **honey** is one the best kinds of honey.
- **Blueweed** (*Echium ulgare* L.) **honey** ranks among the best kinds; it is light amber in color and has a pleasant aroma and very fine flavor.
- **Borage** (*Borago officinalis* L.) **honey** comes from the nectar of the beautiful big blue flowers of borage, cultivated as a valuable honey and medicinal plant.

- **Buckwheat** (*Fagopyrum esculentum*) **honey** is dark, ranging from dark yellow with a reddish tint to dark brown. In contrast to other types of honey, it has a peculiar aroma and specific flavor.
- **Burdock** (*Lappa tamentosa* Lam. and *Lappa major* Gaertn.) **honey** is of a dark olive color and has a sharp spicy aroma and a high viscosity.
- **Carrot** (*Daucus carota* L.) **honey** is dark yellow and pleasantly aromatic. It is made from the nectar of the fragrant white flowers of the biennial umbelliferous carrot.
- **Chestnut** (*Castanea sativa* L.) **honey** is dark and has a faint aroma and an unpleasant flavor.
- **Citrus honey**, one of the best kinds, has an exquisite aroma, similar to that of blossoming oranges, lemons, and tangerines, and an excellent flavor.
- **Colza** (*Barbarea vulgaris* R. Br.) **honey** is greenish yellow, with a faint aroma and good flavor.
- **Coriander** (*Coriandrum sativum* L.) **honey** has a pungent aroma and specific flavor.
- **Cornflower** (*Centaurea cyanus* L.) **honey** is greenish yellow, with an aroma reminiscent of almonds and a peculiar, slightly bitter flavor.
- **Dandelion** (*Taraxacum officinale* L.) **honey** is golden yellow, very thick, rapidly granulates, and has a strong odor and flavor.
- **Dragonhead** (*Dracocephalum moldavicum* L.) **honey** is gathered from the blue-purple flowers of the annual essential-oil plant growing in the wild in the Caucasus, the Altai, the Ukraine, and in some other districts.
- **Eucalyptus** (*Eucalyptus globules* Labill.) **honey** has an unpleasant flavor but is highly valued because it is used in the treatment of lung tuberculosis in popular medicine.
- **Hovenia** (*Hovenia dulcis* Thubg) **honey** resembles linden honey but is somewhat darker. It has a strong aroma and very agreeable flavor.
- **Heather** (*Calhuna ulgaris* L.) **honey** is produced from the nectar in the tiny pink flowers of the heather shrub.
- **Hibiscus** (*Hibiscus cannabinus* L.) **honey**, when freshly extracted, is of a dull yellowish color, turbid, and possesses a very unpleasant flavor.
- **Horehound** (*Marrubium vulgare* L.) **honey** is light in color, with a delicious aroma and flavor.
- **Honeydew honey** is produced not from floral nectar but from the sweet liquid excreted by plant-lice (*Aphididae*), jumping plant-lice (*Psyllidae*), and bark-lice or scale-insects (*Coccidae*). These insects feed on plant juices and their excretions fall on the foliage of trees like dew, hence the term “honeydew.”
- **Hyssop** (*Hyssopus officinalis* L.) **honey** is regarded as one of the best kinds.
- **Lavender** (*Lavandula vera* DC) **honey** is highly valued. It is of a golden color and has a delicate aroma.
- **Linden** (*Tilia*) **honey** is one of the very best kinds and is highly valued for its exceptional flavor.
- **Maple** (*Acer platanoides* L.) **honey** is light in color and has an excellent flavor.
- **Melissa** (*Melissa officinalis* L.) **honey** has an excellent flavor. It is produced from the nectar of the fragrant lilac or pink flowers of melissa, which is widespread in the Caucasus and Crimea and is cultivated in the Ukraine as a medicinal and essential-oil plant.
- **Motherwort** (*Leonurus cardiaca* L.) **honey** is light yellow with a golden tint (straw-colored), a faint aroma, and a fine, specific flavor. It is collected from the pale-lilac flowers of motherwort.
- **Mountain-ash** (*Sorbus aucuparia* L.) **honey** is reddish in color, with a strong aroma and pleasant flavor.
- **Parsnip** (*Pastinaca sativa* L.) **honey** is light, with a fine flavor.

- **Peppermint** (*Mentha piperita* L.) **honey** is produced from the nectar of the aromatic flowers of an essential-oil plant, which is widely cultivated in the Soviet Union.
- **Phacelia** (*Phacelia tanacetifolia* Benth.) **honey** is light green or white and has a delicate aroma and fine, pleasant flavor.
- **Pumpkin** (*Cucurbita pepo* L.) **honey** granulates easily, possesses a golden-yellow color, and an agreeable flavor.
- **Radioactive honey**: Alin Caillas, the well-known French chemist who made an important contribution to the study of honeys, proved in 1908 that some kinds of honey contain **radium**. Glass tubes filled with honey were wrapped in opaque black paper and placed on photographic plates. A month later some of the plates were found to have impressions made by the **radiation of radium**.
- **Rape** (*Brassica napus* var. *oleifera* Metzg.) **honey** is white, sometimes yellow; it has an agreeable aroma but is unpleasantly sweet.
- **Raspberry** (*Rubus idaeus* L.) **honey** is white, with a very pleasant aroma and delicious flavor. Raspberry comb honey is so tasty that it seems to melt in the mouth. This honey comes from the blossoms of the raspberry, which grows in woods and orchards throughout the territories of the former U.S.S.R. It is particularly plentiful in forests of Siberia, the Urals, and Kirov, Gorky, and other regions, and holds a place of importance among fruit and berry plants.
- **Rhododendron** (*Rhododendron ponticum* L.) **honey** has an unpleasant flavor and causes poisoning (general weakness, headache, vomiting, loss of consciousness). There is evidence that the poisoning is due to the presence of alkaloid of andromedotoxin in rhododendron honey.
- **Rock honey** is a peculiar and rare honey. It is made by wild bees, which deposit it in rock crevices. The honey is pale yellow and has a pleasant aroma and flavor. There is little wax in the combs and the honey comes in the form of a solid crystallized mass from which pieces must be chopped off. Unlike ordinary honey, rock honey is not sticky and does not need a special packaging. It can keep unchanged for years.
- **Sage** (*Salvia officinalis* L.) **honey** is of a light-amber or dark-golden color, with a delicate aroma and pleasant flavor.
- **Sainfoin** (*Onobrychis sativa* Lam. or *O. viciaefolia* Scop.) **honey** is golden yellow and has an exceedingly pleasant aroma and flavor. It is produced from the nectar of the pink or red blossoms of the perennial fodder grass sainfoin, which grows wild in Siberia and the Ukraine.
- **Salt-tree** (*Halimodendron halodendron* [Pall.] Voss.) **honey** is light-colored with a yellow tinge.
- **Sow thistle** (*Cirsium oleraceum* Scop.) **honey** is white, with a pleasant aroma and flavor.
- **Sunflower** (*Helianthus annuus* L.) **honey** is golden yellow but turns light amber, sometimes with a greenish tint when it crystallizes. It has a faint aroma and a pleasant, though pungent flavor.
- **Sweet clover** (*Melilotus officinalis* Desr.) **honey** has a delicious flavor and is considered one of the best honeys.
- **Tobacco** (*Nicotiana tabacum* L.) **honey** ranges in color from light to dark, has an unpleasant aroma and a bitter flavor.
- **Tulip-tree** (*Liriodendron tulipifera* L.) **honey** is reddish in color and has a pleasant aroma and flavor.
- **Vetch** (*Vicia tenuifolia* Koth.) **honey** is made from the nectar of the vetch, which grows in Siberia. The honey is transparent, has a fine aroma and flavor.
- **White clover** (*Trifolium repens* L.) **honey** is one of the best light honeys. It is colorless, transparent, and has an excellent flavor.

- **White mustard** (*Sinapis alba* L.) **honey** is golden yellow when liquid and acquires a cream-yellow tinge when it crystallizes.
- **Willow** (*Salix*) **honey** is golden yellow, granulates into a fine-grained creamy mass, and has a fine flavor. The various shrubs and trees of the genus *Salix* (about 170 species) occur everywhere in the Soviet Union.
- **Willow-herb** (*Epilobium angustifolium* L.) **honey** is transparent, with a greenish tinge, and crystallizes into white grains or a cream-like mass (see Yorish, 2001).

## HONEY: AN ANTIOXIDANT

Antioxidants are nutritive and nonnutritive agents that can retard biologically destructive chemical reactions in foods and living organisms. These compounds are thought to protect humans from disease, in part, through their ability to scavenge oxidants and free radicals, absorbing molecular damage that might otherwise compromise the function of essential lipids, proteins, and nucleic acids.

Throughout evolution, plants and animals have been constantly exposed to oxidative stress, high response, organisms have evolved to acquire, synthesize, store, and use antioxidant chemicals and proteins. For example, humans synthesize the antioxidant enzymes Cu–Zn superoxide dismutase (SOD), Mn–SOD, glutathione peroxidase, and catalase, and they can incorporate dietary antioxidants such as plant phenolics, vitamin C, and vitamin E into their tissues.

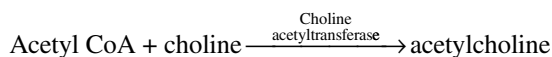
Honey conveys both phenolic antioxidants and increases plasma antioxidant capacity (Nagai et al., 2001; Schramm et al., 2003). Honey contains flavanoids such as **rhamnetin**, **kaempferol**, **naringenin**, **quercetin**, and **apigenin** (see Chapter 31).

## HONEY ENHANCES MEMORY FORMATION

**Learning** and **memory** are closely related to one another, but the terms are not interchangeable. Learning refers to the process by which behavior can be changed as a result of experience or practice. Memory refers to the ability to recall things that have been learned. Ancient civilizations have noted that eating honey regularly improves memory. Honey has **choline**, which is the precursor of **acetylcholine**, the memory molecule, and sphingomyelin.

## NEUROCHEMICAL BASIS OF CHOLINERGIC TRANSMISSION

**Acetylcholine**, an ester of choline and acetic acid, is synthesized in cholinergic neurons according to the following scheme:



The acetylcholine, in turn, is hydrolyzed by both **acetylcholinesterase** and plasma butyrylcholinesterase. **Choline** is actively transported into nerve terminals (synaptosomes) by a high-affinity uptake mechanism. Furthermore, the availability of choline regulates the synthesis of acetylcholine.

**Hemicholinium** blocks the transport of choline into synaptosomes, whereas **botulinum toxin** blocks the calcium-mediated release of acetylcholine. The released acetylcholine is hydrolyzed rapidly by acetylcholinesterase to choline and acetate.

## CLASSIFICATION OF CHOLINERGIC RECEPTORS

**Acetylcholine receptors** are classified as either **muscarinic** or **nicotinic**. The alkaloid muscarine mimics the effects produced by stimulation of the parasympathetic system. These effects are

postganglionic and are exerted on exocrine glands, cardiac muscle, and smooth muscle. The alkaloid **nicotine** mimics the actions of acetylcholine, which include stimulation of all autonomic ganglia, stimulation of the adrenal medulla, and contraction of skeletal muscle.

Dimethylphenylpiperazinium stimulates the autonomic ganglia, tetraethylammonium and **hexamethonium** block the autonomic ganglia, phenyltrimethylammonium stimulates skeletal motor muscle end plates, decamethonium produces neuromuscular blockade, and *d*-tubocurarine blocks both the autonomic ganglia and the motor fiber end plates.

Among the agents cited, only *d*-tubocurarine is useful as a drug (skeletal muscle relaxant); the rest are useful only as research tools. **Cholinesterase**, found in liver and plasma, can hydrolyze other esters such as **succinylcholine** (a skeletal muscle relaxant). Cholinergic peripheral receptors are located on (1) postganglionic parasympathetic fibers, (2) postganglionic sympathetic fibers, (3) all autonomic ganglia, and (4) skeletal end plates.

Honeybee brain contains nicotinic and muscarinic cholinergic receptors (Huang and Knowles, 1990).

Drugs blocking muscarinic cholinergic receptors (such as **atropine**) cause amnesia and drugs inhibiting cholinesterase (such as **physostegmine**) building acetylcholine improves memory. Patients with **Alzheimer's disease**, suffer from impaired cholinergic transmission and benefit from cholinesterase inhibitors such as **tacrine** (tetrahydroaminoacridine).

## HONEY AND THE TREATMENT OF WOUNDS AND BURNS

Honey has a well-established usage as a wound dressing in ancient and traditional medicine. In recent times this has been rediscovered, and honey is in fairly widespread use as a topical antibacterial agent for the treatment of wounds, burns, and skin ulcers, with many reports of its effectiveness. The observations recorded are that inflammation, swelling, and pain are quickly reduced, unpleasant odors cease, sloughing of necrotic tissue occurs without the need for debridement, dressings can be removed painlessly and without causing damage to regrowing tissue, and healing occurs rapidly with minimal scarring, grafting being unnecessary. In many of the cases honey was used on infected lesions not responding to standard antibiotic and antiseptic therapy. It was found to be very effective in rapidly clearing up infection and promoting healing in almost all cases.

The antimicrobial property of honey has been recognized for over 80 years and has been studied by numerous microbiologists since then. The high sugar content of honey is itself sufficient to inhibit the growth of bacteria and fungi, but this action is lost when the honey becomes diluted, as when lymph seeps out from a wound or ulcer into a honey dressing. But honey contains other antimicrobial components as well. In most honeys the major antimicrobial activity is due to hydrogen peroxide. This is produced by the action of an enzyme in honey. The enzyme is inactive until honey becomes diluted as honey contains an inhibitor of this enzyme. Thus, levels of hydrogen peroxide never get high enough to cause any harm to the wound tissues. It is not possible to get too high a level of hydrogen peroxide produced from honey — the rate of production is near flat over a very wide range of concentrations of honey solutions owing to the strong inhibition in high concentrations of honey. Honey also effectively gives a “slow-release” delivery of hydrogen peroxide, as the enzyme keeps on producing hydrogen peroxide over at least 24 h (Williams, 2002). Honey has been used in the treatment of burns and wounds for many centuries, with documents describing this use dating back to 1700 B.C.

A number of properties inherent to honey might contribute to its ability to fight infection and promote healing. Its high sugar content allows it to draw infection and fluid from wounds by a process called “osmosis.” Honey prevents bacterial growth through its acidic pH and through the work of an enzyme that produces small amounts of hydrogen peroxide. Its ability to keep the area around a wound moist and protected promotes fast healing and prevents scarring.

Honey also contains components from the specific plants used by the bees in their production, and it is speculated that some of these components might further add to the antibacterial and wound-

healing effects of certain honeys. The process of pasteurization, used to sterilize commercial honeys, destroys the enzyme involved in the production of hydrogen peroxide, rendering these honeys less antibacterial. Raw honeys maintain their enzymes, and honeys produced for therapeutic use are sterilized through an irradiation process that does not damage their constituents. There are currently two therapeutic honeys available: **Medihoney of Australia** and **active manuka honey** of New Zealand. Both are derived from bees using the flowers of **tea trees** (*Leptospermum* spp.) as their source.

Other studies have compared honey with other wound treatments. In one such study, honey was found to be as effective as, or more effective than, **silver sulfadiazine** (SSD), one of the most common topical treatments for burns. Fifty participants with superficial burns were randomly assigned to have their burns dressed with honey or SSD. Those treated with honey experienced faster reduction in inflammation and better infection control. Eighty-four percent of those treated with honey had satisfactory healing within 7 d and 100% by day 21, whereas 72% of those treated with SSD had satisfactory healing after 7 d and 84% by day 21. In another controlled trial, 900 participants with partial-thickness burns were randomly assigned to receive either honey dressings or other dressings. Honey was applied directly to the burns and covered with sterile dressings on alternate days. Those whose burns were treated with honey had faster healing and less scarring than those treated with other dressings. In the case of full-thickness burns, however, honey has been found to be inferior to other treatments. Honey contains ten **sulfonamides**, **tetracyclines**, and **flumequine** (Kaufmann et al., 2002; Verzegnassi et al., 2002).

### HONEY FOR THE TREATMENT OF PEPTIC ULCERS

Honey is a traditional remedy for dyspepsia and peptic ulcers, but there has been no rational basis for its use. The finding that *Helicobacter pylori* is probably the causative agent in many cases of dyspepsia and peptic ulcers raised the possibility that the antibacterial properties may be responsible for its therapeutic action. Consequently, the sensitivity of *Helicobacter pylori* to honey was tested, using isolates of *Helicobacter pylori* from biopsies of gastric ulcers. All five isolates tested were found to be sensitive in an agar well diffusion assay to a 20% (v/v) solution of a manuka honey with an average level of nonperoxide activity, but none showed sensitivity to a 50% (v/v) solution of a honey in which the antibacterial activity was due primarily to its content of hydrogen peroxide. Assessment of the minimum inhibitory concentration by inclusion of **manuka honey** in the agar showed that the growth of all of a further seven isolates tested was completely inhibited over the incubation period of 72 h by the presence of 5% (v/v) honey (Al Somal et al., 1994).

### HONEY FOR THE TREATMENT OF GASTROENTERITIS

Honey has been found to be effective in treating bacterial gastroenteritis in infants. Used in place of glucose in an oral rehydration fluid, it was found to be as effective as glucose in achieving rehydration, whereas the antibacterial activity cleared the infection in bacterial diarrhea. However, there is little information available on the sensitivity of the gastroenteritis-causing species of bacteria to the antibacterial activity of honey, and which of the antibacterial factors in honey is most effective against them. Thus, honey was tested for its relative antibacterial potency against all the bacterial species that commonly cause gastroenteritis, comparing manuka honey and a honey with the usual hydrogen peroxide activity, also an artificial honey to assess how much of the antibacterial activity was due simply to the acidity and the osmotic effect of the sugar in honey. With some of the species of bacteria the assessment was repeated with additional strains obtained from clinical isolates supplied by medical and animal health laboratories to see if there was any variation in sensitivity between different strains of a species.

Cultures of the bacteria were streaked on nutrient agar plates containing various concentrations of the honeys, and the growth of the bacteria was assessed to find the concentration of honey that

was necessary to prevent growth of the bacteria. The honeys used were a mixed pasture honey with an average level of activity due to hydrogen peroxide and no detectable nonperoxide activity and a manuka honey with an average level of nonperoxide activity. Honey concentrations were in a 5% (v/v) step dilution series initially and then with 1% dilution steps, the honey being diluted with either sterile distilled water (for the pasture honey and artificial honey) or a sterile solution of 0.2% catalase (for the manuka honey). Plates in which inhibition of growth was observed were swabbed with a loopful of sterile water and streaked onto freshly prepared nutrient agar plates that did not contain honey. The plates were then incubated to find any surviving bacteria growing into visible colonies — if the initial inhibition had been due to prevention of growth (bacteriostasis) rather than killing the bacteria (bactericidal activity).

The results showed that honey with an average level of hydrogen peroxide activity is **bacteriostatic** at 4 to 8% (v/v) and **bactericidal** at 5 to 10% (v/v). The nonperoxide activity of an average manuka honey is bacteriostatic at 5 to 11% (v/v) and bactericidal at 8 to 15% (v/v). Activity (just bacteriostatic) was not seen with artificial honey unless it was at 20 to 30% (v/v), clearly showing the importance of factors other than sugar and acidity.

### HONEY IN INFLAMMATORY BOWEL DISEASE

All honeys, in varying degrees, are effective for healing major wounds, cuts, burns, abscesses, skin ulcers, bed sores, eye infections, and varicose ulcers. When honey comes into contact with body moisture, the **glucose oxidase** introduced to the honey by the bee slowly releases hydrogen peroxide at a sufficient level to be effective against bacteria, without any damage to the tissue. Honey is not only antibacterial, but it also draws body fluids and nutrients to the area, and so assists cell growth and prevents scar formation. When used to treat diarrhea, honey promotes the rehydration of the body and causes the earlier clearing of diarrhea, vomiting, and stomach upsets.

Corticosteroids are some of the most important drugs used in the treatment of patients with inflammatory bowel disease. Intrarectal administration of corticosteroids is used in order to obtain topical action of these drugs and thus to reduce adverse systemic side effects.

Bilsel et al. (2002) reported that honey was as effective as **prednisolone** in the treatment of colitis.

### HONEY PROTECTS AGAINST CARCINOGENESIS

Many natural food substances have been shown to protect against carcinogen-induced tumors. **Linoleic acid** isomers were previously shown to protect against dimethylbenz(a)anthracene (DMBA) induced mammary cancer. Also, chronic administration of vitamin D analogues (**deltanoid**) prevented methylnitrosourea (MNU) induced mammary carcinogenesis. Other nutrients used as a whole (natural) or their active ingredients were shown to protect from cancer, e.g., **grapes** and **resveratrol**, **green tea extract** and **epigallocatechin gallate**, and **garlic** and **selenium**. Other nutrients, such as vitamins, which are considered normal constituents of balanced diet, were also demonstrated to inhibit and protect against cancers, e.g., vitamin A and retinoids, vitamin E and selenium, and vitamin C.

Mabrouk et al. (2002) have shown that orally administered honey and nigella grains inhibited methylnitrosourea-induced oxidative stress and carcinogenesis (see also El-khawaga et al., 2003). The role of vitamins as anticancer agents lie in their ability to suppress the oxidative stress associated with the carcinogenic process. Some natural food substances suppress the carcinogenic process through its contents of antioxidants as flavones in tea or work synergistically with vitamin E as lycopene in tomatoes. Lutein in fruits and lutein and glucosinolates in vegetables were also shown to have an anticancer effect.

*Nigella sativa* grains known in the Middle and Far East as black grain or black cumin has an inhibitory effect on clinical carcinogenesis, and the said effects are mediated via inhibition of

inducible nitric oxide synthase, arresting the cell cycle at S/G2 transition and apoptosis. **Propolis** (a product of honeybee hives) that has been used in folk medicine as a potent anti-inflammatory agent contains active component **caffeic acid phenethyl ester** (CAPE).

## HONEY IN THE TREATMENT OF HERPES SIMPLEX LESIONS

Honey has a wide range of antibacterial activities. The conjunctival application of honey can eradicate acute bacterial conjunctivitis due to *Staphylococcus aureus* and *Pseudomonas aeruginosa*. *In vitro* studies have shown that a 30 to 50% dilution of honey in liquid broth inhibits the growth of various human pathogenic bacteria, as well as *Candida albicans*. Two important classes of inhibitors found naturally in honey are flavonoids and phenolic acid (caffeic acid and ferulic acid). Honey has also been reported to have antileishmanial effects, as well as antirubella virus activity. Labial and genital herpes are common viral diseases. Satisfactory curative agents are still unavailable. Al-Waili (2004) investigated the effect of the topical application of honey on recurrent attacks of herpes lesions, labial and genital, as compared to **acyclovir cream**.

Sixteen adult patients with a history of recurrent attacks of herpetic lesions, eight labial and eight genital, were treated by topical application of honey for one attack and acyclovir cream for another attack.

For labial herpes, the mean duration of attacks and pain, occurrence of crusting, and mean healing time with honey treatment were 35%, 39%, 28%, and 43% better, respectively, than with acyclovir treatment. For genital herpes, the mean duration of attacks and pain, occurrence of crusting, and mean healing time with honey treatment were 53%, 50%, 49%, and 59% better, respectively, than with acyclovir. Two cases of labial herpes and one case of genital herpes remitted completely with the use of honey. The lesions crusted in three patients with labial herpes and in four patients with genital herpes. With acyclovir treatment, none of the attacks remitted, and all the lesions, labial and genital, developed crust. No side effects were observed with repeated applications of honey, whereas three patients developed local itching with acyclovir.

Topical honey application is safe and effective in the management of the signs and symptoms of recurrent lesions from labial and genital herpes.

Wounds treated with honey show less edema, less granular and mononuclear cell infiltration, less necrosis, better wound contraction, and lower glycosaminoglycan and proteoglycan concentrations. In postoperative wound infections following cesarean section or hysterectomy, topical honey application hastens the eradication of bacterial infections, reduces antibiotic use and hospital stay, accelerates wound healing, and produces minimal scar formation. In skin diseases, Al-Waili (2004) used honey to treat seborrheic dermatitis and dandruff. A mixture that includes olive oil, beeswax, and natural honey accelerates healing of skin lesions and relieves the signs and symptoms of eczema, psoriasis, and fungal skin infections.

## TREATMENT OF BULLOUS KERATOPATHY WITH HONEY

Honey was used by ancient Egyptians 5000 years ago to treat inflammations and burns of the cornea and conjunctiva. This practice continued through the Greco-Roman period and the Middle Ages, right up to the modern era. Honey is mentioned as a remedy in the Old Testament, the Talmud, and the Koran. It is described in the Talmud as having a propitious effect on the eyes: "Honey enlightens the eyes of man." This prompted a prospective study of topical honey as a hyperosmotic and healing agent in the medical therapy of bullous keratopathy.

Mansour et al. (2004) carried out a prospective study of 24 consecutive patients with bullous keratopathy, who were not immediate surgical candidates. One drop of honey was applied to the cornea after informed consent had been obtained. Patients were instructed to use topical honey three or four times daily.



All corneas had clearing of epithelial edema with collapse of corneal bullae. Median Snellen best corrected visual acuity (VA) improved from finger counting at 50 cm to finger counting at 2 m ( $p = 0.001$ ). After topical application of honey, anterior segment details could be seen and fundus evaluation was possible in two cases. Patients experienced stinging but with repeated usage the discomfort became minimal. Visual acuity improvement and corneal clearing lasted for around 1 h after topical honey.

Bullous keratopathy is a major complication of cataract surgery. In the past, penetrating keratoplasty was considered the most effective therapy for the symptomatic stage of the disease. Other surgical options have included conjunctival flaps, enucleation (reserved for blind, painful eyes) and, more recently, deep phototherapeutic keratectomy and amniotic membrane transplantation. Medical therapy of bullous keratopathy using hypertonic saline (Nad 5%) has been of marginal benefit due to its relatively weak osmotic effect.

Mansour et al. (2004) described a topical medication that can collapse corneal bullae (the osmotic pressure of honey is extremely high, exceeding 2000 milliosmols/kg), prevent bacterial superinfection (honey does not support the vegetative life stage of any bacterial species), and enhance the healing of corneal defects, thereby displaying properties similar to its unique healing facilities in recalcitrant ulcers or burns. Topical honey improved VA in eyes with epithelial corneal edema and in eyes with bullous keratopathy, and allowed anterior and posterior segment visualization. Given its advantages in terms of its antimicrobial, antioxidant, anti-inflammatory, and hygroscopic properties, further evaluation of the long-term effects of honey on bullous keratopathy is warranted (Mansour et al., 2004).

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# 42 Horseradish and Antiplatelet Actions

## INTRODUCTION

**Platelets** provide the initial hemostatic plug at sites of vascular injury. They also participate in reactions that lead to atherosclerosis and pathological thrombosis. Antagonists of platelet function have thus been used in attempts to prevent thrombosis and to alter the natural history of atherosclerotic vascular disease.

Japanese domestic **horseradish**, *wasabi*, containing **isothiocyanates** has **antiplatelet activity**. **Glucosinolates** are found in cell vacuoles of various plants in the family **Cruciferae** such as **horseradish**, **mustard**, **broccoli**, and **wasabi** (*Wasabia japonica*, syn. *Eutrema wasabi*). When plant cells are damaged, glucosinolates are hydrolyzed by **myrosinase (thioglucoside glucohydrolase, EC 3.2.3.1)**, which is also produced in the same family, and yield **isothiocyanates** (Figure 42.1). Most of these Crucifer isothiocyanates are well known for having antimicrobial, fungicidal, and pesticidal activities. A major wasabi flavor compound, **6-methylthiohexyl isothiocyanate (MS-ITC)**, has been shown to possess antimicrobial and platelet aggregation inhibition activities (Morimitsu et al., 2000).

Similarly, it has been shown that consumption of cruciferous vegetables is associated with a lower incidence of cancers. Induction of phase II enzymes such as the **glutathione S-transferase (GST)** and **quinone reductase (QR)** have been demonstrated in **broccoli**, **cabbage**, and **brussel sprouts**. Many natural isothiocyanates derived from cruciferous vegetables and some fruits have been shown to cause induction of phase II enzymes in cultured cells and rodents.

Morimitsu et al. (2000) isolated **6-methylsulfinylhexyl isothiocyanate (MS-ITC)** from wasabi (*W. japonica*, Japanese domestic horseradish) as a potential inhibitor of human platelet aggregation *in vitro* through extensive screening of vegetables and fruits (Figure 42.2).

In the course of another screening for the induction of **GST** activity in RL34 cells, MS-ITC was inadvertently isolated from wasabi as a potential inducer of GST. MS-ITC administered to rodents also showed both activities *in vivo*. As a result of elucidation of the platelet aggregation inhibition and the GST induction mechanisms of MS-ITC, the isothiocyanate moiety of MS-ITC plays an important role for antiplatelet and anticancer activities because of its high reactivity with **sulphydryl (RSH)** groups in biomolecules (GSH, cysteine residue in a certain protein, etc.) (Figure 42.3).

Morimitsu et al. (2000) have shown that after incubation with MS-ITC (5 or 10 min), the treated platelets were washed two times with phosphate-buffered saline, and MS-ITC potently inhibited platelet aggregation induced by thrombin. Then, MS-ITC could not show any effects on **arachidonic acid cascade (phospholipase A<sub>2</sub>, prostaglandin synthase, and thromboxane synthase)** in human platelets.

## ANTIPLATELET DRUGS

### ASPIRIN

Processes including thrombosis, inflammation, wound healing, and allergy are modulated by oxygenated metabolites of arachidonate and related polyunsaturated fatty acids that are collectively

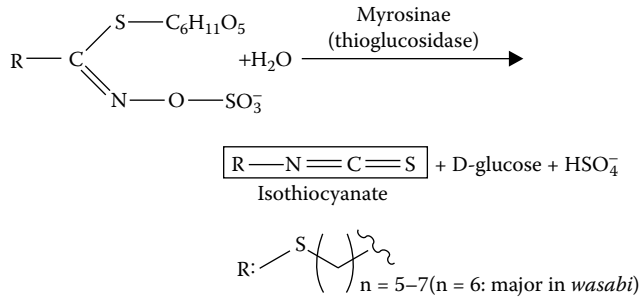


FIGURE 42.1 The enzymatic formation of isothiocyanates from *Brassica* sp.

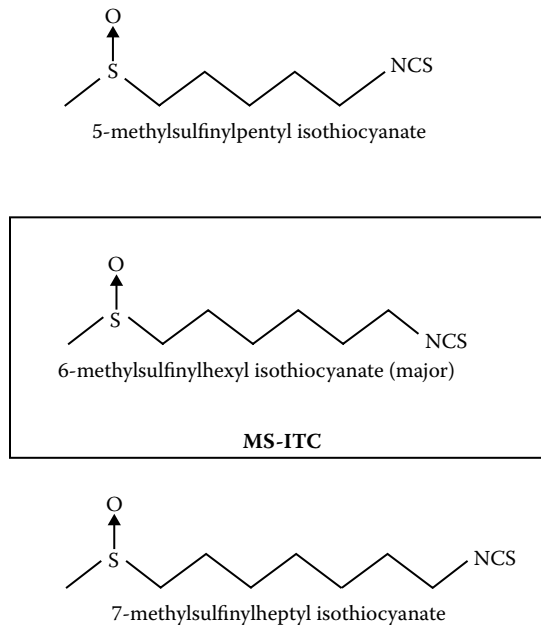
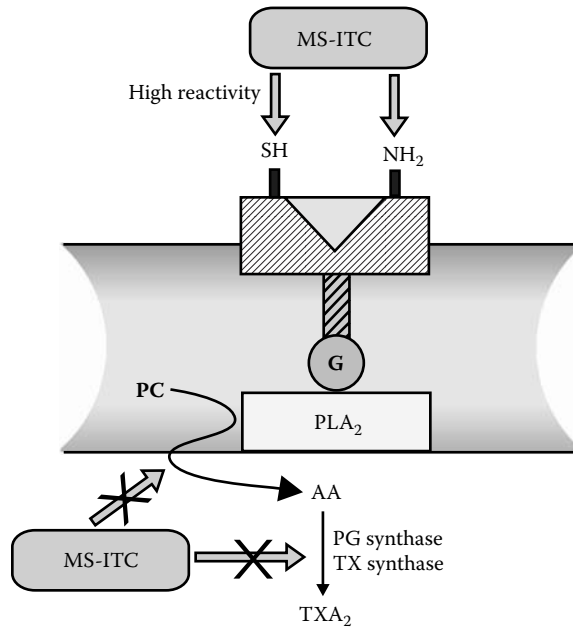


FIGURE 42.2 The chemical structures of platelet aggregation inhibitors, which were also identified as potential inducers of GST in RL34 cells.

termed **eicosanoids**. Interference with the synthesis of eicosanoids is the basis for the effects of many therapeutic agents, including analgesics, anti-inflammatory drugs, and antithrombotic agents.

In platelets, the major cyclooxygenase product is **thromboxane A<sub>2</sub>**, a labile inducer of platelet aggregation and a potent vasoconstrictor. **Aspirin** blocks production of thromboxane A<sub>2</sub> by covalently acetylating a serine residue near the active site of cyclooxygenase, the enzyme that produces the cyclic endoperoxide precursor of thromboxane A<sub>2</sub>. Since platelets do not synthesize new proteins, the action of aspirin on platelet cyclooxygenase is permanent, lasting for the life of the platelet (7 to 10 d). Thus, repeated doses of aspirin produce a cumulative effect on platelet function. Complete inactivation of platelet cyclooxygenase is achieved when 160 mg of aspirin is taken daily. Therefore, aspirin is maximally effective as an antithrombotic agent at doses much lower than required for other actions of the drug. Numerous trials indicate that aspirin, when used as an antithrombotic drug, is maximally effective at doses of 160 to 320 mg/d. Higher doses do not improve efficacy; moreover, they potentially are less efficacious because of inhibition of prostacyclin production, which can be largely spared by using lower doses of aspirin. Higher doses also increase toxicity, especially bleeding.



**FIGURE 42.3** The isothiocyanate moiety of MS-ITC plays an important role for antiplatelet and anticancer activities because of its high reactivity with sulfhydryl (RSH) groups in biomolecules (GSH, cysteine residue in a certain protein).

### DIPYRIDAMOLE

Dipyridamole (Persantine) is a vasodilator that, in combination with **warfarin**, inhibits embolization from prosthetic heart valves and, in combination with aspirin, reduces thrombosis in patients with thrombotic diseases. Dipyridamole by itself has little or no benefit; in fact, in trials where a regimen of dipyridamole plus aspirin was compared with aspirin alone, dipyridamole provided no additional beneficial effect. Dipyridamole interferes with platelet function by increasing the cellular concentration of adenosine **3',5'-monophosphate** (cyclic AMP). This effect is mediated by inhibition of **cyclic nucleotide phosphodiesterase** and by blockade of uptake of **adenosine**, which acts at  $A_2$  receptors for adenosine to stimulate **platelet adenylyl cyclase**. The only current recommended use of dipyridamole is for primary prophylaxis of thromboemboli in patients with prosthetic heart valves; the drug is given in combination with warfarin.

### TICLOPIDINE

Ticlopidine (Ticlid) is a thienopyridine that inhibits platelet function by inducing a thrombasthenia-like state. It interacts with platelet glycoprotein IIb/IIIa in an unknown way to inhibit the binding of fibrinogen to activated platelets. Glycoprotein IIb/IIIa is a fibrinogen receptor that links platelets via fibrinogen to form an aggregated plug; this action allows clot retraction. Thus, ticlopidine inhibits platelet aggregation and clot retraction. Ticlopidine prolongs the template bleeding time, with a maximal effect seen only after several days of therapy; abnormal platelet function persists for several days after treatment is discontinued. It is possible that some metabolite of ticlopidine is the active antithrombotic agent, since the drug is relatively ineffective in inhibiting platelet aggregation when added to platelets *in vitro* compared with its effects on platelets taken from patients who are ingesting the drug. The drug has no effect on eicosanoid metabolism, and it should act independently of aspirin; to date, however, these two agents have not been tested in combination. Ticlopidine currently is used for prevention of thrombosis in cerebral vascular and coronary artery disease. Side effects

include bleeding, nausea, and diarrhea in 10% of patients, and severe neutropenia in approximately 1% of patients. Ticlopidine is recommended for patients unable to tolerate aspirin.

## THERAPEUTIC USES OF ANTICOAGULANT, THROMBOLYTIC, AND ANTIPLATELET DRUGS

### VENOUS THROMBOEMBOLISM

The goal in the treatment of deep venous thrombosis and pulmonary embolism is the prevention of recurrent, fatal embolism.

### MYOCARDIAL INFARCTION

All patients with acute myocardial infarction should be considered for intravenous thrombolytic therapy with **streptokinase**, **tissue plasminogen activator (TPA)**, or anistreplase because these agents are effective in both preserving cardiac function and reducing mortality.

### UNSTABLE ANGINA

Aspirin (160 mg/d) combined with heparin followed by warfarin (INR 2.0 to 3.0) may be the optimal treatment.

### SAPHENOUS VEIN BYPASS GRAFTS

Antiplatelet therapy reduces the risk of occlusion of saphenous grafts, and a “low” dose of aspirin (325 mg/d) is as effective as a higher dose (975 mg/d) or the combination of aspirin and dipyridamole. Rates of occlusion are similar for aspirin begun before or 6 h after surgery, but the incidence of hemorrhage is increased with preoperative administration.

### PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Full-dose heparin therapy, beginning with an intravenous bolus of 10,000 U and continued for 4 to 24 h, is standard practice in patients undergoing angioplasty. Aspirin begun 1 d prior to surgery reduces periprocedural thrombosis and should be continued indefinitely due to its beneficial effect on coronary artery disease.

### ATRIAL FIBRILLATION

More than 50% of patients with cerebral embolism have atrial fibrillation. In the majority of these patients, the underlying cardiac disease is nonvalvular. The risk of ischemic stroke and atrial fibrillation increases with age, reaching a cumulative risk of 35% during a patient's lifetime. Combined results from several randomized trials show that warfarin reduces the risk of stroke in patients with nonrheumatic atrial fibrillation by 68% (to 1.4% per year), with an excess incidence of major hemorrhage (including intracranial) of only 0.3% per year.

### PROSTHETIC HEART VALVES

The risk of embolism associated with mechanical heart valves is 2 to 6% per patient per year despite anticoagulation and is highest with valves in the mitral position. Warfarin therapy (INR 2.5 to 3.5) is recommended in these patients. The addition of enteric-coated aspirin (100 mg/d) to warfarin (INR 3.0 to 4.5) in high-risk patients (preoperative atrial fibrillation, coronary artery disease, history of thromboembolism) with mechanical valves decreases the incidence of systemic embolism and death from vascular causes (1.9 vs. 8.5% per year), but increases the risk of bleeding.

### VALVULAR HEART DISEASE

Rheumatic mitral valve disease is associated with thromboembolic complications at reported rates of 1.5 to 4.7% per year; the incidence in patients with mitral stenosis is approximately 1.5 to 2 times that in patients with mitral regurgitation. The presence of atrial fibrillation is the single most important risk factor for thromboembolism in valvular disease, increasing the incidence of thromboembolism in both mitral stenosis and regurgitation four- to sevenfold. In current practice, patients with nonrheumatic atrial fibrillation at low risk for thromboembolism based on clinical characteristics frequently are treated with aspirin. Warfarin therapy is considered in higher-risk patients, especially those with previous thromboembolism and in whom anticoagulation is not contraindicated due to preexisting conditions.

### CEREBROVASCULAR DISEASE

Most ischemic strokes are due to atherosclerotic cerebrovascular disease. Patients with symptomatic carotid stenosis of > 70% should be considered for **endarterectomy**. Aspirin is used for prophylaxis following transient ischemic attacks and minor stroke.

### PERIPHERAL VASCULAR DISEASE

Antithrombotic therapy for acute peripheral occlusive disease is largely empirical. Thrombolytic therapy typically is reserved for patients in whom the occlusion is not amenable to surgery and for those in whom a possible delay between the initiation of therapy and thrombolysis would not jeopardize the viability of the limb. Evidence that antithrombotic therapy changes the natural course of the peripheral disease is sparse, but these patients are at an increased risk of cardiovascular mortality and should receive long-term **aspirin** therapy. Initial trials suggest that ticlopidine may improve the symptoms of chronic arteriosclerotic arterial insufficiency and also reduce fatal and nonfatal cardiovascular events, but further studies are needed.

### PRIMARY PREVENTION OF ARTERIAL THROMBOEMBOLISM

In view of the perceived benefit of aspirin in the secondary prevention of stroke and myocardial infarction, two large trials involving physicians as subjects were initiated to study the effect of aspirin in the primary prevention of arterial thrombosis. In the American study, 22,000 volunteers (age 40 to 84 years) were randomly assigned to take 325 mg of aspirin every other day or placebo. The trial was halted early, after a mean follow-up of 5 years, when a 45% reduction in the incidence of myocardial infarction and a 72% reduction in the incidence of fatal myocardial infarction were noted with aspirin treatment. However, total mortality was reduced only 4% in the aspirin group, a difference that was not statistically significant, and there was a trend for a greater risk of hemorrhagic stroke with aspirin. Thus, the prophylactic use of aspirin in an apparently healthy population is not recommended at this time, unless there are risk factors for cardiovascular disease.



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# 43 Hypericum (St. John's Wort) and Depression

## INTRODUCTION

The main uses of this herb are as follows:

- *Hypericum* extract has been used for the treatment of mild to moderate mental depression.
- *Hypericum* is thought to affect the synaptosomal uptake of serotonin, dopamine, and norepinephrine.
- From the existing literature, St. John's wort appears to be a safe and effective alternative in the treatment of depression. Tricyclic antidepressants and monoamine oxidase inhibitors can produce serious cardiac side effects, such as tachycardia and postural hypotension, and many unwanted anticholinergic side effects, including dry mouth and constipation. St. John's wort has proved to be free of any cardiac, as well as anticholinergic, side effects normally seen with antidepressant medications. Based upon limited studies, St. John's wort appears to be an acceptable alternative to traditional antidepressant therapy.

More than 3 million people over the age of 85 currently reside in the U.S. and the geriatric population is continually rising. One of the most common disabilities seen in elderly people is major depression, which affects 17% of the population. Between 35 and 45% of hospitalized elderly patients experience a depressive syndrome at some point. Cognitive symptoms of depression may include a loss of interest in activities, suicidal thoughts, depressed mood, and feelings of worthlessness, as well as a number of symptoms that are indistinguishable from other disease states. Depression also presents with somatic symptoms, including weight loss, fatigue, loss of concentration, disturbed sleep, and an excessive concern with health problems.

Because suicide is one of the leading causes of death in elderly people and in other populations, rapid and effective treatment of depression is warranted. Current therapies include the use of electroconvulsive (shock) therapy, psychiatric intervention, and antidepressant drugs such as **tricyclic antidepressants** (TCAs), **monoamine oxidase inhibitors** (MAOIs), and **serotonin-selective reuptake inhibitors** (SSRIs). Recently, in the U.S., the use of **St. John's wort** (*Hypericum perforatum*) has become more prevalent, especially in the treatment of depression.

*Hypericum perforatum* is a herbaceous perennial plant widely distributed throughout Europe, Asia, North Africa, and Canada, notably in British Columbia. In the U.S., it grows wild in northern California and southern Oregon.

St. John's wort was believed in the Middle Ages to have magical powers that would protect one from evil. The plant was originally named after **John the Baptist** and is commonly collected on June 25, **St. John's Day**; it is soaked in olive oil, eventually producing a red oil symbolizing the "**Blood of St. John.**" This oil, exposed to sunlight for several weeks, has a reputation as an anti-inflammatory and healing agent used especially in the treatment of wounds. *Hypericum* has also been used in Europe as a soothing agent, often in the treatment of hemorrhoids. More recently, St. John's wort has been tested for use as an antiviral agent, most specifically in the treatment of AIDS.



Today, *Hypericum* is used widely in Germany for the treatment of depression where it is prescribed approximately 20 times more often than **fluoxetine**, one of the most highly prescribed antidepressants in the U.S., where *Hypericum* is increasingly used as an over-the-counter remedy by a significant portion of the lay population for the treatment of depression. In 1998, *Hypericum* was expected to garner \$400 million in sales in the U.S. and an estimated \$6 billion in Europe, despite a lack of consensus regarding its efficacy among the medical community and the absence of standardization guidelines in the U.S. Furthermore, the specific modes of purported antidepressant activity are not well defined. There is some evidence that *Hypericum* may exert a significant influence on catecholamine neurotransmission via known pathways, including (1) inhibition of neurotransmitter metabolism, (2) modulation of neurotransmitter receptor density and sensitivity, and (3) synaptic reuptake inhibition. Similar to conventional antidepressant pharmacology, these mechanisms may ultimately lead to increased synaptic availability of the neurotransmitters believed to be implicated in clinical depression, namely, serotonin (5-HT), norepinephrine (NE), and dopamine (DA) (Greenson et al., 2001).

## ST. JOHN'S WORT

### BOTANICAL NAME

*Hypericum perforatum* L.

### Family

**Hypericaceae** (*alt.* Clusiaceae = Guttiferae)

### Synonyms

*Hyperici herba*

### COMMON NAMES

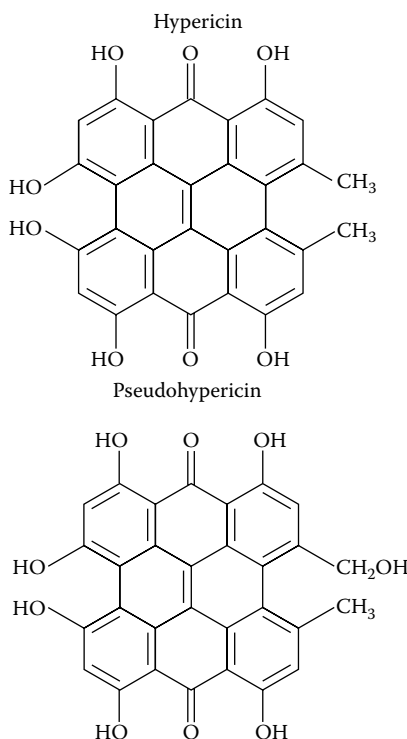
Amber, Amber Touch-and-Heal, Blutkraut, Chassediabie, Corazoncillo, Goatweed, Hardhay, Hartheu, Herba di S. Giovanni, Herbe de Millepertuis, Herbe St. Jean, Herrgottsblut, Hexenkraut, Heirba de San Juan, Hipericon, Hypericum, Iperico, Johannesort, Johannisblut, Johanniskraut, Johnswort, Klamath weed, Millepertuis, Pelatro, Perforata, Qian Ceng Lou, Rosin Rose, Sankt Hans Urt, St. Jan's Kraut, St. John's wort, St. Johnswort, Tipton weed, Toutsaine, Tupfelhartheu, Walpurgiskraut, Zwierboij.

### COMMERCIAL PRODUCTS

The commercial products of **St. John's wort** are derived from the dried flowering tops or aerial parts of *Hypericum perforatum* L.; they are harvested shortly before or during the flowering period. Hypericum preparations include the dried herb (chopped or powdered), tea infusion, liquid extract, dried (hydroalcoholic) extract, oil, and tincture.

### ACTIVE INGREDIENTS

The active ingredients for hypericum include **cyclopseudohypericin**, **hypericin**, **hyperforin**, **isohypericin**, **protohypericin**, and **pseudohypericin**. Other active ingredients include the following flavonoids: **hyperin**, **hyperoside**, **isoquercitrin**, **kaempferol**, **luteolin**, **quercetin**, **quercitrin**, **rutin**, and the following biflavonoids: **amentoflavone** and **I3,I18-biapigenin**. Although the flavonoids, the essential oils, and the phenolic acids are common plant constituents, the **hypericins**,



**FIGURE 43.1** Principal constituents of *Hypericum* (St. John's wort).

**1,3,6,7-tetrahydroxy-xanthone**, and **hyperforin** are characteristic constituents of hypericum (Figure 43.1).

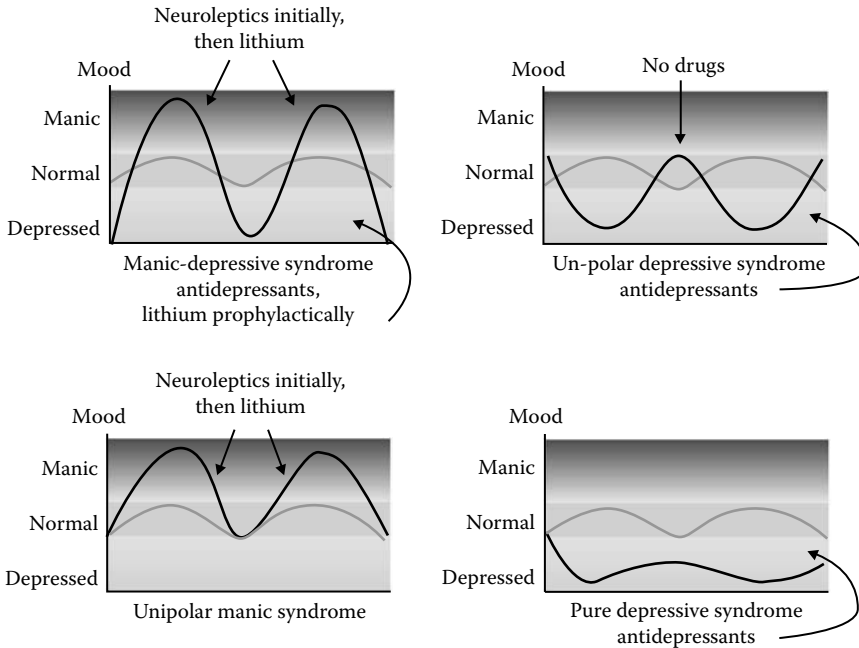
### HYPERICUM (ST. JOHN'S WORT) IN FOLK MEDICINE AND TRADITIONAL SYSTEMS OF MEDICINE

In folk medicine and traditional systems of medicine, various species of *Hypericum* have been used orally to treat anxiety, bed-wetting, dyspepsia, excitability, exhaustion, fibrositis, gastritis, gout, hemorrhage, hysteria, insomnia, irritability, jaundice, migraine headaches, neuralgia, pulmonary complaints, rheumatism, sciatica, and swelling. It also has been used orally as an anthelmintic, an antidiarrheal, and a diuretic. Various dosage forms of hypericum have been used topically as an astringent and to treat injuries or conditions such as blisters, burns, cuts, hemorrhoids, inflammation, insect bites, itching, redness, sunburns, and wounds. *Hypericum* with or without light therapy may be useful for the treatment of **seasonal affective disorder** (SAD), but studies to date have used too few subjects to determine its efficacy. In addition, light therapy combined with hypericum intake may increase the risk of phototoxicity.

**Hypericum** is being combined with other products such as **ma huang** (ephedra) and promoted for weight loss as an alternative to prescription weight loss medications.

### ANTIDEPRESSANTS

Depressive disorders are the most prevalent of psychiatric illnesses, occurring more often among women (16%) than among men (8%). Depression, a recurrent but self-limiting disorder, is classified as (1) exogenous or reactive depression or as (2) endogenous depression. Depression is further



**FIGURE 43.2** The use of antidepressants in bipolar depression.

classified as unipolar and bipolar. Unipolar patients display one type of affective disorder, most commonly depression; bipolar patients usually experience mania and depression (Figure 43.2).

**Symptoms of major depression and dysthymia are:**

- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all or almost all activities
- Marked weight loss or gain, or a decrease or increase in appetite
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt
- Diminished ability to think or concentrate, or indecisiveness
- Recurrent thoughts of death, or suicidal ideation or attempt
- Feelings of hopelessness

**Characteristics of melancholic depression are:**

- Loss of interest or pleasure in all or almost all activities
- Lack of reactivity to usually pleasurable stimuli
- Depression regularly worse in the morning
- Early morning awakening
- Psychomotor retardation or agitation (not merely subjective reports)
- Marked anorexia or weight loss
- No marked personality disturbance before the first major depressive episode
- One or more previous major depressive episodes followed by complete or nearly complete recovery
- Previous good response to specific and adequate somatic antidepressant therapy (e.g., tricyclic drugs, electroconvulsive therapy, monoamine oxidase inhibitors, and lithium)

## NEUROTRANSMITTERS AND THEIR ROLE IN DEPRESSION

Depression has been noted in 10 to 15% of all patients who take **reserpine** for the treatment of hypertension. When used for the treatment of **tuberculosis**, **isoniazid** brings about mood elevation. Reserpine was found to diminish the levels of brain neurotransmitters such as dopamine, serotonin, and norepinephrine, whereas isoniazid, through its **monoamine oxidase inhibitory actions**, augments the levels of these substances. It was thus theorized that too much of one or more of these neurotransmitters might be associated with states of hypomania or mania, whereas too little would correlate with depression.

Other neurotransmitters besides dopamine, norepinephrine, or serotonin may be involved in depression. These include acetylcholine and  $\gamma$ -aminobutyric acid (GABA). Acetylcholine stimulates the **locus ceruleus** through the **muscarinic cholinergic receptors**. Clinical data have shown that cholinergic agonists can cause depression in that the response to muscarinic agonists is augmented in euthymic patients with a history of depression. In addition, **iprindole**, an antidepressant that does not alter the uptake or metabolism of monoamines, has potent anticholinergic properties. Moreover, electroshock treatment, one of the most efficacious of treatments for managing depression, also has little, if any, effect on available measures of the functioning of neurotransmitter systems.

GABA inhibits the action of the locus ceruleus and this is mediated by the GABA<sub>A</sub> receptor-chloride channel system. The plasma and cerebrospinal fluid levels of GABA are low, and **progabide**, a GABA<sub>A</sub> receptor agonist, has antidepressant properties.

## CLASSIFICATION OF ANTIDEPRESSANTS

Drugs used in the treatment of depression are referred to as **thymoleptics**, **thymoanaleptics**, **psychoanaleptics**, **psychic energizers**, and antidepressants.

Antidepressants are divided into the following classes:

- The dibenzapine derivatives are called tricyclic antidepressants and include **imipramine** (Tofranil), **desipramine** (Norpramin), **amitriptyline** (Elavil), **nortriptyline** (Aventyl), **protriptyline** (Vivactil), and **doxepin** (Adapin).
- The monoamine oxidase inhibitors are used occasionally to treat depression. The hydrazine derivatives consist of **isocarboxazid** (Marplan) and **phenelzine sulfate** (Nardil). The nonhydrazine derivatives include **tranilycypromine** (Parnate).
- L-tryptophan is the only member of the monoamine precursors used to treat depression.
- Newer agents include amoxapine, doxepin, fluoxetine, maprotiline, trazodone, mianserin, alprazolam, and bupropion.

## DIBENZAPINE DERIVATIVES

The three-ring nucleus characteristic of the dibenzapine derivatives has given rise to their name of tricyclics or heterocyclics. They resemble the phenothiazine derivatives such as chlorpromazine in structure and function.

Similar to the phenothiazine derivatives (e.g., chlorpromazine), tricyclic antidepressants (e.g., imipramine) may:

- Reduce the seizure threshold and precipitate seizures in patients with epilepsy
- Cause cholestatic jaundice
- Cause movement disorders
- Cause hematological side effects

Unlike the phenothiazine derivatives, the tricyclic antidepressants:

**TABLE 43.1**  
**The Inhibition of Monoamine Uptake by**  
**Antidepressant Inhibition of Reuptake**

Drug	Inhibition of Reuptake	
	Norepinephrine	Serotonin
<b>Older Drugs</b>		
Amitriptyline	+	++
Nortriptyline	++	+
Imipramine	+	+
Desipramine	+++	0
Clomipramine	+	+++
<b>Newer Drugs</b>		
Fluoxetine	0	+++
Bupropion	±	0

*Note:* 0 = no effect; ± = an equivocal effect; + = slight effect; ++ = moderate effect; +++ = large effect.

- May increase motor activity
- Are antidepressant
- Have a very slow onset and long duration of action
- Have a relatively narrow margin of safety
- Have strong anticholinergic effect; in fact, dry mouth is the most common side effect and other anticholinergic effects such as tachycardia, loss of accommodation, constipation, urinary retention, and paralytic ileus have been reported

### CONVERSION TO PHARMACOLOGICALLY ACTIVE METABOLITES

Imipramine is demethylated to desipramine, and amitriptyline is demethylated to nortriptyline. Both metabolites are active antidepressants.

### VARIOUS PROPERTIES OF THE TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants, like some of the phenothiazine derivatives, are sedative in nature. Those compounds containing a tertiary amine (**imipramine**, **amitriptyline**, and **doxepin**) are the most sedative. Those compounds containing a secondary amine (**nortriptyline** and **desipramine**) are less so, and protriptyline has no sedative effect.

Tricyclic antidepressants, like some of the phenothiazine derivatives (e.g., **thioridazine**), have an anticholinergic property. **Amitriptyline** is the strongest in this regard, and desipramine is the weakest.

The tricyclic antidepressants also have cardiovascular actions. In particular, they cause orthostatic hypotension by obtunding the various reflex mechanisms involved in maintaining blood pressure.

Antidepressants may block the uptake of norepinephrine or serotonin (Table 43.1).

### THE SITES OF ACTION OF ANTIDEPRESSANTS

The precise mechanism by which the first-generation tricyclic antidepressants, monoamine oxidase inhibitors, and the newer-generation antidepressants exert their effects is uncertain. However, it is clear that antidepressants exert their effects at both pre- and postsynaptic receptor sites (Figure 43.3 and Figure 43.4).

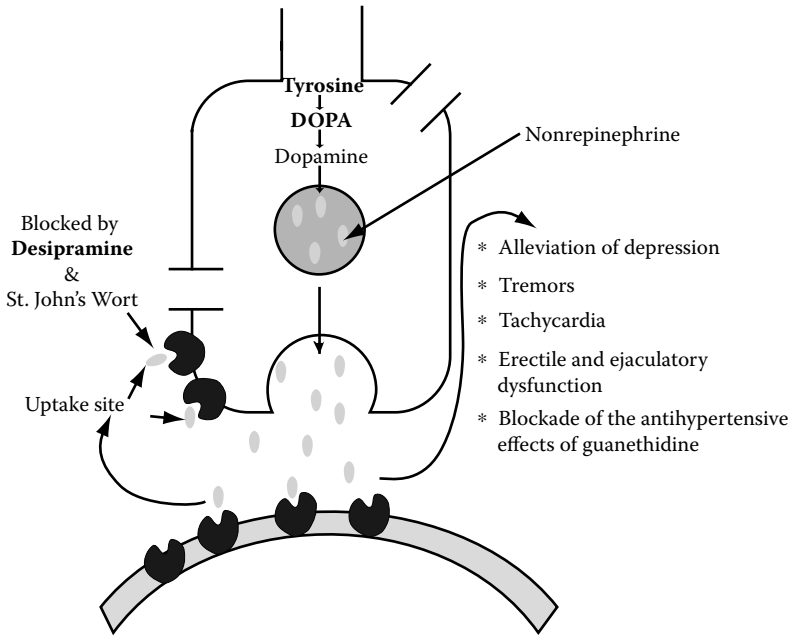


FIGURE 43.3 Desipramine blocks the uptake sites for norepinephrine.

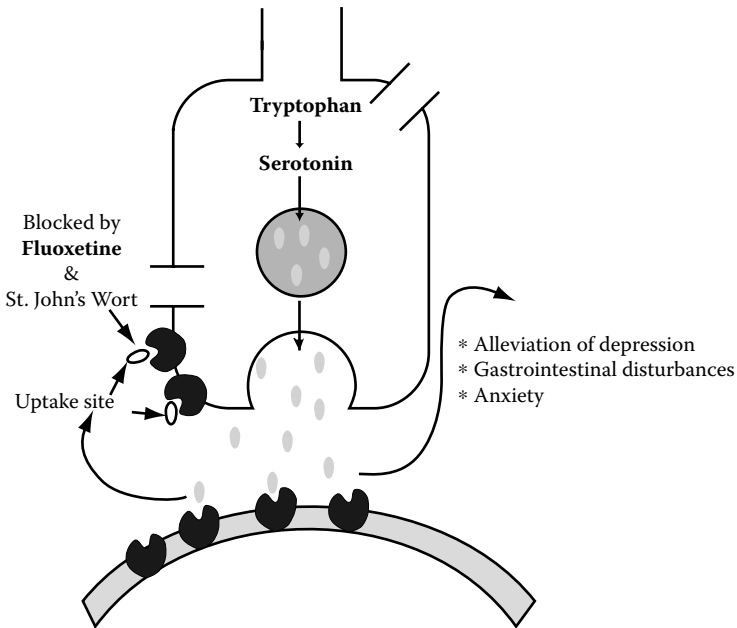


FIGURE 43.4 Fluoxetine blocks the uptake sites for serotonin.

**TABLE 43.2**  
**Selected Side Effects of Antidepressant Drugs**

Drug	Sedation	Anticholinergic Effects	Orthostatic Hypotension
<b>Tricyclic Drugs</b>			
Amitriptyline	+++	+++	+++
Desipramine	+	+	+
Doxepin	+++	++	+++
Imipramine	++	++	++
Nortirptiline	++	+	+
Protriptyline	+	++	+
<b>Monoamine oxidase inhibitors</b>			
Tranlycypromine	0	0	+++
<b>Newer Agents</b>			
Amoxapine	++	+	++
Fluoxetine	0	0	0
Maprotiline	++	+	++
Trazodone	++++	0	++
Alprazolam	+	0	0
Bupropion	0	0	0

*Note:* 0 = no side effect; + = minor side effect; ++ = moderate side effect; +++ = major side effect; ++++ = extreme side effect.

The blockade of norepinephrine and serotonin uptake occurs immediately, but antidepressants are not effective clinically for 2 to 4 weeks. Long-term treatment with antidepressants causes:

- Decreased sensitivity of postsynaptic  $\beta_1$ -adrenergic receptors
- Decreased sensitivity of postsynaptic serotonin receptors
- Decreased sensitivity of  $\alpha_1$ -adrenergic presynaptic receptors
- Increased sensitivity of  $\alpha_1$ -adrenergic postsynaptic receptors (see Table 43.2)

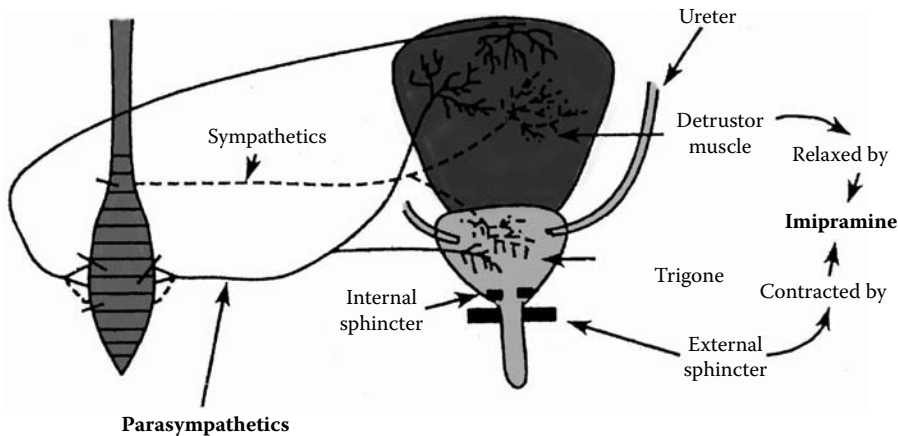
### SIDE EFFECTS OF ANTIDEPRESSANTS

The first-generation tricyclic antidepressants, the monoamine oxidase inhibitors, and the newer agents can cause sedation, insomnia, orthostatic hypotension, or nausea. Because of their anticholinergic properties, they may also produce cardiac toxicities (Table 43.2).

### THERAPEUTIC INDICATIONS

A primary indication for the use of tricyclic antidepressants is endogenous depression. Before treating an endogenous depression, however, it should first be differentiated from sadness. Disabling depression and its vegetative symptoms generally respond to tricyclic antidepressants but sadness does not, although it responds to changes in environmental events. The effective dose of tricyclic antidepressants, which are equivalent drugs, is chosen empirically. The less sedative agents are chosen for apathetic and withdrawn patients. Because the margin of safety for these agents is very narrow, they should not be prescribed in large quantities for a depressed patient who may use them to attempt suicide.

The anticholinergic effect of imipramine has been used successfully in managing enuresis (Figure 43.5).



**FIGURE 43.5** Imipramine is used to manage enuresis.

The pain associated with diabetic peripheral neuropathy, trigeminal neuralgia, or cancer may predispose such patients to depression. Tricyclic antidepressants have been shown to be an effective adjunct in managing these and other similar conditions.

Some episodic phobias are regarded as “masked” depression and thus respond to treatment with tricyclic antidepressants.

**Fluoxetine**, in addition to its antidepressant property, has been used as an appetite suppressant. Imipramine and desipramine have been used as **antibulimic substances**.

Desipramine has been used as part of the **treatment of alcoholism**. Because depression has led to relapsed drinking in people suffering from alcoholism who are striving to maintain sobriety, treatment with antidepressants may reverse or prevent these depressive symptoms. They may also correct the biochemical abnormalities hypothesized to underlie both depression and alcoholism, thus helping to ensure abstinence in recovering alcoholics.

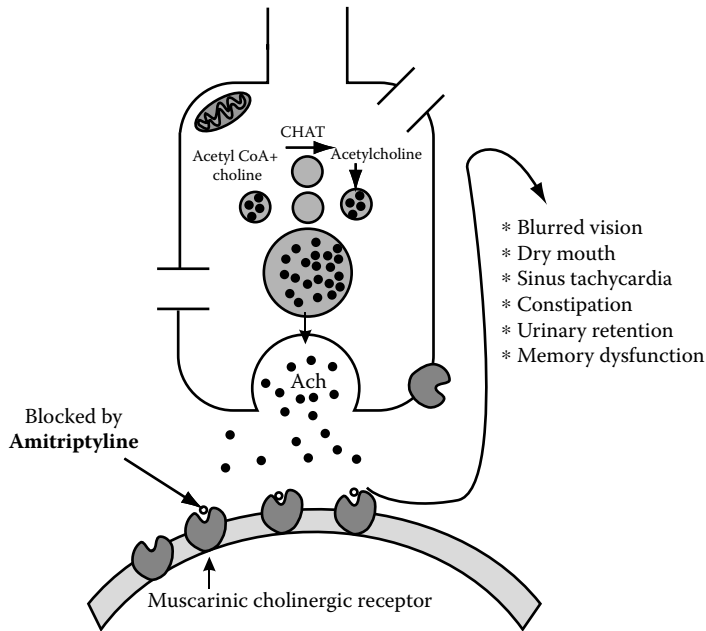
## FATAL OVERDOSES

Currently, overdoses of tricyclics are one of the most serious types of poisoning encountered in clinical practice because the depressed patients who are treated with these drugs are also those who are the most prone to using them for suicidal purposes.

The diagnostic triad of coma, seizures, and cardiac arrhythmias should raise the suspicion of tricyclic overdose, if there is otherwise no verified history of drug intake. Cardiac arrhythmias and conduction abnormalities are the major distinguishing features. A trial dose of intravenously administered **physostigmine** (1 to 4 mg) may suggest the diagnosis because this will awaken the comatose patient or mitigate the arrhythmias. The effects of physostigmine are transient, however, and it is not a definitive treatment. Other problems encountered in such poisonings include neuromuscular irritability, delirium, hyperpyrexia, hypotension, and bladder or bowel paralysis (Figure 43.6).

The cardiac arrhythmias are life-threatening, so the patient must be closely monitored, with facilities available for possible resuscitation. Drugs such as **quinidine** and **procainamide** are contraindicated, but **lidocaine**, **propranolol**, or **phenytoin** has been used safely and effectively. The arterial blood gas levels, pH, and electrolyte concentrations should be monitored so that metabolic acidosis or hypokalemia can be identified that would further aggravate the arrhythmias. Electrical pacing may be required if the antiarrhythmic drugs fail. Hyperpyrexia is treated by cooling. Seizures may be managed by intravenous doses of diazepam.





**FIGURE 43.6** Amitriptyline has potent anticholinergic properties. CHAT = choline acetylase; CoA = coenzyme A; ACh = acetylcholine.

## MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase can metabolize monoamines by oxidative deamination and convert them to inactive acidic derivatives. In general, not only do these agents inhibit the oxidase that metabolizes amines but they also inhibit the oxidase that metabolizes drugs and essential nutrients. Hence, the incidence of drug–drug and drug–food interactions is extremely high with these agents. These agents should be used with extreme caution in conjunction with sympathomimetic amines, ganglionic blocking agents, procaine, and anesthetic agents. They are contraindicated in patients with hyperthyroidism and in combination with tricyclic antidepressants. In the event of poisoning, adrenergic blocking agents such as **phentolamine** may be effective for combating the hypertensive crisis.

### INDICATIONS FOR MONOAMINE OXIDASE INHIBITORS

The high incidence of drug–food and drug–drug interactions rules out monoamine oxidase inhibitors as antidepressants of first choice. However, there are circumstances in which these agents may be used effectively and successfully:

- When a patient has not responded to a tricyclic antidepressant for an adequate trial period and with an appropriate dosage
- When a patient has developed allergic reactions to tricyclics
- When a patient has had previous depressive episodes that responded well to monoamine oxidase inhibitors

## NEWER, NOVEL, OR ATYPICAL ANTIDEPRESSANTS

The newer agents that may have actions that are novel or atypical include maprotiline, amoxapine, fluoxetine, trazodone, bupropion, mianserin, and alprazolam.

**Maprotiline** has relatively minor anticholinergic properties compared to amitriptyline. It has a very large elimination half-life of 36 to 48 h and in large doses produces convulsions.

**Amoxapine** has neuroleptic properties that stem from its dopamine receptor-binding affinity. Similar to the neuroleptics, it may produce movement disorders. In toxic doses, amoxapine may provoke difficult-to-control convulsions.

**Fluoxetine** selectively blocks the uptake of serotonin. It is devoid of anticholinergic properties and hence has little or no effect on the cardiovascular system, including orthostatic hypotension or arrhythmias.

**Trazodone** is perhaps the most sedative antidepressant available. It is devoid of anticholinergic effects and causes postural hypotension as well as rarely serious priapism.

**Bupropion** is free of anticholinergic, antiadrenergic, and cardiotoxic properties. Its structure is related to that of amphetamine and it possesses stimulating effects; hence it may be useful in hyperphagic or obese individuals.

**Mianserin** does not alter the uptake of norepinephrine, serotonin, or dopamine. It is devoid of anticholinergic properties and thus is not cardiotoxic. Mianserin blocks both  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors, and it is sedative in nature.

**Alprazolam** causes pronounced sedation but is devoid of anticholinergic properties. Alprazolam and, to a certain extent, clonazepam are effective in the treatment of panic disorder.

## CONTROL OF MANIC EPISODES IN MANIC-DEPRESSIVE PSYCHOSIS USING LITHIUM

### PHARMACOKINETICS

**Lithium** is given orally as a salt, and the particular salt does not affect the therapeutic action. The anionic partner of lithium — carbonate, chloride, acetate, citrate, or sulfate — serves only as an inert vehicle. Carbonate is by far the most widely used lithium salt. In addition, lithium carbonate contains more lithium, weight for weight, than do the other lithium salts.

Because lithium is not bound to any plasma or tissue proteins, it is widely distributed throughout the body. Lithium ions are eliminated mainly by the kidneys. There is a direct relationship between the amount of sodium chloride ingested and the fraction of filtered lithium resorbed, in that, the lower the sodium intake, the greater is the lithium retention. The contraindications are significant cardiovascular or renal diseases that would compromise its excretion.

### SIDE EFFECTS

Lithium is unique among the psychopharmacological compounds in that it rarely has any undesirable effects on emotional and intellectual functioning. A few unwanted effects are seen in the somatic sphere, and these fall into three overlapping categories:

1. Initially, when the maintenance dose of lithium is being established, the patient may experience gastrointestinal discomforts such as nausea, vomiting, diarrhea, stomach pain, muscular weakness, unusual thirst, frequent urination, a slight feeling of being dazed, tiredness, and sleepiness. These early side effects disappear once the patient is stabilized.
2. From the beginning of treatment, patients exhibit light and barely noticeable hand tremors, which do not respond to antiparkinsonian agents.
3. After several months of continuous therapy with lithium, **diabetes insipidus** and goiter may develop. The kidney tubules then become insensitive to the action of antidiuretic hormone, and its administration is ineffective. Either a dose reduction or discontinuation of the lithium corrects this side effect without leaving any residual pathology. In the

presence of goiter, the patient remains euthyroid. It has been reported that the administration of small amounts of thyroxine may counteract this side effect.

### PHARMACODYNAMICS OF LITHIUM

Lithium is thought to exert its effect by interfering with the calcium-mediated release of norepinephrine, increasing the uptake of norepinephrine, and decreasing the sensitivity of postsynaptic receptor sites to norepinephrine.

In addition, there is increasing evidence that lithium exerts its therapeutic action by interfering with the polyphosphoinositide metabolism in the brain and by preventing inositol recycling through the uncompetitive inhibition of inositol monophosphatase.

### THERAPEUTIC USES OF LITHIUM

The uses of lithium fall into two categories: established and innovative. Among its established uses, lithium salts are used to treat acute mania and as a prophylactic measure to prevent the recurrence of bipolar manic-depressive illness. As an innovative agent, lithium salts have been used with certain success in the management of the following illnesses or conditions.

In combination with tricyclic antidepressants, lithium is used in treating recurrent endogenous depression. In combination with neuroleptics, it is used in the management of schizoaffective disorders. In combination with neuroleptics, it is used to control schizophrenia. Lithium is also used in the case of patients with alcoholism associated with depression and has been used to correct the neutropenia that occurs during cancer chemotherapy.

Lithium has been investigated for use in subduing aggressive behaviors in nonpsychotic but possibly brain-damaged patients. Its use has also been investigated in the management of inappropriate secretion of antidiuretic hormone.

### REGULATORY STATUS OF HYPERICUM

**Hypericum** (as *Hypericum perforatum* L.) has official status (i.e., government approval in some capacity) in several countries throughout the world. In some cases, the status is based on traditional use rather than on controlled trials. Table 43.3 shows the status of hypericum.

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**TABLE 43.3**  
**Regulatory Status of Hypericum**

Country	Regulatory Status
Canada	Authorization has been granted for hypericum preparations as traditional herbal medicines intended to be used as a sedative for relief of restlessness (or nervousness) due to overwork, tiredness, and fatigue. Crude dried herbs of hypericum intended for sale as food, without medicinal representations, may be sold if they conform with the pertinent requirements of the Food Regulations.
France	The flowering tip has traditional use externally for chapped skin, insect bites, minor burns, pruritus, and rash. It is permitted for use in temporary relief of sore throat and hoarseness.
Germany	Hypericum is registered for mild to moderate depressive episodes as specified in the <i>International Classification of Diseases</i> , 10th revision. Commission E has approved the oily hypericum preparations for topical use to treat incised and contused wounds, myalgia, and first-degree burns.

*Note:* St. John's wort is stated to possess sedative and astringent properties. It has been used for excitability, neuralgia, fibrositis, sciatica, wounds, and specifically for menopausal neurosis. St. John's wort is used extensively in homeopathic preparations as well as in herbal products.

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# 44 Ipecac

## IPECACUANHA AND EMETINE

Ipecac, the root of a Brazilian plant, contains several alkaloids of which two, **emetine** and **cephaëline**, produce local irritation and nausea and emesis, by central and local action, without danger of side effects.

Ipecac is the root of *Cephaëlis ipecacuanha*, or of *C. acuminata*, a perennial shrub growing in Brazil and other South American states (Figure 44.1). It contains three alkaloids — **emetin**, **cephaëlin**, and **psychotrin**. The dose of the powdered drug as an expectorant is from 1/2 to 2 grain (0.03 to 0.13 g); as an emetic, 15 to 30 grain (1.0 to 2.0 g) (Table 44.1).

## IPECAC

### HISTORY

**Ipecac** (“**Brazil root**”) was long employed by the native people of Brazil in the treatment of diarrhea. It was sold as a secret remedy to the French government in 1658, and its use in dysentery rapidly spread throughout Europe and India. Its employment was entirely empirical until 1912 when Vedder demonstrated the *in vitro* efficacy of emetine against *E. histolytica* and suggested that ipecac be used in amebic infections. The source of ipecac is the dried root or rhizome of *C. ipecacuanha* or *C. acuminata*, plants native to Brazil and Central America, but also cultivated in India, the Straits Settlements, and the Federated Malay States (see Grollman, 1962).

Emetine was first described in 1817 by Pelletier, the discoverer of **quinine**. However, Pelletier was actually dealing with a mixture of the alkaloids of ipecac, that is, **emetine**, **cephaëline**, and **psychotrine** (see Grollman, 1962).

### ACTIVE PRINCIPLES

The efficacy of ipecac in amebic infections depends upon its content of alkaloids, the principal ones being **emetine** and **cephaëline**. Both are **amebicidal**, but emetine is much more active. Cephaëline is more toxic than emetine, except for the heart, and causes more nausea and vomiting. Emetine constitutes more than one half of the total alkaloidal content of ipecac.

### STATUS AND USE

Ipecac is an amebicidal and emetic agent. Ipecac is official in the U.S.P. in powder form and as a fluid extract and syrup. It is rarely used in the modern therapy of **amebiasis** because its administration results in severe gastrointestinal irritation, nausea, and vomiting. The drug is not employed unless the patient has proved refractory to other methods of treatment. If prescribed, ipecac is given as the powder in salol-coated pills, each containing 0.03 g. The dose is 10 to 15 such pills taken at night before retiring. Ipecac should not be given in divided doses. The full course consists of 100 pills. The patient should be at absolute bed rest during the treatment. All the precautions outlined for emetine therapy must be observed. **Tincture of opium** may be needed to control nausea and vomiting, which, nevertheless, maybe so severe as to necessitate cessation of ipecac administration.



***Cephaelis Ipecacuanha* Willd**

**FIGURE 44.1** Ipecac plant — *Cephaelis* (*Uragoga*) *ipecacuanha*: (a) flowering shoot, (b) flower in longitudinal section, (c) fruit, (d) fruit in transverse section, (e) seed, (f) annulate root.

**TABLE 44.1**  
**The Emetic Doses of Ipecac Preparations**

Preparations	Dose
Fluidextractum ipecacuanhae	As an expectorant 2–5 min (0.1–0.3 cc); as an emetic, 15–30 min (1.0–2.0 cc)
Syrupus ipecacuanhae	As an expectorant, 10–60 min (0.6–4.0 cc); as an emetic, 2–4 fl. Dr. (8.0–15.0 cc)
Vinum ipecacuanhae	As an expectorant, 10–60 min (0.6–4.0 cc); as an emetic, 2–4 fl. Dr. (8.0–15.0 cc)

*Note:* The most commonly used emetics are ipecac and apomorphine. Induced emesis is the preferred means of emptying the stomach in awake patients who have ingested a toxic substance or have recently taken a drug overdose. Emesis should not be induced if there is central nervous system depression or ingestion of certain volatile hydrocarbons and caustic substances. Ipecac syrup is prepared from the dried rhizome and roots of *Cephaelis ipecacuanha* or of *C. accuminata*, plants from Brazil and Central America, in which the alkaloid emetine is its active principal ingredient.

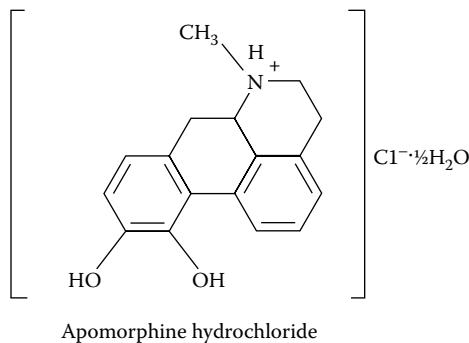
## DRUGS THAT PRODUCE VOMITING (EMETICS)

There are a few important drugs that cause nausea and vomiting as undesirable side actions when used in therapeutic dosage, and perhaps a larger number that induce the state as part of a serious toxic reaction to them in overdose, but the number that is used intentionally to cause the patient to vomit is relatively small. Here, the following four — ipecac, apomorphine, mustard, copper sulfate — are considered as a group.

### SOURCE, NATURE, AND PREPARATIONS

**Ipecac**, which is a mixture of the alcohol-soluble alkaloids from the underground parts of the South American plant, *C. ipecacuanha*, is used almost solely as the U.S.P. ipecac syrup.

**Apomorphine hydrochloride** (Figure 44.2), an alkaloid obtained in the laboratory by rearrangements within the morphine molecule, is a grayish-white, glistening, light-sensitive, and air-sensitive crystalline powder, soluble in both water and alcohol in the proportions of about 1:50; it is available in small amounts in bulk and more easily as 5 mg (1/12 grain) tablets.



**FIGURE 44.2** The structure of apomorphine hydrochloride.

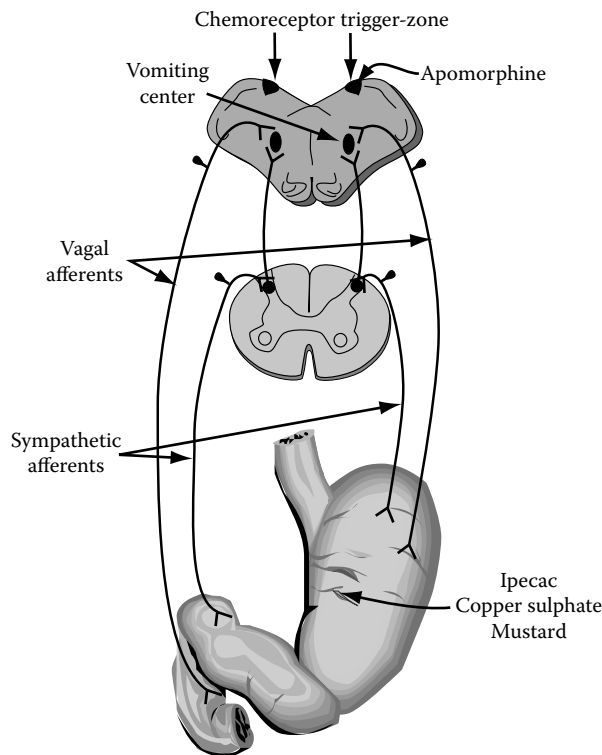
**Black mustard** is a light olive-brown powder obtained by grinding the dried ripe seeds of several varieties of plants of the *Brassica* genus; moisture yields from this, through enzymatic hydrolysis of a contained glycoside, are about 0.6% of the volatile oil of mustard, which has as its main ingredient the irritant compound **allyl isothiocyanate**. Mustard is available in bulk and as the official plaster, the latter used only for the local irritant (**counterirritant**) properties it develops when applied to the skin after moistening with tepid water.

**Copper sulfate** ( $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ) occurs as deep blue crystals or granules that effloresce slowly in dry air; it is freely soluble in water and in glycerin (1:3), slightly soluble in alcohol (1:500), the solutions being acidic; and it is available in bulk.

#### NATURE OF EMETIC ACTION OF IPECAC

There are three sites at which chemical irritation with emetic drugs can initiate vomiting: the gastroduodenal mucosa, the chemoreceptor trigger zone in the caudal portion of the fourth ventricle (area postrema), and the lateral reticular formation of the medulla (vomiting center) (Figure 44.3). The intimate nature of the interferences in cellular metabolism effected by the drugs has not been determined, but it is known at which of these sites the individual drugs act. In Figure 44.3 are shown the points of attack when the drugs are given under clinical circumstances, but this picture must be amplified somewhat with words to bring in the occurrences under experimental conditions as well.

When given orally in therapeutic dosage **ipecac** and **copper sulfate** fire reflex discharges in the gastroduodenal mucosa whose pathways to the vomiting center are afferent fibrils carried in the vagal and sympathetic nerves. In the laboratory, copper sulfate in high doses orally or intravenously also acts at the **chemoreceptor trigger zone**. And **emetine**, an alkaloid obtained from ipecac, likewise has central action when given parenterally. **Apomorphine** acts solely at the



**FIGURE 44.3** Sites of action of emetic drugs as employed clinically.

chemoreceptor trigger zone; mustard is not known to act elsewhere than locally on the gastroduodenal mucosa.

## CLINICAL EFFECTS

Emetics are used rather infrequently because the occasions for making a patient vomit do not arise very often. In the several types of food poisoning it is usually considered advisable, if emptying of the stomach is indicated, to use the tube rather than emetic drugs. This is the case also when potent drugs have been ingested in excessive dosage by accident or with suicidal intent. Even in the case of **phosphorus poisoning**, lavage is most important, although it is undeniable that copper sulfate will precipitate an impermeable coating of **copper phosphide** on the encountered phosphorus particles.

Actually, in the past, perhaps the only three really important uses of emetics under ordinary circumstances were to treat the following:

1. The **fulminating-asthmatic attack**
2. The recalcitrant attack or **paroxysmal atrial tachycardia**
3. The midnight attack of **catarrhal croup** in an infant

In all three instances ipecac is the drug of choice, and it is used not to rid the stomach of noxious contents but to profit by the act of vomiting itself. In the asthmatic attack, with the bronchi blocked with accumulations of mucus, forceful vomiting will release the plugs and often afford truly dramatic relief. It is possible that the retching and vomiting induce a peristaltoid action in the trachea and release the obstructing plugs through what has been called "**tracheal vomiting**." In the case of the arrhythmia, the action comes about through an increase of cardiac vagal influence simply because central, vagal stimulation is an accompaniment of the act of vomiting. It is also this central vagal stimulation that appears to relieve the **glottic spasm in croup**.

## PREVENTION OF FURTHER ABSORPTION OF POISON

### EMESIS

Although emesis is indicated after poisoning by oral ingestion of most chemicals, it is contraindicated in certain situations as follows:

- If the patient has ingested a **corrosive poison**, such as a strong acid or alkali (e.g., drain cleaners), emesis increases the likelihood of gastric perforation and further necrosis of the esophagus.
- If the patient is comatose or in a state of stupor or delirium, emesis may cause aspiration of the gastric contents.
- If the patient has ingested a central nervous system (CNS) stimulant, further stimulation associated with vomiting may precipitate convulsions.
- If the patient has ingested a **petroleum distillate** (e.g., **kerosene**, **gasoline**, or petroleum-based liquid furniture polish), regurgitated hydrocarbons can be aspirated readily and cause **chemical pneumonitis**.

In contrast, emesis should be considered if the solution that is ingested contains potentially dangerous compounds, such as **pesticides**. There are marked differences in the capabilities of various petroleum distillates to produce **hydrocarbon pneumonia**, which is an acute, **hemorrhagic necrotizing process**. In general, the ability of various hydrocarbons to produce **pneumonitis** is inversely proportional to the viscosity of the agent: if the viscosity is high, as with oils and greases,



the risk is limited; if viscosity is low, as with mineral seal oil found in liquid furniture polishes, the risk of aspiration is high.

Vomiting can be induced mechanically by stroking the posterior pharynx. However, this technique is not as effective as the administration of ipecac or apomorphine.

### SYRUP OF IPECAC

The most useful household emetic is **syrup of ipecac** (not **ipecac fluid extract**, which is 14 times more potent and may cause fatalities). Syrup of ipecac is available in 0.5- and 1-fluid ounce containers (approximately 15 and 30 ml), which may be purchased without prescription. The drug can be given orally, but it takes 15 to 30 min to produce emesis; this compares favorably with the time usually required for adequate gastric lavage. The oral dose is 15 ml in children from 6 months to 12 years of age and 30 ml in older children and adults. Because emesis may not occur when the stomach is empty, the administration of ipecac should be followed by a drink of water.

### MONITORING

In dealing with poisoning, serial measurement and charting of vital signs and important reflexes help to judge progress of intoxication, response to therapy, and the need for additional treatment. This monitoring usually requires hospitalization. The classification in Table 44.2 often is used to indicate the severity of CNS intoxication. Treatment with large doses of stimulants and sedatives often can cause more harm than the poison. Chemical antidotes should be used judiciously; heroic measures seldom are necessary.

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**TABLE 44.2**  
**Signs and Symptoms of CNS Intoxication**

Degree of Severity	Characteristics
<i>Depressants</i>	
0	Asleep, but can be aroused, and can answer questions
I	Semicomatose, withdraws from painful stimuli, reflexes intact
II	Comatose, does not withdraw from painful stimuli, no respiratory or circulatory depression, most reflexes intact
III	Comatose, most or all reflexes absent, but without depression of respiration or of circulation
IV	Comatose, reflexes absent, respiratory depression with cyanosis or circulatory, failure and shock, or both
<i>Stimulants</i>	
I	Restlessness, irritability, insomnia, tremor, hyperreflexia, sweating, mydriasis, flushing
II	Confusion, hyperactivity, hypertension, tachypnea, tachycardia, extrasystoles, sweating, mydriasis, flushing, mild hyperpyrexia
III	Delirium, mania, self-injury, marked hypertension, tachycardia, arrhythmias, hyperpyrexia
IV	As in III, plus convulsion, coma, and circulatory collapse

*Note:* As with therapeutic effects, the toxicity of drugs and other chemicals is a function of the concentration of the compound achieved at the site of action. For locally acting external irritants this means that the magnitude of toxicity produced is proportional to the concentration of the substance in the external medium (air or water); for systemically acting agents, the magnitude of the adverse effects produced is proportional to the dose of the toxicant.

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## AMEBIASIS

Amebiasis is an infection of the large intestine produced by *Entamoeba histolytica* that causes symptoms that range from mild diarrhea to fulminant dysentery. Therapy includes treating the asymptomatic carrier of the cysts, as well as the acute amebic dysentery, and the amebic hepatitis and abscess in the symptomatic patient.

### TREATMENT OF THE ASYMPTOMATIC CARRIER

Effective drugs for treating the asymptomatic carrier are the **8-hydroxyquinoline derivatives**, such as **iodoquinol** (the preferred drug) and **difoxanide furoate** (an alternative drug).

### TREATMENT OF ACUTE AMEBIC DYSENTERY

**Dehydroemetine** is given for 5 d and effects rapid relief of the symptoms of acute amebic dysentery. The patient is then switched to **metronidazole**. If the response to metronidazole is not satisfactory, **dehydroemetine plus tetracycline** or **dehydroemetine plus paromomycin** are given along with the metronidazole.

### TREATMENT OF AMEBIC HEPATITIS AND ABSCESS

Amebic hepatitis and abscess are best treated with metronidazole. Dehydroemetine or chloroquine can serve as alternative drugs.



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# 45 Manuka and Fungal Disease

## TEA TREE OILS FROM AUSTRALIA AND NEW ZEALAND

Both Australia and New Zealand have indigenous “tea trees” in the family **Myrtaceae**, which were reputedly used for brewing tea by **Captain Cook**. There is, however, no resemblance between real tea *Camellia sinensis*, **Camelliaceae**, and the taste or odor of these species. The Australian tea tree oil from *Melaleuca alternifolia* and other *Melaleuca* species has strong antimicrobial potential (see Lis-Balchin et al., 2000, for a review and references).

The whole-plant extract had been used originally by aboriginals and the essential oils themselves had been used during the World War II as a general antimicrobial agent and insect repellent, and provided in the first-aid kits of serving Australian soldiers. The essential oil is used today as a strong antimicrobial and antifungal agent in creams, soaps, toothpastes, and other preparations and has been used both externally and internally by both **herbalists** and **aromatherapists** for some years.

There is scant evidence that **Manuka** (*Leptospermum scoparium*) and **Kanuka** (*Kunzea ericoides*) have such potential, but as the essential oils are said to have remarkable powers of healing, based on folk medicinal usage. These oils are being used by some aromatherapists, although there have been no safety or toxicological evaluations performed on them.

Many of the folk-medicinal uses of the New Zealand tea tree oils are related to both species, e.g., the leaves of Manuka and Kanuka were used as vapor baths for colds; an infusion was very astringent and various uses were found for concoctions including urinary complaints and as a febrifuge. Kanuka was applied to scalds and burns, used to stop coughing, and as a sedative; it was also used against dysentery. The decoction of boiled leaves and bark was used to treat stiff backs, etc. Seed capsules were boiled to yield a decoction to apply externally to treat inflammation or to drink for diarrhea; the capsules or leaves were also chewed for dysentery. The water from boiled bark was used for treating inflamed breasts and also to treat mouth, throat, and eye problems.

The antibacterial effect of honey derived from Kanuka and Manuka blossom against *Staphylococcus aureus* was shown and, more recently, Manuka honey was shown to be active against *Helicobacter pylori*. *Leptospermum scoparium* contains **leptospermone**, which has antihelminthic properties and is closely related to compounds having similar properties in male ferns; **leptospermone** has insecticidal properties, and is similar in structure to the insecticide **valone**.

Lis-Balchin et al. (2000) studied three different species of **Myrtaceae** growing in Australia and New Zealand all known as *tea tree* — the Australian tea tree (*Melaleuca alternifolia*), the New Zealand Manuka (*Leptospermum scoparium*), and Kanuka (*Kunzea ericoides*). All three essential oils are used by aromatherapists, although only *Melaleuca* has been tested for toxicity and its antimicrobial effects studied. The pharmacology and antimicrobial activity of the three tea tree oils was determined using guinea pig ileum, skeletal muscle (chick biventer muscle and the rat phrenic nerve diaphragm), and also rat uterus *in vitro*. Differences were shown between the three essential oils in their action on smooth muscle: Manuka had a spasmolytic action, whereas Kanuka and *Melaleuca* had an initial spasmogenic action. In the diaphragm, Manuka and *Melaleuca* decreased the tension and caused a delayed contracture; Kanuka had no activity at the same concentration. The action on chick biventer muscle was, however, similar for all three oils, as was the action on the uterus, in which they caused a decrease in the force of the spontaneous contractions. The latter action suggests caution in the use of these essential oils during childbirth, as cessation of contrac-

tions could put the baby, and mother, at risk. The comparative antimicrobial activity showed greater differences between different samples of Manuka and Kanuka than *Melaleuca* samples. The antifungal activity of Kanuka was inversely proportional to its strong antibacterial activity, whereas Manuka displayed a stronger antifungal effect, although not as potent as *Melaleuca*. The antioxidant activity of Manuka samples was more consistent than that of Kanuka, whereas *Melaleuca* showed no activity. The variability in the Manuka and Kanuka essential oils suggests caution in their usage, as does the fact that the oils have not been tested for toxicity.

## FUNGAL DISEASES

The following are fungal diseases — **histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, cryptococcosis, sporotrichosis, candidiasis, aspergillosis, and mucormycosis.**

## ANTIFUNGAL AGENTS

Antifungal agents consist of either topical or systemic medications. Systemic antifungal agents include:

- Amphotericin B
- Flucytosine
- Ketoconazole
- Griseofulvin
- Nystatin

The topical antifungal agents comprise:

- Clotrimazole
- Econazole
- Miconazole
- Terconazole and butoconazole
- Ciclopirox olamine
- Haloprogin
- Totnaftate
- Naftifine
- Nystatin
- Undecylenic acid
- Benzoic acid

## SYSTEMIC ANTIFUNGAL AGENTS

### AMPHOTERICIN B

Amphotericin B (Fungizone), which is ineffective in ridding infections caused by bacteria, *Rickettsia*, or viruses, is either fungicidal or fungistatic, depending on the drug concentration used or the sensitivity of the particular fungus. Numerous pathogenic yeasts (*Cryptococcus neoformans*), pathogenic yeastlike organisms (*Monilia*), dimorphic fungi (*Blastomyces*), filamentous fungi (*Cladosporeium*), and other fungi are highly sensitive to amphotericin B. Furthermore, the antifungal actions of amphotericin B are enhanced by **flucytosine, minocycline, or rifampin** — agents otherwise devoid of antifungal activity.

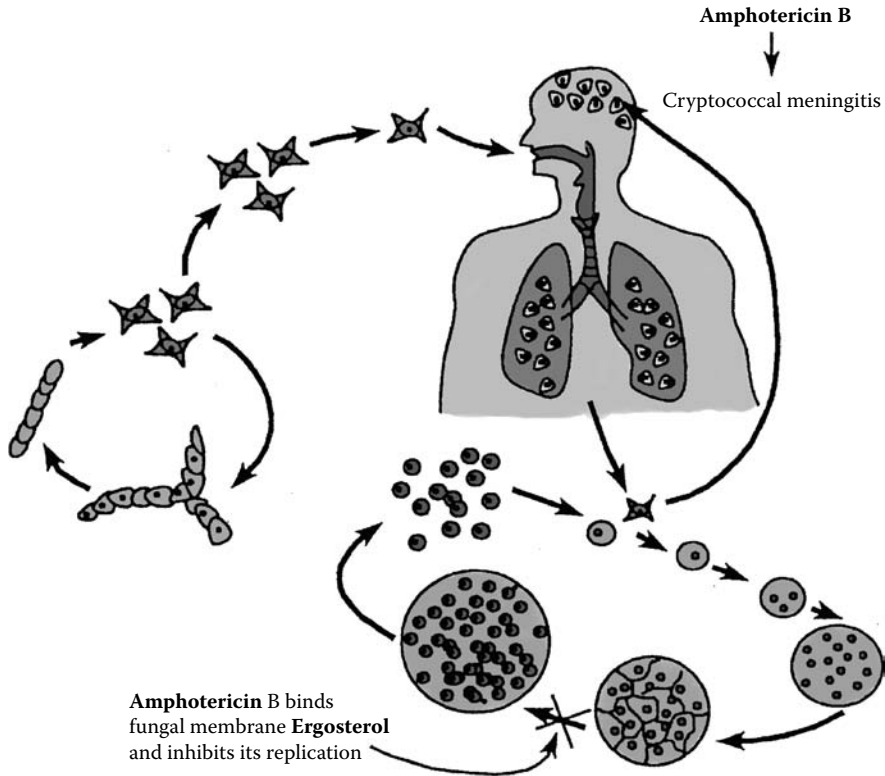


FIGURE 45.1 The mechanism of action of amphotericin B.

### Pharmacodynamics

Amphotericin B imposes its antifungal effects by binding to the sterol moiety of the membrane and damaging its structural and functional integrity (Figure 45.1).

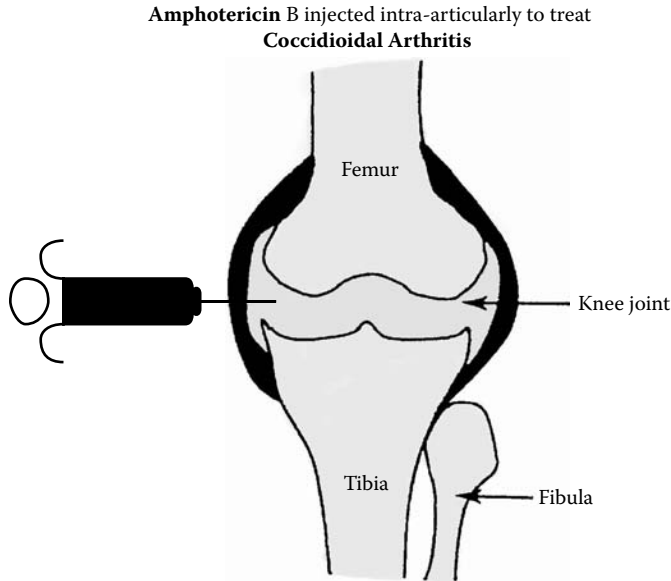
### Pharmacokinetics and Proper Usage

Amphotericin B is available in the form of sterile lyophilized powder. Because it is insoluble in water, it is marketed with sodium deoxycholate for dispersal in sterile water and 5% dextrose. The **polyene antibiotics** — **amphotericin B**, **nystatin**, and **candicidin** — are all poorly absorbed from the gastrointestinal tract. In the plasma, amphotericin B binds to lipoproteins including cholesterol. It is extensively metabolized and the inactive metabolite, or metabolites, are slowly excreted in the urine.

Amphotericin B is the only polyene antibiotic given parenterally. When the intravenous route is contemplated, amphotericin B is dispersed fresh, as discussed, and infused slowly. Amphotericin B should not be administered rapidly because this causes cardiac toxicity. **Heparin** (1000 units) is often added to the infusion suspension to avert the risk of **thrombophlebitis**. Amphotericin B can also precipitate normocytic or **normochromic anemia**, **leukopenia**, and **thrombocytopenia**.

During the infusion of amphotericin B, the patient's temperature will rise, which may or may not be accompanied by hypotension and delirium. Often, **hydrocortisone sodium succinate** is added to the infusion during the initial but not the succeeding alternate-day treatment with amphotericin B.

Amphotericin B is nephrotoxic in most patients and often causes a permanent reduction in the glomerular filtration rate. Furthermore, hypokalemia may occur, requiring the oral administration of potassium chloride.



**FIGURE 45.2** Amphotericin B is used to treat coccidioidal arthritis.

Amphotericin B has been used intrathecally in patients with coccidioidal or **cryptococcal meningitis**. The side effects associated with this route of administration are headache, paraesthesia, nerve palsy, and visual impairment. To treat coccidioidal arthritis, amphotericin B may be injected intraarticularly (Figure 45.2).

### FLUCYTOSINE

**Flucytosine** (Ancobon) possesses clinically useful activity against *Cryptococcus neoformans*, *Candida* species, *Torulopsis glabrata*, and the agents of chromomycosis. Susceptible fungi deaminate flucytosine to **5-fluorouracil**, which becomes an antimetabolite. Flucytosine, which is excreted by the kidney, should be used cautiously in the setting of renal impairment. Flucytosine is a bone marrow depressant. Flucytosine is used in combination with **amphotericin B**.

### KETOCONAZOLE

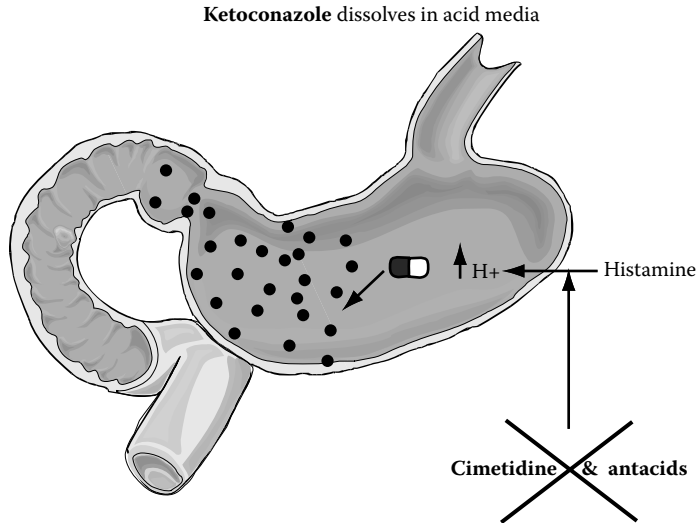
Ketoconazole (Nizoral) has a broad therapeutic potential for a number of superficial and systemic fungal infections. Ketoconazole dissolves in an acidic media; therefore, antacids or histamine<sub>2</sub>-receptor-blocking agents reduce its effectiveness (Figure 45.3). Ketoconazole can cause gastrointestinal disturbances.

### FLUCONAZOLE

Fluconazole, which is absorbed from the stomach, has been shown to be effective in the treatment of the oral and esophageal forms of candidiasis in patients with acquired immunodeficiency syndrome.

### GRISEOFULVIN

Griseofulvin (Fulvicin and Grisactin) is a fungistatic effective against various dermatophytes, including *Microsporum*, *Epidermophyton*, and *Trichophyton*, that produce diseases of the skin, hair, and nails. It exerts its effect by inhibiting fungal mitosis.



**FIGURE 45.3** The action of ketoconazole.

### NYSTATIN

Nystatin (Mycostatin) is poorly absorbed from the gastrointestinal tract. It is both fungistatic and fungicidal but has no effect on bacteria, viruses, or protozoa. It exerts its effect by binding to the sterol moiety and hence damaging the fungal membrane. It is used primarily as a topical agent to treat **candidal infections** of the skin and mucous membrane (**paronychia**, **vaginitis**, and **stomatitis**), and so causes no major toxicities.

## TOPICAL ANTIFUNGAL AGENTS

### CLOTRIMAZOLE

Clotrimazole, which is used only topically, is available as a 1% cream, lotion, or solution (**Lotrimin** and **Mycelex**), as a 1% vaginal cream, as 100- or 500-mg vaginal tablets (**Gyne-Lotrimin**, **Mycelex-G**), and as 10-mg troches (**Mycelex**).

### ECONAZOLE

**Econazole nitrate (Spectazole)** is administered only topically and comes as a water-miscible cream (1%), which is applied twice a day.

### MICONAZOLE

Miconazole nitrate, applied topically, is available as a 2% dermatological cream, spray, powder, or lotion (**Micatin** and **Monistat-Derm**).

### TERCONAZOLE AND BUTOCONAZOLE

Terconazole and **butoconazole nitrate (Femstat)** are available as a 2% vaginal cream. They are used at bedtime for 3 d in nonpregnant females. There is a slower response during pregnancy, which requires a 6-d course of treatment.



### CICLOPIROX OLAMINE

Ciclopirox olamine is available as a 1% cream and lotion applied topically for the treatment of cutaneous candidiasis and tinea corporis, cruris, pedis, and versicolor.

### HALOPROGIN

Haloprogin (Halotex) is available as a 1% cream or solution, which is applied topically. It is applied twice a day for 2 to 4 weeks. It is used principally in the treatment of tinea pedis.

### TOLNAFTATE

Tolnaftate (Aftate, Tinactin, and others) is available in a 1% concentration as a cream, gel, powder, aerosol powder, and topical solution, or as a topical aerosol liquid.

### NAFTIFINE

Naftifine hydrochloride (Naftin) is available as a 1% cream. It is effective for the topical treatment of tinea cruris and corporis.

### UNDECYLENIC ACID

Undecylenic acid (Desenex) is available as a foam, ointment, cream, powder, soap, and liquid, all administered topically.

### BENZOIC ACID AND SALICYLIC ACID

Benzoic and **salicylic acid ointment** is known as **Whitfield's ointment**. It combines the fungistatic action of benzoate with the keratolytic action of salicylate. It contains benzoic acid and salicylic acid in a ratio of 2:1 (usually 6%:3%). It is used mainly in the treatment of tinea pedis.

## AROMATHERAPY CAUTIONS

There is a vogue for many scientifically nonqualified aromatherapists to practice clinical aromatherapy, in which they prescribe the internal usage of essential oils. Internal prescribing involves oral, rectal, and vaginal intake; however, the use of tampons soaked in various potentially toxic essential oils, such as the various tea tree oils, with variable biological potential could have a possible harmful effect on the delicate internal mucosal membranes. The possibility of misdiagnosis of a urogenital condition by medically unqualified aromatherapists or by the patients themselves could also result in serious consequences.

The problem with many Myrtarcae is that of their genetic variation or the production of spontaneous chemotypes, giving many different essential oil compositions with differing bioactivities. The quality of commercial Australian tea tree has now been generally stabilized, mainly by the selection of clones and the blending of different essential oils from different species of *Melaleuca* to conform with the Australian standards, but the problem of diversity remains in other parts of the world where *Melaleuca* species grow, e.g., Zimbabwe, New Zealand, Indonesia, etc. The diversity of Manuka and Kanuka oils is even more pronounced and the use of these New Zealand oils, especially in aromatherapy, may therefore be premature, unless their quality can be assured, and also toxicological studies (that are available for all essential oils used in the food and cosmetics industry) are undertaken (Lis-Balchin et al., 2000).

# 46 Marine Therapeutics

More than 10,000 new compounds have been isolated from bacteria, fungi, microalgae, seaweed, sponges, soft corals, opisthobranch mollusks, bryozoans, echinoderms, and ascidians.

There are two serious obstacles that prevent development of drugs from marine natural products. Obviously, the most important is the “supply issue.” The majority of promising compounds have complex structures, which limits the ability to supply large amounts of samples by chemical synthesis. Usually, yields from organisms are quite low as well. Many researchers believe that these compounds are actually produced by “**symbiotic**” **microorganisms**. Yet bacteria or fungi that produce highly promising metabolites have not been isolated from parent organisms.

Most of the highly bioactive marine metabolites are also highly toxic, which is very serious. If enough materials are available, parent compounds could be modified to reduce their toxicity or to improve their therapeutic efficacy. However, such attempts have not been accomplished because of limited amounts of materials and their highly complex structures, except for readily synthesized substances such as didemnins and dolastatins.

Of course, the discovery of new structures is very important. Marine microbes are relatively new targets for such research. Bacteria and fungi isolated from marine environments, i.e., seawater, sediments, and marine organisms, often produce metabolites identical or similar to those from terrestrial species.

**Phytoplanktons** produce a wide variety of unusual metabolites with strong bioactivities and frequently unprecedented structural features. However, there are some problems — low growth rates, low productivity of metabolites, and complexity of structures are negative factors (Fusetani, 2000). Table 46.1 and Table 46.2 list a few of the more than 10,000 potential drugs that are being isolated from marine life.

**TABLE 46.1**  
**Potential Drugs from Marine Bacteria**

Producing Strains	Sources	Compounds
<b>Anticancer</b>		
<i>Actinomycete</i>	Sediment	Lagunapyrones
<i>Alteromonas haloplanktis</i>	Sediment	Bisucaberin
<i>Alteromonas</i> sp.	Sponge	Alteramide
<i>Bacillus cereus</i>	Mollusk	Homocereulide
<i>Bacillus</i> sp.	Sediment	Halobacillin
<i>Bacillus</i> sp.	Sediment	Isocoumarin
<i>Chaina purpurogena</i>	Sediment	SS-228Y
LL-141352	Tunicate	LL-141352β
<i>Micromonospora</i> sp.	Soft coral	Thiocoraline
<i>Pelagiobacter</i> sp.	Alga	Pelagiomycin
<i>Streptomyces hygroscopicus</i>	Fish gut	Halichomycin
<i>Streptomyces sioyaensis</i>	Sediment	Allemicidin
<i>Streptomyces</i> sp.	Soft coral	Octalacins

*Continued.*

**TABLE 46.1 (Continued)**  
**Potential Drugs from Marine Bacteria**

Producing Strains	Sources	Compounds
<b>Anticancer</b>		
<i>Streptomyces</i> sp.	Sediment	$\gamma$ -Indomycinone
<i>Streptomyces</i> sp.	Sediment	$\delta$ -Indomycinone
<i>Streptomyces</i>	Mollusk	Aburatubolactam C
<i>Vibrio</i> sp.	Driftwood	Acyldepsipeptide
<b>Antibacterial</b>		
<i>Actinomycete</i>	Sediment	Marinone
<i>Alcaligenes faecalis</i>	Mollusk	B-1015
<i>Alteromonas rava</i>	Seawater	Thiomarinol
<i>Bacillus</i> sp.	Marine worm	Loloatins
<i>Chromobacterium</i> sp.	Seawater	Bromopyrroles
Maduromycete	Sediment	Maduralide
Pseudoalteromonas	Alga	Korormicin
Pseudomonad	Seawater	Quinolinol
<i>Pseudomonas aeruginosa</i>	Sponge	Diketopiperazine
<i>Pseudomonas bromoutilis</i>	Seagrass	Pentabromopseudilin
<i>Pseudomonas fluorescens</i>	Ascidian	Andrimid, noiramides
<i>Pseudomonas</i> sp.	Alga	Massetolides
<i>Streptomyces griseus</i>	Sediment	Aplasmomycins
<i>Streptomyces</i> sp.	Sediment	Phenazines
<i>Streptomyces</i> sp.	Sponge	Urauchimycins
<i>Streptomyces</i> sp.	Sediment	Bioxalomycins
<i>Streptomyces tenjimariensis</i>	Sediment	Istamycins
Streptomycete	Sediment	Wailupemycins
<i>Vibrio gazogenes</i>	Sediment	Magnesidins
<i>Vibrio</i> sp.	Sponge	Phenolic
<i>Vibrio</i> sp.	Sponge	Trisindoline
<b>Antiviral</b>		
Unidentified Gram-positive	Sediment	Macrolactins
Unidentified Gram-positive	Sediment	Caprolactins
<b>Anti-inflammatory</b>		
Actinomycete	Jellyfish	Salinamides

**TABLE 46.2**  
**Potential Drugs from Marine Fungi**

Producing Strains	Sources	Compounds
<b>Anticancer</b>		
<i>Aspergillus fumigatus</i>	Fish	Fumiquinazolines
<i>Aspergillus fumigatus</i>	Sediment	Tryprostatins
<i>Aspergillus niger</i>	Sponge	Asperazine
<i>Aspergillus</i> sp.	Sediment	Aspergillamides
<i>Aspergillus versicolor</i>	Alga	Sesquiterpene esters
<i>Fusarium</i> sp.	Wood	Neomangicols
<i>Gymnasella dankaliensis</i>	Sponge	Gymnastatins
<i>Gymnasella dankaliensis</i>	Sponge	Gymnasterones
<i>Leptosphaeria</i> sp.	Alga	Leptosins
<i>Penicillium fellutanum</i>	Fish	Fellutamides
<i>Penicillium</i> sp.	Alga	Cummunesins
<i>Penicillium</i> sp.	Alga	Penochalasin
<i>Penicillium</i> sp.	Alga	Penostatins
<i>Penicillium waksmanii</i>	Alga	Pyrenocines
<i>Periconia</i> sp.	Sea hare	Pericosines
<i>Phomopsis</i> sp.	Coral reef	Phomopsidin
<i>Trichoderma harzianum</i>	Sponge	Trichodenones, harzialactones spiroxins
<b>Antibacterial</b>		
<i>Coniothyrium</i> sp.	Sponge	Hydroxyphenyl
<i>Corollospora pulchelia</i>	Sand	Melinacidins, gancidin
<i>Exophiala pisciphila</i>	Sponge	Exophilin A
<i>Microsphaeropsis</i> sp.	Sponge	Microsphaeropsisin
<i>Preussia aurantiaca</i>	Mangrove	Auranticins
Unidentified fungus	Sponge	Secocurvularin
Unidentified fungus	Sponge	Hirsutanols
<b>Antiviral</b>		
<i>Scytalidium</i> sp.	Seagrass	Halovirs
<b>Antifungal</b>		
<i>Aspergillus</i> sp.	Alga	Mactanamide
<i>Hypoxylon oceanicum</i>	Wood	15G256γ



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# 47 Morphine:

## *Papaver somniferum*

### INTRODUCTION

Morphine is a **narcotic analgesic** in the combination morphine sulfate (*Astramorph PF, Duramorph, MS Contin, Infumorph, Kadian, MSIR, OMS Concentrate, RMS, Roxanol, Roxanol Rescudose, Roxanol SR, Roxanol 100, and Roxanol UD*). Morphine relieves pain by stimulating opiate receptors in the central nervous system (CNS). It is used in moderate to severe acute and chronic pain, as a preoperative sedative and adjunct to anesthesia, and in the management of dyspnea associated with left ventricular failure and pulmonary edema. Morphine is contraindicated in upper airway obstruction and acute asthma.

### OPIOID ANALGESICS IN HISTORY

Although the psychological effects of opium may have been known to the ancient **Sumerians**, the first undisputed reference to poppy juice is found in the writings of **Theophrastus** in the third century B.C. The word **opium** itself is derived from the Greek name for juice, the drug being obtained from the juice of the poppy, *Papaver somniferum*. Arabian physicians were well versed in the uses of opium; Arabian traders introduced the drug to the East, where it was employed mainly for the control of dysenteries. **Paracelsus** (1493–1541) is credited with repopularizing the use of opium in Europe after it had fallen into disfavor because of its toxicity. By the middle of the 16th century, many of the uses of opium were appreciated. In 1680, **Sydenham** wrote, “Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium” (see Grollman, 1962).

Opium contains more than 20 distinct alkaloids. In 1806, **Sertürner** reported the isolation of a pure substance in opium that he named *morphine*. The discovery of other alkaloids in opium quickly followed that of morphine (**codeine** by Robiquet in 1832 and **papaverine** by Merck in 1848). By the middle of the 19th century, the use of pure alkaloids rather than crude opium preparations began to spread throughout the medical world.

In the U.S. opioid abuse was accentuated by the unrestricted availability of opium until the early years of the 20th century and by the influx of opium-smoking immigrants from the East. In addition, the invention of the hypodermic needle led to the parenteral use of morphine and to a more severe variety of compulsive drug abuse.

The problem of addiction to opioids stimulated a search for potent analgesics free of the addictive potential. Just prior to and following World War II, synthetic compounds such as **meperidine** and **methadone** were introduced into clinical medicine, but proved to have typical morphinelike actions. **Nalorphine**, a derivative of morphine, was an exception. Nalorphine antagonized the effects of morphine and was used to reverse morphine poisoning in the early 1950s. Higher doses of nalorphine are analgesic in postoperative patients, but the drug is not used clinically as an analgesic because of side effects such as anxiety and dysphoria. However, its unusual pharmacological profile ushered in the development of new drugs, such as the relatively pure antagonist **naloxone** and compounds with mixed actions (e.g., **pentazocine**, **butorphanol**, and **buprenor-**

**phine**). Such agents enlarged the range of available therapeutic entities and provided tools needed to explore the mechanisms of opioid actions (Goodman and Gilman, 1955).

The complex interactions of morphine and drugs with mixed agonist/antagonist properties, such as nalorphine, led to the proposal of the existence of multiple classes of opioid receptors. This proposal has now been confirmed, first by receptor-binding studies and more recently with the cloning of four distinct but closely related opioid receptors. Soon after the demonstration of the existence of opioid-binding sites, three classes of endogenous opioid peptides were isolated. They are encoded by different genes, are expressed in distinct neuronal pathways or cell types, and have differing selectivities for the various classes of opioid receptors.

## FRIEDRICH WILHELM ADAM SERTÜRNER AND OPIUM

Friedrich Wilhelm Adam Sertürner (1783–1841) was born in Neuhaus close to the German town Paderborn in Westphalia. At the age of 16, he became an apprentice in the pharmacy of Paderborn, moving from there to Einbeck (1806) and later to Hameln (1820). From 1809, he had his own pharmacy. Already during his apprenticeship, he published his first paper on opium (1805), in which he described the discovery of **meconic acid** in the drug. The next year, a further publication followed, announcing another new substance derived from opium. It was characterized by its solubility in acid water, from which it could be precipitated by ammonia. It thus had the character of a weak base. Because it induced sleep in a dog, Sertürner supposed it to be “**der eigentliche betäubende Grundstoff**” (the specific narcotic element) of opium. In his own laboratory, he followed up the study and now called the new substance **morphine** after the god of sleep, **Morpheus**. Its stupendous effects were clearly shown in experiments on Sertürner himself and three young men. Sertürner had in fact discovered a new group of highly active substances, to which the name *alkaloids* was attached in 1818 by W. Meissner. The priority of the discovery was disputed, because Derosne in 1804 had isolated from opium juice crystals, which he considered to be a salt. The crystals were probably a mixture of morphine and narcotine, but Derosne had completely missed the fact that the substance had the nature of a base. Sertürner’s work at first was neglected in Germany, but thanks to the French chemist J. L. Gay-Lussac, its importance was soon recognized, and in 1831 he received from the Institut de France the Monthyon prize (2000 francs) “pour avoir reconnu la nature alcaline de la morphine et avoir ainsi ouvert une voie, qui a produit de grandes découvertes médicales” (for having found the alkaline nature of morphine and thereby opened a way which has led to great medical discoveries). By this time the methods of Sertürner had been successfully applied to different drugs, and especially through the efforts of P. J. Pelletier (1784–1841) and J. B. Caventou (1788–1842), a series of alkaloids such as **quinine**, **strychnine**, **brucine**, **veratrine**, and **emetine** had been isolated, and many more were to follow. Other work by Sertürner, such as that on the composition of corrosive alkalis and on the nature of cholera (which he considered to be caused by a living organism that might be combated by disinfectants or by boiling the water), proved his unusual gifts (see Potter, 1910; Gathercoal and Wirth, 1947).

## OPIUM

**Opium** or **gum opium** is the air-dried, milky exudation obtained by incising the unripe capsules of *Papaver somniferum* Linné or its variety *P. album* DeCandolle. The term *opium* is from the Greek *opion*, meaning poppy juice. *Papaver* is the Latin name for the poppy and *somniferum* is Latin meaning to produce sleep. The opium poppy is an annual herb with large, showy, solitary flowers varying in color from white (var. *album*) to pink or purple (Figure 47.1).

Opium, which is native to Asia Minor, was introduced into India by the Mohammedans in the 15th century; cultivation was begun in Macedonia and Persia about the middle of the 19th century. Opium is commercially produced now in Turkey, the Balkan States, Persia, India, and China. The



**FIGURE 47.1** The oriental poppy (*Papaver somniferum*) from which opium is derived. The unripe pod from which opium juice is obtained is shown together with the flowering plant.

discovery of the medicinal qualities of opium is lost in antiquity. **Theophrastus** (third century B.C.) mentions it, and **Dioscorides** (A.D. 77) distinguishes between the juice of the poppy and an extract of the entire plant.

### CULTIVATION, COLLECTION, AND COMMERCE

The seeds of the opium poppy are sown in October in well-cultivated soil. The seeds germinate in the fall, and the seedlings may be an inch high when snow falls; this protects them from freezing. In the spring, when the plants have attained the height of 6 in., the fields are cultivated and the plants thinned to stand about 2 ft apart. The poppy blossoms in April or May, and the capsules mature in June or July. Each plant bears from five to eight capsules.

The ripening capsules, about 4 cm in diameter, change from bluish green to yellowish in color. This is a critical time for collecting the latex. The capsules are incised with a knife, usually three bladed, the incision made around the circumference of the capsule (see Figure 47.1). The latex tubes open into one another so that it is not necessary to incise them all. Great skill, however, is required so as not to cut through the endocarp, in which case the latex would flow into the interior of the capsule and be lost. The latex, which is at first white, rapidly coagulates and turns brown. This is removed early the following morning, being scraped off with a knife and transferred to a poppy leaf. When sufficient latex is collected, it is kneaded into balls, which are wrapped in poppy leaves and shade-dried. The opium is then inspected and usually packed with the brown winged fruits of a *Rumex*, which prevents cohering. In some districts, the latex is molded or pressed into cakes or other forms, which are then wrapped in paper (Gathercoal and Wirth, 1947).

Opium contains 20 alkaloids in combination with meconic, lactic, and sulfuric acids; the neutral principles are *meconin* and *meconoiasin*, besides glucose, mucilage, resin, pectin, caoutchouc,



fats, essential oil, odorous substances, salts of ammonium, magnesium, and calcium, and water. Its principal alkaloids are the following six:

- **Morphine**,  $C_{17}H_{19}NO_3$ , 2 1/2 to 2% — The principal alkaloid, occurring in the drug in the form of the tribasic meconate. Its properties are anodyne, hypnotic, and narcotic. From it, by a process of dehydration by heat and hydrochloric acid, is prepared the artificial alkaloid *apomorphine*, a powerful emetic and expectorant.
- **Codeine**,  $C_{18}H_{21}NO_3$ , 0.3 to 0.5% — A calmative and, when pure, not very active alkaloid, it is frequently contaminated with other alkaloids. *Apomorphine* may be prepared from it.
- **Narceine**,  $C_{22}H_{29}NO_9$ , 0.2 to 0.7% — It is now believed to have little or no action.
- **Narcotine**,  $C_{22}H_{23}NO_7$ , 2 to 10% — An antiperiodic and a tetanizer, it is wholly devoid of narcotic properties.
- **Thebaine**, or *paramorphine*,  $C_{19}H_{21}NO_3$ , 0.2 to 1% — It is a powerful spinal exaltant and tetanizer, resembling **strychnine** in its action.
- **Papaverine**,  $C_{20}H_{21}NO_4$ , 1% — It stands midway between morphine and codeine in its action on the CNS, but is a comparatively weak poison.

Other alkaloids are **codamine**, **cryptopine**, **gnoscopine**, **hydrocotarnine**, **lanthopine**, **laudanine**, **laudanosine**, **meconidine**, **oxynarcotine**, **papaveramine**, **protopine**, **pseudomorphine**, **rheoadine**, and **tritopine**. Many of them occur only in traces, and some are regarded as probable derivatives of morphine. *Porphyroxin* is said to be a complex combination of several of the alkaloids, and not a proximate principle (Potter, 1910).

## MORPHINE AND OTHER NARCOTIC ANALGESICS

Analgesia means lack of pain, and analgesics are substances that obtund the perception of pain without causing loss of consciousness. However, analgesics should not be given until the cause of pain has been determined. If a proper diagnosis is made, the use of an analgesic may not be necessary. A few examples are cited.

If individuals become dehydrated in hot weather without fluid replenishment, they will suffer painful muscular cramp, known as *stoker's cramp*. This condition may be prevented or corrected by administering sodium chloride and by replenishing the lost fluid. The severe muscular spasm occurring in tetanus is managed by muscle relaxants. The painful epigastric pain associated with acid-pepsin disease is managed with antacids and other medications. The pain associated with gouty arthritis is managed with anti-inflammatory drugs and agents that reduce the synthesis and the pool of uric acid in the body. The headache associated with malignant hypertension is managed with antihypertensive agents.

Although analgesics may ameliorate the pain in all these conditions, their use should not be implemented until the pathology has been discerned and appropriate rehabilitative measures instituted.

## MULTIPLE MEDICATIONS TO TREAT PAINFUL CONDITIONS

In a pathological condition that causes pain, drugs may be used either to care for the acute attack of pain or as prophylaxis to prevent the occurrence of pain. For example, **colchicine** is used during an acute attack of gout, and after the pain has subsided initially, the patient is switched to uricosuric agents such as **probenecid** or an inhibitor of uric acid synthesis such as **allopurinol**.

Drugs used in migraine therapy can be divided into two groups: those that abort an established migraine attack and those used prophylactically to reduce the number of migraine attacks. Each group has drugs that are specific for migrainous headaches and those that are nonspecific but treat the accompanying headache (analgesics), vomiting (antiemetics), anxiety (sedatives and anxioly-

**TABLE 47.1**  
**Endogenous and Synthetic Opioid Peptides**

<b>Selected Endogenous Opioid Peptides</b>	
[Leu <sup>5</sup> ]enkephalin	Tyr-Gly-Gly-Phe-Leu
[Met <sup>5</sup> ]enkephalin	Tyr-Gly-Gly-Phe-Met
Dynorphin A	Tyr-Gly-Gly-Phe-Leu-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln
Dynorphin B	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr
α-Neendorphin	Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys
β-Neendorphin	Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro
β <sub>h</sub> -Endorphin	Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu
<b>Selected Synthetic Opioid Peptides</b>	
DAMGO	[D-Ala <sup>2</sup> , MePhe <sup>4</sup> , Gly <sup>9</sup> ol <sup>5</sup> ]enkephalin
DPDPE	[D-Pen <sup>2</sup> , D-Pen <sup>5</sup> ]enkephalin
DSLET	[D-Ser <sup>2</sup> , Leu <sup>5</sup> ]enkephalin-Thr <sup>6</sup>
DADL	[D-Ala <sup>2</sup> , D-Leu <sup>5</sup> ]enkephalin
CTOP	D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH <sup>2</sup>
FK-33824	[D-Ala <sup>2</sup> , N-MePhe <sup>4</sup> , Met(O) <sup>5</sup> -ol]enkephalin
[D-Ala <sup>2</sup> ]Deltorphin I	Tyr-D-Ala-Phe-Asp-Val-Val-Gly-NH <sup>2</sup>
[D-Ala <sup>2</sup> , Glu <sup>4</sup> ] Deltorphin (Deltorphin II)	Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH <sup>2</sup>
Morphiceptin	Tyr-Pro-Phe-Pro-NH <sup>2</sup>
PL-017	Tyr-Pro-MePhe-D-Pro-NH <sup>2</sup>
DALCE	[D-Ala <sup>2</sup> , Leu <sup>5</sup> , Cys <sup>6</sup> ]enkephalin

*Note:* Three distinct families of peptides have been identified: the *enkephalins*, the *endorphins*, and the *dynorphins*. Each family is derived from a distinct precursor polypeptide and has a characteristic anatomical distribution. These precursors are now designated as proenkephalin (also proenkephalin A), proopi-melanocortin (POMP), and prodynorphin (also proenkephalin).

tics), or depression (antidepressants). The main drugs with specific actions on migraine include ergot alkaloids (**ergotamine**, **dihydroergotamine**), specific serotonin receptor agonists (**sumatriptan**), β-adrenergic receptor antagonists (**propranolol** and **metoprolol**), calcium antagonists (**flunarizine**), and anti-inflammatory agents (**indomethacin**).

## ENDOGENOUS OPIOID PEPTIDES

For many years, pharmacologists considered the possibility that opioids mimic a naturally ongoing process. Investigations isolated opiate-like peptides from the brain that consisted of two similar pentapeptides with the sequences as shown in Table 47.1 through Table 47.3.

## OPIOID RECEPTORS

### THE EVIDENCE FOR MULTIPLE OPIOID RECEPTORS

Opioids produce a large variety of pharmacological responses by interacting with multiple opioid receptors. The indirect evidence for the presence of these multiple receptors is as follows:

- **Nalorphine** produces many of the pharmacological effects of morphine, yet it blocks or reverses the action of morphine.

**TABLE 47.2**  
**Proposed Functions of the Opioid Receptor Types**

Function	Receptor Types	Anatomy
Appetite modulation, eating behavior	$\mu$ , $\delta$ , and $\kappa$	Ventral tegmental area
Cardiovascular regulation	$\mu$ , $\delta$ , and $\kappa$	Nucleus tractus solitarii
Fluid balance	$\kappa$ : diuresis	Hypothalamus and/or pituitary; also possibly kidney ( $\kappa$ )
Endocrine responses	$\mu$ : antidiuresis	Hypothalamus, possible pituitary
Stimulatory effects		
Growth hormone	$\delta$	
Corticotropin	$\mu$ and $\kappa$	
Prolactin	$\mu$ and $\kappa$	
Inhibitory effects		
Luteinizing hormone	$\mu$ and $\delta$	
Vasopressin	$\kappa$	(Also nucleus tractus solitarii)
Oxytocin	$\mu$ and $\kappa$	
Pain inhibition	$\mu$ and $\delta$	Supraspinal
	$\delta$	Spinal medullary reticular formation
	$\kappa$	Spinal
Respiration	$\mu$ and $\delta$ may mediate respiratory depression	Brainstem
Locomotor behavior	$\mu$ : increased activity	A9, A10 DA systems
	$\kappa$ : sedation	A10 DA systems
Thermoregulation	$\mu$ : may mediate hypothermia	Hypothalamus
	$\delta$ : may mediate hyperthermia	

*Note:* DA = dopaminergic.

- **Naloxone**, which does not produce any of the pharmacological effects of morphine, blocks or reverses the action of morphine.
- Subjects who are tolerant to the psychomimetic effects of morphine are not cross-tolerant to the psychomimetic effects of **cyclazocine**.
- The abstinence syndrome associated with morphine is qualitatively different from the abstinence syndrome caused by cyclazocine.
- Agonists–antagonists nalorphine and cyclazocine can induce tolerance to their agonistic effects but not to their antagonistic effects.

### DISTRIBUTION OF OPIOID RECEPTORS

The opioid receptors are distributed widely throughout the neuraxis, but the highest density is found in the limbic structures, thalamic nuclei, and neural areas important for visceral functioning.

### PROPOSED FUNCTIONS OF THE OPIOID RECEPTOR SUBTYPES

The precise functions of the opioid receptor subtypes remain to be delineated. In many studies, it has been established that they modulate the functions of the dopaminergic system. For example, administration of morphine into the area 10 region results in a dopamine-dependent increase in locomotor activity. Electrophysiological studies of area 9 neurons suggest that  $\mu$  and  $\kappa$  opioids have opposite effects on motor behaviors: activation or sedation, respectively. The  $\kappa$  and  $\mu$  agonists have also been found to exert opposite actions with respect to fluid regulation: diuretic and

**TABLE 47.3**  
**Actions and Selectivities of Opioids at the Various Opioid**  
**Receptor Classes**

Opioids	Receptor Types			
	$\mu$	$\delta$	$\kappa_1$	$\kappa_3$
<b>Drugs</b>				
Morphine	+++		+	+
Methadone	+++			
Etorphine	+++	+++	+++	+++
Levorphanol	+++		NA	+++
Fentanyl	+++			
Sufentanil	+++	+	+	
DAMGO	+++			+
Butorphanol	P	NA	+++	NA
Buprenorphine	P	NA	--	NA
Naloxone	----	-	--	--
Naltrexone	----	-	----	--
CTOP	----			-
Diprenorphine	----	--	----	----
$\beta$ -Funaltrexamine	----	-	++	NA
Naloxonazine	----	-	-	-
Nalorphine	----		+	+++
Pentazocine	P		++	+
Nalbuphine	--		++	++
Naloxone benzoylhydrazone	----	-	-	+++
Bremazocine	+++	++	+++	++
Ethylketocyclazocine	P	+	+++	+++
U50,488			+++	
U69,593			+++	
Spiradoline	+		+++	
Nor-Binaltorphimine	-	-	----	-
Naltrindole	-	----	-	-
DPDPE		++		
[D-Ala <sup>2</sup> ,Glu <sup>4</sup> ]deltorphan		++		
DSLET	+	++		
<b>Endogenous Peptides</b>				
Met-enkephalin	++	+++		
Leu-enkephalin	++	+++		
$\beta$ -Endorphin	+++	+++		
Dynorphin A	++		+++	NA
Dynorphin B	+	+	+++	NA
$\alpha$ -Neoendorphin	+	+	+++	NA

*Note:* Activities of drugs are given at the receptors for which the agent has reasonable affinity. + = agonist, - = antagonist, P = partial agonist, NA = data not available or inadequate. DAMGO, CTOP, DPDPE, DSLET. The number of symbols is an indication of potency; the ratio for a given drug denotes selectivity. These values were obtained primarily from animal studies and should be extrapolated to humans with caution. Both  $\beta$ -funaltrexamine and naloxonazine are irreversible  $\mu$  antagonists, but  $\beta$ -funaltrexamine also has reversible  $\kappa$  agonist activity.

antidiuretic effects, respectively. The  $\mu$ ,  $\delta$ ,  $\kappa$  and opioid receptor types have all been implicated in the mediation of analgesia (see Table 47.2).

## MORPHINE AND RELATED COMPOUNDS

The opium alkaloids, which are obtained from *Papaver somniferum*, contain two groups of compounds: compounds with phenanthrene derivatives, consisting of **morphine**, **codeine**, and **thebaine** and compounds with isoquinoline derivatives, consisting of **papaverine** and **noscipine**.

Narcotics are divided into naturally occurring, semisynthetic, and synthetic derivatives. The naturally occurring analgesics consist of morphine and codeine (**methylmorphine**). The semisynthetic analgesics include **hydromorphone** (Dilaudid) and **hydrocodone** (Dicodid). The synthetic analgesics consist of **meperidine** (Demerol), **alphaprodine** (Nisentil), **methadone** (Dolophine), **propoxyphene** (Darvon), and **pentazocine** (Talwin).

The narcotic antagonists are naltrexone and naloxone (Narcan). **Dextromethorphan** (Romilar) is used as an antitussive preparation. Apomorphine is used as an emetic agent.

Narcotic analgesics may have either a high potency (morphine, hydromorphone, oxymorphone, methadone, meperidine, fentanyl, and levorphanol) or low potency (codeine, oxycodone, hydrocodone, propoxyphene, and diphenoxylate). The analgesic agent may be a pure agonist (morphine), pure antagonist (naloxone), or mixed agonist–antagonist (pentazocine).

In discussing the pharmacology of narcotic analgesics, morphine is considered in greater detail as a prototype drug, and all the other compounds are compared with it.

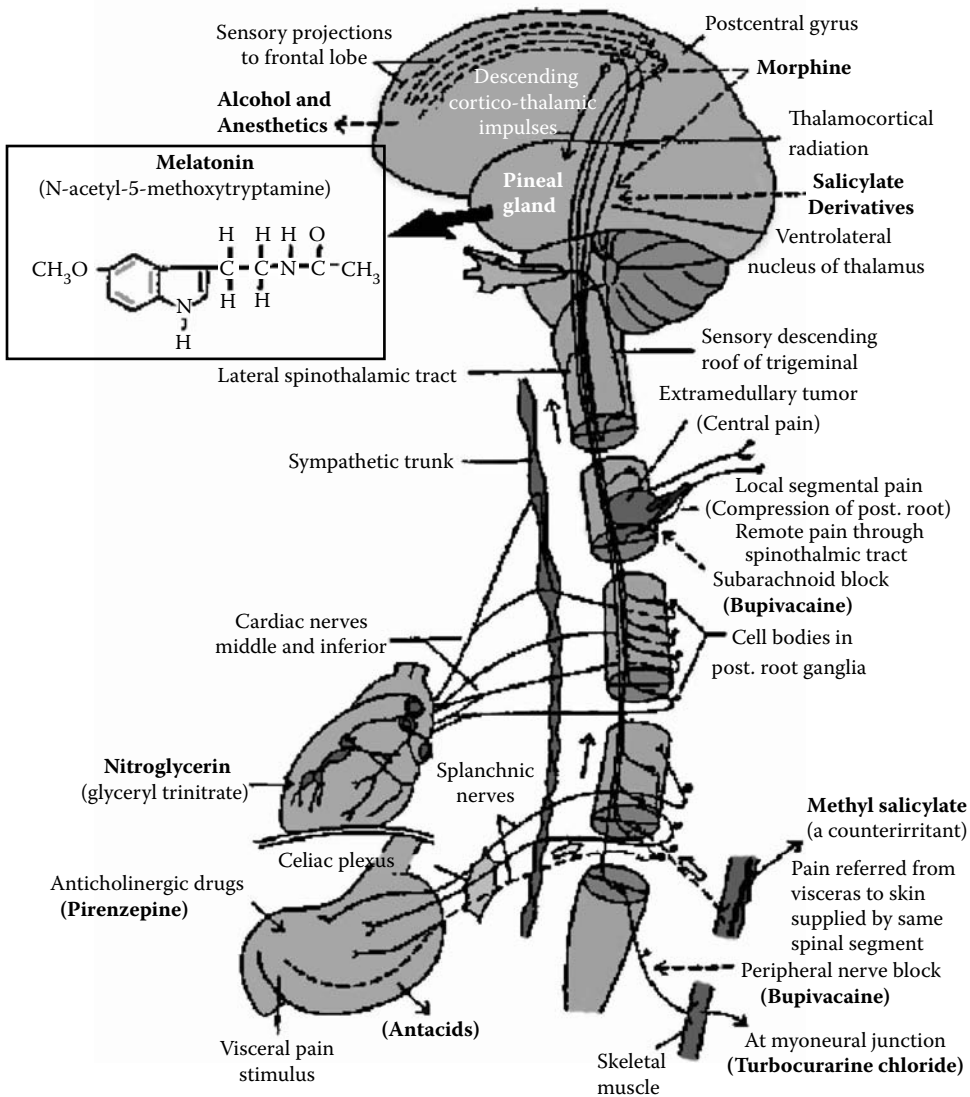
### MORPHINE: A NATURALLY OCCURRING ANALGESIC

#### Effects on the Central Nervous System

The majority of the analgesic agents exert their main action within the CNS, particularly, at the cerebral cortical levels of integration of the pain impulse (Figure 47.2). Many act primarily on the hypothalamic centers, which are also the sites of temperature control, and hence exert an antipyretic as well as an analgesic action. The **salicylates**, for example, are effective antipyretics as well as analgesics. The antirheumatics, used primarily as analgesics in gout and rheumatism, are also included here. In addition to the analgesic property, many drugs are used because of their capacity to relieve pain, but their analgesic action is not dependent on any action on the CNS but rather on the end organ. For example, **amyl nitrite** relieves pain in **angina pectoris** by its action on the coronary blood flow and alleviates pain in biliary colic by reducing the intrabiliary pressure. It, therefore, is not included among analgesics, which act directly on the higher centers involved in the perception of pain. **Morphine**, on the other hand, although not affecting coronary blood flow and actually increasing intrabiliary pressure, nevertheless provides relief from pain in these conditions by its action on the higher cerebral centers and hence is classified as an analgesic.

Pain may be relieved in the following ways:

- By removing its point of origin by drugs (e.g., by regional anesthesia, relief of muscular spasm, etc.) or by surgery (e.g., by excision or denervation of the painful focus)
- By the application of physical measures or anesthetics to the point to which the pain is referred or to the hyperirritable segments of the cord
- By interrupting the impulses that convey the pain by anesthetizing or destroying the nerve tracts
- By modifying the central reception of pain by blocking the facilitating reflexes and thereby raising the pain threshold with analgesic drugs



**FIGURE 47.2** Schematic representation of the pain tracts and their potential interruption at various levels. The figure is organized in 5 sections in relation to the spinal cord, and depicts from bottom up, pain originating in skeletal muscle, stomach (with referral of pain to the skin), heart, spinal cord, and head, respectively. The action of drugs is indicated as of three types: (1) abolition of the pain stimulus, (2) local interruption of the conducting pathways, and (3) elevation of the pain threshold. The spinothalamic tract is shown as a combination of both the right and left sides above the thoracic segment.

- By modifying the central perception, interpretation, and reaction to pain by interrupting the pathways for their transmission in the brain by such drugs as morphine or by such surgical procedures as lobotomy, leucotomy, etc.
- By modifying the central perception of pain of peripheral origin and mitigating psychogenic pain by depressing reflex activity with such drugs as alcohol, the barbiturates, etc.

The ideal analgesic should obliterate pain and diminish the anxiety associated with it; exert a minimal degree of narcosis and stupefaction; be free of such undesirable side effects as constipation,

nausea, respiratory depression, etc.; have no tendency to addiction or the development of tolerance; have a rapid onset and long duration of action; be effective and well tolerated when administered orally; and be relatively inexpensive (Grollman, 1962).

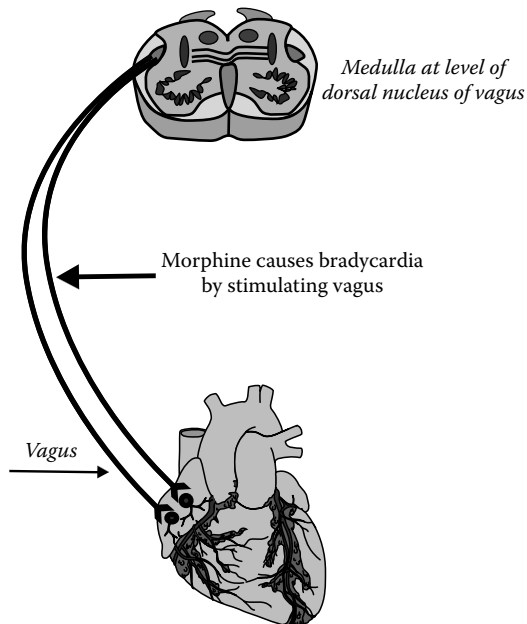
Pain is probably the symptom that most often and most promptly brings the patient to the attention of the physician. The nature of the pain is important in arriving at a correct diagnosis but, once this has been made, relief is in order. The most suitable analgesic to be used in a given patient is dependent upon the nature of the pain, its origin and severity, as well as upon the temperament and personality of the patient. In many cases, narcotics, despite their effectiveness as analgesics, must be excluded because of their potential to cause addiction. The use of a sedative in conjunction with the analgesic is often indicated particularly in nervous individuals.

Experimental evaluation of the analgesic activity of a given drug in humans is difficult, for the reactivity to a painful stimulus varies in different individuals and even in the same individual from time to time. The analgesic action depends on the alteration of the transmission of the pain impulse from the periphery to the cerebral cortex but is modified by psychic factors.

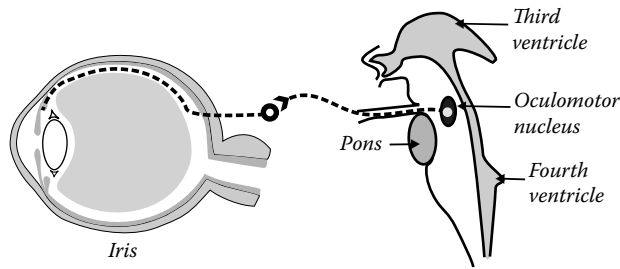
It appears from available evidence that analgesics generally act by altering the patient's reaction to pain rather than by interfering with the pain impulse. This accounts for the great variability in the response elicited in different patients from the same analgesic, as well as for the effectiveness of placebos and suggestion in susceptible individuals.

#### *Morphine Stimulates Parts of the Central Nervous System*

In horses, morphine stimulates the spinal cord in a predictable fashion. This effect is short-lived in humans, and is seldom seen when given in therapeutic doses. Initially, morphine stimulates the vomiting center, and emesis occurs early in cases of intoxication. Depression of the vomiting center then ensues late in intoxication. Morphine stimulates the vagus nerve, causing bradycardia, and stimulates the nucleus of the third cranial nerve (oculomotor), causing miosis (Figure 47.3 and Figure 47.4).



**FIGURE 47.3** Morphine causes bradycardia.



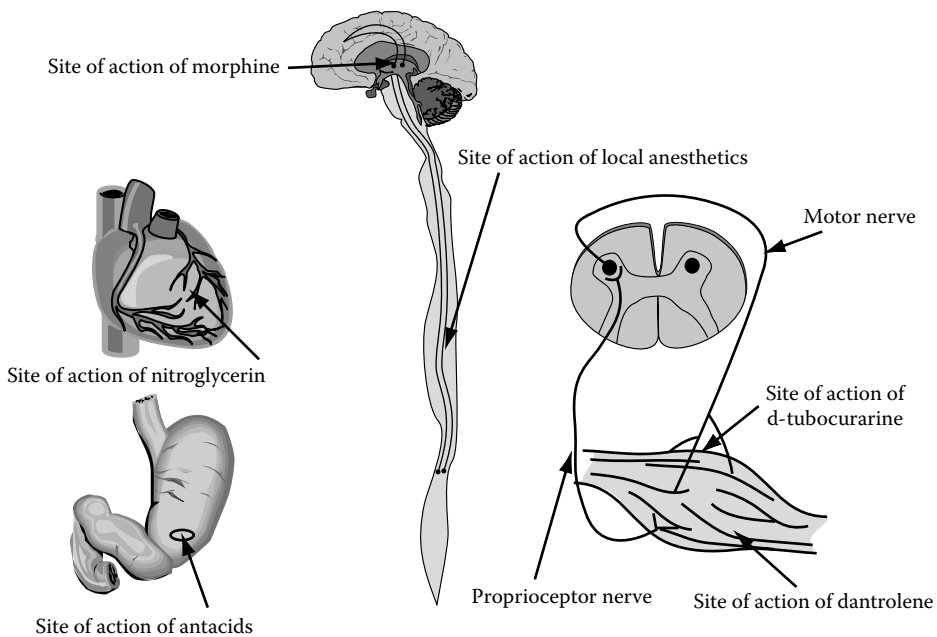
Morphine causes miosis by stimulating the oculomotor nerve

**FIGURE 47.4** Morphine causes miosis by stimulating oculomotor nerve.

**Analgesic Effects**

The relief of pain brought about by morphine is selective, and other sensory modalities such as touch, vibration, vision, hearing, and the like are not obtruded. Morphine does not reduce the responsiveness of nerve endings to noxious stimuli, nor does it impair the conduction of nerve impulses along the peripheral nerves, as seen following the administration of local anesthetics.

Morphine exerts its analgesic effects by elevating the pain threshold and, especially, by altering the patient’s reaction to pain (Figure 47.5). Morphine induces analgesia by activating the opioid, adrenergic, and serotonergic systems within the dorsal horn of the spinal cord that depresses the transmission of pain sensation to the brain. This is accomplished by decreasing the release of pain transmitters such as substance P or



**FIGURE 47.5** Morphine alters the patient’s reaction to pain.



by hyperpolarizing the interneurons within the dorsal horn or in both ways. Morphine activates these mechanisms by interacting with the  $\mu$  receptors located on neurons in the dorsal cord. There is considerable evidence suggesting that this action depends on the activation of the adrenergic system within the dorsal horn. This, in turn, suggests that morphine analgesia could be potentiated by the addition of drugs, such as **clonidine**, that activate the adrenergic system.

In addition, morphine appears to activate the endogenous supraspinal system that is normally activated by pain to protect the body from excessive nonessential pain stimulation. Patients report that the sensation of pain often exists, but, under the influence of morphine, they feel more at ease and comfortable. This euphoria is present in 90 to 95% of patients. Morphine may cause dysphoria in the remaining 5 to 10%.

## Therapeutic Uses of Morphine

### *Local Uses of Opiates*

With the exception of local application of **ethylmorphine** to the conjunctiva or the tympanum to produce hyperemia, there are no rational local uses of opium alkaloids. These drugs are not local anesthetics and relieve pain only by central actions. Indeed, irritation and vesication may result from opium plasters, ointment, or washes applied to the skin or mucosa.

### *Sudorific Action of Morphine*

Although morphine produces some degree of sweating, it is a very poor **diaphoretic** when compared with **pilocarpine** or **methacholine**. The sweating caused by **Dover's powder** is mainly due to the ipecac content. The use of this powder as a diaphoretic for aborting the onset of "colds" due to exposure may conceivably be based on the same rationale as suggested with alcohol.

### *Analgesic Action of Morphine*

The opium alkaloids have no rival for the relief of pain, and when suffering cannot be allayed by nonnarcotic analgesics or other therapeutic measures, morphine may be considered indispensable. In a relatively small dose of 5 to 10 mg, morphine relieves the constant but dull pain originating from the viscera, such as that of coronary, pulmonary, and biliary origin. In somewhat larger doses (10 to 20 mg), morphine relieves the sharp, lancinating, and intermittent pain resulting from bone fractures and other physical injuries. Inoperable and terminal causes of neoplastic diseases usually require the administration of morphine or other narcotics in increasing doses that eventually lead to both tolerance and addiction.

Pain from all parts of the body is dulled by the central action of opium alkaloids. The more severe the pain, the larger the dose of opiate required and the greater the amount of drug that can be tolerated. Thus, for the severe pain due to coronary thrombosis, two to four times the usual therapeutic dose of morphine may be given over a suitable period without the danger of seriously embarrassing respiration. This is in keeping with the general principle that the degree of stupefaction caused by a given amount of a depressant drug is directly proportional to the level of reflex excitability of the nervous system. It is not unusual to administer within an hour from 45 to 60 mg of morphine in 15-mg portions to patients with excruciating pain. However, caution is required in the administration of these large total doses, especially, when they are used for severe pain of a type that may suddenly lessen in severity or even disappear entirely. For example, the pain in coronary occlusion or renal or biliary colic may rapidly decline spontaneously. If patients have already been given a large amount of morphine, they may quickly show signs of morphine poisoning. Close observation of the patient and proper spacing of the doses of morphine will usually prevent such an occurrence.

Pain is a chief diagnostic sign for the physician, and its total abolition may seriously handicap the discovery of the nature of the patient's illness. It has been said of morphine that "it not only puts the patient to sleep but also puts the physician to sleep." Although it is generally unwarranted to make the diagnosis at the cost of unbearable pain, nevertheless there are certain conditions in

which opiates are not usually prescribed until the diagnosis has been made and permission obtained for operation, should it be necessary. These, especially, are the conditions that constitute what is known as the acute surgical abdomen. For example, no single cause, apart from the use of a cathartic, is responsible for more complications or deaths from acute appendicitis than the misuse of opiates.

Nevertheless, it has been claimed that the skillful use of morphine may sometimes aid considerably in the diagnosis of acute abdominal conditions. The patient who is restless, apprehensive, and in severe pain often cannot give a satisfactory or correct history. Rigidity of the abdominal muscles may prevent an adequate physical examination. This rigidity may be due not only to the reflex spinal component as a result of an inflamed viscus but also to a cortical component secondary to intense pain. Morphine in analgesic doses abolishes the cortical component and leaves the spinal reflexes unaffected. In expert hands, the drug may thus be employed to aid in abdominal diagnosis, for which purpose it has been injected intravenously (10 mg) to obtain analgesia and cooperation quickly. Naturally, a baseline history and physical examination are necessary and the patient must be followed up closely.

In patients with pain due to **neoplastic growths** or other chronic diseases, the use of morphine alkaloids should be reserved until nonnarcotic drugs no longer give relief. Then, codeine should be employed in combination with nonnarcotic sedatives and analgesics, and the doses increased until pain can no longer be controlled without morphine, metopon, meperidine, or methadone. The doses should be kept as low as possible so that maximal relief can be given for the longest possible period. Because tolerance develops, one wishes to reserve a margin of susceptibility to cope with the terminal stages when pain may be excruciating. In other words, "the physician should use morphine as a miser spends his gold." If absolutely necessary, of course, morphine is given without stint. When opiates and other analgesics are no longer satisfactory, nerve blocking by injections of alcohol, chordotomy, lobotomy, or other type of neurosurgical intervention may be required if the nature of the lesion allows. In most cases, the euphoria, tranquility, and relief of pain afforded by the wise use of narcotics are a blessing to the patient and family, and death is made easy and comfortable. Narcotic addiction, even in terminal cases, should be avoided if possible; nevertheless, it often occurs despite precautionary measures (Goodman and Gilman, 1955).

For the relief of pain arising from spasm of smooth muscle, as in renal or **biliary** colic, morphine is frequently employed. Other measures including antispasmodics such as atropine, atropine substitutes, theophylline, nitrites, and heat may be employed first; however, if they are ineffective, meperidine, methadone, or opiates must be used. Morphine relieves pain only by a central action and may aggravate the condition producing the pain by exaggerating the smooth muscle spasm. Morphine may also be indispensable for the relief of pain due to acute vascular occlusion, whether this be peripheral, pulmonary, or coronary in origin. In painful acute pericarditis, pleurisy, and spontaneous pneumothorax, morphine is likewise indicated. Carefully chosen and properly spaced doses of codeine or morphine may occasionally be necessary in pneumonia to control pain, dyspnea, and restlessness. Traumatic pain arising from fractures, burns, etc., frequently requires morphine. In shock, whether due to trauma, poisons, or other causes, morphine may be required to relieve severe pain.

The use of opiates in **obstetrical analgesia** is a highly specialized field requiring considerable experience and sound judgment to ensure safety. Morphine has been combined with **scopolamine** in "twilight sleep," but this mixture is not used nearly as much as formerly. Various combinations of meperidine, barbiturate, scopolamine, paraldehyde, and the inhalation anesthetics have made morphine less popular in obstetrical work. The opiates are powerful respiratory depressants. The fetus is especially susceptible to morphine, which greatly increases the incidence of asphyxia in the newborn. Morphine and its derivatives are particularly contraindicated in premature labor because of the untoward effect of such medication on the premature infant.

Postoperatively, narcotics may be employed to control pain and discomfort for the first 1 to 3 d, but if prescribed indiscriminately, they may obscure the outcome of surgery and the course of recovery, as well as prevent the early recognition of complications. For headache, codeine may be

effectively combined with analgesics such as salicylate or acetanilid. Morphine is not used in migraine unless all other measures, including ergotamine, have failed. Great care should be exercised to prevent addiction.

Although morphine is the most potent and effective analgesic known, it possesses many properties and actions that are undesirable, including spasm of smooth muscle, nausea and vomiting, interference with gastrointestinal function, urinary retention, respiratory depression, stupefaction, pruritus and urticaria, tolerance to the analgesic effect, physical dependence, and addiction liability. If one lists the obvious criteria desirable in an analgesic, morphine does not receive a very high score when measured by such criteria. Nevertheless, its proper use often permits maximal benefit with minimal untoward effect, but this requires considerable knowledge of the drug, the patient, and the disease or syndrome being treated.

### Sedation and Sleep

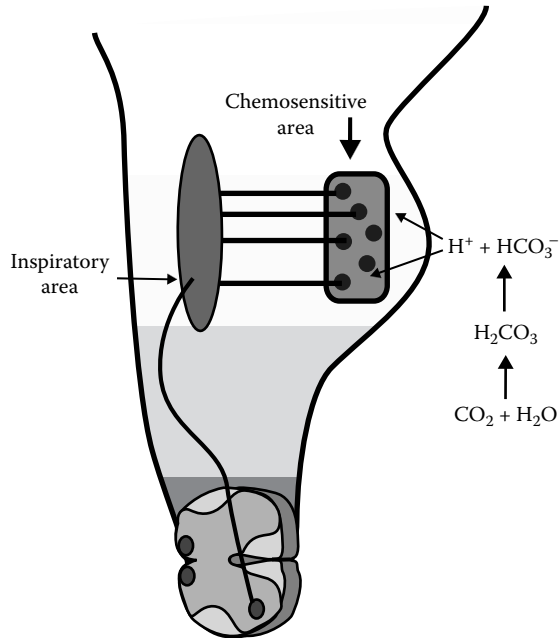
Whenever possible, drugs other than narcotics are to be prescribed for sedation, tranquility, or sleep. In many cases, however, opiates must be resorted to in order to provide the necessary relief from insomnia, restlessness, or excitement and thus conserve the patient's strength. The ordinary non-narcotic somnifacients such as bromides, chloral hydrate, and barbiturates are not analgesic and, when sleeplessness is due to pain or cough, opiates are often required. In certain forms of delirium, mania, and psychoses, and in the hyperexcitable states caused by thyrotoxicosis and certain encephalopathies, opium alkaloids may be needed. In these conditions, smaller doses of morphine produce sedation than are necessary when pain is also present. When sleep and relief from restlessness and apprehension are absolutely essential, as in threatened abortion, internal hemorrhage, congestive heart failure, and massive pulmonary hemorrhage, morphine provides a valuable therapeutic agent.

#### *Cough and Dyspnea*

Cough, especially when unproductive and irritating, interferes with rest and sleep and may be painful. It can also result in cardiac strain and cause pulmonary or cardiovascular accidents. The opiates comprise the so-called **anodyne expectorants**, and codeine in particular deserves preference for quieting an overactive cough reflex. The antitussive dose is kept small (5 to 10 mg) because repeated medication may be necessary. The uniformly effective oral dose of codeine for cough is about 10 mg. Large doses of codeine (over 60 mg) may actually increase the irritability of the respiratory mechanism and cough. Codeine can be effectively incorporated in an expectorant cough mixture for a dry, irritating cough with the object of stimulating secretion of mucus yet reserving the cough reflex for productive expectoration. Coughing should not be unnecessarily depressed, especially if bronchial secretion is profuse, because drainage will then be insufficient and complications may ensue. Small amounts of codeine, or of morphine (2 to 4 mg), will decrease the frequency of coughing without altering significantly the respiratory minute volume.

Certain forms of dyspnea yield only to opiates. Especially in this category is the dyspnea of acute left ventricular failure and pulmonary edema. Most authorities agree that morphine is contraindicated in patients with pulmonary edema caused by chemical respiratory irritants. If needed in such cases for severe pain, its use should be combined with oxygen inhalation and positive-pressure therapy. In bronchial asthma, morphine is usually contraindicated because there is danger of addiction, the drug tends to depress respiration and to constrict bronchioles, and patients with asthma may be allergic to the drug. Deaths have occurred from the use of morphine in asthma.

There is no good evidence that the use of codeine or papaverine shortens the duration of the "common cold." Opiates tend to dry the mucosal lining of the throat and nose, but other measures such as atropine can accomplish this end. If headache and pain require relief, nonnarcotic analgesics should first be employed. If the symptomatic improvement afforded by codeine encourages patients



Morphine depresses respiration by decreasing the responsiveness of the respiratory center to  $\text{CO}_2$

**FIGURE 47.6** Morphine depresses respiration by decreasing the responsiveness of the respiratory center to  $\text{CO}_2$ .

to be ambulatory when they should be in bed, the medication has done harm by increasing the chances for complications and the infection of other individuals (Goodman and Gilman, 1955).

## Side Effects of Morphine

### *Morphine Depresses Respiration*

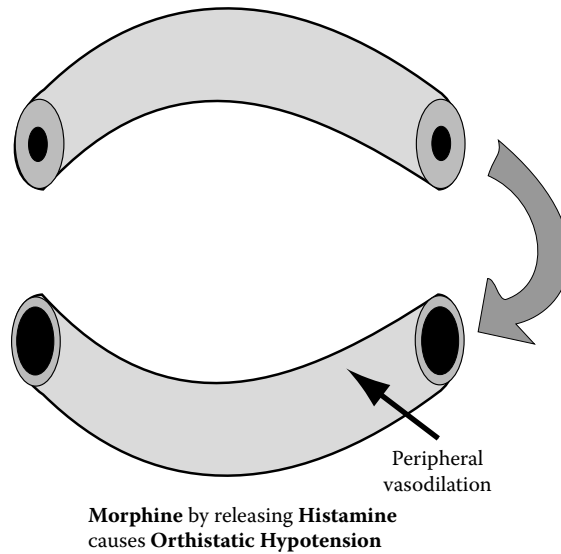
Morphine depresses all phases of respiration (respiratory rate, tidal volume, and minute volume) when given in subhypnotic and subanalgesic doses (Figure 47.6). In humans, a morphine overdose causes respiratory arrest and death. Therefore, morphine and other narcotic analgesics should be used with extreme caution in patients with asthma, emphysema, and cor pulmonale, and in disorders that may involve hypoxia, such as chest wound, pneumothorax, or bulbar poliomyelitis.

### *Morphine Causes Hypotension*

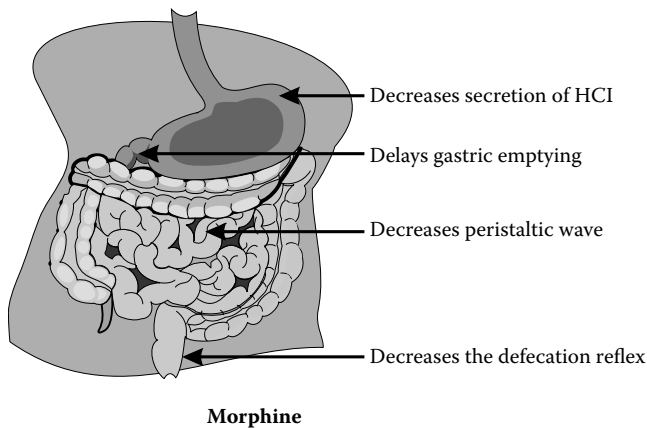
Morphine releases histamine and may cause peripheral vasodilation and orthostatic hypotension (Figure 47.7). The cutaneous blood vessels dilate around the “blush areas” such as the face, neck, and upper thorax. Morphine causes cerebral vasodilation (due to increased carbon dioxide retention secondary to respiratory depression), and hence, it increases the cerebrospinal fluid pressure. Therefore, morphine should be used cautiously in patients with either meningitis or a recent head injury. When given subcutaneously, morphine is absorbed poorly whenever there is either traumatic or hemorrhagic shock.

### *Morphine Causes Constipation*

Morphine decreases the activity of the entire gastrointestinal tract in that it reduces the secretion of hydrochloric acid, diminishes the motility of the stomach, and increases the tone of the upper part of the duodenum. These actions may delay passage of the stomach contents into the duodenum. Both pancreatic and biliary secretions are diminished, which may also hinder digestion. In the large



**FIGURE 47.7** Morphine causes vasodilation.



**FIGURE 47.8** Morphine causes constipation.

intestine, the propulsive peristaltic wave in the colon is reduced; the muscle tone, including that of the anal sphincter, is increased; and the **gastrocolic reflex** (defecation reflex) is reduced. These actions in combination cause constipation, which seems to be a chronic problem among addicts (Figure 47.8).

### Morphine-Induced Addiction

The narcotic alkaloids of opium head the list of addictive drugs, and this fact is a major consideration in their therapeutic use. Opium addiction has existed for centuries in the East, where the drug is habitually smoked by millions of people and the cultural attitude toward its use is quite different from that in the West. In the U.S. and Europe, pure alkaloids are used, and the addiction takes a more serious form. The following discussion applies mainly to morphine and its congeners. Significant variations from the morphine pattern are exhibited by meperidine and methadone. The etiology of narcotic addiction varies, but addicts can seldom be relied upon for accurate information regarding the origin of their addiction. It is likely that only a small percentage becomes addicted as a result of the therapeutic use of opiates; however, many female addicts do acquire their addiction

in this way. The vast majority of addicts are persons classified as neurotic or constitutional psychopathic inferiors, and addiction is only one manifestation of their fundamental personality defect. In this sense, they do not differ from chronic alcohol or barbiturate addicts. Because motivations related to hunger, sexual urges, and pain are reduced by morphine, use of the drug provides an escape mechanism from reality, a way of release from the failures and disappointments of everyday life, and a means of bridging the gap between ambition and accomplishment. Some addicts start their abuse of narcotics out of curiosity or as a means of dissipation with evil associates. When a “thrill” or “kick” is desired, according to the language of the addict, the dose must constantly be increased as tolerance develops, in order to duplicate the original thrill, dreamy state, or euphoria. Many heroin and cocaine addicts are in this category. On the other hand, the few persons who develop addiction accidentally from therapeutic use of a narcotic usually increase their dose as little as possible and continue to take the drug mainly to prevent unpleasant withdrawal symptoms. Aside from personality factors, addicts do not differ from the rest of the population with respect to intelligence or physical fitness or the incidence of psychoses.

There are on record a few authenticated cases of **congenital morphinism**, that is, morphinism in the newborn of addicted mothers; convulsions are a prominent feature. Unless the syndrome is promptly recognized and properly treated, the infant may succumb.

#### *Types of Drug Used*

The opium narcotics used in the U.S. are, particularly, morphine and heroin, especially the former; but juveniles definitely prefer heroin. Heroin has greater addiction liability than other narcotics, produces more euphoria and “stimulation,” requires smaller doses, and is easier to traffic in illicitly. Codeine addiction is rare because the drug produces relatively little euphoria, and is thus less desirable to the potential addict, and because it is quite expensive and bulky in effective amounts. Codeine addicts are usually persons who originally received the drug for clinical purposes. Many narcotic addicts also use cocaine, usually in combination with heroin, and resort to whisky or barbiturate when their supply of narcotic is low. Every conceivable method and route are used to get the narcotic into the body. Morphine and heroin, however, are ordinarily taken hypodermically or intravenously; cocaine and heroin are employed by snuffing. The use of galenical preparations of opium is rare in the U.S. Occasionally, however, a **paregoric addict** is discovered.

#### *Time Required for Addiction*

Addiction occurs after a variable period of time. Although it usually requires more than 2 weeks of repeated use of a narcotic, addiction may develop in a few days and, in some unstable personalities, after only a few doses. Physical dependence has been shown to develop within 2 d by the use of nalorphine. Great care should therefore be exercised not to prescribe a narcotic for a longer period of time than is absolutely necessary, and to avoid clocklike regularity in its administration. The continued employment of an opiate to relieve pain in terminal illnesses or neoplastic diseases does not come under the scope of the present discussion, and addiction under such circumstances is often unavoidable.

#### *Amount of Drug Taken*

The amount of narcotic taken by the addict may be remarkably large. De Quincey in his *Autobiography* and *Confessions of an Opium Eater* remarked that at one time he took 133 dr (over 500 ml) of tincture of opium daily. This is the equivalent of 4.7 g of morphine, or 300 times the single therapeutic dose. A case has been verified of a patient who employed 4.5 g of heroin daily by subcutaneous injection. More often, the total daily dose of heroin, cocaine, or morphine used by addicts ranges between 0.5 and 2 g. The daily dose of paregoric may reach a quart. Addicts cannot be trusted to give an honest report of the amount used because they feel that by exaggerating their needs they will more easily succeed in obtaining what they desire. In estimating the daily requirements of an addict, it is necessary to establish the amount that keeps the person comfortable and prevents withdrawal symptoms.

### *Symptoms and Effects of Morphine Addiction*

The popular conception of the morphine addict, as a cunning, cringing, malicious, and degenerate criminal who is shabbily dressed, physically ill, and devoid of the social amenities could not be farther from the truth. When addicts are properly dressed and fed and receive their daily drug requirement through legitimate medical channels, they cannot easily be distinguished from other persons. They may remain in good health and suffer little inconvenience or physical deficiency unless they cease to take the drug. However, certain serious consequences do occur even under favorable circumstances. To cite but two examples, decrease in libido may lead to marital difficulties, and masking of pain may result in neglect of a pathological process such as malignant neoplasm. The euphoria experienced at first soon disappears unless the dose is continuously elevated. Some addicts take morphine for the euphoria, thrill, or gratification it affords. Such an effect is particularly observed when the drug is taken intravenously; the resulting thrill has the attributes of a sexual orgasmic experience, localized in the abdomen rather than the genitalia. Yet an appreciable number continue their addiction mainly to escape from the distress that quickly follows withdrawal of the narcotic. Brilliant and famous persons have been narcotic addicts, and their affliction often has remained unknown even to their closest associates. The only adequate test of morphine addiction is the occurrence of characteristic withdrawal symptoms upon cessation of the narcotic or upon administration of nalorphine.

Good health and productive work are thus not incompatible with addiction to morphine. As an example may be cited of the case of a physician who was a morphine addict for 62 years and exhibited no evidence of mental or physical deterioration due to the drug, when carefully studied at the age of 84.

Ill health, crime, degeneracy, and a low standard of living are the result not of the pharmacological effects of morphine but of the sacrifice of money, social position, food, and self-respect in order to obtain the drug. Inasmuch as narcotics are ordinarily obtained through illicit channels, the cost is high. It is difficult for a normal person to appreciate how completely the necessity and compulsion to maintain an adequate supply of the narcotic dominate the entire thought, action, and daily life of the addict. The major purpose of existence is to obtain sufficient narcotic for the addict's daily needs.

### **Withdrawal Symptoms**

The character and severity of the untreated abstinence syndrome depend on many factors, including the particular narcotic and total daily dose used, the interval between doses, the duration of addiction, and the health and personality of the addict. The major factor, however, is the intensity of physical dependence on the drug. If it is absolutely clear to the addicts that regardless of their complaints, pleas, and demands they will not receive an opiate, the psychogenic aspect of the withdrawal syndrome is usually less pronounced. For example, those forced against their will to undergo therapy are difficult to manage. On the other hand, many confirmed addicts "take the cure" to be able to start all over again with a dose that is small and, therefore, cheap, which again produces the euphoria that tolerance prevented them from experiencing. Such patients will sometimes plead for a small "pick-up" dose of morphine about the third or fourth day after withdrawal is started. If euphoria is once again experienced from this small dose, they know that their tolerance is broken and that their original susceptibility to morphine is restored. They then continue quietly and cooperatively with the remainder of the treatment, their objective having been attained.

Although psychic factors are undoubtedly important in determining certain features of the withdrawal syndrome, most signs and symptoms have a physiological basis and represent a fundamental imbalance in the homeostatic adaptive mechanisms of the body, which developed in response to the continued use of morphine. At the height of the syndrome, tolerance is still present, and injection of the dose to which the patient was accustomed will quickly relieve all subjective distress and physical signs and completely restore the person's equanimity. By the time withdrawal symptoms have ceased, tolerance has disappeared.

The first changes are noted shortly before the time of the next regularly scheduled dose. Patients volubly express their craving and need for the drug, state that they feel sick, and are apprehensive and irritable. If conditions permit, they will do anything to obtain the drug. This type of activity has been termed purposive in that it is directed toward the goal of obtaining the narcotics. Purposive behavior reaches its peak intensity in 36 to 72 h after the last dose of morphine, then subsides at a variable rate, but craving may persist for months or years. About 8 h after withdrawal, addicts fall into a deep sleep, known as a “yep,” which may last for several hours, but from which they awaken more restless and miserable than before. Nonpurposive abstinence changes are not goal-directed, appear about 15 to 20 h after the last dose, reach their peak intensity in 48 to 72 h after abrupt withdrawal, and are usually entirely gone in 10 to 14 d. This category of behavioral alteration has an organic basis. Prominent features are lacrimation, yawning, sneezing, sweating, anorexia, tremor, restlessness, irritability, muscular weakness, mydriasis, fever, and increased respiratory rate. There then follow increasing irritability, insomnia, marked anorexia, violent yawning, severe sneezing, excessive lacrimation and coryza, and hoarseness. Weakness and depression are pronounced. Vomiting may occur, and colic and diarrhea are usually prominent. Heart rate and blood pressure are elevated. Marked chilliness alternating with flushing and excessive sweating is characteristic. The chilliness is associated with pilomotor activity, and the skin resembles that of a plucked turkey. This feature is the basis of the expression “cold turkey” to signify abrupt morphine withdrawal without substitution therapy. Patients lie on their side in a flexed position and cover themselves with blankets even on hot days.

The failure to take fluid and food, coupled with vomiting, sweating, and diarrhea, results in weight loss, dehydration, ketosis, and disturbance in acid–base balance, usually acidosis. Abdominal cramps and pains in the back and extremities are also quite characteristic; pain is particularly severe in the popliteal region. There may be rigidity in the right lower quadrant; this, combined with abdominal pain and a commonly occurring leucocytosis, may simulate acute appendicitis. Severe muscle tremors and twitchings, headache, diplopia, delirium, and occasionally, mania and seminal emissions in men and orgasms in women complete the dramatic picture. Sometimes, there is cardiovascular collapse; this complication requires the administration of morphine to prevent death.

As symptoms subside, patients begin to eat, drink, and sleep and to regain their composure and weight. Physical recovery from addiction is an irregular process requiring approximately 6 months; of the many physical and laboratory features studied, weight gain proved to be the most important single index of recovery.

The former opinion that the abstinence syndrome is largely psychogenic in origin and merely the manifestation of anxiety and terror is no longer tenable. The typical nonpurposive signs and symptoms of withdrawal occur in addicts who are kept under heavy sedation, as well as in addicts who, for other purposes, have undergone frontal lobotomy prior to narcotic withdrawal (see Goodman and Gilman, 1955).

### Antidiarrheal Effects

Opiate preparations, usually given as **paregoric**, are effective and fast acting antidiarrheal agents. These agents are also useful postoperatively to produce solid stool following an **ileostomy** or **colostomy**. A meperidine derivative, **diphenoxylate**, is usually dispensed with atropine and sold as **Lomotil**. The atropine is added to discourage the abuse of diphenoxylate by narcotic addicts who are tolerant to massive doses of narcotic but not to the CNS stimulant effects of atropine.

### Oliguric Effect

Morphine causes oliguria, which results from (1) pronounced diaphoresis, (2) the relative hypotension and decreased glomerular filtration rate, and (3) the release of antidiuretic hormone from the neurohypophysis. In an elderly patient with prostatic hypertrophy, morphine may cause acute



urinary retention. Morphine may reduce the effectiveness of a diuretic when both drugs are used in combination in the treatment of congestive heart failure.

### Morphine-Induced Tolerance

Tolerance develops to the narcotic and analgesic actions of morphine, so that increasingly larger doses are needed to render patients pain free. Tolerance develops to many effects of morphine such as analgesia, euphoria, narcosis, respiratory depression, hypotension, and antidiuresis. Morphine-induced bradycardia may be experienced. However, no tolerance develops to morphine-induced miosis or constipation. If the administration of morphine is discontinued, the tolerance is lost and the preaddiction analgesic doses of morphine become effective once more.

## NATURAL OPIUM ALKALOIDS

### CODEINE

Codeine given in moderate quantities resembles morphine in its action in humans but is much weaker. Thus, 60 mg of codeine induces sleep and relieves pain to about the same degree as 10 mg of morphine, but the sleep is not so deep and restful, and the subject awakens unrefreshed. Larger quantities may increase the restlessness and exaggerate the reflex excitability. Respiration is slowed down, but to a lesser degree than by morphine. The pupil is slightly contracted, but dilates if the excitement stage follows its administration. Codeine thus depresses the CNS in humans, although there are indications of stimulation also when larger quantities are used. In animals, these symptoms of excitation are more obvious, however, especially in the spinal cord, in which the reflexes are rendered more acute and may finally give rise to spasms.

Codeine acts less on the stomach and bowel than does morphine but, when given in large doses, also causes constipation. It is excreted unchanged in the urine. Tolerance for codeine is difficult to develop, but cases of addiction to it have been reported. They are usually secondary to the use of morphine; that is, the patient, addicted to morphine and unable to secure this drug, resorts to codeine.

Codeine, when incubated with the livers of several mammalian species, is converted to morphine and formaldehyde. The biotransformation products identified in the urine following the administration of codeine include morphine, norcodeine, and free and bound codeine.

**Dihydrocodeine** is somewhat less analgesic, whereas dihydroisocodeine is approximately as analgesic as morphine in comparable doses. Dihydrocodeine is essentially free of such side effects as respiratory depression, nausea, and mood changes induced by codeine and **dihydroisocodeine**.

### PAPAVERINE

Papaverine, as already indicated, is unrelated chemically to morphine and exerts no analgesic or narcotic action. It is essentially free of any effect on the CNS, its principal actions being to depress conduction and prolong the refractory period of the heart and to relax smooth muscle. It also exerts a mild local anesthetic action, counteracting, for example, the pruritus induced by the application of **cowhage** to the skin. Itching apparently is not transmitted by the same nerve fibers as are sensations of pain, because analgesics fail to alleviate the itching induced by cowhage.

Papaverine has a greater tendency to slow down the heart rate than morphine, acting directly on the heart muscle to produce this effect. In addition, it depresses the smooth muscles of arterioles so that when it is perfused through them, the blood pressure is somewhat lowered. However, ordinary amounts administered systemically cause little if any change. In the dog, papaverine significantly raises the fibrillation threshold of the ventricle when administered in therapeutic doses. Large doses lower the threshold for fibrillation, especially if enough is given to cause a sharp drop in blood pressure. However, there is no conclusive proof that papaverine will bring about spontaneous recovery in a fibrillating heart. Its action upon the intestinal tract of the intact animal is without

therapeutic importance. Upon excised tissues (ureter, gall bladder, etc.) papaverine and other **benzyl isoquinoline alkaloids** relax the tone, slow down the contractions, and thus antagonize the action of morphine. Papaverine undergoes complete destruction in the tissues. Tolerance and addiction to papaverine are unknown.

Papaverine, because of its general depressant effect on smooth muscle, has been used in doses of 30 to 60 mg, subcutaneously and intravenously, in peripheral thrombosis and embolism, acute myocardial infarction, angina pectoris, bronchial asthma, renal and biliary colic, and other conditions in which relaxation of smooth muscle is desired. However, the therapeutic effectiveness of papaverine is questionable, and there is no established indication for its use.

The **tetraethyl homologue of papaverine (Perparin<sup>®</sup>, Perperine<sup>®</sup>, Ethaverine<sup>®</sup>, Diquinol<sup>®</sup>)** is more active than papaverine and is used for its spasmolytic effects on the uterus, ileum, and circulatory system.

## NOSCAPINE

**Noscapine (Nectadon<sup>®</sup>), 2-methyl-8-methoxy-6,7-methylenedioxy-1-(6,7-di-methoxy-3-phthalidyl)-1,2,3,4-tetrahydroisoquinoline**, is also one of the isoquinoline derivatives present in opium. Next to morphine, it is the most abundant of the opium alkaloids, present to the extent of 6% in the seed capsules. This drug was formerly known as *narcotine* but, because it is neither chemically nor pharmacologically related to the narcotics, is more appropriately designated as *noscapine*.

Noscapine resembles papaverine in its action on smooth muscle and, in large doses, induces bronchodilation in animals. It is readily absorbed from the gastrointestinal tract, but its metabolic fate is unknown. In experimentally induced cough in animals and humans, noscapine exerts an antitussive action approximately equal to that of codeine, without any of the unpleasant side effects of codeine. It is administered orally in doses of 15 to 30 mg, three or four times daily as an antitussive.

## SYNTHETIC DERIVATIVES OF THE OPIUM ALKALOIDS

Many attempts have been made to modify the morphine molecule or break it down to some constituent that might retain its analgesic action without its tendency to develop tolerance and addiction. However, only very closely related derivatives of morphine have been found to maintain its analgesic action and still retain to a considerable degree the undesirable potentiality to develop tolerance and addiction.

### HEROIN (DIAMORPHINE)

Heroin, a synthetic alkaloid formed from morphine by substituting acetyl for its two hydroxyl groups, resembles morphine in its general effects but acts more strongly on both cerebrum and medulla than does morphine, and is therefore more poisonous, with the usual dose about one fourth that of morphine. The action on respiration is same as that of morphine, and the advantages claimed for heroin by its advocates have not been confirmed by impartial investigation. It is effective, but not more so than is morphine, in the treatment of cough, and is less effective in the treatment of dyspnea. Heroin is excreted mainly in the urine unchanged, but some is found in the stools. In animals, large doses cause excitement and convulsions, observed in humans in cases of poisoning.

Many cases of heroin habit have occurred, and this aspect of the drug's action has brought it into serious disrepute. The fact that it can be administered easily and in small doses makes trafficking in the drug less difficult compared with some of the other narcotics. The social danger from it, moreover, seems to be greater compared with morphine in that it produces a change in the user's personality as shown by his or her utter disregard for the conventions and morals of civilization. Degenerative changes in the individual progress faster than with any of the other narcotic drugs; all the higher faculties of the mind, such as judgment, self-control, and attention, are weakened,

and the addict rapidly becomes a mental and moral degenerate. The heroin habit is most difficult to cure, not only in the active withdrawal period but also in the convalescent stage, and relapse is frequent. Habitueés take it either by snuffing or by hypodermic injection. Because of its marked tendency to addiction and its minor therapeutic value, the manufacture and importation of heroin has been outlawed in the U.S.

### DIHYDROCODEINONE

In this synthetic derivative of codeine, a ketone group replaces the –OH of codeine at position 6 and two H atoms are added at positions 7 and 8. It thus bears the same relation to codeine as **dihydromorphinone (Dilaudid®)** does to morphine. It is marketed as the tartrate under the trade names **Dicodid®** and **Hycodan®** and is used chiefly for the relief of cough.

The risk of addiction is greater in the case of dihydrocodeinone than with codeine, but small doses (5 to 10 mg) are often of value in tuberculosis, measles, atypical pneumonia, etc., conditions in which cough is a troublesome symptom.

### DIHYDROMORPHINONE

Dihydromorphinone hydrochloride (Dilaudid) is five to ten times as potent as, and more toxic than, morphine, but its duration of action is less, as are also its effects on the gastrointestinal tract. Chemically, it differs from morphine in that the alcoholic hydroxyl group of that alkaloid is replaced by ketonic oxygen and the adjacent double bond is removed by hydrogenation. Dihydromorphinone produces analgesia and narcosis and acts upon respiration in a manner similar to morphine, with the difference, however, that it is effective in about quarter the dose. In the dog, restlessness and vomiting are followed by depression, somnolence, analgesia, and slowdown in respiration. In the rabbit, respiration is slowed down very markedly but with some deepening, so that the effect of the slowdown is partially compensated. In humans, the drug is powerfully analgesic as well as markedly depressing to respiration, although nausea, vomiting, and constipation are not so marked as with morphine. Tolerance and addiction occur readily, and the same care should be exercised in prescribing it as in the case of the natural opium alkaloids.

Dihydromorphinone is used in the same manner as morphine for the relief of pain but in much smaller doses — usually 1 to 2 mg. For cough, a dose about half that size is used. Administered orally, dihydromorphinone, is more effective than morphine, and it may also be administered in a rectal suppository. It is principally indicated for acute pain of short duration.

**Oxymorphone (Numorphan®), dihydromorphinone hydrochloride**, is also about ten times as active as morphine and has a rapid onset of action that lasts for about 6 h. It is administered subcutaneously or intramuscularly in doses of 1 ml (1.5 mg) or as a rectal suppository (2 and 5 mg).

**Metopon (methyldihydromorphinone)** manifests the properties of tolerance and liability to addiction, but it is about twice as effective as an analgesic, and its duration of action is equal to that of morphine. Tolerance to metopon and physical dependence on the drug develop more slowly than in the case of morphine. In therapeutic doses, it produces little or no respiratory depression and still less mental dullness. Metopon thus possesses many advantages over morphine but is no longer available commercially.

### DEXTROMETHORPHAN HYDROBROMIDE

The dextrorotatory isomer of **3-methoxy-N-methylmorphinan**, a synthetic morphine derivative (**Romilar hydrobromide®**, **Tusilan®**) is employed exclusively as an antitussive agent. Its levorotatory isomer (in the form of the 3-hydroxy tartrate) is described next. These compounds differ from morphine chemically in lacking the –O– bridge between carbons 4 and 5, the OH group at C<sub>6</sub>, and

the double bond between carbons 7 and 8. Dextromethorphan hydrobromide exhibits little or no central depressant activity and does not produce analgesia, nor does it manifest any addicting effects.

Dextromethorphan hydrobromide is administered orally in doses of 10 to 20 mg one to four times daily to adults. This dose is reduced to a half for children over 4 years of age and to a quarter for children under 4 years of age.

### LEVORPHANOL TARTRATE

The levorotatory isomer of **3-hydroxy-N-methylmorphinan tartrate dihydrate (Levo-dromoran tartrate®)** is a more potent analgesic than morphine with an approximately equal margin of safety, but is longer acting and has a lesser constipating action. Contraindications to its use, including the danger of addiction, are similar to those of morphine.

Levorphanol tartrate is used for the relief of severe pain in cancer, trauma, colic, and myocardial infarction, as well as pre- and postoperatively. It is administered orally or subcutaneously in doses of 2 to 3 mg according to the age and weight of the patient and the severity of pain.

### ETHYLMORPHINE

Ethylmorphine hydrochloride (**Dionine®**) resembles codeine more closely in its action than it does morphine. It is used primarily as a chemotic to produce vasodilatation and edema of the conjunctiva in corneal ulcer and other inflammatory conditions of the eye. For this purpose, it is instilled topically as a 1 to 5% solution in the eye. It has also been used as an antitussive in doses of 15 mg.

### APOMORPHINE

When morphine is acted on by acids and other dehydrating agents, it loses a molecule of water, and a new alkaloid is formed, apomorphine ( $C_{17}H_{17}NO_2$ ), the structural formula of which is shown in Figure 44.2. Through this change, the action of the original alkaloid is considerably modified; apomorphine preserves the stimulant but loses to a great degree the depressant action of morphine on the CNS. This stimulant action extends over the whole CNS but is most developed in the "vomiting center" of the medullar oblangata.

### Symptoms

In humans, apomorphine in doses of 5 to 10 mg induces nausea and vomiting within 10 to 15 min. Very often, the nausea passes off immediately after evacuation of the stomach, but when larger quantities have been administered, repeated vomiting and retching may occur. Occasionally, depression and sleep follow emesis after even small doses.

The attendant symptoms are profuse salivation, increased secretion of the mucous glands of the nose, throat, and bronchial passages, tears, and a cold perspiration. A feeling of depression, muscular weakness, and acceleration of the pulse are also well-known symptoms accompanying nausea and vomiting after apomorphine. These are all to be regarded as sequelae of the emetic action, however, and not as due to direct action of the drug on the glands and other organs. In a few instances, the depression and weakness have passed into alarming collapse, but no actual fatality is recorded from the use of apomorphine.

Very small doses of apomorphine may induce the secondary symptoms without actual vomiting. Thus saliva, perspiration, tears, and other secretions may be augmented by quantities that are too small to act as emetics.

Apomorphine induces vomiting through changes in the medulla oblongata and not by irritation of the stomach. This is shown by the fact that it acts much more quickly and in smaller doses when administered hypodermically or intramuscularly than when swallowed, as well as by the fact that if the medulla is brushed with apomorphine solution, vomiting follows immediately. Moreover, the

movements of vomiting can be induced in animals even after the removal of the stomach and intestines. Large doses may cause such depression of the CNS as to prevent vomiting.

Apomorphine is used chiefly as an emetic (dose, 5 mg) and presents several advantages over other drugs employed for this purpose, inasmuch as it acts more promptly and can be administered by injection whereas most other emetics (ippecac and emetine excepted) have to be given by mouth, which is a serious drawback in cases of poisoning. However, vomiting is not as important a method of treatment now as it was formerly, and emetics are less frequently employed to evacuate the stomach than other measures, such as repeated washing of the stomach by means of the stomach tube. In narcotic poisoning, apomorphine not infrequently fails to act, owing to depression of the vomiting center, and in corrosive poisoning, a certain amount of danger attends its use as the pressure exerted by contraction of the diaphragm and abdominal muscles on the walls of the stomach may lead to rupture of the weakened walls of the organ.

Emetics, when administered in small doses, act as expectorants and are used in inflammatory conditions of the respiratory tract to increase the bronchial secretion and render it less tenacious. The most commonly used expectorants are ippecac, ammonium chloride, and apomorphine. The last named is administered in doses of 1 mg in the form of an elixir or syrup. Apomorphine injected in subemetic doses of 1 to 2 mg is also used as a sedative in the delirium following anesthesia, in acute alcoholic psychosis, and in patients manifesting severe agitation prior to anesthesia.

## NONOPIATE ADDICTING ANALGESICS

The first success in obtaining synthetic substances approaching morphine or its derivatives was **meperidine** (Demerol®) or **isonipecaine** as a substitute for morphine. Following World War II, examination of the files of the German dye trust revealed, among several related products, **methadone**, which has proved to be a valuable analgesic. These compounds, more potent per unit of weight in their analgesic action than morphine, have encouraged the synthesis of other related compounds in the search for an ideal analgesic.

The synthetic substitutes for opium alkaloids, or *opioids* as they have been designated, include the **morphinans**, **meperidines**, **methadones**, **hexamethyleneimines**, and **dithienylbutenylamines**. The two last named groups bear only a slight chemical resemblance to morphine derivatives but possess the branched methyl and tertiary amino group characteristic of methadone. Some of these are as potent as morphine as analgesics, and all of them possess addictive properties. In addition to the drugs to be described, related synthetic agents have been introduced into medicine as analgesics and antitussives. These include **phenadoxone hydrochloride**, **6-(N-morpholino)-4,4-diphenyl-3-heptanone hydrochloride** (Heptalgin®, Heptazone®, Morphodone®), and **dipipanone**, the hydrochloride of *dl*-6-piperidine-4,-diphenyl-heptan-3-one.

### MEPERIDINE (PETHIDINE)

Meperidine (isonipecaine, Demerol®, and Dolantin®) is the **methyl ester of methyl-4-phenylpiperidine-4 carboxylic acid**. It is used in the form of its soluble hydrochloride. The piperidine nucleus is also present in many alkaloids, such as atropine or lobeline, which are not analgesics, as well as in morphine.

### Action

Meperidine shows certain relationships to both morphine and atropine in its action. Similar to morphine, it exerts a generalized depression of the CNS but, in ordinary doses, does not affect the cough reflex. Similar to morphine, it induces euphoria, and its continued use leads to tolerance and addiction. However, its euphoric and sedative effects are less than that of morphine; addiction due to meperidine is more serious than that due to morphine. Meperidine is an effective analgesic,

although less so than morphine. Following its parenteral administration, relief of pain is experienced in about 15 min and lasts for several hours. Similar to atropine, meperidine exerts a spasmolytic action on the gastrointestinal tract except on the duodenum and jejunum. As with morphine, it increases the intrabiliary pressure.

In ordinary doses, meperidine exerts inappreciable effects on respiration and circulation. In large doses, it interferes with the facilitatory function of the pneumotaxic center and the vagal afferent impulses, thereby reducing the rate and depth of respiration. With still higher doses, meperidine produces an irregular respiratory rhythm and ultimately induces apnea. It causes relaxation of the ureter, gall bladder, and bronchi. This action is partly a direct one on the smooth muscle of these structures and, in part, a result of its anticholinergic activity. It does not affect the size of the pupil or alter the tonus of the uterus.

### Undesirable Side Effects

Dizziness, sweating, nausea and vomiting, headache, and occasionally, syncope are sometimes noted following the administration of therapeutic doses of meperidine. Excessive or repeated doses of the drug may induce more serious toxic effects marked by cerebral stimulation similar to that seen in atropine poisoning, with dilatation of the pupils, tachycardia, disorientation, muscle twitching, convulsions, and depression of respiration. Maximum tolerance to the analgesic properties of the drug develops in about 8 weeks. Because of its tendency to addiction, sale of the drug is subject to federal narcotic regulations.

### Metabolism

Meperidine is in part demethylated in the body appearing as **normeperidine** in the urine. It is, however, for the most part hydrolyzed and excreted as free and conjugated **meperidinic acid**. The normeperidine is also partially hydrolyzed to normeperidinic acid, which is partly conjugated. Only a small part of the drug is excreted in an unchanged form. In humans, meperidine is metabolized at the rate of about 17% per hour, so that a single dose exerts its analgesic effect for 3 to 4 h. In the dog, on the other hand, its rapid metabolism (70 to 90% per hour) makes it difficult to induce tolerance or addiction.

### Therapeutic Use

Meperidine is available in the form of tablets (50 mg) for oral use or in solution (50 mg/ml) for intramuscular administration. It is administered in doses of 50 to 100 mg at 3- to 4-h intervals. Because of its antispasmodic effects, it is particularly useful in pain due to colic. It is also used prior to anesthesia, particularly cyclopropane. Meperidine is used in asthma, but its tendency to addiction limits its use in this condition to acute attacks.

Meperidine has replaced morphine to a large extent in medical practice because of the physician's reluctance to use an opiate and the belief that meperidine manifests less undesirable side effects than does morphine. However, both of these assumptions are ill founded. Addiction to meperidine is much less amenable to treatment than is addiction to morphine. Meperidine, similar to morphine and codeine, causes spasm of the upper gastrointestinal tract and typical attacks of biliary colic in biliary tract disease. Meperidine, in doses giving an equal analgesic effect, induces as much respiratory depression as does morphine. Similar to morphine, it also crosses the placental barrier and must therefore be used cautiously in the latter stages of labor.

### METHADONE

Of the synthetic compounds related to meperidine, **methadone** (**Adanon**<sup>®</sup>, **Amidone**<sup>®</sup>, and **Dolophine**<sup>®</sup>) is the most active and has proved to be an effective substitute for morphine. Chemically,

it is **6-dimethylamino-4,4-diphenyl-3-heptanone** and is used as the hydrochloride. Methadone is related to meperidine, morphine, and atropine and contains an asymmetric carbon atom. It was the first synthetic opium substitute not containing a piperidine ring. The levorotatory optical isomer has twice the analgesic power of *d,l*-methadone. **Isomethadone (6-dimethylamino-5-methyl-4,4-diphenyl hexanone-3)** resembles methadone in action but is less active.

### Action

Methadone, in general, exerts a pharmacological action similar to that of morphine. Its action on smooth muscle resembles that of meperidine. *d,l*-Methadone, per unit of weight, is equivalent to morphine in analgesic potency, but *l*-methadone is twice as effective. When used in comparable analgesic doses, methadone is as toxic as morphine and exerts the same effects on the pulse rate and respiration as does morphine. Methadone exerts no sedative effect and, hence, is of no value as a preanesthetic agent.

Similar to morphine and meperidine, methadone has a definite addiction liability, but withdrawal symptoms after prolonged administration come on more slowly and are of less intensity than after morphine. Dogs receiving gradually increasing doses of methadone develop tolerance to its analgesic and narcotic actions, but not to the cardiac slowing and effects on intestinal motility. The parasympathomimetic effects of methadone on the heart and intestine are of central origin and resemble those of morphine.

**Side reactions** to methadone include nausea, diaphoresis, and dizziness, but these are uncommon when minimal doses (2.5 to 5 mg) are used. Such doses have no effect on the temperature, pulse, blood pressure, or respiration. Miosis is produced with doses of 10 mg or more but is less than with morphine.

### Mechanism of Action

Although resembling morphine in its analgesic properties, the mechanism of its action as inferred from *in vitro* studies on brain metabolism appears to be different. Small concentrations of methadone cause an initial period of stimulation of cellular metabolism, which is not observed with morphine. Larger doses (0.005 *M*) reduce the oxygen uptake, a phenomenon not observed with comparable doses of morphine.

### Therapeutic Uses

Methadone is used as an analgesic for the relief of moderate to severe pain. It is effective in conditions in which the analgesic effect of morphine is desirable, and it exerts a satisfactory antitussive action.

In adults, a dose of 2.5 to 10 mg is satisfactory for the relief of most forms of pain. This is administered orally every 3 to 4 h. For suppression of nonproductive cough, 1.25 to 2.5 mg orally every 3 h is usually satisfactory. Where oral administration is undesirable, the drug may be administered subcutaneously, but the oral route is almost as effective as its hypodermic injection. It may also be administered intramuscularly, but should not be injected intravenously.

**Dextromoramide tartrate (Palfium®)**, which is related chemically to methadone, is as effective when administered orally in doses of 5 to 10 mg as when injected.

### ALPHAPRODINE HYDROCHLORIDE

Alphaprodine, **1,3-dimethyl-4-phenyl-4-piperidyl propionate hydrochloride (Nisentil®, Prislidene®)**, resembles meperidine chemically. Its analgesic and depressant actions are less intense, but more prompt and of shorter duration, than those of morphine. It is a potent, short-acting narcotic

used in intense pain of brief duration, as in obstetrics, urologic examinations, and minor surgical procedures. Although producing little or no cumulative effect, tolerance and the liability of addiction can develop.

Alphaprodine hydrochloride is administered by subcutaneous injection in doses of 40 to 60 mg depending upon the weight of the patient. Analgesia occurs within 5 min and lasts about 2 h. Nalorphine is an effective antidote to overdose.

### ANILERIDINE

**Anileridine, ethyl 1-(4-amino phenethyl)-4 phenylisonipecotate** is available in the form of its dihydrochloride for oral administration and as the phosphate for injection (**Leritine**<sup>®</sup>). Its analgesic potency is intermediate between that of meperidine and morphine. Similar to meperidine, it exerts mild antihistaminic and spasmolytic effects, but it is devoid of the constipating effect of opiates. Sedative and direct hypnotic effects are similar to those of meperidine but less than those of morphine.

Anileridine hydrochloride is administered orally in the form of 25 mg tablets repeated every 6 h if necessary, but dosages up to 50 mg or more frequent doses may be desirable for more severe pain. Anileridine phosphate is administered by subcutaneous, intramuscular, or intravenous injection in doses of 25 to 50 mg (1 to 2 ml) at intervals of 4 to 6 h.

### PHENAZOCINE

**Phenazocine (Prinadol**<sup>®</sup>), **1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl- 3-phenethyl-2,6-methano-3-benzazocine hydrobromide**, was synthesized at the National Institutes of Health in a search for new analgesics with low addictive liability. Addiction to phenazocine develops more slowly and is less intense when dosages equivalent to morphine are administered chronically for 30 d. The incidence of side effects (respiratory depression, hypotension, and nausea and vomiting) are less with phenazocine than with morphine.

Phenazocine is administered intramuscularly in doses of 1 to 3 mg every 4 to 6 h. Its depressant effects are potentiated by CNS depressants such as the barbiturates, phenothiazines, and anesthetics so that smaller doses are indicated when these are used concomitantly with the phenazocine.

### PIMINODINE ETHANESULFONATE

**Piminodine (Alvodine**<sup>®</sup>), **ethyl-4-phenyl-1-(3-phenylaminopropyl)piperidine-4-carboxylate ethanesulfonate**, is reputed to be equal to morphine in analgesic potency, but relatively free of the latter's narcotizing action. It is administered in doses of 25 to 50 mg orally every 4 to 6 h, or in doses of 10 to 20 mg subcutaneously or intramuscularly every 4 h as needed. Piminodine is habit forming, requires a narcotic prescription, and should be used with the same precautions as other members of this group. **Levallorphan tartrate, nalorphine, naloxone, or naltrexone** are antidotes to it.

### DEXTROPROPOXYPHENE

Propoxyphene is structurally very similar to methadone and possesses four stereoisomers. **Dextro-propoxyphene** is an analgesic with a potency two thirds that of codeine. **Levopropoxyphene** is an antitussive, but lacks analgesic properties.

**Adverse reactions** to dextropropoxyphene include nausea, vomiting, sedation, dizziness, constipation, and skin rash, with a frequency of incidence somewhat less than that seen with codeine use. Although respiratory depression is a cardinal sign of acute dextropropoxyphene poisoning, the drug apparently does not affect respiration in the usual therapeutic doses of 32 to 65 mg.



## OPIOIDS WITH MIXED ACTIONS: AGONISTS–ANTAGONISTS AND PARTIAL AGONISTS

The analgesia produced by 30 mg of **pentazocine (Talwin)**, a mixed-narcotic agonist and a weak antagonist, is comparable to that elicited by 10 mg of morphine. Its onset and duration of action are shorter than those of morphine. Pentazocine will antagonize some of the respiratory depression and analgesia produced by morphine and meperidine. However, the analgesic action and respiratory depression produced by pentazocine can be reversed by a narcotic antagonist. Pentazocine causes tolerance and addiction, but their emergences are very slow compared with those induced by morphine.

**Nalbuphine** is structurally related to both naloxone and oxymorphone. It is an agonist–antagonist opioid possessing a spectrum of effects that resemble those of pentazocine; however, nalbuphine is a more potent antagonist at  $\mu$  receptors and is less likely to produce dysphoria than is pentazocine.

**Butorphanol** is a **morphinan congener** with a profile of actions similar to that of pentazocine.

**Buprenorphine** is a semisynthetic, highly lipophilic opioid derived from thebaine. It is 25 to 50 times more potent than morphine.

## OPIOID RECEPTOR ANTAGONISTS

**Naloxone (Narcan)** and **naltrexone hydrochloride (Trexan)** reverse the respiratory depressant action of narcotics related to morphine, meperidine, and methadone. They differ from other narcotic analgesics in several respects. Naloxone does not cause respiratory depression, pupillary constriction, sedation, or analgesia. However, it does antagonize the actions of pentazocine. Naloxone neither antagonizes the respiratory depressant effects of barbiturates and other hypnotics nor aggravates their depressant effects on respiration. Similar to nalorphine, naloxone precipitates an abstinence syndrome when administered to patients addicted to opiate-like drugs.

## ANTITUSSIVE PREPARATIONS

**Dextromethorphan (Romilar)** is the dextroisomer of the methyl ether of **levorphanol**. Unlike its levorotatory congener, it possesses no significant analgesic property, exerts no depressant effects on respiration, and lacks addiction liability. It is an antitussive agent with a potency approximately one half that of codeine.

Therapeutic doses of dextromethorphan (15 to 30 mg) produce little or no side effects, whereas excessively high doses (300 to 1500 mg) have been reported to produce a state resembling intoxication accompanied by euphoria.

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# 48 Oats (*Avena sativa* L.) and Their Antioxidant Activity

## INTRODUCTION

The chief medicinal uses of oats are:

- Oats lower cholesterol
- Oats combat heart attack
- Oats control diabetes mellitus

Several classes of compounds with antioxidant activity have been identified in oats (*Avena sativa* L.), including **vitamin E tocols**, **flavonoids**, and **nonflavonoid phenolic acids** (see Handelman et al., 1999).

Grains are the seeds of food grasses and other plants and include barley, corn, millet, oats, rice, rye, the hybrid triticale, and wheat. Buckwheat, usually grouped with grains, is actually a botanical relative of rhubarb. Grains were the first cultivated food. Once humans learned to plant crops, they were able to give up the nomadic way of life and settle down to farming. Usually, the locally grown grain became the staple food of the area: rice in the Far East, oats in Scotland, wheat in the U.S. Grains can be eaten whole, such as brown rice, or processed into cereals or flour for a multitude of other food products.

Grains are:

- An excellent source of starchy carbohydrate and dietary fiber
- A good source of **niacin**, **riboflavin**, other **B vitamins**, **iron**, and **calcium**

**Oats** are used in breakfast cereals and baked goods. Oat bran is high in soluble fiber, which can help lower blood cholesterol levels, thus possibly reducing the risk of **heart attacks**. It also helps the body utilize insulin more efficiently, an important asset in controlling **diabetes**. Products made with oats contain little or no gluten and can usually be tolerated by people with **celiac disease**.

**Whole oats**, called **groats**, consist of the bran, germ, and endosperm of the whole grain with the outer hull removed. Whole oats are softer than wheat grains and can be crushed at home. They are available in specialty food stores.

**Rolled oats** are the most common form of oats and are so called because the whole groats are steamed and then flattened between rollers before being made into flakes. Rolled oats are popularly called **oatmeal**. They are available in three thicknesses, and the thicker the flake, the longer the oats take to cook. **Scotch** or **steel-cut oats** are the thickest, and are sometimes called **Scotch** or **Irish oatmeal**. **Table-cut** or **regular old-fashioned oats**, sold in specialty stores, are nuttier and chewier than quick-cooking oats but are otherwise the same. Quick-cooking or instant oats are the thinnest flakes. Some people think they have a raw taste compared to other oats.

Handelman et al. (1999) treated milled oat groat pearlings, trichomes, flour, and bran with methanol and tested the fractions for antioxidant capacity against low-density lipoprotein (LDL) oxidation and **R-phycoerythrin protein oxidation** in the oxygen radical absorbance capacity

(ORAC) assay. The oxidative reactions were generated by **2,2-azobis(2-amidinopropane) HCl** (AAPH) or  $\text{Cu}^{2+}$  in the LDL assay and by AAPH or  $\text{Cu}^{2+} + \text{H}_2\text{O}_2$  in the ORAC assay and calibrated against a Trolox standard to calculate **Trolox equivalents** (1 Trolox equivalent = 1 TE = activity of 1 mol of Trolox). The antioxidant capacity of the oat fractions was generally consistent with a potency rank of pearlings (2.89 to 8.58 TE/g) > flour (1.00 to 3.54 TE/g) > trichome (1.74 TE/g) = bran (1.02 to 1.62 TE/g) in both LDL and ORAC assays regardless of the free-radical generator employed. A portion of the oat antioxidant constituents may be heat labile as the greatest activity was found among non-steam-treated pearlings. The contribution of oat bran from the fractions accounted for < 5% of the measured antioxidant capacity. AAPH-initiated oxidation of LDL was inhibited by the oat fractions in a dose-dependent manner, although complete suppression was not achieved with the highest doses tested. In contrast,  $\text{Cu}^{2+}$ -initiated oxidation of LDL stimulated peroxide formation with low oat concentrations but completely inhibited oxidation with higher doses. Thus, oats possess antioxidant capacity, most of which is likely derived from polar **phenolic compounds** in the **aleurone**.

In conclusion, phenolic-rich fractions of oats possess an antioxidant capacity that can be assessed quantitatively through their ability to inhibit LDL oxidation and protein oxidation. The greatest degree of antioxidant capacity was associated with compounds extracted with methanol from the aleurone. The identification of the oat constituents from these fractions should be investigated, although candidate compounds include **caffeic acid**, **ferulic acid**, and **avenanthramides**. These compounds may be bioavailable and contribute to the health effects associated with dietary antioxidants and oats.

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# 49 Olives and Olive Oil

**Olives possess potent antioxidants; the lower incidence of coronary heart disease and cancer in the Mediterranean area is attributed to this.**

The impact of the environment on human physiology and pathology has been recognized for decades. In the Mediterranean basin, several components of the diet are derived from plants and fruits. Among them, **olives** and **grapes** have been, at least originally, rather unique to this area.

Because of the particular climate, plants in the Mediterranean basin are subjected to prolonged exposure to sunlight. Thus, many fruits, including olives and grapes, have developed an array of protective compounds that limit the effects of ultraviolet light and the subsequent oxidative damage. Accordingly, the levels, dependent on the rates of synthesis of **anthocyanins**, **flavonoids**, and **phenols** (see Chapter 31) in dark-colored fruits are enhanced by sunlight. Wine and olive oil, which originated in the Mediterranean area, are obtained by pressure techniques from ripe fruits. The compounds responsible for the **organoleptic** and other properties of the fruits are thus transferred to the fluids (Galli and Visioli, 1999).

The observation of a lower incidence of coronary heart disease (CHD) and certain types of cancers in the Mediterranean area led to the hypothesis that a diet rich in grain, legumes, fresh fruits and vegetables, wine in moderate amounts, and olive oil was beneficial to human health. To date, this effect has been mainly attributed to the low saturated fat intake of the Mediterranean diet and its high proportion of monounsaturates, which indeed may favorably affect the plasma **lipid** and **lipoprotein profiles**. Nevertheless, other components of the diet, such as fiber, vitamins, flavonoids, and phenols, may play an important role in disease prevention, acting on different cardiovascular variables.

**Olive oil**, in particular, is the principal source of fat in the Mediterranean diet. The production of olive oil for 1997–1998 in the European Community is estimated to be 1,941,000 tons, which represents 85% of global production. Due to the increasing popularity of the Mediterranean diet, its consumption is expanding to nonproducer countries such as the U.S., Canada, and Japan. Abundance of **oleic acid**, a monounsaturated fatty acid, is the feature that sets olive oil apart from other vegetable oils. In particular, oleic acid (18:1n-9) ranges from 56 to 84% of total fatty acids, whereas **linoleic acid** (18:2n-6), the major essential fatty acid and the most abundant polyunsaturate in the U.S. diet, is present in concentrations between 3 and 21%. Depending on its chemical and **organoleptic properties**, olive oil is classified into different grades that also serve as guidelines to the consumer's preference. In many producing countries, **extra virgin olive oil**, i.e., the one with the highest quality, accounts for just 10% of total production. In addition to triglycerols and free fatty acids, olive oil contains a variety of nonsaponifiable compounds that add to 1 to 2% of the oil and are important for its stability, unique flavor, and taste. By contrast, other edible seed oils lose most of their minor compounds during the refining stages.



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# 50 Onion and Garlic

## INTRODUCTION

Onion (*Allium cepa*) and garlic (*Allium sativum*) exhibit:

- Antimicrobial activities
- Antifungal activities
- Antiviral activities
- Antithrombotic actions
- Antineoplastic effects
- Hypolipidemic properties
- Antiarthritic actions
- Hypoglycemic functions

**Garlic** (*Allium sativum*) and **onion** (*Allium cepa*) are among the oldest of all cultivated plants and originated in central Asia. Garlic has been used as a spice, food, and folklore medicine for over 4000 years and is the most widely researched medicinal plant (see Ali et al., 2000).

**Codex Ebers**, an Egyptian **medical papyrus** dating to about 1550 B.C., gives more than 800 therapeutic formulas of which 22 mention garlic as an effective remedy for a variety of ailments, including heart problems, headache, bites, worms, and tumors.

**Aristotle**, **Hippocrates**, and **Aristophanes** recommended garlic for its medicinal effects. The Roman naturalist **Pliny the Elder** cited numerous therapeutic uses for both garlic and onions. **Discorides**, a chief physician to the Roman army in the 1st century A.D., prescribed garlic as a vermifuge or expeller of intestinal worms. During the first Olympic games in Greece, **athletes** ingested garlic as a stimulant. **Louis Pasteur** reported the antibacterial properties of garlic as early as 1858. In India, garlic has been used for centuries as an **antiseptic lotion** for washing wounds and ulcers. During both world wars, garlic was used as an antiseptic for the **prevention of gangrene**. Many medical practitioners have researched its insecticidal, antimicrobial, antiprotozoal, and anti-tumor activities.

More recently, garlic has been reported to be effective in ailments such as cardiovascular diseases because of its ability to lower serum **cholesterol**. A component of both garlic and onion, **S-methylcysteine sulfoxide** (SMCS) has been shown to reduce both blood cholesterol and the severity of atherosclerosis. Garlic has protective effects against **stroke**, **coronary thrombosis**, **atherosclerosis**, and **platelet aggregation**, as well as **infections** and **vascular disorders**. Furthermore, fibrinolytic activity increases following administration of garlic, thus preventing **atherosclerosis** and ischemic heart disease. Many claims of **antibiotic action**, **hypoglycemic effect**, **antitumor**, **antioxidant**, and **antithrombotic properties** have also been attributed to garlic (and onion) extracts.

## ACTIVE INGREDIENTS IN ONION AND GARLIC

When garlic is cut and the parenchyma is destroyed, **alliin** is the major cysteine sulfoxide liberated. Alliin is acted upon by the enzyme **allinase** (**alliin lyase**) to produce **allicin**. **Allicin** [S-(2-

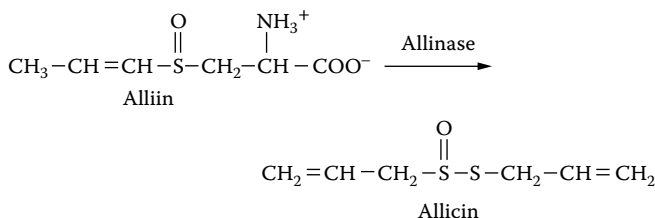


FIGURE 50.1 The structure of allicin.

**propenyl)2-propene-1-sulfinothioate or diallylthiosulfinate]** is an odoriferous compound and the main component of freshly crushed garlic homogenates (Figure 50.1).

Garlic also contains **S-propylcysteine-sulfoxide** (PCSO) and **S-methylcysteine-sulfoxide** (MCSO). PCSO can generate over 50 compounds depending on temperature and water content. The action of allinase on the mixture of alliin, PCSO, and MCSO can produce many other molecules, including **allyl methane thiosulfinate**, **methyl methanethiosulfinate**, and other mixed or symmetrical **thiosulfinites** (R-S-S-R'), where R and R' are methyl, propyl, and allyl groups.

## INHIBITION OF PLATELET AGGREGATION BY ONION AND GARLIC

### ANTICOAGULANTS AND THROMBOLYTIC AGENTS

The clotting of blood, which protects against hemorrhage, involves the sequential initiation, interaction, and completion of several stages in hemostasis. The adhesion and **aggregation of platelets** are mediated via the release of **adenosine diphosphate** (ADP). An extensive number of pharmacological agents, such as **acetylsalicylic acid**, **indomethacin**, **phenylbutazone**, **sulfinpyrazone**, and **dipyridamole**, and foods such as garlic and onion, inhibit both platelet aggregation and thrombus formation, and thus may be of value in the treatment of thrombotic disorders. The formation of fibrin itself occurs by means of a cascading group of reactions involving numerous blood-clotting factors and is accomplished in several stages.

Hemorrhage may result from several causes: an abnormality or deficiency of platelets (**thrombocytopenic purpuras**), a deficiency of **clotting factors** (factors II, VII, IX, or X), **vitamin K deficiency** (vitamin K is necessary for synthesizing clotting factors), or liver diseases that involve the synthesis of clotting factors. Increased clotting may occur in the presence of **thrombosis** (enhanced formation of fibrin), **stasis and phlebitis** (diminished circulation), or **embolism** (dislocation and lodging of blood clots). Although **heparin** is an extremely effective anticoagulant, it has certain limitations that the newer thrombin inhibitors do not have. As a result, these novel inhibitors may have advantages over heparin for use in certain clinical settings.

Thrombin activates platelets, converts fibrinogen to fibrin, activates factor XIII, which stabilizes fibrin, and activates factors V and VIII, which accelerate the generation of **prothrombinase**. Therefore, the inhibition of thrombin is essential in preventing and treating **thromboembolic disorders**.

### AGGREGIN AND PLATELET AGGREGATION

Platelets circulate in blood without adhering to other platelets or to the endothelium. However, when the endothelial cells are perturbed, the platelets adhere and undergo a change in shape, and aggregate. ADP is known to induce the platelet shape change, aggregation, and exposure of fibrinogen-binding sites.

The platelet surface contains aggregin, a membrane protein with a molecular weight of 100 kDa, which has physical and immunochemical properties that differ from those of platelet glycoprotein IIIa.

Binding to aggregin is required for **epinephrine-induced platelet aggregation** to occur. In turn, epinephrine increases the affinity of ADP for its receptor. Thrombin stimulates platelet aggregation independently of ADP, but by raising the level of calcium in the cytoplasm, it activates **platelet calpain**, which in turn cleaves aggregin.

### VITAMIN E AND PLATELET AGGREGATION

**$\alpha$ -Tocopherol**, a natural antioxidant, inhibits platelet aggregation and release. The effect of vitamin E is due to a reduction in platelet **cyclooxygenase** activity and inhibition of **lipid peroxide** formation. It is believed that supplementing the diet with **vitamin E** could play a role in the treatment of thromboembolic disease, especially if it is given in conjunction with an inhibitor of platelet aggregation.

### PLATELET-ACTIVATING FACTOR

A platelet-activating factor, **1-O-alkyl-2-(R)acetyl-sn-glycerol-3-phosphocholine**, is released in the presence of shock and ischemia. The platelet-activating factor antagonist can protect the heart and brain against ischemic injury.

### PLATELET-INHIBITING DRUGS

A combination of **acetylsalicylic acid** and **dipyridimole** has been found to be effective in preventing myocardial reinfarction and occlusion of aortocoronary grafts.

## EICOSANOIDS

All naturally occurring prostaglandins are derived through the cyclization of 20-carbon unsaturated fatty acids such as arachidonic acid, which in turn is synthesized from the essential fatty acid linoleic acid. The prostaglandins are named according to their ring substitutions and the number of additional side-chain double bands, as seen in prostaglandins  $E_1$ ,  $F_{1\alpha}$ , and  $F_{2\alpha}$ .

In addition to serving as a precursor for the synthesis of prostaglandins, arachidonic acid is also a precursor for the synthesis of **prostacyclin**, **thromboxanes**, and **leukotrienes**.

### PHARMACOKINETIC PROPERTIES OF THE EICOSANOIDS

The prostaglandins are inactivated rapidly (half-life < 1 min) by the pulmonary, hepatic, and renal vascular beds through the actions of **prostaglandin dehydrogenase** and **prostaglandin reductase**. In addition, the aliphatic side chain undergoes relatively slow  $\beta$  and  $\omega$  oxidation. The rapid metabolism and removal logically protect the cardiovascular system from the smooth-muscle-stimulating effects of prostaglandins. Prostacyclins are also rapidly metabolized by prostaglandin dehydrogenase. Thromboxane  $A_2$  is hydrated in the blood to thromboxane  $B_2$ . The thromboxanes are metabolized extensively and their metabolites appear in urine.

### PHYSIOLOGY OF THE EICOSANOIDS

The most important known effects of the prostaglandins and other eicosanoids are the contraction and relaxation of smooth muscles:



- **Smooth muscles and vascular smooth muscles:** Prostaglandins  $E_2$  and  $I_2$  cause arteriolar dilation in the systemic and pulmonary vascular beds. Prostaglandins  $F_{2\alpha}$  and  $E_2$ , as well as thromboxane  $B_2$ , constrict the human umbilical cord. Leukotrienes  $C_4$  and  $D_4$ , which release prostaglandin  $E$ , decrease peripheral vascular resistance.
- **Respiratory smooth muscles:** Prostaglandins  $E_1$ ,  $E_2$ , and  $I_2$  cause bronchodilation and oppose the actions of acetylcholine, histamine, and bradykinin. On the other hand, prostaglandin  $F_2$ , leukotrienes  $C_4$  and  $D_4$ , thromboxane  $A_2$ , and 5-HPETE are all bronchoconstricting substances possessing different potencies.
- **Gastrointestinal smooth muscles:** Prostaglandin  $E_2$  contracts longitudinal but relaxes circular smooth muscles, whereas prostaglandin  $F_2$  contracts both.
- **Reproductive smooth muscles:** Prostaglandins  $E_1$ ,  $E_2$ , and  $F_{2\alpha}$  cause contraction of the pregnant and nonpregnant human uterus, and produce laborlike contractions. In contrast to **oxytocin**, this effect is possible in all stages of pregnancy.

In general, the constricting and relaxing effects of the eicosanoids on the smooth muscles are not mediated by means of the classic neurotransmitters such as acetylcholine, catecholamine, or histamine, which is proved by the fact that they are not altered by antihistaminic substances, anticholinergic agents, or either  $\alpha$ - or  $\beta$ -adrenergic receptor-blocking agents.

Prostaglandins exhibit the following effects:

- **Cardiovascular system:** Prostaglandins  $E_2$  and  $F_{2\alpha}$  have positive isotropic effects and generally elicit increases in the cardiac output.
- **Blood:** Prostaglandin  $E_1$  inhibits platelet aggregation, whereas thromboxane  $A_2$  induces platelet aggregation. Prostaglandins  $A_2$ ,  $E_1$ , and  $E_2$  enhance **erythropoiesis** by augmenting the renal cortical release of **erythropoietin**.
- **Kidneys:** Prostaglandins  $E_1$ ,  $E_2$ , and  $I_2$  increase renal blood flow and produce diuresis, natriuresis, and kaliuresis. Prostaglandins  $E_1$  and  $E_2$  antagonize the action of antidiuretic hormones.
- **Endocrine system:** Various prostaglandins have the following effects in the endocrine system:  
 Prostaglandins  $E_1$  and  $F_{2\alpha}$  stimulate the release of **corticotropin**.  
 Prostaglandins  $E_1$  and  $E_2$  enhance the release of **growth hormone**.  
 Prostaglandin  $F_{2\alpha}$  increases the release of **prolactin**.  
 Prostaglandin  $E_2$  increases the release of **luteinizing hormone**.  
 Prostaglandin  $F_{2\alpha}$  reduces progesterone output and causes regression of the **corpus luteum**.
- **Metabolic effects:** Prostaglandin  $E_1$  inhibits basal and **catecholamine-stimulated lipolysis**.
- **Nociception:** Prostaglandins  $E_1$  and  $E_2$  bring about the sensation of pain by sensitizing the afferent nerve endings to noxious chemical and physical stimuli.
- **Inflammatory and immune responses:** The prostaglandins are involved in both the genesis and manifestation of inflammation. Furthermore, prostaglandins are thought to regulate the functions of B and T lymphocytes.
- **Central nervous system:** Prostaglandins  $E_1$  and  $E_2$  cause sedation.
- **Pyrexia:** Prostaglandin  $E_1$  precipitates fever when it is injected intracerebroventricularly.

## THE PHARMACODYNAMICS OF EICOSANOIDS

Some, but not all, of the pharmacological effects of eicosanoids are mediated through alterations in the concentration of cyclic adenosine monophosphate (cyclic AMP). For example, prostaglandins  $E_1$  and  $E_2$  inhibit platelet aggregation by increasing the cyclic AMP concentration. Conversely,

thromboxane  $A_2$ , which induces platelet aggregation, inhibits the synthesis of cyclic AMP. Prostaglandins also regulate the functions of B and T lymphocytes.

### THE THERAPEUTIC USES OF EICOSANOIDS

Prostaglandins are mostly used as **abortifacients**. They may be administered by vaginal suppository (**dinoprostone**), which contains prostaglandin  $E_2$ , by intramuscular injection (**carboprost** and **tromethamine**), which contains **15-methyl prostaglandin  $F_{2\alpha}$** , or by intraamniotic administration (**dinoprost** and **tromethamine**), which contains prostaglandin  $F_{2\alpha}$ . Other possible uses of prostaglandins may include the treatment of ductus arteriosus (prostaglandin  $E_1$ ) to maintain patency, and as a vasodilator (prostaglandin  $E_1$ ) in the management of peripheral vascular diseases. High levels of prostaglandin  $F_{2\alpha}$  may cause dysmenorrhea, as substances such as indomethacin and ibuprofen are effective in relieving these symptoms.

### AGENTS THAT ALTER METABOLISM OF EICOSANOIDS

Additional deleterious or beneficial actions of agents that alter the metabolism of eicosanoids are described in the following text:

- **Interleukin-1, pancreatic  $\beta$  cells, and insulin-dependent diabetes mellitus:** Insulin-dependent diabetes mellitus is an autoimmune disease that causes the gradual destruction of insulin-producing pancreatic  $\beta$  cells. It has been postulated that the infiltration of macrophages into the pancreatic islets plays a key role in the destruction of  $\beta$  cells and that cytokines, especially interleukin-1, which is released locally from macrophages, may be the toxic molecule causing this destruction.
- **Prostaglandin, renin, and the control of arterial pressure:** Arachidonic acid, prostacyclin (prostaglandin  $I_2$ ), and prostaglandin  $E_2$  stimulate the secretion of renin, and this effect is blocked by **indomethacin** or **meclofenamate**. Because stimulation of the sympathetic nervous system increases the release of renin and prostaglandin, it is postulated that a portion of the neurogenically activated renin secretion is governed by prostaglandin-dependent pathways.
- **Aspirin, prostaglandin, and platelet aggregation:** Thromboxane  $A_2$  is a potent vasoconstrictor and a stimulus to platelet aggregation: Prostacyclin, on the other hand, is the principal cyclooxygenase product of the vascular endothelium and has the opposite effect on platelet function and vascular tone. Aspirin inhibits the arachidonic-acid-induced platelet aggregation. It and other nonsteroidal anti-inflammatory drugs block the biosynthesis of prostaglandins and thromboxane  $A_2$  by inhibiting cyclooxygenase.
- **Indomethacin, prostaglandin, and ductus arteriosus:** The patency of the **ductus arteriosus** is maintained in part by a prostaglandin. Indomethacin induces constriction of the ductus during the neonatal period, whereas infusion of prostaglandin  $E_1$  maintains its patency.
- **Aspirin, cyclooxygenase, and the provocation of asthma:** A few people with asthma suffer from a unique syndrome in which the ingestion of 40 to 300 mg of aspirin produces rhinorrhea and acute bronchoconstriction. All cyclooxygenase inhibitors will precipitate bronchospasm in patients with aspirin-evoked asthma.
- **Aspirin, prostaglandin, and hypercalcemia:** Certain solid tumors (**renal cell carcinoma**) cause hypercalcemia, which may be mediated by prostaglandin  $E_2$ . Taking a high dose of aspirin or another nonsteroidal anti-inflammatory agent will lower the serum-calcium level.
- **Indomethacin, cyclooxygenase, and hypertension:** Arthritis and hypertension frequently coexist, and certain nonsteroidal anti-inflammatory agents antagonize the action

of antihypertensive medications. For example, indomethacin will elevate blood pressure in hypertensive patients being treated with diuretics,  $\beta$ -adrenergic receptor antagonists, or converting-enzyme inhibitors. Similar effects are seen with **ibuprofen** and **piroxicam**, but not with aspirin or **sulindac**.

- **Aspirin, prostaglandins, and mastocytosis:** Mastocytosis is a disease of unknown cause that is characterized by the increased proliferation of tissue mast cells, which leads to an episodic release of mediators and the manifestation of prominent symptoms such as vasodilation, flushing, hypotension, and tachycardia. Increased intestinal motility, which is also observed in this disease, may result in abdominal cramping and diarrhea. Additional manifestations of mastocytosis are chest pain, dyspnea, pruritus, and headache. The production of prostaglandin  $D_2$  is elevated in mastocytosis. Histamine is a potent vasodilator and causes contraction of gastrointestinal smooth muscle. However, the symptoms of mastocytosis do not respond to an antihistamine alone, although the episode can be prevented by an antihistaminic agent, or with high doses of aspirin, or some other nonsteroidal anti-inflammatory agent that inhibits the synthesis of prostaglandins.

### EFFECT OF GARLIC AND ONIONS ON EICOSANOID METABOLISM

The effects of onion and garlic on eicosanoid metabolism have mainly been studied by observing the effects of garlic and onion preparations on platelet aggregation and subsequent eicosanoid synthesis.

ADP, thrombin, collagen, and the **calcium ionophore A23187** can induce aggregation of platelets followed by secretion of the contents of storage granules. With the exception of collagen, these agonists can also shift the metabolic balance in platelets toward rapid mobilization. Arachidonic acid (AA) from phospholipid stores and the conversion of AA into eicosanoids occurs. Therefore, platelet aggregation and activation are not always linked.

After liberation, AA is converted into prostaglandin endoperoxides by the action of the enzyme cyclooxygenase. Endoperoxides are rapidly converted into either stable prostaglandins,  $PGE_2$ ,  $PGF_{2\alpha}$ , and  $PGD_2$ , or thromboxane  $A_2$ . AA can also be converted into lipoxygenase-dependent products such as **12-hydroperoxyeicosatetraenoic acid (12-HPETE)** and **12-hydroxyeicosatetraenoic acid (12-HETE)**.

**Onion oil** has been shown to inhibit both the cyclooxygenase and 12-lipoxygenase in platelets, as well as inhibiting platelet aggregation induced by epinephrine, ADP, or AA. Inhibitors of lipoxygenase and cyclooxygenase have been isolated and characterized from onion extracts. More specifically, "**cepaenes**" found in onions have been found to be potent inhibitors of sheep seminal **microsomal cyclooxygenase** and porcine **leukocyte 5-lipoxygenase** (see Ali et al., 2000).

Both aqueous and organic garlic extracts have been found to inhibit several steps of the AA cascade in platelets. Garlic extracts inhibit incorporation of labeled AA into platelet phospholipids, and also inhibit deacylation of platelet phospholipids upon stimulation with the calcium ionophore A23187, resulting in decreased eicosanoid synthesis. In addition, a direct inhibitory effect of garlic extracts on AA-metabolizing enzymes has been observed. More recently, Ali et al. (2000) observed noncompetitive and irreversible inhibition of cyclooxygenase by aqueous extracts of raw garlic. This inhibitory activity was destroyed by boiling the garlic.

### CARDIOVASCULAR AND LIPID-LOWERING EFFECTS OF GARLIC

Diseases related to atherosclerosis such as ischemic heart disease, stroke, and peripheral arterial diseases are associated with elevated serum lipids. Hyperlipidemia is one of the major risk factors for atherosclerosis. The lipid-lowering properties of garlic and onion have been studied in great detail. Intervention studies have reported the effect of garlic on various risk factors with inconsistent results, reflecting variations in protocol design as well as dosage types and garlic preparations used.

It was demonstrated previously that **allicin** extracted from garlic had a lipid-lowering effect on long-term feeding to healthy rats. These studies reported a significant decrease in total serum lipids, phospholipids, and cholesterol in the animals fed allicin compared to control animals.

The **cholesterol-lowering effect of garlic** was also seen in rabbits that were fed 2 g cholesterol/day for 16 weeks. A dose-dependent reduction of serum cholesterol in garlic-fed rats was observed in these experiments.

A study carried out in the U.S. showed a 56% decrease in serum total lipid radioactivity in rats fed the equivalent of 5 g of fresh garlic bulbs/d for 7 d. Rats fed an experimental diet containing cholesterol were treated either with intraperitoneal injections of C-14 labeled acetate or a diet containing C-14 sucrose.

In summary, the consumption of garlic appears to reduce serum cholesterol in experimental animals in a dose-dependent fashion. This may be due to decreased synthesis or increased excretion of cholesterol through the intestinal tract. It has been reported that garlic consumption increases high-density lipoprotein (HDL) levels, which may help to remove excess cholesterol from arterial tissue.

## GARLIC AND CANCER PREVENTION

The anticancer properties of garlic have been known since ancient times. The ancient Egyptians used garlic externally for the treatment of tumors, and Hippocrates and physicians in ancient India are reported to have used garlic externally for cancer treatment.

Although the anticancer properties of garlic have been recognized for centuries, the most recent studies involving garlic have focused on several aspects, including **chemoprevention**. A compound that can inhibit the carcinogenic process is called an anticarcinogen or chemopreventive. The field describing the effects of these agents in inhibiting cancer in animals and humans is called chemoprevention.

Studies on the chemopreventive activity of garlic have utilized a number of different garlic preparations, including fresh garlic extract, aged garlic, garlic oil, and several organosulfur compounds derived from garlic. In addition to studying the anticarcinogenic activity of garlic components, a number of researchers have recently begun to focus on the antimutagenic activity of garlic.

It is clear that the chemopreventive activity of garlic is related to the **organosulfur compounds** (OSCS) derived from garlic. Although how garlic achieves chemoprevention is not fully understood, several modes of action have been proposed on the basis of recent studies.

## ANTICLASTOGENIC EFFECTS OF GARLIC AND ONION

Aqueous garlic extract in combination with **mustard oil** reduces the chromosomal aberrations caused by **sodium arsenate**. Furthermore, both onion and garlic oil decrease the **phorbol-myristate-acetate**-induced tumor promotion.

## ANTIMICROBIAL EFFECTS OF GARLIC AND ONION

Garlic extracts have been shown to inhibit the growth of a variety of bacteria and fungi. In addition, garlic extracts have been shown to have antiviral properties. Onion extracts have also been shown to have antibacterial properties.

A number of studies have focused on identifying the active antimicrobial principles in fresh garlic extract. **Allicin** has been identified as the active agent in garlic extracts. The antifungal activity of allicin has been shown to depend on the sulfhydryl moiety because activity is destroyed by thiols such as **L-cysteine**, **glutathione**, and **mercaptoethanol**. **Ajoene**, a compound found in oil-macerated garlic, has also been shown to have antimicrobial activity (Ali et al., 2000).

## THE ANTIOXIDANT ACTIONS AND OTHER THERAPEUTIC EFFECTS OF GARLIC

Garlic has long been used not only as a flavoring agent for food but also for its medicinal properties. The intrinsic antioxidant activities of **garlic**, **garlic extracts**, and some **garlic constituents** have been widely documented *in vivo* and *in vitro*, as well as the ability of aged garlic extract to decrease  $H_2O_2$  levels *in vitro*.

Studies have shown that 2% garlic feedings for 2 weeks:

- Decrease  $H_2O_2$  generation
- Increase the activity of **superoxide dismutase**
- Increase the activity of **glutathione peroxidase**
- Increase catalase activity in vascular endothelial cells

**Garlic oil** and **S-allyl-cysteine sulfoxide (Alliin)**, a garlic compound, exhibited similar antioxidant properties. Aged garlic extract prevents ischemia and reperfusion injuries to the heart and brain.

## CARDIOPROTECTIVE ACTIONS OF WILD GARLIC (*ALLIUM URSINUM*) IN ISCHEMIA AND REPERFUSION

Ventricular arrhythmias arising predominantly from ischemic heart disease are a major cause of death in Western industrialized countries, and the prevention and pharmacological management of life-threatening arrhythmias remain a great challenge. It is, therefore, important to search for alternative dietary and phytotherapeutic strategies. In the framework of these studies it was found that the feeding of garlic powder (*A. sativum*) and pulverized dried wild garlic (*A. ursinum*) leaves for several weeks has significant protective effects with respect to the size of the ischemic zone and the incidence of arrhythmias.

Rietz et al. (1993) investigated the susceptibility to ventricular arrhythmias under the conditions of cardiac ischemia and reperfusion in the Langendorff heart preparation of rats fed a standard chow for 8 weeks enriched with 2% of pulverized wild garlic leaves. The isolated hearts were perfused with a modified Krebs–Henseleit solution. The incidence of ventricular fibrillation (VF) during 20-min occlusion of the descending branch of the left coronary artery (LAD) was significantly reduced in the wild-garlic group compared to untreated controls (20 vs. 88%). The same holds for the size of the ischemic zone (33.6 vs. 40.9% of heart weight). In the reperfusion experiments (5 min after 10-min ischemia), ventricular tachycardia (VT) occurred in 70% of the wild-garlic group vs. 100% in untreated controls, and VF in 50 vs. 90%. The time until occurrence of extrasystoles, VT, or VR was prolonged. No significant alterations in cardiac fatty acid composition were observed. Although the **prostacyclin** production was slightly increased in hearts of the wild-garlic group, inhibition of **cyclooxygenase** by **acetylsalicylic acid (ASA; aspirin)** could not completely prevent the cardioprotective effects, suggesting that the prostaglandin system does not play a decisive role in the cardioprotective action of wild garlic. Furthermore, a moderate **angiotensin-converting enzyme (ACE)** inhibiting action of wild garlic was found *in vitro* as well as *in vivo* that could contribute to the cardioprotective and blood-pressure-lowering action of wild garlic (Figure 50.2).

## ACE INHIBITORS

ACE inhibitors are used in the following areas.

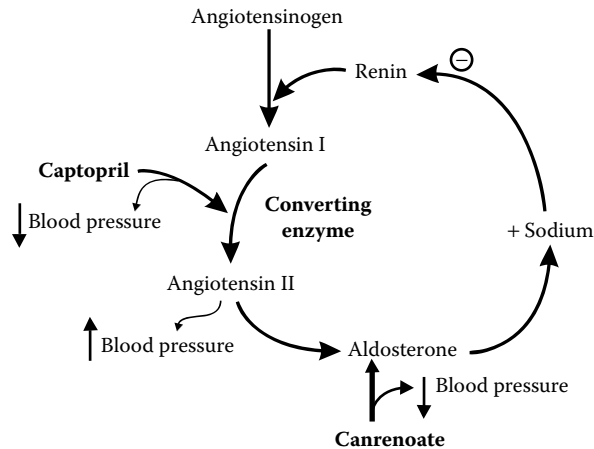


FIGURE 50.2 Captopril and garlic inhibit angiotensin-converting enzyme.

### MYOCARDIAL INFARCTION

The use of ACE inhibitors in myocardial infarction is rapidly evolving. Several large, prospective, randomized clinical studies involving thousands of patients have been published, and these studies provide convincing evidence that ACE inhibitors reduce overall mortality when treatment is begun during the peri-infarction period. In this regard, clinical trials with ACE inhibitors in myocardial infarction can be divided into two groups: (1) treatment for several years postmyocardial infarction of patients with left ventricular systolic dysfunction (with or without overt heart failure) and (2) treatment for several weeks postmyocardial infarction of patients regardless of ventricular function. These studies suggest that, in selected high-risk patients (i.e., those with systolic dysfunction), ACE inhibitors save 40 to 70 lives per 1000 patients. Short-term treatment of unselected patients postmyocardial infarction saves about 5 lives per 1000.

An important issue is when to initiate therapy and how long to maintain treatment. In the CONSENSUS II study, **enalaprilat** was administered intravenously within 24 h of myocardial infarction, and no benefit was demonstrated. This study raised serious questions about giving ACE inhibitors too soon after myocardial infarction. However, in the SMILE study, treatment with oral **zofenopril** was initiated within the first 24 h, and a reduction in mortality was observed within a few days. Most likely, the symptomatic hypotension induced by intravenous enalaprilat explains the negative finding in the CONSENSUS II study. Given the current data findings, an oral ACE inhibitor should be initiated as soon as possible, but no later than 16 d after infarction. In all patients, therapy should be maintained for at least 6 weeks, and in patients with left ventricular systolic dysfunction, ACE inhibitor therapy should be maintained long term. Whether long-term ACE inhibitor therapy would benefit patients without ventricular dysfunction is an open question that is being addressed by two ongoing clinical trials. Doubtless, the dosage of ACE inhibitors and duration of treatment for various categories of patients with ischemic heart disease will continue to be refined in coming years.

### PROGRESSIVE RENAL IMPAIRMENT

The combination of diabetes mellitus and hypertension inexorably leads to diabetic nephropathy and is the major cause of **end-stage renal failure**. In numerous animal studies and in several small clinical trials, ACE inhibitors have been shown to significantly retard the loss of kidney function associated with diabetic nephropathy. A large, prospective, placebo-controlled study has clearly established that **captopril** slows the progression of diabetic nephropathy in patients with insulin-

**dependent diabetes mellitus** and established renal disease. In this regard, captopril significantly reduced proteinuria, the rate of decline in **creatinine clearance**, and the combined end points of dialysis, transplantation, and death. These results support the conclusion that, unless contraindicated, patients with diabetic nephropathy (whether normotensive or hypertensive) should be treated with an ACE inhibitor.

A broader issue is whether or not ACE inhibitors should be used routinely in nondiabetic patients with chronic renal failure. No large, long-term, prospective, and placebo-controlled study has yet addressed this issue; however, when animal studies and small, less-than-adequate clinical trials are viewed in aggregate, the data suggest that ACE inhibitors should be tried in hypertensive patients with progressive renal impairment who are at high risk of developing end-stage renal failure. Because renal impairment predisposes toward ACE inhibitor-induced hyperkalemia, serum  $K^+$  levels should be monitored carefully in such patients. The development of ACE inhibitors that do not inhibit the **intraadrenal renin-angiotensin system** may alleviate this concern. It is likely that future studies will broaden the indications for ACE inhibitors in renal disease.

Several mechanisms participate in the renal protection afforded by ACE inhibitors. Increased glomerular capillary pressure induces glomerular injury, and ACE inhibitors reduce this parameter both by decreasing arterial blood pressure and by dilating renal efferent arterioles. ACE inhibitors increase the permeability selectivity of the filtering membrane, thereby diminishing exposure of the mesangium to proteinaceous factors that may stimulate mesangial cell proliferation and matrix production, two processes that contribute to expansion of the mesangium in diabetic nephropathy. Because angiotensin II is a growth factor, reductions in the intrarenal levels of angiotensin II may further attenuate mesangial cell growth and matrix production.

### **SCLERODERMA RENAL CRISIS**

Before the use of ACE inhibitors, patients with scleroderma renal crisis generally died within several weeks. A few small, observational studies have suggested that captopril markedly improved this otherwise grim prognosis. As stated previously, **garlic behaves like captopril** and inhibits the activity of ACE. Considering the well-known difficulties in the prevention and pharmacological treatment of life-threatening cardiac arrhythmias, it seems appropriate to also systematically investigate dietary and phytotherapeutic interventions. A number of studies have demonstrated the cardioprotective actions of diets enriched with polyunsaturated fatty acids. In addition, the antiarrhythmic effects of various oil diets, particularly fish oil and linseed oil, are well known. Indeed, a dietary supplement of wild garlic can significantly reduce the size of the ischemic zone as well as ischemia- and reperfusion-induced arrhythmias.

Oxygen free-radical generation has been proposed to be a major mechanism particularly in the pathogenesis of reperfusion injury. In this context, studies on the antioxidant and free-radical scavenging activity of garlic and alliin are of great interest. As the compounds of garlic and wild garlic are very lipophilic, they might be incorporated into the myocardial membranes acting as radical scavengers.

### **ANTIOXIDANT ACTIVITY OF ALLICIN, AN ACTIVE PRINCIPLE IN GARLIC**

The use of garlic is rising among health-conscious people. Reports suggest that it has beneficial effects in diseases such as ischemic-reperfusion arrhythmias and infarction, ischemic heart disease, hypertension, hyperlipidemia, peripheral arterial occlusive disease, and hypercholesterolemic atherosclerosis. Reactive oxygen metabolites (ROMs), which include superoxide anion ( $O^{2-}$ ), hydrogen peroxide ( $H_2O_2$ ), and hydroxyl radicals ( $\bullet OH$ ), have been implicated in the pathophysiology of hypercholesterolemic atherosclerosis and ischemia-reperfusion cardiac injury. Antioxidants are effective against ischemia-reperfusion cardiac injury, and hypercholesterolemic atherosclerosis. The

beneficial effects of garlic in these diseases and other undocumented health problems may be due to its antioxidant property. However, it is not known if garlic scavenges  $O^{\cdot-2}$ ,  $H_2O_2$ , or  $\bullet OH$ .  $\bullet OH$  is the most toxic of all the ROMs. The **allicin** (active ingredient of garlic) content of commercial preparations of garlic varies tremendously. **Garlicin** preparations contain 1800 g of allicin per tablet.

Prasad et al. (1995) investigated the ability of **allicin** contained in the commercial preparation **Garlicin** to scavenge **hydroxyl radicals** ( $\bullet OH$ ) using high-pressure liquid chromatography (HPLC).  $\bullet OH$  was generated by photolysis of  $H_2O_2$  (1.25 to 10  $\mu mol/ml$ ) with ultraviolet light and was trapped with salicylic acid, which is hydroxylated to produce  $\bullet OH$  adduct products **2,3-** and **2,5-dihydroxybenzoic acid** (DHBA).  $H_2O_2$  produced a concentration-dependent  $\bullet OH$  as estimated by  $\bullet OH$  adduct products 2,3-DHBA and 2,5-DHBA. Allicin equivalents in **Garlicin** (1.8, 3.6, 7.2, 14.4, 21.6, 28.8, and 36  $\mu g$ ) produced concentration-dependent decreases in the formation of 2,3-DHBA and 2,5-DHBA. The inhibition of formation of 2,3-DHBA and 2,5-DHBA with 1.8  $\mu g/ml$  was 32.36 and 43.2%, respectively, and with 36.0  $\mu g/ml$  the inhibition was approximately 94.0 and 90.0%, respectively. The decrease in  $\bullet OH$  adduct products was due to scavenging of  $\bullet OH$  and not the scavenging of formed  $\bullet OH$  adduct products. Allicin prevented the lipid peroxidation of liver homogenate in a concentration-dependent manner. These results suggest that **allicin scavenges  $\bullet OH$**  and that **Garlicin has antioxidant activity**.

There are numerous commercial garlic preparations available on the market in the form of **garlic powder tablet**, **steam-distilled garlic oils**, and **oil-macerated garlic**. The best garlic powder tablets have been reported to be as active as clove homogenate, whereas steam-distilled oils were 35% as active and oil macerates only 12% as active in the inhibition of whole blood platelet aggregation. **Allicin**, an active principle in garlic, is present only in garlic powder and fresh garlic but not in garlic oil or oil-macerated garlic. The allicin content of commercial garlic powder tablets varies from 160 to 3600  $\mu g/g$ . The results suggest that the claimed beneficial effects of garlic in various diseases could be due to the  $\bullet OH$  scavenging property of allicin in garlic (Figure 50.3).

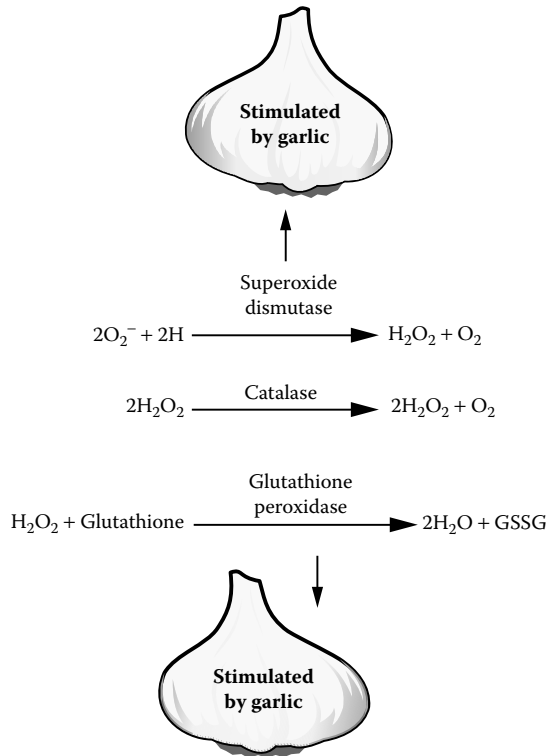
## ATTENUATION OF ISCHEMIC BRAIN DAMAGE BY AGED GARLIC EXTRACTS

Through numerous studies on the mechanism of pathogenesis of cerebral ischemia, various compounds were proposed that could effectively protect the brain against ischemia. Because free radicals are one of the focuses of study in the mechanism of cerebral ischemic injury, a variety of agents that have antioxidant capacity have been developed:

- **Lazaroid** compounds, which do not have glucocorticoid activity, but do have antioxidant properties
- **Transgenic mouse models**, which have enhanced superoxide dismutase (SOD) activity
- **Prostaglandin oligomeric** compounds
- **Aged extract of garlic** (*Allium sativum*)-containing biochemically active substances, including thioallyl compounds

Numagami et al. (1996) examined the effects of an aged garlic extract (AGE) and its thioallyl components on rat brain ischemia using a middle cerebral artery occlusion model and a transient global ischemia model. In focal ischemia, an aged garlic extract, **S-allyl cysteine** (SAC), **allyl sulfide** (AS), or **allyl disulfide** (ADS), was administered 30 min prior to ischemic insult. At 3 d after ischemic insult, water contents of both ischemic and contralateral hemispheres were measured to assess the degree of ischemic damage. The water content of the ischemic control (no drug treatment) group was  $81.50 \pm 0.07\%$  (mean  $\pm$  SEM). It was significantly reduced with the administration of 300 mg/kg of SAC; the water content was  $80.66 \pm 0.11\%$  ( $p < 0.001$ ). The histological observation using **2,3,5-triphenyltetrazolium chloride** staining demonstrated that the administration of SAC reduced infarct volume. Neither AS nor ADS was effective. In global ischemia, the





**FIGURE 50.3** Garlic increases antioxidant mechanisms.

production of reactive oxygen species (ROS) was measured *ex vivo* using a spin-trapping agent,  $\alpha$ -phenyl-*N*-tert-butyl nitron, and electron paramagnetic resonance spectroscopy. The production of ROS had two peaks; first at 5 min and second at 20 min after reperfusion. Both SAC and 7-nitro indazole, a nitric oxide synthase inhibitor, did not attenuate the amount of ROS produced at the first peak but did attenuate the amount of the second peak. The possible involvement of peroxynitrite, which may be formed from superoxide and nitric oxide and is known to be highly toxic in ischemia or reperfusion injury of the brain, was suggested.

### INHIBITION OF FREE-RADICAL GENERATION AND AUGMENTATION OF ANTIOXIDANT ENZYME ACTIVITY IN VASCULAR ENDOTHELIAL CELLS BY GARLIC

Oxygen free radicals such as hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), superoxide anion ( $\text{O}^{2-}$ ), and hydroxyl radical ( $\text{OH}\cdot$ ) have been implicated in mediating various pathological processes such as ischemia, inflammatory diseases, diabetes, and atherosclerosis. Endothelial cell injury is often the first stage of these disorders. Free radicals produced by activated polymorphonuclear neutrophils (PMN) or endothelial cells are critical factors in causing endothelial cell injury. The antioxidant enzymes (see Figure 50.3) superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), either present intracellularly or released into the extracellular milieu, can directly scavenge these oxidants or prevent their conversion to toxic species. They also inhibit PMN adhesion to endothelial cells and therefore play an important role in preventing endothelial cell injury.

Garlic has been shown to prevent atherosclerosis and cancer and to retard the aging process. Alliin from garlic can scavenge  $\text{OH}\cdot$ , and garlic powder has been shown to scavenge both  $\text{OH}\cdot$  and 1,1-diphenyl-2-picrylhydrazyl radicals.

AGE has been shown to prevent oxidant-induced injury of endothelial cells. Wei and Lau (1998) determined the effects of AGE on the generation of hydrogen peroxide and superoxide anion ( $O^{2-}$ ) and the activity of three antioxidant enzymes in bovine pulmonary artery endothelial cell (PAEC). Confluent monolayers of PAEC were incubated with AGE, and oxidative stress was triggered by **hypoxanthine** and **xanthine oxidase** or  $H_2O_2$ . AGE exhibited both concentration- and time-dependent suppression of  $H_2O_2$  and  $O^{2-}$  generation, and also significantly increased the activities of SOD, CAT, and GPX. The results suggest that AGE may be an effective antioxidant in preventing or treating disorders related to endothelial cell injury associated with free radicals.

Oxygen is required for many life-sustaining metabolic reactions. Normal oxygen utilization in mammalian tissues requires an enzymatically controlled four-electron reduction to form water. If oxygen accepts fewer than four electrons, highly reactive free radicals (**oxyradicals**) are generated. One-electron reduction of molecular oxygen yields  $O^{2-}$ ; two-electron reduction results in hydrogen peroxide ( $H_2O_2$ ); and three-electron reduction generates hydroxyl radical ( $OH\bullet$ ). Both activated PMN and reoxygenated endothelial cells can accelerate oxyradical generation. The primary reactant that serves as the ultimate source for these oxyradicals is  $O^{2-}$  derived from the one-electron reduction of oxygen catalyzed by the enzyme **NADPH-oxidase** in PMN. Another source of  $O^{2-}$  is xanthine oxidase (XO) localized within the endothelial cells that utilizes HPX as a substrate. Free radicals contribute to endothelial cell injury, increase microvascular permeability and tissue damage, and play a critical role in mediating various pathological processes such as atherosclerosis, ischemia and reperfusion, and inflammatory diseases.

The antioxidant enzymes SOD, GPX, and CAT play an important role in maintaining physiological levels of  $O^{2-}$  and  $H_2O_2$ . The SODs are a group of enzymes that rapidly catalyze the conversion of  $O^{2-}$  to  $H_2O_2$  and oxygen. GPX is a major enzyme that inactivates a variety of organic peroxides and thus controls the cellular peroxide levels. It also reduces  $H_2O_2$  to water with generation of **oxidized glutathione**. Several studies have indicated that treatment of endothelial cells with SOD or CAT decreased damage caused by free radicals. Other data show that AGE increases the activities of SOD, GPX, and CAT. By inducing activities of antioxidant enzymes, AGE may hasten dismutation of  $O^{2-}$  and decomposition of  $H_2O_2$ . The effects of AGE on  $H_2O_2$  and  $O^{2-}$  generation observed in this study may, therefore, be due to enhanced activities of these antioxidant enzymes. Recently, Wei and Lau (1998) reported that AGE modulates the glutathione-redox cycle with the particular result of increasing the intracellular glutathione levels. The increase in intracellular glutathione may also account for the decrease in  $H_2O_2$  observed in this study.

In summary, Wei and Lau (1998) have shown that AGE inhibited  $H_2O_2$  and  $O^{2-}$  generation and augmented SOD, CAT, and GPX activities. The results suggest that AGE may be an effective antioxidant in preventing endothelial cell damage and may therefore play a significant role in the defense against free-radical-mediated disorders.

## ATTENUATION OF RENAL OXIDATIVE STRESS WITH GARLIC OIL

*Allium sativum*, commonly known as garlic, is a common constituent of the diet. It is used with spices to give foods a special flavor and fragrance. It is also used as a medicinal herb in many countries. Several pharmacological effects of garlic constituents have been reported. These include bactericidal, antibiotic, antitumor, hypolipidemic, hypoglycemic, and antiatherosclerotic activities. Garlic also inhibits **7,12-dimethyl benz[a]anthracene** and **benzo[a]pyrene-induced skin carcinogenesis** in mice. Garlic oil also reduces the tumor induction response in other organs.

**Nitritotriacetic acid** (NTA) is a constituent of various domestic and hospital detergents and is a common water contaminant. NTA forms water-soluble chelate complexes with various metal ions, including iron, at neutral pH. Its iron complex, Fe-NTA, is a known potent nephrotoxic agent. The renal toxicity is assumed to be caused by the elevation of serum free-iron concentration following the reduction of Fe-NTA at the luminal side of the proximal tubule, which generates reactive oxygen species and leads to enhancement of lipid peroxidation.

Iqbal and Athar (1998) showed that Fe-NTA-mediated nephrotoxicity is diminished by 1 week of oral daily pretreatment of male albino Wistar rats with garlic oil given by gavage at 50 or 100 mg/kg body weight/ml corn oil. Intraperitoneal Fe-NTA treatment at a dose level of 9 mg Fe/kg body weight/10 ml enhanced renal microsomal lipid peroxidation and hydrogen peroxide generation, which are accompanied by a decrease in the activities of renal antioxidant enzymes (e.g., catalase, glutathione peroxidase, glutathione reductase, and glutathione *S*-transferase), and a depletion in the level of renal glutathione. Parallel to these changes, a sharp increase in blood urea nitrogen and serum creatinine has been observed. In addition, Fe-NTA treatment also enhanced renal **ornithine decarboxylase** (ODC) activity and increases **[<sup>3</sup>H]thymidine incorporation** into renal DNA. Prophylactic treatment of animals with garlic oil before the administration of Fe-NTA resulted in the diminution of Fe-NTA-mediated injury. The enhancement of renal lipid peroxidation and hydrogen peroxide generation was decreased. In addition, there was recovery of glutathione depletion and inhibition of the activities of antioxidant enzymes. Similarly, in animals given the higher dose of garlic oil (100 mg/kg body weight), the enhanced blood urea nitrogen and serum creatinine levels, which are indicative of renal injury, showed a reduction of about 30 and 40%, respectively, in comparison with the group treated with Fe-NTA alone. Pretreatment with garlic oil also ameliorated the Fe-NTA-mediated induction of ODC activity and enhancement of [<sup>3</sup>H]thymidine incorporation into DNA in a dose-dependent manner. These data suggest that garlic oil is a potent chemopreventive agent and may suppress Fe-NTA-induced nephrotoxicity.

A large number of chemopreventive agents, particularly those that are a part of our diet, afford protection against the onset of various diseases, including cancer. Many of these actions have been related to the abilities of the agent to enhance the activities of carcinogen-metabolizing enzymes or to bind with toxicants, thus reducing their effective critical concentrations. Alternatively, chemopreventive agents act as antioxidants and counteract the increased amount of oxidants generated by toxicants. The medicinal uses and chemical composition of garlic have been widely studied. Garlic and its constituents have been shown to inhibit skin, forestomach, esophageal, and colon carcinogenesis in animal model systems. Garlic oil, which contains a large number of sulfur-containing compounds, has been shown to act as a potent modifier of tissue oxidant response. Therefore, the protection afforded by garlic oil against Fe-NTA-mediated renal damage may be due to the counteracting effect of its antioxidant constituents on Fe-NTA-mediated generation of oxidative stress.

In the study carried out by Iqbal and Athar (1998), garlic oil ameliorated Fe-NTA-induced lipid peroxidation, enhanced generation of H<sub>2</sub>O<sub>2</sub>, and depleted the level of glutathione. In addition, garlic oil reversed Fe-NTA-mediated inhibition of the activities of antioxidant enzymes such as catalase, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase, and GST.

The exact mechanism by which garlic oil may suppress Fe-NTA-mediated renal damage is not known. However, onion and garlic extracts have been shown to inhibit **platelet aggregation** and **prostaglandin synthesis**.

### AMELIORATION OF HYPERLIPIDEMIA IN CHRONIC AMINONUCLEOSIDE NEPHROSIS BY GARLIC

Garlic (*A. sativum* L.) has long been used not only as a flavoring but also as a folk medication. Some of the beneficial effects of garlic have been attributed to its hypolipidemic and antioxidant properties. The hypolipidemic effect of garlic in experimental animals is generally consistent. Long-term exposure to garlic, water-soluble garlic extracts, or garlic oil resulted in decreased serum levels of cholesterol and triglycerides in rats and rabbits fed a high-lipid diet. Perhaps the hypolipidemic action is primarily due to the decrease in hepatic **cholesterolgenesis** in garlic-treated rats by the inhibition of **3-OH-3-methyl glutaryl CoA reductase** (HMG-CoA), the rate-limiting

enzyme, early in cholesterol synthesis; whereas the triacylglycerol-lowering effect of garlic appears to be due to inhibition of fatty acid synthesis.

Pedraza-Chaverri et al. (2000a) studied **nephrotic syndrome** (NS), which is characterized by proteinuria, oxidative stress, and endogenous hyperlipidemia. Hyperlipidemia and oxidative stress may be involved in coronary heart disease and the progression of renal damage in these patients. Garlic has been suggested to be beneficial in various disease states. Some of these effects of garlic may be secondary to its hypolipidemic and antioxidant properties. Therefore, the effect of a 2% garlic diet on acute and chronic experimental NS induced by **puromycin aminonucleoside** (PAN) was studied in this work. Acute NS was induced by a single injection of PAN to rats, which were sacrificed 10 d later. Chronic NS was induced by repeated injections of PAN to rats that were sacrificed 84 d after the first injection. Garlic treatment was unable to modify proteinuria in both acute and chronic NS and was unable to modify hypercholesterolemia and hypertriglyceridemia in acute NS. However, garlic treatment diminished significantly total cholesterol, LDL cholesterol, and triglycerides, but not HDL cholesterol in chronic NS. Garlic induced no change in the percentage of sclerotic glomeruli in chronic NS and a significant decrease in the percentage of sclerotic area of these glomeruli ( $33 \pm 3\%$  in NS + garlic group vs.  $47 \pm 4\%$  in NS group,  $p = 0.0126$ ). The enhanced *in vivo* renal  $H_2O_2$  production, the diminished renal Cu,Zn-SOD and catalase activities in acute NS, and the decreased renal catalase activity in chronic NS were not prevented by garlic treatment. These data indicate that garlic treatment ameliorates hyperlipidemia and renal damage in chronic NS, which is unrelated to proteinuria or antioxidant enzymes.

### AMELIORATION OF GENTAMICIN NEPHROTOXICITY BY GARLIC: RELATION TO ANTIOXIDANT ENZYMES

**Gentamicin (GM)** is an **aminoglycoside antibiotic** commonly used in treating life-threatening Gram-negative bacterial infections. However, 30% of the patients treated with GM for more than 7 d showed some signs of nephrotoxicity. Serious complications resulting from GM-induced nephrotoxicity are a limiting factor for its clinical usage. GM is not metabolized in the body but is essentially eliminated by glomerular filtration and partially reabsorbed by proximal tubular cells. Lysosomes have been shown to be the unique site of GM accumulation into proximal cells. GM induces a **lysosomal phospholipidosis** by inhibiting the activity of **phospholipases A<sub>1</sub> and C** and of **sphingomyelinase**.

A potential therapeutic approach to protecting or reversing renal GM damage would have very important clinical consequences. GM administration in rats provides an excellent model of acute renal failure for studying therapeutic potential in preventing the side effects of acute renal failure pathogenesis in humans.

The pathophysiology of GM nephropathy is yet to be completely understood. However, **reactive oxygen species** (ROS) have been involved in GM-induced nephropathy. It has been found that renal cortical lipoperoxidation, *in vivo* renal  $H_2O_2$  generation, and *in vitro* mitochondrial  $H_2O_2$  generation are increased in GM-treated rats.

Pedraza-Chaverri et al. (2000b) studied the efficacy of garlic in preventing GM-induced nephrotoxicity. Four groups of rats were studied: (1) fed normal diet (CT), (2) treated with GM (GM), (3) fed 2% garlic diet (GA), and (4) treated with GM and 2% garlic diet (GM + GA). Rats were placed in metabolic cages and GM nephrotoxicity was induced by injections of GM (75 mg/kg every 12 h) for 6 d. Lipoperoxidation and enzyme determinations were made in renal cortex on day 7. GM nephrotoxicity was made evident on day 7 by (1) tubular histological damage, (2) enhanced BUN and urinary excretion of **N-acetyl- $\beta$ -D-glucosaminidase**, and (3) decreased creatinine clearance. These alterations were prevented or ameliorated in the GM + GA group. The rise in lipoperoxidation and the decrease in Mn-SOD and GPX activities observed in the GM group were prevented in the GM + GA group. Cu,Zn-SOD activity and Mn-SOD and Cu,Zn-SOD content

did not change. CAT activity and content decreased in the GM, GA, and GM + GA groups. CAT mRNA levels decreased in the GM group. The protective effect of garlic is associated with the prevention of the decrease of Mn-SOD and GPX activities and with the rise of lipoperoxidation in renal cortex (see Figure 50.3).

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# 51 Immunoenhancing Actions of Plantain

## INTRODUCTION

Plants known to stimulate the immune system include but are not limited to:

- American mistletoe, mistletoe, golden bough
- Astragalus, huang qi, milk vetch
- Echinacea
- Garlic
- Ginseng
- Goldenseal
- Lavender
- Live-long, orpine, stonecrop
- Paclitaxel
- Plantain
- Vincristine, vinblastine

Humans have a long history of the use of higher plant extracts for the therapy of diverse maladies. Medicinal plants play a major role in the lives of many people worldwide, and their usage has increased significantly. Epidemiological studies have associated a reduced risk of infectious diseases and cancer with a diet high in fruits and vegetables, and have determined that molecules such as  **$\beta$ -carotene, tocopherols, vitamin C, and flavonoids** confer some of this protective benefit. Finding additional agents for human or agricultural use based upon higher plant extracts may contribute to increasing the number of plant compounds of potentially beneficial application.

*Plantago major*, also known as **plantain, waybread, or dooryard plantain**, is found on roadsides, fields, lawns, and waste places in temperate zones worldwide. *P. major* has been used in traditional medicine as an astringent, anesthetic, anthelmintic, analgesic, analeptic, antiviral, antihistaminic, anti-inflammatory, antirheumatic, antitumor, antiulcer, diuretic, hypotensive, and expectorant. The fresh leaves of *P. major* are crushed and applied to wounds to prevent or cure infection and hasten healing. Moreover, plantain is a rapid pain reliever of stings, bites, and poison ivy. The intracellular fluid from *P. major* has also been shown to possess prophylactic activity against the development of mammary tumors in mice.

Gomez-Flores et al. (2000) designed experiments to evaluate the *in vitro* effects of methanol extracts of *P. major* leaves on the peritoneal macrophage and **thymic lymphocyte functions**. Macrophages play a central role in modulating humoral and cellular immunity against infectious diseases and cancer. Immunomodulatory agents such as **interferon- $\gamma$  (IFN $\gamma$ )** and **lipopolysaccharide (LPS)** are capable of activating them. Activated macrophages produce mediators of cytotoxicity such as **nitric oxide (NO)** and **tumor necrosis factor- $\alpha$  (TNF $\alpha$ )**, which protect the host against the development of infections and tumors. On the other hand, T lymphocytes respond to antigen challenge by proliferating and expanding the antigen-specific lymphocyte clones thus amplifying immune responses. Functional T cell proliferating activity can be studied by the use of polyclonal

mitogens such as **concanavalin A** (Con A) and **phytohemagglutinin** (PHA), which bind to certain sugar residues on T cell surface glycoproteins, including the T cell receptor and CD<sub>3</sub> protein, and stimulate T cell proliferative response.

Gomez-Flores et al. (2000) found that endotoxin-free methanol extracts from *P. major* leaves, at doses of 50, 100, 250, and 500 µg/ml, were associated with  $4.4 \pm 1$ ,  $6 \pm 1$ ,  $12 \pm 0.4$ , and  $18 \pm 0.4$ -fold increases of NO production, and increased TNF production ( $621 \pm 31$ ,  $721 \pm 36$ ,  $727 \pm 36$ , and  $1056 \pm 52$  U/ml, respectively) by peritoneal macrophages, in the absence of IFN $\gamma$  or LPS. NO and TNF production by untreated macrophages was negligible. In addition, *P. major* extracts potentiated ConA-induced lymphoproliferation (3- to 12-fold increases) in a dose-dependent fashion, compared with the effect of ConA alone.

## IMMUNOPHARMACOLOGY

The immune system protects the body from bacteria, viruses, and other harmful microorganisms. It is also able to attack a healthy body and cause life-threatening diseases such as multiple sclerosis. In the past, immunosuppressive agents were used solely in patients undergoing allotransplantation. However, a new understanding of the role of interleukins in the pathophysiology of diseases has spawned new applications for these agents. Moreover, because tissue transplantation, including even bone marrow transplantation, is associated with complications, and because the pharmacokinetics of agents are modified in organ transplant patients, an even greater understanding of the therapeutic refinements of immunomodulating agents is required.

The principal elements in the cellular and molecular cascades that participate in activating immune response and the sites of actions of various immunosuppressive agents are depicted in Figure 51.1. In this process, the immune system is first provoked by either autoantigens or alloantigens. This activates the phagocytic cells that, in turn, communicate their message via helper T-cells by elaborating several mediators collectively called the **cell differentiation complex<sub>3</sub>** (CD<sub>3</sub>). This culminates in **interleukin 2-mediated cell proliferation** (see Figure 51.1).

## THERAPIES THAT ENHANCE OR SUPPRESS THE IMMUNE SYSTEM

### RADIOIMMUNOTHERAPY

Radioimmunotherapy or monoclonal antibody-mediated radioimmunotherapy is a process that couples an antibody to a radioactive isotope to enhance its tumoricidal activity. The long-range  $\beta$ -emitters rhenium-90Y and -188 have now replaced iodine-131 as isotopes.

### CELL TRANSFER THERAPY AND CANCER

Cell transfer therapy is a new approach to strengthening the innate ability of the immune system to fight against cancer (Figure 51.2). In this therapy, lymphocytes are isolated and cultured with interleukin-2 for 3 d to yield lymphokine-activated killer cells, which are then administered to patients along with interleukin-2.

### IMMUNOSUPPRESSIVE AGENTS

The following agents and measures are used for immunosuppressive therapy — corticosteroids, cytotoxic agents (alkylating agents and antimetabolites), cyclosporin A and dihydrocyclosporin C, antilymphocyte globulin and Rho (D) immune globulin (RhoGAM), lymphoid irradiation and thoracic duct drainage, and immunomodulating agents (interferons and their inducers).

Immunosuppressive agents are used in patients undergoing organ transplantation, such as that of the liver, heart, and kidney. One or a combination of agents may be given, including **glucocor-**

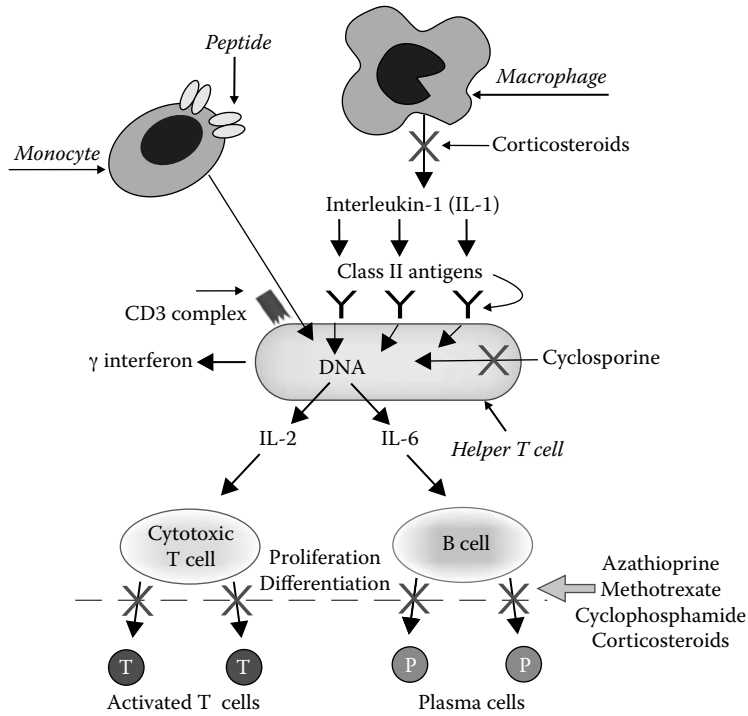


FIGURE 51.1 The sites of actions of immunosuppressive agents.

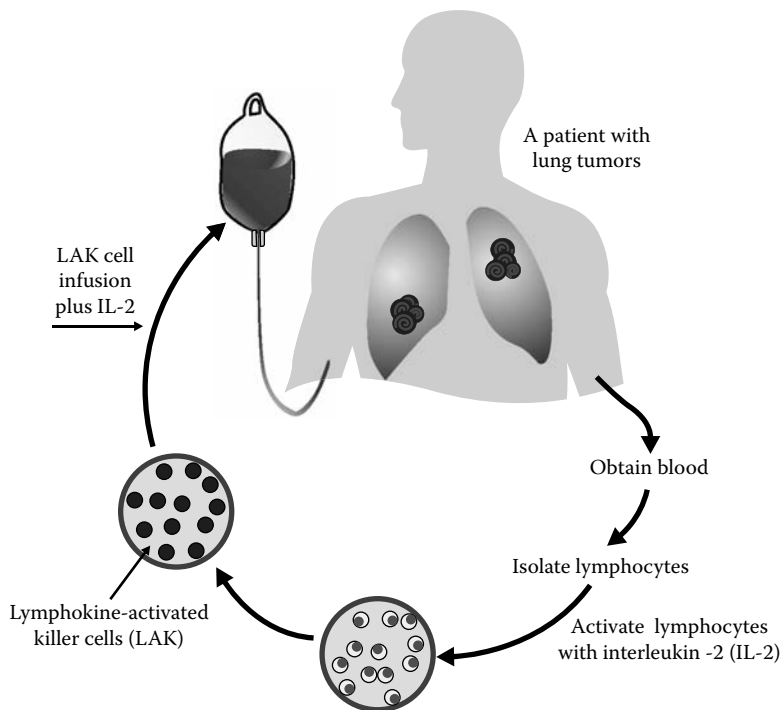


FIGURE 51.2 Cell transfer therapy with lymphokine-activated killer cells.



**ticosteroids, azathioprine, and cyclophosphamide.** In addition, a combination of drug therapy and other ameliorative techniques that bring about lymphocyte depletion, such as thoracic duct drainage or total lymph node irradiation, may be indicated.

Immunosuppressive agents are used in the treatment of autoimmune diseases. For example, the treatment approach to chronic active hepatitis not attributable to drugs, Wilson's disease, or  $\alpha_1$ -antitrypsin deficiency consists of prednisone combined with azathioprine. Azathioprine by itself is not effective in this disorder. **Idiopathic thrombocytopenic purpura** is treated with corticosteroids and splenectomy, and immunosuppressive agents are used in refractory cases. Hemolysis due to warm-reacting autoimmune antibodies (**autoimmune hemolytic anemia**) involving **immunoglobulin G** (predominantly IgG<sub>1</sub> and IgG<sub>3</sub>) is initially treated with prednisone. If this proves unsuccessful, splenectomy (in younger patients) or immunosuppression using azathioprine or cyclophosphamide (in older patients) is carried out next.

Acute rheumatic fever is treated with anti-inflammatory agents such as aspirin. Corticosteroids are reserved for those patients with severe carditis who do not respond to or are unable to take salicylates.

Myasthenia is treated with cholinergic drugs, which actually have no influence on the course of the disease itself, or with therapeutic regimens such as thymectomy, corticosteroids, or immunosuppressive agents, which are intended to induce remission of the disease. Immunosuppressive agents are used in isoimmune disorders such as **Rh hemolytic disease of the newborn**.

Immunomodulating agents are being investigated for their potential application in immunodeficiency disorders, chronic infections, and neoplasms.

The immunosuppressive agents are not without their problems, however. With the exception of **RhoGAM**, the currently available immunosuppressive agents are nonspecific in their actions, and generalized and prolonged immunosuppression increases the susceptibility to infections and the risk of **lymphoreticular cancer**.

## CORTICOSTEROIDS

Corticosteroids such as prednisone or dexamethasone have lympholytic properties. They reduce the lymphoid contents of the lymph nodes and the spleen without influencing the myeloid or erythroid stem cells. Corticosteroids have the following pharmacological effects on immunosuppression:

- They inhibit prostaglandin E<sub>2</sub> and leukotriene synthesis.
- They reduce the macrophage-mediated lysosomal contents.
- They reduce the activity of the lymphocyte-mediated chemotactic factor and lymphotoxin.
- They increase the catabolism of immunoglobulins such as IgG.
- They are able to lyse T helper cells.
- They interfere with the ability of reticuloendothelial macrophages to attack and destroy antibody-coated cells.

Prednisone is used in the treatment of autoimmune diseases, both organic-specific autoimmune diseases such as **myasthenia gravis** and idiopathic thrombocytopenic purpura and nonorgan-specific autoimmune diseases such as **lupus erythematosus, rheumatoid arthritis, and periarteritis nodosa**. In addition, prednisone is used in patients receiving organ transplants and is of paramount value in countering the problems associated with organ rejection.

## CYTOTOXIC COMPOUNDS AS ALKYLATING AGENTS

As an alkylating agent, **cyclophosphamide** (Cytoxan) and its active metabolites destroy the rapidly proliferating lymphocytes and, hence, are potent immunosuppressive agents. Those metabolites that are devoid of alkylating properties also lack an immunosuppressive capability. Because the

biotransformation to active metabolites takes place in the liver, inducers of microsomal enzymes influence both the therapeutic spectrum and the toxicity of cyclophosphamide. When used in combination with prednisone and antilymphocyte globulin, cyclophosphamide prolongs the survival of organ and skin allografts. It is also effective in the treatment of **T cell-dependent autoimmune diseases** such as **chronic lymphocytic thyroiditis**.

### Antimetabolites

When injected, **azathioprine** (Imuran) is rapidly converted to **6-mercaptopurine**. The half-life of azathioprine after intravenous injection is 10 to 20 min, and that of **6-mercaptopurine** is somewhat longer. The cytotoxic activity of these thiopurines is due to the conversion of mercaptopurine to 6-thiouric acid, a noncarcinostatic metabolite. This action is thought to block the excess synthesis of inosinic acid from its precursors, glutamine and **phosphoribosylpyrophosphate**. In addition, unlike cyclophosphamide, azathioprine is a potent anti-inflammatory substance that can cause a reduction in the number of monocytes and neutrophils at inflammatory sites. Antibody responses are also inhibited by azathioprine. Studies in humans have shown that azathioprine decreases the  $\gamma$ -globulin and antibody levels, thus influencing IgG rather than IgM production. This makes azathioprine an effective immunosuppressant in the early phases of immune responses. It is less effective or completely ineffective in altering either the effector phase or already established reactivities.

Azathioprine is an effective agent in suppressing the immune system in patients undergoing renal transplantation and in patients suffering from **acute glomerulonephritis**, the renal component of **systemic lupus erythematosus**, prednisone-resistant **idiopathic thrombocytopenic purpura**, and functioning **autoimmune hemolytic anemia**. Azathioprine depresses bone marrow functioning, which is its chief side effect.

### Cyclosporin A and Dihydrocyclosporin C

Cyclosporin A, a fungal metabolite, is a cyclic polypeptide that consists of 11 amino acids. It has a biologic half-life of 4 to 6 h and displays a preferential T cell cytotoxic property, in that it inhibits the factors that stimulate T lymphocyte proliferation. Cyclosporin A has been used as the sole immunosuppressant (without prednisone or other drugs) for cadaveric transplants of the kidney, pancreas, and liver. Cyclosporin A has been observed to cause reversible hepatic toxicity and nephrotoxicity.

**Dihydrocyclosporin C**, another fungal metabolite, is even more selective than cyclosporin A, in that it suppresses T lymphocyte production with only marginal effects on the antibody response.

### Antilymphocyte Globulin

The antilymphocyte globulin is obtained through the immunization of horses with human lymphoid cells or with fetal thymus cells. The antilymphocyte antibody destroys the T cells and impairs delayed hypersensitivity and cellular immunity without altering humoral antibody formation. The pattern of immunosuppression obtained with antilymphocyte globulin is identical to that brought about following thoracic duct drainage that depletes the numbers of small lymphocytes.

### Rho (D) Immune Globulin

RhoGAM is a solution of human IgG containing antibodies against the Rho (D) antigen of the red blood cells. It is administered to a mother after the birth of her **Rh-negative** baby as a prophylactic measure to prevent **erythroblastosis fetalis** (hemolytic disease of the newborn) in infants born in succeeding pregnancies. Treatment with RhoGAM may also be indicated in Rh-negative mothers who have had ectopic pregnancies, miscarriages, or abortions in which the blood type of the fetus is unknown.

### Immunomodulating Agents

In addition to its antiviral actions, interferon has an antiproliferative effect and modifies the functions of macrophages and natural killer cells. **Thymosin**, a protein synthesized by the epithelioid component of the thymus, may be potentially valuable in patients with **DiGeorge's syndrome** or other **T cell deficiency states**. **Levamisole** augments T cell-mediated immunity and may be of value in the immunodeficiency associated with **Hodgkin's disease**.

### SUMMARY

The regulation of immune parameters by *P. major* leaf extract (plantain) may be clinically relevant in numerous diseases including chronic viral infections, tuberculosis, AIDS, and cancer.

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# 52 Plants and Diabetes

## INTRODUCTION

The following are the plants used to treat diabetes:

- *Acacia arabica*
- *Artemisia herba alba*
- *Cleome droserifolia*
- *Eugenia jambolana*
- *Ficus bengalensis*
- *Glossostemon bruguieri*
- *Lagerstraemia speciosa*
- *Lythrum salicaria*
- *Momordica charantia*
- *Opuntia cactus*
- *Panax ginseng*
- *Petiveria alleaceae*
- *Phaseolus vulgaris*
- *Swertia chirayita*
- *Swertia japonica*

Hypoglycemic natural products comprise **flavonoids**, **xanthenes**, **triterpenoids**, **glycosides**, **alkyldisulfides**, **aminobutyric acid derivatives**, **guanidine**, **polysaccharides**, and **peptides** (see Wang and Ng, 1999). The mechanisms of actions of these hypoglycemic plants are uncertain. They either enhance the release of insulin or enhance the peripheral utilization of glucose.

## ANTIDIABETIC AGENTS

Diabetes mellitus results from disturbances in the metabolism of carbohydrates, lipids, and proteins. Normally, the blood glucose level is maintained within a range of 80 to 130 mg/ml. When the level rises above 180 mg/ml, the glucose spills into the urine, causing glucosuria. The utilization of glucose by most tissues, including muscle and adipose tissue, is insulin dependent. The brain is an exception in that its utilization of glucose is insulin independent. In the absence of insulin, organs other than the brain are able to make use of amino acids and fatty acids as alternative sources of energy.

The release of insulin is closely coupled with the glucose level. Hypoglycemia results in a low level of **insulin** and a high level of **glucagon** and, hence, favors the processes of **glycogenolysis** and **gluconeogenesis**.

Growth hormone is one of the glucose counterregulatory hormones. It is released in response to hypoglycemia and has intrinsic hyperglycemic actions and causes insulin resistance.

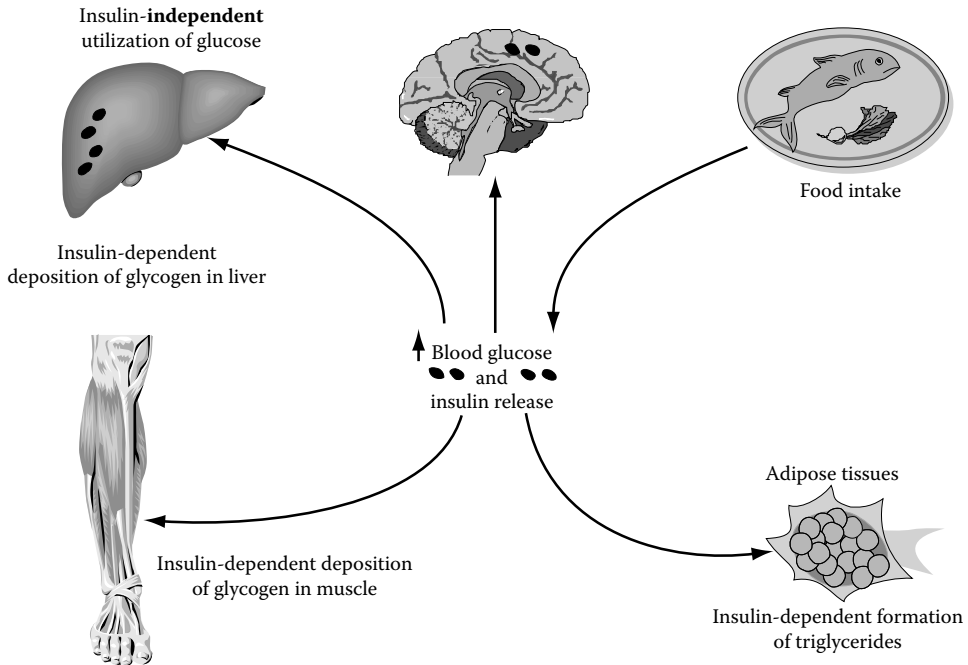


FIGURE 52.1 Glucose intake enhances glycogen storage.

### EFFECTS OF FOOD ON INSULIN RELEASE

Following ingestion of a meal or the administration of glucose (e.g., in a glucose tolerance test), the glucose level rises, causing the release of insulin and inhibiting the release of hyperglycemic glucagon. Excess glucose is transformed into glycogen in the liver and the muscles. The high level of amino acids and free fatty acid fosters the respective formation of proteins in the muscles and triglycerides in the adipose tissues (Figure 52.1).

### EFFECTS OF FASTING ON INSULIN RELEASE

In a nondiabetic fasting subject, the ensuing hypoglycemia not only discourages the release of insulin but also activates the homeostatic mechanisms that block the action of insulin and convert the storage forms of fuel into utilizable glucose. Consequently, a number of hormones including glucagon, epinephrine, and glucocorticoid are released, and these convert glycogen into glucose, triglyceride into free fatty acid, and proteins into amino acids (gluconeogenesis), respectively (Figure 52.2). Furthermore, the uptake and utilization of glucose in the peripheral tissue decrease. The muscles and other tissues utilize amino acids and free fatty acid, thus providing the brain with an adequate supply of glucose.

### METABOLIC CONSEQUENCES OF DIABETES MELLITUS

In an individual with diabetes who suffers from a deficiency of insulin, all of the aforementioned measures that apply to a fasting individual may also occur. However, the consumption of a meal or the administration of glucose will instead cause pronounced hyperglycemia because the insulin-dependent utilization of glucose by muscles and adipose tissues is lacking (Figure 52.3). The elevated glucose level thus surpasses the renal threshold, and glucose may appear continuously in the urine. The osmotic diuretic effects of glucose cause **polyuria** and **polydipsia**, and the chronic

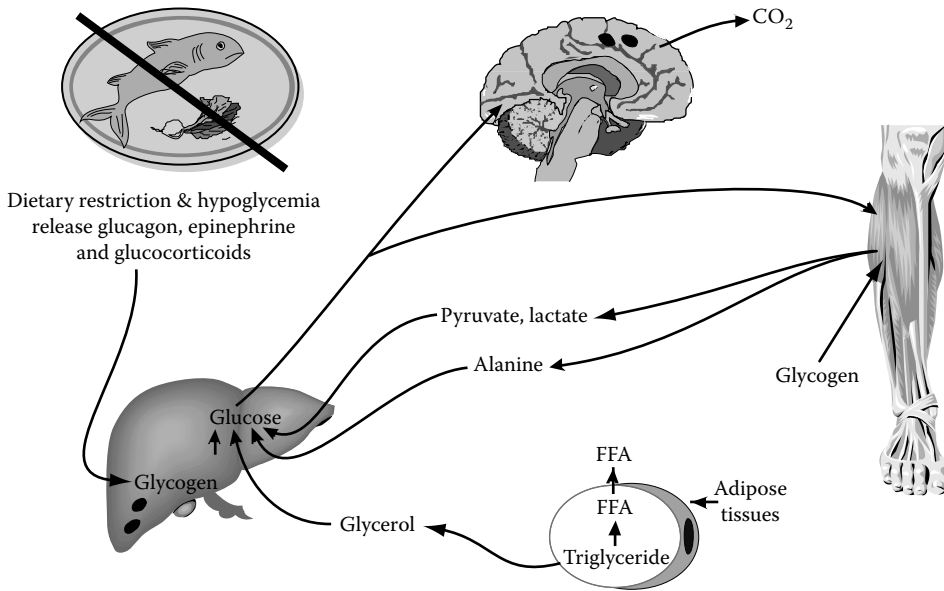
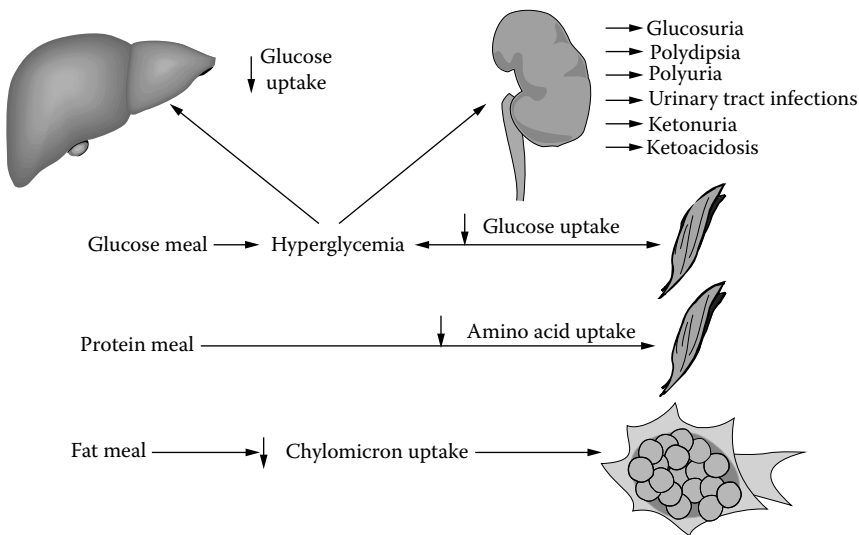


FIGURE 52.2 During fasting, glycogen is converted into glucose. FFA = free fatty acid.



Biochemical abnormalities in an untreated patient with diabetes mellitus

FIGURE 52.3 Consequences of hyperglycemic states.

**glucosuria** may lead to urinary tract infection. Because the conversion to triglyceride does not take place, free fatty acids are metabolized to ketone bodies, causing ketonuria and ketoacidosis (acetone or **fruity breath**). The continuous destruction of muscular proteins may ultimately lead to muscle wasting and weight loss.

### DIABETES MELLITUS AND PREGNANCY

Early in pregnancy, glucose homeostasis is altered by the increasing levels of **estrogen** and **progesterone**, which lead to  $\beta$ -cell hyperplasia and an increased insulin response to a glucose load. During

the second half of pregnancy, rising levels of human placental lactogen and other contrainsulin hormones synthesized by the placenta modify maternal utilization of glucose and amino acids. The actions of **lactogen** are responsible, in part, for the diabetogenic state associated with pregnancy.

## CLASSES OF DIABETES MELLITUS

There are two types of diabetes mellitus — type I, or **insulin-dependent diabetes mellitus**, and type II, or **noninsulin-dependent diabetes mellitus**.

Patients with type I diabetes may have islet cell antibodies and human leukocyte antigens (HLA). They are dependent on insulin to prevent ketosis and hence have **insulinopenia**. Affected individuals consist mostly of children and young adults.

Patients with type II diabetes, who are noninsulin-dependent, are not prone to ketosis. This type of diabetes is not an autoimmune disorder nor is it associated with HLA. The patients are generally older (> 40 years), may or may not be obese, and may or may not have been treated with insulin for the control of their hyperglycemia.

## SIGNS AND SYMPTOMS OF DIABETES

The signs and symptoms of diabetes consist of thirst, anorexia, nausea, vomiting, abdominal pain, headache, drowsiness, weakness, coma, severe acidosis, **air hunger (Kussmaul's breathing)**, sweetish odor of the breath, hyperglycemia, decreased blood bicarbonate level, decreased blood pH, and plasma that is strongly positive for ketone bodies.

## COMPLICATIONS OF DIABETES

There are a number of complications that arise as the result of poorly treated or unstabilized diabetes.

### VASCULAR COMPLICATIONS

Vascular complications may be manifested by **microangiopathy** (thickening of the capillary basement membrane), **intracapillary glomerulosclerosis** (thickening of the glomerular capillary basement membrane, which leads to a nephrotic syndrome characterized by edema, albuminuria, or renal failure), and microangiopathy of the blood vessels supplying the retina (**diabetic retinopathy**). In fact, diabetes is still the leading cause of blindness in the world. In addition, there may be atherosclerosis of the peripheral arteries.

### NEUROPATHY

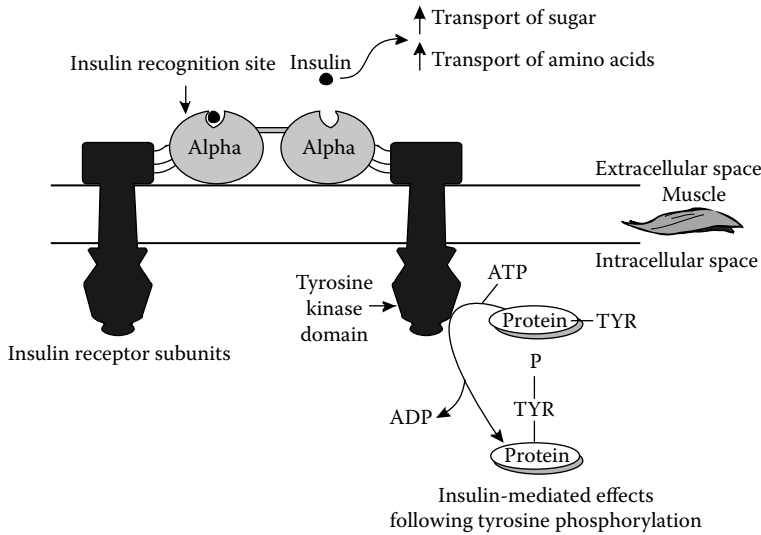
Diabetic neuropathy may be associated with **neuropathic ulcer**, ptosis, **diplopia**, **strabismus**, loss of deep tendon reflexes, ankle drop, wrist drop, **paresthesia**, **hyperalgesia**, **hyperesthesia**, and orthostatic hypotension (because of autonomic dysfunction).

## THE INSULIN RECEPTOR

### STRUCTURE AND FUNCTION

When insulin binds to specific membrane receptors on target cells, this initiates a wide spectrum of biologic activities:

- Enhancing the transport of sugar and amino acids
- Stimulating anabolic pathways
- Stimulating growth and development by triggering RNA and DNA synthesis



**FIGURE 52.4** The insulin receptor. ATP = adenosine triphosphate; ADP = adenosine diphosphate; TYR = tyrosine.

The insulin receptor is a disulfide-linked oligomer consisting of two  $\alpha$  and two  $\beta$  chains, with molecular weights of 130,000 and 95,000, respectively (Figure 52.4). Cross-linking studies using iodine-125-labeled insulin have shown that the insulin-binding domain is situated primarily in a subunit. In addition, it has been observed that proteolysis of the  $\beta$  subunit does not appreciably influence insulin binding. Insulin binding to the  $\alpha$  subunit was found to induce rapid phosphorylation of the intracellular domain of the  $\beta$  subunit. The  $\beta$  subunit contains a putative adenosine triphosphate (ATP)-binding site and an intrinsic tyrosine-specific kinase as part of the receptor. The enzymatic activity of the receptor is activated by insulin binding, which results in increased tyrosine phosphorylation of the  $\beta$  subunit as well as the production of a number of other cellular proteins.

### TERMINATION OF INSULIN SIGNAL

The insulin receptor is internalized, and this action terminates the insulin signal at the surface of the cell. Once internalized, some of the receptors are degraded and others are recycled back to the membrane. In addition, phosphatases are able to dephosphorylate the phosphorylated insulin receptor. This dephosphorylation reduces kinase activity and decreases the responsiveness to insulin.

### CLINICAL SYNDROMES ASSOCIATED WITH CELLULAR DEFECTS IN INSULIN RECEPTOR

A number of disorders are associated with the development of insulin resistance. Although some cases are due to autoimmune responses such as the development of anti-insulin or **anti-insulin receptor antibodies**, insulin resistance often results from defects at the cellular level in the insulin receptor or in postreceptor function.

## TREATMENT OF DIABETES MELLITUS

### DIETARY TREATMENT

The American Diabetes Association currently makes the following nutritional recommendations for people with diabetes:



1. Achieve and maintain ideal body weight.
2. Derive 55 to 60% of total caloric intake from carbohydrates.
3. Consume foods containing unrefined carbohydrate with fiber, attempting to take in 40 g of soluble fiber per day.
4. Consume only modest amounts of sucrose.

## DRUG TREATMENT

The drug therapy of diabetes includes eliminating obesity (which causes resistance to both endogenous and exogenous forms of insulin), exercising (to promote glucose utilization and reduce insulin requirement), dieting (to restrict intake of excess amounts of carbohydrates), and taking insulin (primarily in polyuric, polydipsic, and ketonuric patients).

Insulin preparations that are commercially available differ in their relative onset of action, maximal activity, and duration of action. Conjugation of the insulin molecule with either zinc or protamine, or both, will convert the normally rapidly absorbed parenterally administered insulin to a preparation with a more prolonged duration of action. The various formulations of insulin are usually classified as short acting (0.5 to 14 h), intermediate acting (1 to 28 h), and long acting (4 to 36 h). The duration of action can vary, however, depending on injection volume, injection site, and blood flow at the site of administration.

### Insulin

Insulin preparations are fast, intermediate, or long acting, as summarized in Table 52.1. Crystalline (regular) insulin may be used as a supplemental injection or for instituting corrective measures in the management of infection and trauma, for postoperative stabilization, and for the rehabilitation of patients recovering from ketoacidosis and coma. In addition, NPH (isophane) contains regular insulin.

Ultralente or semilente insulin is used to eliminate nocturnal and early-morning hyperglycemia.

#### *Complications of Insulin Therapy*

Hypoglycemia is a primary complication of insulin therapy and may result from either an excess of insulin or a lack of glucose, or both. Severe hypoglycemia may cause headache, confusion, double vision, drowsiness, and convulsions. The treatment of this hypoglycemia may include the administration of glucose or glucagon.

**TABLE 52.1**  
**Properties of Insulin Preparations**

Type	Added Protein	Action (h)		Duration
		Onset	Peak	
Rapid				
Regular (crystalline)	None	0.3–0.7	2–4	5–8
Semilente	None	0.5–1.0	2–8	12–16
Intermediate				
NPH (Isophane)	Protamine	1–2	6–12	18–24
Lente	None	1–2	6–12	18–24
Slow				
Ultralente	None	4–6	16–18	20–36
Protamine zinc	Protamine	4–6	14–20	24–36

**TABLE 52.2**  
**Comparison of Orally Administered Sulfonylurea Hypoglycemic Agents**

Characteristic	Tolbutamide	Acetohexamide	Tolazamide	Chlorpropamide	Glipizide	Glyburide
Relative potency	1	2.5	5	6	100	150
Duration of action (h)	6–10	12–18	16–24	24–72	16–24	18–24
Extent of protein binding (%)	> 98	~ 90	> 98	~ 95	> 98	> 98
Hepatic metabolism	Yes	Yes	Yes	Yes	Yes	Yes
Urinary excretion	Yes	Yes	Yes	Yes	Yes	Yes
Fecal excretion (% of dose)	Negligible	Negligible	Negligible	Negligible	12	50
Dose (mg) range	500–3000	250–1500	100–1000	100–500	2.5–40	1.25–20
Diuretic	Yes	Yes	Yes	No	No	Yes
Antidiuretic	Yes	No	No	Yes	No	No
Disulfiram-like effects	No	No	No	Yes	No	No

*Note:* Although insulin has the disadvantage of having to be injected, it is without question the most uniformly effective treatment of diabetes mellitus available. Insulin remains the drug of choice in severe cases of diabetes and in IDDM, though some milder forms of diabetes mellitus that do not respond to diet management alone can be treated with oral hypoglycemic agents. The success of oral hypoglycemic drug therapy is usually based on restoration of normal blood glucose levels and absence of glycosuria.

**Lipodystrophy** can also result from insulin therapy and is characterized by atrophy of subcutaneous fat. Insulin edema is manifested by a generalized retention of fluid. Insulin resistance arises when there is an excess insulin requirement that exceeds 200 units per day.

#### *Agents That Alter the Release of Insulin*

The release of insulin is enhanced by certain physiological substances (glucose, leucine, arginine, gastrin, secretin, and pancreozymin) and by certain pharmacological agents (oral **hypoglycemic agents**). The release of insulin is also inhibited by some physiological substances (epinephrine and norepinephrine) as well as by some pharmacological substances (**thiazide diuretics**, **diazoxide**, and **chlorpromazine**).

#### **Oral Hypoglycemic Agents**

Oral hypoglycemic agents have advantages over insulin because, by releasing insulin and by decreasing the release of glucagon, they mimic physiological processes and cause fewer allergic reactions. Furthermore, they are effective in an oral form, thus eliminating the need for daily injections. The properties of these agents are described in Table 52.2.

The mechanisms that underlie the hypoglycemic actions of sulfonylureas are as follows:

##### Pancreatic

- Improved insulin secretion
- Reduced glucagon secretion

##### Extrapancreatic

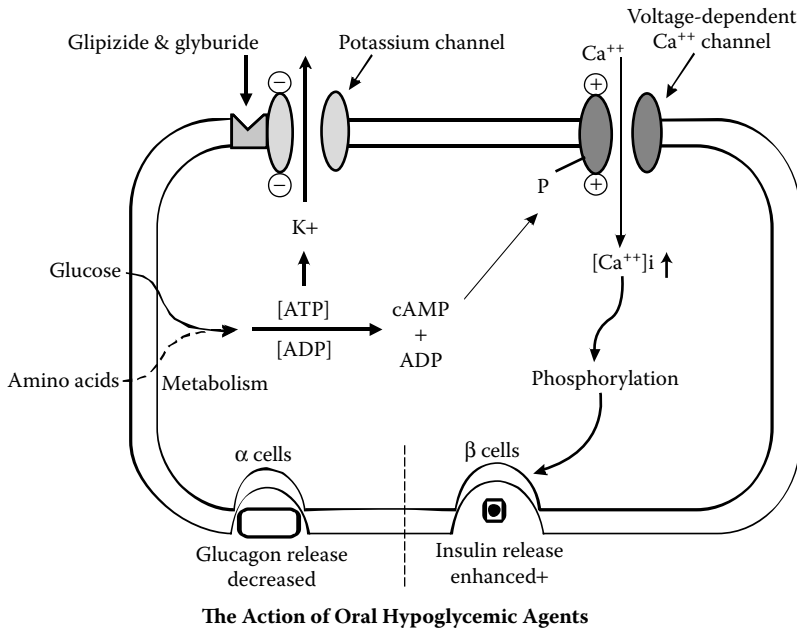
- Improved tissue sensitivity to insulin

##### Direct

- Increased receptor binding
- Improved postbinding action

##### Indirect

- Reduced hyperglycemia
- Decreased plasma concentrations of free fatty acids
- Reduced hepatic insulin extraction



**FIGURE 52.5** The actions of glipizide. ATP = adenosine triphosphate; ADP = adenosine diphosphate; cAMP = cyclic adenosine monophosphate.

### RECEPTORS FOR SULFONYLUREA AND THEIR MECHANISM OF ACTION

Sulfonylureas such as **glyburide** and **glipizide** bind to **sulfonylurea receptors** located on the surface of  $\beta$  cells and trigger insulin releases at nanomolar concentrations (Figure 52.5). Sulfonylureas bind to **ATP-sensitive potassium channels** and inhibit potassium efflux through these channels. The inhibition of ATP-sensitive potassium channels then leads to depolarization of the  $\beta$  cell; this opens voltage-dependent calcium channels and allows the entry of extracellular calcium. The rising level of cytosolic-free calcium next triggers the release of insulin. An increase in the cyclic adenosine monophosphate levels in the cells can also open the voltage-dependent calcium channels, thus increasing calcium-influx into the cells.

### TREATMENT OF DIABETIC KETOACIDOSIS

**Diabetic ketoacidosis** may either result from or be aggravated by infection, surgery, trauma, shock, emotional stress, or failure to take sufficient amounts of insulin. Treatment is focused on reversing the hypokalemia by administering potassium chloride and on offsetting the acidosis by providing bicarbonate. The dehydration and electrolyte imbalance are treated with appropriate measures and **crystalline zinc insulin** is administered to counter the hyperglycemia.

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# 53 Pomegranate

The botanical name of pomegranate is *Punica grantum* and it is known by various common names as *anar*, pomegranate, and seeded apple. The following are the properties and benefits of pomegranate:

- It contains **polyphenol**.
- It is a potent antioxidant (see Chapter 8 and Chapter 31).
- It reduces arterial plaque.
- It inhibits **angiotensin-converting enzyme** and reduces systolic blood pressure.
- It is a vasodilator and acts by regulating **nitric oxide**.
- It contains **phytoestrogen** and minimizes the sequelae of menopause.

Another phytohormonal menopause aid is pomegranate seeds. Many cultures have considered the pomegranate a **symbol of fertility and rejuvenation**.

Pomegranate first appeared in Persia (4000 B.C. to 3000 B.C.) and gradually moved toward China, India (100 B.C.), North Africa, Europe, Mexico (1521), and the U.S. (1792). Pomegranate is one of the first fruits cultivated by humans. In Greek mythology, the pomegranate symbolized death and fertility; in ancient Chinese culture, it was a symbol of immortality. One of the earliest cultivated fruits, it is also called a “**gift from God**” in the Bible and also in the Koran.

Pomegranates contain **polyphenols** that are potent antioxidants with three times the antioxidant effect of red wine or green tea. The effect of these chemicals may provide protection against heart disease and cancer (see Chapter 31). The juice of wild pomegranates yields **citric acid and sodium citrate** for pharmaceutical purposes. Pomegranate juice is used for treating dyspepsia and is considered beneficial in **leprosy**.

The bark of the stem and root contains several alkaloids including **isopelletierine**, which are active against tapeworms. Either a decoction of the bark, which is very bitter, or the safer, insoluble **Pelletierine tannate** may be employed. Overdoses of pomegranate are emetic and purgative, and produce dilation of pupils, dimness of sight, muscular weakness, and paralysis. Because of their **tannin** content, extracts of the bark, leaves, immature fruit, and fruit rind have been used as astringents to halt diarrhea, dysentery, and hemorrhages. Dried, pulverized flower buds are employed as a remedy for bronchitis. In Mexico, a decoction of the flowers is gargled to relieve oral and throat inflammation. The leaves, seeds, roots, and bark have displayed hypotensive, antispasmodic, and anthelmintic activity in bioassay.

Pomegranate juice not only appears to prevent hardening of the arteries by reducing blood vessel damage, but the antioxidant-rich juice may also reverse the progression of this disease. Beneficial effects of pomegranate juice on hardening of the arteries are probably largely due to its high antioxidant content. Controlled studies have shown that the antioxidant level in pomegranate juice was higher than that found in other fruit juices, including blueberry, cranberry, orange, and even red wine (see Gil et al., 2000; Kaplan et al., 2001; Aviram and Dornfeld, 2002; Aviram et al., 2000, 2002).



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# 54 Pycnogenol

## INTRODUCTION

The following are the main characteristics of pycnogenol:

- It is obtained from the bark of the French maritime pine *Pinus maritima*.
- It is an antioxidant.
- It is a vasorelaxant.
- It inhibits angiotensin-converting enzyme.
- It improves capillary circulation.

The term *pycnogenol* describes an entire class of **flavonoids** composed of **flavan-3-ol derivatives**, which is now utilized throughout the world as a nutritional supplement and as a phytochemical remedy for various diseases ranging from chronic inflammation to circulatory dysfunction. *Thesaurus medicaminum* (pine bark) was considered helpful for **wound healing**. Pycnogenol was said to be used by Hippocrates. In old Europe, pine bark was utilized against **inflammation** and to overcome the symptoms of **scurvy**. Other uses of pycnogenol were suggested by the naturalist **Hieronymus Boch** and included topical application on **skin ulcers** and general use against **skin disorders**. In the New World, **Native Americans** utilized the bark of the pine as a food, a beverage, and a remedy for various conditions, such as inflamed wounds or ulcers, now recognized to have free-radical involvement. Pine bark was used for many conditions that are now known to involve **vitamin C deficiency**, such as **scurvy**, skin disorders, and wound healing. This indicates an interaction between **vitamin C** and flavonoids, which was also suggested by **Albert Szent-Gyorgyi**, who won a Nobel Prize for his discovery of vitamin C.

Pycnogenol is exclusively prepared from the bark of the *P. maritima* found in France in a region of the **Bay of Biscay** called **Landes de Gascogne**. The climatic conditions in this region strongly influence the characteristics of this subspecies of *Pinus*. Various efforts to cultivate the same subspecies in other geographic areas, such as the **Iberian Peninsula** and **Korea**, have failed, indicating the uniqueness of the environmental conditions necessary for the growth of the French maritime pine (Packer et al., 1999).

Grape seed extract, which is another widely used plant extract similar to pycnogenol, contains **procyanidins**, which have a strong antioxidant activity.

## ANTIOXIDANT ACTIVITY OF PYCNOGENOL

**Phenolic acids, polyphenols, and flavonoids** in particular are composed of one or more aromatic rings bearing one or more hydroxyl groups and are therefore potentially able to quench free radicals by forming resonance-stabilized phenoxyl radicals. **Superoxide radical anion ( $O_2^{\cdot-}$ )**, **hydroxyl radical (HO)**, **lipid peroxyl radical**, and the **reactive nitrogen species**, such as **nitric oxide radical (NO)**, and **peroxynitrite (ONOO<sup>-</sup>)**, which are among the most important free radicals in the biologic environment and in human health and disease, have been investigated either *in vitro* or *in vivo*. Moreover, as suggested by the early reports from the laboratory of Szent-Gyorgyi (Benthath et al., 1936), flavonoids may have a fundamental role in the antioxidant network, interplaying together

with other antioxidants and in particular with ascorbic acid, thus significantly contributing to cellular and extracellular defenses against oxidative stress.

One of the earliest studies addressing the antioxidant activity of various **procyanidins** *in vitro* reported strong scavenging activity against free radicals such as the stable radical **1,1-diphenyl-2-picryl-hydrazyl** (DPPH) and the oxygen free radicals  $O_2^{\cdot-}$  and HO, as assessed by ESR spectroscopy.

The capacity of pycnogenol to protect cellular systems has also been investigated, particularly in cultured endothelial cells and macrophages. In a bovine line of cultured normal endothelial cells (pulmonary artery endothelial, PAEC), preincubation with 20 to 80  $\mu\text{g/ml}$  pycnogenol is associated with significant protection from both lipid peroxidation and cell damage induced by **tert-butylhydroperoxide** (t-BHP). At 60  $\mu\text{g/ml}$ , pycnogenol completely inhibited the release of **lactate dehydrogenase** after T-BHP treatment, suggesting significant protection from oxidative stress-induced cytotoxicity. The generation of **thiobarbituric acid reactive substances** (TBARS) was also significantly decreased, indicating that the protective effect was due, at least in part, to the antioxidant activity of pycnogenol. In the same cellular system, pycnogenol induced a dose-dependent decrease in the steady-state production of both  $O_2^{\cdot-}$  and hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), and decreased the rate of  $\text{H}_2\text{O}_2$  accumulation following treatment with xanthine/xanthine oxidase (X/XO) as a superoxide-generating system. The effect on both the steady state and the clearance of reactive oxygen species ( $O_2^{\cdot-}$  and  $\text{H}_2\text{O}_2$ ) after X/XO treatment was attributed to the effects of pycnogenol on **glutathione** (GSH) levels and on the enhancement of the activity of the enzymatic machinery that regulates GSH redox status. A significant increase in GSH levels, an increased activity of the GSH redox enzymes (glutathione reductase and glutathione peroxidases), and an increase in the enzymatic activity of both superoxide dismutase (SOD) and catalase were observed.

### VASORELAXANT ACTIVITY

Pycnogenol is commonly suggested to lower the risk of cardiovascular diseases and also to serve as a therapeutic alternative to established pharmacology for mild pathological conditions of blood vessels. The rationale behind this is the link between cardiovascular disease and free-radical-induced stress. However, besides its strong antioxidant capacity, pycnogenol has been reported to have other activities related to cardiovascular functionality, such as **vasorelaxant activity, inhibition of angiotensin-converting enzyme**, and the ability to **enhance microcirculation by increasing capillary resistance**.

The effects of pycnogenol on circulation can be seen as the outcome of two different activities — relaxation of arterial walls and increase of capillary resistance. The combination of these effects results in an increase of peripheral blood flow and a facilitation of microcirculation. Early studies suggested a strong vasoactivity of **procyanidins** extracted from sources such as **wine** and **grape seed**, which have recently been confirmed for pycnogenol.

### INHIBITION OF PLATELET AGGREGATION

Pycnogenol inhibits platelet aggregation induced by cigarette smoking without the adverse effect on bleeding time that characterizes aspirin use.

### ENHANCEMENT OF MICROCIRCULATION

Pycnogenol enhances microcirculation and reduces capillary resistance in spontaneous hypertensive animals.

## INHIBITION OF ELASTASE ACTIVITY

The fragmentation of elastic fibers is a classical histological hallmark of the inflammatory response associated with several pathological conditions and the aging process. The dramatic proteolytic activity results from an imbalance between natural inhibitors, such as  $\alpha$ -1 antitrypsin and  $\alpha$ -2 macroglobulin, and leads to **elastolysis**. **Elastin**, together with **collagen**, is an important component of blood vessels, contributing to their integrity, elasticity, and permeability. Studies have reported an inhibitory effect of **procyanidins** on elastase activity *in vitro* and *in vivo*.

## REGULATION OF INFLAMMATORY RESPONSE

Inflammation is a multifactorial cellular response that is of fundamental importance in the maintenance of homeostasis when the organism is challenged by noxious agents (e.g., bacteria, viruses, irritating agents) or by tissue mechanical injury. Inflammation is associated with a dramatic rise in the number of polymorphonuclear leukocytes and monocytes in the affected tissue and with the release of inflammatory mediators such as **prostaglandins** and **cytokines**. Under ideal conditions, inflammation results in the complete recovery of the integrity of the affected tissue, but if the response to the triggering stimulus is not subjected to tight regulation, cellular and extracellular components of the organism adjacent to the inflammation site can be injured, inducing a condition known as *chronic inflammatory disease*. Indeed, a chronic inflammatory-like environment characterizes the pathogenesis of various diseases such as **atheriosclerosis**, **arthritis**, and **Crohn's disease**, and it is thought to be among the causative factors of more than 30% of human **cancers**. Thus, it is tremendously important to localize the inflammatory response, which on one hand increases the ability of the immune machinery to destroy the noxious agent and on the other hand provides an efficient defense from self-inducing damage.

Pycnogenol reduces the production of **interleukin-6** and restores the activity of **natural killer cells** in retrovirus-infected animals. Pycnogenol delays the development of immune dysfunctions secondary to retrovirus infection by restoring the imbalanced cytokine secretion by **T helper 1** and **T helper 2 cells**.

## MODULATION OF MACROPHAGE ACTIVITY

Pycnogenol affects the activity of **nitric oxide synthase** and the production of nitric oxide in murine macrophages (RAW 264.7 cell line) activated by **endotoxin** (the lipopolysaccharide) and **tumor necrosis factor** (TNF).

## SUMMARY

In conclusion, pycnogenol is a complex mixture mainly composed of **oligomeric procyanidins** and other **flavonoids** and **polyphenols**. A wide spectrum of biologic activities has been described for the mixture. Pycnogenol has been reported to significantly affect circulation, inflammation, and the immune response. The molecular bases of pycnogenol activity are manifold but mainly appear to depend on its capacity to efficiently scavenge reactive oxygen and reactive nitrogen species. Other major biologic effects are probably due to its ability to specifically bind to proteins, therefore affecting both structural and functional characteristics. Finally, pycnogenol has been demonstrated to participate in the cellular antioxidant network and to be able to affect the expression of those genes that are regulated by cell redox status (see Packer et al., 1999).





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# 55 *Pygeum africanum* and Permixon for the Treatment of Patients with Benign Prostatic Hyperplasia

## INTRODUCTION

Symptomatic **benign prostatic hyperplasia** (BPH) is a common medical problem in older men. As many as 40% of men aged 60 years or older have lower urinary tract symptoms consistent with **bladder outlet obstruction**. Treatment goals in the vast majority of men are to relieve bothersome symptoms that reduce quality of life. In the U.S., treatment for benign prostatic hyperplasia costs more than \$2 billion per year and accounts for 1.7 million physician office visits annually (Ishani et al., 2000).

The management of lower urinary tract symptoms suggestive of clinical symptomatic BPH remains somewhat controversial. Treatment options range from watchful waiting, for those patients wishing to delay any active therapy, to minimally invasive treatment, such as **transurethral needle ablation of the prostate** and **transurethral microwave therapy**, to surgical interventions in the form of **transurethral prostatectomy** or **open enucleation of the prostate**. Most patients present with difficulties in urination for which a variety of medical therapies are available, including synthetic **5- $\alpha$ -reductase inhibitors**,  $\alpha$ -blockers, and plant extracts (Boyle et al., 2000).

Medicinal herbs, or phytotherapy, have been used extensively for benign prostatic hyperplasia in Europe and are being used more commonly in the U.S. Sales of herbal medicine reached \$4 billion in the U.S. in 1998, and sales of **saw palmetto extract** for treatment of symptoms attributable to benign prostatic hyperplasia exceeded \$20 million, making it the seventh most commonly purchased medicinal herbal preparation.

A recent survey demonstrated that one third of men choosing nonsurgical therapy for benign prostatic hyperplasia were using herbal preparations alone or in combination with prescription medications. There is emerging evidence that several plant extracts are well tolerated and provide at least short-term improvement in urologic symptoms and flow.

*Pygeum africanum*, an extract from the bark of the **African prune tree**, has been used in Europe since 1969 to treat men with mild to moderate symptoms of benign prostatic hyperplasia. The mechanism of action of *P. africanum* is not known. In animal models, *P. africanum* modulates bladder contractility, has anti-inflammatory activity, decreases production of leukotrienes and other 5-lipoxygenase metabolites, inhibits fibroblast production, affects adrenal androgens, and restores the secretory activity of prostate epithelium.

In a study involving 1562 men, Ishani et al. (2000), by using *P. africanum* (100 mg/d) for at least 30 d showed that *P. africanum* modestly, but significantly, improved urologic symptoms and flow measures.

## URINARY SYMPTOMS AND FLOW MEASURES

*P. africanum* improved specific urinary symptoms and flow measures. In six double-blind trials involving 430 participants, men receiving *P. africanum* were more than twice as likely to be rated by their physician as having overall improvement in symptoms compared with men taking placebo. *P. africanum* reduced **nocturia** compared with placebo. *P. africanum* also increased **peak urine flow** compared with placebo. Additionally, *P. africanum* reduced **residual urine volume**.

## PERMIXON IN THE TREATMENT OF SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA

Permixon is a standardized lipid-sterolic extract of *Serenoa repens* and is a registered trademark of Pierre Fabre Médicament, Castres, France. Its major mechanism of action is still uncertain; however, several activities have been demonstrated. It repeatedly exerts antiandrogenic activity in the form of a noncompetitive inhibition of **5- $\alpha$ -reductase types I and II**, resulting in decreased prostatic **dihydrotestosterone** content in patients with BPH treated with this compound. Permixon also appears to inhibit *in vitro* **basic fibroblast growth factor** and **epidermal growth factor-induced prostate epithelial cell proliferation** and decrease epidermal growth factor concentrations in human prostate tissue. It also exerts an anti-inflammatory effect through the inhibition of the enzymes responsible for **prostaglandin** and **leukotriene synthesis**.

To assess the effects of Permixon in men with lower urinary tract symptoms and BPH, a meta-analysis of all available clinical trial data was undertaken. Boyle et al. (2000), in randomized clinical trials involving 2859 patients, found that Permixon in the treatment of men with BPH revealed a significant improvement in peak flow rate and reduction in nocturia.

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# 56 Reserpine

## INTRODUCTION

**Reserpine is a neuroleptic and an antihypertensive medication obtained from *Rauwolfia serpentina*.** It has the following characteristics:

**Rauwolfia (Raudixin, Rauserpa, etc.)**, the powdered whole root of the *Rauwolfia* plant, is a tan, bitter, fine amorphous powder with a slight odor, sparingly soluble in alcohol and only very slightly soluble in water.

**Alseroxylon (Rauwiloid)**, an alkaloidal fraction from *Rauwolfia* root, is a reddish-brown amorphous powder with a characteristic odor.

**Deserpidine (Harmony)** is an alkaloid from *Rauwolfia* root.

**Rescinnamine (Moderil)** is an alkaloid of the **alseroxylon fraction** of *Rauwolfia* root.

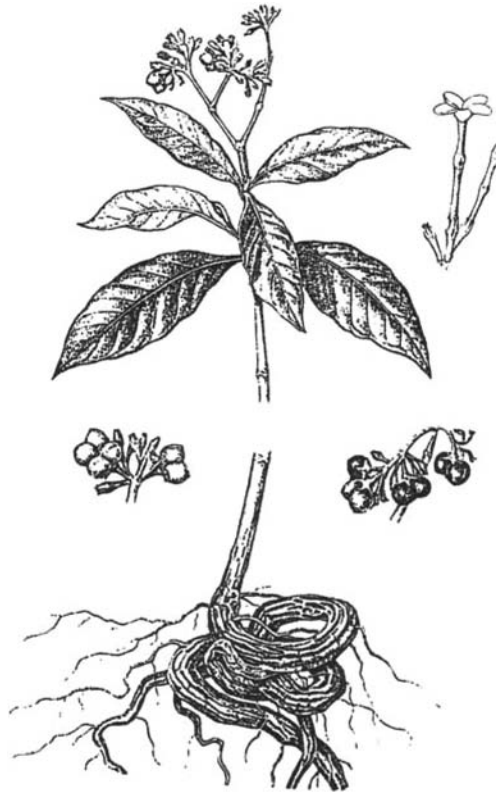
**Syrosingopine (Singoserp)** is a preparation made from reserpine by hydrolysis and reesterification.

## THE RAUWOLFIA ALKALOIDS

*Rauwolfia serpentina* Benth, which derives its name from **Leonhart Rauwolf**, a 16th century botanist, and its serpentine root (Figure 56.1), has long been used in India for a variety of ailments. The discovery of its tranquilizing action, particularly in lowering the blood pressure, led to its introduction into Western medicine. The *Rauwolfia* alkaloids are derived from a family of tropical and semitropical plants related to **oleander** and **periwinkle**. They vary from small shrubs to tall trees. The important species from which the alkaloids are derived include *Rauwolfia serpentina* (*Ophioxylon serpentinum* or **Indian snakeroot**), *R. micrantha*, *R. vomitoria*, and *R. hirsuta* (*Canescens heterophylla*).

## CHEMISTRY

The first alkaloid of this group to be isolated and synthesized was **reserpine** (Serpasil®), which has the structure shown in Figure 56.2. Reserpine is an indole derivative related to **yohimbine**, which is also present in preparations of *Rauwolfia*. A number of related alkaloids have been isolated from *Rauwolfia*, some of which are used clinically, e.g., **rescinnamine**, the 3:4:5-trimethoxycinnamic acid ester of methyl reserpate and **deserpidine** (11-desmethoxyreserpine), which lacks the methoxy group of ring A of reserpine. **Deserpidine** has also been designated as **canescine**, **recanescine**, and **raunormine**. Other alkaloids present in *Rauwolfia* include **serpine**, **serpagine** (**serpagene** or **raupine**), **rauhimbine**, **reserpinine**, **ajmaline** (or **rauwolfine**), **serpentine**, **ajmalicine**, etc. **Syrosingopine**, a synthetic derivative prepared from reserpine by hydrolysis and reesterification, is used in treating hypertension (Grollman, 1962).



**FIGURE 56.1** A flowering *Rauwolfia serpentina* plant. Note the serpentine root from which the plant obtains its name (snakeroot).

## PHARMACOLOGY

Reserpine and its related alkaloids exert their principal action on the posterior hypothalamus and the reticular formation of the brain stem, inducing a facilitative effect on the transmission of impulses in these areas. This effect on the central nervous system is readily demonstrated experimentally when the drugs are administered to a monkey. Following its injection, a state of repose gradually develops during which it is possible to handle and stroke a previously untamed animal safely with the bare hands. The animal shows less natural curiosity and interest than it normally displays toward its surroundings. Although it appears to be asleep, it may be aroused readily; it eats normally and does not appear to sleep more than usual. The electroencephalogram remains normal in contrast to the sleep pattern seen following the administration of barbiturates. The drug thus acts primarily as a tranquilizer and inactivating agent rather than as a soporific or hypnotic agent. In patients also, the drug induces quiet with an inner calm and less active response to external stimuli. Spontaneous activity is reduced and although the patients often complain of being sleepy, they do not actually sleep. However, drowsiness, mild dizziness, and fatigue often accompany reserpine therapy.

The peripheral effects of reserpine are similar to those resulting from stimulation of the parasympathetic nervous system. Thus, there is bradycardia, constriction of the pupil, increased motor activity of the intestinal tract, and an increase in the volume and hydrochloric acid content of gastric juice following its intravenous administration. This increased secretion may be effectively prevented for several hours by the use of an anticholinergic drug. However, the tranquilizing effect of well-tolerated doses of reserpine may bring about a secondary decrease in gastric acidity. Hence,

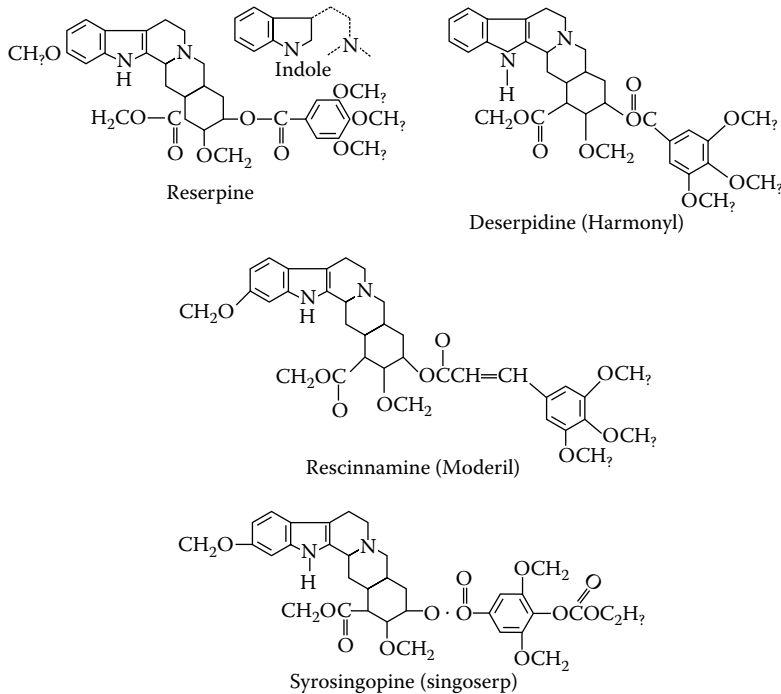


FIGURE 56.2 The structures of reserpine and related compounds.

no consistent change in volume, free hydrochloric acid concentration, or its output is observed after prolonged oral administration. The increased motility of the bowel may cause diarrhea, which has been noted in the unanesthetized dog following administration of the drug. When administered parenterally, reserpine induces a gradual increase in bladder tone that is not blocked by ganglionic blocking agents. The effect of reserpine on cardiovascular activity, intestinal motility, and pupillary size suggest that the posterior hypothalamus is its primary site of action because it does not antagonize the effects of sympathetic substances, such as epinephrine, or norepinephrine nor does it potentiate the effects of acetylcholine.

In the unanesthetized dog, reserpine selectively depresses the sympathetic centers and induces facilitation of the parasympathetic centers in the diencephalon. The latter effect accounts for the bradycardia, miosis, aggravation of bronchial asthma, renal and biliary colic, and ulcerative colitis observed in some patients receiving the drug.

### MECHANISM OF ACTION

Large single doses of reserpine (1 to 5 mg/kg) in animals cause a progressive decline in the **serotonin** content in the intestine. After 16 h, about 90% of it disappears and the level remains low for about 48 h, after which it gradually rises to its normal level again in the course of about 7 d. Similar changes occur in the platelets. The brain is more sensitive to the effects of reserpine so that 80% of the serotonin originally present disappears within 1 hr, and the liberation of serotonin may be observed in doses as low as 0.05 mg/kg.

It therefore appears that the main action of reserpine is to produce a biochemical change so that the cells no longer retain a high concentration of serotonin. In other words, the binding of serotonin is prevented. Thus, after the administration of **5-hydroxytryptophan** (a precursor of serotonin) to rabbits pretreated with reserpine, serotonin is rapidly formed but remains in a free form. Presumably, free serotonin, before it is metabolized to **5-hydroxyindole acetic acid** by amine

oxidase, acts to produce the central action of reserpine. Reserpine affects the serotonin-binding sites by an unknown mechanism releasing serotonin, but it also causes a depletion from the body stores of **epinephrine** and **norepinephrine**.

Reserpine enters the brain rapidly after its intravenous administration, reaching a maximum level almost immediately. The drug is metabolized rapidly, presumably in the liver, and disappears from the brain in 8 h. However, the inability to take up serotonin persists with its pharmacological effect because apparently new binding sites for serotonin must be produced. This explains the persistence of the tranquilizing effect after reserpine medication is discontinued and the cumulative effect of the customary small daily doses of this drug. Although the drug is present in the body for only a few hours and a single dose is too small to affect serotonin or exert a tranquilizing action, each dose inactivates a sufficient number of the binding sites of serotonin so that the typical effects of free serotonin are produced. This phenomenon also explains the appearance of signs of over-dosage in patients who have been taking the *Rauwolfia* drugs for a long time.

Similar to serotonin, the *Rauwolfia* alkaloids potentiate the action of barbiturates and alcohol. This potentiating action is mediated through serotonin. The alkaloids also exert an antiveratrinic and antiarrhythmic action on the isolated heart.

## PREVENTION OF THE STORAGE OF NOREPINEPHRINE BY RESERPINE

### NEUROCHEMICAL BASIS OF ADRENERGIC TRANSMISSION

Dopamine, norepinephrine, and epinephrine are classified as catecholamines.

Tyrosine is converted to dopa by the rate-limiting enzyme **tyrosine hydroxylase**, which requires **tetrahydrobiopterin**, and is inhibited by  **$\alpha$ -methyltyrosine**. Dopa is decarboxylated to dopamine by **L-aromatic amino acid decarboxylase**, which requires **pyridoxal phosphate (vitamin B<sub>6</sub>)** as a coenzyme. **Carbidopa**, which is used with levodopa in the treatment of parkinsonism, inhibits this enzyme. Dopamine is converted to norepinephrine by **dopamine  $\beta$ -hydroxylase**, which requires **ascorbic acid (vitamin C)**, and is inhibited by **diethyldithiocarbamate**. Norepinephrine is converted to epinephrine by **phenylethanolamine N-methyltransferase (PNMT)**, requiring **S-adenosylmethionine**. The activity of PNMT is stimulated by corticosteroids.

The catecholamine-synthesizing enzymes are not only able to synthesize dopamine and norepinephrine from a physiologically occurring substrate such as levodopa, but also from exogenous substrates such as  **$\alpha$ -methyldopa**, which is converted to  **$\alpha$ -methyldopamine** and in turn to  **$\alpha$ -methylnorepinephrine**.  $\alpha$ -methyldopamine and  $\alpha$ -methylnorepinephrine are called **false transmitters** and, in general (except for  $\alpha$ -methylnorepinephrine), are weaker agonists.  $\alpha$ -methyldopa is used in the management of hypertension.

In addition to being synthesized in the peripheral nervous system, dopamine is synthesized in the corpus striatum and in the mesocortical, mesolimbic, and tuberoinfundibular systems. Norepinephrine is synthesized and stored primarily in sympathetic noradrenergic nerve terminals, as well as in the brain and the adrenal medulla. Epinephrine is synthesized and stored primarily in the adrenal medulla and, to a certain extent, in the hypothalamic nuclei.

In sympathetic nerve terminals, as well as the brain, the adrenal medulla, and sympathetic postganglionic terminals, there are osmophilic granules (synaptic vesicles) that are capable of storing high concentrations of catecholamine (a complex with adenosine triphosphate, or ATP, and protein). The stored amines are not metabolized by the intersynaptosomal mitochondrial enzyme (monoamine oxidase).

In addition to releasing norepinephrine (through exocytosis), the stimulation of sympathetic neurons also releases ATP, storage protein, and dopamine  $\beta$ -hydroxylase. The released norepinephrine interacts with receptor sites located postsynaptically ( $\alpha_1$ ) to produce the desired effects.

The action of norepinephrine is terminated by reuptake mechanisms, two of which have been identified. **Biogenic amine Uptake 1** is located in the presynaptic membrane, requires energy for the transport, is sodium and temperature dependent, and is inhibited by ouabain (a cardiac glycoside), cocaine (a local anesthetic), and imipramine (an antidepressant). **Biogenic amine Uptake 2** is located extraneuronally in various smooth muscles and glands, requires energy, and is temperature dependent. Approximately 20% of the amine is either taken up by the Uptake 2 mechanism or is metabolized.

### CATECHOLAMINE METABOLISM

There are two enzymes capable of metabolizing catecholamines. The first is **monoamine oxidase (MAO)**, a mitochondrial enzyme that oxidatively deaminates catecholamines, tyramine, serotonin, and histamine. MAO is further subclassified as either monoamine oxidase A, which metabolizes norepinephrine and is inhibited by tranylcypromine, and monoamine oxidase B, which metabolizes dopamine and is inhibited by 1-deprenyl. **Catechol-O-methyltransferase (COMT)**, a soluble enzyme present mainly in the liver and kidney, is also found in postsynaptic neuronal elements. About 15% of norepinephrine is metabolized postsynaptically by COMT.

### ADRENERGIC NEURONAL-BLOCKING DRUGS

Reserpine (Serpasil) depletes the store of catecholamine peripherally and centrally and attenuates, but does not abolish, sympathetic reflexes. Reserpine is useful in the management of mild to moderate hypertension. Its onset of action is very slow (2 to 3 weeks) when given orally. The side effects of reserpine are manifested by cholinergic hyperactivity such as diarrhea, bradycardia, and nasal stuffiness. Reserpine can activate a peptic ulcer (cholinergic dominance) and cause depression (depletes norepinephrine stores). Reserpine and propranolol have potential cardiac depressant activity and should not be used together.

Although the *Rauwolfia* compounds were pioneers among **tranquilizing agents (neuroleptics)**, they are hardly used for that purpose anymore for two main reasons: first, they tend to cause serious depressions; second, the **phenothiazine derivatives** and newer neuroleptics such as **clozapine** are as effective, act more rapidly, and are infrequently followed by depression.

### SIDE EFFECTS

Although the *Rauwolfia* alkaloids show a low degree of acute toxicity, their continued use may be accompanied by serious side effects. One of the most troublesome symptoms observed in the therapeutic use of *Rauwolfia* alkaloids is nasal congestion and stuffiness, which may be so severe as to necessitate discontinuing of therapy. Increased motility of the bowel, diarrhea, and increased gastric secretion resulting from its action on the autonomic nervous system are frequently observed. Skin eruptions, epistaxis, and peptic ulceration are rare complications.

The more serious side effects observed in patients receiving reserpine for long periods involve the nervous system and include withdrawal from the environment, unhappiness, depression, lack of ambition, crying spells, introspection, and lethargy. Bizarre dreams and nightmares may necessitate cessation of therapy. **Loss of libido** is a frequent complaint among males. A parkinsonian-like syndrome may result from prolonged therapy or excessive dosage.





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# 57 Rhubarb

## INTRODUCTION

**Rhubarb** (the “wondrous drug”) is a purgative agent, and is an effective remedy in “Oketsu Syndrome,” a blood stagnation syndrome. It consists of the rhizomes of *Rheum palmatum* L., *R. tanguticum* Maxim., *R. officinale* Baill., Baill., *R. coreanum* Nakai, and *R. undulatum* L., and is used in remedies for blood stagnation syndrome (called “**Oketsu syndrome**” in Japanese traditional medicine) as well as a **purgative agent** in Japanese, Korean, and Chinese traditional medicines. Among them, the rhizome of *R. undulatum*, a Korean rhubarb, is considered to have a reduced purgative but more potent effect on Oketsu syndrome than other kinds of rhubarbs.

## RHUBARB AND ITS LAXATIVE PROPERTIES

The medicinal parts are the dried underground parts free of the stem remnants, the smaller roots, and most of the root bark in the dried form. **Garden rhubarb** is *Rheum ponticum*.

The inflorescence is an erect panicle foliated to the tip. The flowers consist of narrow, red, pink, or whitish yellow petals, which are curved and located far back in the mature flowers to facilitate wind pollination. The fruit is red-brown to brown, and oval. It is angular, about 10.2 to 7.8 mm wide and usually has scarios wings. The nutlet is 6 to 10 mm long and 7 mm in diameter.

The plant is a large, sturdy herbaceous perennial. The stem grows to over 1.5 m high. The leaves are orbicular-cordate, palmate-lobed, somewhat rough on the upper surface, or smooth and three- to five-ribbed. The lobes are oblong-ovate to lanceolate, dentate or pinnatisect. The root system consists of a tuber, which after a number of years measures 10 to 15 cm in diameter and has arm-thick lateral roots.

The plant is indigenous to the western and northwestern provinces of China and is cultivated in many regions around the world. The main producers are China and Russia.

Rhubarb consists of the dried underground parts of *R. palmatum*, *R. officinale*, or of both species. Stem parts, roots, and most of the bark are removed from the rhizomes.

Rhubarb contains:

- **Anthracene derivatives** (3 to 12%): chief components 1- or 8 $\beta$ -glucosides of the **aglycones rheumemodin, aloë-emodin, rhein, chrysophanol, physcion** (together 60 to 80%), 8,8'-diglucosides of dianthrones (10 to 25%), including, among others, **sennosides A and B**
- **Tannins**: gallo tannins, including, among others, **galloylglucose, galloylsaccharose, lindleyine, isolindleyine**
- **Flavonoids** (2 to 3%)
- **Naphthohydroquinone glycosides**

Rhubarb is a laxative, primarily owing to its influence on the motility of the colon, inhibiting stationary and stimulating propulsive contractions. This results in an accelerated intestinal passage and, because of the active chloride secretion, an increase in the water and electrolyte content of stool.

Rhubarb is indicated in constipation, bowel movement relief with anal fissures, hemorrhoids, after recto-anal surgery and in preparation for diagnostic interventions of the gastrointestinal tract.

Rhubarb is contraindicated in cases of intestinal obturation, acute inflammatory intestinal disease, appendicitis, and abdominal pain of unknown origin. Spasmodic gastrointestinal complaints can occur as a side effect of the purgative effect of the drug. Long-term use leads to losses of electrolytes, in particular  $K^+$  ions, and as a result of this, to hyperaldosteronism, inhibition of intestinal motility, and enhancement of the effect of cardioactive steroids; in rare cases it also leads to heart arrhythmias, nephropathies, edemas, and accelerated bone deterioration.

The question of the increase in probability of the appearance of carcinomas in the colon following long-term administration of anthracene drugs has not yet been fully clarified. Recent studies show no connections between the administration of anthracene drugs and the frequency of carcinomas in the colon. Potassium deficiency can cause an increase in the effect of cardiac glycosides.

## CONSTIPATION

Constipation may be defined as the passage of excessively dry stools, infrequent stools, or stools of insufficient size. Constipation is a symptom and not a disease. It may be of brief duration (e.g., when one's living habits or diet change abruptly) or it may be a lifelong problem, as occurs in congenital aganglionosis of the colon (**Hirschsprung's disease**). The causes of constipation are multiple and include the following:

- Functional causes
  - Fiber-deficient diets
  - Variants of irritable bowel syndrome
  - Debilitation and extreme old age
- Colonic diseases
  - Chronic obstructive lesions (e.g., tumors or strictures)
  - Ulcerative colitis
  - Collagen vascular diseases
- Rectal diseases
  - Stricture (e.g., ulcerative colitis)
  - Painful conditions (fissure or abscess)
- Neurologic diseases
  - Hirschsprung's disease
  - Spinal cord injuries and disease
  - Parkinson's disease
  - Cerebral tumors and cerebrovascular disease
- Metabolic diseases
  - Porphyria
  - Hypothyroidism
  - Hypercalcemia
  - Pheochromocytoma
  - Uremia

Use of the following drugs may also lead to constipation:

- Anticholinergic drugs contained in many of the over-the-counter medications
- Antiparkinsonian drugs possessing anticholinergic properties (e.g., **trihexyphenidyl** and **ethopropazine**)
- Antihistaminic drugs with anticholinergic properties (e.g., **diphenhydramine**)
- Neuroleptics with anticholinergic properties (e.g., **thioridazine**)

- Antidepressants with anticholinergic properties (e.g., **amitriptyline**)
- Anticonvulsants with anticholinergic properties (e.g., **carbamazepine**)
- Analgesics (e.g., morphine, codeine, and **diphenoxylate**)
- Ganglionic blocking agents (e.g., **mecamylamine hydrochloride** and **pempidine**)
- Antacids (calcium- or aluminum-containing compounds)

## LAXATIVES AND CATHARTICS

Although often used interchangeably, the terms *laxative* and *cathartic* have slightly different meanings. A laxative effect refers to the excretion of a soft, formed stool; catharsis implies a more fluid and complete evacuation.

### IRRITANTS

Irritant agents used in the treatment of constipation include **cascara sagrada**, **castor oil**, **senna**, **rhubarb**, **phenolphthalein**, and **acetphenolisatin**. Phenolphthalein is a constituent of many over-the-counter preparations, including Correctol™, Ex-Lax™, and Feen-A-Mint™. Most of these agents, with the exception of castor oil, are slow in their onset of action (24 h).

Phenolphthalein is thought to exert its effect by inhibiting the movement of water and sodium from the colon into the blood and by stimulating mucus secretion. If misused on a prolonged basis, a consequential loss of mucus may lower the plasma protein level. Castor oil is hydrolyzed to **ricinoleic acid**, the active cathartic. It has an onset of action of 2 to 6 h.

The misuse of any of these agents has been shown to cause hypokalemia, dehydration, and a cathartic colon (resembling ulcerative colitis). Phenolphthalein-containing products may color alkaline urine red.

### BULK SALINE LAXATIVES

Bulk saline laxatives fall into two categories: inorganic salts (magnesium sulfate, magnesium citrate, milk of magnesia, sodium sulfate, and sodium phosphate) and organic hydrophilic colloids (**methycellulose**, **carboxymethylcellulose** (Metamucil), plantago seed, agar, psyllium, bran, and fruits). They exert their effects by absorbing and retaining water, increasing bulk, stimulating colonic peristaltic movements, and lubricating and hydrating the desiccated fecal materials.

These agents are more effective when administered with water. The onset of action of organic salts is relatively fast (2 to 6 h) and that of colloids is relatively slow (1 to 3 d). These agents, which are very effective and safe, should not be used when the intestinal lumen has been narrowed. The prolonged use of saline cathartics may create problems for certain individuals. For example, magnesium salts have been known to cause hypermagnesemia, coma, and death in patients with renal insufficiency. Sodium salts may also be responsible for causing congestive heart failure.

### LUBRICANTS

These consist of mineral oil and **dioctyl sodium sulfosuccinate** (Colace™). Colace is used in the pharmaceutical industry as an emulsifying and dispersing substance. Both agents are taken orally. These agents, which do not influence peristalsis, soften desiccated stools or delay the desiccation of fecal materials. They are especially useful in patients with painful bowel movements resulting from inspissated stools or inflammation of the anal sphincter such as occurs with hemorrhoids or anal fissures. Colace is also useful for patients for whom the consequences of “straining at stool” may be harmful.

When used for a long time, mineral oil may come to interfere with the absorption of fat-soluble vitamins and other essential nutrients. Lipid pneumonitis may evolve if mineral oil is used as a vehicle for drugs that are taken nasally.

## OTHER USES OF LAXATIVES

Laxatives have the following other uses:

- **Poisoning:** Laxatives are used to hasten the elimination and reduce the absorption of a poison that has been taken.
- **Anthelmintics:** Laxatives are used before and after treatment with anthelmintic drugs.
- **Radiology:** Laxatives are used to clean the gastrointestinal tract before radiographic techniques are performed.

## ANTIOXIDANT PROPERTIES OF RHUBARB

Japanese scientists believe that the **anti-oketsu effects** of rhubarb are brought about by the inhibition of the production of nitric oxide, inhibition of platelet aggregation, antiallergic effects, and its anti-inflammatory properties. Matsuda et al. (2001) studied and reported that the methanolic extracts from five kinds of rhubarb were found to show scavenging activity for **1,1-diphenyl-2-picrylhydrazyl (DPPH) radical** and **superoxide anion radical** ( $O_2^{\cdot-}$ ) generated by the **xanthine/xanthine oxidase** system and/or on lipid peroxidation by **tert-butyl hydroperoxide** (*t*-BuOOH) in the erythrocyte membrane ghost system.

Two new **anthraquinone glucosides** were isolated from the rhizome of *R. undulatum* L. together with two anthraquinone glucosides, a naphthalene glucoside, and ten stilbenes. In the screening test for radical-scavenging activity of rhubarb constituents, stilbenes and a **naphthalene glucoside** showed activity, but **anthraquinones** and **sennosides** did not. In addition, most stilbenes inhibited lipid peroxidation of erythrocyte membrane by *tert*-butyl hydroperoxide. Detailed examination of the scavenging effect on various related compounds suggested the following structural requirements: (1) phenolic hydroxyl groups are essential to show the activity, (2) galloyl moiety enhances the activity, (3) glucoside moiety reduces the activity, and (4) dihydrostilbene derivatives maintain the scavenging activity for the DPPH radical, but they show weak activity for superoxide anion. In addition, several stilbenes with both the 3-hydroxyl and 4-methoxyl groups inhibited xanthine oxidase.

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# 58 Saffron

## INTRODUCTION

The following are the main uses of saffron:

- Has antitumor effects
- Scavenges free radicals
- Exhibits hypolipidemic properties
- Attenuates alcohol-induced memory impairment
- Is an aromatic and tasty spice in preparing many foods

*Crocus sativus* L., commonly known as **saffron**, is used in folk medicine as an **antispasmodic, eupeptic, gingival sedative, anticatarrhal, nerve sedative, carminative, diaphoretic, expectorant, stimulant, stomachic, aphrodisiac, and emmenagogue**. Furthermore, modern pharmacological studies have demonstrated that saffron extract or its active constituents have **antitumor effects, radical scavenger properties, and hypolipemic effects** (see Rios et al., 1996).

## ANTIOXIDANT EFFECT OF SAFFRON

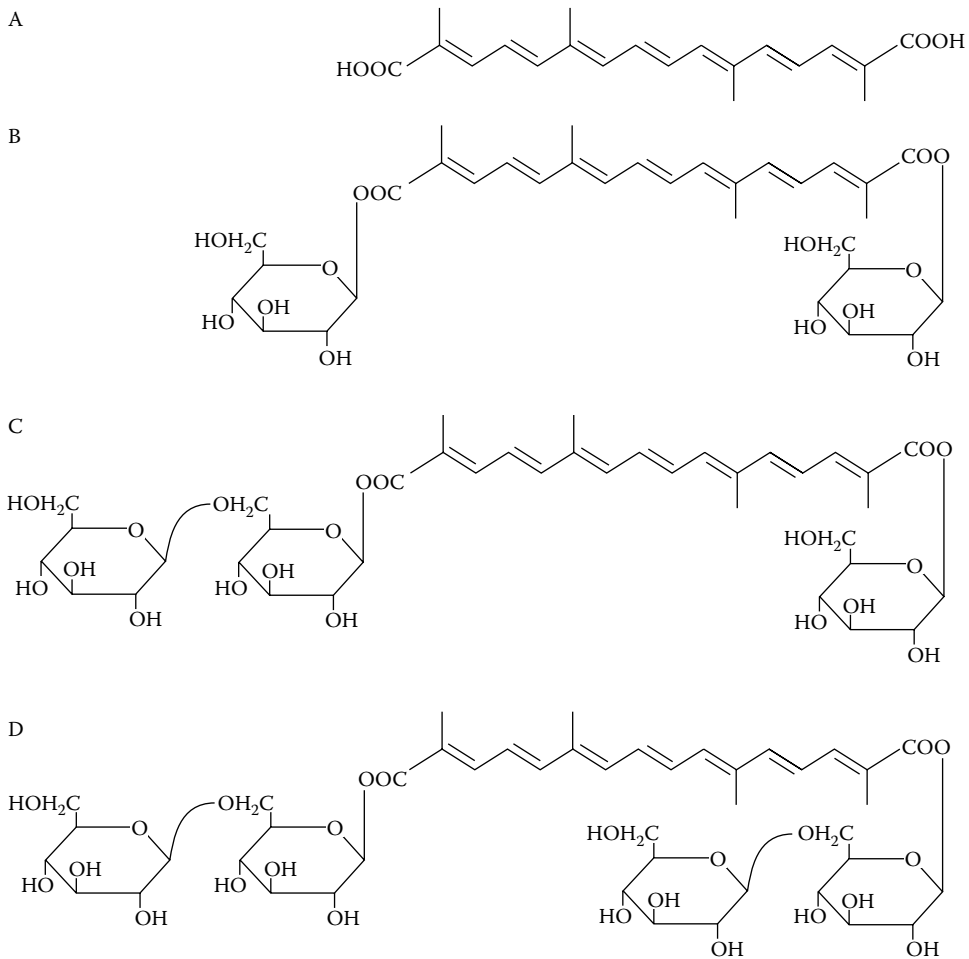
Saffron extract contains many **carotenoids** such as **crocetin, crocetin di-glucose ester, crocetin gentiobiose glucose ester, and crocin** (crocetin di-gentiobiose ester), whose chemical structures are shown in Figure 58.1. These carotenoids scavenge free radicals, especially superoxide anions, and so may protect cells from oxidative stress. Indeed, it has been demonstrated that these carotenoids are useful in **sperm cryoconservation** and in protecting hepatocytes from toxins.

Accumulating evidence suggests that cellular stress induced by free radicals is responsible for a variety of central nervous system (CNS) neurodegenerative disorders, including **Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis**, and in pathological conditions such as ischemia and excitotoxicity. The importance of preventing oxidative-stress-induced neuronal damage has recently been emphasized. Because of its powerful antioxidant activity, saffron extract, crocetin, or crocin could be useful in the therapy of brain neurodegenerative disorders, although their effects have not yet been evaluated.

## EFFECT OF SAFFRON ON LEARNING AND MEMORY

CNS neurodegenerative disorders often accompany the impairment of memory and other cognitive functions. This impairment is probably due to selective neuronal death in the cerebral cortex and hippocampus, brain regions that are crucially involved in learning and memory. It has recently been found that the alcohol extract of pistils of *C. sativus* L. (CSE) affects learning and memory in mice. Oral administration of CSE (125 to 500 mg/kg) alone had no effect on learning behavior of mice in passive avoidance tests, but significantly improved ethanol-induced impairment of memory acquisition.

The effect of CSE was reproduced by **crocin**, a major constituent in CSE. Oral administration of crocin (50 to 200 mg/kg) alone had no effect, but significantly improved ethanol-induced



**FIGURE 58.1** Chemical structures of crocetin (A), crocetin diglucose ester (B), crocetin gentiobiose glucose ester (C), and crocin (D).

impairment of memory acquisition in mice. Picrocrocin, another constituent in CSE, was ineffective in the same experiment. These results indicate that **crocin** has a specific, preventive effect on ethanol-induced impairment of learning and memory.

### POSSIBLE MOLECULAR TARGET OF CROCIN

The induction of **long-term potentiation (LTP)** in CA1 and dentate gyrus regions of the hippocampus essentially requires the activation of the ***N*-methyl-D-aspartate (NMDA)** type of glutamate receptors.  $\text{Ca}^{2+}$  influx into postsynaptic cells through NMDA receptors channels the activation of enzymes linked to the induction of LTP. Furthermore, ethanol has been considered to inhibit the induction of LTP by suppressing the activity of the NMDA receptor channel complex. In rat hippocampal slices and single hippocampal neurons, ethanol inhibited NMDA receptor-mediated synaptic excitation, and the inhibitory effect of ethanol was significantly attenuated by crocin, but not by crocetin diglucose ester. Crocin is likely to prevent ethanol-induced inhibition of hippocampal LTP by antagonizing the inhibitory effect of ethanol on NMDA receptors, although it is not clear whether crocin acts directly on the NMDA receptor channel complex or indirectly modulates NMDA receptor functions (see Figure 13.4). In addition, because the antagonizing effect of crocin

against ethanol on NMDA receptor functions was smaller than that observed in behavioral and LTP experiments, this action of crocin cannot account solely for the antagonism against **ethanol-induced memory impairment**. Further investigations are necessary to explore other molecular targets of crocin. Saffron extract contains many carotenoids with powerful antioxidant effects, and may protect CNS neurons from oxidative damage. Saffron extract or its constituents, especially crocin, improves the impairment of certain types of learning and memory. Therefore, saffron and its active constituents should be useful for the therapy of CNS neurodegenerative disorders accompanying the impairment of memory and cognitive functions.

In addition, the finding that crocin specifically prevents ethanol-induced memory impairment and inhibition of hippocampal LTP is of great significance in the following respects. First, the consistency of effects of crocin on learning behavior and LTP further supports the hypothesis that hippocampal LTP is involved in memory formation. Second, crocin should be useful as a new pharmacological tool for studying the mechanism of ethanol-induced memory impairment. Further investigation on molecular targets of crocin may give new insight into the mechanism underlying memory formation and LTP (Abe and Saito, 2000).





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# 59 Salicylate

## INTRODUCTION

Salicylate (aspirin) is found in willow, wintergreen, and sweet birch, and:

- Is an antirheumatic agent
- Causes analgesia
- Reduces fever
- Has anti-inflammatory activity
- Inhibits platelet aggregation
- Has neuroprotective effects in an animal model of Parkinson's disease
- May bring about chemoprevention of colorectal cancer
- May prevent Alzheimer's disease
- Could be used in the treatment of reflux esophagitis

## SOURCE

**Salicinum**, Salicin,  $C_{13}H_{18}O_7$ , is a glucoside obtained from several species of *Salix*, the **willow**, and *populus*, the **poplar**, trees of the nat. ord. **Salicaceae**. It is found also in *Gaultheria procumbens*, the **wintergreen**, nat. ord. **Ericaceae**; and in *Betula lenta*, the **sweet birch**, nat. ord. **Betulaceae**; the volatile oils of which, distilled from the leaves of the former and from the bark of the latter, consist almost entirely of **methyl salicylate**.

**Salicin** occurs in colorless or white and silky, shining crystalline needles, or a crystalline odorless powder, of very bitter taste, permanent in the air, of neutral reaction, soluble in 28 parts water and in 30 parts alcohol, in 0.7 parts of boiling water and in 2 parts of boiling alcohol; almost insoluble in ether or chloroform.

*Salix nigra*, the **pussy willow**, grows along streams in the Southern states. It was used in the late 19th century as a "**sexual sedative**."

**Acidum salicylicum**, **salicylic acid**,  $HC_7H_5O_3$ , is a monobasic organic acid, existing naturally in combination in various plants, but generally prepared synthetically from phenol. It occurs in light, fine, white prismatic needles, or a crystalline powder, which is odorless, sweetish, but having an acrid aftertaste and acid reaction, permanent in the air. It is soluble in about 450 parts cold water, but readily soluble in water containing 8% of borax or 10% of sodium phosphate. It is soluble in 2H parts alcohol, in 14 parts boiling water, in 2 parts ether, in 80 parts chloroform, and is very soluble in boiling alcohol.

## OFFICIAL SALICYLATES USED IN THE EARLY 20TH CENTURY

The following are the official salicylates used in the early 20th century:

- **Lithii Salicylas**, **Lithium Salicylate**,  $LiC_7H_5O_3$ , is a white, or grayish-white powder, odorless, sweetish, very soluble in water and in alcohol.

- **Sodii Salicylas**, *Sodium Salicylate*,  $\text{NaC}_7\text{H}_5\text{O}_3$ , is a white, amorphous powder, soluble in 1 part water and in 6 parts alcohol and also in glycerin.
- **Strontii Salicylas**, *Strontium Salicylate*, is a white, crystalline powder, soluble in 18 parts water and in 66 parts alcohol.
- **Methylis Salicylas**, *Methyl Salicylate*, is an ester, produced synthetically, and is the principal constituent of Oil of Gaultheria and Oil of Betula. It is soluble in all proportions in alcohol or glacial acetic acid.
- **Phenylis Salicylas**, *Phenyl Salicylate*, *Salol*,  $\text{C}_{13}\text{H}_{10}\text{O}_3$ , is the salicylic ester of phenyl, and occurs as a white, crystalline powder, odorless and almost tasteless, nearly insoluble in water, soluble in 10 parts alcohol, and very soluble in ether, chloroform, and oils. On warming with an alkali, it splits up into salicylic acid 60, and phenol 40, frequently repeated, in compressed tablets or in cachets, or suspended by mucilage of acacia or of tragacanth.
- **Oleum Betulae**, *Oil of Betula (Oil of Sweet Birch)*, is a volatile oil distilled from the bark of *Betula lenta*, the sweet birch. It is identical with methyl salicylate and nearly identical with Oil of Gaultheria.
- **Oleum Gaultheriae**, *Oil of Gaultheria*, *Oil of Wintergreen*, consists almost entirely of methyl salicylate, and is almost identical to the preceding compounds.

## ANALGESICS–ANTIPYRETICS AND ANTI-INFLAMMATORY AGENTS

The development of aspirin was a significant landmark in the history of medicine because it stimulated the development of a family of medicines, collectively known as the **nonsteroidal anti-inflammatory drugs** (NSAIDs). NSAIDs such as **ibuprofen**, **naproxen**, and **sulindac** are valuable drugs used for the alleviation of pain, inflammation, and fever, and they are commonly prescribed for the treatment of rheumatoid disorders such as arthritis. The world market for NSAIDs now exceeds \$6 billion (Vainio and Morgan, 1997).

Despite the introduction of many new drugs, **aspirin (acetylsalicylic acid)** is still the most widely prescribed analgesic–antipyretic and anti-inflammatory agent and is the standard for the comparison and evaluation of the others. Prodigious amounts of the drug are consumed in the U.S.; some estimates place the quantity as high as 10,000 to 20,000 tons annually. Aspirin is the common household analgesic; yet, because the drug is so easily available, its usefulness is often underrated. Despite the efficacy and safety of aspirin as an analgesic and antirheumatic agent, it is necessary to be aware of its role in **Reye's syndrome** and as a common cause of lethal drug poisoning in young children, as well as its potential for serious toxicity if used improperly.

Salicylates and allied compounds have analgesic, antipyretic, uricosuric, and anti-inflammatory properties. Their mechanisms of action differ from those of the anti-inflammatory steroids and the opioid analgesics. They are classified into the following categories:

### **Salicylate derivatives**

Acetylsalicylic acid (aspirin)

### **Pyrazolone derivatives**

Phenylbutazone (Butazolidin)

Oxyphenbutazone (Oxalid, Tandearil)

Sulfinpyrazone (Anturane)

### **Paraaminophenol derivatives**

Acetaminophen (Tylenol, Datriol)

Phenacetin (Acetophenetidin)

**Propionic acid derivatives**

Ibuprofen (Motrin)  
Naproxen (Naprosyn)  
Fenoprofen (Nalfon)  
Flurbiprofen (Ansaid)  
Ketoprofen (Orudis)

**Other related compounds**

Indomethacin (Indocin)  
Sulindac (Clinoril)  
Mefenamic acid (Ponstel)  
Tolmetin (Tolectin)  
Piroxicam (Feldene)  
Diclofenac sodium (Voltaren)

**Drugs used in the treatment of gout**

Colchicine  
Allopurinol  
Uricosuric agents

**Drugs used in the treatment of arthritis**

Aurothioglucose (Solganal)  
Gold sodium thiomalate (Myochrysine)  
Auranofin (Ridaura)

The pharmacology of acetylsalicylic acid (aspirin) is discussed in detail as a prototype drug, and all the other drugs are compared to it.

## MECHANISM OF ACTION OF ASPIRIN

The mechanism by which these drugs act to reduce mild to moderate pain is based on the relationship between drugs such as aspirin and **prostaglandin** synthesis. Studies in humans have shown that intravenous administration of certain prostaglandins elicits headache and pain and produces hyperalgesia, sensitizing the individual to stimuli that normally would not produce pain. Aspirin and related compounds inhibit the enzyme **cyclooxygenase** and prevent the formation of **prostaglandin endoperoxides**, PGG<sub>2</sub> and PGH<sub>2</sub>, which are normally formed from **arachidonic acid**.

## ASPIRIN AND ITS USES

### ASPIRIN-INDUCED ANALGESIA

**Unlike the narcotic analgesics such as morphine**, aspirin does not depress respiration, is relatively nontoxic, and lacks addiction liability. Aspirin is a weak or mild analgesic that is effective for ameliorating short, intermittent types of pain such as neuralgia, myalgia, and toothache. It does not have the efficacy of morphine and cannot relieve the severe, prolonged, and lancinating types of pain associated with trauma such as burns or fractures. Similar to morphine, it produces analgesia by **raising the pain threshold** in the thalamus, but unlike morphine, it does not alter the patient's reactions to pain. Because aspirin does not cause hypnosis or euphoria, its site of action has been postulated to be subcortical (see also Figure 44.2). In addition to raising the pain threshold, the anti-inflammatory effects of aspirin may contribute to its analgesic actions. However, no direct association between the anti-inflammatory and analgesic effects of these compounds should be expected. For example, aspirin has both analgesic and anti-inflammatory properties, whereas **acetaminophen** has analgesic but not anti-inflammatory properties. Furthermore, potent anti-inflammatory agents such as **phenylbutazone** have only weak analgesic effects.

### ASPIRIN-INDUCED ANTIPYRESIS

Aspirin does not alter the normal body temperature, which is maintained by a balance between heat production and dissipation. In a fever associated with infection, increased oxidative processes enhance heat production. Aspirin acts by causing cutaneous vasodilation, which prompts perspiration and enhances heat dissipation. This effect is mediated via the hypothalamic nuclei, as proved by the fact that a lesion in the preoptic area suppresses the mechanism through which aspirin exerts its antipyretic effects. The antipyretic effects of aspirin may be due to its inhibition of hypothalamic prostaglandin synthesis. Although aspirin-induced diaphoresis contributes to its antipyretic effects, it is not an absolutely necessary process, because antipyresis takes place in the presence of atropine.

### URICOSURIC EFFECTS OF ASPIRIN

Small doses (600 mg) of aspirin cause hyperuricemia, but large doses (> 5 g) have a uricosuric effect. Aspirin inhibits uric acid resorption by the tubules in the kidneys.

### ANTI-INFLAMMATORY EFFECTS OF ASPIRIN

Aspirin has an anti-inflammatory action as well as antirheumatic and antiarthritic effects, and may therefore be used in the treatment of rheumatic fever. However, it cannot alter the cardiac lesion and other visceral effects of the disease. Aspirin is extremely effective in managing rheumatoid arthritis and allied diseases involving the joints, such as ankylosing spondylitis and osteoarthritis. It is thought that aspirin and indomethacin exert their anti-inflammatory effects by inhibiting prostaglandin synthesis through the inhibition of cyclooxygenase. The presynthesized prostaglandins are released during a tissue injury that fosters inflammation and pain. Furthermore, aspirin reduces the formation of prostaglandin in the platelets and leukocytes, which is responsible for the reported hematological effects associated with aspirin.

### ASPIRIN AND CARDIOVASCULAR DISEASE

The current thinking concerning the role of aspirin in the prevention of cardiovascular disease is that it is beneficial in the event of myocardial infarction and stroke. It is effective because, in platelets small amounts of aspirin acetylate irreversibly bind to the active site of **thromboxane A<sub>2</sub>**, a potent promoter of platelet aggregation.

### ASPIRIN AND THE PREMENSTRUAL SYNDROME

The menstrual cycle is associated with two potentially incapacitating events: dysmenorrhea and the premenstrual syndrome. Substantial evidence indicates that the excessive production of prostaglandin F<sub>2a</sub> is the major source of painful menstruation. The NSAIDs approved for the treatment of dysmenorrhea are aspirin, ibuprofen, **mefenamic acid**, and **naproxen**.

## SIDE EFFECTS OF ASPIRIN

### EFFECTS OF SALICYLATE ON RESPIRATION

Aspirin both directly and indirectly stimulates respiration. In analgesic doses, aspirin increases oxygen consumption and carbon dioxide production. However, increased alveolar ventilation balances the increased carbon dioxide production; thus, the partial pressure of CO<sub>2</sub> (PCO<sub>2</sub>) in plasma does not change. In the event of salicylate intoxication (e.g., 10 to 12 g of aspirin given in 6 to 8 h in adults, and an even smaller dosage in children, whose brains are far more sensitive to salicylate intoxication), salicylate stimulates the medullary centers directly and this causes hyperventilation

characterized by an increase in the depth and rate of respiration. The  $\text{PCO}_2$  level declines, causing hypocapnia, and the blood pH increases, causing respiratory alkalosis. The low  $\text{PCO}_2$  then decreases the renal tubular resorption of bicarbonate and compensates for the alkalosis.

If the salicylate level continues to rise, the respiratory centers become depressed, the  $\text{PCO}_2$  level becomes elevated, and the blood pH becomes more acidic, causing respiratory acidosis. Dehydration, reduced bicarbonate levels, and the accumulation of **salicylic acid**, **salicyluric acid** resulting from metabolism of aspirin, and lactic and pyruvic acid resulting from deranged carbohydrate metabolism may cause metabolic acidosis.

### TREATMENT OF ASPIRIN POISONING

The supportive treatment of aspirin poisoning may include gastric lavage (to prevent the further absorption of salicylate), fluid replenishment (to offset the dehydration and oliguria), alcohol and water sponging (to combat the hyperthermia), the administration of vitamin K (to prevent possible hemorrhage), sodium bicarbonate administration (to combat acidosis) and, in extreme cases, peritoneal dialysis and exchange transfusion.

### THE GASTROINTESTINAL EFFECT OF ASPIRIN

Although innocuous in most subjects, therapeutic analgesic doses of aspirin may cause epigastric distress, nausea, vomiting, and bleeding. Aspirin can also exacerbate the symptoms of peptic ulcer, characterized by heartburn, dyspepsia, and erosive gastritis. Furthermore, compounds possessing anti-inflammatory properties (aspirin, phenylbutazone, and oxyphenbutazone) are associated with a higher incidence of gastrointestinal toxicity than compounds devoid of anti-inflammatory properties (phenacetin and acetaminophen).

### THE HEMATOPOIETIC EFFECT OF ASPIRIN

Aspirin reduces the leukocytosis associated with acute rheumatic fever. When given on a long-term basis, it also reduces the hemoglobin level and the hematocrit. Aspirin use can cause reversible hypoprothrombinemia by interfering with the function of vitamin K in prothrombin synthesis. Therefore, aspirin should be used with caution in patients with vitamin K deficiency, preexisting hypoprothrombinemia, or hepatic damage; in patients taking anticoagulants; and in patients scheduled for surgery. Aspirin leads to hemolytic anemia in individuals with **glucose 6-phosphate dehydrogenase deficiency**. An aspirin tolerance test is used diagnostically in **von Willebrand's disease**, because aspirin will further prolong the bleeding time if the disease exists. Aspirin prevents platelet aggregation and may be helpful in the treatment of thromboembolic disease. In addition to aspirin, indomethacin, phenylbutazone, sulfinpyrazone, and dipyridamole prevent platelet aggregation, whereas epinephrine, serotonin, and prostaglandins promote platelet aggregation and hence are procoagulants. The erythrocyte sedimentation rate is often elevated in infections and inflammations, but aspirin therapy will yield a false negative.

### NEW USES OF ASPIRIN

Although the uses of NSAIDs are identical to the uses of the plant extracts that contained **salicylic acid**, namely, inflammation, pain, and fever, these drugs are increasingly used for other indications, such as:

- In the case of aspirin, there are numerous reports of beneficial effects of low-dose aspirin in the secondary **prophylaxis of cardiovascular disease** (myocardial infarction and stroke). Aspirin clearly reduces the risk of myocardial infarction and stroke among patients who already have manifestations of cardiovascular disease.

- More recently, growing evidence has suggested that aspirin and other NSAIDs might have another public health indication: **colorectal cancer** might be prevented by regular aspirin use. Administration of **sulindac** to affected individuals induced polyp regression that was reversed by cessation of sulindac administration. A large body of epidemiological evidence point to an inverse association between aspirin use and colorectal cancer risk.
- In the case of **reflux esophagitis**, the combination of low-dose NSAIDs coupled to an acid inhibitor (to simultaneously reduce gastrototoxicity and the reflux of gastric juice) may have potent healing properties. The presence of the NSAID may also help to reduce the risk of reflux-related complications such as esophageal carcinoma.
- Other potential indications for NSAID use is prevention and treatment of **Alzheimer's disease**. In a recent review of 15 published studies, 14 suggest that NSAID treatment prevents or ameliorates symptoms of Alzheimer's disease (see Vainio and Morgan, 1997).

### SALICYLATE PROTECTS AGAINST MPTP-INDUCED PARKINSONISM

Since the chance discovery of the neurotoxic effects of 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (**MPTP**) in humans, it has been thought that a similar type of environmental toxin might be responsible for idiopathic Parkinson's disease and that an understanding of the neurotoxic effects of MPTP might lead to prevention of this debilitating disorder. MPTP is metabolized to the 1-methyl-4-phenylpyridinium ion (**MPP<sup>+</sup>**) by **monoamine oxidase (MAO) B**, and this highly toxic metabolite is selectively taken up into dopaminergic neurons via the dopamine transporter (see Figure 13.3). **MPP<sup>+</sup>** is a **mitochondrial toxin** that selectively inhibits **complex I** of the respiratory chain, leading evidently to energy compromise and to the production of potentially cytotoxic **free radicals**. Accumulating evidence suggests that oxidative stress is also a feature of Parkinson's disease neuropathology, as is mitochondrial complex I deficiency. MPTP produces a selective lesion of the nigrostriatal dopamine system that closely mimics the neuropathological and symptomatic sequelae of Parkinson's disease. Blockade of either MAO-B or **dopamine uptake** is known to protect against the neurotoxic effects of MPTP in laboratory animals.

MPTP decreases glutathione levels and increases the levels of reactive oxygen species and the degree of lipid peroxidation in mouse brain slices *in vitro* and increases the levels of reactive oxygen species in mouse brain *in vivo*. MPTP neurotoxicity *in vitro* is reduced by glutathione. *In vitro* studies have shown that **MPP<sup>+</sup>** neurotoxicity can be reduced by vitamin E, vitamin C, **coenzyme Q**, and mannitol (but not by superoxide dismutase, catalase, allopurinol, or dimethyl sulfoxide).  $\beta$ -Carotene, vitamin C, and *N*-acetylcysteine partially protect against the neurotoxic effects of MPTP in mice, as do nicotinamide, coenzyme Q, and the free-radical spin trap ***N*-tert-butyl- $\alpha$ -(sulfophenyl) nitron**.

Aubin et al. (1998) reported that the neurotoxic effects of the dopamine-selective neurotoxin MPTP (15 mg/kg, s.c.), in mice, were totally prevented by systemic administration of **salicylate** (ED<sub>50</sub> = 40 mg/kg, i.p.), **aspirin** (ED<sub>50</sub> = 60 mg/kg, i.p.), or the soluble lysine salt of aspirin, **Aspegic** (ED<sub>50</sub> = 80 mg/kg, i.p.). The protective effects of aspirin are unlikely to be related to cyclooxygenase inhibition, because **paracetamol** (100 mg/kg, i.p.), **diclofenac** (100 mg/kg, i.p.), **ibuprofen** (20 mg/kg, i.p.), and **indomethacin** (100 mg/kg, i.p.) were ineffective. **Dexamethasone** (3 to 30 mg/kg, i.p.), which, similar to aspirin and salicylate, has been reported to inhibit the **transcription factor NF- $\kappa$ B**, was also ineffective. Aspirin or salicylate (100  $\mu$ M) had no effect on dopamine uptake into striatal synaptosomes or on monoamine oxidase B activity. The neuroprotective effects of salicylate derivatives could perhaps be related to hydroxyl radical scavenging. This was suggested by the fact that hydroxylated metabolites of salicylate (2,3- and 2,5-dihydrobenzoic acid) were recovered in brain tissue following the combined administration of MPTP and

aspirin to a greater extent than following aspirin alone. The surprising neuroprotective effects of aspirin in an animal model of Parkinson's disease warrant further clinical investigation.

## HEALTH EFFECTS OF SALICYLATES IN FOODS

Salicylates are found in fruits and vegetables. Salicylate-elimination diets have been used successfully in the treatment of asthma and chronic urticaria in **aspirin-sensitive individuals** (Swain et al., 1985; Perry et al., 1996).

### ASPIRIN-INDUCED ASTHMA

The drugs most commonly associated with the induction of acute episodes of asthma are aspirin, coloring agents such as tartrazine,  $\beta$ -adrenergic antagonists, and sulfiting agents. It is important to recognize drug-induced bronchial narrowing because its presence is often associated with great morbidity. Furthermore, death sometimes has followed the ingestion of aspirin (or other nonsteroidal anti-inflammatory agents) or  $\beta$ -adrenergic antagonists. The typical **aspirin-sensitive respiratory syndrome** primarily affects adults, although the condition may be seen in childhood. This problem usually begins with **perennial vasomotor rhinitis** that is followed by a **hyperplastic rhinosinusitis** with **nasal polyps**. Progressive asthma then appears. On exposure to even very small quantities of aspirin, affected individuals typically develop ocular and nasal congestion and acute, often severe episodes of airways obstruction. The prevalence of aspirin sensitivity in subjects with asthma varies from study to study, but many authorities feel that 10% is a reasonable figure. There is a great deal of cross-reactivity between aspirin and other nonsteroidal anti-inflammatory compounds. **Indomethacin, fenoprofen, naproxen, zomepirac sodium, ibuprofen, mefenamic acid, and phenylbutazone** are particularly important in this regard. On the other hand, **acetaminophen, sodium salicylate, choline salicylate, salicylamide, and propoxyphene** are well tolerated. The exact frequency of cross-reactivity with tartrazine and other dyes in aspirin-sensitive subjects with asthma is also controversial; again, 10% is the commonly accepted figure (Table 59.1). This peculiar complication of aspirin-sensitive asthma is particularly insidious, however, in that tartrazine and other potentially troublesome dyes are widely present in the environment and may be unknowingly ingested by sensitive patients.

Patients with aspirin sensitivity can be desensitized by daily administration of the drug. Following this form of therapy, cross-tolerance also develops to other NSAIDs. The mechanism by which aspirin and other such drugs produce bronchospasm has not yet been elucidated but may be related to aspirin-induced preferential generation of leukotrienes. Immediate hypersensitivity does not seem to be involved. The availability of effective inhibitors of **leukotriene** synthesis or receptor activity should aid materially in the treatment of this problem.  $\beta$ -Adrenergic antagonists regularly obstruct the airways in people with asthma as well as in others with heightened airway reactivity, and should be avoided by such individuals. Even the selective  $\beta_1$  agents have this propensity, particularly at higher doses. In fact, the local use of  $\beta_1$  blockers in the eye for the treatment of glaucoma has been associated with worsening asthma.

Sulfiting agents, such as **potassium metabisulfite, potassium and sodium bisulfite, sodium sulfite, and sulfur dioxide**, which are widely used in the food and pharmaceutical industries as sanitizing and preserving agents, can also produce acute airway obstruction in sensitive individuals. Exposure usually follows ingestion of food or beverages containing these compounds, e.g., salads, fresh fruit, potatoes, shellfish, and wine. Exacerbation of asthma has been reported following the use of sulfite-containing topical ophthalmic solutions, intravenous glucocorticoids, and some inhalational bronchodilator solutions. The incidence and mechanism of action of this phenomenon are unknown. When suspected, the diagnosis can be confirmed by either oral or inhalational provocations (see Habtemariam, 2000).



**TABLE 59.1**  
**Naturally Occurring Salicylates in Food**

	Type	mg/100 g
<b>Fruits</b>		
Apples	Granny Smith	0.59
	Jonathan	0.38
	Red Delicious	0.19
	Golden Delicious	0.08
Apricot, fresh		2.58
Avocado, fresh		0.60
Cantaloupe, fresh	Edible portion	1.50
Cherry, fresh	Sweet	0.85
Dates, dried		4.50
Figs, dried	Calamata	0.64
Grapes, fresh	Sultana	1.88
Grapefruit, fresh		0.68
Guava, canned		2.02
Kisi fruit, fresh		0.32
Lemon, fresh		0.18
Loquat, fresh		0.26
Mandarin, fresh		0.56
Mango, fresh		0.11
Mulberry, fresh		0.76
Nectarine, fresh		0.49
Orange, fresh		2.39
Passionfruit, fresh		0.14
Peach, fresh		0.58
Pear, fresh	With skin	0.31
Persimmon, fresh		0.18
Pineapple, fresh		2.10
Plum, fresh	Red	0.11
Pomegranate, fresh		0.07
Raisins, dried		6.62
Raspberries, fresh		5.14
Rhubarb, fresh		0.13
Strawberry, fresh		1.36
Tangelo, fresh		0.72
Watermelon, fresh		0.48
<b>Vegetables</b>		
Alfalfa, fresh		0.70
Asparagus, fresh		0.14
Beans, fresh	Broad	0.73
	Green (French)	0.11
Bean sprouts, fresh		0.06
Beets, fresh		0.18
Broccoli, fresh		0.65
Brussels sprouts, fresh		0.07
Carrot, fresh		0.23
Cauliflower, fresh		0.16
Chicory, fresh		1.02
Chickpeas, dried		0.00
Chives, fresh		0.03

**TABLE 59.1 (Continued)**  
**Naturally Occurring Salicylates in Food**

	Type	mg/100 g
Cucumber	No peel	0.78
Eggplant	With peel	0.88
Endive, fresh		1.90
Leek, fresh		0.08
Mushroom, fresh		0.24
Olive, canned	Black	0.34
	Green	1.29
Onion, fresh		0.16
Parsnip, fresh		0.45
Peas, fresh	Green	0.04
Peppers, fresh	Green chili	0.64
	Red chili	1.20
	Yellow chili	0.62
	Green sweet	1.20
Potato, fresh	White, with peel	0.12
Pumpkin, fresh		0.12
Radish, fresh	Red, small	1.24
Shallots, fresh		0.03
Spinach		
Fresh		0.58
Frozen		0.16
Squash	Baby	0.63
Sweet corn, fresh		0.13
Sweet potato, fresh	White	0.50
	Yellow	0.48
Tomato		
Fresh		0.13
Juice	Heinz	0.12
Paste	Campbell	0.57
Sauce	Heinz	2.48
Turnip, fresh		0.16
Watercress, fresh		0.84
Zucchini, fresh		1.04
<b>Spices</b>		
Allspice	Powder, dry	5.20
Aniseed	Powder, dry	22.80
Bay leaf	Leaves, dry	2.52
Basil	Powder, dry	3.40
Canella	Powder, dry	42.60
Cardamom	Powder, dry	7.70
Caraway	Powder, dry	2.82
Cayenne	Powder, dry	17.60
Celery	Powder, dry	10.10
Chili	Flakes, dry	1.38
	Powder, dry	1.30
Cinnamon	Powder, dry	15.20
Cloves	Whole, dry	5.74

*Continued.*

**TABLE 59.1 (Continued)**  
**Naturally Occurring Salicylates in Food**

	Type	mg/100 g
Coriander	Leaves, fresh	0.20
Cumin	Powder, dry	45.00
Curry	Powder, dry	218.00
Dill	Fresh	6.90
	Powder, dry	94.40
Fennel	Powder, dry	0.80
Fenugreek	Powder, dry	12.20
Five spice	Powder, dry	30.80
Garam masala	Powder, dry	66.80
Garlic	Bulbs, dry	0.10
Ginger	Root, fresh	4.50
Mace	Powder, dry	32.20
Mint	Garden, fresh	9.40
Mixed herbs	Leaves, dry	55.60
Mustard	Powder, dry	26.00
Nutmeg	Powder, dry	2.40
Oregano	Powder, dry	66.00
Paprika	Hot powder, dry	203.00
	Sweet powder, dry	5.70
Parsley	Leaves, fresh	0.08
Pepper	Black powder, dry	6.20
	White powder, dry	1.10
Pimiento	Powder, dry	4.90
Rosemary	Powder, dry	68.00
Sage	Leaves, dry	21.70
Soy Sauce	Liquid	0.00
Tabasco sauce	Liquid	0.45
Tarragon	Powder, dry	34.80
Turmeric	Powder, dry	76.40
Thyme	Leaves, dry	183.00
Vanilla	Essence, liquid	1.44
Worcestershire	Sauce, liquid	64.30
<b>Miscellaneous</b>		
<i>Alcohol</i>		
Benedictine		0.94
Brandy	Hennessy	0.40
Cointreau		0.66
Drambuie		1.68
Gin	Gilbey's	0.00
Rum	Captain Morgan	1.28
Tia Maria		0.83
Wine	Cabernet Sauvignon	0.86
	Champagne	1.02
	Claret	0.90
	Claret (reserve)	0.35
	Dry white	0.10
	Riesling	0.81
	Rose Vermouth	0.37
		0.46

**TABLE 59.1 (Continued)**  
**Naturally Occurring Salicylates in Food**

	Type	mg/100 g	
<i>Beverages</i>			
Coca-Cola	Liquid	0.25	
Coffee	International Roast	0.96	
	Maxwell House Instant (powder)	0.84	
	Nescafe Instant (granules)	0.59	
	Herbal tea	Chamomile, bag	0.06
	Fruit, bag	0.36	
	Peppermint, bag	1.10	
	Rose hip, bag	0.40	
Tea	Burmese green, leaves	2.97	
	Bushells, bag	4.78	
	Golden Days decaf, bag	0.37	
	Harris, bag	4.00	
	Indian green, leaves	2.97	
	Peony Jasmine, leaves	1.90	
	Old Chinese, leaves	1.90	
	Tetley, bag	5.57	
	Twinings		
		Earl Grey, bag	3.00
	English Breakfast, bag	3.00	
<b>Negligible</b>			
<i>Cereals</i>			
Maize	Meal, dry	0.43	
<i>Dairy</i>			
Cheese	Blue Vein	0.05	
	Camembert	0.01	
	Mozzarella	0.02	
<i>Meats</i>			
Liver	Fresh	0.05	
Prawn	Fresh	0.04	
Scallop	Fresh	0.02	

*Note:* Pain serves the useful function of alerting an individual that some component of a physiological system has gone awry. Ideally, the pain can be alleviated by removal of the underlying cause. In many situations, however, the stimulus of the pain is either not easily defined or is not readily removable. Therefore, the physician is often faced with the necessity of treating pain as a symptom. Aspirin, a member of the salicylate family, is the most extensively employed analgesic agent. Of the remaining nonnarcotic analgesic drugs, only two aniline derivatives, acetaminophen and phenacetin, and one arylalkanoic acid derivative, ibuprofen, are sufficiently safe to be used in general, nonprescription preparations. Although other agents have important therapeutic applications, toxicity limits their usefulness.

*Source:* From Swain, A.R., Dutton, A.P., and Truswell, A.S., Salicylates in foods, *J. Am. Diet Assoc.*, 85, 950–960, 1985.

## ASPIRIN AND OTHER NATURAL INHIBITORS OF TUMOR NECROSIS FACTOR- $\alpha$ PRODUCTION, SECRETION, AND FUNCTION

**Tumor necrosis factor (TNF)** (also known as **cachectin**) was originally discovered by its antitumor activity, but it is now recognized to be one of the most pleiotropic cytokines acting as a host defense factor in immunological and inflammatory responses. Among its many different activities, TNF has effects on the vascular endothelium, which lead to upregulation of various cell adhesion molecules such as intercellular **adhesion molecule-1 (ICAM-1)**, **vascular cell adhesion molecule-1 (VCAM-1)**, and **endothelial-leucocyte adhesion molecule-1 (ELAM-1)**. The regulated expression of these adhesion molecules and their counterreceptors on leucocytes mediates the adhesion and extravasation of white blood cells during inflammatory reaction. Although mediation of inflammation and antitumor activity by TNF could be beneficial to the host, overproduction of TNF is the basis for the development of various diseases. There is now overwhelming evidence to suggest that TNF mediates the **wasting disease**, cachexia, associated with chronic diseases such as cancer and AIDS. TNF also plays pivotal roles in the development of pathologies such as **disseminated intravascular coagulation** and death in septic shock and **cerebral malaria**, and a range of inflammatory diseases including **asthma**, **dermatitis**, **multiple sclerosis**, **inflammatory bowel disease**, **cystic fibrosis**, **rheumatoid arthritis**, **multiple sclerosis**, and **immunological** diseases. It is thus clear that suppression of TNF production/release or inhibition of its function could benefit in the treatment of these TNF-mediated diseases (Janeway and Travers, 1994).

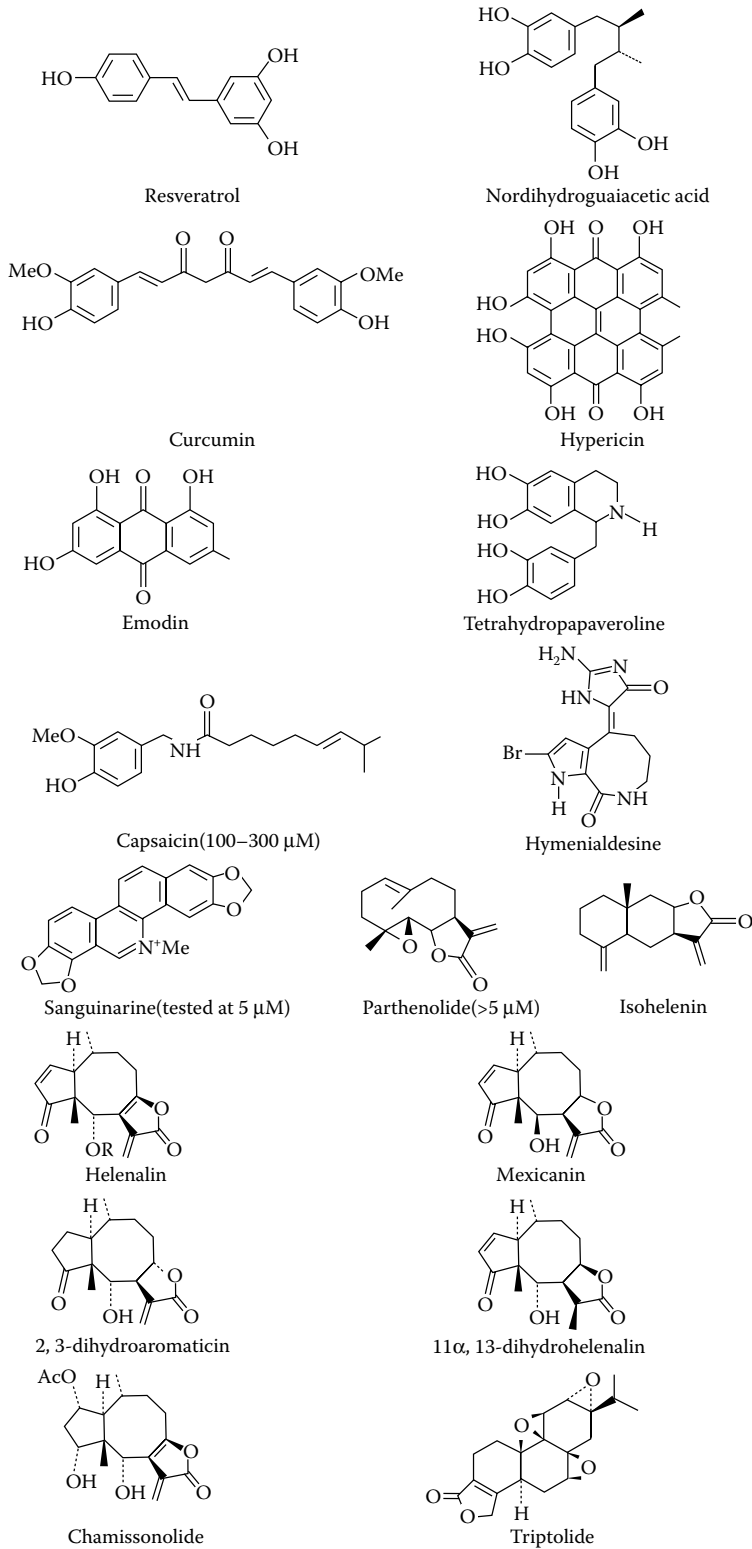
Potential target sites for inhibitory small-molecular-weight natural products could be broadly divided into three areas:

1. Inhibition of TNF production and secretion
2. TNF receptor antagonism
3. Inhibition of TNF function through modulation of its signal transduction pathways

### INHIBITION OF TNF PRODUCTION AND SECRETION

Monocytes and macrophages are the principal TNF factories in the body, but it has now emerged that other cell types including T lymphocytes, mast cells, neutrophils, keratinocytes, astrocytes, microglial cells, smooth muscle cells, and many others are known to produce TNF. The induced (e.g., by **bacterial endotoxins** and **proinflammatory cytokines**) release of TNF from most of these cells requires *de novo* protein synthesis, which can be targeted by drugs at transcriptional, translational, and posttranslational levels. It is now well established that one crucial step in the transcriptional activation of TNF gene is the transcription factor, NF- $\kappa$ B mobilization. NF- $\kappa$ B is sequestered in the cytoplasm by **inhibitory proteins I $\kappa$ B**, which are phosphorylated by a cellular kinase, leading to degradation and translocation of NF- $\kappa$ B to the nucleus. The potential target of NF- $\kappa$ B in TNF-mediated diseases is evident, because inappropriate regulation of NF- $\kappa$ B has been shown to be associated with diseases such as septic shock, graft vs. host reaction, acute inflammatory condition, acute-phase response, radiation damage, atherosclerosis, and cancer. Of the known natural inhibitors of TNF production (Figure 59.1), the two classical anti-inflammatory agents **aspirin** and **salicylic acid** have been shown to act *in vitro* through inhibition of I $\kappa$ B degradation and the subsequent inhibition of NF- $\kappa$ B activation. Other anti-inflammatory agents reported for inhibition (at  $\mu$ M concentration range) of NF- $\kappa$ B activation and the subsequent TNF release include **resveratrol** and **quercetin**, **nordihydroguaiaretic acid**, **butylated hydroxyanisole** and **tetrahydropapaveroline**, **curcumin**, **myricetin**, **epigallocatechin-gallate**, **4-hydroxy-2-nonenal**, and **capsaicin**.

Although the underlying mechanism has not yet been clearly established, many other natural products have been shown to inhibit TNF production. These include the antipsoriatic phenolic



**FIGURE 59.1** Structure of naturally occurring inhibitors of TNF production/function.

compound **anthraline**, **lignans-woorenosides II-V**, **lariciresinol glycoside**, **pinoresinol**, **eudesmin** and, to some extent, **magnolol** and **lirioresinol-B dimethyl ether**; **flavonoids** — **naringin**, **epicatechin**, some **isoprenoid-substituted flavones** of *Artocarpus* spp., namely, **heterophyllin**, **artocarpin E**, **artobiloxanthone**, **cycloartobiloxanthone**, **cycloheterophyllin**, and **morusin**, and **silymarin**, which is known to be a mixture of **silydianin** and **silibinin**; **alkaloids** — **anisodamine**, **quinine** (at concentrations that block potassium channels), **fangchinoline**, **isotetrandrine**, and **colchicine**; **terpenoids** — **cynaropicrin**, **reynosin**, **santamarin**, and **dehydrocostus lactone** and the anti-inflammatory **saponin**, **esculentoside A**, both of which have also been shown to suppress the serum level of TNF *in vivo*; long-chain fatty acids - $\omega$ -fatty acids of fish oil origin, **docosahexaenoic acid (DHA)** and **eicosahexaenoic acid (EPA)**, but also to some extent saturated fatty acids, **stearic acid**, **palmitic acid**, and **anandamide**. The hepatoprotective compound, **tetrahydroswertianolin**, which inhibits the d-galactoseamine (DGalN)/LPS liver injury, has been shown to suppress the serum level of TNF. Of the fungal metabolites, the immunosuppressive agent **cyclosporin A** has been demonstrated to suppress TNF production both *in vitro* and *in vivo*. Another fungal metabolites of interest are **trichodimerol** and **tetracycline**, both of which have been shown to inhibit TNF secretion. Inhibition of TNF release at higher concentrations (mM range) of the antibiotic tetracycline has been shown to be associated with retention of membrane-associated TNF, suggesting possible metalloproteinase blocking activity. Processing of the TNF precursor (pro-TNF) to mature biologically active TNF by metalloproteinases has been one of the anti-inflammatory target sites for synthetic agents. The other possible natural metalloproteinase inhibitor is the immunosuppressive and psychoactive agent  $\Delta^9$ -**tetrahydrocannabinol**, which has been reported to inhibit TNF production through action at a posttranscriptional level. Other natural products of fungal origin with TNF production inhibitory effects are the antibiotic **erythromycin**, **cytochalasin D**, the toxic metabolite **aflatoxin B<sub>1</sub>**, and known kinase inhibitors **herbimycin A** and **staurosporin**.

### INHIBITORS OF TNF-MEDIATED CYTOTOXICITY

Although TNF toxicity to tumor cells and augmentation of this effect by drugs could be beneficial, the unwanted systemic cytotoxicity of TNF associated with various diseases needs to be modulated. As with TNF release, the cytotoxic response of TNF could be targeted at the various levels of TNF signaling. Experimentally, potential inhibitors of TNF cytotoxicity could easily be studied using TNF-sensitive cell lines, including by far the most commonly used, L929 cells. In the presence of protein synthesis inhibitors such as **actinomycin D** (usually 2  $\mu\text{g/ml}$ ), TNF induces DNA fragmentation within 6 h followed by cell death within 24 h. Based on this L929 cell-based bioassay, a number of phenolic compounds (**3,4-dihydroxybenzoic acid** and **caffeic acid** and also neurotransmitters **dopamine** and **noradrenaline**), which possess the catecholic functional moiety, have been shown to suppress TNF cytotoxicity. These effects of catechols, including that of **nordihydroguaiaretic acid**, are not related to their antioxidant action, because related antioxidants failed to protect cells from TNF cytotoxicity. Further studies on the mechanism of action of catechols revealed that inhibition of TNF cytotoxicity by catechols is related to their iron-chelating activity and the subsequent inhibition of **lipoxigenase enzymes**. On the basis of these findings, large numbers of flavonoids were tested for their inhibitory effect on TNF cytotoxicity *in vitro*. It appears that all **flavonols** tested (**galangin**, **kaempferol**, **kaempferide**, **quercetin**, **myricetin**, **morin**, and **rutin**) inhibited TNF cytotoxicity and the C-3 free hydroxy group of these structural groups appears to play a pivotal role in the observed protective effect. In contrast to this protective effect of flavonols, no protective activity was observed for the **flavones** (**chrysin**, **apigenin**, and **luteolin**) tested. In fact, **apigenin** and **chrysin**, which possess one (C-4') hydroxy group or none on the B-ring, respectively, enhanced the TNF cytotoxicity. **Epicatechin** and **flavanones** that bear the catecholid functional moiety (**eriodictyol** and **taxifolin**) were protective, whereas other flavanones without this *o*-dihydroxy functionality either failed to protect (**pinocembrin**, **isosakuranetin**, **hesperetin**) or enhanced (**naringenin**) TNF cytotoxicity. It is worth noting that all protective flavonoids and

other catecholic compounds were effective when they were added as post-TNF treatment. Because some of the flavonoids showed enhancement of TNF cytotoxicity, the clinical use of such compounds for inhibition of TNF cytotoxicity needs detailed analysis of their structural moiety *ex vivo* and *in vivo*.

Other agents that have been reported to inhibit TNF cytotoxicity *in vitro*, but with as yet unknown mechanism of action, include butylated **hydroxyanisol**, **pyridoxin**, **retinoic acid (vitamin A**, both the *cis* and *trans* form) and, to a lesser extent, **carotene**. Two **lignanamides**, **tribulusamides A** and **B**, have been shown to inhibit TNF cytotoxicity in DGalN-sensitized cultured mouse hepatocytes, and the **sesquiterpene lactones** **germacrone**, **neocurdione**, **curdione**, and **curcumenol** have been reported to inhibit *in vivo* liver injury induced by coadministration of TNF and DGalN. These latter compounds, as well as **gentiopicroside** and **sweroside**, have also been shown to inhibit the endotoxin/DGalN-induced liver injury *in vivo*, which is now known to be TNF dependent. Whether the compounds act through direct inhibition of the TNF-induced cytotoxicity in liver cells, however, remains to be proved.

In conclusion, although the complete biochemical pathways for TNF production and action have yet to be fully elucidated, several target sites have been identified. Of these targets, the transcription factor NF- $\kappa$ B is most interesting because NF- $\kappa$ B regulates TNF production and, in turn, TNF regulates NF- $\kappa$ B reciprocally to produce its biological effects. A number of natural products widely known for their anti-inflammatory activities have been shown to modulate TNF release and function through suppression of NF- $\kappa$ B activation. Other targets for natural products that have been demonstrated to inhibit TNF production are kinase enzymes and the cAMP system. There appear to be very few compounds inhibiting TNF production/function at the posttranslational level and the long-awaited TNF receptor antagonist is still not available (see Habtemariam, 2000).





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# 60 Sex Herbs

## INTRODUCTION

The following herbs are used to improve sexual function:

- **Anise** imitates the female hormone estrogen, increasing sexual intensity and satisfaction
- **Epimedium**, a Chinese herb, has a testosterone-like substance and enhances a woman's sexual desire
- **Fenugreek** augments breast size and is used to elevate sex drive
- **Fennel** prolongs orgasm, allowing men to enjoy sex for a longer period of time
- **Guarana** seed tea has aphrodisiac effect
- **Quebracho** (in South America) and **Sheng Jing** (in China) are used in male infertility and erectile dysfunction (impotence)

**Erectile dysfunction** (ED) is a condition defined by the inability to attain or maintain penile erection sufficient for satisfactory sexual intercourse (Roybal and Skowronski, 1999; Bivalacqua and Hellstrom, 2001; Giuliano and Rampin, 2000; Salonia et al., 2003). In 1995, it was estimated that approximately 152 million men worldwide suffered from ED, with projections for 2025 growing to a prevalence of 322 million affected men. In the past, ED was believed to be caused by nonspecific psychological causes; however, in the past two decades, the majority of cases have been attributed to an organic etiology. Although ED patients can have a number of medical conditions, organic ED is usually associated with vascular risk factors such as arteriosclerosis, hypertension, diabetes mellitus, Peyronie's disease, and renal disease. In addition, pelvic trauma and pelvic surgery (radical prostatectomy or radical cystectomy) can cause ED by either vascular or nerve damage.

Since the early 1980s, understanding about the pharmacology of the erectile mechanism has advanced significantly. Basic research in corporal cavernosal smooth muscle (CCSM) physiology and identification of the central mediators involved in the erectile process has contributed to the development of pharmacological agents that can effectively treat ED patients. At present, the diagnosis and treatment of ED has evolved to the point where virtually every patient suffering from ED can be successfully treated. **Vacuum erection devices, intracavernosal injection therapy, intraurethral suppositories**, oral medications, **penile vascular procedures**, and **surgical implantation of prosthetic devices** offer most men a viable option to correct their ED. However, despite the overall success and efficacy of the aforementioned therapies, there are implicit side effects, complications, and contraindications. Therefore, the development of future therapeutic options for the treatment of ED should focus on those strategies with fewer adverse effects and an absence of contraindications. Gene therapy for the treatment of ED may become a viable and relatively noninvasive therapeutic option (Bivalacqua and Hellstrom, 2001).

## IMPOTENCE

A variety of endocrine, vascular, neurological, and psychiatric diseases disrupt normal sexual and reproductive function in men. Furthermore, sexual dysfunction may be the presenting symptom of systemic disease.

## NORMAL SEXUAL FUNCTION

Penile erection is initiated by neuropsychological stimuli that ultimately produce vasodilation of the sinusoidal spaces and arteries within the paired corpora cavernosa. Erection is normally preceded by **sexual desire** (or **libido**), which is regulated in part by androgen-dependent psychological factors. Although nocturnal and diurnal spontaneous erections are suppressed in men with androgen deficiency, erections may continue for long periods in response to erotic stimuli. Thus, the continuing action of testicular androgens appears to be required for normal libido but not for the erectile mechanism itself.

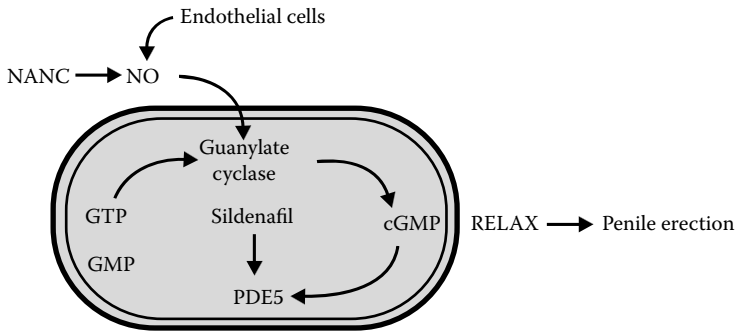
The penis is innervated by sympathetic, parasympathetic, and somatic fibers. Somatic fibers in the dorsal nerve of the penis form the afferent limb of the erectile reflex by transmitting sensory impulses from the penile skin and glans to the S2–S4 dorsal root ganglia via the pudendal nerve (Giuliano and Rampin, 2000; Salonia et al., 2003). Unlike the corpuscular-type endings in the penile shaft skin, most afferents in the glans terminate in free nerve endings. The efferent limb begins with parasympathetic preganglionic fibers from S2–S4 that pass in the pelvic nerves to the pelvic plexus. Sympathetic fibers emerging from the intermediolateral gray areas of T11–L2 travel through the paravertebral sympathetic chain ganglia, superior hypogastric plexus, and hypogastric nerves to enter the pelvic plexus along with parasympathetic fibers. Somatic efferent fibers from S3–S4 that travel in the **pudendal nerve** to the ischiocavernosus and bulbocavernosus muscles and postganglionic sympathetic fibers that innervate the smooth muscle of the epididymis, vas deferens, seminal vesicle, and internal sphincter of the bladder mediate rhythmic contraction of these structures at the **time of ejaculation**.

Autonomic nerve impulses, integrated in the pelvic plexus, project to the penis through the cavernous nerves that course along the posterolateral aspect of the prostate before penetrating the pelvic floor muscles immediately lateral to the urethra. Distal to the membranous urethra, some fibers enter the corpus spongiosum, whereas the remainder enter the corpora cavernosa along with the terminal branches of the pudendal artery and exiting cavernous veins. If disruption of the cavernous nerves occurs following pelvic trauma or surgery, erectile impotence may ensue.

The brain exerts an important modulatory influence over spinal reflex pathways that control **penile function** (Giuliano and Rampin, 2000). A variety of visual, auditory, olfactory, and imaginative stimuli elicit erectile responses that involve cortical, thalamic, rhinencephalic, and limbic input to the medial preoptic-anterior hypothalamic area, which acts as an integrating center. Other areas of the brain, such as the **amygdaloid complex**, may inhibit sexual function.

Although the parasympathetic nervous system is the primary effector of erection, the transformation of the penis to an erect organ is a vascular phenomenon. In the flaccid state the arteries, arterioles, and sinusoidal spaces within the corpora cavernosa are constricted due to sympathetic-mediated contraction of smooth muscle in the walls of these structures. The venules between the sinusoids and the **densetunica albuginea** surrounding the cavernosa open freely to the emissary veins. Erection begins when relaxation of the sinusoidal smooth muscles leads to dilation of the sinusoids and a decrease in peripheral resistance, causing a rapid increase in arterial blood flow through internal **pudendal and cavernosa arteries**. Expansion of the sinusoidal system compresses the venules against the interior surface of the tunica albuginea, resulting in venous occlusion. The increase in intracorporeal pressure leads to rigidity; less than complete expansion of the sinusoidal spaces leads to less than complete rigidity.

Erection occurs when adrenergic-induced sinusoid tone is antagonized by sacral parasympathetic stimulation that produces sinusoidal relaxation primarily by synthesis and release of the nonadrenergic-noncholinergic (NANC) neurotransmitter **nitric oxide (NO)**. The contribution of acetylcholine-dependent release of NO from the vascular endothelium is uncertain. *In vitro* electrical stimulation of isolated corpus cavernosum strips (with or without endothelium) produces sinusoidal relaxation by release of neurotransmitters within nerve terminals that is resistant to adrenergic and cholinergic blockers. Inhibitors of the synthesis of NO or of **guanosine monophosphate (GMP)**,



**FIGURE 60.1** Mechanism of action of sildenafil in corpus cavernosal smooth muscle cells. NANC: Non-adrenergic, noncholinergic; NO: nitric oxide; PDE5: Phosphodiesterase Type 5.

as well as **nitric oxide scavengers**, block sinusoidal relaxation (Figure 60.1). A variety of neuropeptides found in corporal tissues, including **vasoactive intestinal peptide (VIP)** and **calcitonin gene-related peptide (CGRP)**, produce tumescence when injected into the penis but have uncertain physiological roles. Norepinephrine plays an important role in the adrenergic mechanism of detumescence (Gingell and Lockyer, 1999).

**Seminal emission** and **ejaculation** are under control of the sympathetic nervous system. Emission results from  $\alpha$ -adrenergic-mediated contraction of the **epididymis**, **vas deferens**, **seminal vesicles**, and **prostate**, which causes seminal fluid to enter the prostatic urethra. Concomitant closure of the bladder neck prevents retrograde flow of semen into the bladder, and antegrade ejaculation results from contraction of the muscles of the pelvic floor including the bulbocavernosus and *ischiocavernosus muscles*.

**Orgasm** is a psychosensory phenomenon in which the rhythmic contraction of the pelvic muscles is perceived as pleasurable. Orgasm can occur without either erection or ejaculation or in the presence of retrograde ejaculation (Gingell and Lockyer, 1999).

## FAILURE OF ERECTION

The organic causes of erectile impotence can be grouped into endocrine, drug, local, neurological, and vascular causes (Table 60.1).

## THERAPY

**Sheng Jing** (Table 60.2) has been tested in 202 patients, given twice a day for 60 d. The results showed “a significant improvement in sperm density, motility and grade, levels of **follicle-stimulating hormone (FSH)**, **luteinizing hormone (LH)**, and **testosterone (T)** and reduction in serum anti-sperm antibody titers. Sperm density increased from  $16.2 \times 10^6/\text{ml}$  to  $56.1 \times 10^6/\text{ml}$ . Sperm density in men with severe oligospermia ( $2.1 \times 10^6/\text{ml}$ ) also experienced significant improvements ( $17.9 \times 10^6/\text{ml}$ ). Sperm motility increased from 34% to 46%. They reported a 78% pregnancy rate in the 148 couples available for follow-up” (Crimmel et al., 2001).

In addition, the efficacy of **acupuncture** on penile erection has been tested. Organic disease was excluded by a combination of nocturnal penile tumescence monitoring and pharmacologically enhanced duplex ultrasonography. Twenty-nine patients with a mean age of 40 years received a series of ten treatments over a 4-week period. If no improvement was observed, they received a second course of ten treatments. Mean follow-up was 8 months. Of the patients, 69% demonstrated successful results, defined as having two or more erections per week that were satisfactory for intercourse (Crimmel et al., 2001).

**TABLE 60.1**  
**Some Organic Causes of Erectile Impotence in Men**

	<b>Endocrine Causes</b>
Testicular failure	
Hyperprolactinemia	
	<b>Drugs</b>
<i>Antiandrogens</i>	
Histamine (H <sub>2</sub> ) blockers (e.g., cimetidine)	
Spironolactone	
Ketoconazole	
Finasteride	
<i>Antihypertensives</i>	
Central-acting sympatholytics (e.g., clonidine and methyldopa)	
Peripheral-acting sympatholytics (e.g., guanadrel)	
β-blockers	
Thiazides	
<i>Anticholinergics</i>	
<i>Antidepressants</i>	
Monoamine oxidase inhibitors	
Tricyclic antidepressants	
<i>Antipsychotics</i>	
<i>Central nervous system depressants</i>	
Sedatives (e.g., barbiturates)	
Antianxiety drugs (e.g., diazepam)	
<i>Drugs of habituation or addiction</i>	
Alcohol	
Methadone	
Heroin	
Tobacco	
	<b>Penile Diseases</b>
Peyronie's disease	
Previous priapism	
Penile trauma	
	<b>Neurological Diseases</b>
Anterior temporal lobe lesions	
Diseases of the spinal cord	
Loss of sensory input	
Tabes dorsalis	
Disease of dorsal root ganglia	
Disease of nervi erigentes	
Radical prostatectomy and cystectomy	
Rectosigmoid operations	
Diabetic autonomic neuropathy and various polyneuropathies	
	<b>Vascular Diseases</b>
Aortic occlusion (Leriche syndrome)	
Atherosclerotic occlusion or stenosis of the pudendal or cavemosa arteries	
Arterial damage from pelvic radiation	
Venous leak	
Disease of the sinusoidal spaces	

*Note:* Sexuality is an integral part of one's identity; it is a reflection of how one feels about oneself and how one interacts with others. Sexual function refers to the physiological ability to perform in a sexually satisfying manner, with or without a partner. Drugs can influence both sexuality and sexual function.

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**TABLE 60.2**  
**Ingredients of the Chinese Herbal Formula Sheng Jing**

Western Name	Chinese Name
Antler gelatin	Lu jiao jiao
Epimedium	Yin yang huo
Curculigo	Xian mao
Cherokee rosa	Jin ying zi
Schizandra	Wu wei zi
Loranthus	Sang Ji Sheng
Rehmannia	Shu di huang
Lycium	Gou qi zi
Cuscuta	Tu si zi
Dendrobium	Shi hu
Morinda	Ba Ji Tian
Rubus	Fu Pen Zi
Achyranthes	Huai niu xi
Scripus	San leng
Zedoaria	E zhu

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### DRUGS THAT STIMULATE SEXUAL BEHAVIOR

Various clinically used or experimental drugs enhance sexual interest or potency as a side effect in humans.

#### LEVODOPA

Levodopa (L-dopa) is a natural intermediate in the biosynthesis of catecholamines in the brain and peripheral adrenergic nerve terminals. In the biologic sequence of events it is converted to dopamine, which in turn serves as a substrate of the neurotransmitter norepinephrine. Levodopa is used successfully in the treatment of **Parkinson's syndrome**, a disease characterized by dopamine deficiency. When levodopa is administered to an individual with this syndrome, the symptoms of Parkinson's disease are ameliorated, presumably because the drug is converted to dopamine and thereby counteracts the deficiency. Individuals treated with levodopa, especially older men, have been observed to experience a **sexual rejuvenation**. This effect has led to the belief that levodopa stimulates sexual powers. Consequently, studies with younger men complaining of decreased erectile ability have shown that levodopa increases libido and the incidence of penile erections. Overall, however, these effects are short lived and do not reflect continued satisfactory sexual function and potency. Thus, levodopa is not a true aphrodisiac. The increased sexual activity experienced by parkinsonian patients treated with levodopa may reflect improved well-being and partial recovery of normal sexual functions that were impaired by Parkinson's disease.

#### AMYL NITRITE

Amyl nitrite, a drug used in the past to treat **angina pectoris**, is alleged to enhance sexual activity in humans. As a vasodilator and smooth muscle stimulant, amyl nitrite has been reported to intensify the orgasmic experience for men if inhaled at the moment of orgasm. This effect is probably the result of relaxation of smooth muscles and consequent vasodilation of the genitourinary tract. No effects of amyl nitrite on libido have been reported, but a loss of erection or delayed ejaculation may result. Women generally experience negative effects on orgasm when taking this drug.

## VITAMIN E

Much has been said about the positive effects of vitamin E ( $\alpha$ -tocopherol) on sexual performance and ability in humans. Unfortunately, there is little scientific rationale to substantiate such claims. The primary reasons for attributing a positive role in sexual performance to vitamin E come from experiments on vitamin E deficiency in laboratory animals. In such experiments the principal manifestation of this deficiency is infertility, although the reasons for this condition differ in males and females. In female rats there is no loss in ability to produce apparently healthy ova, nor is there any defect in the placenta or uterus. However, fetal death occurs shortly after the first week of embryonic life, and fetuses are reabsorbed. This situation can be prevented if vitamin E is administered any time up to day 5 or 6 of embryonic life. In the male rat the earliest observable effect of vitamin E deficiency is immobility of spermatozoa, with subsequent degeneration of the germinal epithelium. Secondary sex organs are not altered and sexual vigor is not diminished, but vigor may decrease if the deficiency continues.

Because of experimental results such as these, vitamin E has been conjectured to restore potency or to preserve fertility, sexual interest, and endurance in humans. No evidence supports these contentions, but because sexual performance is often influenced by mental attitude, a person who believes vitamin E may improve sexual prowess may actually find improvement. The only established therapeutic use for vitamin E is for the prevention or treatment of vitamin E deficiency, a condition that is rare in humans.

## SILDENAFIL (VIAGRA)

Sildenafil increases the release of **nitric oxide** and increases the levels of **cyclic guanosine monophosphate (cGMP)**, a smooth muscle relaxant. Sildenafil enhances the effects of nitric oxide by inhibiting **phosphodiesterase 5**, an enzyme found primarily in the penis that degrades cGMP. As a result, increased levels of cGMP in the corpus cavernosum enhance smooth muscle relaxation, the inflow of blood, and erection. Sildenafil has no effect in the absence of sexual stimulation (see Figure 60.1).

This is an exciting new era in the treatment of ED. Since the development of such a highly effective oral preparation as sildenafil, much more research activity will be generated to produce competing therapies. Locally applied, rapidly absorbed preparations will almost certainly have a role to play. Combination therapy has to date not been extensively studied. The potential of utilizing centrally acting drugs or sildenafil in combination with locally applied preparations in the more clinically challenging patient is an exciting therapeutic opportunity. Much as been achieved in the past 15 years in the field of andrological research and much will be achieved in the very near future for the benefit of patients (Gingell and Lockyer, 1999).

## EMERGING PHARMACOLOGICAL THERAPIES FOR ERECTILE DYSFUNCTION

In addition to **Sheng Jing** and acupuncture, which are old (Crimmel et al., 2001), and gene therapy, which is novel and new (Bivalacqua and Hellstrom, 2001), other emerging therapeutics for erectile dysfunction are the following:

- Phosphodiesterase inhibitors (**sildenafil, viagra**)
- Cyclic AMP activators (**vasoactive intestinal polypeptide**)
- $\alpha$ -Adrenergic receptor antagonists (**phentolamine, yohimbine**)
- Dopaminergic receptor agonists (**apomorphine**)
- $\alpha$ -Melonocyte stimulating hormone
- Potassium channel modulators

- Endothelin antagonists
- Nitric oxide donors
- Drugs topically applied to penis (transdermal or transglandular nitroglycerine, capsaicine, papaverine, or prostaglandin E<sub>1</sub>)
- **Viagra (Sildenafil)** — In March 1998, the FDA announced that Viagra®, a new drug from Pfizer, Inc., has been approved as treatment for male sexual dysfunction
- **Cialis (Tadalafil)** — Works fast — within 30 min in some patients — and can work up to 36 hours.
- **Vardenafil (Levitra)** — Levitra is an FDA-approval oral prescription medication for the treatment of ED in men.

The **Herbal Virility** herbs and minerals have been claimed to show specific improvements in the following areas:

- **Catuaba (bark)** — Increases libido, relieves fatigue, aphrodisiac, nerve tonic.
- **Tribulus (aerial)** — Boosts testosterone levels and sperm production, aids in increasing libido and male infertility.
- **L-Arginine (HCL)** — Increases blood flow to the genital area and gives erections that are harder, last longer and can be more frequent.
- **Asian ginseng (root)** — Arousing, stimulating, energy enhancing effect. Increases physical performance and activity.
- **Orchic substance (bovine)** — Extract from bovine testes used to increase testosterone levels.
- **Maca (tuber)** — Aphrodisiac, increases sexual desire, may help to increase sperm count.
- **Stinging nettle (leaves)** – Body tonic, rich nutritional content of vitamins and minerals, helps in recovery and preventing exhaustion.
- **Orexis ingredients:**
  - **Tribulus terrestris** — A plant found throughout Australia, Asia, Africa, and North and South America. It contains saponins, polysaccharides, sterols, flavonoids, and fatty acids, many of which are indicated to have general health benefits. *Tribulus terrestris* is a natural testosterone enhancer, shown in clinical studies to increase testosterone levels by aiding in the production of the luteinizing hormone (LH), a hormone that influences sex drive. Tribulus terrestris has been used to increase fertility and aid impotence.
  - **Epimedium** — An important supplement in traditional Chinese medicine and is gaining popularity in Western homeopathy as well. Epimedium is a leafy plant that grows best at higher altitudes. Its leaves contain a variety of healthful flavonoids, polysaccharides, and sterols, as well as an alkaloid called **magnafloine**. Its exact mechanism of action is still somewhat a mystery, but it has shown success for many years in boosting sexual desire, aiding erectile function, and fighting fatigue. Clinical practitioners have long used epimedium to treat erectile problems, to improve libido, and to restore sexual vitality.
  - **Yohimbe extract** — Yohimbe (*Pausinystalia yohimbe*) is an evergreen botanical native to Africa containing a substance called **yohimbine**, together with additional similar compounds called *indole alkaloids*. Synthesized yohimbine has been used medicinally for many decades. Yohimbe is a traditional male aphrodisiac recognized worldwide for the treatment of impotence. Today, the drug yohimbine is considered an effective treatment for erectile dysfunction. Yohimbine acts similar to Viagra and increases penile blood flow, and may also increase the amount of cGMP, a substance required for the stimulation and maintenance of erections.



- **Muirá pauma** — **Muirá puama** is a native shrub of Brazil. It has long been used to improve libido and increase sexual potency.
- ***Panax ginseng*** — Ginseng is traditionally used to overcome general weakness and deliver extra energy. It also has demonstrated aphrodisiac powers. Used to combat impotence, infertility, and premature ejaculation, it normalizes blood pressure while rejuvenating and revitalizing the body. It also promotes the growth of nerve tissue. A key ingredient of ginseng is **ginsenoside**, which alters blood flow to the brain and penis and can build blood and sperm.
- **Catuaba bark extract** — Catuaba has a long history in herbal medicine as an aphrodisiac. The Tupi Indians in Brazil first discovered the qualities of the plant Andover the last centuries.
- **Damiana** (*Turnera aphrodisiaca*) — Found throughout Mexico, Central America, and the Caribbean, the Latin name of this herb suggests its use as an **aphrodisiac**.
- **Orexis** is advertised to increase sexual performance immediately and effectively.

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# 61 Sponges and Steroids

## INTRODUCTION

All marine organisms have been proved to be a veritable cornucopia of unusual steroid metabolites, but some believe that marine sponges may provide the most diverse and biogenetically unprecedented array of unconventional steroids in the entire animal kingdom. These steroids are potent inhibitors of histamine release, are anti-inflammatory agents, immunosuppressants, antineoplastic agents, and antiviral agents. However, their full therapeutic potential remains to be delineated.

Unconventional steroids often co-occur with conventional ones and are sometimes present in small amounts; however, many exceptions are reported for some sponges that are found with unusual structures as the predominant steroids rather than cholesterol or the conventional 3,β-hydroxy sterols. It is, therefore, particularly interesting when a sponge contains unusual steroids in large quantities, as these very likely play a functional (rather than metabolic) role in maintaining the integrity of membranous structures. It has been hypothesized and, to some extent, documented that the uniqueness of sterols in cell membranes of sponges is related to the other membrane components, particularly the phospholipids. These latter compounds seem to have head groups and fatty acids very different from those of higher animals; therefore, the structural modifications exhibited by the sponge sterols may be a sort of structural adjustments for a better fit with other membrane components.

The highly functionalized steroids have recently attracted considerable attention because of their biological and pharmacological activities. Remarkable examples are **herbasterol** (which is **ichthyotoxic**) **xestobergsterols**, and **contignasterol**, potent inhibitors of histamine release from rat mast cells induced by anti-IgE, and **halistanol disulfate B**, an endothelin-converting enzyme inhibitor. Most of the oxygenated cholesterol derivatives have been shown to exert a cytotoxic activity on human cancer cells lines *in vitro*. Also, enzymatic transformations leading to **secosterols**, i.e., ring cleavage products of cholesterol, may result in the formation of products with cell division-inhibitory properties. Finally, the recent discovery of the antiviral properties of **sulfated polyhydroxysterols** has increased interest in these compounds (see Aiello et al., 1999).

## EXAMPLES OF STEROIDS FOUND IN SPONGES

### POLYOXYGENATED STEROIDS

Six new **3β,5,6β-trihydroxysterols** with a saturated nucleus have been isolated from two different populations of the sponge *Cliona copiosa*, collected from two different sites of the bay of Naples. Successively, several new **D5-3β-hydroxy-7-ketosteroids** and the related  $\Delta^5$ -**3β, 7β**, and  $\Delta^5$ -**3β,7α-dihydroxysteroids** have been described as constituent of the same species.

### STEROID SULFATES

Several **sulfated polyhydroxysterols** have been recently isolated from sponges. Most of these natural products are characterized by the **2β,3α,6α-tri-O-sulfate** functions together with additional alkylation in the side chain. These steroids are of interest not only because of their structures but

also because of their physiological activities, which include an **antihuman immunodeficiency virus** (HIV) effect and a high inhibitory action on some enzymes.

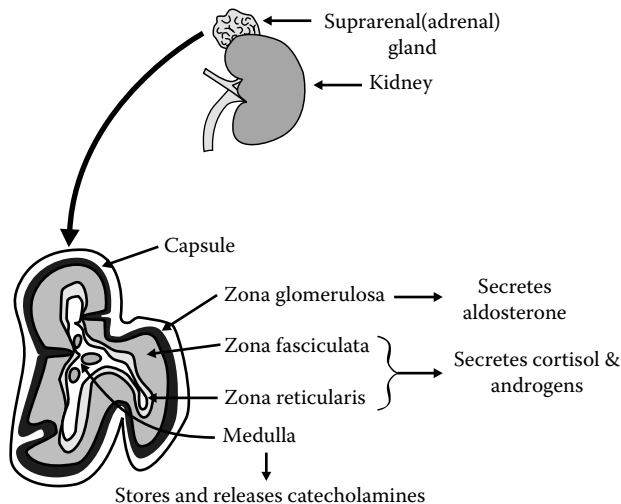
### STEROIDS WITH UNCONVENTIONAL SIDE CHAINS

Steroids isolated from sponges frequently contain substantially modified side chains, such as those with high degrees of alkylation or other unusual functionalization. Biosynthetic studies have been performed on the mechanism and scope of sterol side-chain dealkylation in sponges:

- **25S-26-Methyl-24-methylenecholest-4-en-3-one** has been isolated from the marine fossil sponge *Neosiphonia supertes*.
- **Baikalosterol** is a novel steroid with a **24-ethyl-26-nor-22,25-diene** group in the side chain isolated from the sponge *Baicalospongia bacilifera*, a common species of the **Baikal lake**.
- **Sutinasterol** contains a C<sub>12</sub> side chain that is presumably the product of quadruple bioalkylation. It represents the 94% of the steroid fraction of a *Xestospongia* sponge.
- A new cytotoxic sterol, **biennmasterol**, possessing the rare 22,25-diene side chain, has been isolated from the Okinawan sponge *Bienma* sp.
- **Topsentinols** A through J, ten new 7-hydroxysterols with unusual polyalkylated side chains, have been isolated from the Okinawan marine sponge *Topsentia* sp.
- Two new sterols, **epipolasterol** and **22,23-dihydroepipolasterol**, have been found in *Epipolasis* sp.
- There are 22 steroid components present in the deep-water sponge *Stelodoryx chlorophylla*, from New Caledonia.

### ADRENAL STEROIDS

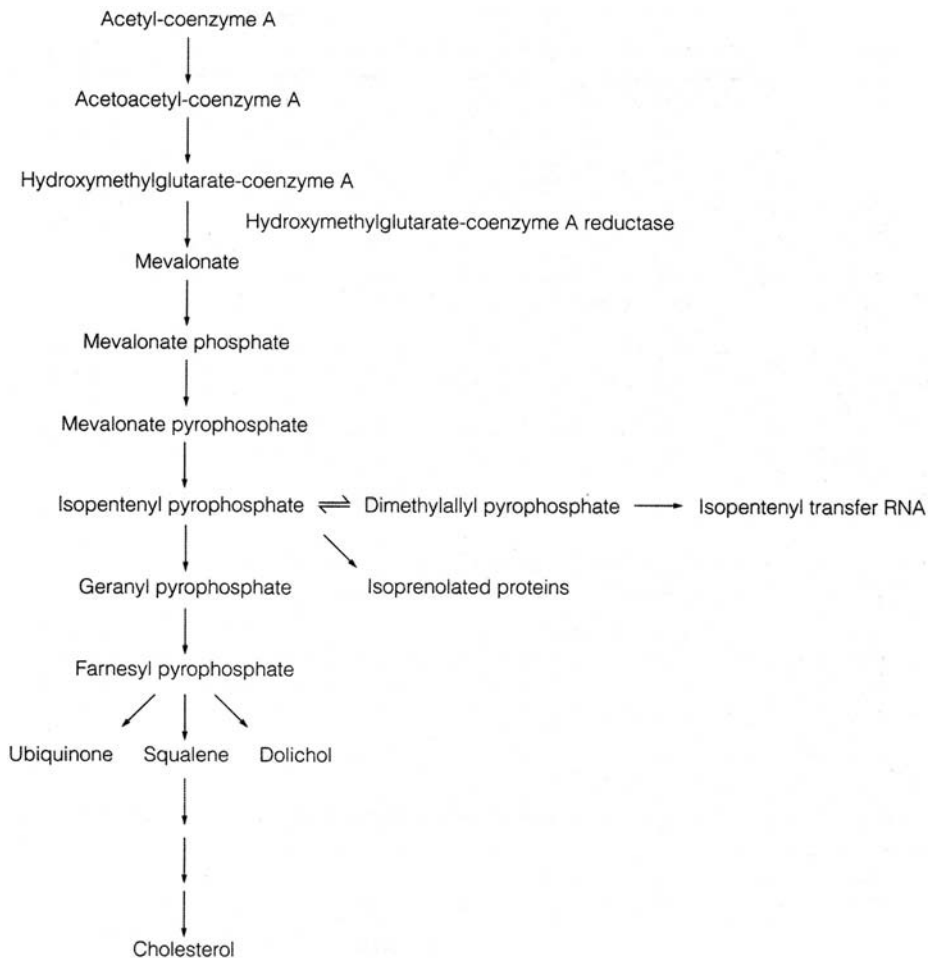
The adrenal gland, which is located at the cap of the kidney, is divided histologically into three zones: the outer zone or zona glomerulosa, the middle zone or zona fasciculata, and the inner zone or zona reticularis. The adrenal cortex synthesizes cholesterol and pregnenolone through the interaction of a group of enzymatic reactions (Figure 61.1).



**FIGURE 61.1** The sites of synthesis of aldosterone, cortisol, and androgens.

## THE SYNTHESIS OF CHOLESTEROL

Cholesterol, which is essential for the synthesis of adrenal, ovarian, and testicular steroid hormones, originates from two sources. The body synthesizes approximately 2 g of cholesterol per day, according to the following pathway:



In addition, between 300 and 800 mg of cholesterol is ingested per day, depending on a person's diet. On average, between 300 and 1500 mg of cholesterol is excreted per day.

## CLASSIFICATION OF ADRENAL STEROIDS

The adrenal steroids are divided into three major categories: **glucocorticoids**, **mineralocorticoids**, and **sex hormones**.

### The Glucocorticoids

The glucocorticoids mainly influence carbohydrate metabolism and, to a certain extent, protein and lipid metabolism. The main glucocorticoid is cortisol, with a daily secretion of 15 mg. Cortisol is synthesized through the 11- $\beta$ -hydroxylation of **11-deoxycortisol**. Besides cortisol, the adrenal

gland also synthesizes and releases a small amount of **corticosterone**, whose synthesis from **11-deoxycorticosterone** is catalyzed by 11- $\beta$ -hydroxylase. A deficiency of 11- $\beta$ -hydroxylase causes the following:

- Diminished secretion of cortisol
- Diminished secretion of corticosterone
- Enhanced compensatory secretion of adrenocorticotropic hormone (ACTH)
- Enhanced secretion of 11-deoxycortisol and 11-deoxycorticosterone
- Enhanced secretion of androgens

The clinical manifestations of 11- $\beta$ -hydroxylase deficiency are virilization, resulting from the overproduction of androgen, and hypertension, stemming from the overproduction of deoxycorticosteroids.

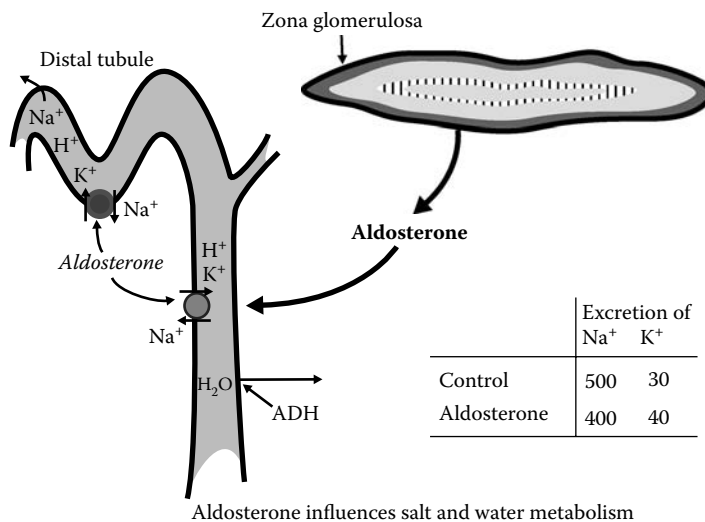
The glucocorticoids work by binding to specific intracellular receptors in target tissues. The receptor hormone complex is then transported into the nucleus in which the complex interacts with the DNA, thus augmenting the synthesis of specific RNAs.

Cortisol, corticosterone, aldosterone, and the synthetic steroids used in steroid therapy (e.g., prednisolone, dexamethasone, and triamcinolone) are glucocorticoid agonists and therefore elicit glucocorticoid responses. A number of other steroids bind to the glucocorticoid receptor and thus suppress glucocorticoid responses.

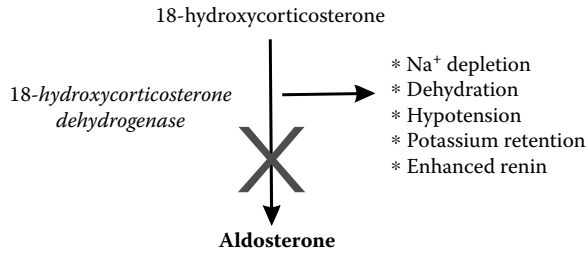
### The Mineralocorticoids

The mineralocorticoids influence salt and water metabolism and in general conserve sodium levels. They promote the resorption of sodium and the secretion of potassium in the cortical collecting tubules and possibly the connecting segment. They also elicit hydrogen secretion in the medullary collecting tubules (Figure 61.2).

The main mineralocorticoid is aldosterone, with a daily secretion of 100  $\mu$ g. Aldosterone is synthesized from 18-hydroxycorticosterone by a dehydrogenase. The consequence of 18-hydroxycorticosterone dehydrogenase deficiency is diminished secretion of aldosterone, and the clinical manifestations consist of sodium depletion, dehydration, hypotension, potassium retention, and enhanced plasma renin levels (Figure 61.3).



**FIGURE 61.2** The action of aldosterone. ADH = antidiuretic hormone.



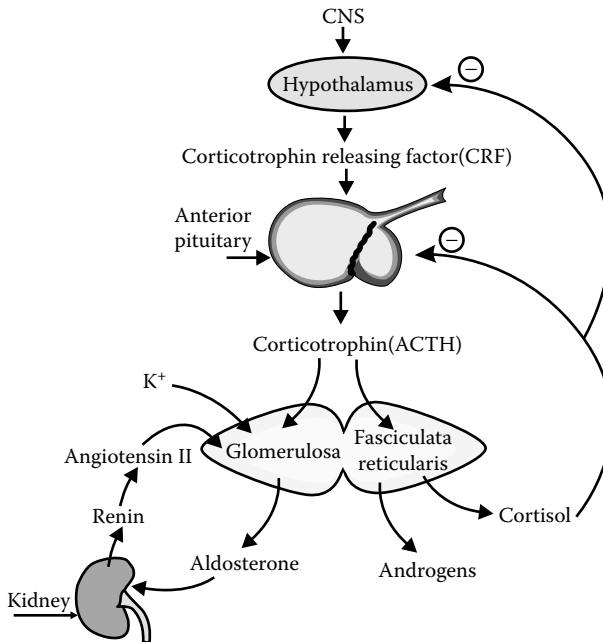
**FIGURE 61.3** The consequences of hydroxycorticosterone dehydrogenase deficiency.

**The Sex Hormones**

Small quantities of progesterone, testosterone, and estradiol are also produced by the adrenal gland. However, they play a minor role compared to the testicular and ovarian hormones. Progesterone, which is the precursor of cortisol, aldosterone, testosterone, and estradiol, is synthesized from **5-pregnenolone** by **3-β-ol-dehydrogenase**. Deficiency of this enzyme results in cortisol and aldosterone deficiencies. Such patients require replacement therapy with both glucocorticoids and mineralocorticoids.

**REGULATION OF ADRENAL STEROID BIOSYNTHESIS**

Adrenal glucocorticoid and androgen production is controlled predominantly by the hypothalamic–pituitary axis, whereas the production of aldosterone by the zona glomerulosa is predominantly regulated by the **renin-angiotensin system** and potassium concentration. The hypothalamus, pituitary, and adrenal form a neuroendocrine axis whose primary function is to regulate the production of both cortisol and some of the adrenal steroids (Figure 61.4).



**FIGURE 61.4** The action of aldosterone on renin–angiotensin system.

## ADRENOCORTICOTROPIC HORMONES

Corticotropin-releasing factor and arginine vasopressin, which are released predominantly by the paraventricular nucleus of the hypothalamus, are important regulators of corticotropin (ACTH) release, which in turn triggers the release of cortisol and other steroids by the adrenal gland. Both the administration of certain psychoactive agents and emotional arousal originating from the limbic system are able to modify the functions of the pituitary–adrenal axis and stimulate the synthesis of cortisol.

ACTH elicits the following effects:

- ACTH enhances the synthesis of pregnenolone.
- ACTH activates adenylate cyclase and elevates the cyclic adenosine monophosphate level.
- ACTH enhances the level of adrenal steroids, especially cortisol.
- ACTH reduces the level of ascorbic acid.

The level of cortisol is thought to directly control the secretion of ACTH through a negative feedback mechanism that may be directed at both the hypothalamus and the anterior pituitary gland. Conversely, a reduced concentration of cortisol or cortisol-like substances eliminates the negative effect and enhances the release of ACTH (see Figure 61.4).

The **metyrapone test** may be used diagnostically to evaluate the proper functioning of the anterior pituitary gland. When administered orally, metyrapone has the following effects:

- Inhibits the activity of 11- $\beta$ -hydroxylase, which is necessary for the synthesis of cortisol, corticosterone, and aldosterone
- Promotes the release of corticotropin, which in turn increases production of the precursors (**11-deoxycortisol** and **11-deoxycorticosterone**)
- Enhances the appearance of **17-hydroxycorticosteroids** and **17-ketogenic steroids**

In the event that the pituitary gland is nonfunctional, and therefore cannot stimulate ACTH secretion, the levels of these urinary metabolites will not increase.

## ACTIONS AND PHARMACOLOGICAL APPLICATIONS OF GLUCOCORTICOIDS

The glucocorticoids possess a plethora of physiological actions, including a role in differentiation and development. They are vital in the treatment of adrenal insufficiency and are used extensively in large pharmacological doses as anti-inflammatory and immunosuppressive agents. Some of the nonendocrine conditions for which they may be used include arthritis, tenosynovitis, systemic lupus erythematosus, acute rheumatic carditis, bronchial asthma, organ transplantation, ulcerative colitis, cerebral edema, and myasthenia gravis.

The relative anti-inflammatory potency and sodium-retaining properties of several steroids are listed in Table 61.1.

- **Glucose metabolism:** Cortisol has an anti-insulin effect and aggravates the pathological consequences of diabetes mellitus. It increases gluconeogenesis, inhibits the peripheral utilization of glucose, and causes hyperglycemia and glucosuria.
- **Protein metabolism:** Cortisol promotes the breakdown of proteins and inhibits protein synthesis. This leads to muscle wasting in the quadriceps–femoris groups, and muscular activities may become difficult as a result. The effect of cortisol is opposite to that of insulin.
- **Glycogen metabolism:** The effects of glucocorticoids on glycogen accumulation appear to be predominantly, although not exclusively, insulin dependent, because glycogen

**TABLE 61.1**  
**Actions of Glucocorticoids**

<b>Steroid</b>	<b>Anti-Inflammatory Potency (% Compared to Cortisol)</b>	<b>Sodium Retention (% Compared to Cortisol)</b>
Betamethasone	20	0
Dexamethasone	20	0
Fludrocortisone	12	100
Paramethasone	6	0
Triamcinolone	5	0
Methylprednisolone	4	0
Prednisolone	3	0.8
Prednisone	2.5	0.8
Cortisol	1	1

*Note:* The glucocorticoids mainly influence carbohydrate metabolism and, to a certain extent, protein and lipid metabolism.

accumulation is markedly reduced in pancreatectomized animals. Glucocorticoid-stimulated increases in insulin secretion promote further glycogen accumulation.

- **Lipid metabolism:** Cortisol causes the abnormal deposition of a fat pad called “buffalo hump.”
- **Electrolytes and water metabolism:** Cortisol use can bring about hypernatremia, hypokalemia, and hypercalciuria.
- **Uric acid:** Cortisol use causes hyperuricemia by suppressing the renal tubular resorption of uric acid.
- **Gastric hydrochloric acid:** Cortisol promotes the production of gastric hydrochloric acid.
- **Blood coagulation:** Cortisol, similar to epinephrine, augments the coagulability of blood.
- **Anti-inflammatory action:** Cortisol exerts its anti-inflammatory effect in part by blocking the release and action of histamine. In addition, it decreases the migration of polymorphonuclear leukocytes.
- **Hematological effects:** Cortisol produces eosinophilia and causes the involution of lymphoid tissues.
- **Leukocytes:** The administration of glucocorticoids to human subjects brings about lymphocytopenia, monocytopenia, and eosinopenia. In addition, glucocorticoids block a number of lymphocytic functions (Table 61.2).
- **Immunosuppression:** Although considered to be immunosuppressive, therapeutic doses of glucocorticoids do not significantly decrease the concentration of antibodies in the circulation. Furthermore, during glucocorticoid therapy, patients exhibit a nearly normal antibody response to antigenic challenge.

### Central Nervous System Effects

Glucocorticoids, which do penetrate the blood–brain barrier, affect behavior, mood, and neural activity, and are able to regulate the permeability of the blood–brain barrier to other substances. Hence, they are used to treat brain edema. Both glucocorticoid deficiency and excess may cause mood swings and, rarely, psychosis. Patients receiving glucocorticoids have a feeling of well-being. On the other hand, patients with spontaneously evolving **Cushing’s syndrome**, which involves the overproduction of glucocorticoids, are commonly depressed. Patients with **Addison’s disease**, which is caused by a deficiency of cortisol and aldosterone, tend to be depressed, negativistic,



**TABLE 61.2**  
**Immunological Mediators Whose Production or Actions**  
**Can Be Blocked by Glucocorticoids**

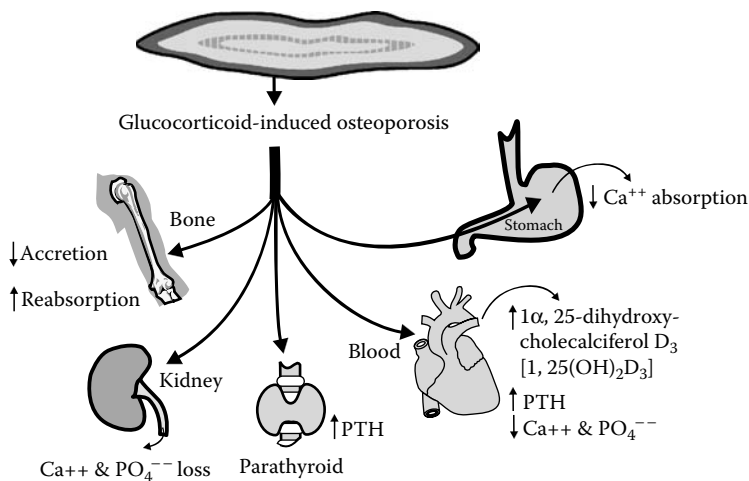
Bradykinin  
 Cachectin (tumor necrosis factor)  
 Colony-stimulating factor  
 Histamine  
 Interleukin-1 (lymphocyte-activating factor)  
 Interleukin-2 (T-cell growth factor)

*Note:* The glucocorticoids possess a plethora of physiological actions, including a role in differentiation and development. They are vital in the treatment of adrenal insufficiency and are used extensively in large pharmacological doses as anti-inflammatory and immunosuppressive agents.

irritable, seclusive, and apathetic. Patients with Addison's disease also suffer from anorexia, whereas a glucocorticoid excess stimulates the appetite. In addition, high doses of glucocorticoids can affect sleep, with a trend toward increased wakefulness and a reduction in rapid-eye-movement (REM) sleep, an increase in stage II sleep, and an increase in the time to the first REM sleep.

### Calcium Metabolism

Glucocorticoids affect bone metabolism in a variety of ways (Figure 61.5). Mild hyperkalemia can occur in Addison's disease. Conversely, glucocorticoids are used to treat certain hypercalcemias, largely granulomatous conditions such as sarcoidosis in which the steroid blocks the formation of 1- $\alpha$ ,25-dihydroxycholecalciferol [1- $\alpha$ ,25-(OH) $_2$ D $_3$ ] by the granulomatous tissues. However, most hypercalcemias are not responsive to glucocorticoid and, in general, glucocorticoid excess does not result in lower serum calcium levels. Serum phosphate levels are lowered and urinary calcium and phosphorus concentrations are elevated in glucocorticoid excess states. Glucocorticoid excess ultimately leads to osteoporosis, the major limitation to their long-term use (see Figure 61.5).



**FIGURE 61.5** Actions of vitamin D on calcium metabolism. PTH = parathyroid hormone.

## Contraindications to Glucocorticoid Therapy

Besides the adverse effects just described, glucocorticoid therapy is contraindicated under the following circumstances: diabetes mellitus, digitalis therapy, glaucoma, hypertension, infection, osteoporosis, peptic ulcer, tuberculosis, and viral infection.

## ADRENAL DISORDERS — CUSHING'S SYNDROME

Cushing's syndrome is a rare condition, occurring in one of 1000 individuals but seen primarily in the female population, that appears in the third or fourth decade of life. A basophilic adenoma of the anterior pituitary gland, hyperplasia, adenoma, and carcinoma of the adrenal cortex may all cause Cushing's syndrome. Patients typically have red cheeks, a moon face, a buffalo hump, thin skin, high blood pressure, a pendulous abdomen with red striae, poor wound healing, osteoporosis, and some signs of virilism (enlarged clitoris). The treatment of Cushing's syndrome may include the following:

- Removal of the microadenoma using the transsphenoidal route to approach the pituitary gland
- Removal of the entire adenohipophysis and life-long treatment with cortisol, thyroxine, and sex hormones
- Bilateral adrenalectomy

## REPRODUCTIVE PHARMACOLOGY

In the absence of pituitary gonadotropins, the gonads fail to develop properly and removal of the pituitary gland causes reproductive failure.

### STEROID HORMONES

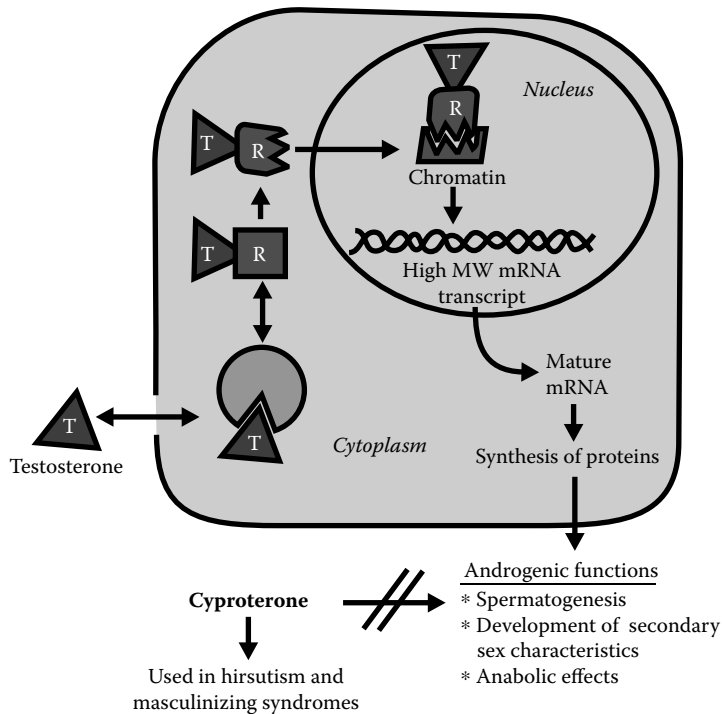
#### Receptors

All classes of steroid hormones bind to specific cytoplasmic receptors in their respective target tissues, and are then translocated to the nucleus. For example, testosterone, a lipid-soluble substance, enters the cell and is enzymatically reduced to **dihydrotestosterone by 5- $\alpha$  reductase**. **Dihydrotestosterone** then becomes bound to a specific androgen receptor site located in the cytoplasm. This complex becomes activated and is then translocated to the nucleus, where it binds to the chromatin acceptor site consisting of DNA and nonhistone chromosomal proteins. This interaction results in the transcription of a specific messenger RNA that is then relocated to the cytoplasm and translated on the cytoplasmic ribosomes, resulting in the synthesis of a new protein that sponsors the androgenic functions (Figure 61.6).

#### Receptor Antagonists

Similar to neurotransmitters, steroid hormones are classified as either agonists or antagonists, as in the following table.

Hormone	Agonist	Antagonists
Estrogen	Estrogen	Nafoxidine, tamoxifen
Androgen	Testosterone	Flutamide, finasteride
Progesterone	Progesterone	Mifepristone

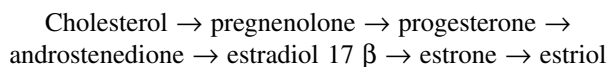


**FIGURE 61.6** The steroid hormones and their receptors. The vitamin D, thyroid hormone, and estrogen receptors are all concentrated in the cell nucleus. However, the importance of steroid (S) and receptor (R) complex formation in the cytoplasm can be judged by the fact that antiestrogenic substances such as clomiphene and nafoxidine reduce the specific uptake of estrogen and hence reduce estrogen-induced uterine growth. Progesterone receptors are present in female reproductive tissues. Androgen receptors exist in male genital and accessory sex tissues. Glucocorticoid receptors are present in most mammalian tissues. Aldosterone receptors are found in mineralocorticoid target tissues such as the kidney, bladder, parotid gland, and gut.

**Tamoxifen** decreases the rate of proliferation of breast cancer cells *in vitro* by inhibiting the estrogen-dependent production of specific proteins and growth factors that exert autocrine effects on cell division. Antiandrogenic compounds antagonize the effects of testosterone and are of value in the treatment of hirsutism and other **masculinizing syndromes**.

## Estrogens

Estrogens are synthesized mainly in the ovaries, the placenta, and the adrenal glands. A minute amount of estradiol is synthesized in the testes. Estrogens are synthesized according to the following scheme.



### Physiological Actions

Estrogen dramatically influences the growth and development of the female reproductive organs, as summarized in Table 61.3.

### Biochemical Actions

The uterus and vagina are sensitive to the biochemical actions of estrogens, which are as follows:

**TABLE 61.3**  
**Summary of the Physiological Actions of Estrogen**

Organs	Action
Uterus	Estrogens participate in the growth and development of muscular and mucosal elements of the uterus, the oviducts, and the fallopian tubes.
Myometrium	Estrogens stimulate the growth of the myometrium at puberty and during pregnancy.
Endometrium	Estrogens increase the endothelium and “rebuild” the endometrial lining in the proliferative phase.
Vagina	Estrogens increase the epithelial layer in the vaginal tract and enhance glandular secretion.
Breast	Estrogens influence the breast tissue at puberty, during each ovulatory cycle, and during pregnancy; they participate in duct formation, and, in conjugation with progesterone, oxytocin, and other hormones, prepare the breasts for lactation.

*Note:* Estrogens cause the growth of the uterus, fallopian tubes, and vagina. Estrogens also are responsible for the expression of female secondary sex characteristics during puberty. These include breast enlargement, the female distribution of body hair, female body contours as determined by subcutaneous fat deposition, and skin texture. Estrogens can stimulate the release of growth hormone and exert a positive effect on nitrogen balance. These effects contribute to the growth spurt during puberty. Closure of the bone epiphyses signaling the end of long bone growth is also estrogen mediated. Estrogens maintain bone mass by inhibiting bone resorption. This action of estrogen may be mediated by stimulating calcitonin production. Additionally, progestins antagonize loss of bone. In males, estrogens stimulate the growth of the stromal cells in the accessory sex organs.

- *Early events* — release of histamine, synthesis of cyclic adenosine monophosphate (cyclic AMP), stimulation of RNA polymerase, and increased excitability of the myometrium.
- *Intermediate events* — synthesis of RNA and DNA, imbibition of water, and stimulation of certain enzymes.
- *Late events* — increased secretory activity, morphological changes, increased protein synthesis, stimulation of lipid and carbohydrate metabolism, and increased gravimetric responses.

### *Estrogen Preparations*

The estrogen preparations are basically divided into three groups: natural steroids, semisynthetic steroids, and nonsteroidal chemical compounds possessing estrogenic activities (Table 61.4). Transdermal estrogen (**Estraderm**) equals the efficacy of the oral preparation.

### *Therapeutic Uses*

Estrogens are used extensively in the treatment of endocrine and nonendocrine diseases, a few of which are as follows:

- Menopause — as a replacement therapy.
- Atrophic vaginitis — to thicken epithelial cells and to cause mucosal cells to proliferate.
- Primary hypogonadism — to correct ovarian failure.
- Osteoporosis — estrogen by itself or with hypercalcemic steroid is used in the treatment of osteoporosis.
- Primary amenorrhea — to cause endometrium to proliferate.
- Uterine bleeding — to reverse estrogen deficiency (in this case, oral contraceptives containing 80 to 100  $\mu\text{g}$  of estrogen are recommended).
- Postpartum lactation — to relieve postpartum painful breast engorgement and prevent postpartum lactation; bromocriptine is also effective.
- Control of height — to cause closure of the epiphyses in unusually tall young girls.
- Dermatological problems — used with some success in the treatment of acne.

### Adverse Effects

Low-dose estrogens are safe only when taken for a limited period. The most often reported side effects are breakthrough bleeding, breast tenderness, and very infrequent gastrointestinal upsets. When estrogens are used in large doses or injudiciously, they may cause thromboembolic disorders, hypertension in susceptible individuals, and cholestasis.

Estrogens are contraindicated in patients with estrogen-dependent neoplasms such as carcinoma of the breast or endometrium. Vaginal adenocarcinoma has been reported in young women whose mothers were treated when pregnant with them with diethylstilbestrol in an effort to prevent miscarriage.

### Antiestrogens

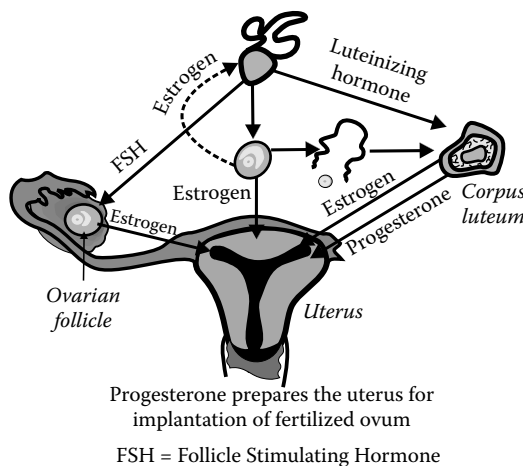
**Clomiphene** (Clomid) and **tamoxifen** (Nolvadex) modify or inhibit the actions of estrogens. They accomplish this by binding to the cytoplasmic estrogen receptors that are then translocated to the nucleus. By diminishing the number of estrogen-binding sites, they interfere with the physiological actions of estrogens. Furthermore, by interfering with the normal hypothalamic and hypophyseal feedback inhibition of estrogen synthesis, these agents cause an increased secretion of **luteinizing hormone**, **follicle-stimulating hormone**, and **gonadotropins**. This leads to ovarian stimulation and ovulation. Clomiphene has been used successfully in some cases of infertility but causes multiple births. Antiestrogens are able to arrest the growth of estrogen-dependent malignant mammary cells. Clomiphene has been used in certain cases of disseminated breast cancer (see Figure 61.6).

### PROGESTERONE

Progesterone is synthesized by the ovaries, the adrenal glands, and the placenta. In a nonpregnant woman, it is produced by the corpus luteum during the latter part of the menstrual cycle under the influence of luteinizing and luteotropic hormones. In a pregnant woman, it is produced initially by the corpus luteum under the influence of chorionic gonadotropins and is synthesized by the placenta after failure of the corpus luteum (Figure 61.7).

Progesterone is not only an important progestin, but is also an important precursor for androgen. It is synthesized according to the following scheme:

Acetate → cholesterol → pregnenolone → progesterone → testosterone → estradiol



**FIGURE 61.7** The actions of progesterone. FSH = follicle-stimulating hormone.

**TABLE 61.4**  
**Progesterone and Selected Progestins**

Agent	Actions and Indications
Progesterone (Progekan)	Must be given intramuscularly, brief duration of action
Ethisterone (17 $\alpha$ -ethinyltestosterone)	Effective orally
Ethinodiol acetate	Potent progestin
Hydroxyprogesterone caproate (Delalutin)	Long-acting, given intramuscularly
Medroxyprogesterone acetate (Provera)	Effective orally
Megestrol acetate (Megace)	Orally effective antifertility agent
Northindrone (Norethisterone)	Potent oral progestin, mild androgenic effect
Norethynrel	Used as an antifertility agent
Norgestrel (18-homonorethisterone)	Potent progestin

Progesterone is absorbed rapidly when given orally and has a plasma half-life of 5 min. It is completely metabolized in the liver and is cleared completely during first passage through the liver.

#### *Physiological Actions*

Progesterone initially prepares the uterus for implantation of the fertilized egg and prevents uterine contraction that would expel the fetus (see Figure 61.7). Progesterone has been used in the past to prevent **threatened abortion**. In addition, progesterone exerts effects on the secretory cells of the mammary glands. Progesterone competes with aldosterone and causes a decrease in sodium resorption; therefore, it antagonizes **aldosterone-induced sodium retention**. Progesterone increases the body temperature and decreases the plasma level of many amino acids.

#### *Progesterone and Progestins*

In the treatment of progesterone-related disorders, progesterone, which must be injected and has a short duration of action, has been replaced by the **progestins**. These newer synthetic derivatives of progesterone are effective orally and have a longer duration of action. Unlike progesterone, some of these agents have androgenic, estrogenic, and even glucocorticoid-like effects (see Table 61.4).

#### *Therapeutic Uses*

The following are the therapeutic uses of progestins:

- **Dysfunctional uterine bleeding:** Progestins are used in the treatment of dysfunctional uterine bleeding, which may occur as a result of insufficient estrogen or because of continued estrogen secretion in the absence of progesterone, and as **antifertility agents**.
- **Amenorrhea:** Progestins such as medroxyprogesterone are useful in the diagnosis and treatment of amenorrhea.
- **Dysmenorrhea:** Because prostaglandin F<sub>2</sub> is capable of inducing contraction in the uterus, agents that are able to block the synthesis of prostaglandin, such as aspirin or aspirin-like substances, have been shown to be effective in easing dysmenorrhea. For sexually active women, oral contraceptives have been found to be effective in relieving dysmenorrhea.
- **Endometriosis:** Endometriosis, which was formerly treated by surgical removal of the ovaries and uterus, is now treated with the continuous administration of progestin, or with progestin combined with estrogen. In addition, progestin may be useful in the management of **endometrial carcinoma**.
- **Suppression of postpartum lactation:** Estrogen, progesterone, and bromocriptine (a dopamine receptor agonist) are all effective in suppressing postpartum lactation.

## Antifertility Agents

Oral contraceptive medications are among the most prescribed and effective drugs. The failure rates associated with various methods of contraception are cited in the following table.

Method	Failure Rate (%)
Sterilization	0.0
Oral contraceptive	2.5
IUD	4.8
Condom	9.6
Diaphragm	14.4
Spermicide	17.7
Rhythm method	18.8

The most common type of oral contraceptive is the combination preparation and these are listed in Table 61.5.

### *Mechanism of Action*

The antifertility agents suppress ovulation by the following methods:

- Inhibiting the release of **hypophyseal ovulation-regulating gonadotropin**
- Producing thick mucus from the cervical glands and hence impeding the penetration of sperm cells into the uterus
- Impeding the transfer of the ovum from the oviduct to the uterus
- Preventing implantation of the fertilized ovum should fertilization take place (Figure 61.8)

### *Adverse Metabolic Effects*

The following are the various adverse metabolic effects of oral contraceptives.

- The incidence of venous and arterial thrombosis is related to the dose of estrogen.
- Blood pressure is increased.
- The incidence of myocardial infarction is higher among older women.
- Adverse alterations in the levels of high-density lipoproteins, cholesterol, and low-density lipoproteins are produced by progestins.
- The estrogen component of the preparation accelerates the development of gallbladder disease.

### *Potential Beneficial Effects*

The potential benefits of oral contraceptive use consist of the following:

- Reduced menstrual blood loss and thus less iron deficiency anemia
- Reduced incidence of menorrhagia and irregular bleeding
- Lower incidence of breast and endometrial cancers
- Less incidence of salpingitis and increased bone density

## ANDROGENS

Testosterone, the male sex hormone, is responsible for the development and maintenance of the male sex organs (the penis, prostate gland, seminal vesicle, and vas deferens) and secondary sex characteristics. In addition, testosterone has anabolic effects. Similar to progesterone, testosterone is metabolized very rapidly by the liver by the first-pass mechanism, and hence requires structural

**TABLE 61.5**  
**Composition and Doses of Some Oral Contraceptives**

Estrogen (mg)		Progestin <sup>a</sup> (mg)		Representative Trade Names
<b>Combinations<sup>b</sup></b>				
0.05	Ethinyl estradiol	1.0	Norethindrone acetate	Loestrin 1/20
0.03	Ethinyl estradiol	0.3	Norgestrel	Lo/Orval
0.03	Ethinyl estradiol	1.5	Norethindrone acetate	Loestrin 1.5/30
0.03	Ethinyl estradiol	0.15	Levonorgestrel	Nordette
0.035	Ethinyl estradiol	0.4	Norethindrone	Ovcon 35
0.035	Ethinyl estradiol	0.5	Norethindrone	Brevicon
0.035	Ethinyl estradiol	1.0	Ethinodiol diacetate	Demulen 1/35
0.035	Ethinyl estradiol	1.0	Norethindrone	Ortho-Novum 1/35
0.05	Mestranol	1.0	Norethindrone	Ortho-Novum 1/50
0.05	Ethinyl estradiol	0.5	Norgestrel	Ovral
0.05	Ethinyl estradiol	1.0	Ethinodiol diacetate	Demulen 1/50
0.05	Ethinyl estradiol	1.0	Norethindrone	Ovcon 50
0.05	Ethinyl estradiol	1.0	Norethindrone acetate	Norlestrin 1/50
0.05	Ethinyl estradiol	2.5	Norethindrone acetate	Norlestrin 2.5/50
<b>Sequential<sup>c</sup></b>				
0.03, 0.04, 0.03	Ethinyl estradiol	0.05, 0.75, 0.125	Levonorgestrel	Tri-Levlen
0.035	Ethinyl estradiol	0.5, 1.0, 0.5	Norethindrone	Tri-Norinyl
0.035	Ethinyl estradiol	0.5, 0.75, 1.0	Norethindrone	Ortho-Novum 7/7/7
0.035	Ethinyl estradiol	0.5, 1.0	Norethindrone	Ortho-Novum 10/11
<b>Minipills<sup>d</sup></b>				
—		0.35	Norethindrone	Micronor
—		0.075	Norgestrel	Ovrette
<b>Postcoital Medications</b>				
Ethinyl estradiol and norgestrel (combination available as Ovral)		100 µg ethinyl estradiol and 1 mg norgestrel (two Ovral tablets) taken twice 12 h apart		
Ethinyl estradiol		2.5 mg twice daily for 5 d		
Conjugated estrogens		10 mg three times daily for 5 d		
Estrone		5 mg three times daily for 5 d		
Diethylstilbestrol		25 mg twice daily for 5 d		

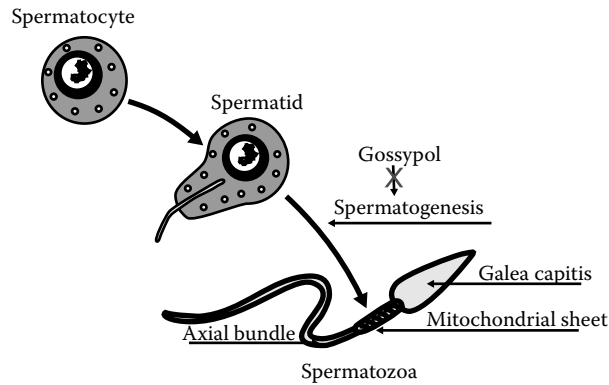
<sup>a</sup> Of the progestins used, norgestrel is strongly androgenic; the others have moderate androgenic activity.

<sup>b</sup> Combination tablets are taken for 21 d and are omitted for 7 d. These preparations are listed in order of the increasing content of estrogen.

<sup>c</sup> These preparations include fixed-dose tablets with the same or different amounts of estrogen and variable amounts of progestin. With biphasic preparations, the first set of tablets is taken for 10 d and the second for 11 d, followed by 7 d of no medication. With triphasic preparations, each set of tablets is taken for 5 to 10 d in three sequential phases, followed by 7 d of no medication.

<sup>d</sup> Minipills are taken daily continually.





**FIGURE 61.8** Actions of oral contraceptive medications.

modifications in order to be effective. For example, the 17-OH group of testosterone may be modified by the addition of propionic acid, which yields **testosterone propionate**, cyclopentyl propionic acid, which yields testosterone cypionate, or enanthate, which yields testosterone enanthate. In addition, the 17 position may be methylated to yield methyltestosterone or a fluorine and a methyl group may be inserted to yield fluoxymesterone. In general, these agents are more effective when given orally and have a longer duration of action than testosterone itself (Table 61.6).

**TABLE 61.6**  
**Examples of Anabolic and Androgenic Steroids**

**Steroids with Anabolic Activities**

Dromostanolone propionate (Drolban)  
Ethylestrenol (Maxibolin)  
Methandrostebolone (Dianabol)  
Nandrolone decanoate (Deca-Durabolin)  
Nandrolone phenpropionate (Durabolin)  
Oxandrolone (Anavar)  
Oxymetholone (Adroyd)  
Stanozolol (Winstrol)  
Testolactone (Teslac)

**Steroids with Androgenic Properties**

Fluoxymesterone (Halotestin)  
Methyltestosterone (Metandren)  
Testosterone (Android-T)  
Testosterone propionate cypionate (Depotestosterone)  
Testosterone enanthate (Delatestryl)

*Note:* Androgens are steroid hormones that are secreted primarily by the testis but also by the mammalian adrenal gland and ovaries. Testosterone, the principal androgen secreted by the testis, and other androgenic compounds possess virilizing activities that serve to regulate both differentiation and secretory function of the male sex accessory organs. Androgens also exhibit protein anabolic activity in skeletal muscle, bone, and kidneys; this effect results in a positive nitrogen balance and increased protein synthesis. In recent years, compounds have been synthesized that possess a preponderance of either virilizing or protein anabolic activity. As a class, the androgens are reasonably safe drugs, having limited and relatively predictable side effects.

### Therapeutic Uses

Testosterone and its derivatives are used in the treatment of **hypogonadism (eunuchoidism)**, hypopituitarism, accelerated growth, aging in men, osteoporosis, anemia, endometriosis, promotion of anabolism, suppression of lactation, and breast carcinoma.

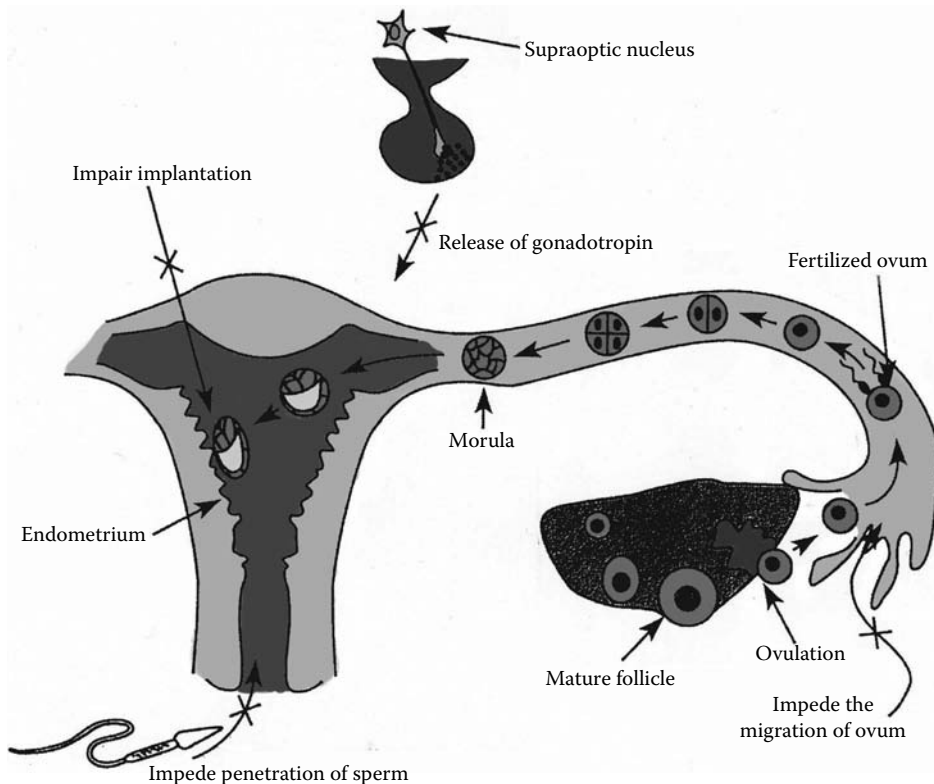
Hormonal therapy with testosterone should be reserved primarily for patients with hypogonadal disorders. There are two important warnings about the indiscriminate use of intramuscular testosterone in patients with serum testosterone levels in the normal range. First, many impotent patients are older and may have **adenocarcinoma of the prostate**, thus exogenous testosterone may accelerate the growth of the neoplasm. Second, although testosterone may induce a marked increase in libido, patients may still be unable to achieve adequate erection.

### Side Effects

One of the side effects of testosterone compounds is masculinization in women (such as hirsutism, acne, depression of menses, and clitoral enlargement) and of their female offspring. Therefore, androgens are contraindicated in pregnant women. Prostatic hypertrophy may occur in males, which leads to urinary retention. Therefore, androgens are contraindicated in men with prostatic carcinoma.

### Antiandrogens

**Cyproterone** inhibits the action of androgens and **gossypol** prevents spermatogenesis without altering the other endocrine functions of the testis (Figure 61.9).



**FIGURE 61.9** The action of gossypol on spermatogenesis.



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# 62 Taxol (Paclitaxel) and Cancer Chemotherapy

## INTRODUCTION

Taxol is an antineoplastic agent. This compound, first isolated from the bark of the **Western yew tree** in 1971, exhibits unique pharmacological actions as an inhibitor of mitosis, differing from the **vinca alkaloids** and **colchicine derivatives** in that it promotes rather than inhibits microtubule formation. Following its introduction into clinical trial, the drug was approved for treatment of **cisplatin-refractory ovarian cancer** in 1992 and has promising activity against **cancers of the breast, lung, esophagus, and head and neck**.

Malignant neoplastic diseases may be treated by various approaches: surgery, radiation therapy, immunotherapy, or chemotherapy, or a combination of these. The extent of a malignant disease (staging) should be ascertained in order to plan an effective therapeutic intervention. Plants have antineoplastic activities.

A significant portion of the product derived from plants serve either as **protective agents against various pathogens** (e.g., insects, fungi, or bacteria) or **growth regulatory molecules** (e.g., hormonelike substances that stimulate or inhibit cell division and morphogenesis).

## CHEMICAL GROUPS OF NATURAL PRODUCTS WITH ANTICANCER PROPERTIES

Plant-derived natural products with documented anticancer and antitumor properties can be classified into the following chemical groups (Kintzios and Barberaki, 2004):

- Aldehydes
- Alkaloids
- Flavonoids
- Glycosides
- Lignans
- Lipids
- Quinones
- Phenols and derivatives
- Polysaccharides
- Proteins
- Terpenoids

**Aldehydes** are volatile substances found (along with alcohols, ketones, and esters) in minute amounts and contributing to the formation of odor and flavor of plant parts. Plants containing aldehydes with anticancer properties include the following:

- *Cinnamomum cassia*
- *Mondia whitei*
- *Rhus vulgaris*
- *Sclerocarya caffra*

**Alkaloids** are weak bases, capable of forming salts, which are commonly extracted from tissues with an acidic, aqueous solvent. Alternatively, free bases can be extracted with organic solvents (see Chapter 11). Plants containing alkaloids with anticancer properties include the following:

- *Aconitum napellus*
- *Acronychia baueri*, *A. haplophylla*
- *Annona purpurea*
- *Brucea antidysenterica*
- *Calycodendron milnei*
- *Cassia leptophylla*
- *Chamaecyparis* sp.
- *Chelidonium autumnale*
- *Ervatamia microphylla*
- *Eurycoma longifolia*
- *Fagara macrophylla*
- *Nauclea orientalis*
- *Psychotria* sp.
- *Strychnos usabarensis*

**Flavonoids** are widely distributed colored phenolic derivatives. Related compounds include flavones, flavonols, flavanonols, xanthenes, flavanones, chalcones, aurones, anthocyanins, and catechins (see Chapter 29). Plants containing flavonoids with anticancer properties include:

- *Acrougehia porteri*
- *Angelica keiskei*
- *Annona densicoma*, *A. reticulata*
- *Claopodium crispifolium*
- *Eupatorium altissimum*
- *Glycyrrhiza inflata*
- *Gossypium indicum*
- *Polytrichum obioense*
- *Psorospermum febrifugum*
- *Rhus succedanea*
- *Zieridium pseudobtusifolium*

**Glycosides** are carbohydrate ethers that are readily hydrolysable in hot water or weak acids. Most frequently, they contain glucose and are named by designating the attached alkyl group first and replacing the *-ose* ending of the sugar with *-oside*.

Basis of anticancer/antitumor activity — Glycosides are mainly cytotoxic against certain types of cancer and also demonstrate antiviral and antileukemic properties. Plants containing glycosides with anticancer properties include the following:

- *Phlomis armeniaca*
- *Phyllanthus* sp.
- *Plumeria rubra* (iridoids)

- *Scutellaria salviifolia*
- *Wikstroemia indica*

**Lignans** are colorless, crystalline, solid substances widespread in the plant kingdom (mostly as metabolic intermediaries) and having antioxidant, insecticidal, and medicinal properties. Plants containing lignans with anticancer properties include the following:

- *Brucea* sp.
- *Juniperus virginiana*
- *Magnolia officinalis*
- *Plumeria* sp.
- *Wikstroemia foetida*

**Lipids** include fatty acids (aliphatic carboxylic acids), fatty acid esters, phospholipids, and glycolipids. Plants containing lipids with anticancer properties include the following:

- *Nigella sativa*
- Sho-saiko-to, luzen-taiho-to

**Quinones** are a diverse group of substances generally soluble in organic solvents and not saponified by alkali. They are yellow to red pigments, often constituents of wood tissues, and have toxic and antimicrobial properties. Plants containing quinines with anticancer properties include the following:

- *Kigelia pinnata*
- *Koelreuteria henryi*
- *Landsburgia quercifolia*
- *Mallotus japonicus*
- *Nigella sativa*
- *Rubia cordifolia*
- *Sargassum tortile*
- *Wikstroemia indica*

**Phenols and derivatives** are the main aromatic compounds of plants, whose structural formulas contain at least one benzene ring. They serve as odors, fungicides, or germination inhibitors.

**Coumarins** are especially common in grasses, orchids, citrus fruits, and legumes. Plants containing phenols with anticancer properties include the following:

- *Acronychia laurifolia*
- *Angelica gigas*, *A. decursiva*, *A. keiskei*
- *Gossypium indicum*

**Polysaccharides** and generally carbohydrates represent the main carbon sink in the plant cell. Polysaccharides commonly serve nutritional (e.g., starch) and structural (e.g., cellulose) functions in plants. Some polysaccharides are cytotoxic against certain types of cancer, such as mouse skin cancer, or tumor lines *in vitro* (e.g., mouse Sarcoma-180). However, most polysaccharides exert their action through stimulation of the immune system (cancer immunotherapy). Plants containing polysaccharides with anticancer properties include the following:

- *Angelica acutiloba*
- *Angelica sinensis*

- *Burcea javanica*
- *Cassia angustifolia*, *Sargassum thunbergii*
- *S. fulvellum*, *Tamarindus indica*

**Proteins**, similar to carbohydrates, belong to the most essential constituents of the plant body, as they are the building molecules of structural parts and the enzymes. Proteins are indirectly cytotoxic against certain cancer types, acting mainly through the inhibition of various enzymes (L-asparaginase, Tyrosine kinase) or by inducing apoptotic cell death. Plants containing proteins are the following:

- *Acacia confuse*
- *Ficus cunia*
- *Glycyrrhiza uralensis*
- *Momordica charantia*
- *Momordica indica*
- *Rubia* sp., *R. cordifolia*

**Terpenoids** are diverse, widely distributed compounds commonly found under groups such as essential oils, sterols, pigments, and alkaloids. They exert significant ecological functions in plants. *Mono-* and *sesquiterpenoids* are found as constituents of steam-distillable essential oils. *Di-* and *triterpenoids* are found in resins. Terpenoids and sterols often possess alkaloidal properties, thus being cytotoxic *in vivo* and *in vitro* against various cancer types, such as human prostate cancer, pancreatic cancer, lung cancer, and leukemia. Plants containing terpenoids and sterols with anti-cancer properties include the following:

- *Aristolochia versicolor*
- *Brucea antidysenterica*
- *Casearia sylvestris*
- *Crocus sativus*
- *Glycyrrhiza* sp.
- *Mallotus anomalus*
- *Melia* sp.
- *Maytenus* sp.
- *Neurolaena lobata*
- *Polyalthia barnesii*
- *Rabdosia trichocarpa*
- *Seseli mairei*
- *Stellera chamaejasme*

## CANCER CHEMOTHERAPY

Before discussing the specific pharmacokinetics and pharmacodynamics of each class of antineoplastic agent, several fundamental concepts and therapeutic objectives will be considered first.

Because a single cancerous cell is capable of multiplying rapidly and eventually causing the host's death, one of the therapeutic objectives is to eradicate the last neoplastic cell. Unlike normal cells, cancerous cells multiply ceaselessly and, unless arrested, they will kill the host. In the early phase, cancerous cells grow exponentially. However, as the tumor grows in mass, the time needed for the number of cells to double also increases. The kinetics of cell multiplication are said to follow a **Gompertzian growth curve**. Tumor growth may be divided into three phases: (1) the subclinical phase, in which  $10 \times 10^4$  cells are present, (2) the clinical phase, in which  $10 \times 10^8$

cells (1-cm<sup>3</sup> nodule) are present, and (3) the fatal phase, in which the number of cancerous cells equals or exceeds  $10 \times 10^{12}$ .

Most human cancerous cells evolve from the single clone of a malignant cell. As a tumor grows, significant mutation takes place, producing cells that exhibit diversified morphological and biochemical characteristics.

During the subclinical phase, the rapidly growing cell population is uniform in character and thus highly sensitive to drug treatment; this is the reason for the importance of early diagnosis and treatment. During the clinical phase, the nondividing and slowly growing cells are nonuniform in character and less sensitive to drug treatment, thus necessitating the need for multiple-drug treatment.

Cell destruction with antineoplastic agents follows a first-order kinetic, indicating that the drugs kill a constant fraction of cells and not a constant number of cells. This concept is depicted mathematically in the following table.

No. of Treatments	% Killed	No. of Tumor Cells Killed Each Treatment	No. of Surviving Tumor Cells
Strat	—	—	1,000,000
1	90	900,000	100,000
2	90	90,000	10,000
3	90	9,000	1,000
4	90	900	100
5	90	90	10
6	90	9	1

Cytotoxic drugs are not specific in their actions. They arrest not only cancerous cells, but also normal cells, especially those of the rapidly proliferating tissues such as the bone marrow, lymphoid system, oral and gastrointestinal epithelium, skin and hair follicles, and germinal epithelium of the gonads. Consequently, the therapeutic regimen must be carried out using high-dose intermittent schedules and not a low-dose continuous approach. Succeeding doses are given as soon as the patient has recovered from the previous treatment.

Antineoplastic agents may be teratogenic, carcinogenic, or immunosuppressant, and they exert their lethal effects on different phases of cell cycle by being either cell-cycle specific or nonspecific.

The management of cancer includes treatment with **alkylating agents** (nitrogen mustards and alkyl sulfonates), **antimetabolites** (methotrexate and purine analogues), **natural products** (vinca alkaloids and taxol), miscellaneous compounds (hydroxyurea, procarbazine, and *cis*-platinum), **hormones** (estrogens and corticosteroids), and **radioactive isotopes**.

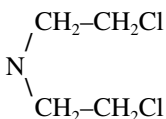
## ALKYLATING AGENTS

The alkylating agents exert their antineoplastic actions by generating highly reactive **carbonium ion intermediates** that form a covalent linkage with various nucleophilic components on both proteins and DNA. The 7 position of the purine base guanine is particularly susceptible to alkylation, resulting in miscoding, depurination, or ring cleavage. **Bifunctional alkylating agents** are able to cross-link either two nucleic acid molecules or one protein and one nucleic acid molecule. Although these agents are very active from a therapeutic perspective, they are also notorious for their tendency to cause carcinogenesis and mutagenesis. Alkylating agents that have a nonspecific effect on the cell-cycle phase are the most cytotoxic to rapidly proliferating tissues.

## NITROGEN MUSTARDS

The activity of nitrogen mustards depends on the presence of a **bis-(2-chloroethyl) grouping**:





This is present in **mechlorethamine** (Mustargen), which is used in patients with Hodgkin's disease and other lymphomas, usually in combination with other drugs, such as in **MOPP therapy** (mechlorethamine, Oncovin [vincristine], procarbazine, and prednisone). It may cause bone marrow depression.

### CHLORAMBUCIL

Chlorambucil (Leukeran) is the least toxic nitrogen mustard and is used as the drug of choice in the treatment of chronic lymphocytic leukemia. It is absorbed orally, is slow in its onset of action, and may cause bone marrow depression.

### CYCLOPHOSPHAMIDE

Cyclophosphamide (Cytoxan and Endoxan) is used in the treatment of Hodgkin's disease, lymphosarcoma, and other lymphomas. It is employed as a secondary drug in patients with acute leukemia and in combination with doxorubicin in women with breast cancer. A drug combination effective in the treatment of breast cancer is **cyclophosphamide, methotrexate, fluorouracil, and prednisone** (CMFP). Cyclophosphamide is also an immunosuppressive agent. The toxicity of cyclophosphamide causes alopecia, bone marrow depression, nausea and vomiting, and hemorrhagic cystitis.

### ALKYL SULFONATE

The **alkyl sulfonate busulfan** (Myleran) is metabolized to an alkylating agent. Because it produces selective myelosuppression, it is used in cases of chronic myelocytic leukemia. It causes pronounced hyperuricemia stemming from the catabolism of purine.

### NITROSOUREAS

Carmustine (BCNU), lomustine (CCNU), and semustine (methyl-CCNU) generate alkyl carbonium ions and isocyanate molecules and hence are able to interact with DNA and other macromolecules. These agents, which are lipid soluble, cross the blood-brain barrier and are therefore effective in treating brain tumors. They are bone marrow depressants.

### TRIAZENES

**Dacarbazine (DTIC-Dome)** is metabolized to an active alkylating substance. It is used in the treatment of malignant melanoma and causes myelosuppression.

## ANTIMETABOLITES

Antimetabolites are structural analogues of naturally occurring compounds and function as fraudulent substances for vital biochemical reactions.

### FOLIC ACID ANALOGUES

Methotrexate (Amethopterin) is a folic acid antagonist that binds to **dihydrofolate reductase**, thus interfering with the synthesis of the active cofactor **tetrahydrofolic acid**, which is necessary for

the synthesis of thymidylate, purine nucleotides, and the amino acids serine and methionine. Methotrexate is used for the following types of cancer:

- **Acute lymphoid leukemia:** During the initial phase, vincristine and prednisone are used. Methotrexate and mercaptopurine are used for maintenance therapy. In addition, methotrexate is given intrathecally, with or without radiotherapy, to prevent meningeal leukemia.
- **Diffuse histiocytic lymphoma:** Cyclophosphamide, vincristine, methotrexate, and cytarabine (COMA).
- **Mycosis fungoides:** Methotrexate.
- **Squamous cell, large-cell anaplastic, and adenocarcinoma:** Doxorubicin and cyclophosphamide, or methotrexate.
- **Head and neck squamous cell:** *Cis*-platinum and bleomycin, or methotrexate.
- **Choriocarcinoma:** Methotrexate.

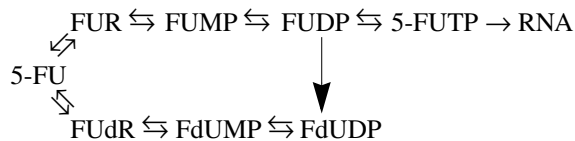
Tumor cells acquire resistance to methotrexate as the result of several factors, including the following:

- The deletion of a high-affinity, carrier-mediated transport system for reduced folates.
- An increase in the concentration of dihydrofolate reductase.
- The formation of a biochemically altered reductase with reduced affinity for methotrexate.

To overcome this resistance, higher doses of methotrexate need to be administered. The effects of methotrexate may be reversed by the administration of **leucovorin**, the reduced folate. This leucovorin “rescue” prevents or reduces the toxicity of methotrexate, which is expressed as mouth lesions (stomatitis), injury to the gastrointestinal epithelium (diarrhea), leukopenia, and thrombocytopenia.

## PYRIMIDINE ANALOGS

**Fluorouracil** and **fluorodeoxyuridine** (floxuridine) inhibit pyrimidine nucleotide biosynthesis and interfere with the synthesis and actions of nucleic acids. To exert its effect, fluorouracil (5-FU) must first be converted to nucleotide derivatives such as 5-fluorodeoxyuridylylate (5-FdUMP). Similarly, floxuridine (FUdR) is also converted to FdUMP by the following reactions:



FdUMP inhibits **thymidylate synthetase**, and this in turn inhibits the essential formation of DTTP, one of the four precursors of DNA. In addition, 5-FU is sequentially converted to 5-FUTP, which becomes incorporated into RNA, thus inhibiting its processing and functioning.

Fluorouracil is used for the following types of cancer:

- **Breast carcinoma:** Cyclophosphamide, methotrexate, fluorouracil, and prednisone (CMP + P). The alternate drugs are doxorubicin and cyclophosphamide.
- **Colon carcinoma:** Fluorouracil.
- **Gastric adenocarcinoma:** Fluorouracil, doxorubicin (Adriamycin), and mitomycin (FAM), or fluorouracil and semustine.

- **Hepatocellular carcinoma:** Fluorouracil alone or in combination with lomustine.
- **Pancreatic adenocarcinoma:** Fluorouracil.

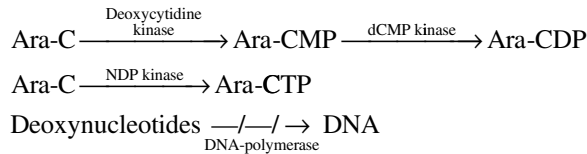
Resistance of 5-FU occurs as the result of one or a combination of the following factors:

- Deletion of uridine kinase
- Deletion of nucleoside phosphorylase
- Deletion of orotic acid phosphoribosyltransferase
- Increased thymidylate kinase

Because 5-FU is metabolized rapidly in the liver, it is administered intravenously and not orally. 5-FU causes myelosuppression and mucositis.

### DEOXYCYTIDINE ANALOGS

**Cytosine arabinoside (Cytarabine, Cytosar, and Ara-C)** is an analog of deoxycytidine, differing only in its substitution of sugar arabinose for deoxyribose. It is converted to Ara-CTP, and thereby inhibits DNA polymerase according to the following reactions:



Cytosine arabinoside is used in the treatment of acute granulocytic leukemia. Doxorubicin; daunorubicin and cytarabine; cytarabine and thioguanine; or cytarabine, vincristine, and prednisone are the combinations of agents employed.

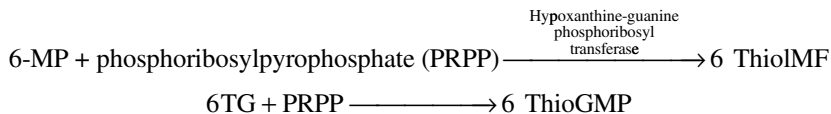
Resistance to cytosine arabinoside may stem from the following factors:

- The deletion of deoxycytidine kinase
- An increased intracellular pool of dCTP, a nucleotide that competes with Ara-CTP
- Increased cytidine deaminase activity, converting Ara-C to inactive Ara-U

The toxic effects of cytosine arabinoside are myelosuppression and injury to the gastrointestinal epithelium, which causes nausea, vomiting, and diarrhea.

### PURINE ANTIMETABOLITES

6-Mercaptopurine (6MP) and 6-thioguanine (6TG) are analogues of the purines hypoxanthine and guanine, which must be activated by nucleotide formation, according to the following scheme:



ThioIMP and ThioGMP are feedback inhibitors of **phosphoribosylpyrophosphate amidotransferase**, which is the first and rate-limiting step in the synthesis of purine. In addition, these analogues inhibit the *de novo* biosynthesis of purine and block the conversion of inosinic acid to

adenylic acid or guanylic acid. The triphosphate nucleotides are incorporated into DNA, and this results in delayed toxicity after several cell divisions. **6-Mercaptopurine** is used in the treatment of acute lymphoid leukemia. Maintenance therapy makes use of both methotrexate and 6-mercaptopurine. Mercaptopurine is absorbed well from the gastrointestinal tract. It is metabolized through (1) methylation of the sulfhydryl group and subsequent oxidation and (2) conversion to 6-thiouric acid by the aid of xanthine oxidase, which is inhibited by allopurinol. Mercaptopurine may cause hyperuricemia. Its chief toxicities are hepatic damage and bone marrow depression.

Thioguanine is used in patients with acute granulocytic leukemia, usually in combination with cytosine arabinoside and daunorubicin.

## NATURAL PRODUCTS

### VINCA ALKALOIDS

The vinca alkaloids (**vinblastine**, **vincristine**, and **vindesine**), which bind to tubulin, block mitosis with metaphase arrest. Vinca alkaloids are used for the following types of cancer:

- **Acute lymphoid leukemia:** In the induction phase, vincristine is used with prednisone.
- **Acute myelomonocytic or monocytic leukemia:** Cytarabine, vincristine, and prednisone.
- **Hodgkin's disease:** Mechlorethamine, Oncovin (vincristine), procarbazine, and prednisone (MOPP).
- **Nodular lymphoma:** Cyclophosphamide, Oncovin (vincristine), and prednisone (CVP).
- **Diffuse histiocytic lymphoma:** Cyclophosphamide, Adriamycin (doxorubicin), vincristine, and prednisone (CHOP); bleomycin, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), and prednisone (BACOP); or cyclophosphamide, Oncovin (vincristine), methotrexate, and cytarabine (COMA).
- **Wilms' tumor:** Dactinomycin and vincristine.
- **Ewing's sarcoma:** Cyclophosphamide, dactinomycin, or vincristine.
- **Embryonal rhabdomyosarcoma:** Cyclophosphamide, dactinomycin, or vincristine.
- **Bronchogenic carcinoma:** Doxorubicin, cyclophosphamide, and vincristine.

The chief toxicity associated with vinblastine use is bone marrow depression. The toxicity of vincristine consists of paresthesia, neuritic pain, muscle weakness, and visual disturbances. In addition, both vinblastine and vincristine may cause alopecia.

### DACTINOMYCIN

The antibiotics that bind to DNA are nonspecific to the cell-cycle phase. Dactinomycin (actinomycin D and Cosmegen) binds to double-stranded DNA and prevents RNA synthesis by inhibiting DNA-dependent RNA polymerase. It is administered intravenously in the treatment for pediatric solid tumors such as **Wilms' tumor** and **rhabdomyosarcoma** and for gestational **choriocarcinoma**. Dactinomycin causes skin reactions, gastrointestinal injury, and delayed bone marrow depression.

### MITHRAMYCIN

The mechanism of action of mithramycin (Mithracin) is similar to that of dactinomycin. It is used in patients with advanced disseminated tumors of the testis and for the treatment of hypercalcemia associated with cancer. Mithramycin may cause gastrointestinal injury, bone marrow depression, hepatic and renal damage, and hemorrhagic tendency.

## DAUNORUBICIN AND DOXORUBICIN

Daunorubicin (**Daunomycin** and **Cerubidine**) and doxorubicin (**Adriamycin**) bind to and cause the intercalation of the DNA molecule, thereby inhibiting DNA template function. They also provoke DNA chain scission and chromosomal damage.

Daunorubicin is useful in treating patients with acute lymphocytic or acute granulocytic leukemia. Adriamycin is useful in cases of solid tumors such as sarcoma, metastatic breast cancer, and thyroid cancer. These agents cause stomatitis, alopecia, myelosuppression, and cardiac abnormalities ranging from arrhythmias to cardiomyopathy.

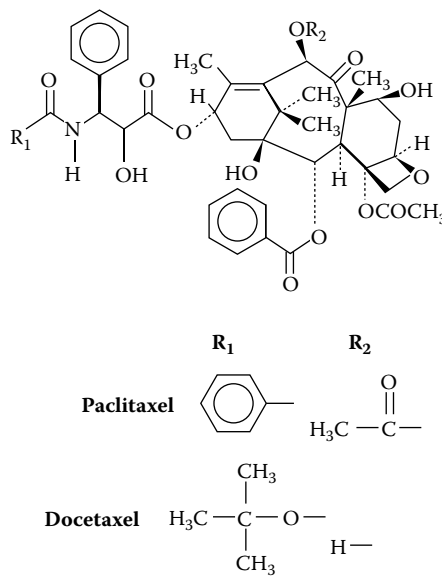
## BLEOMYCIN

Bleomycin (**Blenoxane**) causes chain scission and fragmentation of DNA. With the exception of the skin and lungs, most tissues can enzymatically inactivate bleomycin. Bleomycin is used in the management of squamous cell carcinoma of the head, neck, and esophagus in combination with other drugs in patients with testicular carcinoma and in the treatment of Hodgkin's disease and other lymphomas. Bleomycin causes stomatitis, ulceration, hyperpigmentation, erythema, and pulmonary fibrosis.

## PACLITAXEL AND DOCETAXEL

Paclitaxel (**Taxol**) is a diterpenoid compound that contains a complex taxane ring as its nucleus (Figure 62.1). The side chain linked to the taxane ring at carbon 13 is essential for its antitumor activity. Modification of the side chain has led to identification of a more potent analogue, docetaxel (Taxotere), which has clinical activity against breast and ovarian cancers. Originally purified as the parent molecule from yew bark, paclitaxel can now be obtained for commercial purposes by semisynthesis from **10-desacetylbaccatin**, a precursor found in yew leaves. It also has been successfully synthesized from simple off-the-shelf reagents in a complex series of reactions.

Taxol binds specifically to the  $\beta$ -tubulin subunit of microtubules and appears to antagonize the disassembly of this key cytoskeletal protein, with the result that bundles of microtubules and



**FIGURE 62.1** Chemical structures of paclitaxel (taxol) and its more potent analog, docetaxel (taxotere).

aberrant structures derived from microtubules appear in paclitaxel-treated cells. Arrest in mitosis follows. Cell killing is dependent on both drug concentrations and duration of cell exposure. Paclitaxel has undergone initial phases of testing in patients with metastatic ovarian and breast cancer; it has significant activity in both diseases, including diseases in patients that have progressed on standard primary combination regimens. Response rates in relapsed patients range from 20 to 50%, depending on the treatment history and the regimen employed. Early trials indicate significant response rates in lung, head and neck, esophageal, and bladder carcinomas as well.

Paclitaxel exerts its primary toxic effects on the bone marrow. Neutropenia usually occurs 8 to 11 d after a dose and reverses rapidly by 15 to 21 d. Many patients experience myalgias for several days after receiving paclitaxel. In high-dose schedules, a stocking-glove sensory neuropathy can be disabling, particularly in patients with underlying diabetic or alcoholic neuropathy (see Suffness, 1995).

## MISCELLANEOUS ANTINEOPLASTIC AGENTS

### ASPARAGINASE

Normal cells are able to synthesize asparagine but neoplastic tissues must obtain it from external sources. By metabolizing asparagine, asparaginase (Elspar) deprives the neoplastic tissues of asparagine, and in turn inhibits protein and nucleic acid synthesis. The resistant tumors are thought to possess higher than ordinary amounts of asparagine synthetase. Asparaginase, which is prepared from *Escherichia coli*, is used to induce remission of acute lymphocytic leukemia. Asparaginase causes malaise, anorexia, chills, fever, and hypersensitivity reactions. In general, it does not damage the bone marrow or other rapidly growing tissues as much as other antineoplastic agents do.

### HYDROXYUREA

Hydroxyurea suppresses DNA synthesis by inhibiting ribonucleoside diphosphate reductase, which catalyzes the reduction of ribonucleotides to deoxyribonucleotides. Hydroxyurea is used in chronic cases of granulocytic leukemia that are unresponsive to busulfan. In addition, it is used for acute lymphoblastic leukemia. Hydroxyurea may cause bone marrow depression.

### CIS-PLATINUM

*Cis*-platinum (cisplatin) binds to intracellular DNA, causing both interstrand and intrastrand cross-linking. It is a cell-cycle phase nonspecific agent. *Cis*-platinum, which is ineffective orally, is used for testicular, bladder, and head and neck cancers. It precipitates nephrotoxicity, ototoxicity, and gastrointestinal injury.

### CARBOPLATIN

Carboplatin is a promising second-generation platinum agent. Because it is less reactive, it causes less nephrotoxicity, myelosuppression, and thrombocytopenia.

### PROCARBAZINE

Procarbazine (Matulane) inhibits DNA, RNA, and protein synthesis through the operation of an unknown mechanism. It is effective in patients with Hodgkin's disease when given in combination with mechlorethamine, vincristine, and prednisone (MOPP). Procarbazine causes neurotoxicity, bone marrow depression, and gastrointestinal injury.

**ETOPOSIDE**

Etoposide is used to combat several types of tumors, including testicular and small-cell lung cancers, lymphoma, leukemia, and Kaposi's sarcoma.

**CANCER CHEMOTHERAPY-INDUCED EMESIS**

Nausea and vomiting are frequent side effects of radiotherapy and cancer chemotherapy. The incidence of this is relatively low for bleomycin, vincristine, and chlorambucil but is high for the remaining agents. Besides **prochlorperazine** and **metoclopramide** (dopamine receptor-blocking agents), **nabilone** (a cannabinoid), **batanopride**, **granisetron**, and **ondansetron** (all serotonin receptor-blocking agents) have been shown to be effective in ameliorating these symptoms.

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# 63 Tomatoes and Medicine

## LYCOPENE AND PROSTATE CANCER

Tomatoes, watermelons, pink grapefruits, papaya, rosehip, and berries contain lycopene. The role of tomatoes in medicine can be summarized as follows:

- Tomato-based food products such as tomato paste, tomato sauce, and tomato-based soups are rich in **carotenoid compounds** and are frequently consumed in the U.S. Foods such as these, which are high in carotenoid content, are of interest because of the demonstrated association between consumption of fruits and vegetables and reduced risk of lung and other epithelial cancers in humans. Unlike other fruits and vegetables where nutritional content such as vitamin C is diminished upon cooking, processing of tomatoes increases the concentration of bioavailable lycopene. Thus, processed tomato products such as tomato juice, soup, sauce, and ketchup contain the highest concentrations of lycopene. There is evidence that frequent intake of such products is associated with reduced risk of cardiovascular disease, cancer (especially prostate cancer), diabetes, osteoporosis, and even male infertility.
- **Lycopene**, the predominant carotenoid in tomatoes (*Solanum lycopersicum*), exhibits the highest antioxidant activity and **singlet oxygen quenching** ability of all dietary carotenoids.
- Carotenoids are substances with very special and remarkable properties that no other groups of substances possess, which form the basis of their many varied functions and actions in all kinds of living organisms. Without carotenoids, **photosynthesis** and all life in an oxygen atmosphere would be impossible.
- Some common carotenoids found in nature are **all-trans- $\beta$ -carotene**, **lycopene**,  **$\alpha$ -carotene**,  **$\beta$ -cryptoxanthin**, **canthaxanthin**, **zeaxanthin**, **antheraxanthin**, **violaxanthin**, **lutein**, **9-cis- $\beta$ -carotene**, and **15,15-cis-phytoene**.
- Lycopene, in addition to possessing antioxidant activities, **induces gap junction communication**, inhibits the growth of chemically transformed cells, and retards cell proliferation. Unlike  $\beta$ -carotene, lycopene does not have provitamin A activity. Carotenoids have recently been implicated in the prevention of or protection against serious human health disorders such as cancer and heart disease. At present, available data point to a possible role of lycopene in human health, which may be related to its antioxidant activities and influence on cell growth and intercellular communication. However, more information is required to firmly establish its role in health protection and to identify the underlying biochemical mechanisms. Lycopene might interact with other food components providing additive or synergistic effects. One important aspect of lycopene research is the bioavailability of this compound and its metabolism to derivatives, which might also exhibit biological activities contributing to its potential cancer-preventing property.



## HISTORY OF CAROTENOIDS

**Lycopene** was introduced into the Western world after the Spanish conquistador **Hernando Cortes** was offered some tomatoes by the **Aztec emperor Montezuma**. Cortes disregarded this courteous gesture and went on to conquer Mexico from 1529 to 1531. In the states bordering Mexico — Texas, New Mexico, Arizona, and California — tomatoes and other Mexican-Indian foods soon began to be adopted but also made their way to Europe. In Italy, tomatoes were mentioned as early as in 1554 and were then slowly assimilated. Their initial color was yellow (pomo d'oro); they obtained their red appearance only after years of cultivation. Today, tomatoes, the major source of lycopene, are an important part of the Mediterranean diet.

Awareness of lycopene as a potentially beneficial carotenoid in the nutritional and medical sciences is less than 10 years old. Therefore, comparatively few scientific data are available from animal and human studies. But in this short time, a number of features of lycopene have emerged that are unique among the common carotenoids, quite apart from its exceptionally high singlet oxygen quenching capacity *in vitro*. The most obvious distinction is that unlike the other hydrocarbon carotenoids,  $\alpha$ - and  $\beta$ -carotene, lycopene has no provitamin A activity.

## PHYSICOCHEMICAL NATURE OF CAROTENOIDS

Similar to other carotenoids, lycopene is a natural pigment synthesized by plants and microorganisms, but not by animals. More than 600 carotenoids have been identified in nature. Inasmuch as they all possess many conjugated double bonds — usually 9 to 13, each can form many geometric isomers.  $\beta$ -Carotene, for example, with nine double bonds in its polyene chain that are free to assume *cis/trans* configurations, can theoretically form 272 isomers, whereas its asymmetric isomer,  $\alpha$ -carotene, can form 512. Thus, the total possible number of compounds in the class, including all possible isomers, easily exceeds 200,000. As they are nonpolar, they are largely associated with lipophilic parts of the cell, including membranes.

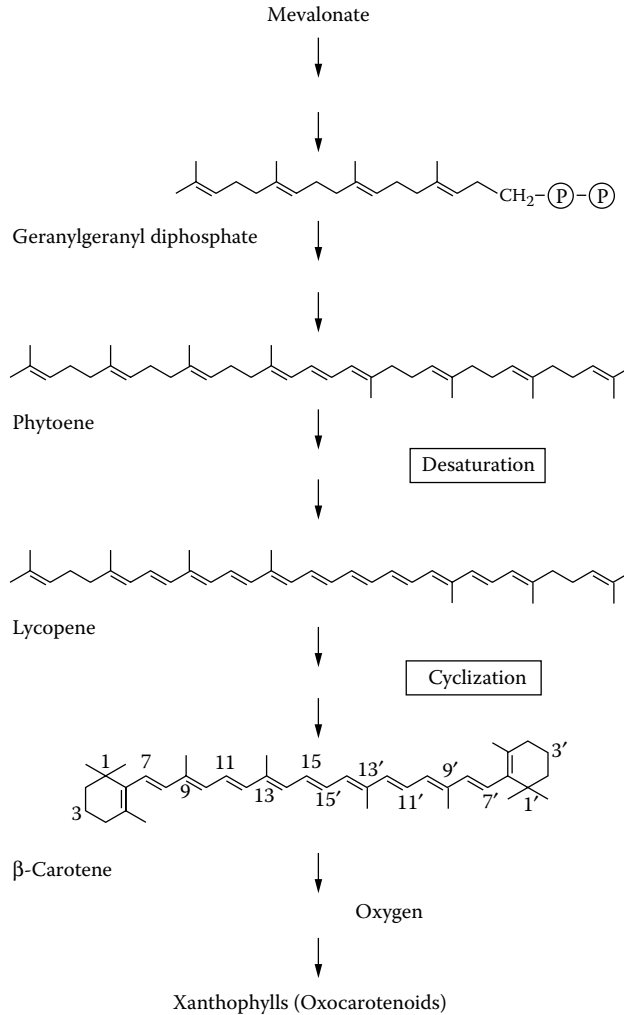
## LYCOPENE: AN IMPORTANT CAROTENOID IN TUMOR SUPPRESSION

Carotenoids are important plant pigments found in the photosynthetic pigment–protein complex of plants, photosynthetic bacteria, fungi, and algae and are responsible for the bright colors of various fruits and vegetables. Among the more than 600 different carotenoids, there are well-known compounds such as lycopene and  $\alpha$ - and  $\beta$ -carotene (Figure 63.1 and Figure 63.2), which are widely used as sources for vitamin A or as food colorants.

Carotenoids are tetraterpenes formed by tail-to-tail linkage of two C-20 units and, in many carotenoids, the end groups are modified into five- or six-membered rings giving monocyclic or dicyclic compounds. Lycopene is an acyclic carotenoid that contains 11 conjugated double bonds arranged linearly in the all-*trans* form. It belongs to the subgroup of carotenes consisting only of hydrogen and carbon atoms.

## CAROTENOID CONTENT OF FRUITS AND VEGETABLES

Carrots, tomatoes, and dark green vegetables are rich in specific carotenoids. Numerous epidemiological studies have shown that the increased intake of fruits and vegetables is associated with a reduced risk of lung and other epithelial cancers. Accurate food composition data have been prepared to test the association between dietary intake of specific carotenoids and disease incidence (Table 63.1).



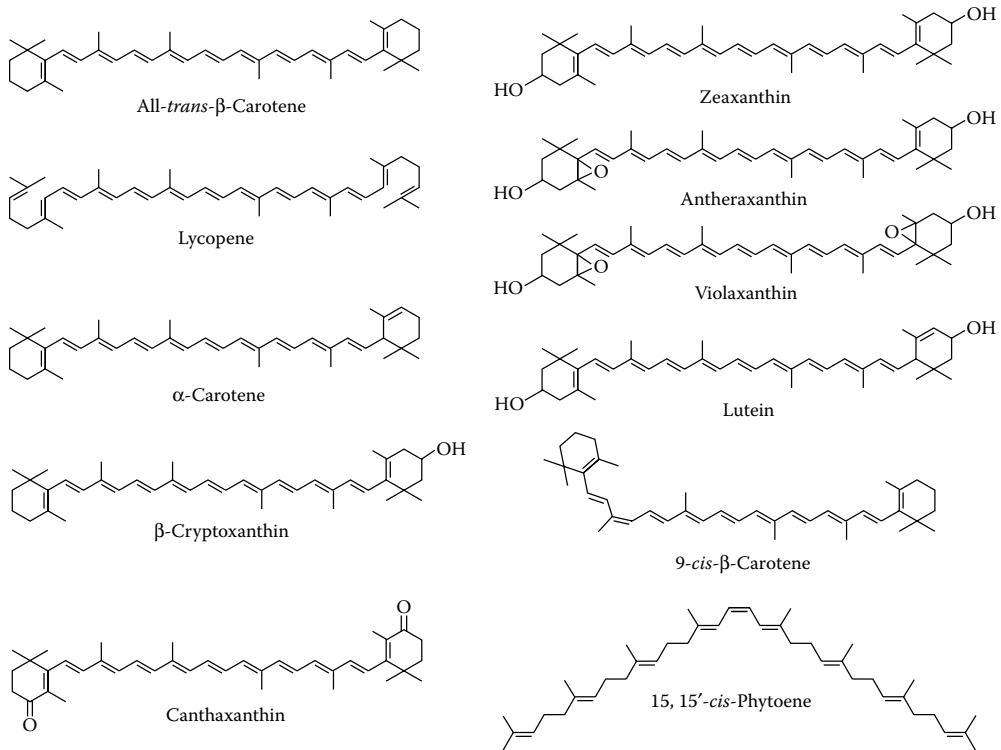
**FIGURE 63.1** Starting with mevalonate, carotenoids are biosynthesized by a special branch of the terpenoid pathway. The first C-40 hydrocarbon unit formed is phytoene, a carotenoid with three conjugated double bonds, which then is enzymatically desaturated to successively yield β-carotene, neurosporene, and lycopene. Other carotenoids such as β-carotene and oxocarotenoids are produced from lycopene following cyclization and hydroxylation reactions. Thus, lycopene is a central molecule in the biosynthesis pathway of carotenoids.

### DISTRIBUTION OF LYCOPENE IN HUMANS

It is conceivable that the different carotenoids have specialized functions in different tissues as has been shown for the xanthophylls lutein and zeaxanthin, which are virtually the only carotenoids occurring in the macular area of the retina. The distribution of lycopene in human tissues is shown in Table 63.2 and Table 63.3.

### CONCENTRATIONS OF CAROTENOIDS IN HUMAN ORGANS

The uneven but wide tissue distribution of most dietary carotenoids may indicate an active biological role for these compounds (see Chapter 20). The organs with the greatest number of low-density lipoprotein (LDL) receptors and the highest rates of lipoprotein uptake (adrenals, testes, and liver)



**FIGURE 63.2** Essentially all carotenoids, which are widespread in nature, possess certain common chemical features — a polyisoprenoid structure, a long conjugated chain of double bonds in the central portion of the molecule, and near symmetry around the central double bond. This basic structure can be modified in a variety of ways, most prominently by cyclization of the end groups and by the introduction of oxygen functions, to yield a large family of > 600 compounds, exclusive of *cis/trans* isomers.

**TABLE 63.1**  
**Lycopene Content of Foods**

Foods	States	Content (mg/100 g) <sup>a</sup>
Tomatoes	Fresh, raw	2937
	Fresh, cooked	3703
	Sauce, canned	6205
	Paste, canned	6500 (range 65400–15,000)
	Fresh, raw	3100 (range 879–4200)
	Juice, canned	8580 (range 5000–11,600)
Apricot	Catsup	9900
	Dried	864
	Canned, drained	65
Grapefruit	Raw	5
	Pink, raw	3362
Guava	Juice	3340
	Raw	5400 (range 5340–5500)
Rosehip	Puree, canned	780
Watermelon	Fresh, raw	4100 (range 2300–7200)
Papaya	Fresh	2000–5300

<sup>a</sup> Edible portion as wet weight.

**TABLE 63.2**  
**Concentration of Lycopene in Human Tissues (nmol/g Wet Tissue)**

	Testis	Adrenal	Liver	Ovary	Fat	Kidney	Brainstem
Lycopene (range)	4.34 (0.41–9.38)	1.90 (0.19–5.60)	1.28 (0.10–4.08)	0.25 (0.14–0.38)	0.20 (0.00–0.51)	0.15 (0.03–0.34)	Not detectable
	11.43 (3.26–63.9)	11.56 (2.04–58.5)	1.31 (0.16–10.3)	0.15 (0.09–5.56)	0.699 (0.02–3.70)	0.21 (0.05–1.20)	
Total carotenoids	7.6 ± 6.9 <sup>a</sup> 14.3	9.7 ± 7.8 18.3	5.1 ± 3.6 <sup>a</sup> 2.7	0.9 ± 0.5 <sup>a</sup> 1.4	0.8 ± 0.8 <sup>a</sup> 1.8	0.9 ± 0.7 <sup>a</sup> 0.53	< 0.04

<sup>a</sup> SEM.**TABLE 63.3**  
**Median Levels of Tissue Carotenoids (ptg/g Wet Tissue Range)**

Organs	n	Total					
		Carotenoids	Zeaxanthin	Crypto-Xanthin	Lycopene	α-Carotene	β-Carotene
Liver	13	2.7	0.292	0.035	1.31	0.112	0.977
Pancreas	13	2.0	0.443	0.040	0.687	0.106	0.670
Fat	12	1.8	0.788	0.025	0.699	0.050	0.202
Kidney	12	0.53	0.090	0.019	0.210	0.030	0.167
Adrenal	11	18.3	0.908	0.160	11.56	0.617	5.04
Spleen	11	0.52	0.097	0.020	0.100	0.050	0.235
Heart	7	0.44	0.035	0.025	0.188	0.050	0.123
Testes	5	14.3	0.211	0.068	11.430	0.257	2.34
Thyroid	3	0.43	0.047	0.020	0.155	0.050	0.135
Ovary		1.4	0.425	0.080	0.150	0.164	0.530

*Note:* Total carotenoids (mg/g wet tissue), as the sum of the major carotenoid fractions listed in the table.

generally contain the greatest amounts of carotenoids. It is generally believed that the carotenoids are primarily transported in blood by the LDL and that the LDL particles themselves take up the carotenoids by a passive mechanism.

Most of the organs (thyroid, spleen, kidney, liver, pancreas, and heart) investigated appear similar in that lycopene and β-carotene are the predominant carotenoids found in these organs, with an approximately equal percentage distribution between them. Selectively, the cellular uptake of individual carotenoids may be based upon the selective transport of the individual carotenoids.

## TOMATOES, LYCOPENE, AND CANCER RISK

Dietary recommendations to increase intake of citrus fruits, cruciferous vegetables, green and yellow vegetables, and fruits and vegetables high in vitamin A and C to lower cancer risk have been made by several organizations, including the National Research Council of the National Academy of Sciences, the National Cancer Institute, the American Cancer Society, the World Cancer Research Fund, and the American Institute for Cancer Research.

### LUNG AND PLEURAL CANCERS

One of the cancer sites for which a benefit of fruits and vegetables has been most apparent is for cancers of the lung (the leading cause of cancer death worldwide). Although the focus has been

on  $\beta$ -carotene, the literature shows that several groups, including leafy green and yellow/orange vegetables, are associated with a lower risk of lung cancer.

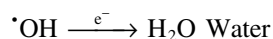
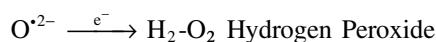
The relationship between tomatoes, lycopene, and other types of cancer are summarized as follows:

- **Stomach cancer:** Although it has become relatively uncommon in most economically developed countries, stomach or gastric cancer remains one of the major causes of cancer death in the world. Inverse associations between tomato consumption and risk of gastric cancer were observed in the U.S, Israel, Italy, Spain, Poland, Belgium, and Sweden. The consistent inverse association observed in diverse populations strongly suggests a protective effect of tomato and lycopene consumption on gastric cancer.
- **Colorectal cancer:** Cancers of the colorectum are common in economically developed areas. Five studies have reported on tomato intake in relation to colorectal cancer risk. One study in the U.S. reported statistically significant inverse associations between tomato consumption and colon cancer risk for men and women.
- **Oral/laryngeal/pharyngeal cancer:** Only three case-control studies have reported on tomato intake in relation to oral cancers. One study in China reported that high consumption of tomatoes was related to approximately half the risk of oral cancer. A similar finding was observed between tomato consumption and cancers of the oral cavity and pharynx in Italy.
- **Esophageal cancer:** Esophageal cancers have received little study regarding tomatoes and lycopene. One study in Iran, which has extremely high rates of esophageal cancer, particularly in men, found a 39% statistically significant reduction in risk for men who consumed tomatoes frequently, but no relationship was apparent for women.
- **Pancreatic cancer:** Four studies have examined tomato or lycopene status in relation to risk of pancreatic cancer; all of these studies support an inverse association.
- **Prostate cancer:** Three studies report data on the relationship between tomato or lycopene consumption and reduced prostate cancer (Giovannucci, 1999, 2005; Kirsh et al., 2006; Limpens et al., 2006; Matos et al., 2006; Stacewicz-Sapuntzakis and Bowen, 2005).
- **Bladder cancer:** Tomato or lycopene does not reduce the risk of bladder cancer.
- **Breast cancer:** Dietary-based studies do not support an association between tomato intake and risk of breast cancer.
- **Ovarian cancer:** No association between tomato consumption and ovarian cancer exists.

## QUENCHING OF REACTIVE OXYGEN BY LYCOPENE

**Oxidative stress** may be defined as that state in which “exposure to free radicals or other oxidants represent a challenge to normal function, or even to survival.” Such situations may arise from an increase in exposure to radicals/oxidants or may be the result of a decreased antioxidant capacity.

A *radical* is defined as an atom or group of atoms with an unpaired electron. Because free radicals are missing an electron in their outer shell, they are highly reactive, and in excess they can damage or kill cells in culture or cause lesions in an organism. The formation of oxygen radicals and their metabolites is summarized as follows:

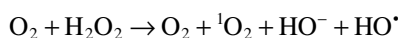


Therefore, the sequential addition of a single electron results in the formation of superoxide anion, hydrogen peroxide, hydroxyl radical, and water.

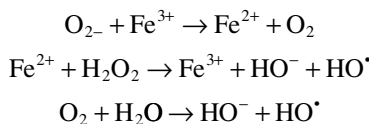
Hydroxyl radicals ( $\cdot\text{OH}$ ) are the most damaging free radicals. Although they exist only for a fraction of a second, they are able to destroy vital enzymes, cause linking of DNA, unleash proteolytic enzymes, tear apart polysaccharides, and cause lipid peroxidation altering membrane permeability and associated functions.

There are at least nine separate steps in which free radicals can be generated, which include the following items:

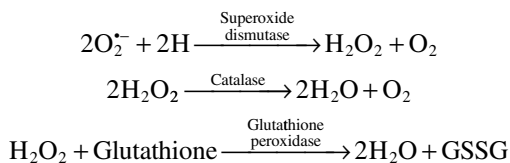
### Haber–Weiss reaction



### Fenton reaction



A number of enzymes (antioxidants) prevent oxidative damage from the reactive products of oxygen that are formed during normal metabolic events. These are



In addition, a number of compounds, such as vitamin E,  $\beta$ -carotene, uric acid, vitamin C, retinoic acid, iron chelators, vitamin E, glutathione, and zinc metallothionein (see Figure 13.4) have been shown to have antioxidant activities. Many of the putative biologic effects and health benefits of lycopene and other carotenoids are hypothesized to occur via protection against oxidative damage. The ability of lycopene to quench  ${}^1\text{O}_2$  or oxygen radicals is only beginning to be investigated in experimental systems. The quenching of  ${}^1\text{O}_2$  by lycopene and other carotenoids can occur through physical or chemical means. Physical quenching predominates and leaves the carotenoid intact, whereas chemical quenching is responsible for the decomposition of the carotenoid (“bleaching”). Physical quenching involves the transfer of excitation energy from  ${}^1\text{O}_2$  to the carotenoid, thereby producing ground-state oxygen and a carotenoid in the excited triplet state. The excess energy is dissipated as heat through rotational and vibrational interactions with the surrounding solvent and structures. The regeneration of the ground-state carotenoid allows it to function as a catalyst and undergo additional cycles of  ${}^1\text{O}_2$  quenching. The quenching capacity of carotenoid depends primarily on the number of conjugated double bonds, which accounts for the exceptionally high capacity exhibited by lycopene compared with many other carotenoids.

Lycopene may also interact with reactive oxygen species such as hydrogen peroxide and nitrogen dioxide. A recent study showed that lycopene was exceptionally potent and twice as effective as  $\beta$ -carotene in protecting lymphocytes from  $\text{NO}_2$  radical cell death and membrane damage.  $\beta$ -Carotene is an efficient scavenger of peroxy radicals, especially at low oxygen tension. Although less research has focused on lycopene, current studies suggest that lycopene is a more potent scavenger of oxygen radicals than other major dietary carotenoids.



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# 64 Ulcer Therapy with Herbal Medicine

## INTRODUCTION

Phytogetic agents have traditionally been used by herbalists and indigenous healers for the prevention and treatment of **peptic ulcer**. Botanical compounds with antiulcer activity include **flavonoids** (i.e., quercetin, naringin, silymarin, anthocyanosides, sophoradin derivatives), saponins (i.e., from *Panax japonicus* and *Kochia scoparia*), **tannins** (i.e., from *Linderae umbellatae*), and **gums** and mucilages (i.e., gum guar and myrrh). Among herbal drugs, **licorice**, **aloe gel**, and **capsicum** (chili) have been used extensively and their clinical efficacy documented. Also, ethno-medical systems employ several plant extracts for the treatment of peptic ulcer. Despite progress in conventional chemistry and pharmacology in producing effective drugs, the plant kingdom might provide a useful source of new antiulcer compounds for development as pharmaceutical entities or, alternatively, as simple dietary adjuncts to existing therapies (Borrelli and Izzo, 2000).

## ACID-PEPSIN DISEASE

The medical treatment of esophageal, gastric, and duodenal ulcer includes relieving the symptoms, accelerating healing, preventing complications, and preventing recurrence. Drug treatment includes the use of antacids, anticholinergic drugs, histamine H<sub>2</sub>-receptor antagonists, and inhibitors of H<sup>+</sup>K<sup>+</sup>-ATPase.

## PATHOGENESIS OF PEPTIC ULCER

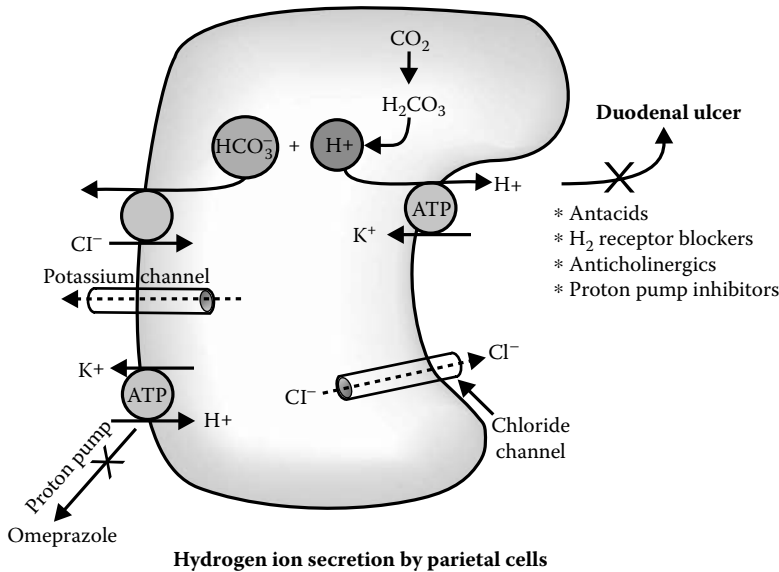
- The normal gastroduodenal mucosa has the following three defense mechanisms for resisting injury arising from the acid and peptic activity in gastric juice.
- The surface epithelial cells, which secrete mucus and bicarbonate
- The gastric mucosal cells, which have a specialized apical surface membrane that resists the diffusion of acid back into the cells
- The mucosal cells, which possess intrinsic mechanisms that resist injury, for example, by extruding back-diffused hydrogen ions using a basolateral carrier (e.g., sodium-hydrogen or sodium-bicarbonate exchange) (Figure 64.1)

About a third of the patients with duodenal ulcer suffer from an excess secretion of gastric acid. This may be due to an increase in the mass of acid-secreting gastric mucosa or to vagal hyperactivity, or both.

## PHYSIOLOGY OF GASTRIC ACID SECRETION

The parietal cells release hydrogen ions through the diversified mechanisms outlined in Figure 31.1. These mechanisms include the following:





**FIGURE 64.1** Omeprazole inhibits proton pump. H<sub>2</sub> = histamine<sub>2</sub>.

- **Histamine** stimulation of parietal cell function by increasing the formation of cyclic adenosine monophosphate (cyclic AMP)
- **Acetylcholine** and **gastrin** stimulation of parietal cell function by increasing the level of cytosolic calcium
- **Prostaglandin** inhibition of gastric acid secretion by blocking the formation of cyclic adenosine monophosphate
- **Omeprazole** inhibition of H<sup>+</sup>K<sup>+</sup>-ATPase

## DRUG THERAPY

### ANTACIDS

Because acid-pepsin disease rarely occurs in the absence of gastric acid and pepsin, antacids are highly effective in its overall management. Antacids consist of a mixture of magnesium, aluminum, and calcium compounds. Their efficacy is based on their inherent ability to react with and neutralize gastric acid. Sodium bicarbonate, which may leave the stomach rapidly, can cause alkalosis and sodium retention. Calcium salts may produce hypercalcemia, which can be detrimental in patients with impaired renal function. **Aluminum salts** may decrease the absorption of **tetracyclines** and anticholinergic drugs.

### ANTICHOLINERGIC DRUGS

Vagal impulses elicit the release of acetylcholine in the parietal cells and in the gastric mucosal cells containing gastrin, a peptide hormone. Both the directly released acetylcholine and the indirectly released gastrin then stimulate the parietal cells to secrete hydrogen ions into the gastric lumen.

The most useful anticholinergic drugs are **proprantheline** (Pro-Banthine), **pirenzepine**, and **telenzepine**, which antagonize muscarinic cholinergic receptors (M<sub>1</sub> receptors). All three agents depress gastric motility and secretion. The production of pepsin is also reduced. Proprantheline may be used as adjunctive therapy with antacids but not as a sole agent. The side effects and contrain-

dications of propantheline use are identical to those of atropine (prostatic hypertrophy, urinary retention, glaucoma, and cardiac arrhythmias).

The timing of medication is critical in ulcer therapy. Anticholinergic drugs should be given about 30 min before meals and antacids about 1 h after meals. A double dose of an antacid is often taken just before bedtime.

### HISTAMINE-RECEPTOR ANTAGONISTS

There are two types of histamine receptors: H<sub>1</sub> receptors, which are blocked by agents such as **diphenhydramine** and other antiallergic compounds, and H<sub>2</sub> receptors, which are blocked by **cimetidine** (Tagamet), **ranitidine** (Zantac), **famotidine** (Pepcid), and **nizatidine** (Axid). Cimetidine has no effect on most H<sub>1</sub> receptor-mediated effects, such as bronchoconstriction.

The clinical use of H<sub>2</sub>-receptor antagonists stems from their capacity to inhibit gastric acid secretion, especially in patients with peptic ulceration. Cimetidine, which is far more efficacious than anticholinergic drugs, is used in the treatment of duodenal ulcers and gastrinoma, and in patients suffering from gastroesophageal reflux. It is absorbed orally, has a plasma half-life of 2 h, and is excreted mainly unchanged by the kidney. The doses of cimetidine must be reduced in the presence of impaired renal function. The few and infrequent adverse effects of cimetidine use include the following:

- Gynecomastia (may bind to androgen receptor sites)
- Galactorrhea (especially in patients with gastrinoma)
- Granulocytopenia, agranulocytosis (very rare)
- Mental confusion (especially in elderly people)
- Restlessness, seizures, and reduced sperm count

Ranitidine is more effective than cimetidine and allegedly has fewer side effects.

### INHIBITORS OF H<sup>+</sup>K<sup>+</sup>-ATPASE

The proton pump (H<sup>+</sup>K<sup>+</sup>-ATPase) of the apical membrane of the parietal cells is the ultimate mechanism that governs acid secretion. Among a family of benzimidazole derivatives, **omeprazole** (Losec) promotes the healing of ulcers in the stomach, duodenum, and esophagus, and is of special value in patients who do not respond to H<sub>2</sub>-receptor antagonists.

## ACTIVE HERBAL PRODUCTS WITH ANTIULCER ACTIVITY

### FLAVONOIDS

Flavonoids are a group of about 4000 naturally occurring compounds with a wide range of biological effects, including antiulcer activity. They are important constituents of the human diet (a daily diet contains approximately 1 g of flavonoids per day) and are also found in several medicinal plants used in folk medicine around the world. Several mechanisms have been proposed to explain the gastroprotective effect of flavonoids:

- Increase of mucosal **prostaglandin** content
- Decrease of **histamine** secretion from mast cells by inhibition of histidine decarboxylase
- Inhibition of *Helicobacter pylori* growth

In addition, flavonoids have been found to be free-radical scavengers, and free radicals play an important role in ulcerative and erosive lesions of the gastrointestinal tract. In relation to their

**TABLE 64.1**  
**Flavonoids with Anticancer Activity**

Flavonoids	Ulcer Model
Anthocyanosides	Pylorus ligated, reserpine, phenylbutazone
Catechin	Stress
Genistin	Phenylbutazone, serotonin pylorus ligated, stress, reserpine
Hypolaetin-8-glucoside	Stress, ethanol, acetylsalicylic acid
Kaempferol	Ethanol
Leucocyanidin	Aspirin
Luteolin-7-glycoside	Pylorus ligated, stress, reserpine, phenylbutazone, serotonin
5-Methoxyflavone	Indomethacin
Myricetin 3-O-D-galactoside	Stress, pylorus ligated, ethanol
Naringin	Ethanol, stress, pylorus ligated
Quercetin	Stress, ethanol, reserpine
Rutin	Ethanol
Silymarin	Stress
Ternatin	Ethanol, indomethacin, stress
Vexibinol	HCl, ethanol

low toxicity and to the properties reported, flavonoids could have a therapeutic potential ideal for treatment of gastrointestinal diseases associated with *H. pylori* infection, i.e., type B gastritis and duodenal ulcer (Table 64.1).

## QUERCETIN

Quercetin is the most abundant of the flavonoid molecules and it is found in many medicinal botanicals, including *Thea sinensis*, *Glycyrrhiza glabra*, *Hypericum perforatum*, *Ginkgo biloba*, and many others. It has been reported to prevent gastric mucosal lesions produced by cold-restraint stress, pylorus ligation, reserpine, and ethanol or acidified ethanol. Quercetin increases the amount of neutral glycoproteins in the gastric mucosa. As these proteins are the most abundant and possibly the most important in the gastric mucosa, it can be assumed that their quantitative replacement is a return to normality of the mucosa, and thus a recovery of the defensive capacity against aggression from absolute ethanol.

Stimulation of local **prostaglandin** production is possibly one protective mechanism as quercetin stimulates the enzyme cyclooxygenase and, in addition, the **cyclooxygenase** inhibitor, **indomethacin**, reverses the protective effect of quercetin on ethanol-induced ulceration. The increase in prostaglandin synthesis may explain the increase in the amount of mucus observed and its participation in ulcer prevention. Other possible mechanisms include the following:

- Inhibition of the **gastric proton pump**
- Inhibition of the **lipoygenase pathway**
- Inhibition of **platelet activating** synthesis
- Inhibition of lipid peroxidation
- Scavenging of free radicals associated with a significant enhancement in **glutathione peroxidase** activity

An interesting aspect of the antiulcer effect of quercetin is that it has been shown to inhibit the growth of *Helicobacter pylori* in a dose-dependent manner *in vitro*.

## NARINGIN

Naringin has been shown to prevent gastric mucosal ulceration in several animal models, including restraint stress, pyloric occlusion, and ethanol-induced chronic ulcer. In ethanol-treated rats, naringin significantly reduced the ulcer index and increased the **hexosamine** content of the gastric mucus without affecting prostaglandin E<sub>2</sub> and the total protein content. Thus, the gastroprotective action of naringin could be explained, at least in part, through a complex nonprostaglandin-dependent mechanism that involves an increase in the glycoprotein content and viscosity of the gastric mucosa. Naringin also possesses antioxidant and superoxide anion scavenger properties that could contribute to its gastroprotective effect.

## ANTHOCYANOSIDES

Anthocyanosides, extracts from *Vaccinium myrtillus*, exert a significant preventive and curative antiulcer activity. Protective effects have been observed not only on ulcer induced by ligation of the pylorus, by reserpine, and by phenylbutazone, in which oral treatment was given before or simultaneously with ulcer formation, but also in ulcer induced by restraint or by acetic acid, in which the animal received treatment when the lesions were already established. The antiulcer activity is not exerted through a blockade of gastric secretion, but it is, in part, attributed to the increase in the mucus of the stomach wall. Anthocyanosides are thought to act by influencing the biosynthesis of the **mucopolysaccharides**, thus improving the efficiency of the mucus barrier at the gastric level.

## SOPHORADIN DERIVATIVES

Sophoradin has been isolated from the root of the ancient Chinese medical plant *Sophora subprostrata*, a plant used in China for the treatment of digestive diseases. Flavonoids derived from sophoradin are known to exhibit gastroprotective and ulcer-healing properties. **Solon**, a synthetic flavonoid derived from sophoradin, has been shown to have antiulcer and gastroprotective effects by influencing the formation and metabolism of prostaglandins in the gastric mucosa.

## SAPONINS

Saponins are widely distributed in plants and are a particular form of **glycosides**. They are so-called because of their soaplike effect, which is due to their **surfactant properties**. They also have hemolytic properties and, when injected into the bloodstream, are highly toxic. When taken by mouth, saponins are comparatively harmless. According to the structure of the **aglycone** or **sapogenin** two kinds of saponin are recognized, the steroidal and triterpenoid type.

Plant materials often contain triterpenoid saponin in considerable amounts. With regard to plants with antiulcer activity, **licorice root** contains about 2 to 12% of **glycyrrhizic acid** and the seeds of the **horse chestnut** up to 13% of aescin. Several plants containing high amounts have been shown to possess antiulcer activity in several experimental ulcer models (Table 64.2).

Among these, saponins isolated from the rhizome of *Panax japonicus* and the fruit of *Kochia scoparia* (that contain approximately 20% of saponins) have been demonstrated to possess gastroprotective properties. Some **oleanolic acid oligoglycosides**, extracted from *P. japonicus* and *K. scoparia*, showed protective effects on ethanol- and indomethacin-induced gastric damage. Moreover, a methanol extract of *P. japonicus* rhizome was demonstrated to possess protective activity also on stress- or HCl-induced ulcers. The protective activities of all these active saponins are not due to inhibition of gastric acid secretion but probably due to activation of mucous membrane protective factors.

**TABLE 64.2**  
**Plants Containing Saponins with Antiulcer Activity**

Botanical Name	Part Plant	Ulcer Model
<i>Calendula officinalis</i>	Rhizome	Caffeine-arsenic, butadiene, pylorus ligated
<i>Calliandra portoticensis</i>	Leaves	Stress, pylorus ligated, <i>Escherichia coli</i>
<i>Glycyrrhiza glabra</i>	Root	Acetic acid, pylorus ligated
<i>Kochia scoparia</i>	Fruit	Ethanol, indomethacin
<i>Panax binnatifidus</i>	Rhizome	Psychological stress
<i>P. japonicus</i>	Rhizome	Stress, HCl
<i>Pyrenacantha staudtii</i>	Leaves	Indomethacine, serotonin, stress
<i>Rhigiocarya racemifera</i>	Leaves	Indomethacine, reserpine, serotonin
<i>Spartium junceum</i>	Flowers	Ethanol
<i>Veronica officinalis</i>	Aerial parts	Indomethacin, reserpine

**Aescin** is a mixture of saponins obtained from the seeds of *Aesculus hippocastanum* (horse chestnut). Aescin has been shown to possess antiulcer activity in various ulcer models (cold restraint and pylorus-ligated), an effect which is, in part, due to inhibition of gastric acid and pepsinogen secretion. However, aescin also prevents gastric lesions due to absolute ethanol, a model of gastric ulceration in which acid and pepsin do not play a significant role; thus, the protective effect of aescin involves other mechanisms, such as improvement of blood flow. It is unlikely that prostaglandins or the maintenance of surface mucus gel could play a role in aescin-induced gastroprotection as this saponin does not enhance prostaglandin E<sub>2</sub> levels, nor does it increase the amount (or the composition) of mucus in ethanol-induced gastric ulceration.

### TANNINS

Tannins are used in medicine primarily because of their astringent properties, which are due to the fact that they react with the proteins of the layers of tissue with which they come into contact. Tannins are known to “tan” the outermost layer of the mucosa and to render it less permeable and more resistant to chemical and mechanical injury or irritation; however, the correlation between the molecular structures of tannins and the astringent/antiulcer activity is not known.

When a low concentration of tannins is applied to the mucosa, only the outermost layer is tanned, becoming less permeable and affording an increased protection to the subjacent layers against the action of bacteria, chemical irritation and, to a certain extent, against mechanical irritation. High concentrations of tannins cause coagulation of the proteins of the deeper layer of the mucosa, resulting in inflammation, diarrhea, and vomiting.

Several plants with antiulcer active which contain tannins have been reported (Table 64.3).

**TABLE 64.3**  
**Plants Containing Tannins with Antiulcer Activity**

Botanical Name	Part Plant	Ulcer Model
<i>Calliandra portoticensis</i>	Leaves	Stress, pylorus ligated, <i>E. coli</i>
<i>Entandrophragma utile</i>	Bark	Ethanol
<i>Linderae umbellatae</i>	Stem	Stress
<i>Mallotus japonicus</i>	Bark	(Clinical study)
<i>Rhigiocarya racemifera</i>	Leaves	Indomethacin, reserpine, serotonin
<i>Veronica officinalis</i>	Aerial parts	Indomethacin, reserpine

A crude extract of *Linderae umbellatae* exhibited antipeptic and antiulcerogenic activity, and these effects were considered ascribable to the presence of tannins or related compounds. Nine condensed tannins (monomers, dimers, trimers, and tetramers) have been isolated and their antipeptic and antiulcer activity confirmed experimentally (pylorus ligated in rats and stress-induced gastric lesions in mice).

Marked differences were observed among monomers, dimers, trimers, and tetramers. Monomers and dimers did not inhibit peptic activity *in vitro*, whereas trimers displayed higher inhibition of peptic activity than tetramers (although tetramers showed higher astringency than trimers). In pylorus-ligated mice, trimers and tetramers clearly suppressed the peptic activity of gastric juice and also monomers and dimers slightly suppressed the peptic activity of mouse gastric juice *in vivo*. As monomers and dimers are inactive *in vitro*, it is possible that their activity *in vivo* is not related to the direct inhibition of pepsin, but related to influence on the secretion mechanism of pepsin.

## GUMS AND MUCILAGES

Gums and mucilages are usually brittle, amorphous, transparent, or translucent substances, which readily absorb water to form gelatinous masses or viscous colloidal solutions. The colloidal character of gums, mucilages, and other mucoids accounts largely for their use as therapeutic agents. Mucilaginous drugs have the property of covering and protecting the mucosa of the stomach and are used in the treatment of gastric ulcer. Plants containing mucilages traditionally used in several countries in the treatment of gastric ulcer include *Althaea officinalis*, *Cetraria islandica*, *Malva sylvestris*, *Matricaria chamomilla*, and *Aloe* species.

Guar gum is obtained from the endosperm of the seed of *Cyamopsis tetragonolobus*, a plant long cultivated in India and Pakistan and nowadays also grown in the U.S. The main constituent is a **galactomannan**, a  $\beta$ -1,4-linked d-mannose linear polysaccharide with an  $\alpha$ -1,6-linked d-galactose residue attached to every other D-mannose unit. Proposed mechanisms are reduced acidity, increased local mucosal supply of energy, and mechanical protection. Moreover, guar gum, in duodenal ulcer patients, decreases gastric acidity and the rate of emptying of gastric contents, probably because of its effects on viscosity and neutralization of gastric acidity.

**Myrrh**, an oleo-gum-resin obtained from *Commiphora molmol*, contains up to 60% gum and up to 40% resin. Myrrh pretreatment produced a dose-dependent protection against the ulcerogenic effects of different necrotizing agents such as ethanol, indomethacin, sodium hydroxide, or hypertonic sodium chloride. The protective effect of myrrh is attributed to its effect on mucus production or increase in nucleic acid and nonprotein sulfhydryl concentration, which appears to be mediated through its free-radical-scavenging, thyroid-stimulating, and prostaglandin-inducing properties.

## HERBAL DRUGS WITH ANTIULCER ACTIVITY

### LICORICE

Licorice, the root and rhizome of different varieties of *Glycyrrhiza glabra* (Leguminosae), has been extensively used in medicine for its antiulcer activity. The principal constituent of licorice is **glycyrrhizinic acid**, a triterpenoid saponin. This chemical class is known to offer protection against ulcers.

**Carbenoxolone** derives from the hydrolysis of glycyrrhizinic acid after its extraction from licorice root. Carbenoxolone was the first drug found to accelerate peptic ulcer healing by a mechanism not involving the inhibition of acid secretion. Several mechanisms of action have been proposed as follows to explain the pharmacological activity of carbenoxolone:

- Stimulates gastric mucus production
- Enhances the rate of incorporation of various sugars into gastric mucosal glycoproteins
- Promotes mucosal cell proliferation

- Inhibits mucosal cell exfoliation
- Inhibits prostaglandin degradation
- Increases the release of PGE<sub>2</sub> and reduces the formation of thromboxane B<sub>2</sub>
- Regulates DNA and protein synthesis in gastric mucosa

More recently, nitric oxide has been claimed to contribute to the antiulcer effect of carbenoxolone.

In excess, carbenoxolone produces effects similar to those of aldosterone excess (sodium retention and hypokalaemia leading to hypertension, edema, and cardiac failure).

## ALOE GEL

Two distinct preparations of *Aloe* plants are most used medicinally. The resinous leaf exudate (named aloe) is used as a laxative, and the mucilaginous gel (named aloe vera or aloe gel) from the leaf parenchyma is used as a remedy against a variety of skin disorders. Aloe gel had a prophylactic effect and was also curative if given as a treatment for stress-induced gastric ulceration in rats. A **lectin fraction** (glycoprotein) from *Aloe arborescens*, Aloctin A, had an antiulcer effect and another high-molecular-weight fraction, not containing glycoprotein, was very effective in healing ulcer induced by mechanical or chemicals stimuli but not those induced by stress. This fraction contained substances with molecular weights between 5,000 and 50,000 Da, which were considered both to suppress peptic ulcers and to heal chronic gastric ulcers. In addition, a component from Cape Aloe exudate, named **aloe ulcin**, suppressed ulcer growth and l-histidine decarboxylase.

## CAPSICUM (CHILI)

Capsicum, also known as chili or **paprika**, is the fruit of various *Capsicum* species. It is widely used as a spice and, traditionally, it has been used internally for **colic, flatulent dyspepsia, chronic laryngitis, insufficiency of peripheral circulation**, and externally for neuralgia. **Capsaicin** (the active pungent ingredient) has been used extensively as a probe to elucidate the function of sensory neurons in various organs and systems (including the stomach), because of its ability to excite and later defunctionalize a subset of primary afferent neurons.

Chili, as well as capsaicin, has a protective effect on ethanol- or aspirin-induced lesion formation in the gastric mucosa; in addition, capsaicin and long-term chili intake (360 mg daily for 4 weeks) protects against hemorrhagic-shock-induced gastric mucosal injury, an effect that may be mediated by capsaicin-sensitive afferent neurons. The pathophysiological basis of gastric protection by chili (capsaicin) remains unclear. An increase in gastric mucosal blood flow has been described and this may be related to the release of **calcitonin-gene-related peptide** and **nitric oxide** rather than to the production of prostaglandins. The protective effect of capsicum could also involve **vanilloid receptors** because **resiniferatoxin**, an ultrapotent analogue of capsaicin present in the latex of *Euphorbia resinifera* (Euphorbium), also displays antiulcer activity and both capsaicin and resiniferatoxin act on vanilloid (capsaicin) receptors.

Chili causes dyspepsia in patients with or without ulcer, and patients with ulcer are often advised to avoid its use. Therefore, patients with peptic ulcer consume less **chili** than controls. Nevertheless, epidemiological and clinical data suggest that chili ingestion may have a beneficial effect on human peptic ulcer disease. For examples, chili has a gastroprotective effect on aspirin-induced gastric mucosal injury in humans. In addition, chili ingestion has no detrimental effect on the healing rates of patients with duodenal ulcer and it does not cause macroscopic gastroduodenal mucosal injury in humans. By contrast, chili increases DNA loss and microbleeding, suggesting the occurrence of cellular damage (see Borrelli and Izzo, 2000).

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# 65 Valerian

## INTRODUCTION

Valerian is used in the treatment of insomnia and stress and anxiety. The important active compounds of valerian are the **valepotriates** (iridoid molecules) and **valeric acid**. These compounds are found exclusively in valerian. Originally, it was thought that just the valepotriates were responsible for valerian's sedative effects but, recently, an aqueous extract of valerian has also been shown to have a sedative effect. As the valepotriates are not soluble in water, it was concluded that valeric acid also possesses sedative action and is the chemical factor responsible for the sedative effect noted in human clinical trials with aqueous extracts of valerian (Murray, 1995). **Valerian inhibits the uptake of GABA and enhances the release of GABA.**

## VALERIAN IN THE MANAGEMENT OF INSOMNIA

**Insomnia** is one of the most common complaints in general medical practice and its treatment is predicated upon proper diagnosis. A variety of pharmacological agents are available for the treatment of insomnia. The "perfect" hypnotic would allow sleep to occur with normal sleep architecture, rather than produce a pharmacologically altered sleep pattern. It would not cause next-day effects, either of **rebound anxiety** or continued sedation. It would not interact with other medications. It could be used chronically without causing dependence or rebound insomnia on discontinuation. Regular moderate exercise meets the criteria, but often is not effective by itself, and patients with significant cardiorespiratory disease may not be able to exercise. However, even small amounts of exercise often are effective in promoting sleep. Although the precise function of sleep is not known, adequate sleep improves the quality of daytime wakefulness, and hypnotics should be used judiciously to avoid its impairment.

The National Institute of Mental Health Consensus Development Conference divided insomnia into three categories as follows:

1. **Transient insomnia** lasts less than 3 d and usually is caused by a brief environmental or situational stressor. It may respond to attention to sleep hygiene rules. If hypnotics are prescribed, they should be used at the lowest dose and for only 2 to 3 nights.
2. **Short-term insomnia** lasts from 3 d to 3 weeks and is usually caused by an ongoing personal stressor such as illness, grief, or job problems. Again, sleep hygiene education is the first step. Hypnotics may be used adjunctively for 7 to 10 nights. Hypnotics are best used intermittently during this time, with the patient skipping a dose after 1 to 2 nights of good sleep.
3. **Long-term insomnia** is insomnia that lasts for more than 3 weeks; no specific stressor may be identifiable. A more complete medical evaluation is necessary in these patients, but most do not need an all-night sleep study.



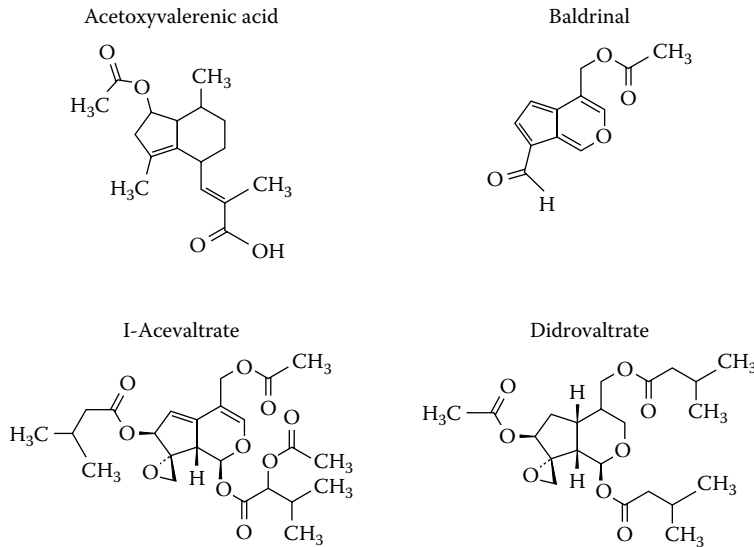


FIGURE 65.1 Principal constituents of valerian.

## THE USE OF VALERIAN IN FOLK MEDICINE AND TRADITIONAL SYSTEMS OF MEDICINE

In folk medicine and traditional systems of medicine, various species of valerian have been used as an oral infusion to treat **migraine headaches, hysteria, nervous unrest, neurasthenia, fatigue, seizures, stomach cramps** that cause vomiting, and other nervous conditions. Valerian also has been used internally as a spasmolytic, a carminative, and a stomachic, and externally on cuts, sores, and acne. Some herbalists recommend it as a possible vermifuge. In Chinese medicine, valerian is used to treat the aforementioned conditions, as well as chronic headache, numbness due to rheumatic conditions, colds, menstrual difficulties, and bruises. Because there has been no extensive research conducted on uses other than the sedative properties of valerian and its constituents, these other uses cannot be scientifically evaluated.

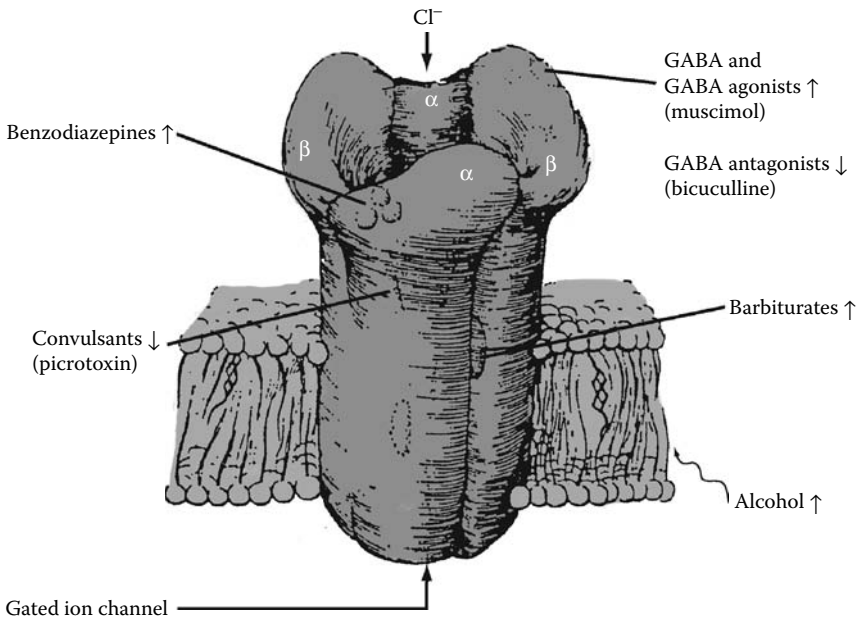
### VALERIAN

The commercial valerian products consist of, or are derived from, the rhizome, roots, and stolons of *Valeriana officinalis* L. The crude herb is dried and may be used as is or to prepare an extract that can be used to make an oral solution, tablet, capsule, or tea. Active constituents of valerian include **acetoxyvaleric acid, 1-acevaltrate, baldrinal, didrovaltrate, hydroxyvaleric acid, kessane derivatives, valeranone, valeranal, valeric acid, and valtrate** (Figure 65.1).

Valerian is used in the short-term treatment of insomnia characterized by difficulty in falling asleep and poor sleep quality. *Valeriana officinalis* L. inhibits reuptake of and stimulates the release of  $\gamma$ -aminobutyric acid (GABA), contributing to its sedative properties.

### $\gamma$ -AMINOBTYRIC ACID

GABA is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS). GABA is primarily synthesized from glutamate by the enzyme **L-glutamic acid-1-decarboxylase (GAD)**; it is subsequently transaminated with  $\alpha$ -oxoglutarate by **GABA- $\alpha$ -oxoglutarate transaminase (GABA-T)** to yield glutamate and succinic semialdehyde.



**FIGURE 65.2** Schematic model of the GABA<sub>A</sub> receptor. The receptor spans the cell membrane. GABA binds to the outside of the receptor, causing an influx of Cl<sup>-</sup> ions through the channel. Benzodiazepines and barbiturates interact with different recognition sites on the receptor and increase the effectiveness of GABA.

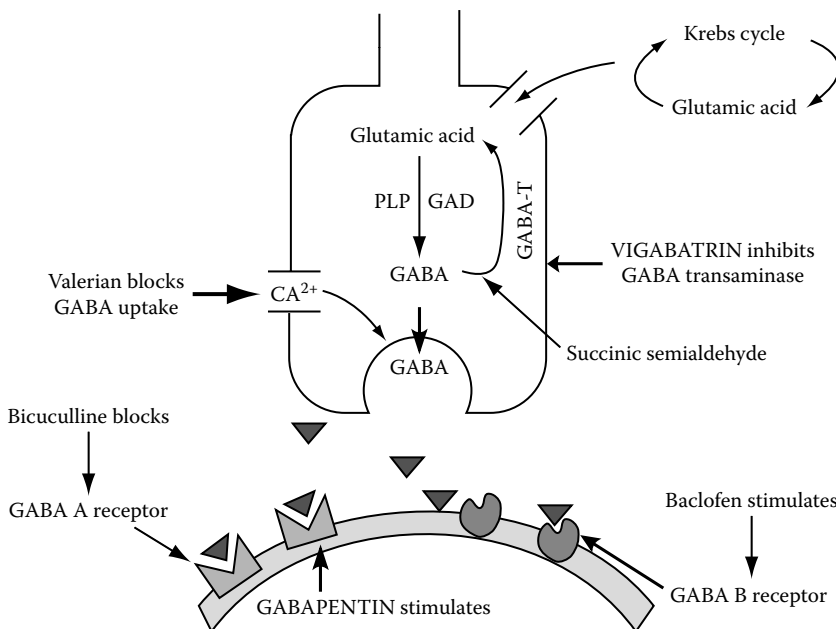
Two types of GABA receptors have been identified in mammals, a GABA<sub>A</sub> and a GABA<sub>B</sub> receptor. The GABA<sub>A</sub> receptor (or recognition site), when coupled with GABA, induces a shift in membrane permeability (primarily to chloride ions), causing a hyperpolarization of the neuron. This GABA receptor appears to be part of a macromolecule that contains, in addition to the GABA<sub>A</sub> receptor, a **benzodiazepine receptor** and the **chloride ionophore** (chloride channel) (Figure 65.2).

## BASIC MECHANISMS OF EPILEPSY

The basic mechanisms underlying convulsive disorders are so diverse that to seek a single cause would be a gross oversimplification. Rather, a number of different disorders, singly or in combination, may result in seizure discharge. However, one of the better-characterized defects concerns GABA and its role as a neurotransmitter. Biochemical lesions that interrupt the synthesis, storage, release, or postsynaptic actions of inhibitory neurotransmitters such as GABA lead to disinhibition of neurons.

The synthesis of GABA is achieved by decarboxylation of glutamate, which is mediated by GAD, a rate-limiting enzyme. The importance of this **pyridoxal phosphate**-dependent enzyme in the etiology of epilepsy is illustrated by a patient who suffered from seizures and who was found at autopsy to have reduced levels of pyridoxal phosphate as well as reduced GAD activity and GABA levels in the occipital cortex, which exhibited gliosis. Several compounds that have been found to lower the threshold for seizures or frankly to elicit seizures have also been found to inhibit GAD. Hence, reducing available GABA levels appears to represent a possible epileptogenic mechanism.

Several agents related to GABA metabolism and its receptors have been found to possess some degree of antiepileptic activity. Specific benzodiazepine and barbiturate receptors have been identified in the postsynaptic membrane, which, when activated by a benzodiazepine or barbiturate, enhance GABA binding to postsynaptic GABA receptors, resulting in prolonged chloride conductance and increased inhibition.



**FIGURE 65.3** The actions of drugs on GABAergic transmission. GABA =  $\gamma$ -aminobutyric acid; GAD = glutamic acid decarboxylase; PLP = pyridoxal phosphate. Substances that stimulate GABA<sub>A</sub> receptors (GABApentin) are anticonvulsants, those blocking GABA<sub>A</sub> receptors (Bicuculline) cause convulsive seizures, and those inhibiting GABA transaminase (Valproate) are anticonvulsants.

The anticonvulsant agents have been developed based on the knowledge of such epileptogenic mechanisms as illustrated by GABA deficiency (Figure 65.3).

## THE ANXIOLYTIC AGENTS

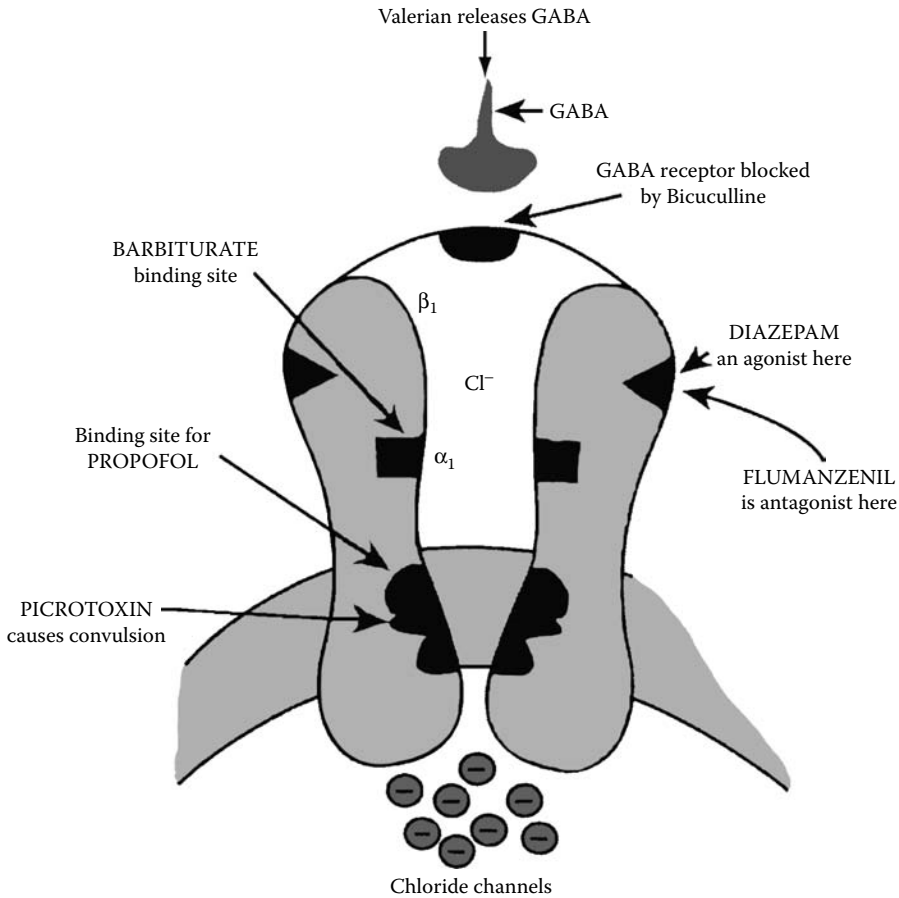
The anxiolytic agents consist of benzodiazepine derivatives and azaspirodecanedione derivatives.

The benzodiazepine derivatives class of antianxiety agents shares the property of binding to a benzodiazepine receptor, part of the GABA receptor–chloride channel complex whose function it modulates allosterically. Not only the anxiolytic effects of the benzodiazepines, but also the anti-convulsant, sedative, or muscle relaxant effects seem to be mediated by the GABA-related mechanism. Besides the direct involvement of the GABA system, in parallel or more downstream to this, several other neurotransmitters such as serotonin have been suggested to participate in different aspects of benzodiazepine action.

The azaspirodecanedione derivatives include **bupirone**, **gepirone**, and **ipsapirone**.

## PHARMACODYNAMICS OF BENZODIAZEPINES

The neurochemical basis for anxiety is only partially understood. Various manifestations of anxiety, such as palpitations and tremulousness, may be viewed as hyperactivity of the adrenergic system, and  $\beta$ -adrenergic receptor-blocking agents are effective for the treatment of acute stress reactions, adjustment disorders, generalized anxiety, panic disorder, and agoraphobia. The discovery of the benzodiazepine–GABA receptor–chloride ionophore complex furnished additional evidence that this complex participates in the etiology and manifestation of anxiety (Figure 65.4).



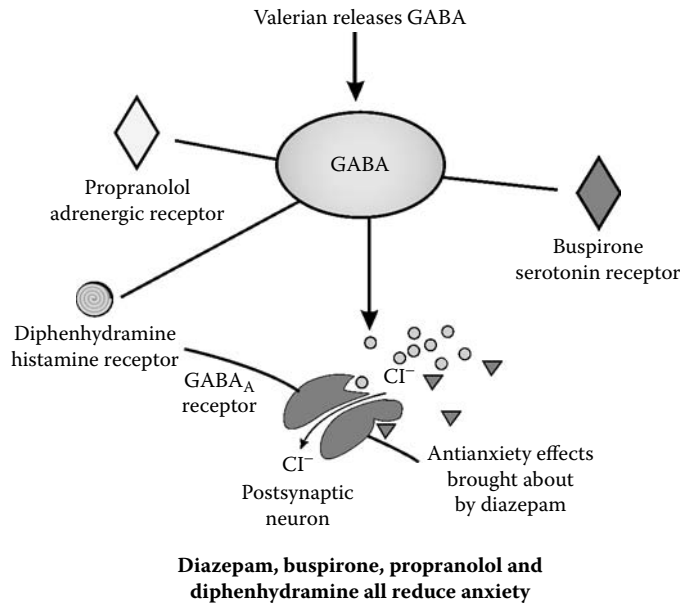
**FIGURE 65.4** GABA–benzodiazepine–chloride channel complex. GABA = g-aminobutyric acid.

## GABA RECEPTORS

GABA is the major neurotransmitter in the brain that mediates inhibition. Virtually every neuron in the brain is inhibited by GABA. GABA receptors have been divided into two types: A and B. The GABA<sub>A</sub> receptors are stimulated by GABA, **muscimol**, and **isoguvacine**, and are inhibited by the convulsants **bicuculline** and **picrotoxin**. GABA<sub>A</sub> receptors are associated with a chloride channel. GABA<sub>B</sub> receptors are stimulated by GABA and (–)**baclofen**, and are inhibited by **phaclofen**. GABA<sub>B</sub> receptors seem to be coupled to calcium and potassium channels, and possibly to second-messenger systems.

## BENZODIAZEPINE-BINDING SITES

The binding sites for benzodiazepines are divided into central and peripheral types. The central or neuronal benzodiazepine receptors are influenced by GABA, linked to chloride channel, and responsible for mediating the anxiolytic, sedative, and anticonvulsant properties of the benzodiazepines. The peripheral or nonneuronal benzodiazepine receptors are found in a variety of tissues, including the kidney, heart, lung, liver, adrenal gland, testis, intestinal smooth muscles, mast cells, platelets, several cell lines, and nonneuronal elements in the central nervous system (CNS).



**FIGURE 65.5** The anxiolytic effect of buspirone. GABA = g-aminobutyric acid.

The released GABA may modulate by inhibiting the functions of other neurons such as the noradrenergic, cholinergic, dopaminergic, and serotonergic neurons (Figure 65.5). Therefore, because benzodiazepine facilitates GABAergic functions, the anticonvulsant, muscle relaxant, sedative, hypnotic, and antianxiety effects of benzodiazepine may be elicited by GABAergic neurons and active metabolites, with longer half-lives. Consequently, it may be necessary to reduce the doses of those benzodiazepines with active metabolites.

Benzodiazepines may depict two- or three-compartment disposition kinetics. For example, a benzodiazepine derivative given in a suitable dose at night may impose dose-dependent effects, in that the concentration attained at night may be in the hypnotic range, whereas the concentration of the drug or its active metabolite or metabolites during the following day may be sufficient to produce antianxiety effects.

It is generally accepted that the pharmacology of benzodiazepine derivatives is identical qualitatively but varies quantitatively. In other words, the sedative, hypnotic, anticonvulsant, muscle relaxant, and anxiolytic properties reside to various degrees in all of them. Nevertheless, they do exhibit pharmacological specificity, making it necessary to select a particular drug for its desired therapeutic effect.

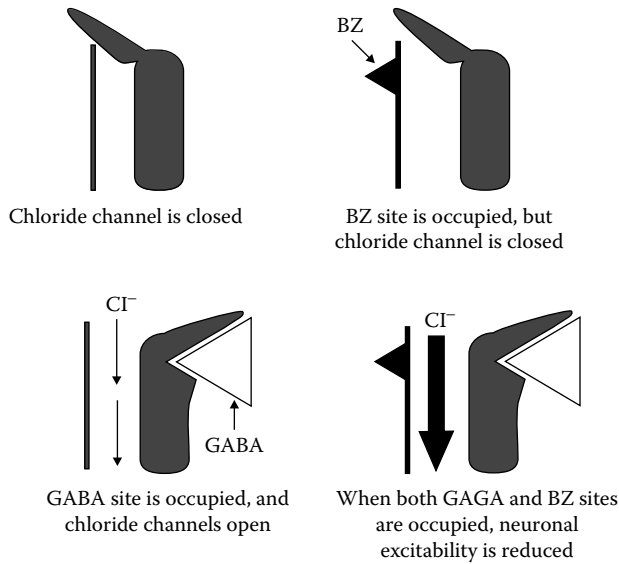
## MODE OF ACTION OF BENZODIAZEPINE DERIVATIVES

### ANTI-ANXIETY EFFECTS

Benzodiazepines, by facilitating GABAergic actions, exert their anxiety-reducing effects by depressing the hyperactivity of neuronal circuits in the limbic system. In addition, they may inhibit the hyperexcitability of hippocampal cholinergic and serotonergic neurons (see Figure 65.5).

### MUSCLE RELAXANT ACTIVITY

Benzodiazepines enhance presynaptic inhibition by releasing GABA from interneurons and by facilitating the action of glycine in the spinal cord and brain stem. Glutamate and aspartate have



**FIGURE 65.6** Diazepam opens the chloride channel. BZ = benzodiazepine; GABA =  $\gamma$ -aminobutyric acid.

excitatory effects on neurons, whereas GABA, glycine, and taurine have inhibitory actions in the CNS. Besides existing in spinal interneurons, excluding the cuneate nucleus, glycine is an inhibitory transmitter in the reticular formation.

### SEDATIVE EFFECTS

The sleep-promoting effects of benzodiazepines may relate to their ability to reduce hyperarousability and emotional tension. The anterograde amnesia produced by high doses may be due to their interference with hippocampal functions.

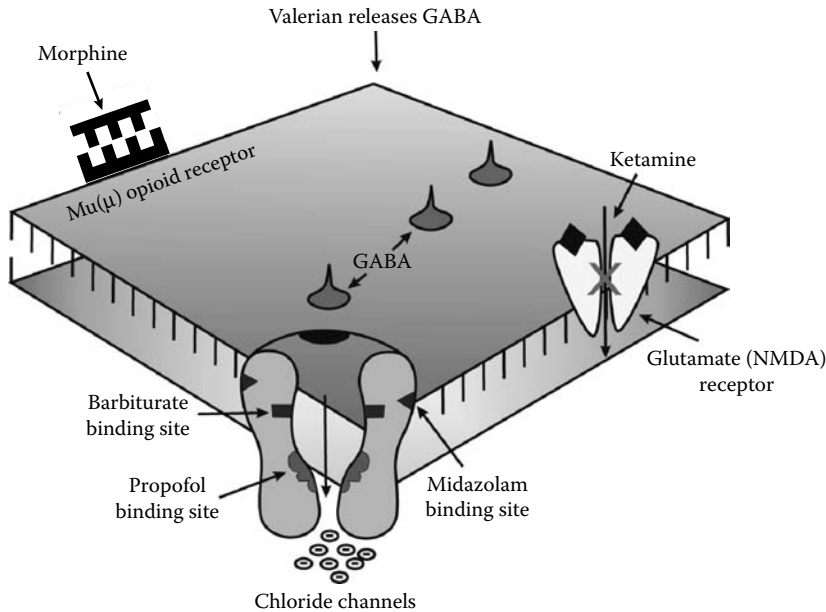
### ANTICONVULSANT ACTIVITY

Benzodiazepine derivatives are thought to exert their anticonvulsant activity by facilitating GABAergic transmission. Substances that inhibit the synthesis of GABA (e.g., **isoniazid**) or block the GABA recognition site (e.g., **bicuculline**) cause convulsions (Figure 65.6).

## MODE OF ACTIONS OF THE GENERAL ANESTHETICS

General anesthetics alter the excitation of the neuronal membrane and modify impulse conduction. Specifically, the general anesthetics have the following common properties: (1) They decrease the activity of neurons by increasing their threshold to fire, and (2) they prevent the action potential from rising to a normal rate by interfering with sodium influx (Figure 65.7).

Barbiturates and benzodiazepines act at two distinct recognition sites on the GABA<sub>A</sub> receptor/chloride channel molecular complex to potentiate GABA-mediated Cl<sup>-</sup> conductance and neuronal inhibition. The depressant effects of morphinelike opioids on neuronal activity are mediated by the  $\mu$ -opioid receptors. **Ketamine** appears to act not only by enhancing neuronal inhibition but also by blocking neuronal excitation. Ketamine binds to the **phencyclidine receptor**, a site located within the cation channel that is gated by the ***N*-methyl-D-aspartate type of glutamate receptor**. Binding to this receptor blocks cation conductance through the channel, thereby blocking the actions of glutamic acid, the principal excitatory neurotransmitter in the brain.



**FIGURE 65.7** The sites of action of general anesthetics. GABA =  $\gamma$ -aminobutyric acid.

## GLYCINE

Glycine is another inhibitory CNS neurotransmitter. Whereas GABA is located primarily in the brain, glycine is found predominantly in the ventral horn of the spinal cord. Relatively few drugs are known to interact with glycine; the best-known example is the convulsant **strychnine**, which appears to be a relatively **specific antagonist of glycine** (Figure 65.8).

## SEDATIVES AND HYPNOTICS

Sedatives and hypnotics may be divided into two categories: barbiturates and nonbarbiturates.

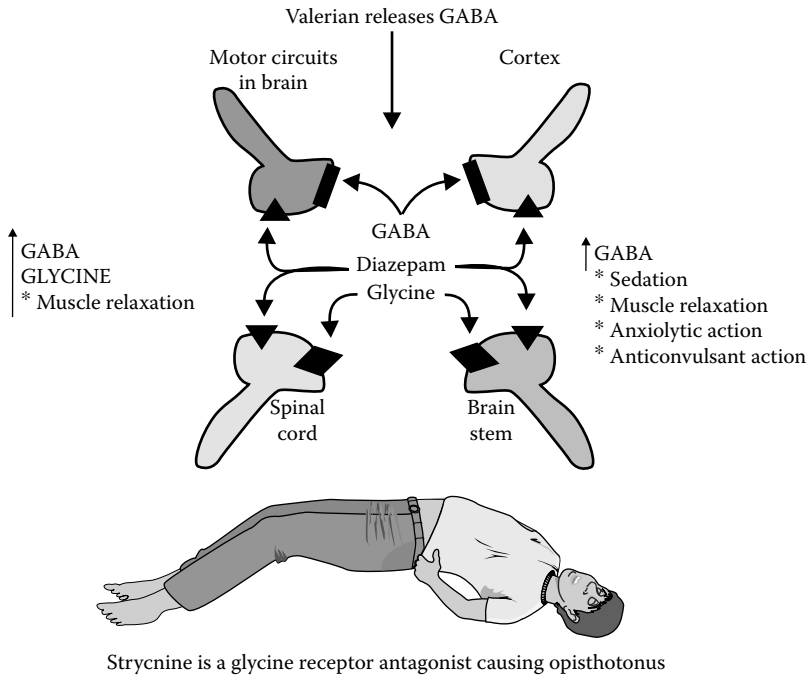
### THE BARBITURATES

The barbiturates were used extensively in the past as hypnotic sedatives, but have been replaced by the much safer benzodiazepine derivatives. They do continue to be used as anesthetics and as anti-convulsants. The primary mechanism of action of barbiturates is to increase inhibition through the **GABA system**. Anesthetic barbiturates also decrease excitation via a decrease in calcium conductance.

### Classification

The most commonly used barbiturates are as follows:

- **Thiopental** (Pentothal)
- **Methohexital** (Brevital)
- **Secobarbital** (Seconal)
- **Pentobarbital** (Nembutal)
- **Amobarbital** (Amytal)
- **Phenobarbital** (Luminal)



**FIGURE 65.8** The actions of GABA and glycine. GABA =  $\gamma$ -aminobutyric acid.

Barbiturates are classified according to their duration of action; these are ultrashort acting (thiopental and methohexital), short to intermediate acting (pentobarbital, secobarbital, and amobarbital), and long acting (phenobarbital).

In general, the more **lipid soluble** a barbiturate derivative is, the greater is its plasma and tissue-binding capacity, the extent of its metabolism, and its storage in adipose tissues. In addition, very lipid-soluble substances have a faster onset of action and a shorter duration of action.

Barbiturates do not raise the **pain threshold** and have no **analgesic** property. In anesthetic doses, they depress all areas of the CNS, including the hypothalamic thermoregulatory system, respiratory center, and vasomotor centers, as well as the **polysynaptic pathways in the spinal column**. In addition, some, such as phenobarbital, but not all, are anticonvulsants. In toxic doses, barbiturates cause oliguria.

### Pharmacokinetics

Barbiturates are absorbed orally and distributed widely throughout the body. They are metabolized in the liver by aliphatic oxygenation, aromatic oxygenation, and *N*-dealkylation.

The inactive metabolites are excreted in the urine. The administration of **bicarbonate** enhances the urinary excretion of barbiturates that have a pK of 7.4 (**phenobarbital** and **thiopental**). This generalization is not true of other barbiturates. The long-term administration of barbiturates activates the cytochrome P-450 drug-metabolizing system.

### Acute Toxicity

Acute barbiturate toxicity is characterized by **automatism**, or a state of drug-induced confusion, in which patients lose track of how much medication they have taken and take more. Death results from respiratory failure. The treatment of poisoning consists of supporting the respiration, preven-



tion of hypotension, diuresis, hemodialysis, and in the event of phenobarbital poisoning, the administration of **sodium bicarbonate**. Tolerance does not develop to lethal doses.

### Addiction

The abrupt withdrawal from barbiturates may cause tremors, restlessness, anxiety, weakness, nausea and vomiting, **seizures**, delirium, and cardiac arrest.

### Selection of Drugs

The selection of a barbiturate is in part determined by the duration of action desired and by the clinical problems at hand. An ultrashort-acting drug is used for inducing anesthesia. For treating epilepsy, a long-acting drug is used, whereas, in a sleep disorder, a short-acting or an intermediate-type drug is used, depending on whether patients have difficulty falling asleep or if they have difficulty staying asleep.

## NONBARBITURATE SEDATIVES AND HYPNOTICS — BENZODIAZEPINE DERIVATIVES

**Flurazepam** (Dalmane), **temazepam** (Restoril), and **triazolam** (Halcion) are all marketed as hypnotic agents, but other benzodiazepine derivatives are also effective as hypnotic agents (Table 65.1).

**TABLE 65.1**  
**Characteristics of Benzodiazepines**

Benzodiazepines	Active Metabolites	Half-Life	Marketed As
Long acting			
Chlordiazepoxide	Yes	2–4 d	—
Diazepam	Yes	2–4 d	—
Flurazepam	Yes	2–3 d	Hypnotic
Chlorazepate	Yes	2–4 d	—
Clonazepam	Yes	2–3 d	Anticonvulsant
Prazepam	Yes	2–4 d	—
Halazepam	Yes	2–4 d	—
Intermediate acting			
Oxazepam	No	8–12 h	Anxiolytic
Lorazepam	No	10–20 h	—
Temazepam	No	10–20 h	Hypnotic
Alprazolam	No	14 h	—
Short acting			
Triazolam	No	2–5 h	Hypnotic
Midazolam	No	2–3 h	—

*Note:* Benzodiazepines have only a limited capacity to produce profound and potentially fatal CNS depression. Although coma may be produced at very high doses, benzodiazepines cannot induce a state of surgical anesthesia by themselves and are virtually incapable of causing fatal respiratory depression or cardiovascular collapse unless other CNS depressants also are present. Because of this measure of safety, benzodiazepines have substantially replaced older agents for the treatment of insomnia or anxiety.

**TABLE 65.2**  
**Regulatory Status of Valerian**

Country	Regulatory Status
Australia	<i>Valeriana officinalis</i> L. is acceptable as an active ingredient in the “listed products” category of the Therapeutic Goods Administration
Belgium	Subterranean parts, powder, extract, and tincture are permitted as traditional tranquilizers
Canada	The Health Protection Branch of Health Canada allows products containing valerian as a single medicinal ingredient in the form of crude dried root in tablets, capsules, powders, extracts, tinctures, drops, or tea bags intended to be used as sleeping aids/sedatives
France	Valerian root (from <i>Valeriana officinalis</i> L.) has traditional use in symptomatic treatment of neurotonic conditions of adults and children, particularly in cases of minor sleep disturbances
Germany	Commission E has approved valerian for restlessness and nervous disturbances of sleep
U.K.	Valerian is included in the General Sale List of the Medicines Control Agency and permitted in “traditional herbal remedies” as a sedative and to promote natural sleep

*Note:* Valerian consists of the dried rhizome and roots of *Valeriana officinalis* Linné (Fam. Valerianaceae). It has been employed as an antianxiety agent and sleep aid for more than 1000 years. The drug contains from 0.3 to 0.7% of an unpleasant-smelling volatile oil containing bornyl acetate and the sesquiterpenoids, valerenic acid, and acetoxyvalerenolic acid. Also present is a mixture of lipophilic iridoid principles known as valepotriates. These bicyclic monoterpenoids are quite unstable and occur only in the fresh plant or in material dried at temperatures under 40°C. Although the specific active principals of valerian have not been determined, it is possible that a combination of the sesquiterpenoids and the valepotriates may be involved. The drug may be administered as a tea prepared from 2 to 3 g of the dried herb or equivalent amounts of a tincture or extract may be employed.

## REGULATORY STATUS

Valerian (as *Valeriana officinalis* L.) has official status (i.e., government approval in some capacity) in many countries throughout the world. In some cases, the status is based on traditional use rather than controlled trials. Table 65.2 shows the regulatory status of valerian.



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# 66 Vitamins and Diet

## INTRODUCTION

Vitamins are found in the following:

- Vegetables
- Fruits
- Nuts
- Greens

Vitamins are organic dietary substances necessary for the maintenance of normal metabolic function. Only small amounts of the vitamins are required for normal health. In the body, they act as components of the important enzyme systems that catalyze the reactions by which proteins, fats, and carbohydrates are metabolized. Some of the vitamins (e.g., vitamin K) may be formed by bacteria in the gut, whereas vitamin D is synthesized by exposure of the skin to sunlight. With these exceptions, vitamins must be ingested in the food. Restricted diets or disorders of the gastrointestinal tract, interfere with absorption, leading to vitamin deficiency. When pronounced, such deficiencies give rise to easily recognizable clinical syndromes (**beriberi, pellagra, rickets, scurvy**), which have long been recognized. Milder forms of avitaminosis are much more common and also give rise to disability and ill health (see Wilson, 2005; Berkner, 2005; Singh et al., 2005).

The **fat-soluble vitamins** are A, D, E, and K. The **water-soluble vitamins** are **thiamine** (vitamin B<sub>1</sub>), **riboflavin**, **nicotinic acid** (niacin) and **nicotinamide**, **pyridoxine** (vitamin B<sub>6</sub>), **pantothenic acid**, **biotin**, **para-aminobenzoic acid**, **choline**, **inositol**, and other lipotropic agents, **ascorbic acid** (vitamin C), the **riboflavonoids**, **folate**, and **vitamin B<sub>12</sub>** (see Figure 66.1 and Figure 66.2, and Table 66.1).

## NUTRITIONAL ACTIONS OF VITAMINS

### PART ONE: FAT-SOLUBLE VITAMINS

The sources and medicinal characteristics of various vitamins are given in the following text.

#### Vitamin A

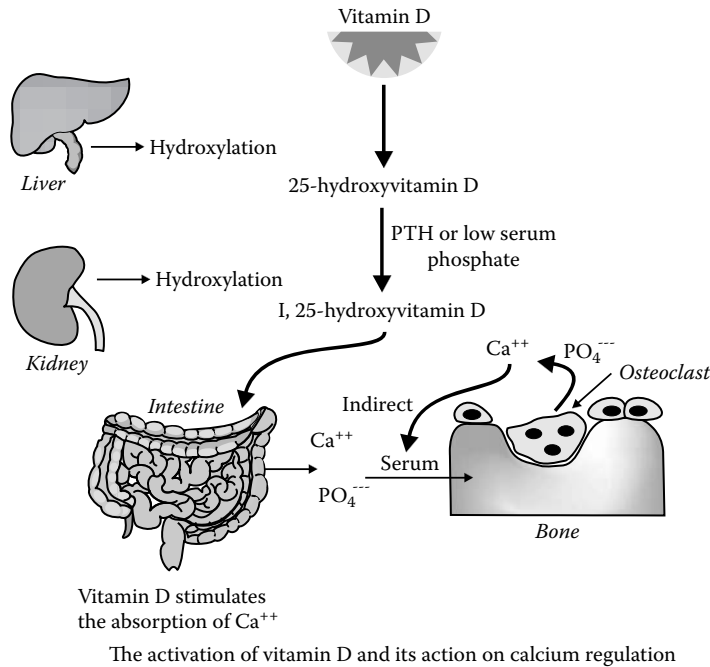
It is obtained from **retinols** in animal products or **β-carotene** in plant foods.

#### Retinols

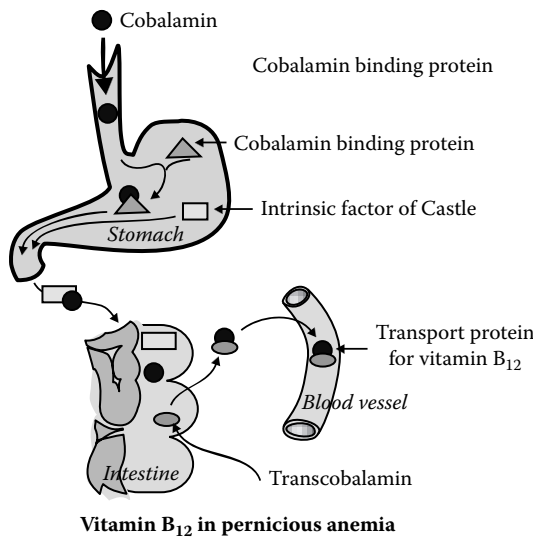
Sources are liver, salmon, and other cold-water fish, egg yolks, and fortified milk and dairy products.

#### Beta Carotene

Sources are orange and yellow fruits and vegetables, such as carrots, squash, and cantaloupes; leafy green vegetables.



**FIGURE 66.1** Vitamins D<sub>3</sub> and D<sub>2</sub> are produced by ultraviolet irradiation of animal skin and plants, respectively. The precursor of vitamin D<sub>3</sub> in skin is 7-dehydrocholesterol, or **provitamin D**. In humans, the storage, transport, metabolism, and potency of vitamins D<sub>2</sub> and D<sub>3</sub> are identical, and the net biologic activity of vitamin D *in vivo* results from the combined effects of the hydroxylated derivatives of vitamins D<sub>2</sub> and D<sub>3</sub>.



**FIGURE 66.2** Both **vitamin B<sub>12</sub>** and **folic acid** are essential for the synthesis of DNA, and this process is impaired in patients with megaloblastic anemia.

**TABLE 66.1**  
**Vitamins: Their Coenzymatic Functions**

<b>Fat-Soluble Vitamins</b>	
A, retinol	Rhodopsin, visual cycle, night vision
K, menadiol	Blood clotting factors II, VII, IX, and X
D, calciferol	Calcium and phosphorus homeostasis
E, tocopherol	Antioxidant, glutathione oxidase
<b>Water-Soluble Vitamins</b>	
C, ascorbate	Antioxidant, regulation of intracellular oxidation-reduction potentials, hydroxylation reactions that require copper or iron
B <sub>1</sub> , thiamin	Oxidative decarboxylation of amino acids, transketolase
B <sub>2</sub> , riboflavin	Flavin mononucleotide and flavin adenine dinucleotide, essential for oxidative systems and oxygen transport
B <sub>3</sub> , pantothenic acid	As CoA precursor, necessary for acyl transfers
B <sub>5</sub> , niacin	Endogenous source for tryptophan; component of NAD and its phosphorylate, NADP; assists in hydrogen transfer of glycolysis, fatty acid synthesis, and tissue respiration
B <sub>6</sub> , pyridoxine	Nitrogen metabolism: transamination, racemization, decarboxylation, cleavage, synthesis, dehydration, and desulfhydration
B <sub>12</sub> , cyanocobalamin	Methylation of homocysteine to methionine, conversion of methyl malonyl CoA to succinyl CoA
Biotin	Cofactor for some carboxylases; acetyl CoA carboxylase, pyruvate carboxylase, $\beta$ -methylcrotonyl carboxylase, and methylmalonyl carboxylase
Folic acid	Transport of single carbon fragments, especially nucleic acid synthesis and metabolism of some amino acids

*Note:* A vitamin is defined as an organic dietary substance required in trace amounts ( $\mu\text{g}$  to  $\text{mg/d}$ ) by humans for health.

- Prevents **night blindness**; needed for growth and cell development; maintains healthy skin, hair, and nails, as well as gums, glands, bones, and teeth; may help prevent lung cancer.
- Symptoms of deficiency include night blindness, stunted growth in children, dry skin and eyes, increased susceptibility to infection.
- Symptoms of excess include headaches and blurred vision, fatigue, bone and joint pain, appetite loss and diarrhea, dry, cracked skin, rashes, and itchiness, hair loss. It can cause birth defects if taken in high doses before and during early pregnancy.

### Vitamin K

It is found in spinach, cabbage, and other green leafy vegetables; pork, liver, and green tea.

- Essential for proper blood clotting.
- Symptoms of deficiency include excessive bleeding and easy bruising.
- In excess may interfere with anticlotting drugs; possible jaundice.

### VITAMIN K DERIVATIVES

Menadiol Sodium Diphosphate  
 (Synkayvite)

### Vitamin D (Calciferol)

It is found in fortified milk and butter, egg yolks, fatty fish; and fish-liver oils. It is also made by the body on exposure to the sun.

- Necessary for calcium absorption, helps build and maintain strong bones and teeth.
- Symptoms of deficiency include weak bones, leading to rickets in children and osteomalacia in adults.
- Symptoms of excess include headaches, loss of appetite, diarrhea, and possible calcium deposits in heart, blood vessels, and kidneys.

### **Vitamin E (Tocopherols)**

**(a Tocopherol) (Aquasole E, CEN-E, Eprolin Gelseas, Episilan-M, E-Vital, Pheryl-E 400, Tocopher-Caps, Vita-Plus E, Vitera E)**

Vitamin E, a fat-soluble vitamin, is used in vitamin E deficiency in premature infants and in patients with impaired fat absorption (including patients with **cystic fibrosis**) and in **biliary atresia**. Sources are eggs, vegetable oils, margarine, and mayonnaise; nuts and seeds; fortified cereals; green leafy vegetables.

- Protects fatty acids, maintains muscles and red blood cells, important antioxidant.
- Symptoms of deficiency are unknown in humans.
- Symptoms of excess include excessive bleeding, especially when taken with aspirin and other anticlotting drugs.

## **PART TWO: WATER-SOLUBLE VITAMINS**

### **Biotin**

Sources are egg yolks, soybeans, cereals, and yeast.

- Biotin is necessary for energy metabolism.
- Symptoms of deficiency include scaly skin, hair loss, depression, elevated blood cholesterol levels.
- Symptoms of excess have not been reported.

### **Folate (Folic Acid, Folacin)**

It is found in liver; yeast, broccoli and other cruciferous vegetables, avocados, legumes, and many raw vegetables.

- It is needed to make DNA, RNA, and red blood cells, and to synthesize certain amino acids.
- Symptoms of deficiency include abnormal red blood cells and impaired cell division, anemia, weight loss and intestinal upsets; deficiency may cause birth defects.
- Symptoms of excess include an inhibition with absorption of phenytoin, an antiepileptic agent, causing seizures in epileptics taking this drug; large doses may inhibit zinc absorption.

### **Niacin (Vitamin B<sub>3</sub>, Nicotinic Acid, Nicotinamide)**

It is found in lean meats, poultry, and seafood, milk, eggs, legumes, fortified breads and cereals.

- It is needed to mobilize energy; promotes normal growth. Large doses lower cholesterol.
- Symptoms of deficiency include diarrhea and mouth sores, pellagra (in extreme cases).
- Symptoms of excess include hot flashes, liver damage, elevated blood sugar and uric acid.

**Pantothenic Acid (Vitamin B<sub>5</sub>)**

It is found in almost all foods.

- Aids in energy metabolism, normalizing blood sugar levels, and synthesizing antibodies, cholesterol, hemoglobin, and some hormones.
- Symptoms of deficiency include fatigue, low blood sugar, numbness, digestive problems, and lowered immunity.
- Symptoms of excess include diarrhea and edema.

**Riboflavin (Vitamin B<sub>2</sub>)**

Sources are fortified cereals and grains, lean meat and poultry, milk and other dairy products, raw mushrooms.

- Essential for energy metabolism; aids adrenal function.
- Symptoms of deficiency include vision problems and light sensitivity, mouth and nose sores, swallowing problems.
- May interfere with cancer chemotherapeutic agents.

**Thiamine (Vitamin B<sub>1</sub>)**

Sources are pork, legumes, nuts and seeds, fortified cereals, and grains.

- Energy metabolism; helps maintain normal digestion, appetite, and proper nerve function.
- Symptoms of deficiency include depression and mood swings, loss of appetite and nausea, muscle cramps. In extreme cases, muscle wasting and beriberi.
- When given in excess, may cause deficiency of other vitamins.

**Vitamin B<sub>6</sub> (Pyridoxine, Pyridoxamine, Pyridoxal)**

It is found in meat, fish, and poultry, grains and cereals, green leafy vegetables, potatoes, and soybeans.

- Promotes protein metabolism; metabolism of carbohydrates and release of energy, proper nerve function, synthesis of red blood cells.
- Symptoms of deficiency include convulsive seizures, depression and confusion, itchy, scaling skin, red tongue, weight loss.
- Symptoms of excess may include sensory nerve deterioration.

**Vitamin B<sub>12</sub> (Cobalamins)**

It is found in all animal products.

- Needed to make red blood cells, DNA, RNA, and myelin (for nerve fibers).
- Symptoms of deficiency may include pernicious anemia, nerve problems and weakness, smooth or sore tongue.

**Vitamin C (Ascorbic Acid)**

Sources are citrus fruits and juices, melons, berries, and other fruits, peppers, broccoli, potatoes, and many other fruits and vegetables.



- Strengthens blood vessel walls, promotes wound healing, promotes iron absorption, helps control blood cholesterol and prevent atherosclerosis.
- Symptoms of deficiency include loose teeth and bleeding gums, bruises, loss of appetite, dry skin, poor healing. In extreme cases, scurvy and internal hemorrhages.
- Symptoms of excess include diarrhea, kidney stones, urinary tract irritation, iron buildup, bone loss (see Gardner, 1982; Weiss, 1997).

## THE IMPORTANCE OF VITAMIN A IN HUMAN NUTRITION

Night blindness apparently was first described in Egypt around 1500 B.C. Although this disease was not then linked to dietary deficiency, topical treatment with roasted or fried liver was recommended, and **Hippocrates** later recommended eating beef liver as a cure for the affliction. The relationship to nutritional deficiency was definitively recognized in the 1800s. **Ophthalmia brasiliensis**, a disease of eyes that affected primarily poorly nourished slaves, was first described in 1865. In 1887, endemic night blindness was reported to occur among the **Orthodox Russian Catholics** who fasted during Lent. More pertinent was the observation that the nurslings of mothers who fasted were prone to develop spontaneous sloughing of the cornea (Marcus and Coulson, 1996).

## DIETARY SOURCES OF VITAMIN A

The major dietary sources for preformed vitamin A are vertebrate animal products that are rich in vitamin A esters (liver, kidney, oil, dairy products, and eggs). Liver and oil, particularly from fish, are the major dietary sources of preformed vitamin A. Levels in milk and eggs depend on dietary **retinoid** and **carotenoid** intake. Freshwater fish are a source of **vitamin A<sub>2</sub> (3,4-dehydroretinol)**, which shows reduced vitamin A activity. Levels of retinal in food are very low, whereas **retinoic acid** has not been found.

**Plants are the major source for dietary provitamin A.** As mammals and humans cannot synthesize **carotenoids**, dietary provitamin A is obtained from plant sources that contain carotenoids having **2,6,6-trimethyl-1-cyclohexen-1-yl rings, such as  $\beta$ -carotene**. More than 600 carotenoids have been identified in plants and algae, which together biosynthesize about 0.1 billion tons of carotenoids each year. However, only about ten carotenoids, including  $\beta$ -carotene, are nutritionally significant members of the provitamin A class that can be oxidatively metabolized to **retinal** in mammals and humans by such organs as the intestine, liver, and kidney and then reduced to **retinol**.

**Provitamin A** carotenoids are the major dietary source of retinol for many residents of developed countries, including the U.S., and for most residents of poor countries.  $\beta$ -Carotene-rich vegetables and fruits (20 to 85% of carotenoid content) include dark-green leafy, bright yellow, orange, or red vegetables and fruits, whose total carotenoid content can range from less than 0.2 mg/100 g (lettuce leaves) to over 35 mg/100 g (oil from red palm fruit). The major dietary source of vitamin A varies with country. For example, in the U.S. it is orange carrots (6 to 12 mg/100 g), in Japan yellow-green vegetables, in Singapore dark-green leafy vegetables, and in Brazil and emerging South Asian and African countries unrefined **red palm oil** (37 to 165 mg/100 g). Grains have variable carotenoid content. For example, cereal seed contains only about 10  $\mu$ g/100 g wet weight of metabolizable carotenoids, in which  $\beta$ -carotene predominates, whereas the content in corn varies from 1 to 5.5 mg/100 g (field corn) or 200 to 700  $\mu$ g retinol equivalents (RE)/100 g (yellow sweet corn). (One RE = 1  $\mu$ g retinol or 6  $\mu$ g  $\beta$ -carotene.) Other sources are sorghum (< 31  $\mu$ g/100 g) and green soybeans, cowpeas, lima beans, and peas (200 to 700  $\mu$ g/100 g). Root vegetables, such as orange carrots, yams, and sweet potatoes, are a major carotenoid source in which  $\beta$ -carotene predominates (90%). Taro has lower concentrations. Fruits show greater variation in their  $\beta$ -carotene content than vegetables, and their levels are generally lower than those found

in leafy vegetables. Other natural sources of carotenoids are lobster, shrimp, and crab, which incidentally, do not contain retinol or its esters.

Other sources are vitamin A–fortified prepared foods, including sugar, monosodium glutamate, and dried milk, that are distributed to vitamin A-deficient population groups. Creams and ointments containing vitamin A esters are used to treat skin disorders, such as acne and psoriasis. Recently, because of the reported efficacy of topical retinoic acid in the treatment of photo-induced skin damage, retinol esters are added to cosmetics for use against the appearance of age-related wrinkles and lines. Commercially prepared foods (margarine, butter, soft drinks, crustacean products, pastries, cheese, desserts) may contain carotenoids as colorants to increase visual appeal (Dawson, 2000).

### ACTION OF VITAMIN A

Although the term *vitamin A* has been used to denote specific chemical compounds, such as **retinol** or its esters, this term now is used more as a generic descriptor for compounds that exhibit the biological properties of retinol. **Retinoid** refers to the chemical entity retinol or other closely related naturally occurring derivatives. Retinoids also include structurally related synthetic analogues, which need not have retinol-like (**vitamin A**) activity. The structural formulas for the vitamin A family of retinoids are shown in Figure 66.3. Retinol (vitamin A<sub>1</sub>), a primary alcohol, is present in esterified form in the tissues of animals and saltwater fish, mainly in the liver. A closely related compound, **3-dehydroretinol** (vitamin A<sub>2</sub>), is obtained from the tissues of freshwater fish and usually occurs mixed with retinol.

A number of geometric isomers of retinol exist because of the possible *cis*–*trans* configurations around the double bonds in the side chain. Fish liver oils contain mixtures of the stereoisomers; synthetic retinol is the all-*trans* isomer. Interconversion between isomers readily takes place in the body. In the visual cycle, the reaction between retinal (**vitamin A aldehyde**) and **opsin** to form **rhodopsin** only occurs with the 11-*cis* isomer.

Ethers and esters derived from the alcohol also show activity *in vivo*. The ring structure of **retinol** ( $\beta$ -ionone), or the more unsaturated ring in **3-dehydroretinol** (dehydro- $\beta$ -ionone), is essential for activity; hydrogenation destroys biological activity. Of all known derivatives, all-*trans*-retinol and its aldehyde, retinal, exhibit the greatest biological potency *in vivo*; 3-dehydroretinol has about 40% of the potency of all-*trans*-retinol.

**Retinoic acid** (vitamin A acid), in which the alcohol group has been oxidized, shares some but not all of the actions of retinol. Retinoic acid is ineffective in restoring visual or reproductive function in certain species in which retinol is effective. However, retinoic acid is very potent in promoting growth and controlling differentiation and maintenance of epithelial tissue in vitamin A–deficient animals. Indeed, all-*trans*-retinoic acid (**tretinoin**) appears to be the active form of vitamin A in all tissues except the retina, and is 10- to 100-fold more potent than retinol in various systems *in vitro*. Isomerization of this compound in the body yields 13-*cis*-retinoic acid (**isotretinoin**), which is nearly as potent as tretinoin in many of its actions on epithelial tissues but may be as much as fivefold less potent in producing the toxic symptoms of hypervitaminosis A.

### VITAMIN A AND CARCINOGENESIS

Because vitamin A regulates epithelial cell differentiation and proliferation, there has been considerable interest in the apparent ability of retinol and related compounds to interfere with **carcinogenesis**. Vitamin A deficiency in humans enhances susceptibility to carcinogenesis.

### VITAMIN A AND IMMUNE FUNCTION

It has been known for many years that vitamin A deficiency is associated with increased susceptibility to bacterial, parasitic, and viral infections. Decreased resistance to infections has been

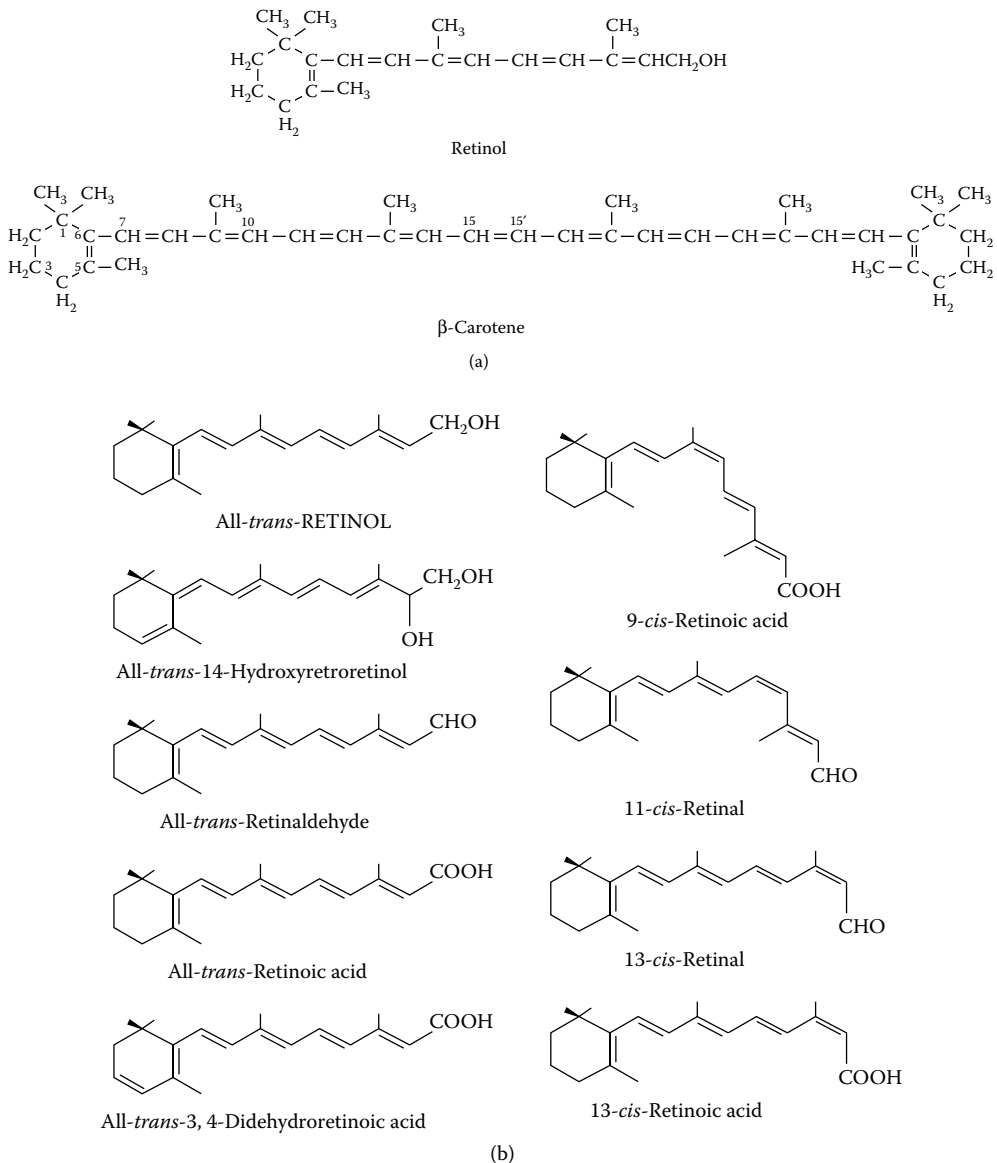


FIGURE 66.3 (a) β-Carotene, (b) the vitamin A family.

demonstrated in numerous animal models of vitamin A deficiency, and even marginal vitamin A status increases the severity and duration of infectious illness.

### SYMPTOMS OF DEFICIENCY

Tissue reserves of retinoids in the healthy adult are sufficiently large to require long-term dietary deprivation to induce deficiency. Vitamin A deficiency occurs more commonly in chronic diseases affecting fat absorption, such as **biliary tract or pancreatic insufficiency**, **sprue**, **Crohn's disease involving the terminal ileum**, and **portal cirrhosis**; deficiency may also occur following **partial gastrectomy** or during extreme, chronic dietary inadequacy.

Signs and symptoms of mild vitamin A deficiency are easily overlooked. Skin lesions, such as **follicular hyperkeratosis** and infections, are among the earliest signs of deficiency, but the most

recognizable manifestation is **night blindness**, even though its onset occurs only when vitamin A depletion is severe. Children may grow more slowly, although this may be recognized only after correction of the deficiency. In general, rapidly proliferating tissues are more sensitive to vitamin A deficiency than are slowly growing tissues and may revert to an undifferentiated state more readily.

## Eye

**Keratomalacia**, characterized by desiccation, ulceration, and xerosis of the cornea and conjunctiva, is occasionally seen as an acute symptom in the very young who are ingesting severely deficient diets. Usually, it is foreshadowed by night blindness, which appears as the earliest ocular sign of deficiency. Ultimately, severe visual impairment and even blindness result.

## Bronchorespiratory Tract

Changes in the bronchorespiratory epithelium from mucus secretion to keratinization lead to increased incidence of respiratory infections in the deficiency state. There also is a decrease in elasticity of the lung and other tissues.

## Skin

Keratinization and drying of the epidermis occur, and papular eruptions involving the pilosebaceous follicles may be found, especially on the extremities.

## Genitourinary System

Urinary calculi are frequent concomitants of vitamin A deficiency. The epithelium of the urinary tract shares in the general pathological changes of all epithelial structures. Epithelial debris thus may provide the nidus around which a calculus is formed. Abnormalities of reproduction include impairment of spermatogenesis, degeneration of testes, abortion, resorption of fetuses, and production of malformed offspring.

## Gastrointestinal Tract

The intestinal mucosa shows a reduction in the number of goblet cells without keratinization. Alterations in intestinal epithelium and metaplasia of pancreatic ductal epithelium are common. They may be responsible for the diarrhea occasionally seen in vitamin A deficiency.

## Sweat Glands

These glands may undergo atrophy and keratinizing squamous-cell metaplasia.

## Bone

Vitamin A deficiency is associated with faulty modeling of bone, with production of thick, cancellous bone instead of thinner, more compact bone.

## Miscellaneous

Often both taste and smell are impaired in vitamin-A-deficient individuals, undoubtedly a result of a keratinizing effect. Hearing also may be impaired. Vitamin A deficiency can interfere with erythropoiesis, which may be masked by abnormal losses of fluid. Nerve lesions, increased cerebrospinal fluid pressure, and hydrocephalus have been reported.

## THERAPEUTIC USES

### Vitamin A Deficiency Diseases

The normal requirement of vitamin A for adults is supplied by an **adequate diet**. The rational uses of retinol are in the treatment of vitamin A deficiency and as prophylaxis in high-risk subjects during periods of increased requirement, such as infancy, pregnancy, and lactation. Once vitamin A deficiency has been diagnosed, intensive therapy should be instituted. The patient should then be maintained on a proper diet.

There are many types of preparations that contain retinol. Absorption is greatest for aqueous preparations, intermediate for emulsions, and slowest for oil solutions. Whereas oil-soluble preparations may lead to greater hepatic storage of the vitamin, water-miscible preparations usually provide higher concentrations in plasma. Vitamin A is available as capsules. **Tretinoin** (all-*trans*-retinoic acid; Retin A) is available for topical use. **Isotretinoin** (13-*cis*-retinoic acid; Accutane) is available for oral use, as is **etretinate** (Tegison).

During pregnancy and lactation, it is advisable to increase the maternal intake of vitamin A by about 25%. As the typical North American diet readily provides adequate intake of the vitamin, supplementation is not routinely indicated.

In **kwashiorkor** and other severe vitamin A deficiencies in children, a single intramuscular injection of 30 mg of retinol as the water-miscible palmitate has been advocated, followed by intermittent oral treatment with retinoids.

### Dermatological Diseases

Vitamin A may be helpful in certain diseases of the skin, such as acne, psoriasis, **Darier's disease**, and **ichthyosis**.

### Cancer and Other Uses

Considerable interest has focused on the possibility that vitamin A and other retinoids may find important roles in **cancer chemoprevention** and therapy (Marcus and Coulson, 1996).

### EXCESSIVE VITAMIN A INTAKE (HYPERVITAMINOSIS A)

High doses of vitamin A can produce the toxic side effects of the acute or chronic hypervitaminosis A syndrome, which in humans is characterized by the following:

- Hypercalcemia (osteosclerosis or bone loss, and soft tissue calcification)
- Related bone and joint pain
- Inflammation of the mucous membranes of the lip (**cheilitis**), the mouth (**stomatitis**), the eye (**conjunctivitis**), and skin capillaries (**erythema**)
- Desquamation (scaling of skin)
- Hair loss (alopecia)
- Fatigue
- Irritability
- Headache
- Intestinal disturbances (diarrhea, nausea, and vomiting)
- Low-grade fever
- Liver dysfunction (hypertriglyceridaemia, **Dissè space fibrosis**, and blood flow obstruction)
- Birth defects (teratogenicity and embryotoxicity)

Acute hypervitaminosis A in humans requires doses of at least 600 mg in adults and 100 mg in children; chronic hypervitaminosis A requires 20 to 50 mg daily for several years (Dawson, 2000).

### VITAMIN A (RETINOL) (AQUASOL A)

Vitamin A, a fat-soluble vitamin, is indicated for severe vitamin A deficiency with **xerophthalmia**. (See the section “Importance of Vitamin A in Human Nutrition.”)

## AGING AND DIET

Although aging is inevitable, many of the degenerative changes that prevail among elderly people are not, if preventative steps are taken.

### BASIC DIETARY RECOMMENDATIONS

The National Institute on Aging recommends that an older person’s daily diet include the minimum number of servings outlined in the following table. Sugar, salt, and fats should be used sparingly; alcohol should be consumed only in moderation, defined as one drink a day for women and two for men (see Gardner, 1982; Weiss, 1997).

Food Group	Provides
<p><b>Starches (Complex Carbohydrates)</b>  <b>At least five servings:</b> Whole grains, breads, and cereals; brown rice, kasha, millet, and other grains; dried beans, peas, lentils, and other legumes; potatoes, pasta, and other starchy foods</p>	Thiamine, riboflavin, niacin, folate, B <sub>6</sub> and other B vitamins; fiber; and complete protein when grains and legumes are combined
<p><b>Vegetables and Fruits</b>  <b>At least five servings:</b> Fresh vegetables and fruits, including dark green leafy vegetables, such as broccoli, cabbage, kale, and spinach; yellow vegetables, such as carrots and squash; citrus fruits, berries, tomatoes, bananas, and other fruits</p>	Vitamins C and A, beta carotene, riboflavin, folate, various minerals, and fiber; these are needed to prevent deficiency disorders and may protect against cancer
<p><b>High-Protein Foods</b>  <b>At least two servings:</b> Lean beef, lamb, chicken and other poultry; fish and other seafood; eggs, tofu, and a combination of grains and legumes</p>	Thiamine, riboflavin, niacin, and vitamins E, B <sub>6</sub> , and B <sub>12</sub> ; iron, zinc, and other minerals; canned sardines and salmon with bones provide calcium
<p><b>Dairy Products</b>  <b>At least two servings:</b> Low-fat milk, cheese, yogurt, and other milk products (Choose lactose-reduced milk and yogurt if one has trouble digesting regular milk)</p>	Protein, calcium, vitamins A and D; needed to prevent the loss of bone minerals that frequently occurs with increasing age

### ANTIOXIDANTS, PROTECTIVE PLANT CHEMICALS, PREVENTING DISEASES

Because plants are also susceptible to cancer and viruses, they have developed their own protective substances, called **phytochemicals** (from phyton, the Greek term for plant). Evidence from research is accumulating that many phytochemicals also protect humans against cancer and other diseases (Weiss, 1997).

Phytochemicals	Functions	Sources
Allylic sulfides	May stimulate production of protective enzymes	Garlic, onions
Bioflavonoids	Antioxidant; inhibit cancer-promoting hormones	Most fresh fruits and vegetables
Catechins (tannins)	Antioxidant	Berries, green tea
Curcumin	Protects against tobacco-induced carcinogens	Turmeric, cumin
Genistein	Inhibits tumor growth	Broccoli and other cruciferous vegetables
Indoles	Inhibit estrogen, which stimulates some cancers; induce protective enzymes	Broccoli, cabbage, cauliflower, mustard greens
Isoflavones	Inhibit estrogen uptake; destroy cancer enzymes	Beans, peanuts and other legumes, peas
Isothiocyanates	Induce production of protective enzymes	Horseradish, mustard, radishes
Lignans	Inhibit estrogen and block prostaglandins	Fatty fish, flaxseed, walnuts
Limonoids	Induce protective enzymes	Citrus fruits
Lycopene	Antioxidant, may protect against prostate cancer	Pink grapefruit, tomatoes, watermelon
Monoterpenes	Some antioxidant properties; aid in activity of protective enzymes	Basil, citrus fruits, broccoli, orange and yellow vegetables
$\omega$ -3 fatty acids	Inhibit estrogen; reduce inflammation	Canola oil, flaxseed, walnuts, fatty fish
Phenolic acid	Inhibits nitrosamines; enhances enzyme activity	Berries, broccoli, cabbage, carrots, citrus fruits, eggplant, parsley, peppers, teas, tomatoes, whole grains
Protease	Destroys enzyme inhibitors that promote cancer spread	Soybeans
Quercetin	Inhibits cellular mutation, carcinogens, clot formation, and inflammation	Grape skins, red and white wine
Terpenes	Stimulate anticancer enzymes	Citrus fruits

## ESSENTIAL TRACE MINERALS

The trace minerals identified as essential to humans and for which deficiency states have been described are **zinc, copper, manganese, selenium, chromium, iodine, molybdenum, and iron**. Each of these minerals participate in a variety of biologic functions and is necessary for normal metabolism. Other trace minerals essential to humans but for which deficiency states have not been recognized include **nickel, vanadium, cobalt, and silicon** (Table 66.2).

**Zinc deficiency** is clinically characterized by the development of a moist **eczematous dermatitis** most apparent in the nasolabial folds and around orifices. Other presenting signs and symptoms may include **hypogeusia** (blunted sense of taste), **alopecia**, diarrhea, rash (which may vary from papular, scaly lesions to weeping, open erosions), apathy, and depression. Clinical zinc deficiency occurs most frequently in the setting of abnormal losses, such as in **Crohn's disease**, malabsorption states, and fistula losses, or from prolonged inadequate intake, such as with zinc-free parenteral nutrition.

**Copper deficiency** may present as hematological changes (**anemia, leukopenia, and neutropenia**) and skeletal demineralization. In severe cases, such as in **Menkes' syndrome**, copper deficiency is further manifested as hypothermia, depigmentation of hair and skin, progressive mental deterioration, and growth retardation. Factors predisposing to copper deficiency include malabsorption states, protein-losing enteropathy, nephrotic syndrome, copper-free parenteral nutrition, and copper-deficient enteral nutrition.

**Chromium deficiency** is characterized by glucose intolerance but also may include neuropathy, increased free fatty acid concentrations, and a low respiratory quotient. Chromium deficiency has been identified in the setting of long-term, chromium-free parenteral nutrition.

**Manganese deficiency** has been reported only in association with chemically defined manganese-deficient oral diets. The symptoms include nausea, vomiting, dermatitis, color changes in hair, hypocholesterolemia, and growth retardation.

**TABLE 66.2**  
**Assessment of Trace Mineral Status**

Trace Minerals	Signs of Deficiency
Chromium	Glucose intolerance, peripheral neuropathy, increased free fatty acid levels, low respiratory quotient
Copper	Neutropenia, hypochromic anemia, osteoporosis, decreased hair and skin pigmentation; dermatitis, anorexia, diarrhea
Iodine	Hypothyroid goiter, hypothyroidism
Manganese	Nausea, vomiting, dermatitis, color changes in hair, hypocholesterolemia, growth retardation
Molybdenum	Tachycardia, tachypnea, altered mental status, visual changes, headache, nausea, vomiting
Selenium	Muscle weakness and pain, cardiomyopathy
Zinc	Dermatitis, hypogeusia, alopecia, diarrhea, apathy, depression

*Note:* The **macrominerals** required by the human body are distinguished from microminerals only by the magnitude of their requirement. The daily requirements for these minerals range from about 0.3 g for sodium and magnesium to 2.0 g for potassium. Sodium and potassium are alkali metals, calcium and magnesium are alkali earths, and chloride and phosphate are accompanying anions. Water is not a mineral, but it is the oxide of hydrogen, which is in group I in the periodic table. Water makes up about 60% of body weight and should be grouped with other substances that contribute to the matrix portion of the body. It has the highest requirement of any essential nutrient, namely 1 ml/kcal of energy expended, which for most persons exceeds 2 k/d.

**Selenium deficiency** has been described in patients receiving long-term selenium-free total parenteral nutrition. Myopathy and abnormal **glutathione peroxidase** concentrations are most frequently observed.

**Molybdenum deficiency** in humans has rarely been observed. The presenting symptoms included tachycardia, tachypnea, headache, night blindness, nausea, vomiting, central scotomas, lethargy, disorientation, and ultimately coma.

**Iodine deficiency** may result in goiter formation. However, not everyone will experience goiter formation with an iodine-deficient diet. Iodine is needed for synthesis of the thyroid hormones thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>).

Patients with **iron deficiency** anemia present with fatigue, weakness, and pallor, and possibly also with glossitis, headache, dysphagia, fingernail changes, gastric atrophy, and paresthesias. Inadequate intake of iron, malabsorption, and blood loss from any origin are the principal causes of iron deficiency anemia.

### FOODS THAT HELP (SEE WEISS, 1997; GARDNER, 1982)

The following is an extensive list of various foods, their properties, and benefits.

#### APPLES

- Low in calories and high in soluble fiber that help lower cholesterol

#### APRICOTS

- A rich source of beta carotene, iron, and potassium
- High in fiber, low in calories
- Dried apricots and apricot leather are nutritious, fat-free snack foods



**ARTICHOKES**

- A good source of folate, vitamin C, and potassium
- Low in calories, high in fiber

**ASPARAGUS**

- A good low-calorie source of folate and vitamins A and C
- Stalks high in fiber

**AVOCADOS**

- A rich source of folate, vitamin A, and potassium
- Useful amounts of protein, iron, magnesium, and vitamins C, E, and B<sub>6</sub>

**BANANAS**

- A good source of potassium, folate, and vitamins C and B<sub>6</sub>

**BEANS**

- High in folate and vitamins A and C
- Mature (shelled) beans are high in protein and iron

**BEAN SPROUTS**

- Some are high in folate; others are fair to good sources of protein, vitamin C, B vitamins, and iron

**BEEF AND VEAL**

- Major sources of high-quality protein
- Contain a wide range of nutrients, especially vitamin B<sub>12</sub>, iron, and zinc

**BEER**

- Lower in alcohol concentration than wine and hard liquor
- Contains modest amounts of niacin, folate, vitamin B<sub>6</sub>, and some minerals

**BEETS**

- A good source of folate and vitamin C
- The greens are a rich source of potassium, calcium, iron, beta carotene, and vitamin C
- Low in calories

**BIOFLAVONOIDS**

- Thought to function as antioxidants and also to enhance the antioxidant effects of vitamin C
- Believed to be instrumental in proper capillary function
- Some appear to be natural antibiotics and anticancer agents

**BLACKBERRIES**

- Low in calories and high in fiber
- A good source of vitamin C and bioflavonoids; also contain folate, vitamin E, iron, and calcium
- Contain anticancer chemicals
- Contain **salicylate**

**BLUEBERRIES**

- A good source of dietary fiber
- Provide some vitamin C and iron
- May protect against some intestinal upsets
- May help prevent some urinary tract infections

**BREAD**

- A good source of protein and complex carbohydrates
- High in niacin, riboflavin, and other B complex vitamins
- Some provide good amounts of iron and calcium
- Whole-grain breads are high in fiber

**BRUSSELS SPROUTS**

- An excellent source of vitamin C
- A good source of protein, folate, vitamin A, iron, and potassium
- Contain bioflavonoids and other substances that protect against cancer

**BUCKWHEAT**

- A good source of iron and magnesium
- High in starches, protein, and fiber

**BUTTER AND MARGARINE**

- Add flavor to many foods
- Improve flavor, moistness, and texture of baked goods
- Good sources of vitamins A and D
- Margarine made with polyunsaturated oils has essential fatty acids

**CABBAGE**

- An excellent source of vitamin C
- Low in calories and high in fiber
- May help prevent colon cancer and malignancies stimulated by estrogen
- Juice helps heal peptic ulcers

**CAFFEINE**

- Temporarily enhances mental alertness and concentration
- Can improve athletic performance by temporarily increasing muscle strength and endurance
- May abort an asthma attack by relaxing constricted bronchial muscles

**CAKES, COOKIES, AND PASTRIES**

- In small amounts, a good source of quick energy
- Delicious occasional snacks or desserts

**CARROTS**

- An excellent source of  $\beta$ -carotene, the precursor of vitamin A
- A good source of dietary fiber and potassium
- Help prevent night blindness
- May help lower blood cholesterol levels and protect against cancer

**CAULIFLOWER**

- An excellent source of vitamin C
- A good source of folate and potassium
- Low in calories and high in fiber

**CELERIAC**

- A good source of fiber, including the soluble type that lowers elevated blood cholesterol levels
- A good source of potassium; also provides some vitamin C
- Low in calories

**CELERY**

- Low in calories and high in fiber
- A good source of potassium
- May reduce inflammation and protect against cancer

**CEREALS**

- High in complex carbohydrates
- Many are high in fiber
- Some are reasonable sources of protein; adding milk makes a bowl of cereal a high-protein dish
- Enriched cereals are high in iron, niacin, thiamine, and riboflavin, along with other B vitamins
- Iron-fortified infant cereals are ideal introductory solid foods

**CHEESE**

- High in protein and calcium
- A good source of vitamin B<sub>12</sub>
- Cheddar and other aged cheeses may fight tooth decay

**CHERRIES**

- A low-calorie fat-free snack or dessert
- A good source of vitamin C
- High in pectin, a soluble fiber that lowers cholesterol

**CHESTNUTS**

- Rich in folate and vitamins C and B<sub>6</sub>
- A good source of iron, phosphorus, riboflavin, and thiamine
- Much lower in fat and calories than almost all other nuts

**CHILIES**

- An excellent source of vitamins A and C
- May help relieve nasal congestion
- May help prevent blood clots that can lead to a heart attack or stroke

**CHOCOLATE AND CANDY**

- Flavorful source of quick energy
- Eating chocolate elevates some people's moods

**COCONUTS**

- A useful source of iron and fiber
- High in easy-to-digest fatty acids

**COFFEE**

- Stimulates the central nervous system
- Can help one stay awake and alert

**CORN**

- A good source of folate and thiamine
- A fair amount of vitamins A and C, potassium, and iron
- Air-popped unbuttered popcorn is low in calories and very high in fiber

**CRANBERRIES**

- A fair source of vitamin C and fiber
- Juice helps prevent or alleviate cystitis and urinary tract infections
- Contain bioflavonoids, thought to protect eyesight and help prevent cancer

**CUCUMBERS**

- Low in calories
- A good source of fiber
- A fair source of vitamin C and folate

**CURRANTS**

- An excellent low-calorie source of vitamin C and potassium
- High in bioflavonoids

**DATES**

- An excellent source of potassium
- A good source of iron and calcium
- High in fiber

**EGGPLANTS**

- Low in calories (unless cooked in fat)
- Meaty flavor and texture lends itself to vegetarian dishes

**EGGS**

- An excellent source of protein, vitamin B<sub>12</sub>, and many other nutrients

**FENNEL**

- An excellent source of vitamins A and C (especially the leaves)
- A good source of potassium, calcium, and iron
- High in fiber and low in calories

**FIBER**

- Helps prevent constipation
- Relieves the symptoms of diverticulosis and hemorrhoids
- May help reduce risk of colon cancer
- Plays a role in lowering elevated blood cholesterol levels
- Useful as a means of controlling weight

**FIGS**

- A rich source of magnesium, potassium, calcium, and iron
- High in fiber

**FRUITS**

- Excellent sources of vitamin C, beta carotene, and potassium; lesser amounts of other vitamins and minerals

- Contain bioflavonoids, which protect against cancer and other diseases
- High in fiber and low in calories
- A source of natural sugars that provide quick energy

### **FISH**

- An excellent source of complete protein, iron, and other minerals
- Some are high in vitamin A
- Contains omega-3 fatty acids

### **FLOURS**

- A concentrated source of starch
- Enriched flours are a good source of calcium, iron, and B vitamins

### **GARLIC**

- May help lower high blood pressure and elevated blood cholesterol
- May prevent or fight certain cancers
- Antiviral and antibacterial properties help prevent or fight infection
- May alleviate nasal congestion

### **GINGER**

- May prevent motion sickness
- Can help to quell nausea
- Ginger wine may help to relieve menstrual cramps

### **GOOSEBERRIES**

- A good source of vitamin C, potassium, and bioflavonoids
- Fair amounts of iron and vitamin A
- High in fiber, low in calories

### **GRAINS**

- An excellent source of starchy carbohydrate and dietary fiber
- A good source of niacin, riboflavin, other B vitamins, iron, and calcium

### **GRAPEFRUIT**

- High in vitamin C and potassium
- A good source of folate, iron, calcium, and other minerals
- Pink and red varieties are high in beta carotene, a precursor of vitamin A
- High in fiber, low in calories
- Contain bioflavonoids and other plant chemicals that protect against cancer and heart disease

### **GRAPES**

- High in pectin and bioflavonoids

- A fair source of iron, potassium, and vitamin C
- A low-calorie sweet snack and dessert
- Contains **salicylate**

### **GUAVAS**

- An excellent source of vitamin C
- High in pectin and other types of soluble dietary fiber
- Good amounts of potassium and iron

### **HONEY**

- A source of quick energy
- Adds flavor to foods and beverages and improves the shelf life of baked goods
- Contains choline
- Memory enhancer and neuroprotectant

### **ICE CREAM**

- A good source of calcium
- Provides protein and digestible, high-calorie nutrition during an illness

### **KALE**

- An excellent source of beta carotene and vitamins C and E
- A good source of folate, calcium, iron, and potassium
- Contains bioflavonoids and other substances that protect against cancer

### **KIWI FRUITS**

- An excellent source of vitamin C
- A good source of potassium and fiber
- Can be used as a meat tenderizer

### **KOHLRABI**

- High in vitamin C, potassium, and cancer-preventing antioxidants and bioflavonoids
- High in dietary fiber

### **LAMB**

- A rich source of minerals, including iron, phosphorus, and calcium
- An excellent source of protein and B-complex vitamins

### **LEEKs**

- A good source of vitamin C, with lesser amounts of niacin and calcium

**LEGUMES**

- Contain more protein than any other plant-derived food
- A good source of starch, B-complex vitamins, iron, potassium, zinc, and other essential minerals
- Most are high in soluble fiber

**LEMONS**

- An excellent source of vitamin C
- A low-calorie alternative to oil dressings
- May relieve dry mouth
- Lettuce and other salad greens
- Low in calories and high in fiber
- Some varieties are high in beta carotene, folate, vitamin C, calcium, iron, and potassium

**LIMES**

- An excellent source of vitamin C
- Can be used to flavor and tenderize meat, poultry, and fish
- Peels contain **psoralens**, which increases sun sensitivity

**MALTED MILK, MALT EXTRACTS**

- Good food for convalescents
- Sugar provides quick energy
- Malt extract is a good source of niacin, iron, and potassium
- Warm malted milk promotes sleep

**MANGOES**

- An excellent source of beta carotene and vitamin C
- A good source of vitamin E and niacin
- High in potassium and iron
- Low in calories, high in fiber

**MAYONNAISE**

- A good source of vitamin E, depending upon the type of oil used
- Contains small amounts of vitamin A and some minerals

**MELONS**

- Sweet and flavorful, yet low in calories
- Yellow varieties are high in vitamin A
- Most are good sources of vitamin C and potassium
- Some are high in **pectin**, a soluble fiber that helps control blood cholesterol levels



## MILK AND MILK PRODUCTS

- The best source of calcium
- A good source of vitamins A and D, riboflavin, phosphorus, and magnesium
- Low-fat dairy products are low in cholesterol and high in protein

## MUSHROOMS AND TRUFFLES

- Fat-free and very low in calories
- Rich in minerals
- High glutamic acid content may boost immune function

## NECTARINES

- A fairly rich source of **beta carotene** and potassium
- Provide moderate amounts of vitamin C
- High in **pectin**, a soluble fiber
- The pits contain **cyanide** and should not be eaten

## NUTS AND SEEDS

- Rich in vitamin E and potassium
- Most are high in minerals, including calcium, iron, magnesium, and zinc
- Some are good sources of folate, niacin, and other B vitamins
- A good source of protein, especially when combined with legumes
- Some are high in fiber
- **Cashew shells** contain **urushiol**, the same irritating oil that is in poison ivy; heating inactivates urushiol, so toasted cashews are safe to eat; the raw nuts, however, should never be eaten
- Molds that grow on nuts (especially peanuts) create **aflatoxins**, substances that cause liver cancer

## OILS

- Provide essential fatty acids needed for hormone production
- Make possible the absorption of fat-soluble vitamins A, D, E, and K
- Oils may contain toxic compounds. For example, **Myristicin** is the compound that flavors nutmeg and mace; it is also found in black pepper and carrot, parsley, and celery seeds. Used in culinary quantities, myristicin is only a flavoring. In massive doses, it causes hallucination. **Thujone**, the anise-flavored oil in wormwood, caused an epidemic of brain disease in drinkers addicted to the now-banned liquor **absinthe**. **Sassafras** contains a toxic oil similar to thujone, which is why it is no longer used to make root beer. Very high doses of **menthol**, from peppermint, may cause dangerous irregularities in the heart's rhythm (Weiss, 1997)

## OKRA

- A good source of vitamins A and C, folate, and potassium
- High in dietary fiber and low in fat and calories

**OLIVES**

- High in monounsaturated fats, which benefit blood cholesterol levels
- A modest, low-calorie source of vitamin A, calcium, and iron

**ONIONS**

- The green tops are a good source of vitamin C and beta carotene
- May lower elevated blood cholesterol
- Reduce the ability of the blood to clot
- May help lower blood pressure
- Mild antibacterial effect may help prevent superficial infections

**ORANGES**

- An excellent source of vitamin C
- A good source of **beta carotene**, folate, thiamine, and potassium

**ORGAN MEATS**

- An inexpensive source of protein
- Liver and kidneys are excellent sources of vitamins A and B<sub>12</sub>, folate, niacin, iron, and other minerals
- Most are good sources of potassium

**PAPAYAS**

- An excellent source of vitamins A and C and potassium
- Papayas contain **papain**, an enzyme that is similar to the digestive juice **pepsin**. Because this enzyme breaks down protein, papain extract from papayas is marketed as a meat tenderizer

**PARSNIPS**

- Low in calories and high in fiber and carbohydrates
- A flavorful alternative to potatoes
- A useful source of vitamin C, folate, and potassium

**PASTA**

- An excellent source of starches
- A useful source of protein, B vitamins, iron, and other minerals
- Low in fat and sodium
- Can be served in many different ways

**PEACHES**

- A good source of vitamin A, with useful amounts of vitamin C and potassium
- A good source of dietary fiber

**PEARS**

- A good source of vitamin C and folate
- A good source of dietary fiber

**PEAS AND PEA PODS**

- A good source of vitamins A and C, thiamine, **riboflavin**, and potassium
- High in **pectin** and other types of fiber
- Provide complete protein when served with grain products

**PEPPERS**

- An excellent low-calorie source of vitamins A and C

**PICKLES AND OTHER CONDIMENTS**

- Sauerkraut is a good source of vitamin C, iron, potassium, and other nutrients.
- Pickles are low-calorie snacks.
- A diet that is high in pickled or other salt-cured foods and condiments has been linked to an increased risk of stomach and esophageal cancers. This is thought to stem from their high levels of nitrates, which are converted to cancer-causing nitrosamines during digestion. Vitamins A and C, beta carotene, and other antioxidants are thought to inhibit the cancer-causing potential of nitrosamines; eating ample fresh vegetables and fruits may counteract any risk from pickled foods (Weiss, 1997).

**PINEAPPLES**

- A good source of vitamin C, with useful amounts of vitamin B<sub>6</sub>, folate, thiamine, iron, and magnesium

**PLUMS**

- A useful source of vitamin C, riboflavin and other B vitamins, and potassium

**PORK**

- Fresh, lean pork is a good source of high-quality protein and B vitamins.
- Ham and bacon have high levels of vitamin C, which is added as a preservative.
- Nitrites in cured pork products form cancer-promoting **nitrosamines**.

**POULTRY**

- An excellent source of protein
- Lower in saturated fat than red meats
- A good source of vitamin A, the B vitamins, and minerals

**PRUNES**

- A rich source of vitamin A
- High in B vitamins, vitamin E, potassium, and iron
- Help to relieve constipation

**PUMPKINS**

- A rich source of beta carotene
- A good low-calorie source of vitamin C and potassium
- High in fiber
- The seeds are a good source of protein, iron, B vitamins, vitamin E, and fiber
- Can be stored for long periods of time

**QUINCES**

- A good source of vitamin C, iron, and potassium
- High in **pectin**, a soluble fiber
- **Seeds contain a cyanide compound**

**QUINOA**

- An excellent source of iron, magnesium, potassium, phosphorus, zinc, and other minerals
- A good source of B-complex vitamins
- High in protein

**RADISHES**

- A useful source of vitamin C
- Low in calories and high in fiber
- Contain **salicylate**

**RASPBERRIES**

- A rich source of vitamin C
- Contain useful amounts of folate, iron, and potassium
- Provide bioflavonoids, which may protect against cancer
- High in fiber
- Contain **salicylate**
- Contain **oxalic acid**, which can aggravate kidney and bladder stones in susceptible persons

**RHUBARB**

- High in vitamin C and potassium
- Contains **oxalic acid**, which inhibits calcium and iron absorption
- **Leaves are highly poisonous**

## RICE

- Enriched varieties provide B vitamins and iron
- Makes a complete protein when combined with beans and other legumes
- A starchy food that provides energy and contributes to protein synthesis
- **Gluten-free** and suitable for people with **celiac disease**
- Easy to digest and useful in restoring bowel function after a bout of diarrhea
- Rarely, if ever, causes food allergies
- Diets high in white rice may be deficient in **thiamine**
- A substance in brown rice can inhibit absorption of iron and calcium

## SALAD DRESSINGS

- Add flavor and interest to lettuce and other salad greens
- A good source of vitamin E

## SALT AND SODIUM

- Helps to maintain fluid balance, regulate blood pressure, and transmit nerve impulses
- Improves the flavor of many foods
- A useful food preservative
- Promotes fluid retention and may contribute to high blood pressure

## SAUCES AND GRAVIES

- Used sparingly, sauces complement flavors and enhance appearance of other food.
- **Salsa-style garnishes** supply fiber and antioxidant vitamins, provided they are carefully prepared.
- **Pasta sauces** based on fresh vegetables and olive oil are good sources of vitamins, fiber, complex carbohydrates, and unsaturated fat.
- Traditional sauces made from butter, flour, cream, and egg yolks are very high in cholesterol.
- Asian-style sauces are high in salt and should be avoided by people on low-sodium diets.

## SEAWEED

- An excellent source of **iodine**
- Provides a wide spectrum of minerals, including calcium, copper, iron, magnesium, and potassium
- Some types rich in the B vitamins, vitamin C, and  $\beta$ -carotene
- Some are a good source of protein

## SHELLFISH

- A low-fat source of high-quality protein
- A rich source of minerals, including calcium, fluoride, iodine, iron, and zinc
- A good source of B-group vitamins

### SMOKED, CURED, AND PICKLED MEATS

- Preserved meats have more concentrated minerals (but generally lower vitamin content) than fresh.
- Used sparingly, they add flavor without excessive fat or calories.
- Cured meats have more concentrated fat than fresh meats.
- Nitrites in preserved meats may form cancer-causing **nitrosamines**.
- High sodium content makes most unsuitable for people on low-salt diets.
- Preserved meats must be carefully handled to prevent food poisoning.
- Sausages made with corn solids or syrup or cereal fillers may cause symptoms in people sensitive to these grains.
- Cured meats may contain high levels of **tyramine**, which triggers **migraine** in susceptible people and causes serious hypertension in patients taking a monoamine oxidase inhibitor such as **tranlycypromine**.

### SNACKS AND DIPS

- Snacks can help a person meet recommendations in the **food guide pyramid**.
- Fruit and vegetable snacks are fat-free and high in vitamins and minerals.
- Well-timed low-calorie snacks can take the edge off hunger and help to prevent overeating at mealtimes.

### SOFT DRINKS

- Carbonated drinks are refreshing and may provide a quick energy boost from their sugar or caffeine.
- Sipping ginger ale or cola can help to quell nausea and provide energy for people unable to take solid food.
- High phosphorus content may interfere with calcium absorption.
- Caffeine may cause health problems in adults or behavior and development problems in children.

### SOUPS

- Can be highly nourishing
- An ideal food for convalescents
- Easy to make and economical
- Commercial varieties are often high in salt and fat

### SPINACH

- A rich source of vitamin A and folate
- High in vitamin C and potassium
- A vegetarian source of protein
- Contains **oxalic acid**, which reduces iron and calcium absorption, and can accelerate the formation of kidney and bladder stones

## SQUASH

- Summer varieties provide some folate and vitamins A and C
- Winter varieties are extremely rich in vitamin A and are a good source of vitamin C, folate, and potassium

## STRAWBERRIES

- An excellent source of vitamin C
- A good source of folate and potassium
- Low in calories and high in fiber
- Provide anticancer bioflavonoids
- Contain **oxalic acid**, which reduces mineral absorption and may aggravate kidney and bladder stones

## TANGERINES

- A good source of vitamin C, beta carotene, and potassium
- Contain **pectin**, a soluble fiber that helps control blood cholesterol

## TEA

- Tea is a refreshing stimulant that is almost calorie-free if consumed plain.
- Tea contains **antioxidants** and **bioflavonoids**, which may lower the risk of cancer, heart disease, and stroke.
- Green tea is high in vitamin K.
- Tea contains **tannins** that may provide protection against **dental decay**.
- Herbal teas are caffeine-free.
- Tannins decrease iron absorption if tea is consumed with meals.
- Tea has a diuretic effect that increases urination.
- Tea may cause insomnia in caffeine-sensitive people.

## TOMATOES

- A useful source of vitamins A and C, folate, and potassium
- A good source of **lycopene**, an antioxidant that protects against some cancers

## TURNIPS

- A useful source of vitamin C, as well as some calcium and potassium
- A low-calorie source of fiber
- May protect against certain cancers
- Contain substances that interfere with the production of thyroid hormones
- Vegetables
- Many are rich in vitamins A, C, and E, folate and other B vitamins, and potassium and other minerals
- High fiber content promotes regular bowel function
- Rich in bioflavonoids and other chemical compounds that help prevent disease
- **Goitrogens** in **cruciferous vegetables** may interfere with thyroid function

**VINEGAR**

- Basis for a low-calorie salad dressing
- Can be used to preserve other foods

**WATERCRESS**

- A good source of **beta carotene**, a precursor of vitamin A, and vitamin C
- A useful source of calcium, iron, and potassium
- Rich in **antioxidants**, which help prevent cancer and other diseases

**WINE**

- Moderate consumption may decrease the risk of heart disease and certain cancers.
- Wine increases the absorption of calcium, magnesium, phosphorus, and zinc.
- Pigments, such as **anthocyanins** and **tannins**, may protect against viruses and inhibit the formation of **dental plaque**.
- Wine promotes relaxation.

**YAMS AND SWEET POTATOES**

- A rich source of  $\beta$ -carotene
- A good source of vitamins C and B<sub>6</sub>, folate, and potassium
- Naturally sweet and high in fiber

**YOGURT**

- An excellent source of calcium and phosphorus
- Provides useful amounts of vitamin A, several B vitamins, and zinc
- More digestible than milk for people with lactose intolerance
- Immunostimulant

**ZUCCHINI**

- Low in calories
- A good source of vitamins A, C, and folate

**ZWIEBACK**

- An ideal finger food for teething babies
- A nonperishable alternative to bread
- Provides some of the same nutrients found in bread





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# 67 Wheat Germ

## INTRODUCTION

Wheat germ contains coenzyme Q<sub>10</sub>, which synthesizes ATP and stabilizes mitochondria. In 1977, Peter Mitchell received a Nobel Prize for work on coenzyme Q<sub>10</sub> and energy transfer. Coenzyme Q<sub>10</sub> protects against mitochondrial diseases. It is efficacious in heart diseases and is a neuroprotectant, and hence is effective in Parkinson's disease.

The usual definition of a *neuroprotectant* is an agent that aims to prevent neuronal death by inhibiting one or more of the pathophysiological steps in the processes that follow injury to the central nervous system (CNS) or ischemia due to occlusion of an artery or hypoxia due to any cause. This definition has now been extended to include protection against neurodegeneration and neurotoxins. The extended definition includes interventions that slows or halts the progression of neuronal degeneration.

Wheat germ is the embryo of wheat berry. It is a good source of coenzyme Q<sub>10</sub>, vitamin E, choline, most of the B vitamins, the minerals calcium, magnesium, phosphorus, and several trace elements. This chapter provides information only on coenzyme Q<sub>10</sub>, which is useful in the treatment of the pleiotropic manifestation of the following diseases:

### **Mitochondrial diseases**

#### **Bone marrow**

Pearson's syndrome with pancytopenia

#### **Brain**

Ataxia

Stroke

Seizures

Dementia

Migraine

#### **Eye**

Ophthalmoplegia

Optic neuropathy

Pigmentary retinal degeneration

Cataract

Corneal dystrophy

#### **Heart**

Cardiomyopathy

Conduction blocks

Wolff–Parkinson–White syndrome

#### **Inner ear**

Sensorineuronal deafness

#### **Intestine**

Malabsorption

Pseudo-obstruction

**Kidney**

Fanconi's syndrome  
Glomerulopathy

**Liver**

Hepatopathy

**Pancreas**

Diabetes mellitus  
Exocrine dysfunction

**Skeletal muscle**

Myopathy  
Fatigue  
Weakness

**Other**

Short stature  
Episodic nausea and vomiting  
Hypoparathyroidism  
Lactic acidosis  
Elevated cerebrospinal fluid protein  
Peripheral neuropathy  
Myoclonus

**Neurodegenerative disease**

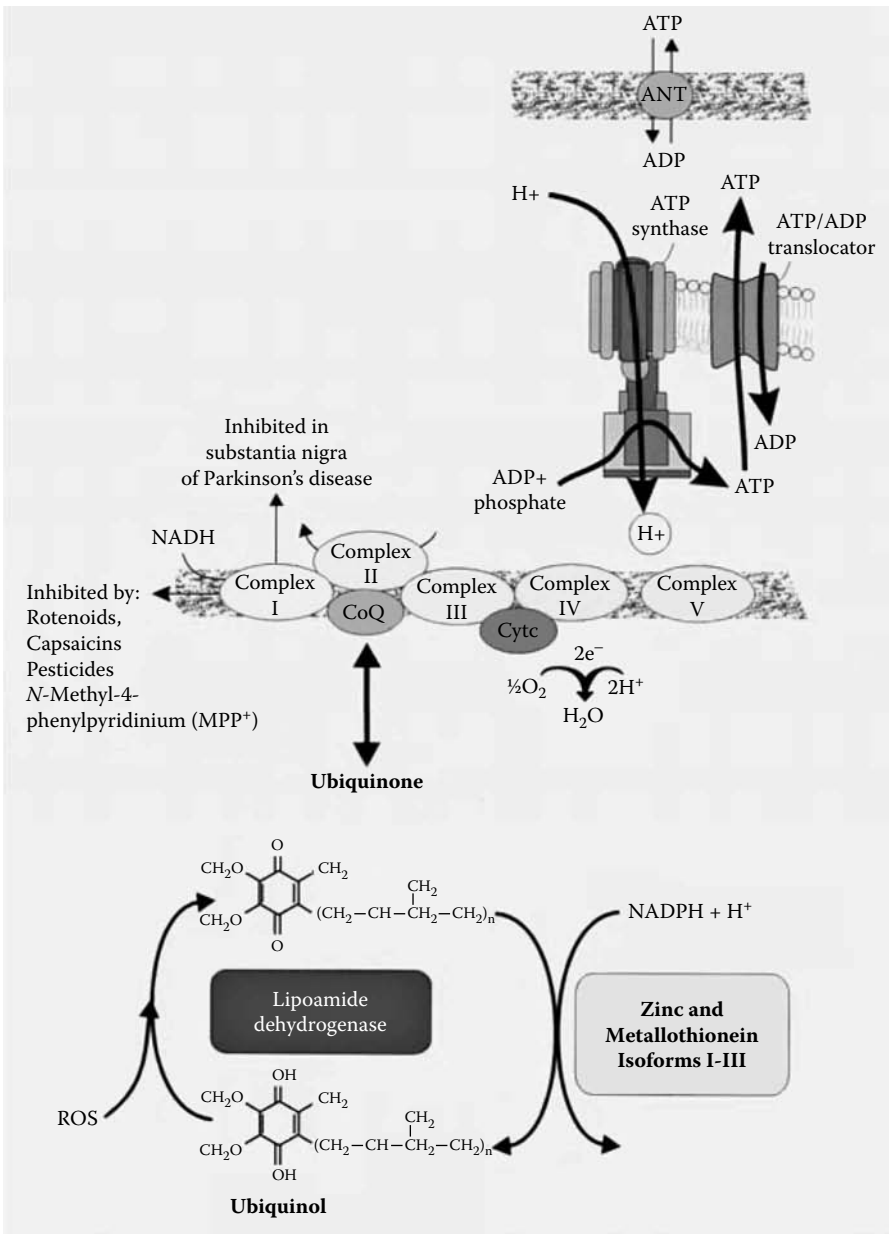
Parkinson's disease  
Huntington's disease  
Amyotrophic lateral sclerosis

In this chapter, mitochondrial dysfunctions will be briefly reviewed, but the neuroprotective effects of coenzyme Q<sub>10</sub> in neurodegenerative disease will be discussed in detail. For additional documentations, the readers should consult the two volumes on mitochondrial ubiquinone (coenzyme Q<sub>10</sub>) biochemical, functional, medical, and therapeutic aspects in human health and disease (Ebadi et al., 2001).

Human mitochondrial DNA (mtDNA) deletion mutations have been found in a number of neurodegenerative diseases, including Kearns–Sayre syndrome, Leber's hereditary optic neuropathy, Alzheimer's disease (AD), and Parkinson's disease (PD), and with aging. Abnormalities in mitochondrial metabolism likewise have been associated with neurodegenerative disease, e.g., Huntington's disease (HD). In addition, a decline of aerobic energy metabolism in the affected tissue is often associated with the progression of these neurodegenerative diseases. A decline in aerobic metabolism has been observed in aging tissues. **Ubiquinone** (coenzyme Q<sub>10</sub>), in addition to its function as an electron and proton carrier in mitochondrial electron transport coupled to ATP synthesis, acts in its reduced form (**ubiquinol**) as an antioxidant, inhibiting lipid peroxidation in biological membranes and protecting mitochondrial inner-membrane proteins and DNA against oxidative damage accompanying lipid peroxidation. Ubiquinol is the only known lipid-soluble antioxidant that animal cells can synthesize *de novo* and for which there exists enzymic mechanisms that can regenerate it from its oxidized product formed in the course of its antioxidant function. Tissue ubiquinone levels are subjected to regulation by physiological factors that are related to the oxidative activity of the organism. They increase under the influence of oxidative stress and decrease during aging (see Figure 67.1 and Ebadi and Pfeiffer, 2005).

## MITOCHONDRIAL DYSFUNCTION IN NEURODEGENERATION

Numerous toxins are known to interfere with mitochondrial respiratory chain function. These have been used in the development of pesticides and herbicides, and accidental use in man has



**FIGURE 67.1** Mitochondria produce energy by recycling electrons from food down the respiratory chain through a series of protein complexes (I–V) in the mitochondrial inner membrane. Complex I and II collect electrons from catabolism of fats, protein, and carbohydrates and transfer them to ubiquinone (CoQ<sub>10</sub>). The electrons then move sequentially through cytochrome c, complex V, and finally react with oxygen generating protons, which are pumped across the inner mitochondrial membrane producing a proton gradient. Complex V (ATP synthase) uses the potential energy stored in the proton gradients to condense ADP and inorganic phosphate into ATP. **Ubiquinone** (coenzyme Q<sub>10</sub>) is a mitochondrial stabilizer that protects against drug-induced parkinsonism. Ubiquinone becomes converted to another antioxidant **ubiquinol** by zinc-dependent enzyme (see Ebadi and Pfeiffer, 2005).

led to the development of animal models for human disease. The propensity for mitochondrial toxins to induce neuronal cell death may well reflect not only their metabolic pathways but also the sensitivity of neurons to the inhibition of oxidative phosphorylation. Thus, the accidental exposure of humans to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and to 3-nitropropionic acid has led to primate models of PD and HD, respectively. These models were made all the more remarkable when identical biochemical deficiencies were identified in relevant areas of humans suffering from the respective idiopathic diseases. The place of complex I deficiency in PD remains undetermined, but there is recent evidence to suggest that, in some cases at least, it may play a primary role. The complex II/III deficiency in HD is likely to be secondary and induced by other pathogenetic factors. The potential to intervene in the cascade of reactions involving mitochondrial dysfunction and cell death offers prospects for the development of new treatment strategies either for neuroprotection in prophylaxis or rescue (Cooper and Schapira, 1997).

### **TOXIN MODELS OF PARKINSON'S DISEASE**

A variety of toxins have been shown to give rise to selective neuronal loss and a parkinsonian syndrome in either humans, other primates, or rodents. These agents include manganese, iron, cyanide, azide,  $\beta$ -carbolines, isoquinolines, and MPTP.

### **TOXIN MODELS OF HUNTINGTON'S DISEASE**

Excitotoxic lesions generated in primates using NMDA receptor agonists such as quinolinic acid cause neuronal loss similar to that found in HD, emphasizing the potential role of excitotoxicity in HD. Intrastratial injections of the reversible succinate dehydrogenase inhibitor, malonate, into rats caused a decrease in ATP levels and increased lactate and excitotoxic lesions, which could be prevented by NMDA antagonists.

3-nitropropionic acid (3NP), an irreversible inhibitor of succinate dehydrogenase (complex II) of the mitochondrial respiratory chain, when administered to rats or primates can also result in selective neuronal loss. In China, children exposed to 3NP from a fungal contaminant of sugar cane developed gastrointestinal disturbances followed by encephalopathy and coma, which was followed by dystonia upon recovery. In mice, 3NP caused bilateral symmetric lesions of the caudate and putamen not dissimilar to that seen with excitotoxins. When administered chronically, 3NP resulted in striatal neuronal loss, and similar to HD, NADPH diaphorase neurons were spared; and in primates chronic administration produced apomorphine-inducible movement disorder involving choreiform and dystonic movements similar to HD with lesions similar to those found in HD.

### **ALZHEIMER'S DISEASE**

As in HD, there is evidence for a defect of energy metabolism in Alzheimer's disease. For instance, there is evidence from positron emission tomography (PET) that glucose metabolism is depressed in the parietal, temporal, and posterior cingulate cortices and this glucose utilization declines progressively with time. Of particular interest is the recent demonstration by PET that cognitively normal individuals homozygous for the apolipoprotein 4 allele, which carries a substantial risk of subsequent development of AD, had significantly reduced rates of glucose metabolism in a pattern identical to AD patients.

Deficiencies of complexes II and IV have been described in AD hemibrains (see Cooper and Schapira, 1997 for a review and references).

## INCREASE IN BRAIN MITOCHONDRIAL CONCENTRATIONS AND EXERTION OF NEUROPROTECTIVE EFFECTS BY COENZYME Q<sub>10</sub>

Coenzyme Q (ubiquinone) is an essential cofactor in the electron transport chain in which it accepts electrons from complex I and II. Coenzyme Q also serves as an important antioxidant in both mitochondria and lipid membranes. Coenzyme Q is a lipid-soluble compound composed of a redox active quinoid moiety and a hydrophobic "tail." The predominant form of coenzyme Q in humans is coenzyme Q<sub>10</sub>, which contains ten isoprenoid units in the tail, whereas the predominant form in rodents is coenzyme Q<sub>9</sub>, which has nine isoprenoid units in the tail. Coenzyme Q is soluble and mobile in the hydrophobic core of the phospholipid bilayer of the inner membrane of the mitochondria in which it transfers electrons one at a time to complex III of the electron transport chain.

There has been considerable interest in the use of coenzyme Q<sub>10</sub> for the treatment of mitochondrial disorders. Several reports found both clinical and biochemical improvement in patients with mitochondrial disorders. If defects in energy metabolism and oxidative damage play a role in the pathogenesis of neurodegenerative diseases, then treatment with coenzyme Q<sub>10</sub> could exert beneficial therapeutic effects. Oral administration of coenzyme Q<sub>10</sub> significantly attenuates lesions produced by intrastratial administration of malonate in rats, as well as malonate-induced depletions of ATP and increases in lactate concentrations. Matthews et al. (1998) studied and showed that feeding 12- to 24-month-old rats with coenzyme Q<sub>10</sub> resulted in significant increases in cerebral cortex mitochondrial concentrations of coenzyme Q<sub>10</sub>. Furthermore, oral administration of coenzyme Q<sub>10</sub> markedly attenuated striatal lesions produced by systemic administration of 3-nitropropionic acid and significantly increased life span in transgenic mouse model of familial amyotrophic lateral sclerosis. These results show that oral administration of coenzyme Q<sub>10</sub> increases brain mitochondrial concentrations. The authors interpreted these results to suggest that coenzyme Q<sub>10</sub> can exert neuroprotective effects that might be useful in the treatment of neurodegenerative diseases (Matthews et al., 1998; Sharma et al., 2004; Ebadi et al., 2004; Sharma and Ebadi, 2004).

### NEUROPROTECTIVE AND NEURORESTORATIVE STRATEGIES FOR PARKINSON'S DISEASE

Advances in understanding the molecular mechanisms of cell death and the pathogenesis of sporadic and familial PD are creating new opportunities for the development of neuroprotective and neurorestorative therapies (Dawson and Dawson, 2002; Ebadi and Pfeiffer, 2005).

PD is the second most common neurodegenerative disease afflicting about 1% of people over 65 years old and 4 to 5% of people over 85. Because of its prevalence, PD is a major societal health problem with significant economic consequences. Early in the disease, dopamine (DA)-containing neurons in the substantia nigra pars compacta (SNc) degenerate, leading to slowed movement, rigidity, rest tremor and disturbances in balance. As the disease progresses, many patients develop cognitive dysfunction, including anxiety, depression and dementia. In contrast to other neurodegenerative disorders, there is relatively good symptomatic therapy for PD, which consists mainly of dopamine replacement and adjuvant surgical therapy that relieves most motoric symptoms (Dawson and Dawson, 2001).

### EFFICACY OF COENZYME Q<sub>10</sub> IN PARKINSON'S DISEASE

Coenzyme Q<sub>10</sub> and vitamin E are found in wheat germ. Furthermore, studies in mice have shown that administration of coenzyme Q<sub>10</sub> elevate the level of mitochondrial  $\alpha$ -tocopherol (Lass et al., 1999). Beal and his colleagues (2002) investigated the potential usefulness of coenzyme Q<sub>10</sub> in animal models of PD, amyotrophic lateral sclerosis (ALS), and HD. It has been demonstrated that coenzyme Q<sub>10</sub> can protect against striatal lesions produced by the mitochondrial toxins malonate and 3-nitropropionic acid. These toxins have been utilized to model the striatal pathology, which

occurs in HD. It also protects against 1-methyl-1,2,3,6-tetrahydro-pyridine (MPTP) toxicity in mice. Coenzyme Q<sub>10</sub> significantly extended survival in a transgenic mouse model of ALS. Coenzyme Q<sub>10</sub> can significantly extend survival, delay motor deficits and weight loss, and attenuate the development of striatal atrophy in a transgenic mouse model of HD. In this mouse model it showed additive efficacy when combined with the *N*-methyl-D-aspartate (NMDA) receptor antagonist, remacemide. Coenzyme Q<sub>10</sub> is presently being studied as a potential treatment or early PD as well as in combination with remacemide as a potential treatment for HD.

Müller et al. (2003) postulated that oxidative stress, nigral mitochondrial complex I deficiency, and visual dysfunction seen in PD were due to coenzyme Q<sub>10</sub> deficiency. Furthermore, they showed that coenzyme Q<sub>10</sub> supplementation provided symptomatic benefit in patients with PD.

Shultz et al. (2002) in a multicenter, randomized, parallel group, placebo-controlled, and double blind trial showed that coenzyme Q<sub>10</sub> slowed the functional decline seen in PD. Coenzyme Q<sub>10</sub> was safe and well tolerated at dosage of up to 1200 mg/d. Less disability developed in subjects assigned to coenzyme Q<sub>10</sub> regimen.

### THE NEUROPROTECTIVE ROLE OF VITAMIN E

The nervous system is very vulnerable to the damaging effects of highly reactive free radicals. Free radicals have been implicated in the development of a number of chronic and acute conditions and diseases involving the brain or neurological tissue. The brain contains high amounts of polyunsaturated fatty acids that are susceptible to oxidative damage, receives a large amount of oxygen, and is relatively deficient in certain antioxidant enzymes. Thus, vitamin E and other antioxidants are critically important in protecting the brain and neural tissues from oxidative damage. Furthermore, dietary intake of vitamin E may reduce risk of Parkinson's disease.

Albert Saint George, who discovered vitamin C (ascorbic acid) and won a Nobel Prize in physiology and medicine, is reported to have said 15 years before discovery of coenzyme Q<sub>10</sub> that eating wheat germ keeps you healthy and young. Wheat germ has coenzyme Q<sub>10</sub> which protects the mitochondria and enhances the level of ATP. In addition, wheat germ has vitamin E which is an antioxidant. Moreover, it has choline (also found in the honey and lecithin), which is the precursor to acetylcholine, the memory molecule. Coenzyme Q<sub>10</sub>, in addition to being efficacious in treating PD and other neurological disorders, has also been advocated in many other disorders including but not limited to bacterial sepsis, cardiac dysfunction, coronary artery disease, restoring respiratory function, aging, and multiple sclerosis (for detailed discussions and references, see Ebadi et al., 2001; Sinatra and Roberts, 2005).

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# 68 Wine

## INTRODUCTION

The following are the benefits of wine:

- Decreases the risk of heart disease and certain cancers
- Increases the absorption of calcium, magnesium, phosphorus, and zinc
- Contains **anthocyanins** and tannins, which protect against viruses and inhibit the formation of dental plaque
- Promotes relaxation
- Wine should be avoided during pregnancy as it causes **fetal alcohol syndrome**, a form of mental retardation. **Epidemiologists have suggested that the countries in which atherosclerosis incidence is low are those countries in which red wine consumption is high.**

## EFFECTS OF RED WINE

**Moderate consumption of red wine** may decrease the risk of heart disease and certain cancers. The pigments found in grapes, such as **anthocyanins** and tannins, may protect against viruses and inhibit the formation of dental plaque.

Red wine is made from **purple grapes**, but white wine is not necessarily made from white grapes. Many white wines are made from purple grapes, but the skins are removed before they color the fermenting juice, called **must**. The grape skins contain most of the **bioflavonoids**, **phenols**, **tannins**, and other compounds that give wine its flavor and possibly healthful properties. The protectors against atherosclerosis in red wine are its **polyphenolic flavonoids**, **quercetin**, and **catechin**. It was interesting to learn from epidemiologists that a high consumption of **green tea** was also geographically associated with low rates of cancer and to observe that the induction by **dimethylbenzanthracene** of skin squamous carcinomas was reduced in mice by green tea or its polyphenolic fraction or agents, especially **mezelein**. These green tea polyphenols also protect against ***N*-nitrosorbis (oxoprophy)** amine-induced pancreatic duct epithelial hyperplasia and carcinoma (Mathé, 1999).

## ALCOHOL

The term **alcohol** usually implies ethyl alcohol, although actually there are a large number of alcohols that vary in physical structure from liquids to waxy solids. Of the host of known alcohols, only two are frequently consumed by humans. They are **glycerol**, from the digestion of fats, and **ethyl alcohol**, from alcoholic beverages. The quantity of glycerol in our food is usually insufficient to cause any pharmacological effect. On the other hand, the amounts of ethyl alcohol commonly ingested do produce pharmacological effects of varying degree. The major portion of this chapter is devoted to ethyl alcohol.



**TABLE 68.1**  
**Alcoholic Beverages**

Beverage	Raw Material	Malting	Distillation	Alcohol Content (Percent by Volume)	Calories <sup>a</sup> (per 100 cc)
Wine	Grape juice	No	No	10–22	60–175
Hard cider	Apple juice	No	No	8–12	35–60
Beer	Cereals	Yes	No	3.5–6	40–60
Ale	Cereals	Yes	No	6–8	55–70
Brandy	Wine	No	Yes	40–55	225–300
Whisky	Cereals	Yes	Yes	40–55	225–300
Rum	Molasses	No	Yes	40–55	225–300
Gin	Neutral spirits plus orange peel and juniper berries	No	Usually	40–55	225–300
Vodka	Neutral spirits	No	No	40–55	225–300
Milk (for comparison)					60–80

<sup>a</sup> Almost half the calories in beer and about one-third of the calories in ale are furnished by unfermented carbohydrate. Sweet wine may contain 4 to 10% sugar.

The ethyl alcohol in all alcoholic beverages results from the **fermentation of a sugar by yeast**. If a cereal is the raw material for the beverage, it must first be malted to convert the starch to **maltose**, as yeast will not ferment starch. Malt is produced by moistening barley and allowing it to sprout. At this stage, the grain contains **maltose** and a large amount of the enzyme **diastase**. The sprouted barley is next dried at a temperature sufficient to kill the sprout without injuring the enzyme and is then ground. A **mash** is prepared by incubating a mixture of ground cereal, water, and malt. Mash for brewing beer is filtered, and the liquid, or **wort**, is then treated with yeast. For making **whisky**, yeast is added directly to the malted mash. After fermentation, the liquid portion, or distiller's beer, is run through a simple still. The distillate, or raw whisky, is mostly water and alcohol, plus traces of other volatile products of the fermentation. If a more efficient fractionating still is used, only water and alcohol are recovered. This product, **neutral spirits**, contains 90 to 95% of alcohol by volume. Information regarding some common alcoholic beverages is given in Table 68.1.

Wines containing more than 16% of alcohol are fortified by the addition of neutral spirits. In making beer, a small amount of **hops** is added to give it a bitter flavor. Whisky must be aged by storage in a **charred oak barrel**. This causes esterification of some of the organic acids with the higher alcohols and adds extractives plus color from the charred wood. Blended whisky is a mixture of aged whisky with neutral spirits and water. Some blended whisky contains less than half aged whisky. Whisky, brandy, and wine contain a small percent of **fusel oil**, which is composed of the higher homologues of ethyl alcohol, chiefly **isoamyl alcohols**, and acids such as **capric acid**.

With wines and distilled liquors, the bottle label must state the percentage of alcohol expressed by volume or as a number followed by the word *proof*. In the U.S., the proof number is twice the percentage of alcohol by volume. The term proof originated in an old English custom of testing the alcohol content of whisky. The whisky was poured over gunpowder and a flame applied to it. If the gunpowder exploded, the whisky was said to be of "**proof strength**." For the whisky to ignite it must contain at least 50% of alcohol by volume. In Great Britain and Canada proof whisky must contain a little over 57% alcohol by volume.

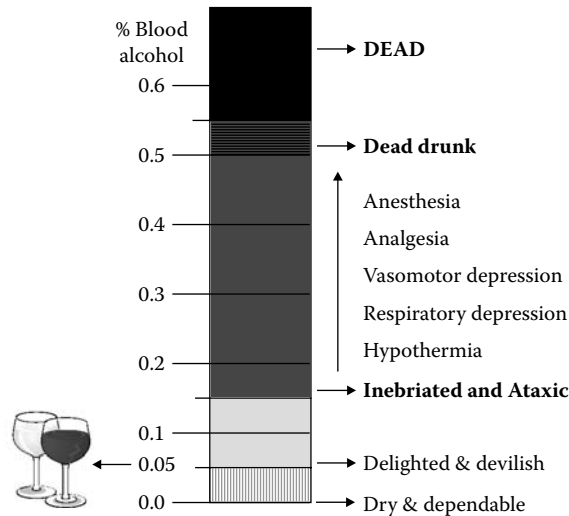


FIGURE 68.1 The dose-dependent actions of ethanol.

## THE PHARMACOLOGY OF ALCOHOL

### EFFECTS OF ETHYL ALCOHOL

#### Central Nervous System

As a CNS depressant, ethyl alcohol (ethanol) obeys the law of descending depression, in that it first inhibits the cerebral cortex, then the cerebellum, spinal cord, and medullary center.

#### Acute Intake of Alcohol

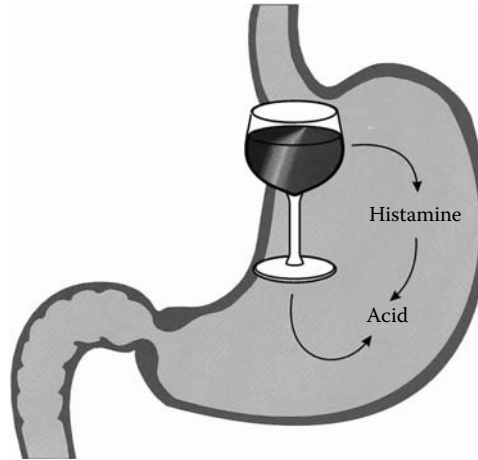
Taken in small quantities, alcohol brings about a feeling of well-being. When consumed in large quantities, alcohol produces more boisterous behavior. Self-control is lost and judgment is impaired. Alcohol works by depressing the inhibitory control mechanism and the reticular activating system. If a large amount of alcohol is consumed within a short time, unconsciousness and general anesthesia ensue. Death is due to respiratory and cardiac failure (Figure 68.1).

#### Cardiovascular System

Alcohol produces dilation of the skin vessels, flushing, and a sensation of warmth. Alcohol also interferes with the normal cutaneous vasoconstriction in response to cold. The body heat is therefore lost very rapidly and the internal temperature consequently falls. At toxic alcohol levels, the hypothalamic temperature-regulating mechanism becomes depressed and the fall in body temperature becomes pronounced. For these reasons, consuming alcoholic beverages for the purpose of keeping warm in cold weather is obviously irrational.

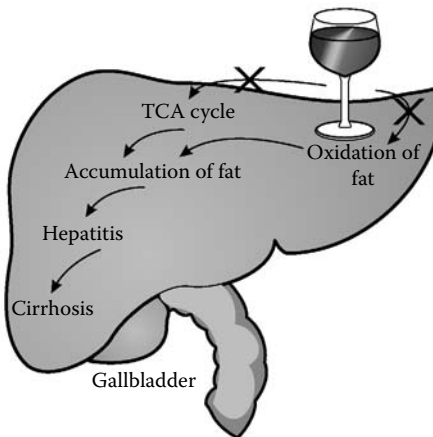
#### Gastrointestinal Effects

As a gastric secretagogue, alcohol stimulates the secretion of gastric juice, which is rich in acid and pepsin. Therefore, the consumption of alcohol is contraindicated in subjects with untreated acid-pepsin disease (Figure 68.2). In addition, alcohol releases **histamine**, which in turn releases gastric juice. This effect is not blocked by **atropine**.



**Ethanol is a gastric secretagogue**

**FIGURE 68.2** Ethanol aggravates acid-pepsin diseases.



**Ethanol causes cirrhosis**

**FIGURE 68.3** Ethanol causes hepatic failure. TCA = tricarboxylic acid.

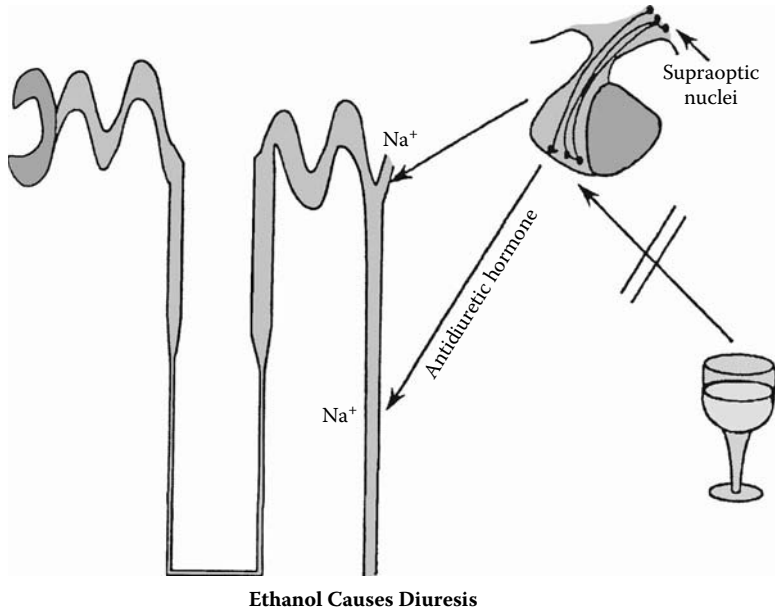
In toxic doses (20%), gastric secretion is inhibited and peptic activity is depressed. From this, it is easy to deduce that small amounts of alcohol stimulate appetite and aid digestion, but large amounts may produce indigestion. Alcohol is also a carminative substance in that it facilitates the expulsion of gas from the stomach.

### Liver

Alcohol enhances the accumulation of fat in the liver. In alcoholics, this fat accumulation continues and **cirrhosis of the liver** may ensue; however, the two phenomena are not related (Figure 68.3).

### Endocrine Glands

Alcohol may release epinephrine, which leads to transient hyperglycemia and hyperlipemia. Therefore, alcohol consumption is contraindicated in those with diabetes. Alcohol causes diuresis by



**FIGURE 68.4** Ethanol inhibits the secretion of antidiuretic hormone.

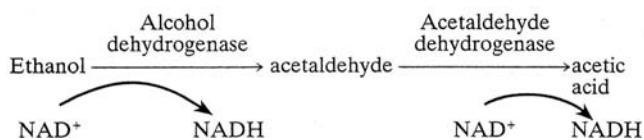
increasing fluid intake and by inhibiting the secretion of **antidiuretic hormone** elaborated by the posterior pituitary gland (Figure 68.4).

### Fetal Alcohol Syndrome

Alcohol has teratogenic effects that are manifested by CNS dysfunction.

### PHARMACOKINETICS OF ETHANOL

Alcohol is absorbed from the small intestine. Patients who have undergone gastrectomy may therefore become intoxicated relatively fast. The absorption that takes place through unbroken skin is negligible. As a water-soluble substance with a small molecular weight, alcohol is distributed uniformly throughout all tissues and tissue fluids. It passes across the placental barrier, is found in spinal fluid, and accumulates in the brain. Consequently, any physiological fluids (urine, blood, spinal fluid, breast milk, or saliva) are suitable for determining the concentration of alcohol. The metabolism of ethanol, which shows genetic polymorphism, is catalyzed primarily by **alcohol dehydrogenase** with zero-order kinetics, according to the following scheme.



The rate-limiting factor in the metabolism of ethanol is the availability of  $\text{NAD}^+$ .

Ethanol is not metabolized by **cytochrome P-450 enzymes (microsomal drug-metabolizing systems, or MEDS)**. However, it is metabolized to a certain extent by the **microsomal ethanol-oxidizing system (MEOS)**.

Although ethanol is not metabolized by the microsomal drug-metabolizing system, it inhibits it and increases the rate of its synthesis. This effect may create a significant alcohol–drug interaction in both nonalcoholics and alcoholics who are taking medications.

## POISONING AND TOXICITY

### ACUTE POISONING

Poisoning may be characterized by inebriation, muscular incoordination, blurred vision, impaired reaction time, excitement due to loss of inhibitions, impairment of consciousness, coma, tachycardia, and slow respiration. A blood alcohol level of 80 mg/dl can produce recognizable features of drunkenness; a level above 300 mg/dl is life threatening. In children, severe hypoglycemia and convulsions may also occur.

Acute poisoning is treated with gastric aspiration and lavage combined with intensive supportive therapy, including thorough assessment of the patient plus measures to prevent respiratory failure. In cases of very severe poisoning, peritoneal dialysis or hemodialysis may be necessary.

### DELIRIUM TREMENS

Delirium tremens usually arises in chronic alcohol abusers. The clinical features may include hallucinations, intense fear, sleeplessness, restlessness, agitation, delirium, and sometimes grand mal convulsions. In addition, tachycardia, hypotension, and clover-shaped ST changes in the electrocardiogram are evident.

The treatment of patients during a delirium tremens episode includes the intravenous administration of another CNS depressant (usually diazepam) during the acute phase, followed by the oral administration of chlordiazepoxide or oxazepam. In addition, other medications and dietary management may become essential.

### CHRONIC TOXICITY

Prolonged alcohol consumption in malnourished individuals causes far more deleterious effects. These include the following:

- **Neuropathy**, which is characterized by dysesthesia, paralysis, and trophic skin changes.
- **Myopathy**, which is manifested by rhabdomyolysis, muscle pain and cramps, elevated serum creatine and phosphokinase levels, and myoglobinuria.
- **Wernicke–Korsakoff syndrome**, stemming from thiamine deficiency and characterized by confusion, ataxia, and ocular abnormalities (nystagmus and lateral rectus muscle palsy).
- **Cerebellar degeneration**, degeneration of the cerebellar cortex, especially the Purkinje cells, causing ataxia and truncal instability.
- **Amblyopia**, decreased visual acuity and color perception.
- **Marchiafava–Bignami disease**, resulting from central demyelination of the corpus callosum (also seen in chronic cyanide intoxication, which causes progressive dementia).
- **Central pontine myelinolysis**, characterized by progressive bulbar weakness and quadriparesis.

## TREATMENT OF ALCOHOLISM

Alcoholism is the most prevalent substance use disorder in the U.S., affecting approximately 7.4% of the population at some point in their lifetime. The magnitude of this problem is huge, involving

the loss of 100,000 lives and costs of \$ 18.5 billion per year (National Institute on Alcohol Abuse and Alcoholism, 2000). It is the number-one substance chosen by both adults and teenagers.

Detoxification refers to the clearing of alcohol from the body and the readjustment of all systems to functioning in the absence of alcohol. The alcohol withdrawal syndrome at the mild end may include only headache and irritability, but about 5% of alcoholic patients have severe withdrawal symptoms manifested by tremulousness, tachycardia, perspiration, and even seizures (rum fits). The presence of malnutrition, electrolyte imbalance, or infection increases the possibility of cardiovascular collapse.

Significant progress has been made in establishing safe and effective medications for alcohol withdrawal. Pharmacotherapy with a **benzodiazepine** is the treatment of choice for the prevention and treatment of the signs and symptoms of alcohol withdrawal. Many patients detoxify from alcohol without specific treatment or medications. However, it is difficult to determine accurately which patients require medication for alcohol withdrawal. Patients in good physical condition with uncomplicated, mild to moderate alcohol withdrawal symptoms usually can be treated as outpatients.

### **DISULFIRAM: AN ALCOHOL SENSITIZING AGENT**

In 1951, disulfiram was the first medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcohol dependence other than detoxification. Disulfiram inhibits a key enzyme, **aldehyde dehydrogenase**, involved in breakdown of ethyl alcohol. After drinking, the alcohol–disulfiram reaction produces excess blood levels of **acetaldehyde**, which is toxic in that it produces facial flushing, tachycardia, hypotension, nausea and vomiting, and physical discomfort. Opioid receptors antagonists, such as **naloxone** and naltrexone (see Chapter 47) that block opioid receptors have been found to decrease alcohol consumption (Cornish et al., 2004).



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# 69 Yogurt and the Immune System

## INTRODUCTION

- The following are the benefits of yogurt:
- An excellent source of calcium and phosphorus
- Provides vitamin A, several B vitamins, and zinc
- More digestible than milk for people with lactose intolerance
- A probiotic agent
- An immunoenhancing agent

Yogurt is defined as a coagulated milk product that results from fermentation of lactic acid in milk by *Lactobacillus bulgaricus* and *Streptococcus thermophilus*. Other **lactic acid bacteria** (LAB) species can be combined with *L. bulgaricus* and *S. thermophilus*. In the finished product, the LAB must be alive and in substantial amounts. LAB have been used for thousands of years to produce fermented food and milk products. Fermented products contain a variety of fermenting microorganisms belonging to various genera and species, all of which produce lactic acid (Meydani and Ha, 2000).

With few exceptions, milk and yogurt have similar vitamin and mineral compositions. During fermentation, **vitamin B<sub>12</sub>** and vitamin C are consumed and **folic acid** is produced. The differences in other vitamins between milk and yogurt are small and depend on the strain of bacteria used for fermentation. Although milk and yogurt have similar mineral compositions, some minerals, e.g., calcium, are more bioavailable from yogurt than from milk. In general, yogurt also has less lactose and more lactic acid, galactose, peptides, free amino acids, and face fatty acid than does milk.

## IMMUNE SYSTEM FUNCTIONS

The main functions of the immune system are to eliminate invading viruses and foreign microorganisms, to rid the body of damaged tissue, and to destroy neoplasms in the body. Healthy humans have two immune mechanisms: **acquired (specific) immunity**, which responds to specific stimuli (antigens) and is enhanced by repeated exposure, and **innate (nonspecific) immunity**, which does not require stimulation and is not enhanced by repeated exposure. Innate immune mechanisms consist of physical barriers, such as mucous membranes, and the phagocytic and cytotoxic function of neutrophils, monocytes, macrophages, and lymphatic cells (NK cells). **Acquired immunity** can be classified into two types on the basis of the components of the immune system that mediate the response, i.e., **humoral immunity** and **cell-mediated immunity**. Humoral immunity is mediated by immunoglobulins produced by **bone-marrow-derived lymphocytes** (B lymphocytes) and is responsible for specific recognition and elimination of extracellular antigens. Cell-mediated immunity is mediated by cells of the immune system, particularly **thymus-derived lymphocytes** (T lymphocytes).



Cell-mediated immunity is responsible for delayed-type hypersensitivity (DTH) reactions, foreign graft rejection, resistance to many pathogenic microorganisms, and tumor immunosurveillance. In addition to their involvement in nonspecific immunity, macrophages are important in cell-mediated immunity as antigen-presenting cells and through the production of regulatory mediators such as cytokines and eicosanoids. Several *in vitro* and *in vivo* tests were developed to assess the function of immune cells. Although the study of immune response in animals and humans is based on similar principles, the methods used to separate cells, the types of stimuli used *in vitro*, and the antigen used for *in vivo* challenge vary. In addition, the type of antibody used to measure different mediators or to determine cell-surface proteins is species specific.

### IN VITRO INDEXES OF IMMUNE FUNCTION

To study immune function *in vitro*, immune cells are first separated from whole blood, lymphoid tissues, and gut-associated immune cells. The cells are then maintained and cultured with and without various immune cell stimuli. To measure the activity of isolated phagocytes, the cells are incubated with bacteria or other engulfable materials with or without opsonin for a limited time and then stained for uptake of foreign bodies. Lymphocytes are usually stimulated for varying lengths of time by a variety of stimuli (mitogens, antigens, and other stimulator or target cells) for measurement of their proliferative or cytotoxic activity or release of immunologically active molecules such as antibodies, cytokines, and eicosanoids.

### PHAGOCYtic ACTIVITY

The ability to perform phagocytosis and kill microbes, including bacterial pathogens, is a major effector function of **macrophages**. These properties of macrophages are particularly important for host defense against facultative intracellular organisms, which can replicate within macrophages. The pathogenesis of facultative intracellular bacteria is determined by their ability to survive within macrophages. Several organisms were used previously as targets to determine macrophage killing. These include *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Listeria monocytogenes*, and *Candida albicans*.

Bacteria bind to complement components and the bacterium–complement complexes bind complement receptors on the surface of macrophages. Phagocytosis may also be mediated by specific antibodies that function as **opsonins**, which bind to particles, rendering them susceptible to phagocytosis. The bacterium–antibody complex then binds the macrophages via the **Fc receptor** and phagocytosis begins.

Measurement of phagocytic activity of macrophages was among the earliest techniques for evaluating the immunological effects of LAB. This assay measures the ability of macrophages to bind, internalize, and phagocytose bacteria. Monocytes or macrophages isolated from human peripheral blood mononuclear cells (PBMCs) or from the peritoneal cavity of animals are mixed with bacteria in suspension and incubated at 37°C. Extracellular bacteria are then removed through washing and centrifugation or through washing only over sucrose. The degree of phagocytosis is determined by examining stained cells under oil-immersion microscopy and quantifying the number of internalized bacteria in each cell. This method takes into account not only the percentage of phagocytic cells but also the strength of the phagocytic ability of these cells, i.e., how many bacteria are internalized by each cell.

### LYMPHOCYTE PROLIFERATION ASSAY

Measurement of the proliferative response of lymphocytes is the most commonly used technique for evaluating cell-mediated immune response. Quantitative analysis of proliferative response

involves measuring the number of cells in culture in the presence and absence of a stimulatory agent such as an antigen or a mitogen. The most common polyclonal mitogens used to test the proliferation of lymphocytes are **concanavalin A** (ConA), **phytohemagglutinin**, **lipopolysaccharide** (LPS), and **pokeweed mitogen**. T and B lymphocytes are stimulated by different polyclonal mitogens. ConA and phytohemagglutinin stimulate T cells, LPS stimulates both T and B cells, and pokeweed mitogen stimulates both T and B cells. When mitogens are used, prior exposure of the host to the mitogens is not necessary. However, to measure antigen-specific proliferation, the host should be exposed to the antigen before the cells are stimulated with that antigen *in vitro*. Lymphocytes normally exist as resting cells in the G<sub>0</sub> phase of the cell cycle.

When stimulated with polyclonal mitogens, lymphocytes rapidly enter the G<sub>1</sub> phase and progress through the cell cycle. Measuring incorporation of [<sup>3</sup>H]thymidine into DNA is the most commonly used method for estimating changes in the number of cells. The proliferative assay is used to assess the overall immunological competence of lymphocytes, as manifested by the ability of lymphocytes to respond to proliferation signals. Decreased proliferation, observed in chronic diseases such as cancer, HIV infection, and in the aging process, may indicate impaired cell-mediated immune function.

## CYTOKINE PRODUCTION

Cytokines, which are protein mediators produced by immune cells, are involved in the regulation of cell activation, growth and differentiation, inflammation, and immunity. Measurement of cytokine production, as determined by techniques such as bioassay, radioimmunoassay, and enzyme-linked immunosorbent assay, has been used to examine various immune functions.

**Interleukin-2** (IL-2) is a T-cell growth factor produced by T-helper (T<sub>H</sub>1) and NK cells. As an autocrine and paracrine growth factor, IL-2 induces proliferation and differentiation of T and B cells. IL-2 is responsible for the progress of T lymphocytes from the G<sub>1</sub> to the S phase in the cell cycle and also for stimulation of B cells for antibody synthesis. IL-2 stimulates the growth of NK cells and enhances the cytolytic function of these cells, producing **lymphokine-activated killer** (LAK) cells. IL-2 can also induce interferon (IFN) $\gamma$  secretion by NK cells. IFN $\gamma$  is an important macrophage-activating lymphokine. IL-2 secreted in culture media or biological fluids can be measured by immunoassay or bioassay, the most common of which uses the IL-2-dependent cytotoxic T lymphocyte line. Proliferation of cytotoxic T lymphocyte line cells reflects IL-2 activity. IL-2 activity in samples can be calculated according to a standard curve generated by adding varying concentrations of recombinant IL-2. Enzyme-linked immunosorbent assay is also used to measure IL-2. Although this assay is more specific than is the cytotoxic T lymphocyte line in measuring IL-2 protein concentrations, it does not differentiate between biologically active and nonactive proteins. Under most conditions, changes in IL-2 production are associated with the change in lymphocyte proliferation, although sometimes these changes do not correlate with one another.

IFN $\gamma$  is involved in the induction of other cytokines, particularly T<sub>H</sub>2 cytokines, such as IL-4, IL-5, and IL-10. Because of its role in mediating macrophages and NK cell activation, IFN $\gamma$  is important in host defense against intracellular pathogens (such as *Mycobacterium tuberculosis* and *L. monocytogenes*) and viruses and against tumors. It was suggested that mice and humans continuously produce small amounts of IFN $\gamma$ , which may produce a state of alertness against tumor cells, pathogenic bacteria, and viruses. Because of the short half-life of IFN $\gamma$ , plasma concentrations of IFN $\gamma$  are low and difficult to measure, potentially making treatment-induced changes in plasma IFN $\gamma$  concentrations difficult to detect. IFN $\gamma$  produced by PBMCs or purified T cells has been shown to be more sensitive to yogurt-induced changes than is plasma IFN $\gamma$ . In addition to *ex vivo* production of IFN $\gamma$ , 2-5 A synthetase activity was used as an index of the biological responsiveness of cells to IFN $\gamma$ . 2-5 A synthetase is an IFN $\gamma$ , 2-5 inducible enzyme. The amount of 2-5 A synthetase in different organs of mice increases several fold after treatment of mice with IFN or IFN inducers, such as viral and synthetic double-stranded RNAs.

## YOGURT COMPONENTS WITH POTENTIAL IMMUNOSTIMULATORY EFFECTS

Although yogurt has long been known to bolster host-defense mechanisms against invading pathogens, the components responsible for these effects have not been fully defined. The immunostimulatory effects of yogurt are believed to be due to the bacterial components of yogurt. However, the mechanism or mechanisms responsible for these effects have not been fully determined. After entering the intestine, live or biologically active LAB particles may activate specific and nonspecific immune responses of gut-associated lymphoid tissue and the systemic immune response. The immunogenicity of intestinal bacteria depends on the degree of contact with lymphoid tissue in the intestinal lumen. Therefore, dead bacteria are generally less efficient as antigens than are live bacteria, because dead bacteria are rapidly dislodged from the mucosa. Some studies, however, showed no difference in immunogenicity between viable and nonviable bacteria.

LAB are Gram-positive bacteria with cell wall components such as **peptidoglycan**, **polysaccharide**, and **teichoic acid**, all of which have been shown to have immunostimulatory properties. In addition to cell wall components, immunostimulatory effects were observed with antigens originated from the cytoplasm of some strains of LAB.

Nonbacterial milk components and components produced from milk fermentation may also contribute to the immunostimulatory activity of yogurt. Peptides and free fatty acids generated by fermentation have been shown to enhance the immune response. Milk components such as whey protein, calcium, and certain vitamin and trace elements also can influence the immune system.

Many investigators have studied the therapeutic effects of yogurt and LAB commonly used in yogurt production on diseases such as cancer, infection, gastrointestinal disorders, and asthma. Because the immune system is an important contributor to all of these diseases, the immunostimulatory effects of yogurt were studied by several investigators. Most of these studies used animal models; few human studies on the immunostimulatory effects of yogurt have been conducted.

Although the results of these studies mostly support the notion that yogurt has immunostimulatory effects, poor study design, lack of appropriate controls, and short duration of most of the studies limit the value of the conclusions that can be drawn from them. Most early animal and human studies included too few animals or subjects in each group and most did not include statistical analysis. Although more recent studies addressed these points, none provided the statistical basis for the selected number of subjects; that is, it seems that no power calculations were performed.

Most studies used short-term feeding protocols, which might induce a transient adjuvant effect rather than a long-term stimulation of the immune response. This was shown by several studies in which a maximum effect was seen with 2 to 5 d of yogurt consumption, after which the stimulatory effect of yogurt or yogurt bacteria diminished significantly. Furthermore, most studies investigated the effect of intravenous or intraperitoneal administration or *in vitro* application of yogurt bacteria on different variables of the immune response. Because yogurt is usually consumed orally and because bacterial and nonbacterial components of yogurt may be altered in the gastrointestinal tract, the results of these studies may not reflect those that would be found if the yogurt had been consumed orally. Also, many studies lacked a placebo group or did not use a randomized, blinded design.

Most animal and human studies investigated the effects of yogurt on *in vitro* indexes of the immune response, whereas very few examined variables of the immune system *in vivo*. Because a quantitative correlation between *in vitro* tests of the immune system and resistance to diseases is not yet available, care should be taken in using the *in vitro* results as supporting evidence for health benefits of yogurt. Further, although most past studies focused on the peripheral immune response, the gut-associated immune system is increasingly being recognized as playing an important role in host defense. This aspect of the immune response is particularly relevant to determining the beneficial effects of yogurt because the systemic effects of yogurt may depend on the interaction of the yogurt bacterial components with the immune cells of the gut.

Despite the design problems of previous studies, these studies provide a strong rationale for the hypothesis that increased yogurt consumption, particularly in immunocompromised populations such as elderly people, may enhance immunity. This hypothesis, however, needs to be substantiated by well-designed, randomized, double-blind, placebo-controlled human studies of adequate duration in which several *in vitro* and *in vivo* indexes of the immune response are tested. In particular, clinically relevant indexes such as response to vaccine and DTH should be included, as should a systematic evaluation of the gut-associated immune response. Future studies should use recent technical advances in fluorescent tagging of yogurt bacteria to enable an understanding of the immunostimulatory effects of yogurt. Information on the mechanisms by which yogurt protects is essential before the scientific community accepts claims regarding the health benefits of yogurt.

Although yogurt has long been believed to be beneficial for host-defense mechanisms, the components responsible for these effects or the way in which these components exert their immunological modifications are not completely understood. The presence of LAB is thought to be essential for yogurt to exert immunostimulatory effects but components of nonbacterial yogurt, such as whey protein, short peptides, and CLA, are believed to contribute to the beneficial effects of yogurt as well. It is proposed that the LAB that survive through the gastrointestinal tract, whether intact or modified, can bind to the luminal surface of M cells. LAB-bound M cells reaching to the dome region of PP cells stimulate local immune response, resulting in production of IFN $\gamma$  by  $\gamma$ T cells. This may increase the M-cell population with subsequent rapid amplification of bacterial translocation, which can further activate the local immune system, resulting in stimulation of the local and the systemic immune response. As mentioned previously, further studies are needed to substantiate this.

Finally, once the efficacy of yogurt in improving the immune response has been shown in humans, the benefits of these effects will need to be shown in large clinical trials in which the main outcomes are the incidences and severity of infectious disease. Infectious disease rather than other immune-related diseases are suggested because such studies can be conducted in a relatively short (e.g., 1 h) time compared with studies of diseases such as cancer.



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# Index

## A

- Abrin, 161
- Absorption of drugs, 3–4, 6–9, 315
- blood flow, 8
  - buccal, 4
  - degree of ionization, 7–8
  - factors controlling, 6–9
  - gastric emptying time, 8–9
  - interaction at site of, 33–34
  - ionization, 7–8
  - sublingual, 4
  - surface area, 8
- Absorption of poisons, 431–433, 524
- Ace inhibitors, 484–486
- myocardial infarction, 485
  - progressive renal impairment, 485–486
  - scleroderma renal crisis, 486
- Acetylcholine
- action of, 163
  - precursors, 305
  - releasing agent, 305
- Acetylcholinesterase, structure of, 374
- Acetylcholinesterase inhibitors, 302–304
- cholinesterase inhibition, 302–303
  - clinical applications, 303
  - drug-drug interactions, 303
  - overdosage, 303
  - pharmacokinetics, 303
  - pharmacology, 302–303
  - physostigmine, 303
  - side effects, 303
  - tetrahydroaminoacridine, 302–304
  - therapy, 303–304
- Achillea, 283
- Acid-pepsin disease, 591
- Acupressure, 65
- Acupuncture, 66, xvii
- Addiction to opioids, 460–462
- symptoms, 462
  - time required for, 461
- Addison's disease, xx
- Administration of drugs, 2–5
- bioavailability, 3–4
  - buccal absorption, 4
  - drugs absorption, 3–4
  - duration of action, 2
  - intranasal delivery, 4–5
  - iontophoresis, drug delivery by, 3
  - liposomal drug delivery system, 3
  - nature of drugs, 2–3
  - particle size, 4
  - phonophoresis, drug delivery by, 3
  - rectal administration, 5
  - special circumstances, 3
  - sublingual absorption, 4
- Adrenal steroids, 554–561
- adrenocorticotrophic hormones, 558
  - biosynthesis, 557
  - cholesterol synthesis, 555
  - classification, 555–557
  - glycocorticoids, 555–556, 558–561
  - mineralocorticoids, 556–557
  - sex hormones, 557
- Adrenergic neuronal-blocking drugs, 519
- Adrenocorticotrophic hormones, 558
- Adverse drug reactions, 31–36
- Aesculus hippocastanum*. See Horse chestnut
- Aggregin, 42
- Aging
- bioavailability of nutrients, 343–344
  - diet and, 621–622
  - vitamin intake, 344, 621–622
- Agnus castus, 85
- Agrimony, 85
- Agrippina, xviii
- AIDS, aloe for, 153
- Albumin, 10
- Alcohol, 647–649
- acute intake of alcohol, 649
  - cardiovascular system, 649
  - central nervous system, 649
  - chronic toxicity, 652
  - dehydrogenase inhibition, 335–336
  - delirium tremens, 652
  - disulfiram, 653
  - effects of, 649–651
  - endocrine glands, 650–651
  - fetal alcohol syndrome, 651
  - gastrointestinal effects, 649–650
  - liver, 650
  - pharmacokinetics, 651–652
  - pharmacology of, 649–652
  - poisoning, 652
    - acute, 652
    - red wine, effects of, 647
    - toxicity, 652
- Alcoholism, treatment of, 652–653
- Aldehyde, 335–336

- Aldo-keto-reductase enzymes. *See* Caronyl reductase inhibition
- Aldose reductase inhibition, 335
- Alfalfa, 85
- Algae, 139–142
- Alkaloids, 143–150, 319–321, xix
- Alkyl sulfonate, 112
- Alkylating agents, 112–115
- Allergic reactions, 31–32
- Allicin, antioxidant activity, 486–487
- Allium sativum*. *See* Garlic
- Allium ursinum*. *See* Garlic
- Allopurinol, xanthine oxidase, 28
- Aloe, 85, 151–152, 160–161, xvii
  - AIDS, 153
  - asthma, 153
  - cancer, 152–153
  - chemical composition, 152
  - colon function, 151–162
  - constipation, 153–154
  - diabetes, 153
  - therapeutic uses of, 152–154
- Aloe barbadensis*. *See* *Aloe vera*
- Aloe ferox*. *See* *Aloe vera*
- Aloe gel, 598
  - skin ailments, 153
- Aloe vera*, 86
  - gel, 61
  - leaf, xxi
- Alpha<sub>1</sub>-acid glycoprotein, 10
- Alpha-methyl dopa, 29
- Alphaprodine hydrochloride, 470–471
- Alternative therapies, 65–84
  - acupressure, 65
  - acupuncture, 66
  - aromatherapy, 66
  - auricular therapy, 66
  - ayurveda, 66–67
  - biodynamic massage, 67
  - bioenergetic therapy, 67
  - Chi Kung medicine, 67–68
  - Chinese herbalism, 68
  - chiropractic medicine, 68
  - crystal therapy, 68
  - cupping therapy, 68–69
  - dietary therapy, 69, 71–72, 81–82
    - anti-Candida diet, 81
    - exclusion diet, 81
    - food combining diet, 81
    - liver diet, 81
    - low blood sugar diet, 81
    - macrobiotic diet, 82
    - vegan diet, 81
    - vegetarian diet, 81
  - Eastern herbal medicine, 69–70
  - environmental therapies, 70
  - flower remedies, 70–71
  - food therapy, 71–72
  - gem therapy, 68
  - geopathic therapy, 72
  - Gestalt therapy, 72
  - herbal medicine, 72–74
  - homeopathy, 74
  - hydrotherapy, 74
  - hypnosis, 74
  - hypnotherapy, 74
  - iridology, 74–75
  - Japanese medicine, 75
  - light therapy, 75
  - massage therapy, 75
    - baby massage, 76
    - biodynamic massage, 76
    - reflexology, 76
    - Shiatsu, 75
    - sports massage, 76
    - therapeutic massage, 75
  - moxibustion, 76
  - myotherapy, 76
  - Native American herbal medicine, 76–77
  - naturopathy, 77
  - nutritional therapy, 69
  - osteopathy, 77
  - Persian medicine, 77
  - polarity therapy, 78
  - psychic healing, 78
  - psychological therapies, 78–79
    - analytical therapy, 78
    - behavioral therapy, 79
    - humanistic therapy, 79
    - integrative therapy, 79
    - meditation therapy, 79
    - sound therapy, 79
  - rationale for use, 65
  - reflexology, 79–80
  - Reiki therapy, 80
  - relaxation therapies, 80
    - rolfing medicine, 80
  - shamanistic medicine, 80–81
  - t'ai chi chuan, 81
  - tibetan medicine, 82
  - transcendental meditation, 82
  - transpersonal therapies, 83
  - tree remedies, 70–71
  - visualization therapy, 83
  - yoga, 83
- Alzheimer's disease, 192
  - acetylcholine precursors, 305
  - acetylcholine-releasing agent, 305
  - acetylcholinesterase inhibitors, 302–304
    - cholinesterase inhibition, 302–303
    - clinical applications, 303
    - drug-drug interactions, 303
    - overdosage, 303
    - pharmacokinetics, 303
    - pharmacology, 302–303
    - physostigmine, 303
    - side effects, 303
    - tetrahydroaminoacridine, 302–304
    - therapy, 303–304
  - cholinergic agonists, 305
  - cholinergic enhancement strategies, 301–302
  - cognitive impairment treatment, 301

- noncholinergic neurotransmitter replacement, 305–307
  - anti-inflammatory agents, 306–307
  - antioxidants, 305–306
  - desferrioxamine, 306
  - drugs affecting glutamate receptor sites, 305
  - monoaminergic drugs, 305
  - nerve growth factor, 306
  - neuropeptides, 305
  - nootropics, 305
- therapeutic objectives in, 301
- wheat germ, 644–646
- Amebiasis, 433
- American dwarf palm, 61
- Amikacin, 385
- Aminonucleoside nephrosis, 490–491
- Amphotericin B, 436–438
- Amyl nitrite, 549
- Amyotrophic lateral sclerosis, 192
- Analgesia, 530–531, xxi
- Analytical therapy, 78
- Anandamide, 227–228
- Androgens, 566–569
  - antiandrogens, 569
  - side effects, 569
  - therapeutic uses, 569
- Anesthesia, 263
  - quinine as, 251
- Angelica, 86
- Angina, 412
- Angiotensin antagonists, 363–365
- Anileridine, 471
- Aniseed, 86
- Anisotropine methylbromide, 208
- Antacids, 592
- Anthelmintics, 524
- Anthocyanosides, 595
- Anti-Candida diet, 81
- Antibiotics, 58–59
- Anticholinergic agents, 592–593
  - contraindication to, 205, 377
- Anticholinesterase agents, 374
- Anticipatory nausea, cannabis, 233
- Anticoagulants, 38–42
- Antidepressants, 417–418, 424–425
  - classification of, 419
  - side effects of, 422
  - sites of action of, 420–422
- Antiemetic drugs, dosage, cost, 234
- Antiemetic effects, cannabis, 230–234
- Antifungal agents, 436–440
- Antilymphocyte globulin, 497
- Antimalarial agents, 56–57
- Antimetabolites, 113, 497
- Antimicrobial activity of plants, 385–386
- Antineoplastic agents, 59–60, 116–117
  - oxidative stress and, 117–118
- Antioxidant vitamins, 345–346
- Antioxidants, 107–124, 305–306, 337, 403, 524–525, 621–622
  - alkyl sulfonate, 112
  - alkylating agents, 112–115
  - allicin, 486–487 (*See also* Garlic)
  - antimetabolites, 113
  - antineoplastic agents, 116–117
    - oxidative stress and, 117–118
  - asparaginase, 116
  - beta-carotene, 120
  - bleomycin, 116
  - cancer-chemotherapy-induced emesis, 117
  - cancer therapy, 110
  - carboplatin, 117
  - cereal grains, antioxidant activity, 108
  - chemotherapy, 110–112
    - side effects, 118–123
  - chlorambuch, 112
  - cis-platinum, 117
  - coenzyme Q<sub>10</sub>, 119
  - cyclophosphamide, 112
  - dactinomycin, 116
  - daidzein, 122
  - daunorubicin, 116
  - deoxycytidine analogs, 114–115
  - dietary, 107–124
  - disease prevention, cure, antioxidants in, 107
  - doxorubicin, 116
  - Du-Zhong, antioxidant actions of, 108–110
  - etoposide, 117
  - flavonoids, 337
  - folic acid analogs, 113
  - fruits, antioxidant capacity, 107–108
  - garlic, 484, 486–489, 491–492
  - genistein, 122
  - glutamine, 121
  - glutathione, 120
  - honey, 403
  - hydroxyurea, 117
  - mithramycin, 116
  - N-acetylcysteine, 121
  - natural products, 115–116
  - nitrogen mustards, 112
  - nitrosoureas, 113
  - oats, 473–474
  - oxidative stress, 110
  - parkinsonism, 192
  - plant chemicals, 621–622
  - procarbazine, 117
  - purine antimetabolites, 115
  - pycnogenol, 509–510
  - pyrimidine analogs, 113–114
  - quercetin, 122–123
  - rhubarb, 524
  - saffron, 525
  - selenium, 121–122
  - triazenes, 113
  - vegetables, antioxidant capacity, 107–108
  - vinca alkaloids, 115–116
  - vitamins, 118–119, 345–346
- Antiplatelet actions, 409–414
  - angina, 412
  - antiplatelet drugs, 409–412
  - aspirin, 409–411

dipyridamole, 411  
 ticlopidine, 411–412  
 arterial thromboembolism, prevention, 413  
 atrial fibrillation, 412  
 cerebrovascular disease, 413  
 drugs, herbs with, 44–47  
 myocardial infarction, 412  
 percutaneous transluminal coronary angioplasty, 412  
 peripheral vascular disease, 413  
 prosthetic heart valves, 412  
 saphenous vein bypass grafts, 412  
 valvular heart disease, 413  
 venous thromboembolism, 412  
 Antipyretics, 530–531  
 Antituberculosis efficacy, natural products, 383–384  
 Antitussive preparations, 472, xxi  
 Antiulcer herbs, 593–597  
 Anxiolytic agents, 602  
 Apomorphine, 467–468  
 Apples, as vitamin source, 623  
 Apricots, 86  
   as vitamin source, 623  
 Aquasol A. *See* vitamin A  
*Arctostaphylos UVA-URSI*. *See* UVA-URSI  
 Arnica, 86  
 Aromatase inhibition, 334–335  
 Aromatherapy, 66  
 Aromatic nucleus, aliphatic bases with, 144  
 Arrow poisons, xviii  
 Artemisia, 283–284  
 Arterial thromboembolism, 413  
 Artichokes, 86  
   as vitamin source, 624  
 Asafoetida, 86  
 Ascorbic acid. *See* Vitamin C  
 Ashwaganda, xxi  
 Asian ginseng root, 99, xxiv  
 Asparaginase, 116  
 Asparagus, as vitamin source, 624  
 Aspirin, 409–411, xx  
   analgesia, 531  
   anti-inflammatory effects of, 532  
   antipyresis, 532  
   asthma, 535–539  
   cardiovascular disease, 532  
   gastrointestinal effect of, 533  
   hematopoietic effect of, 533  
   mechanism of action, 531  
   new uses of, 533–534  
   poisoning, 533  
   premenstrual syndrome, 532  
   side effects of, 532–533  
   tumor necrosis factor-alpha, inhibition, 540–542  
   uricosuric effects of, 532  
   uses of, 531–532  
 Asteraceae groups, 283–285  
 Asthma, aloe for, 153  
 Astragalus leaf, xxii  
*Astragalus membranaceus*. *See* Astragalus leaf  
 Atrial fibrillation, 412  
 Atrophic gastritis, xxi

Atropine, 199  
   dose-dependent effects of, 203, 376  
   pharmacological actions of, 203  
 Auricular therapy, 66  
 Australia, tea tree oils from, 435–436  
 Autonomic nervous system, 199  
   division, 372–373  
     functions of, 200–202  
     somatic, comparison of, 199–200  
 Avarol, 394–395  
 Avarone, 394–395  
*Avena sativa*. *See* Oats  
 Avens, 86  
 Avocados, as vitamin source, 624  
 Ayurveda, 66–67

## B

Baby massage, 76  
 Baccharis, 284  
 Bananas, as vitamin source, 624  
 Banisterine, 163–194  
   Parkinson's disease, 168–169, 190–193  
 Barbiturates, 606–608  
   acute toxicity, 607–608  
   addiction, 608  
   classification, 606–607  
   pharmacokinetics, 607  
   selection of drugs, 608  
 Bayberry, 87  
 Bean sprouts, as vitamin source, 624  
 Beans, as vitamin source, 624  
 Beef, 624  
 Beer, as vitamin source, 624  
 Beets, as vitamin source, 624  
 Behavioral therapy, 79  
 Behcet's syndrome, colchicine, 279  
 Belladonna, 195–208, xviii  
   anisotropine methylbromide, 208  
   anticholinergic agents, contraindications to, 205  
   atropine, 199  
     dose-dependent effects of, 203  
     pharmacological actions of, 203  
   autonomic nervous system, 199  
     division, functions of, 200–202  
   belladonna, 198–199  
   chemistry, 197–198  
   cholinergic receptor blocking agents, 203  
   cholinergic receptor classification, 202–203  
   cholinergic transmission, neurochemical basis of, 200  
   clidinium bromide, 208  
   glycopyrrolate, 208  
   hexocyclium methylsulfate, 208  
   historical uses of, 203–204  
   homatropine methylbromide, 207  
   hyoscyamine, 205  
   ipratropium, 206–207  
   isopropamide iodide, 208  
   mepenzolate bromide, 208  
   methantheline, 207

- methoscopolamine, 207
  - muscarinic receptor antagonists, synthetic, 204–205
  - nightshade family, 195–198
    - drugs from, 198
  - preparation of leaves, 199
  - preparation of root, 199
  - propantheline, 207
  - quaternary ammonium muscarinic receptor antagonists, 206
  - scopolamine, 205–206
  - Solanaceae, 195–198
    - botany of, 198
  - somatic, autonomic nervous systems, comparison of, 199–200
  - substitutes for, 206–208
  - tertiary-amine muscarinic receptor antagonists, 208
  - tridihexethyl chloride, 208
  - Bellenamine, 396–397
  - Benign prostatic hyperplasia, permixon, 513–514
  - Benzodiazepine-binding sites, 603–604
  - Benzodiazepine derivatives, 608–609
    - antianxiety effects, 604
    - anticonvulsant activity, 605
    - mode of action of, 604–605
    - muscle relaxant activity, 604–605
    - sedative effects, 605
  - Benzodiazepines, 233
    - pharmacodynamics of, 602–603
  - Benzoic acid, 440
  - Beta carotene, 611–613
  - Beta-carotene, 53, 120
  - Betulinic acids, 393–394
  - Bier's block. *See* Intravenous regional anesthesia
  - Bilberry fruit, xxii
  - Biliary cirrhosis, colchicine, 279
  - Bioavailability, 3–4
  - Biodynamic massage, 67, 76
  - Bioenergetic therapy, 67
  - Bioflavonoids, as vitamin source, 624
  - Biotin, 614
  - Biotransformation, 17–19, 349–350
    - drug interactions, 35–36
    - hepatic drug metabolism, 17
    - lethal synthesis, 350
    - metabolic activation of drugs, 349
    - metabolite conversion, 349–350
    - nonhepatic metabolism, 17–18
      - intestinal epithelium, 18
      - lung, 18
      - plasma, 17–18
    - precursor activation, 349
  - Black cohosh, 87, xxiii
  - Black tea, 379–382
    - anticarcinogenic actions, 381–382
    - antioxidant properties, 379–380
    - dental caries, 381
    - skin cancer, 380–381
  - Blackberries, as vitamin source, 625
  - Bleomycin, 116
  - Blepharoclonus, 191
  - Blepharospasm, 191
  - Blood-brain barrier, 12
  - Blood flow
    - drug absorption and, 8
    - in drug clearance, 22–23
  - Blood schizonticides, 248
  - Bloodroot, 87
  - Blue cohosh, 87
  - Blue flag, 87
  - Blueberries, as vitamin source, 625
  - Blueberry, 209–212
  - Bogbean, 87
  - Boldo, 87
  - Bone, vitamin intake, 619
  - Boneset, 87
  - Borage, 88
  - Botulinum toxin, 213–216
    - botulism antitoxin, trivalent equine, 213
    - ear disorders, 216
    - hypersecretion of glands, 216
    - movement disorders, 215
    - neuromuscular disorders, 215
    - nose disorders, 216
    - ophthalmic disorders, 214–215
    - pain, 216
    - pelvic floor disorders, 216
    - rationale for treatment with, 214–216
    - smooth muscle overactivity, 216
    - spasticity, 215
    - throat disorders, 216
    - type A, 213
    - uses of, 213–214
  - Bowel activity, 154–155
  - Bread, as vitamin source, 625
  - Breast cancer, carotenoids, 240
  - Bronchial asthma, 28
  - Bronchorespiratory tract, vitamin intake, 619
  - Broom, 88
  - Brussels sprouts, 217–220
    - oxidative DNA damage, effects on, 217–219
    - as vitamin source, 625
  - Buccal absorption, 4
  - Buchu, 88
  - Buckwheat, as vitamin source, 625
  - Bullous keratopathy, honey for, 407–408
  - Bupivacaine, 266
  - Burdock, 88
  - Burnet, 88
  - Burns, honey for, 404–405
  - Butoconazole, 439
  - Butter, as vitamin source, 625
- C**
- Cabbage, as vitamin source, 625
  - Caffeine, 53, 262
    - as vitamin source, 625
  - Cakes, as vitamin source, 626
  - Calamus, 88
  - Calanolides, 395
  - Calciferol. *See* Vitamin D

- Calcium, 328
- Calcium antagonists, 328
- Calcium-channel blockers, 328
- Calendula, 88–89
- Calendula officinalis*, xvii
- Camellia sinensis*. *See* Green tea
- Cancer
  - alkylating agents
    - alkyl sulfonate, 576
    - chlorambucil, 576
    - cyclophosphamide, 576
    - nitrogen mustards, 575–576
    - nitrosoureas, 576
    - triazenes, 576
  - aloe for, 152–153
  - antimetabolites
    - deoxycytidine analogs, 578
    - folic acid analogues, 576–577
    - purine antimetabolites, 578–579
    - pyrimidine analogs, 577–578
  - chemotherapy, 110, 571–582
    - alkylating agents, 575–576
    - antimetabolites, 576–579
    - antineoplastic agents, 581–582
    - asparaginase, 581
    - bleomycin, 580
    - carboplatin, 581
    - chemotherapy, emesis induced by, 582
    - cis-platinum, 581
    - dactinomycin, 579
    - daunorubicin, 580
    - docetaxel, 580–581
    - doxorubicin, 580
    - emesis, 117
    - etoposide, 582
    - hydroxyurea, 581
    - mithramycin, 579
    - natural products, 579–581
    - paclitaxel, 580–581
    - procarbazine, 581
    - vinca alkaloids, 579
  - vitamin intake, 620
- Candy, as vitamin source, 627
- Cannabinoid receptor, 227
- Cannabinoids, 233
- Cannabis, 221–236
  - anandamide, 227–228
  - anticipatory nausea, 233
  - antiemetic drugs, dosage, cost, 234
  - antiemetic effects, 230–234
  - benzodiazepines, 233
  - botanical properties, 224–225
  - cannabinoids, 233
  - central nervous system cannabinoid receptors, 228
  - delayed emesis, 233
  - dexamethasone, 231–232
  - for dyskinesia, 234–236
  - in history, 223–224
  - Huntington's chorea, 229
  - inebriation, 225–226
  - metoclopramide, 232–233
  - for migraine, 230
  - movement disorders, 228–229
  - multiple-day cisplatin chemotherapy, 233
  - multiple sclerosis, 229
  - neuroprotection, 229–230
  - ondansetron, 231
  - phenothiazines, 233
  - psychoactive effects, 221–223
  - receptor, 227
  - receptor subtypes, 226–227
  - therapeutic potential, 228–230
  - vomiting
    - caused by cancer therapy, 231–232
    - central control of, 230–231
    - physiology of, 230
- Cannabis sativa*. *See* Marijuana
- Cantil. *See* Mepenzolate bromide
- Capsaicin, 53
- Capsicum, 89, 237–238, 598, xxii
- Carbamazepine, 328
- Carbidopa, 191
- Carboplatin, 117
- Carcinogenesis
  - honey for, 406–407
  - vitamin intake, 617
- Cardiac glycosides, congestive heart failure, 355–366
  - angiotensin antagonists, 363–365
  - digitalis, 355–356
    - toxicity, 361–362
  - dopamine receptors, 362–363
    - drugs acting on, 362–363
  - electrophysiological effects of, 360–361
  - endothelium-dependent, 364–365
  - independent vasodilators, 364–365
  - modes of action, 360
  - myocardial contraction, biochemical basis of, 359–360
  - phosphodiesterase, drugs inhibiting, 363
  - positive inotropic action of, 360
  - receptor-dependent vasodilation, 364
  - vasodilators, 363–365
- Cardiovascular disease
  - carotenoids, 240–241
  - folate, 345
- Cardiovascular drugs, 57
- Cardiovascular effects, cocaine, 258
- Cardiovascular system, effects of alcohol, 649
- Caronyl reductase inhibition, 335
- Carotenoids, 239–242, 583–590
  - breast cancer, 240
  - cardiovascular disease, 240–241
  - in fruits, vegetables, 584–585
  - head cancer, 240
  - history of, 584
  - lung cancer, 587–588
  - lycopene, 584, 588–589
    - cancer risk, 587–588
    - distribution in humans, 585
  - prostate cancer, 583
  - macular degeneration, 241
  - neck cancer, 240
  - organ concentrations, 585–587

- physicochemical nature of, 584
- pleural cancer, 587–588
- prostate cancer, 240
- Carrier-mediated transport, 5–6
- Carrots, as vitamin source, 626
- Cascara, 89
- Cascara sagrada, 89, 160
- Cassia, 89
- Castor oil, 161
- Catapres. *See* Clonidine hydrochloride
- Cathartics, 158–162, 523
  - abrin, 161
  - aloe, 160–161
  - anthraquinone, 159–160
  - bryonia, 162
  - cascara sagrada, 160
  - castor oil, 161
  - classification of, 159
  - colocynth, 162
  - croton oil, 161–162
  - elaterin, and bryonia, 162
  - emodin, 159–160
  - ipomea, 162
  - jalap, 162
  - podophyllum, resin of, 162
  - rhubarb, 160
  - ricin, 161
  - scammonium, ipomea, 162
  - senna, 160
- Cat's claw, 89, xxii
- Caulerpa, toxicity of, 142
- Cauliflower, as vitamin source, 626
- Cayenne peppers. *See* Capsicum
- Celeriac, as vitamin source, 626
- Celery, 89
  - as vitamin source, 626
- Cellular sites of actions, 27–28
  - drug-coenzyme interactions, 27
    - folic acid, 27
    - isoniazid, pyridoxal phosphate, 27
    - trimethoprim-sulfamethoxazole, 27
  - drug-enzyme interactions, 27–28
    - allopurinol, xanthine oxidase, 28
    - bronchial asthma, 28
    - hyperuremic states, 28
    - xanthine oxidase, 28
- Centaury, 89
- Central nervous system, 452–455, 649
  - cannabinoid receptors, 228
  - cocaine effects, 258
  - drugs, 57–58
- Cephalis acuminata*. *See* Ipecacuanha
- Cephalis ipecacuanha*. *See* Ipecacuanha
- Cereals
  - antioxidant activity, 108
  - as vitamin source, 626
- Cerebrovascular disease, 413
- Cereus, 89
- Chamomile, 90, xxii
- Chamomile (German), 90
- Chamomile (Roman), 90
- Chaparral, 90
- Chaste berry, xxii
- Cheese, as vitamin source, 626
- Chemotherapy, 110–112, 571–582. *See also* Cancer, chemotherapy
  - alkylating agents, 575–576
    - alkyl sulfonate, 576
    - chlorambucil, 576
    - cyclophosphamide, 576
    - nitrogen mustards, 575–576
    - nitrosoureas, 576
    - triazenes, 576
  - antimetabolites, 576–579
    - deoxycytidine analogs, 578
    - folic acid analogues, 576–577
    - purine antimetabolites, 578–579
    - pyrimidine analogs, 577–578
  - antineoplastic agents, 581–582
  - asparaginase, 581
  - bleomycin, 580
  - cancer chemotherapy, 574–575
  - carboplatin, 581
  - cis-platinum, 581
  - dactinomycin, 579
  - daunorubicin, 580
  - docetaxel, 580–581
  - doxorubicin, 580
  - emesis induced by, 117, 582
  - etoposide, 582
  - HIV, 387–398
    - avarol, 394–395
    - avarone, 394–395
    - bellenamine, 396–397
    - betulinic acids, 393–394
    - calanolides, 395
    - curcumin, 395–396
    - curcumin analogs, 395–396
    - cyanovirin-N, 391
    - daicalin, 394
    - dicafeoylquinic acid, 395–396
    - equisetin, 396
    - etiologial agent, 388
    - flavonoids, 392–393
    - glycyrrhizin, 393
    - herbal products, 387–388
    - hypericin, 397
    - illimaquinone, 395
    - immune system components, 390–391
    - ingenol derivatives, 392
    - inophyllums, 395
    - L-chicoric acid, 395–396
    - life cycle of, 390
    - life cycle of HIV, 388–389
    - mannose-specific plant lectins, 393
    - melittin, 396
    - phloroglucinol derivatives, 394–395
    - polyphemusins, 393
    - pseudohypericin, 397
    - psychotrine, 394–395
    - siamycins, 393



- sulfated polysaccharides, 392
  - trichosantin, 396
- hydroxyurea, 581
- mithramycin, 579
- natural products, 579–581
- paclitaxel, 580–581
- procarbazine, 581
- side effects, 118–123
- vinca alkaloids, 579
- Cherries, as vitamin source, 627
- Chestnuts, as vitamin source, 627
- Cheyenne, xxvi
- Chi, xix, xvii, xx
- Chi Kung medicine, 67–68
- Chili. *See* Capsicum
- Chilies, as vitamin source, 627
- Chinese herbalism, 68
- Chinese traditional medicine
  - drug therapy in, 50–53
  - herbal classification, 51–53
- Chiropractic medicine, 68
- Chlorambuch, 112
- Chlorprocaine, 265
- Chocolate, 243–244
  - as vitamin source, 627
- Choctaw, xxvi
- Cholesterol-lowering agents, 60–61
- Cholesterol synthesis, 555
- Cholinergic agonists, 305
- Cholinergic enhancement, 301–302
- Cholinergic receptor agonists, 374
- Cholinergic receptor blocking agents, 203, 375–376
- Cholinergic receptors
  - classification of, 202–203
  - honey, 403–404
- Cholinergic transmission
  - cholinesterase inhibitors, 374–375
    - irreversible, antidote, 375
  - ginseng, 371–378
    - acetylcholinesterase, structure of, 374
    - anticholinergic agents, contraindication to, 377
    - anticholinesterase agents, 374
    - antineoplastic effects, 377–378
    - autonomic nervous system, division, 372–373
    - cholinergic receptor agonists, 374
    - cholinergic receptor blocking agents, 375–376
    - classification of, 373–374
    - CNS actions, 377
    - dose-dependent effects of atropine, 376
    - immunomodulatory effects, 377–378
    - neurochemical basis of, 373
    - synthetic muscarinic receptor antagonists, 376–377
- honey, 403–404
- neurochemical basis of, 200
- synthetic muscarinic receptor antagonists
  - cardiology, 376
  - gastroenterology, 376–377
  - neurology, 377
  - ophthalmology, 376
  - preoperative uses, 376
- Cholinesterase inhibition, 302–303
  - classification of, 374–375
  - irreversible, antidote, 375
- Ciclopirox olamine, 440
- Cimicifugae racemosae rhizome*. *See* Black cohosh
- Cinchona tree, 245–252
  - as anesthetic, 251
  - antipyretic action, 251
  - antiseptic action, 251
  - blood schizonticides, 248
  - cinchonism, 252
  - colds, 252
  - colloids, 250–251
  - composition, 245–247
  - digestion, 251
  - headaches, 252
  - malaria, quinine for, 247
  - neuralgias, 252
  - Peruvian bark, 245
  - quinine, 250–252
  - quinine sulfate, 248–250
  - skeletal muscle, 252
  - skin eruptions, 252
  - sunburn prophylaxis, 251
  - ulcers, 251
  - varieties, 245
- Cinnamon, 90
- Cis-platinum, 117
- Citalopram, 166–167
- Classification of headaches, 323
- Cleopatra, xviii
- Clidinium bromide, 208
- Clivers, 90
- Clonidine hydrochloride, 328
- Clotrimazole, 439
- Clove, 90
- Coagulation, agents interfering with, 43
- Cobalamins. *See* Vitamin B<sub>12</sub>
- Coca, 253–275
  - alkalinization, 261–262
  - allergic reactions, 258–259
  - anesthesia, 263
  - anesthetics, for open wounds, ulcers, 263
  - botanical properties, 255–256
  - bupivacaine, 266
  - caffeine, 262
  - cardiovascular effects, 258
  - central nervous system effects, 258
  - chemical composition, 256–257
  - chlorprocaine, 265
  - cocaine
    - addiction, 270
    - dopamine biosynthesis, 271–272
    - dopamine transport, 271
    - effect of, 259
    - eye, actions on, 263
    - as local anesthetic, 256–257
    - local anesthetic action, 259
    - psychostimulant, 270–271
    - withdrawal symptoms, 272
  - commercial properties, 255

- conduction anesthesia, 264
- dosage, 268–269
- emesis, 265
- epidural anesthesia, 268
- epidural opiate analgesia, 268
- epinephrine anesthetic combinations, 262
- etidocaine, 266
- field block anesthesia, 266
- incoordination, 265
- infiltration anesthesia, 266
- intravenous regional anesthesia, 267
- ischemia, 263
- lidocaine, 266
- local anesthesia, pharmacology of, 257–258
- local anesthetics, 265–266
  - application, 262
  - clinical uses, 266–268
- local vascular action, 262
- mepivacaine, 266
- methylene blue, 262
- nerve block anesthesia, 267
- ophthalmic anesthesia, 263
- oxalic acid, 262
- plant, 254
- potassium synergism, 261
- prilocaine, 266
- procaine, 265
- site of action, 261
- spinal anesthesia, 264, 267
- sterilization, 269
- tetracaine, 266
- theophylline, 262
- Cocaine
  - addiction, 270
  - convulsions, 265
  - dopamine biosynthesis, 271–272
  - dopamine transport, 271
  - effect of, 259
  - eye, actions on, 263
  - as local anesthetic, 256–257, 259–265
  - local anesthetic action, 259
  - psychostimulant, 270–271
  - withdrawal symptoms, 272
- Coconuts, as vitamin source, 627
- Codeine, 464
- Coenzyme Q<sub>10</sub>, 45, 119
- Coffee, as vitamin source, 627
- Cola, 91
- Colchicine, 53, 279, xxvii
  - Behcet's syndrome, 279
  - biliary cirrhosis, 279
  - familial Mediterranean fever, 279
  - gout, 275–280
    - allopurinol, 276
    - cell division, 277
    - hyperuricemia, 275–276
    - insulin, 277
    - melanin, 277
    - pharmacokinetics, 278
    - pharmacological properties, 277
    - prophylactic uses, 279
    - therapeutic uses, 278
    - toxic effects, 278
    - uricosuric agents, 276
  - psoriasis, 279
- Colds, quinine, 252
- Colocynth, 162
- Colon function, aloe, 151–162
- Colon movements, 154–155
  - duodenocolic reflex, 155
  - gastrocolic reflex, 155
  - haustrations, 154
  - propulsive movements, 154–155
- Coltsfoot, 91
- Comfrey, 91
- Compositae, 281–286
  - achillea, 283
  - artemisia, 283–284
  - Asteraceae groups, 283–285
  - baccharis, 284
  - elephantopus, 285
  - helenium, 285
  - montanoa, 285
  - packera, 285
  - parthenium, 285
  - sesquiterpene lactones, 281–282
  - sesquiterpene neurotoxicity, 282–283
  - tanacetum parthenium, 282–283
  - tithonia, 285
- Conduction anesthesia, 264
- Congestive heart failure, 355–366
  - angiotensin antagonists, 363–365
  - digitalis, 355–356
    - toxicity, 361–362
  - dopamine receptors, 362–363
    - drugs acting on, 362–363
  - electrophysiological effects of, 360–361
  - endothelium-dependent, 364–365
  - independent vasodilators, 364–365
  - modes of action, 360
  - myocardial contraction, biochemical basis of, 359–360
  - phosphodiesterase, drugs inhibiting, 363
  - positive inotropic action of, 360
  - receptor-dependent vasodilation, 364
  - vasodilators, 363–365
- Constipation, 157–158, 522–523
  - aloe, 153–154
  - causes, 158
  - definition, 157
- Cookies, as vitamin source, 627
- Corn, as vitamin source, 627
- Corn silk, 91
- Corticosteroid-binding globulin, 10
- Corticosteroids, 496
- Cortisone acetate, xx
- Couchgrass, 91
- Cough, 458–459
- Coumarin, herbs with, 44–47
- Cowslip, 91
- Cranberry, 91
  - fruit, xxiii

juice, 61  
 as vitamin source, 627  
 Cranial neuralgias, 328  
*Crataegus laevigata*. See Hawthorn  
*Crataegus monogyna*. See Hawthorn  
 Crocin, molecular target, 526–527  
 Croton oil, 161–162  
 Crow, xxvi  
 Crystal therapy, 68  
 Cucumbers, as vitamin source, 628  
 Cupping therapy, 68–69  
 Curare, 287–295  
   cardiovascular effects, 294  
   erythrina alkaloids, 294–295  
   histamine release, 294  
   mechanism of action of, 289–290  
   methonium compounds, 295  
   muscular effects, 294  
   neuromuscular blockade, 290–291  
     acid-base balance, 293  
     age, 294  
     disease states, 294  
     drug interactions, 292–293  
     electrolytes, 293  
     factors affecting, 292–295  
     hypothermia, 293  
     side effects of, 294  
   neuromuscular junction, 289  
   nicotinic cholinergic receptors, 289  
   ocular effects, 294  
   skeletal muscle relaxants, 288–295  
 Curcumin, 395–396  
   analogs, 395–396  
 Currants, as vitamin source, 628  
 Cushing's syndrome, 561  
 Cyanovirin-N, 391  
 Cyclic nucleotide phosphodiesterase inhibition, 333  
 Cyclooxygenase inhibition, 333  
 Cyclophosphamide, 112  
 Cycloserin, 385  
 Cyclosporin A, 497  
 Cyproheptadine, 328  
 Cytokines  
   actions of, 179  
   production, 657

## D

Dactinomycin, 116  
 Daffodils, 297–300  
   compounds found in, 297–301  
   galanthamine, 299–301  
     antinociceptive effects of, 300  
     chemistry of, 299  
     pharmacokinetics of, 299–300  
     pharmacological mechanisms, 299  
     to treat depression, 300  
   lycorine, 299  
 Daicalin, 394  
 Dakota, xxvi

Damiana, 92  
 Dandelion, 92  
 Danshen, 45–46  
 Darbid. See Isopropamide iodide  
 Daunorubicin, 116  
 Decongestant, ephedrine as, 311–318  
   absorption, 315  
   actions of, 311  
   allergic disorders, 316  
   bronchi, 314  
   bronchial asthma, 315  
   cardiovascular, 313–314  
   central nervous system, 315  
   enuresis, 317  
   ephedra, 312  
   eye, 314  
   gastrointestinal musculature, 314  
   glands, 314–315  
   heart block, 316  
   history, 311–312  
   myasthenia gravis, 317  
   mydriasis, 316  
   organ systems, effect on, 313–315  
   pharmacological properties, 313  
   pilotator muscles, 314  
   routes of administration, 315  
   skeletal muscle, 315  
   smooth muscle, 314  
   spinal anesthesia, 316  
   therapeutic uses, 315–317  
   toxicity, 317–318  
   urinary bladder, 314  
 Defecation, 155–157  
 Defecation reflexes, 155–157  
   autonomic reflexes affecting, 157  
   bowel activity, autonomic reflexes affecting, 157  
   intestino-intestinal reflex, 157  
   peritoneo-intestinal reflex, 157  
   reno-intestinal reflex, 157  
   somato-intestinal reflex, 157  
   vesico-intestinal reflex, 157  
 Delaware, xxvi  
 Delayed emesis, cannabis, 233  
 Delirium tremens, 652  
 Dental caries, black tea, 381  
 Deoxycytidine analogs, 114–115  
 Deprenyl, for parkinsonism, 192  
 Depression  
   antidepressants, 417–418, 424–425  
     classification of, 419  
     side effects of, 422  
     sites of action of, 420–422  
   dibenzapine derivatives, 419–424  
   galanthamine, 300  
   hypericum, 415–426  
   lithium  
     manic-depressive psychosis, 425–426  
     pharmacodynamics of, 426  
     pharmacokinetics, 425  
     regulatory status of hypericum, 426

- side effects, 425–426
  - therapeutic uses of lithium, 426
  - monoamine oxidase inhibitors, 424
    - indications for, 424
  - neurotransmitters, 419
  - overdoses, 423–424
  - St. John's wort, 416–417
  - tricyclic antidepressants, 420
  - Dermatological diseases, vitamin intake, 620
  - Desferrioxamine, 306
  - Devil's claw, 46, 92
  - Dexamethasone, 231–232
  - Dextromethorphan hydrobromide, 466–467
  - Dextropropoxyphene, 471
  - Diabetes, 499–506, xx
    - aloe for, 153
    - antidiabetic agents, 499–500
    - classes of, 502
    - complications, 502
    - diabetic ketoacidosis, treatment of, 506
    - dietary treatment, 503–504
    - drug treatment, 504
    - insulin, 504–506
    - insulin receptor, 502–503
    - insulin release
      - effects of fasting, 500
      - effects of food, 500
    - metabolic consequences of, 500–501
    - neuropathy, 502
    - oral hypoglycemic agents, 505–506
    - pregnancy, 501–502
    - sulfonylurea, receptors for, 506
    - symptoms of, 502
    - treatment, 503–506
    - vascular complications, 502
  - Diabetic ketoacidosis, treatment of, 506
  - Diamorphine. *See* Heroin
  - Dibenzapine derivatives, 419–424
  - Dicaffeoylquinic acid, 395–396
  - Diet, 503–504, 621. *See also* Dietary therapy
    - aging and, 621–622
    - antioxidants, 107–124
    - in curing, preventing diseases, 107
    - sources of vitamin A, 616–617
    - vitamins and, 611–640
  - Dietary Supplement Health and Education Act, 127
  - Dietary supplements, 126–128
    - laws regulating, 126–128
  - Dietary therapy, 69, 71–72, 81–82, 503–504
    - anti-Candida diet, 81
      - Dietary Supplement Health and Education Act, 127
    - exclusion diet, 81
    - food combining diet, 81
    - liver diet, 81
    - low blood sugar diet, 81
    - macrobiotic diet, 82
    - vegan diet, 81
    - vegetarian diet, 81
  - Digestion, quinine, 251
  - Digitalis, 355–356, xix
    - toxicity, 361–362
  - Dihydrocodeinone, 466
  - Dihydrocyclosporin C, 497
  - Dihydroergotoxine. *See* Ergoloid mesylates
  - Dihydrogenated ergot alkaloids. *See* Ergoloid mesylates
  - Dihydromorphinone, 466
  - Dipyridamole, 411
  - Distribution of drugs, 9–10
  - Disulfiram, 653
  - Divine plowman, xvii
  - DNA ligase I inhibition, 336–337
  - DNA polymerase inhibition, 336
  - Domoic acids, 141–142
  - Dong quai, 92
  - DOPA decarboxylase inhibition, 335
  - Dopamine
    - action of, 163
    - biosynthesis of, 271–272
    - transport, 271
  - Dopamine receptors, 362–363
    - drugs acting on, 362–363
  - Dose-response relationship, 14
  - Drosera, 92
  - Drug-coenzyme interactions, 27
    - folic acid, 27
    - isoniazid, pyridoxal phosphate, 27
    - trimethoprim-sulfamethoxazole, 27
  - Drug-drug interactions, 31–36
  - Drug-enzyme interactions, 27–28
    - allopurinol, 28
      - xanthine oxidase, 28
    - bronchial asthma, 28
    - hyperuremic states, 28
    - xanthine oxidase, 28
      - hyperuremic states, 28
  - Drug metabolite kinetics, 19–20, 350
  - DSHEA. *See* Dietary Supplement Health and Education Act
  - Du-Zhong, antioxidant actions of, 108–110
  - Duodenal ulcer, xxi
  - Duration of drug action, 2
  - Dyskinesia, cannabis, 234–236
- ## E
- Ear disorders, botulinum toxin, 216
  - Eastern herbal medicine, 69–70
  - Echinacea, 92
  - Echinacea angustifolia*, xxvii
  - Echinacea angustifolia* roots, xxvi
  - Econazole, 439
  - Efficacy, drugs, 14–16
  - Eggplant, 309–310
    - as vitamin source, 628
  - Eggs, as vitamin source, 628
  - Eicosanoids, 479–482
    - agents altering metabolism, 481–482
    - metabolism, 482
    - pharmacokinetic properties, 479
    - physiology of, 479–480
    - therapeutic uses of, 481

- Elder, 92  
 Elecampane, 93  
 Elephantopus, 285  
 Eleutherococcus. *See* Ginseng  
*Eleutherococcus senticosus*. *See* Siberian ginseng root  
 Emesis, 431–432. *See also* Vomiting  
   cancer-chemotherapy-induced, 117  
   chemotherapy induced, 117  
 Emetic doses, 429  
 Emetics. *See* Vomiting  
 Emetine, 427  
 Emodin, 159–160  
 Endocrine system, interaction of drugs with, 29–30  
   alpha-methyl dopa, 29  
   prolactin, 29–30  
   renin, 29  
 Endogenous opioid peptides, 449  
 Endorphin, xvii  
 Enhancement of drug action, 16  
 Enkephalin, xvii  
 Enuresis, 317  
 Environmental therapies, 70  
 Enzyme induction, inhibition, 351–352  
 Ephedra alkaloids, 98  
 Ephedrine, 98, 311–318  
   absorption, 315  
   actions of, 311  
   allergic disorders, 316  
   bronchi, 314  
   bronchial asthma, 315  
   cardiovascular, 313–314  
   central nervous system, 315  
   enuresis, 317  
   ephedra, 312  
   eye, 314  
   gastrointestinal musculature, 314  
   glands, 314–315  
   heart block, 316  
   history, 311–312  
   myasthenia gravis, 317  
   mydriasis, 316  
   organ systems, effect on, 313–315  
   pharmacological properties, 313  
   pilomotor muscles, 314  
   routes of administration, 315  
   skeletal muscle, 315  
   smooth muscle, 314  
   spinal anesthesia, 316  
   therapeutic uses, 315–317  
   toxicity, 317–318  
   urinary bladder, 314  
 Epidural anesthesia, 268  
 Epidural opiate analgesia, 268  
 Epilepsy, mechanisms of, 601–602  
 Epinephrine anesthetic combinations, 262  
 Epithelium, intestinal, drug metabolism, 18  
 Equisetin, 396  
 Erectile dysfunction, 547  
   new therapies, 550–552  
 Ergoloid mesylates, 329  
 Ergot, headache and, 319–330, xix  
   alkaloids, 319–321  
   calcium antagonists, 328  
   calcium-channel blockers, 328  
   carbamazepine, 328  
   classification of headaches, 323  
   clonidine hydrochloride, 328  
   cranial neuralgias, 328  
   cyproheptadine, 328  
   efficacy, 321–324  
   ergoloid mesylates, 329  
   methylphenidate, 328  
   methysergide, 326  
   migraine, 326–328  
     serotonin, 324–326  
     sumatriptan, 324–326  
   serotonergic abnormalities, 325  
   serotonin  
     actions of, 324–325  
     metabolism of, 324  
     receptors, 325  
   serotonin receptor antagonists, 325  
   sumatriptan  
     antimigraine action of, 326  
     clinical efficacy of, 325–326  
     side effects of, 326  
   trigeminal and glossopharyngeal neuralgias, 328–329  
 Erythrina alkaloids, 294–295  
 Estrogens, 562–564  
   adverse effects, 564  
   antiestrogens, 564  
   biochemical actions, 562–563  
   estrogen preparations, 563  
   physiological actions, 562  
   therapeutic uses, 563  
 Ethambutol, 385  
 Ethylmorphine, 467  
 Etidocaine, 266  
 Etoposide, 117  
 Eucalyptus, 93  
 Euphorbia, 93  
 European blueberry. *See* Bilberry fruit  
 Evening primrose, 93  
   oil, 61, xxiii  
 Exclusion diet, 81  
 Excretion site, interactions at, 36  
 Eye, vitamin intake, 619  
 Eyebright, 93  
 Eyelids  
   fluttering (*See* Blepharoclonus)  
   involuntary closure (*See* Blepharospasm)

## F

- Facilitated transport, 6  
 Factors controlling absorption of drugs, 6–9  
   blood flow, 8  
   ionization, 7–8  
   surface area, 8  
 FAD-containing monoamine oxidase inhibition, 335

- False unicorn, 93
- Familial Mediterranean fever, colchicine, 279
- Familial paroxysmal polyserositis. *See* Familial Mediterranean fever
- Fat-soluble vitamins, 611–613
- FDAMA. *See* Food and Drug Administration Modernization Act
- Fennel, as vitamin source, 628
- Fenugreek, 93
- Fetal alcohol syndrome, 651
- Feverfew, 44–45, 62, 93–94
- Fiber, as vitamin source, 628
- Fibrin, formation of, 42
- Fibrinolysis, 43
- Field block anesthesia, 266
- Figs, as vitamin source, 628
- Figwort, 94
- Fish, as vitamin source, 629
- Five-element theory, Chinese traditional medicine, 51
- Flavonoids, 331–340, 392–393, 593–594
  - alcohol dehydrogenase inhibition, 335–336
  - aldehyde, 335–336
  - aldose reductase inhibition, 335
  - antioxidant properties of flavonoids, 337
  - aromatase inhibition, 334–335
  - caronyl reductase inhibition, 335
  - cyclic nucleotide phosphodiesterase inhibition, 333
  - cyclooxygenase inhibition, 333
  - DNA polymerase inhibition, 336
  - DOPA decarboxylase inhibition, 335
  - FAD-containing monoamine oxidase inhibition, 335
  - genotoxicity, excessive flavonoid intake, 337–338
  - histidine decarboxylase, 335
  - HIV-1 proteinase inhibition, 334
  - human DNA ligase I inhibition, 336–337
  - hyaluronidase inhibition, 335
  - lipoygenase, 333
  - mutagenicity, excessive flavonoid intake, 337–338
  - ornithine decarboxylase inhibition, 334
  - pharmacodynamics of, 332–337
  - phospholipase A<sub>2</sub> inhibition, 333
  - protein kinase C inhibition, 332–333
  - reverse transcriptase inhibition, 333–334
  - RNA polymerase inhibition, 336
  - safe flavonoid intake, 339
  - sialidase inhibition, 337
  - topoisomerase inhibition, 334
  - xanthine oxidase inhibition, 334
- Flaxseed, 341–342
  - oil, xxiii
- Flour, as vitamin source, 629
- Flower remedies, 70–71
- Fluconazole, 438
- Flucytosine, 438
- Folacin. *See* Folate
- Folate, 614
  - antioxidant vitamins, 345–346
  - cardiovascular disease, 345
  - deficiency of vitamin B<sub>12</sub>
    - with agency, 344
    - effects of, 344–345
  - gastrointestinal effects, 344
  - hematological effects, 344
  - hematological status, 344
  - neurological effects, 344
  - replacement therapy, 345
  - in fruit, 343–346
  - gestation, 345
  - vitamin B<sub>12</sub>, 343
    - with aging, 343–344
    - folic acid, relationship, 346
    - megaloblastic anemias, 346
- Folic acid, 27. *See also* Folate
  - vitamin B<sub>12</sub>, relationship, 346
- Folic acid analogs, 113
- Food, Drug, and Cosmetic Act, 126
- Food and Drug Administration, xviii
- Food and Drug Administration Modernization Act, 127–128
- Food combining diet, 81
- Food-drug interactions, 347–354
  - biotransformation, 347, 349–350
    - lethal synthesis, 350
    - metabolic activation of drugs, 349
    - metabolite conversion, 349–350
    - precursor activation, 349
  - drug metabolite kinetics, 350
  - enzyme induction, inhibition, 351–352
  - grapefruit juice, cytochrome P-450 enzymes, 352–353
  - hepatic drug metabolism, 347
  - influence of age, 351
  - liver disease, 351
  - mixed-function oxidation reaction pathway, 348–349
  - nonhepatic metabolism, 347–348
    - intestinal epithelium, 348
    - lung, 348
    - plasma, 347–348
  - P-450, multiple isoenzymes, 348
  - pharmacogenetics, 350–351
- Food of gods, xix
- Food therapy, 71–72
- Foxglove, 355–366
- Frangula, 94
- Frankincense, xvii
- Fruit, folate in, 343–346. *See also* Folate
  - antioxidant vitamins, 345–346
  - cardiovascular disease, 345
  - deficiency of vitamin B<sub>12</sub>
    - with agency, 344
    - effects of, 344–345
    - gastrointestinal effects, 344
    - hematological effects, 344
    - hematological status, 344
    - neurological effects, 344
    - replacement therapy, 345
    - gestation, 345
    - vitamin B<sub>12</sub>, 343
      - with aging, 343–344
      - folic acid, relationship, 346
      - megaloblastic anemias, 346
- Fruit as vitamin source, 628–629
- Fucus, 94

Fumitory, 94

Fungal disease

- amphotericin B, 436–438
- antifungal agents, 436
- aromatherapy, cautions, 440
- benzoic acid, 440
- butoconazole, 439
- ciclopirox olamine, 440
- clotrimazole, 439
- econazole, 439
- fluconazole, 438
- flucytosine, 438
- griseofulvin, 438
- haloprogin, 440
- ketoconazole, 438
- manuka, 435–440
- miconazole, 439
- naftifine, 440
- nystatin, 439
- salicylic acid, 440
- systemic antifungal agents, 436–439
- tea tree oils, 435–436
- terconazole, 439
- tolnaftate, 440
- topical antifungal agents, 439–440
- undecylenic acid, 440

## G

Galanthamine, 299–301

- antinociceptive effects of, 300
- chemistry of, 299
- pharmacokinetics of, 299–300
- pharmacological mechanisms, 299
- to treat depression, 300

Gamma-aminobutyric acid, 600–601

Garlic, 45, 62, 94, 477–492

- ace inhibitors, 484–486
  - myocardial infarction, 485
  - progressive renal impairment, 485–486
  - scleroderma renal crisis, 486
- active ingredients, 477–478
- aggregin, 478–479
- allicin, antioxidant activity, 486–487
- aminonucleoside nephrosis, 490–491
- anticlastogenic effects of, 483
- anticoagulants, 478
- antimicrobial effects of, 483
- antioxidant actions, 484
- cancer prevention, 483
- cardioprotective actions, 484
- cardiovascular effects, 482–483
- eicosanoids, 479–482
  - agents altering metabolism, 481–482
  - metabolism, 482
  - pharmacodynamics of, 480–481
  - pharmacokinetic properties, 479
  - physiology of, 479–480
  - therapeutic uses of, 481
- free-radical generation, 488–489

gentamicin nephrotoxicity, 491–492

ischemic brain damage, attenuation of, 487–488

lipid-lowering effects, 482–483

platelet-activating factor, 479

platelet aggregation, 478–479

platelet aggregation inhibition, 478–479

platelet-inhibiting drugs, 479

renal oxidative stress attenuation, 489–490

thrombolytic agents, 478

vitamin E, 479

as vitamin source, 629

Gastric acid secretion, physiology of, 591–592

Gastric carcinoma, xxi

Gastric emptying time, alteration in, 34

Gastric pH, alteration of, 33–34

Gastrocolic reflex, 155

Gastroenteritis, honey for, 405–406

Gastrointestinal tract

deficiency of vitamin B<sub>12</sub>, 344

vitamin intake, 619

Gem therapy, 68

General anesthetics, mode of actions of, 605–606

Genistein, 122

Genitourinary system, vitamin intake, 619

Gentamicin nephrotoxicity, 491–492

Gentian, 94

Geopathic therapy, 72

Gestalt therapy, 72

Gestation, folate in, 345

Ginger, 45, 94–95, xxiii

root, 62

as vitamin source, 629

Ginkgo, 45, 95, 367–370, xxiv

leaf, 62

monoamine oxidase inhibition, 367–368

nitric oxide, 368–370

*Ginkgo biloba*. See Ginkgo

Ginseng, 46, 95

cholinergic transmission, 371–378

acetylcholinesterase, structure of, 374

anticholinergic agents, contraindication to, 377

anticholinesterase agents, 374

antineoplastic effects, 377–378

autonomic nervous system, division, 372–373

cholinergic receptor agonists, 374

cholinergic receptor blocking agents, 375–376

classification of, 373–374

CNS actions, 377

dose-dependent effects of atropine, 376

immunomodulatory effects, 377–378

neurochemical basis of, 373

synthetic muscarinic receptor antagonists, 376–377

cholinesterase inhibitors, 374–375

irreversible, antidote, 375

CNS actions, 377

synthetic muscarinic receptor antagonists

cardiology, 376

gastroenterology, 376–377

neurology, 377

ophthalmology, 376

preoperative uses, 376

- Glossopharyngeal neuralgia, 328–329
- Glutamine, 121
- Glutathione, 120
- Glycine, 606
- Glycocorticoids, 555–556, 558–561
- Glycoproteins, 10
- Glycopyrrolate, 208
- Glycyrrhiza glabra*. *See* Licorice
- Glycyrrhizin, 393
- Glyoxaline group, 146
- Golden seal, 95
- Goldenseal root, xxiv
- Gooseberries, as vitamin source, 629
- Gout, colchicine, 275–280
  - allopurinol, 276
  - cell division, 277
  - hyperuricemia, 275–276
  - insulin, 277
  - melanin, 277
  - pharmacokinetics, 278
  - pharmacological properties, 277
  - prophylactic uses, 279
  - therapeutic uses, 278
  - toxic effects, 278
  - uricosuric agents, 276
- Gracilaria, toxicity of, 142
- Grains, as vitamin source, 629
- Grape seed extract, xxiv
- Grapefruit
  - juice, cytochrome P-450 enzymes, 352–353
  - as vitamin source, 629
- Grapes, as vitamin source, 629–630
- Gravel root, 95
- “Green” revolution, xviii
- Green tea, 46, 379–382, xxiv
  - anticarcinogenic actions, 381
  - anticarcinogenic effects, 381–382
  - antioxidant properties, 379–380
  - dental caries, 381
  - skin cancer, 380–381
- Griseofulvin, 438
- Ground ivy, 96
- GSH. *See* Glutathione
- Guaiacum, 96
- Guavas, as vitamin source, 630
- Gums, with ulcers, 597
- H**
- Half-life, drug, 23
- Haloprogin, 440
- Hamisheh bahar*, xvii
- Haustrations, colon, 154
- Hawthorn, 62, 96, xxv
- Head cancer, carotenoids, 240
- Headache
  - alkaloids, 319–321
  - calcium, 328
  - calcium antagonists, 328
  - calcium-channel blockers, 328
  - carbamazepine, 328
  - cinchona tree, 252
  - classification of headaches, 323
  - clonidine hydrochloride, 328
  - cranial neuralgias, 328
  - cyproheptadine, 328
  - efficacy, 321–324
  - ergoloid mesylates, 329
  - ergot, 319–330, xix
  - ergot and, 319–330
  - methylphenidate, 328
  - methysergide, 326
  - migraine, 326–328
    - prevention, treatment, 326–328
    - serotonin, 324–326
    - sumatriptan, 324–326
  - quinine, 252
  - serotonergic abnormalities, 325
  - serotonin
    - actions of, 324–325
    - metabolism of, 324
    - receptors, 325
  - serotonin receptor antagonists, 325
  - sumatriptan
    - antimigraine action of, 326
    - clinical efficacy of, 325–326
    - side effects of, 326
  - trigeminal and glossopharyngeal neuralgias, 328–329
- Heavy sedation, xxi
- Helenium, 285
- Hematological system, deficiency of vitamin B<sub>12</sub>, 344
- Hemostasis, stages in, 41
- Henbane, xviii
- Hepatic drug metabolism, 17, 347
- Hepatic first-pass effect, 9
- Herb-drug interactions, 37–48
  - agggregin, 42
  - anticoagulants, 38–42
  - antiplatelet drugs, herbs with, 44–47
  - coagulation, agents interfering with, 43
  - coenzyme Q<sub>10</sub>, 45
  - coumarin, herbs with, 44–47
  - danshen, 45–46
  - devil’s claw, 46
  - feverfew, 44–45
  - fibrin, formation of, 42
  - fibrinolysis, 43
  - garlic, 45
  - ginger, 45
  - ginkgo, 45
  - ginseng, 46
  - green tea, 46
  - hemostasis, stages in, 41
  - hirudin, 43
  - MedWatch program, 47
  - oral anticoagulants, 44
  - papain, 46
  - platelet-activating factor, 42
  - platelet aggregation, 42
  - platelet-inhibiting drugs, 42–43
  - salicylate, herbs with, 44–47



- thrombin, 43
- thrombolytic agents, 38–42
- vitamin E, 46–47
  - platelet aggregation, 42
  - warfarin, 47
  - alternative therapies and, 38
- Heroin, 465–466
- Herpes simplex, honey for, 407
- Hexocyclium methylsulfate, 208
- Hidatsa, xxvi
- Hirudin, 43
- Histamine, xx
- Histamine-receptor antagonists, 593
- Histidine decarboxylase, 335
- HIV, 387–398
  - avarol, 394–395
  - avarone, 394–395
  - bellenamine, 396–397
  - betulinic acids, 393–394
  - calanolides, 395
  - curcumin, 395–396
  - curcumin analogs, 395–396
  - cyanovirin-N, 391
  - daicalin, 394
  - dicafeoylquinic acid, 395–396
  - equisetin, 396
  - etiological agent, 388
  - flavonoids, 392–393
  - glycyrrhizin, 393
  - herbal products, 387–388
  - hypericin, 397
  - illimaquinone, 395
  - immune system components, 390–391
  - ingenol derivatives, 392
  - inophyllums, 395
  - L-chicoric acid, 395–396
  - life cycle of HIV, 388–389
    - immunopharmacology, 390
  - mannose-specific plant lectins, 393
  - melittin, 396
  - phloroglucinol derivatives, 394–395
  - polyphemusins, 393
  - pseudohypericin, 397
  - psychotrine, 394–395
  - siamycins, 393
  - sulfated polysaccharides, 392
  - trichosantin, 396
- HIV-1 proteinase inhibition, 334
- Holy thistle, 96
- Homatropine methylbromide, 207
- Homeopathy, 74
- Honey, 399–408
  - as antioxidant, 403
  - bullous keratopathy, 407–408
  - burns, 404–405
  - carcinogenesis, 406–407
  - cholinergic receptors, 403–404
  - cholinergic transmission, 403–404
  - curative properties, 400
  - gastroenteritis, 405–406
  - herpes simplex, 407
  - inflammatory bowel disease, 406
  - memory formation, 403
  - peptic ulcers, 405
  - as vitamin source, 630
  - wounds, 404–405
- Hops, 96
- Horehound
  - black, 96
  - white, 96
- Horse chestnut, 62, 96–97
- Horseradish, 97, 409–414
  - angina, 412
  - antiplatelet drugs, 409–412
    - aspirin, 409–411
    - dipyridamole, 411
    - ticlopidine, 411–412
  - arterial thromboembolism, prevention, 413
  - atrial fibrillation, 412
  - cerebrovascular disease, 413
  - myocardial infarction, 412
  - percutaneous transluminal coronary angioplasty, 412
  - peripheral vascular disease, 413
  - prosthetic heart valves, 412
  - saphenous vein bypass grafts, 412
  - valvular heart disease, 413
  - venous thromboembolism, 412
- Humanistic therapy, 79
- Huntington's disease, 644
  - cannabis, 229
- Hyaluronidase inhibition, 335
- Hydrangea, 97
- Hydrastis canadensis*. *See* Goldenseal root
- Hydrocortisone, xix
- Hydrocotyle, 97
- Hydrotherapy, 74
- Hydroxyurea, 117
- Hyoscyne. *See* Scopolamine
- Hyoscyamine, 205
- Hypericin, 397
- Hypericum, 415–426
  - antidepressants, 417–418, 424–425
    - classification of, 419
    - side effects of, 422
    - sites of action of, 420–422
  - dibenzapine derivatives, 419–424
  - lithium
    - manic-depressive psychosis, 425–426
    - pharmacodynamics of, 426
    - pharmacokinetics, 425
    - regulatory status of hypericum, 426
    - side effects, 425–426
    - therapeutic uses, 426
  - monoamine oxidase inhibitors, 424
    - indications for, 424
  - neurotransmitters, 419
  - overdoses, 423–424
  - tricyclic antidepressants, 420
- Hypericum perforatum*. *See* Hypericum; St. John's wort
- Hypersecretion of glands, botulinum toxin, 216
- Hyperuremic states, 28
  - xanthine oxidase, 28

Hypnosis, 74  
 Hypnotherapy, 74  
 Hypnotics, 606–609  
 Hypoglycemic agents, 505–506  
 Hypolipaeemics. *See* Cholesterol-lowering agents

## I

Iatrogenic reactions, 31  
 Ice cream, as vitamin source, 630  
 Idiosyncratic reactions, 32  
 Illimaquinone, 395  
 Immune system, 377–378, 658–659  
   components of, 390–391  
   vitamin intake, 617–618  
   yogurt and, 655–659  
 Immunoenhancing cytokines, xvii  
 Immunomodulators, 61  
 Impotence, 545, xxi  
*In vitro* indexes of immune function, 656  
 Indole derivatives, 147–148  
 Infiltration anesthesia, 264, 266  
 Inflammatory bowel disease, honey for, 406  
 Inflammatory peptides, xvii  
 Ingenol derivatives, 392  
 Inophyllums, 395  
 Insomnia, valerian with, 599–600  
 Insulin, 504–506, xx  
 Insulin-dependent diabetes mellitus, xx  
 Insulin receptors, 502–503  
 Insulin release  
   effects of fasting, 500  
   effects of food, 500  
 Integrative therapy, 79  
 Interleukin 1, 188–189  
 Interleukin 6, 188–190  
 Intestinal epithelium, drug metabolism, 18  
 Intranasal delivery, 4–5  
 Intrathecal opiate analgesia, 268  
 Intravenous regional anesthesia, 267  
 Ion pair transport, 6  
 Ionization, drug absorption and, 7–8  
 Iontophoresis, drug delivery by, 3  
 Ipecac, 427–434  
   amebiasis, 433  
   emesis, 431–432  
   emetic doses, 429  
   emetine, 427  
   ipecacuanha, 427  
   poison, absorption prevention, 431–433  
   syrup of ipecac, 432  
   vomiting, drugs producing, 429–431  
 Ipecacuanha, 62, 427  
 Ipratropium, 206–207  
 Iridology, 74–75  
 Ischemia, 263  
 Isoniazid, xx  
   pyridoxal phosphate, 27  
 Isopropamide iodide, 208  
 Isoquinoline, derivatives of, 147

Ispaghula, 97  
   husk, 63  
 Ivy, 96

## J

Jalap, 162  
 Jamaica dogwood, 97  
 Japanese medicine, 75  
 Juniper, 97  
 Juvenile-onset diabetes mellitus, xx

## K

Kainic acid, 140–141  
 Kale, as vitamin source, 630  
 Kava-kava, 63, 97  
 Ketoacidosis, diabetic, treatment of, 506  
 Ketoconazole, 438  
 Kidneys, rate of excretion of drugs by, 21–22  
 Kiowa, xxvi  
 Kiwi fruits, as vitamin source, 630  
 Kohlrabi, as vitamin source, 630

## L

L-chicoric acid, 395–396  
 Lady's slipper, 97  
 Lamb, as vitamin source, 630  
 Lao Tzu, xx  
 Laws regulating dietary supplements, 126–128  
 Laws regulating herbs, 126–128  
 Laxatives, 523  
   bulk saline, 523  
   properties, 521–522  
 Learning, saffron, 525–526  
 Leeks, as vitamin source, 630  
 Legumes, as vitamin source, 631  
 Lemon verbena, 97  
 Lemons, as vitamin source, 631  
 Leprosy, 384–385  
 Levodopa, 549  
 Levorphanol tartrate, 467  
 Librax, 208  
 Licorice, 98, 597–598, xxv  
 Lidocaine, 266  
 Liferoot, 98  
 Light therapy, 75  
 Lime flower, 98  
 Limes as vitamin source, 631  
*Linum usitatissimum*. *See* Flaxseed  
 Lipoproteins, 11  
 Liposomal drug delivery system, 3  
 Lipoxygenase, 333  
 Lithium  
   manic-depressive psychosis, 425–426  
   pharmacodynamics of, 426  
   pharmacokinetics, 425  
   regulatory status of hypericum, 426

- side effects, 425–426
- therapeutic uses of lithium, 426
- Liver
  - diet and, 81
  - disease of, 351
  - effects of alcohol, 650
- Lobelia, 98
- Local anesthesia, pharmacology of, 257–258
- Local anesthetics, 265–266
  - application, 262
  - clinical uses, 266–268
- Low blood sugar diet, 81
- Lung, drug metabolism, 18
- Lung cancer, carotenoids, 587–588
- Lycopene, 584, 588–589
  - cancer risk, 587–588
  - distribution in humans, 585
  - prostate cancer, 583
- Lycorine, 299
- Lymphocyte proliferation assay, 656–657

## M

- Ma huang. *See* Ephedrine
- Macrobiotic diet, 82
- Macular degeneration, carotenoids, 241
- Madder, xvii
- Mallotojaponin, 394–395
- Malted milk, malt extracts, as vitamin source, 631
- Mangoes, as vitamin source, 631
- Mannose-specific plant lectins, 393
- Manuka, 435–440
  - amphotericin B, 436–438
  - antifungal agents, 436
  - aromatherapy, cautions, 440
  - benzoic acid, 440
  - butoconazole, 439
  - ciclopirox olamine, 440
  - clotrimazole, 439
  - econazole, 439
  - fluconazole, 438
  - flucytosine, 438
  - griseofulvin, 438
  - haloprogin, 440
  - ketoconazole, 438
  - miconazole, 439
  - naftifine, 440
  - nystatin, 439
  - salicylic acid, 440
  - systemic antifungal agents, 436–439
  - tea tree oils, 435–436
  - terconazole, 439
  - tolnaftate, 440
  - topical antifungal agents, 439–440
  - undecylenic acid, 440
- Margarine, as vitamin source, 625
- Marigold, xvii
- Marijuana, 63, xviii. *See also* Cannabis
  - Marine therapeutics, 441–444
    - bacteria, potential drugs from, 441–442
    - fungi, potential drugs from, 443
  - Marshmallow, 98
  - Massage therapy, 75
    - baby massage, 76
    - biodynamic massage, 76
    - reflexology, 76
    - Shiatsu, 75
    - sports massage, 76
    - therapeutic massage, 75
  - Mate, 99
  - Matricaria recutita*. *See* Chamomile
  - Mayonnaise, as vitamin source, 631
  - Meadowsweet, 99
  - Medicatrix naturae*. *See* Naturopathy
  - Meditation therapy, 79
  - MedWatch program, 47
  - Melaleuca alternifolia*. *See* Tea tree oil
  - Melittin, 396
  - Melons, as vitamin source, 631
  - Memory. *See also* Alzheimer's disease
    - honey for, 403
    - saffron, 525–526
  - Mentha piperita*. *See* Peppermint
  - Mepenzolate bromide, 208
  - Meperidine, 468–469
  - Mepivacaine, 266
  - Meskwaki, xxvi
  - Metabolism of drugs, factors modifying, 20–21
    - age, influence of, 20
    - enzyme induction, inhibition, 20–21
    - liver disease, 20
    - pharmacogenetics, 20–21
  - Methadone, 10, 469–470
  - Methantheline, 207
  - Methonium compounds, 295
  - Methoscopolamine, 207
  - Methylene blue, 262
  - Methylphenidate, 328
  - Methysergide, 326
  - Metoclopramide, 232–233
  - Miconazole, 439
  - Migraine
    - cannabis, 230
    - prevention, treatment, 326–328
    - serotonin, 324–326
    - sumatriptan, 324–326
  - Milk, as vitamin source, 632
  - Milk thistle fruit, xxv
  - Mineralocorticoids, 556–557
  - Minocycline, 385
  - Mistletoe, 99
  - Mithramycin, 116
  - Mitochondrial diseases, 641
  - Mixed-function oxidation reaction pathway, 18, 348–349
  - Molecular biology, multiple isoenzymes of P-450, 18
  - Monoamine oxidase
    - inhibition, 367–368, 424
    - indications for, 424

Parkinson's disease, 168–169  
*in situ* hybridization, 167–168  
 Monoaminergic drugs, 305  
 Montanoa, 285  
 Morphine, 445–472  
   addiction, 460–462  
     symptoms, 462  
     time required for, 461  
   agonists-antagonists, 472  
   alpropridine hydrochloride, 470–471  
   analgesic action, 456–458  
   analgesic effects, 455–456  
   anileridine, 471  
   antidiarrheal effects, 463  
   antitussive preparations, 472  
   apomorphine, 467–468  
   central nervous system, 452–455  
   codeine, 464  
   constipation, 459–460  
   cough, 458–459  
   cultivation, 447–448  
   dextromethorphan hydrobromide, 466–467  
   dextropropoxyphene, 471  
   dihydrocodeinone, 466  
   dihydromorphinone, 466  
   dyspnea, 458–459  
   endogenous opioid peptides, 449  
   ethylmorphine, 467  
   heroin, 465–466  
   hypotension, 459  
   levorphanol tartrate, 467  
   local uses, 456  
   meperidine, 468–469  
   methadone, 469–470  
   morphine-induced tolerance, 464  
   multiple opioid receptors, 449–450  
   natural opium alkaloids, 464–465  
   nonopiate addicting analgesics, 468–471  
   noscapine, 465  
   oliguric effect, 463–464  
   opioid analgesics, 445–446  
   opioid receptor antagonists, 472  
   opioid receptors, 449–452  
     distribution of, 450  
   opium, 446–447  
   pain, medications, 448–449  
   papaverine, 464–465  
   partial agonists, 472  
   phenazocine, 471  
   piminodine ethanesulfonate, 471  
   respiration, 459  
   sedation, 458–459  
   side effects, 459–460, 469  
   sleep, 458–459  
   stoker's cramp, 448  
   sudorific action, 456  
   synthetic derivatives, opium alkaloids, 465–468  
   therapeutic uses, 456–458  
   withdrawal symptoms, 462–463  
 Motherwort, 99

Movement disorders  
   botulinum toxin, 215  
   cannabis, 228–229  
 Moxibustion, 76  
 MPTP-induced parkinsonism, 534–535  
 Mucilages, 597  
 Multiple-day cisplatin chemotherapy, 233  
 Multiple isoenzymes, P-450, molecular biology, 18  
 Multiple opioid receptors, 449–450  
 Multiple sclerosis, cannabis, 229  
 Muscarinic receptor antagonists, 376–377  
   cardiology, 376  
   gastroenterology, 376–377  
   neurology, 377  
   ophthalmology, 376  
   preoperative uses, 376  
   synthetic, 204–205  
 Mushrooms, as vitamin source, 632  
 Myasthenia gravis, 317  
 Mycobacterial diseases, 384–386  
 Myocardial contraction, biochemical basis of, 359–360  
 Myocardial infarction, 412  
 Myotherapy, 76  
 Myrrh, 99, xvii

## N

N-acetylcystine, 121  
 Naftifine, 440  
 Narcissine. *See* Lycorine  
 Naringin, 595  
 Native American herbal medicine, 76–77, xxvi  
 Nature of drugs, 2–3  
 Naturopathy, 77  
 Neck cancer, carotenoids, 240  
 Necrotizing peptides, xvii  
 Nectarines, as vitamin source, 632  
 Nerve block anesthesia, 267  
 Nerve growth factor, 306  
 Nervous system, deficiency of vitamin B<sub>12</sub>, 344  
 Nettle, 99  
 Neuralgias, quinine, 252  
 Neurodegeneration, 642–644  
 Neuromuscular blockade, 287–295  
   cardiovascular effects, 294  
   erythrina alkaloids, 294–295  
   factors affecting, 292–295  
     acid-base balance, 293  
     age, 294  
     disease states, 294  
     drug interactions, 292–293  
     electrolytes, 293  
     hypothermia, 293  
   histamine release, 294  
   mechanism of action of, 289–290  
   methonium compounds, 295  
   muscular effects, 294  
   neuromuscular junction, 289  
   nicotinic cholinergic receptors, 289  
   ocular effects, 294

side effects of, 294  
skeletal muscle relaxants, 288–295

Neuronal elements, interactions of drugs with, 29

Neuropeptides, 305

Neuroprotection, cannabis, 229–230

Neurotransmitters, 419

Neurotrophins, xvii

New Zealand, tea tree oils from, 435–436

Newborn  
  drug therapy in, 13  
  drugs in, 13

Niacin, 614

Nicotine, xix

Nicotinic cholinergic receptors, 289

Nightshade family, 195–198  
  drugs from, 198

Nitrogen mustards, 112

Nitrosoureas, 113

NLEA. *See* Nutrition Labeling and Education Act

Noncholinergic neurotransmitter replacement, 305–307  
  anti-inflammatory agents, 306–307  
  antioxidants, 305–306  
  desferrioxamine, 306  
  drugs affecting glutamate receptor sites, 305  
  monoaminergic drugs, 305  
  nerve growth factor, 306  
  neuropeptides, 305  
  nootropics, 305

Nonhepatic metabolism, 17–18, 347–348  
  intestinal epithelium, 18, 348  
  lung, 18, 348  
  plasma, 17–18, 347–348

Nonopiate addicting analgesics, 468–471

Nootropics, 305

Nordihydroguaiaretic acid, 53–56

Norepinephrine, storage prevention, by reserpine, 518–519

Noscapine, 465

Nose disorders, botulinum toxin, 216

Nucleic acid, drug interactions, 28–29

Nutrition Labeling and Education Act, 126–127

Nuts, as vitamin source, 632

Nystatin, 439

## O

Oats, 473–474

*Oenothera biennis*. *See* Evening primrose

Oils, as vitamin source, 632

Okra, as vitamin source, 632

Olive oil, 475–476

Olives, 475–476  
  as vitamin source, 633

Omaha-Ponca, xxvi

Ondansetron, 231

Onion, 477–492  
  active ingredients, 477–478  
  aggregin, 478–479  
  anticlastogenic effects of, 483  
  anticoagulants, 478  
  eicosanoids, 479–482

agents altering metabolism, 481–482  
  metabolism, 482  
  pharmacodynamics of, 480–481  
  pharmacokinetic properties, 479  
  physiology of, 479–480  
  therapeutic uses of, 481

platelet-activating factor, 479

platelet aggregation, 478–479

platelet-inhibiting drugs, 479

thrombolytic agents, 478

vitamin E, 479

Onions  
  antimicrobial effects of, 483  
  as vitamin source, 633

Ophthalmic anesthesia, 263

Ophthalmic disorders, botulinum toxin, 214–215

Opioid analgesics, 445–446

Opioid receptor antagonists, 472

Opioid receptors, 449–452  
  distribution of, 450

Opium, 446–447

Opium alkaloids  
  natural, 464–465  
  synthetic derivatives, 465–468

Oral anticoagulants, 44

Oral contraceptive, xx

Oral hypoglycemic agents, 505–506

Oranges, as vitamin source, 633

Organ meats, as vitamin source, 633

Ornithine decarboxylase inhibition, 334

Osteopathy, 77

Oxalic acid, 262

Oxidative stress, chemotherapeutic effectiveness, antioxidants, 110

## P

Pacific yew, xix

Packera, 285

Paclitaxel. *See* Taxol

Panax. *See* Ginseng

*Panax*. *See* Asian ginseng root

Pantothenic acid, 615

Papain, 46

*Papaver somniferum*. *See* Morphine

Papaverine, 464–465

Papayas, as vitamin source, 633

Parkinsonism, 163–194  
  antioxidative therapy, 192  
  banisterine, 168–169, 190–193  
  deprenyl antioxidative therapy, 192  
  MPTP-induced, 534–535  
  selegiline, 163–194  
  tocopherol antioxidative therapy, 192  
  wheat germ, 644–646

Parsley, 99

Parsley piert, 100

Parsnips, as vitamin source, 633

Parthenium, 285

Particle size, drug, 4

- Passionflower, 100  
Passive diffusion, 5  
Pasta, as vitamin source, 633  
Pastries, as vitamin source, 626  
Pathilon. *See* Tridihexethyl chloride  
Pawnee, xxvi  
Pea pods, as vitamin source, 634  
Peaches, as vitamin source, 633  
Pears, as vitamin source, 634  
Peas, as vitamin source, 634  
Pelvic floor disorders, botulinum toxin, 216  
Pennyroyal, 100  
Peppermint, xxv  
Peptic ulcer  
    honey for, 405  
    pathogenesis of, 591  
Percutaneous transluminal coronary angioplasty, 412  
Periactin. *See* Cyproheptadine  
Periphera dopa decarboxylase inhibitor, 191  
Peripheral vascular disease, 413  
Periwinkle plant, xxvii  
Permixon, benign prostatic hyperplasia, 513–514  
Pernicious anemia, xxi  
Persian medicine, 77  
Pertensive medications, xxi  
Pethidine. *See* Meperidine  
Phagocytic activity, 656  
Pharmacokinetic interactions, 33  
Pharmacologic antagonism, drugs, 16  
Pharmacologic receptor sites, nature, type, 13–14  
Phenanthrene, 147  
Phenazocine, 471  
Phenothiazines, 233  
Phloroglucinol derivatives, 394–395  
Phosphodiesterase, drugs inhibiting, 363  
Phospholipase A<sub>2</sub> inhibition, 333  
Physiologic antagonism, drugs, 16  
Physostigmine, 303  
Pickles, as vitamin source, 634  
Pilewort, 100  
Pilocarpine, 56  
Piminodine ethanesulfonate, 471  
Pineapples, as vitamin source, 634  
Pinocytosis, 6  
Pioneers scientists in herbal medicine, 128–138  
*Piper methysticum*. *See* Kava-kava  
Piperidine rings, alkaloids with, 146–147  
Placental barrier, 12–13  
*Plantago ovato*. *See* Ispaghula  
Plantain, 100, 493–498  
    alkylating agents, 496–498  
    antilymphocyte globulin, 497  
    antimetabolites, 497  
    cell transfer therapy, 494  
    corticosteroids, 496  
    cyclosporin A, 497  
    dihydrocyclosporin C, 497  
    immunomodulating agents, 498  
    immunopharmacology, 494  
    immunosuppressive agents, 494–496  
    radioimmunotherapy, 494  
    rho (D) immune globulin, 497  
Plasma  
    drug metabolism, 17–18  
    protein-binding sites, interactions at, 34–35  
    proteins, binding of drugs to, 10–11  
Platelet-activating factor, 42  
Platelet aggregation, 42  
    vitamin E, 42  
Platelet-inhibiting drugs, 42–43  
Pleural cancer, carotenoids, 587–588  
Pleurisy root, 100  
Plums, as vitamin source, 634  
Podophyllotoxin, xxvii  
Podophyllum resin, 162  
Poisoning  
    absorption, 431–433, 524  
    alcohol, 652  
Pokeweed, 100  
Polarity therapy, 78  
Polyoxygenated steroids, 553  
Polyphemusins, 393  
Pomegranate, 507–508  
Poplar, 100–101  
Pork, as vitamin source, 634  
Potassium synergism, 261  
Potency, drugs, 14–16  
Poultry, as vitamin source, 634  
Prana, xx  
Pregnancy, 13  
    diabetes in, 501–502  
Prevent pregnancy, xx  
Prickly ash  
    northern, 101  
    southern, 101  
Prilocaine, 266  
Procaine, 265, xix  
Procarbazine, 117  
Progesterone, 564–566  
    adverse metabolic effects, 566  
    antifertility agents, 566  
    physiological actions, 565  
    potential beneficial effects, 566  
    progestins, 565  
    therapeutic uses, 565  
Progestins, 565  
Prolactin, 29–30  
Propantheline, 207  
Propulsive movements, colon, 154–155  
Prostate cancer, carotenoids, 240  
Prosthetic heart valves, 412  
Protein kinase C inhibition, 332–333  
Prunes, as vitamin source, 635  
Pseudohypercin, 397  
Psoriasis, colchicine, 279  
Psychic healing, 78  
Psychological therapies, 78–79  
    analytical therapy, 78  
    behavioral therapy, 79  
    humanistic therapy, 79  
    integrative therapy, 79

meditation therapy, 79  
 sound therapy, 79  
 Psychotrine, 394–395  
 Psyllium seed products, xix  
 Pulsatilla, 101  
 Pumpkins, as vitamin source, 635  
 Purine antimetabolites, 115  
 Purine bases, 148–149  
 Pycnogenol, 509–512
 

- antioxidant activity, 509–510
- elastase activity inhibition, 511
- inflammatory response regulation, 511
- macrophage activity modulation, 511
- microcirculation enhancement, 510
- platelet aggregation inhibition, 510
- vasorelaxant activity, 510

*Pygeum africanum*, 513–514  
 Pyridine group, 144–146  
 Pyridoxal. *See* Vitamin B<sub>6</sub>  
 Pyridoxamine. *See* Vitamin B<sub>6</sub>  
 Pyridoxine. *See* Vitamin B<sub>6</sub>  
 Pyrimidine analogs, 113–114  
 Pyrrolidine, 144
 

- alkaloids with, 146–147

## Q

Quarzan, 208  
 Quassia, 101  
 Quaternary ammonium muscarinic receptor antagonists, 206  
 Queen's delight, 101  
 Quercetin, 122–123, 594  
 Quinces, as vitamin source, 635  
 Quinine, 56, 248–252
 

- as anesthetic, 251
- antipyretic action, 251
- antiseptic action, 251
- cinchonism, 252
- colds, 252
- colloids, 250–251
- digestion, 251
- headaches, 252
- malaria, 247
- neuralgias, 252
- skeletal muscle, 252
- skin eruptions, 252
- sunburn prophylaxis, 251
- ulcers, 251

 Quinoa, as vitamin source, 635  
 Quinoline, derivatives of, 147

## R

Radiology, to clean gastrointestinal tract, 524  
 Radishes, as vitamin source, 635  
 Rasagiline, dopaminergic neurons, 169–171  
 Raspberry, 101
 

- as vitamin source, 635

*Rauwolfia* alkaloids, 515  
 Recently evaluated herbal products, 61–63  
 Receptor antagonists, 561–562  
 Receptor-mediated endocytosis, 6  
 Receptor-specific interaction, 26–27  
 Rectal administration, 5  
 Red clover, 101
 

- blossoms, xxv

 Red wine, effects of, 647  
 Reflex zone therapy. *See* Reflexology  
 Reflexology, 76, 79–80  
 Reiki therapy, 80  
 Relaxation therapies, 80  
 Renal excretion, drugs, 21  
 Renin, 29  
 Reproductive pharmacology, 561–569
 

- androgens, 566–569
  - antiandrogens, 569
  - side effects, 569
  - therapeutic uses, 569
- progesterone, 564–566
  - adverse metabolic effects, 566
  - antifertility agents, 566
  - physiological actions, 565
  - potential beneficial effects, 566
  - progesterone and progestins, 565
  - therapeutic uses, 565
- steroid hormones, 561–564
  - estrogens, 562–564
  - receptor antagonists, 561–562
  - receptors, 561

 Reserpine, 515–520
 

- adrenergic neuronal-blocking drugs, 519
- adrenergic transmission, neurochemical basis of, 518–519
- catecholamine metabolism, 519
- chemistry, 515–516
- mechanism of action, 517–518
- norepinephrine, storage prevention, 518–519
  - by reserpine, 518–519
- pharmacology, 516–517
- Rauwolfia* alkaloids, 515
- side effects, 519

 Retinoids, in cancer chemoprevention, 620  
 Retinol, 611, 616, 621. *See also* Vitamin A
 

- deficiency, 620
- excessive intake, 620–621
- sources of, 616–617

 Reverse transcriptase inhibition, 333–334  
 Rho (D) immune globulin, 497  
 Rhubarb, 102, 160, 521–524
 

- anthelmintics, 524
- antioxidant properties, 524
- bulk saline laxatives, 523
- cathartics, 523
- constipation, 522–523
- laxative properties, 521–522
- laxatives, 523
- lubricants, 523
- poisoning, absorption, 524

radiology to clean gastrointestinal tract, 524  
 as vitamin source, 635

Riboflavin, 615

Rice, as vitamin source, 636

Ricin, 161

Rifampin, 385

Ritalin. *See* Methylphenidate

RNA polymerase inhibition, 336

Robinul. *See* Glycopyrrolate

Rolfing medicine, 80

Rosemary, 102, 237–238

Rue, xvii

## S

Saffron, 525–528  
 antioxidant effects, 525  
 crocin, molecular target, 526–527  
 learning, effect on, 525–526  
 memory, effect on, 525–526

Sage, 102

Salad dressings, as vitamin source, 636

Salicylate, 529–544  
 analgesics, 530–531  
 anti-inflammatory agents, 530–531  
 antipyretics, 530–531  
 aspirin  
 analgesia, 531  
 anti-inflammatory effects of, 532  
 antipyresis, 532  
 asthma, 535–539  
 cardiovascular disease, 532  
 gastrointestinal effect of, 533  
 hematopoietic effect of, 533  
 mechanism of action, 531  
 new uses of, 533–534  
 poisoning, 533  
 premenstrual syndrome, 532  
 side effects of, 532–533  
 tumor necrosis factor-alpha, inhibition, 540–542  
 uricosuric effects of, 532  
 uses of, 531–532  
 early use of, 529–530  
 effects on respiration, 532–533  
 in foods, 535  
 herbs with, 44–47  
 MPTP-induced parkinsonism, 534–535  
 source of, 529  
 TNF-mediated cytotoxicity, inhibitors of, 542–543

Salicylic acid, 440

Salt, as vitamin source, 636

Saphenous vein bypass grafts, 412

Saponins, 595–596

Sarsaparilla, 102

Sassafras, 102

Sauces, as vitamin source, 636

Saw palmetto, 102, xxv

Scopolamine, 56, 205–206, xix

Seaweed, as vitamin source, 636

Sedatives, 606–609

Seeds, as vitamin source, 632

Selegiline, 164–167, 192  
 antiapoptotic actions, 187–188  
 ATP-sensitive potassium channel, 176–177  
 calmodulin antagonist, 175–176  
 clinical pharmacokinetics, 165–166  
 cytokines, 188–189  
 dopaminergic neuron protection, 172–175, 182–185  
 insulin-like growth factor-I restoration, 181–182  
 MPTP-induced neurotoxicity protection, 171–172  
 neurotrophic-like action of, 177–181  
 nitric-oxide-induced apoptosis protection, 186–187  
 Parkinson's disease, 163–194  
 peroxynitrite-induced apoptosis protection, 186–187  
 striatal superoxide dismutase, 185–186

Selenium, 121–122

Senega, 103

Senna, 103, 160

Serotonergic abnormalities, 325

Serotonin  
 actions of, 324–325  
 metabolism of, 324  
 migraine, 324–326  
 receptors, 325

Serotonin receptor antagonists, 325

Sesquiterpene  
 lactones, 281–282  
 neurotoxicity, 282–283

Sex herbs, 545–552  
 amyl nitrite, 549  
 erectile dysfunction, 547  
 new therapies, 550–552  
 impotence, 545  
 levodopa, 549  
 normal sexual function, 546–547  
 sexual behavior, drugs stimulating, 549–550  
 sildenafil, 550  
 vitamin E, 550

Sex hormones, 557

Sexual behavior, drugs stimulating, 549–550. *See also* Sex herbs

Shamanistic medicine, 80–81

Shellfish, as vitamin source, 636

Shepherd's purse, 103

Shiatsu massage, 75

Sialidase inhibition, 337

Siamycins, 393

Siberian ginseng root, xxiv

Sildenafil, 550

*Silybum marianum*. *See* Milk thistle

Sinemet. *See* Periphera dopa decarboxylase inhibitor

Site of action of drugs, herbs, 13, 25, xxi

Skin  
 ailments, aloe gel for, 153  
 cancer, black tea, 380–381  
 eruptions, quinine, 252  
 vitamin intake, 619

Skullcap, 102–103

Skunk cabbage, 103

Slippery elm, 103

Smoked meats, as vitamin source, 637



- Smooth muscle overactivity, botulinum toxin, 216
- Snacks, as vitamin source, 637
- Soft drinks, as vitamin source, 637
- Solanaceae, 195–198  
botany of, 198
- Solanaceous plants, xix
- Somatic, autonomic nervous systems, comparison of, 199–200
- Sophoradin derivatives, 595
- Sound therapy, 79
- Soups, as vitamin source, 637
- Soybean oil, xix
- Spasticity, botulinum toxin, 215
- Spinach, as vitamin source, 637
- Spinal anesthesia, 264, 267
- Sponges, 553–570. *See also* Steroids  
steroids found in, 553–554  
polyoxygenated steroids, 553  
steroid sulfates, 553–554
- Sports massage, 76
- Squash, as vitamin source, 638
- Squill, 103
- St. John's wort, 63, 103–104, 415–426  
antidepressants, 417–418, 424–425  
classification of, 419  
side effects of, 422  
sites of action of, 420–422  
dibenzapine derivatives, 419–424  
lithium  
manic-depressive psychosis, 425–426  
pharmacodynamics of, 426  
pharmacokinetics, 425  
regulatory status of hypericum, 426  
side effects, 425–426  
therapeutic uses, 426  
monoamine oxidase inhibitors, 424  
indications for, 424  
neurotransmitters, 419  
overdoses, 423–424  
tricyclic antidepressants, 420
- Steroid sulfates, 553–554
- Steroids  
adrenal disorders, 561  
adrenal steroids, 554–561  
Cushing's syndrome, 561  
reproductive pharmacology, 561–569  
in sponges, 553–554  
with unconventional side chains, 554
- Stigmasterol, xix
- Stoker's cramp, 448
- Stone root, 104
- Strawberries, as vitamin source, 638
- Structure-activity relationship, 25–26
- Strychnine, xviii
- Substitutes for, 206–208
- Sudorific action, 456
- Sulfamethoxazole, trimethoprim, interactions, 27
- Sulfated polysaccharides, 392
- Sulfonylurea, receptors for, 506
- Sumatriptan  
antimigraine action of, 326  
clinical efficacy of, 325–326  
migraine, 324–326  
side effects of, 326
- Sunburn prophylaxis, quinine, 251
- Supersensitivity to drug, 33
- Surface area, drug absorption and, 8
- Sweat glands, vitamin intake, 619
- Syrup of ipecac, 432
- ## T
- Tachyphylaxis, 32–33
- T'ai chi chuan, 81
- Tanacetum parthenium, 282–283
- Tangerines, as vitamin source, 638
- Tannins, 596–597
- Tansy, 104
- Tao, xx
- Taoism, xx
- Taxol, 571–582, xix  
alkylating agents, 575–576  
alkyl sulfonate, 576  
chlorambucil, 576  
cyclophosphamide, 576  
nitrogen mustards, 575–576  
nitrosoureas, 576  
triazenes, 576  
antimetabolites, 576–579  
deoxycytidine analogs, 578  
folic acid analogues, 576–577  
purine antimetabolites, 578–579  
pyrimidine analogs, 577–578  
antineoplastic agents, 581–582  
asparaginase, 581  
bleomycin, 580  
cancer chemotherapy, 574–575  
carboplatin, 581  
chemotherapy, emesis induced by, 582  
cis-platinum, 581  
dactinomycin, 579  
daunorubicin, 580  
docetaxel, 580–581  
doxorubicin, 580  
etoposide, 582  
hydroxyurea, 581  
mithramycin, 579  
natural products, 579–581  
paclitaxel, 580–581  
procarbazine, 581  
vinca alkaloids, 579
- Tea tree oil, 63, 435–436
- Teas, 379–382. *See also* Black tea; Green tea; White tea  
as vitamin source, 638
- Tegretol. *See* Carbamazepine
- Terconazole, 439
- Tertiary-amine muscarinic receptor antagonists, 208
- Tetracaine, 266
- Tetrahydroaminoacridine, 302–304
- Tetrahydrocannabinol, 56
- Theobroma cacao*, xix

Theophylline, 56, 262  
 Therapeutic index, 16–17  
 Therapeutic massage, 75  
 Thiamine, 615  
 Thistle, 96  
 Throat disorders, botulinum toxin, 216  
 Thrombin, 43  
 Thrombolytic agents, 38–42  
 Thyme, 104  
 Thyroxine-binding globulin, 10  
 Tibetan medicine, 82  
 Ticlopidine, 411–412  
 Tissue localization of drugs, 11  
 Tithonia, 285  
 TM. *See* Transcendental meditation  
 TNF-mediated cytotoxicity, inhibitors of, 542–543  
 Tocopherol. *See* Vitamin E  
 Tolerance to drug, 32–33  
 Tolnaftate, 440  
 Tomatoes, 583–590  
   carotenoids  
     in fruits, vegetables, 584–585  
     history of, 584  
     organ concentrations, 585–587  
     physicochemical nature of, 584  
   lung cancer, 587–588  
   lycopene, 584, 588–589  
     cancer risk, 587–588  
     distribution in humans, 585  
     prostate cancer, 583  
   pleural cancer, 587–588  
   as vitamin source, 638  
 Topoisomerase inhibition, 334  
 Trace minerals, 622–623  
 Tral. *See* Hexocyclium methylsulfate  
 Transcendental meditation, 82  
 Transpersonal therapies, 83  
 Transport mechanisms, 5–6  
   carrier-mediated transport, 5–6  
   facilitated transport, 6  
   ion pair transport, 6  
   passive diffusion, 5  
   pinocytosis, 6  
   receptor-mediated endocytosis, 6  
 Tree remedies, 70–71  
 Triazines, 113  
 Trichosantin, 396  
 Tricyclic antidepressants, 420  
 Tridihexethyl chloride, 208  
*Trifolium pretense*. *See* Red clover  
 Trigeminal neuralgia, 328–329  
 Trimethoprim, sulfamethoxazole, 27  
   interactions, 27  
*Triticum* species. *See* Wheat bran  
 Truffles, as vitamin source, 632  
 Tuberculosis, 383–386, xx  
   amikacin, 385  
   antimicrobial activity, 385–386  
   antituberculosis efficacy of natural products, 383–384  
   cycloserin, 385  
   ethambutol, 385

herbal plants, 383–386  
 leprosy, 384–385  
 minocycline, 385  
 mycobacterial diseases, 384–386  
 rifampin, 385  
 Turmeric, 237–238  
 Turnips, as vitamin source, 638

## U

Ubiquinone. *See* Coenzyme Q<sub>10</sub>  
 Ulcer therapy, 591–598  
   acid-pepsin disease, 591  
   aloe gel, 598  
   antacids, 592  
   anthocyanosides, 595  
   anticholinergic drugs, 592–593  
   antiulcer herbs, 593–597  
   capsicum, 598  
   drug therapy, 592–593  
   flavonoids, 593–594  
   gastric acid secretion, physiology of, 591–592  
   gums, 597  
   herbal drugs, 597–598  
   histamine-receptor antagonists, 593  
   licorice, 597–598  
   mucilages, 597  
   naringin, 595  
   peptic ulcer, pathogenesis of, 591  
   quercetin, 594  
   quinine, 251  
   saponins, 595–596  
   sophoradin derivatives, 595  
   tannins, 596–597  
*Uncaria tomentosa*. *See* Cat's claw  
 Undecylenic acid, 440  
 UVA-URSI, 104, xxvi

## V

*Vaccinium macrocarpon*. *See* Cranberry  
*Vaccinium myrtillus*. *See* Bilberry fruit  
*Vaccinium* species. *See* Cranberry  
 Valerian, 104, 599–610, xxvi  
   anxiolytic agents, 602  
   barbiturates, 606–608  
     acute toxicity, 607–608  
     addiction, 608  
     classification, 606–607  
     pharmacokinetics, 607  
     selection of drugs, 608  
   benzodiazepine-binding sites, 603–604  
   benzodiazepine derivatives, 608–609  
     antianxiety effects, 604  
     anticonvulsant activity, 605  
     mode of action of, 604–605  
     muscle relaxant activity, 604–605  
     sedative effects, 605  
   benzodiazepines, pharmacodynamics of, 602–603

- epilepsy, mechanisms of, 601–602
- GABA receptors, 603
- gamma-aminobutyric acid, 600–601
- general anesthetics, mode of actions of, 605–606
- glycine, 606
- hypnotics, 606–609
  - with insomnia, 599–600
  - regulatory status, 609
  - sedatives, 606–609
- Valpin. *See* Anisotropine methylbromide
- Valvular heart disease, 413
- Vasodilation, receptor-dependent, 364
- Vasodilators, 363–365
  - independent, 364–365
- Vasopressor, 317–318
  - ephedrine as, 311–318
    - absorption, 315
    - actions of, 311
    - allergic disorders, 316
    - bronchi, 314
    - bronchial asthma, 315
    - cardiovascular, 313–314
    - central nervous system, 315
    - enuresis, 317
    - ephedra, 312
    - eye, 314
    - gastrointestinal musculature, 314
    - glands, 314–315
    - heart block, 316
    - history, 311–312
    - myasthenia gravis, 317
    - mydriasis, 316
    - organ systems, effect on, 313–315
    - pharmacological properties, 313
    - pillomotor muscles, 314
    - routes of administration, 315
    - skeletal muscle, 315
    - smooth muscle, 314
    - spinal anesthesia, 316
    - therapeutic uses, 315–317
    - toxicity, 317–318
    - urinary bladder, 314
- Veal, as vitamin source, 624
- Vegan diet, 81
- Vegetables, antioxidant capacity, 107–108
- Vegetarian diet, 81
- Venous thromboembolism, 412
- Vervain, 104
- Viagra. *See* Sildenafil
- Vimosidine, xxvii
- Vinblastine, xix, xxvii
- Vinca alkaloids, 115–116, xxvii
- Vincristine, xix, xxvii
- Vinegar, as vitamin source, 639
- Vinleurosine, xxvii
- Vinorelbine, xxvii
- Visualization therapy, 83
- Vitamin A, 611, 616, 621
  - deficiency diseases, 620
  - excessive intake, 620–621
- Vitamin A deficiency diseases, 620
- Vitamin B<sub>1</sub>. *See* Thiamine
- Vitamin B<sub>2</sub>. *See* Riboflavin
- Vitamin B<sub>3</sub>. *See* Pantothenic acid
- Vitamin B<sub>6</sub>, 615
- Vitamin B<sub>12</sub>, 343, 615
  - with aging, 344
    - bioavailability of, 343–344
    - folic acid, relationship, 346
    - megaloblastic anemias, 346
- Vitamin C, 119, 615–616
- Vitamin D, 613–614
- Vitamin E, 46–47, 118–119, 550, 614
  - neuroprotective role, 646
  - for parkinsonism, 192
  - platelet aggregation, 42
- Vitamin K, 613–614
- Vitamins, 611–640. *See also under* specific vitamin
  - action of, 617–621
  - aging, 621–622
  - antioxidants, 621–622
  - beta carotene, 611–613
  - biotin, 614
  - bone, 619
  - bronchorespiratory tract, 619
  - cancer, 620
  - carcinogenesis, 617
  - dermatological diseases, 620
  - dietary recommendations, 621
  - dietary sources, 616–617
  - excessive vitamin A intake, 620–621
  - eye, 619
  - fat-soluble vitamins, 611–613
  - folate, 614
  - foods, 623–639
  - gastrointestinal tract, 619
  - genitourinary system, 619
  - immune function, 617–618
  - niacin, 614
  - nutritional actions, 611–616
  - pantothenic acid, 615
  - retinoids, in cancer chemoprevention, 620
  - retinols, 611 (*See also* Vitamin A)
  - riboflavin, 615
  - skin, 619
  - sweat glands, 619
  - therapeutic uses, 620
  - thiamine, 615
  - trace minerals, 622–623
  - water soluble vitamins, 614–616
- Vitex Agnus-Castus*. *See* Chaste berry
- Vitis vinifera*. *See* Grape seed extract
- Volume of distribution of drugs, 12
- Vomiting
  - caused by cancer therapy, cannabis, 231–232
  - central control of, cannabis, 230–231
  - drugs producing, 429–431
  - physiology of, 230

**W**

- Warfarin, 47
  - alternative therapies and, 38
- Water soluble vitamins, 614–616
- Watercress, as vitamin source, 639
- Wheat bran, 63
- Wheat germ, 641–646
  - Alzheimer's disease, 644–646
  - Huntington's disease, 644
  - mitochondrial diseases, 641
  - neurodegeneration, 642–644
  - Parkinson's disease, 644–646
  - vitamin E, neuroprotective role, 646
- White tea, benefits of, 381–382
- Wild carrot, 104
- Wild lettuce, 105
- Willow, 105
- Wine, 647–654
  - acute intake of alcohol, 649
  - alcoholism, treatment of, 652–653
  - cardiovascular system, 649
  - central nervous system, 649
  - chronic toxicity, 652
  - delirium tremens, 652
  - disulfiram, 653
  - effects of, 649–651
  - endocrine glands, 650–651
  - fetal alcohol syndrome, 651
  - gastrointestinal effects, 649–650
  - liver, 650
  - pharmacokinetics, 651–652
  - pharmacology of, 649–652
  - poisoning, 652
    - acute, 652
  - red wine, effects of, 647
  - toxicity, 652
  - as vitamin source, 639

- Winnebago, xxvi
- Witch hazel, 105
- Withania somnifera*. *See* Ashwaganda
- Wounds, honey for, 404–405

**X**

- Xanthine oxidase, 28
  - hyperuremic states, 28
- Xanthine oxidase inhibition, 334

**Y**

- Yams, as vitamin source, 639
- Yang, xix, xx
- Yarrow, 105
- Yellow dock, 105
- Yew species, xix
- Yin, xix, xx
- Yoga, 83
- Yogurt
  - immune system, 655–659
    - cytokine production, 657
    - immune function, *in vitro* indexes, 656
    - lymphocyte proliferation assay, 656–657
    - phagocytic activity, 656
  - as vitamin source, 639
- Yucca, 105

**Z**

- Zingiber officinale*. *See* Ginger
- Zollinger-Ellison syndrome, xxi
- Zucchini, as vitamin source, 639
- Zwieback, as vitamin source, 639



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