As the field of nutritional medicine is developing, there is generally a lack of laboratory technology to help the hard pressed clinician in selecting diets or supplements.

This book makes the provocative suggestion that the present disease model is out-moded and old-fashioned. It outlines a new model in which inappropriate oxidative metabolism is responsible for loss of efficiency in tissues. Since the nervous system is the most "oxygen hungry" tissue in the body, nervous symptoms are frequently generated as an early warning of malnutrition, especially that caused by ingestion of “empty calories”.

Dr. Lonsdale uses the metabolism of vitamin B-l and the symptoms of Beri-Beri to illustrate the effect of inefficient redox, emphasizing the generic effect that this has on the hypothalamic-autonomic-endocrine axis. The biochemical lesion caused by thiamin pyrophosphate deficiency is easily measured in a clinical laboratory by measuring the activity of erythrocyte transketolase. Using a test of this nature points the way to the methodology of other cofactor deficiencies. More importantly, however, it is one method of assessing hypo-oxidative stress.

This book was originally published in 1987 and, before it had a chance to become better known, most of the books were burned in a fire at the publisher’s warehouse. Its title was “A Nutritionst’s Guide to the Clinical Use of Vitamin B-1” but I have changed this title since it is really a monogram, reporting the many facets of clinical and animal research performed during my tenure at Cleveland Clinic Foundation. This centered on the surprisingly versatile activity of thiamin and its derivatives in both clinical and laboratory improvements in many different conditions. Thus, the obvious conclusion was that efficient oxidation is a key factor in many human diseases.

It is becoming obvious that the model for drug-based modern medicine is broken. Hospitals are now dangerous places in which to be treated and there must be a shift to accepting the ancient proverb that “prevention is better than cure”. We have to recognize that the human body is an extraordinary “machine” that is designed with breathtaking beauty. Disease is produced by loss of efficiency in the biochemistry and electricity that it uses to create energy for its 70 to 100 trillion cells to function. The most modern

research has shown that an important part of this is intracellular communication.

It is a good concept to think of the body as being like an orchestra. The organs can be compared with the various instruments, each of which has a program that enables it to participate in the “Symphony o f Health”. It is inconceivable that this complex would function properly if there was not a “conductor”. The limbic system of the brain is visualized as a computer that enables the organs to work together in “playing that symphony”, thus analogized as the “conductor”.

Thus, if the genetic program is complete in a given individual, all he/she has to do is to “obey the rules set by Mother Nature”. In the modern world, that is simply not happening and we are moving further and further away from our biologic origins. Through the new science of epigenetics, we have learned that our genes can be manipulated by diet and lifestyle factors and “God made food” is the only fuel that we were designed to ingest.

In proof reading the text in preparation for placing this book in the “Soil and Health Library” I have added small sections of updating since more is known about some of the patients described. Readers will encounter some work on amino acid ratios in comparing threatened SIDS infants with patients suffering from Reye’s syndrome, a disease that is now a more or less extinct issue since aspirin as its cause is known. But I would hasten to add that the true underlying cause of both SIDS and Reye’s syndrome is still not defined in biochemical terms. Although not truly showing us this cause in finite terms, it is a hint that biochemistry plays a very important role in both and it may lead to further research.

Hans Selye studied the way in which animals adapt to stresses imposed by him in his experiments. He formulated the concept of “diseases of adaptation”. Perhaps a more accurate phraseology would be to call them “diseases of maladaptation” as they apply to humans living in the modern world.

The discerning reader will soon note that most of the references are old. In the modern era it has been generally accepted that “if the reference is old it is already out of date”. It is to be noted, however, that the references given here are from an era when much thought was being given to

vitamins as therapeutic agents. The simple facts are that the results were “too good to be true” and threatened the pharmaceutical industry. Drugs could be patented and make money whereas naturally occurring substances could not. Vitamin therapy fell into disrepute and was classified as “quackery” by an onslaught of politically driven motives.

Healing requires energy and it is a natural process. An orthopedist is a technician who realigns the fractured bones. The healing takes place from within and this applies to all diseases. We have centered on the concept of “kill the enemy”, the bacteria, viruses, cancer cells. Little thought has been given to how we can assist the natural defensive mechanisms by stimulating energy synthesis. The reappearance of the ancient form of therapy known as holistic medicine under the general title of Complementary Alternative Medicine is truly a paradigm shift in concept. The majority of the present medical profession and the pharmaceutical industry will not change. It will be the intelligent consumer that will force the issue eventually

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DEDICATION

To my wife, Adèle.

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Expert technical assistance in the laboratory was provided by Mrs. Judy Goodman.

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PREFACE

By Dr. Myron Brin, M.D.
Fellow, Charles A. Dana Research Institute for Scientists Emeriti

The metabolic functions of thiamine have been studied extensively in man and experimental animals for over 50 years. Thiamine supports normal metabolism in every tissue of the body. Yet the signs and symptoms of the deficient condition have not been fully explained.

Dr. Lonsdale proposes that restricted availability of vitamin coenzymes disrupts cellular energy balance This has an adverse effect upon the function of the autonomic nervous system, thereby resulting in tissue/organ pathology. He draws upon the literature extensively to support his hypothesis.

Many of the studies Dr. Lonsdale presents used subjects as their own controls. In some cases he used functional enzyme/coenzyme tests to contribute specificity to the conclusions. These tests were developed some years ago to determine severity of marginal or preclinical deficiency. The latter is a state of vitamin depletion in which non-specific physiological entities such as feeling of well-being, maintenance of body weight, rates of drug metabolism, levels of immunocompetence, modified behavior, etc., are adversely affected before the onset of the classical deficiency syndrome.

Accordingly, Dr. Lonsdale has developed a general theme based upon both clinical and experimental data. While acceptance of his hypothesis on the origin of stress may not be universal, at least initially, it is worthy of consideration. In fact, stimulation of additional research on this subject would be an important contribution to nutritional science.

FOREWORD

Much has happened since this book was started. There is burgeoning interest in the science and art of nutrition from the public, but as yet there is little real interest from the medical profession. Most physicians do not know that the chemistry of the body can be influenced by nutritional means and have yet to grasp the fact that nutrients are the only real weapons in the continuing struggle against disease. The body knows what to do with them, and uses them to enhance its natural mechanisms of defense. The scientific community is awakening to the fact that cellular mechanisms are not autonomous and rely on to and fro communication with control mechanisms in the brain. Holistic medicine is gradually overcoming the stigma placed upon its conception, as a realization dawns that the body is a machine which has to run its "mental" and "physical" components in a state of harmony.

The fact is that the human body was using Einsteinian physics before the theory of relativity was discovered. It takes fuel, combines it with oxygen in a process of oxidation and yields from it a carefully modulated supply of energy. To biochemists the underlying mechanism is known as redox and its normal function is dependent upon an astoundingly complicated series of biochemical events which rely heavily on cell membrane physiology. The net result is conversion of matter to energy.

Chance experience with a thiamine dependent child suffering from intermittent episodes of cerebellar ataxia was responsible for research which then led to the writing of this book. However, one of the basic things that was learned by the author is that no nutrient works on its own. It only operates within a complicated network of nutrients which together enable the live cell to use oxygen efficiently and thereby release energy. The energy must be channeled appropriately and not wasted.

If it were technologically possible to perform a test which gave a calibration for efficient utilization of cellular oxygen it could become the gold standard for ascertaining the nature of the nutrients required to improve redox. Oxidative deficiency is as lethal at one extreme as excessive oxidation is at the other. Now that medicine has to struggle with the emergent idea of free oxygen radical pathology and the appropriate therapeutic use of antioxidants, we are beginning to see in perspective how redox becomes important clinically. In fact we are at last beginning to learn how deviant redox causes the nervous system to react reflexly and express behaviour in neurotransmitter and endocrine terms.

The experience with thiamine recorded in this work is obviously a very small part of the total solution and it is not in any way intended to suggest that it is any more important than any of its nutrient relatives. It seems to be a vital concept that the efficient burning of calories will occur when there is a reasonable ratio of oxidant fuel to nutrient oxidants. It does appear, however, that thiamine has a role in the cell membrane as well as its better known function in the citric acid cycle and other oxidant enzymes. Hence, knowledge of its biochemistry, as it is presently known, introduces us to the complete picture of energy metabolism, even to release of acetyl choline into the synaptosome. It was felt to be important that the clinical situations outlined in the book should be described only in order to illustrate the emergent concept of the development in vitamin and mineral therapy which is so rewarding to both patient and physician.

Beriberi may be viewed as the classic expression of the nervous system in a hypo-oxidative state, whereas loss of control of membrane function alters the mechanism of electron transfer so that coupling control is partially lost and oxygen is wasted in formation of free oxygen radicals. Perhaps the entire field of health and loss of health is governed by the simple principles of an intact "machine" in relation to its efficient use of oxygen. Hence, bacteria and viruses are merely environmental stressors in the same fundamental bracket as any other stress force and it is the defense which is critical and must be assisted through increased redox efficiency.

There are, therefore, only three variables that have to be considered in dealing with the deviation from health (ease) to disease. The first is constitution, which is the way the individual is put together; the second is the nature of environmental stress

encountered; the third is redox efficiency. The last is the only variable which we can control through the quality of the fuel (nutrition).

The clinical work reported here was carried out over a period of more than ten years in a large private clinic. The thiamine tetrahydrofurfuryl disulfide (TTFD) was provided by Takeda Chemical Industries in Osaka, Japan, and used under FDA Independent Investigator License 11019.

INTRODUCTION

Hippocrates recommended dietary therapy almost exclusively, and his fame must have been derived from his success as a physician. It is, therefore, hardly new to discuss diet in relation to disease. Biochemistry has made spectacular advances in this century and enabled a more scientific approach to nutrition. If such an approach really works, then it has the fundamental quality of safety which was one of the principles of therapy most emphasized by Hippocrates.

Consider the recent history of medicine. It is only a few hundred years since circulation of the blood was discovered. Bleeding the patient was as irrational in the light of present knowledge as was trephining the skull to let out evil spirits. Both of them must have worked, or appeared to work, or the practice would have been rapidly discontinued. Polycythemia and hypertension might have responded to the first procedure, and raised intracranial pressure, from any source, to the second. Until the discovery of penicillin there was no specific therapy, and its value depends on the fact that it is destructive to bacterial life processes with a large margin of safety to the patient. But even penicillin is occasionally lethal, and many of the antibiotics that have since evolved possess numerous toxic qualities.

The powerful drugs that are used today have one thing in common. They are essentially physiologic inhibitors, and much of the discussion about any one of them in a manual emphasizes the side-effects, or unwanted actions, of which the physician must be aware and attempt to avoid by proper dose. The principle must assume, therefore, that the disease is brought about by abnormally active function which has to be suppressed. A typical example of the use of this principle is propranolol to block adrenergic receptors in hypertension, and it is not without interest that the same drug has been used for schizophrenia, [1,2] although the two conditions are generally thought of as entirely different disease entities. The conclusion is that in both cases the symptoms arise from, or are connected with, an unbalanced and excessive activity of the adrenergic component of autonomic and endocrine function. It is well known that autonomic response is normally balanced in terms of the entire system and a proper mixture of adrenergic and cholinergic drive gives rise to the control of function. Presumably the excessive and persistent adrenergic drive in the two disease states is based on one of two possibilities: excessive adrenergic and normal cholinergic component; or normal adrenergic and ablated or subnormal cholinergic component.

The nutritional approach to therapy is an attempt to restore balance in the system, and makes use of biochemical knowledge. It is readily apparent that if this hypothesis is true, the two forms of therapy should be able to work together. But if one component of the total system is subnormal, then a suppression of activity of the normal opposing component would lead to two subnormal members and might result in deterioration rather than improvement of the patient.

This hypothesis also involves an understanding of the concept that was studied for many years by Selye [3] and followed up by others.[4,5,6] Selye was struck by the similarity of appearance in all sick patients, irrespective of the cause. It dawned upon him that this appearance represented something to do with the individual being overwhelmed by the nature of the attack, whether it be from infection, trauma, or environment. He called the attacking force "stress," just the same as an engineer refers to the press or weight which he applies to a metal bar to test its tensile strength. If there is a genetically built-in defect in an individual such as an enzyme deficiency, the "machine" is partially crippled and the attacking force — or stress factor — would be expected to worsen the situation in terms of the response of the total organism by exposing the symptoms related to the defective enzyme. A rather typical example of this is in maple syrup disease. When the patient has an infection such as a simple cold, branched chain amino acids increase in concentration and keto acids derived from the abnormal metabolism are found in urine.[7] This might be referred to as the host response resistance. The enzyme defect is analogically equivalent to a molecular fault in the tested metal which would quickly develop stress lines and thus be detectable by the engineer from x-ray studies or other technical means. Selye's concept goes further than that. His reasoning would

embrace the fact that the steel bar might be built as well as the tensile strength of the metal would allow. Reversing the analogy, therefore, this would mean that a genetic defect would quickly show up as "stress lines" in an organism, but might just as easily appear if the organism were intact, assuming the force to be great enough to overwhelm the "normal tensile strength." Since all organisms, including man, are under stress, as indeed is the metal in the analogy, it is not really surprising that the idea of stress as a cause of disease is not readily accepted.

If the argument is accepted thus far, the next question to be asked is how the total organism meets stress and how its total commitment to survival is organized. Selye repeatedly emphasized that this was a normal response and was concerned by its breakdown as the cause of disease. He emphasized, too, that the mechanism could be improved with practice and might be the key to adaptation, hence the concept that he called "the diseases of adaptation." The physiology of stress response is the well known fight-or-flight reflex, primarily adrenergic and capable of extraordinary "superhuman" power; the secret of success in rescue work, battle engagements, or other emergency events which raise the average human being to above average. What happens if this reflex is chronically sustained in a poorly adapted individual? We can assume that the total commitment to survival calls up every ounce of usable energy and, even in the event that bioenergy regeneration proceeds during the crisis, there may come a time when the use of energy stores exceeds the ability to supply it. Could this perhaps be what we call "shock?" The third aspect that must therefore be considered in the hypothesis is the process of energy production. What is known about bioenergy and how can it be fitted into the various disease patterns? Essentially, it is necessary to think in Einsteinian terms of the interchangeability of matter and energy. The cell, as a single live unit of the whole organism, adapted to its highly specialized role within the species, has to take in fuel and burn it just the same as any internal combustion engine. It does it by unlocking the energy of glucose and building up an ionic gradient which synthesizes ATP by the process of oxidative phosphorylation. The ATP formed can then be used to perform work. If a state of alarm existed for long enough and without respite, it does not seem to be illogical to contemplate that it might result in a deficit of available ATP. The location of the deficit might be related to the organ or system which is called upon most heavily and is likely to originate sensory signals or symptoms which attempt to notify the brain of the crisis that is developing. This could be a protective mechanism which results in the whole organism seeking rest, or a local effect such as the sensations created in a limb after exercise. If this be true, then functional disease patterns could well be the forerunner of organ or system structural disease, and would represent the clearest indication that more trouble might be ahead if the signals are ignored. We know that physical rest is not necessarily the answer, for the activated brain of insomnia could be seen as part of the energy using fight-or-flight mechanism, and the deficit continues to build up in the brain itself. It is here where nutritional therapy might be most valuable by providing the raw materials which the cell cannot synthesize but which may be squandered in carrying out the multitude of reactions which represent the cellular response to stress as defined above.

Perhaps one of the factors which has been insufficiently studied is the relation between calories offered and the potential for completely oxidizing them. Like a choked internal combustion engine, hydrocarbons representing incomplete oxidation products could form and circulate in the blood before elimination in urine. Such calories are sometimes referred to as "empty" or "naked," the best example perhaps being alcohol.

In the pages that follow, an attempt has been made to look at the mechanisms involved and to try to understand how knowledge of them might be used to our advantage. Nutrition is primarily a preventive approach and there is no doubt that medicine is swinging towards a realization that prevention is indeed better than cure. We may have to accept that cataracts, for example, are incurable except by surgical means, but are in many instances preventable, as Heffley and Williams showed in animal studies.[8] The old adage that surgery is an admission of medical failure may well be invoked if the physician is unable to perceive the warning signals that herald the biochemical changes leading to organic damage. If preventive measures are advised and are successful, it is virtually impossible to prove. How could a physician

claim that the patient would have developed cataracts without such a measure being taken? It is only in the long run, by making cataract surgery a thing of the past or a relative rarity, that medicine would be able to claim that the measures represent a useful change in man's ability to maintain a healthier existence.

Studies of nutritional therapy have, for the most part, been on the basis of pure clinical observation, which is likely to be subjectively biased. Efforts are being made to obtain more objective biochemical measurements which, hopefully, will support the observations and bring credibility to a field which continues, quite rightly, to be under skeptical observation.

One of the most alarming factors that will have to be considered when nutritional therapy begins, is the effect of what we have termed "paradox." The patient's symptoms, particularly if they have been long standing, are apt to become considerably worse for an unpredictable period, varying from a few days to a few months. Biochemical changes may appear to reflect this. For example, creatine may increase drastically before diminishing and hypoaminoaciduria may become hyperaminoaciduria before becoming normal. This is not new. Paradox was very visible in beri-beri patients and we have the modern counterpart of unpredictability from dextroamphetamine and barbiturates, particularly in children. This makes double blind studies very difficult since the period of authentic administration has to be long enough, and it appears to "overlap" the placebo period if the authentic compound has been used first in the random selection.

Another difficulty we have recognized is that nutritional therapy is not often successful from the use of a single agent. In some instances we have obtained remission only by the addition of other vitamins or nutrients, and hormone replacement may be required. Since our experience has strongly suggested that a thorough knowledge of the physiology of autonomic activity is required, chapter one reviews the more important of the autonomic nervous system features. Chapter two reviews what is known of autonomic dysfunction, and how it appears to be a relevant feature of many different disease entities. From then on, the book seeks to show that interpretation of autonomic function, by understanding the "balanced" relation between cholinergic and adrenergic activities, may be used in order to "decode" the true meaning of the signals (symptoms) experienced by the patient and observed by the physician (signs).

Chapter 1

THE AUTONOMIC NERVOUS SYSTEM

Before considering a dysautonomic response it is necessary to review the known features of the autonomic system relatively familiar to the neurophysiologist, but to some extent forgotten by the practicing physician. No attempt will be made to deal with this in detail since the information is readily available in a textbook of physiology.[1]

GENERAL ARRANGEMENT AND FUNCTIONS

Also known as the vegetative, visceral or involuntary nervous system, the autonomic nervous system controls the activities of the heart, blood vessels, glands, and all smooth muscles. The ganglia are situated outside the central nervous system and the nervous functions are coordinated with those of the somatic nervous system. The integration of the two systems is brought about by reflex pathways at various levels. The two systems may be compared in order to simplify concepts.

In a somatic spinal reflex three neurones are involved. The afferent has its cell body in the dorsal root ganglion and transmits impulses to the ventral horn through the connector neurone whose cell lies in the dorsal horn of grey matter. Efferent impulses are then relayed to the ventral horn cell and its axon which leaves via the ventral root. Similarly, there are three neurones in the autonomic system. There is an afferent, proceeding from an internal organ, and the nutrient cell lies in the dorsal root ganglion or its cranial equivalent, and a central process is sent into the grey matter adjacent to the dorsal horn; its axon passes out ventrally to the excitor cell which is situated peripherally outside the central nervous system. Excitor cells form masses or ganglia, and from them the postganglionic fibers pass to the innervated tissue either to excite or to inhibit the action.

The whole system falls into three outflow tracts anatomically. The parasympathetic system is the craniosacral outflow in connection with the nuclei of the Illrd, Vlth, IXth and Xth cranial nerves and the second and third sacral segments of the spinal cord. The sympathetic system flows from the entire thoracic region of the cord and its first two lumbar segments.

When stimulated, the sympathetic and parasympathetic nerves produce antagonistic effects on the organs which they both supply, and under natural conditions they act synergistically to produce a balanced action. Thus, increased rate of the heart is produced mainly by decreased vagal tone, but also by increased sympathetic tone. It is also necessary to consider normal autonomic reaction so that the observed clinical changes can be fitted into either the expected normal response or the unexpected abnormal. Although much of the anatomy is known, all that is required for our purposes is to delineate the various physiologic phenomena and then to discuss them in terms of neurotransmission from a biochemical standpoint.

SYMPATHETIC SYSTEM

The Eye. Structures of the eye supplied by the sympathetic system are:

1) dilator pupillae muscles.
2) smooth muscle fibers in the upper and lower lids, called respectively the superior and inferior tarsal muscles which retract the upper and lower lids.
3) smooth muscle fibers of the retroocular muscle of Müller which lies in the orbital fascia and pushes the globe forward. This is important in considering exophthalmos as a sign of adrenergic overdrive and enophthalmos as a sign of its interruption.

Stimulation of the cervical sympathetic causes dilatation of the pupil and retraction of the lids resulting in a "staring" gaze. The effect on the globe in man is variable, although it can move the dog's globe forward by as much as 5 mm. The blood vessels are constricted. Section of the cervical sympathetic causes Horner's syndrome; constricted pupil, narrowed palpebral fissure, ptosis of the upper lid, and

slight elevation of the lower lid, together with diminished sweating of the face on the same side. The blood vessels arc dilated. There is a center in the superior colliculi for the control of sympathetic fibers to the eye. The path from midbrain to the connector cells in the thoracic cord is the tectospinal tract, so that a disturbance in brain stem, cervical or upper thoracic cord, upper chest, neck or interior of skull can lead to changes in sympathetic innervation of the eye.

Skin. Fibers to the eccrine sweat glands are anatomically sympathetic but functionally cholinergic. The apocrine sweat glands are probably activated by circulating adrenalin. The erector pili muscles are smooth muscle fibers which erect the hairs and produce the appearance of goose skin in man when stimulated. Smooth muscles around the anus and vagina are stimulated by the sympathetic system as is the retractor penis muscle. The cutaneous arterioles, veins and capillaries are sympathetically innervated, causing vasoconstriction, although some fibers have been shown to be dilator in function.

Thoracic Viscera. Connector fibers in animals go to the stellate ganglion and in man to all three ganglia of the cervical sympathetic chain. Postganglionic fibers go to the heart and increase the force of contraction, rate, conductivity, and excitability. The bronchi are dilated by inhibition of smooth muscle action in their walls and pulmonary arteries are constricted. The coronary arteries are dilated. The cardiac innervation is important to our understanding of the prolonged QT syndrome which causes sudden death in humans, and which can be treated by surgical removal of the stellate ganglion or by the use of propranolol.[2] Other causes of sudden death have been described, believed to be related to autonomic action on the heart in at least some cases.[3]

Limbs. Sympathetic postganglionic fibers reach the limbs via the appropriate spinal nerves and are distributed to large arteries, skin, and skeletal muscle vessels. Some preganglionic fibers in the lower limb end in ganglia outside the sympathetic chain which might account for some failures of symparhectomy.[4]

Abdomen. Preganglionic fibers to abdominal structures pass through the ganglia of the sympathetic chain without relaying and continue as the splanchnic nerves which are therefore still preganglionic. They relay in the celiac, superior mesenteric, renal, spermatic and ovarian ganglia, and in the hypogastric ganglia on the lateral walls of the rectum. Postganglionic fibers pass to the various organs via the large arteries which supply them. The system is distributed to the small and large intestine and related sphincters. It supplies the pyloric sphincter, pyloric region of the stomach, and cardiac sphincter. There are no sympathetic fibers to the esophagus. Electrical stimulation of splanchnic nerves causes inhibition of peristaltic movements and diminution of tone throughout the intestine, together with stimulation of the sphincters which become tightly closed. This distribution of functional response is emphasized since it is theoretically possible to produce pathophysiologic or functional changes by a chronically unbalanced autonomic stimulation of one system relative to the other. Sympathetic stimulation throughout the splanchnic area causes arteriolar constriction, and forms an important part of "peripheral resistance" where shifts in blood volume take place. The detrusor muscle of the bladder is inhibited, whereas the sphincter and trigonal area are contracted. The muscle coat of the epididymis, ejaculatory ducts, seminal vesicles and prostate are stimulated with the result that ejaculation of semen occurs. The ureters, uterus, Fallopian tubes and *vas deferens* receive both motor and inhibitory fibers without supply from the parasympathetic. Understanding of the physiological effects within the organs of reproduction is necessary to appreciation of common abnormalities and distortions of sexual relationships such as impotence, failure to ejaculate, or unusual emotional states during coitus. Although the parasympathetic system is yet to be considered in this discourse, it is worth drawing attention to the fact that erection of the penis is caused by stimulation of this system and, therefore, the completion of successful coitus in man is highly dependent upon a balanced relation between adrenergic and cholinergic stimulus. Sympathetic secretory fibers are supplied to the adrenal medulla and cause discharge of adrenalin and noradrenalin. Thus, all forms of both physical and psychic stimulus, which may be viewed generally as stressful, will produce a compound adrenergic response involving both the autonomic and endocrine systems.

PARASYMPATHETIC SYSTEM

Anatomically the system consists of the sacral and cranial divisions. Connector cells for the sacral outflow lie in the second and third segments of the sacral cord, the preganlionic fibers passing out in their corresponding ventral roots to form a single nerve on each side called the pelvic nerves. The cell ganglia are found in the vicinity of the substance of the innervated organs. Relays in the hypogastric ganglia on the lateral walls of the rectum supply the bladder, prostate, most of the large intestine and the blood vessels of the penis. Functionally, the system stimulates the detrusor muscle of the bladder and inhibits the sphincter. The colon and rectum contract and the anal sphincters are relaxed. Erection of the penis and clitoris is stimulated.

The cranial outflow of the parasympathetic system is intimately related to certain cranial nerves, and it is necessary to review the anatomy in terms of the normal and abnormal responses which have to be interpreted in consideration of the overall autonomic balance.

CRANIAL NERVES

Tenth Nerve. Afferent neurones have their cell bodies in the nodose and jugular ganglia. The central axons enter the medulla and pass to the dorsal nucleus of the vagus and the nucleus of the *tractus solitarius.* The dorsal nucleus, situated in the floor of the fourth ventrical, contains connector cells for both somatic and autonomic systems or the equivalent of both dorsal horn and lateral horn cells of the cord. There are also cells which give rise to fibers ending in the *nucleus ambiguus* which supplies the muscles of the larynx, and certain preganlionic fibers pass into the vagus nerve without relaying to reach some viscera where their appropriate ganglia are found in the substance of the organ. Ganglion cells for regulating functional control of the heart lie in the sinuatrial and atrioventricular nodes. The postganglionic fibers supply the nodes, the bundle of His and its ramification, the musculature of the atrium and the base of the ventricles. The apex of the ventricles does not receive parasympathetic innervation. Constrictor fibers are distributed to the coronary arteries. This innervation carries a tonic stream of inhibitory impulses to the heart, slowing its rate, shortening the period of systole and reducing contractility.

Constrictor fibers pass to the smooth muscle in the walls of bronchi, and parasympathetic outflow is distributed throughout the alimentary canal from the esophagus to the cecum, and is motor to the peristaltic muscles while relaxing the sphincters. Auerbach's plexus, lying between the circular and longitudinal muscle coats, forms the ganglionic neurones to the muscle coat of the intestine, although only one in every hundred muscle fibers receives a nerve ending. Fibers also relay in Meissner's plexus in the submucous coat, the postganglionic fibers passing to the mucous membrane. Arterioles are dilated by this system. Secretory fibres go to the glands in the stomach, the secreting alveoli of the pancreas, and the islets of Langerhans. The functional significance of a distribution to the gallbladder, liver, and kidneys is unknown.

Ninth Nerve. The dorsal nucleus is continuous with the corresponding nucleus of the vagus and is a compound fusion of cells equivalent to the dorsal and lateral horn cord cells. Connector cells give rise to fibers which pass via the tympanic nerve and the small superficial petrosal nerve to the otic ganglion where relays send postganglionic fibers which join the auriculotemporal nerve to reach the parotid gland and supply it with secretory and vasodilator fibers. Afferent fibers from the posterior third of the tongue enter the brain stem along the ninth cranial nerve and pass to the dorsal nucleus, so that afferent impulses readily produce a reflex flow of parotid saliva.

Seventh Nerve. The nucleus is similar in structure to that already outlined in the ninth and tenth nerves. Preganglionic fibers join the facial nerve and pass via the great superficial petrosal nerve to the sphenopalatine ganglion. Relays distribute postganglionic fibers to the lacrimal gland and to the smooth muscle, vessels, and the glands in the palate and nasopharynx. Other preganglionic fibers pass from the facial nerve via the *chorda tympani* to the lingual nerve and relay in ganglia in the vicinity of the submaxillary and sublingual glands, giving rise to secretory and vasodilatory fibers. The *nervus intermedius* conveys taste fibers from the anterior two thirds of

the tongue to the dorsal nucleus and establishes a reflex arc for secretion of saliva from these glands.

Third Nerve. The preganglionic fibers leave the third nerve to end in the ciliary ganglion, relaying motor fibers to the ciliary muscle and pupillary sphincter.

AUTONOMIC BALANCE

It is obvious that the opposing forces of the sympathetic and parasympathetic systems is the key to maintaining a balance of function throughout the entire organism. If the entire sympathetic system is removed in the cat or dog under experimental conditions, apparent "good health" remains. Reproduction in the female occurs, the blood pressure shows only a temporary fall, and the blood vessels maintain a sufficient degree of tone for peripheral resistance. The heart rate and size of pupil quickly return to normal.

With emotional stimulus, however, there is no change in blood sugar, no increase in red blood cell count and no rise of blood pressure as would be normally seen. The animals are sensitive to cold and lose heat more rapidly than intact animals. They are apparently able to maintain a placid existence, but do not respond to stress as well — although even this is not always in evidence, for some of the animals are able to run or fight as vigorously as intact animals. It is possible that alternative "back up" mechanisms of adaptation may be mediated through the endocrine system alone, as was shown by the detailed writings of Selye and others, to which reference has already been made. Balance between the two systems in an intact animal must be maintained by a constant supply of afferent or "input" signals, and the response is dependent upon the result of data processing which is carried out in the central control within the brain. The brain stem, hypothalamus, and cerebral cortex all play a part in the control.

Central Control of the Autonomic System. The vasomotor center, situated in the floor of the fourth ventricle maintains arteriolar and venous tone by means of vasoconstrictor fibers relayed in the sympathetic system. Asphyxia increases the frequency of the tonic impulses and there is variation with the phases of respiration. The respiratory centers are directly connected with the vasomotor center and are related functionally. Stimulation of an inspiratory center in the medial region of the medullary reticular formation causes an inspiratory movement which is sustained during the stimulus. Stimulation of a more dorso laterally placed expiratory center causes expiration. An apneustic center in the lower and mid pons and a pneumotaxic center in the rostral pons constitute the higher centers for autonomic respiratory control. The exact relation of these centers with the overall function of automatic respiration is poorly understood, but it is clear that the mechanism is dependent also on afferent vagal impulses which are stimulated by stretch receptors in pulmonary tissue and bronchioles. It is also clear that lesions within the brain stem and pons can have differing effects on the rate and patterning of automatic respiration, and that obstructive phenomena in the respiratory tract can have important effects on the central mechanism by afferent vagal impulses.

The physiology of the hypothalamus is easier to understand when it is recognized as a neuroendocrine organ, representing the bridge between the reception of afferent nervous impulses and the "executive command" which is mediated through a combination of efferenr autonomic and somatic impulses and the endocrine system. The bodily changes produced by emotional stimuli are well recognized and certainly do not require detailing. Kaada [5] showed that the limbic system represents the primary area of control of autonomic function in the forebrain, and the hypothalamus is considered to be part of this system. The impact of emotional input and expressions of anger, pleasure, fear and so forth, are best considered by referring to a textbook of physiology. Some aspects of function must be mentioned in reference to later discussion.

From a functional point of view the hypothalamus was described by Chatfield [6] as being divided into an anterior portion, "stimulation of which gives rise mostly to parasympathetic responses, and a posterior portion, stimulation of which gives rise

mostly to sympathetic responses." Stimulation of posterior hypothalamic nuclei causes hypertension, tachycardia, vasoconstriction, shivering and pupillary dilation. Somatic responses involve struggling in the anesthetized animal. Ablation removes this response and the body temperature responds passively to its surroundings, the animal being unable to protect itself against rising environmental temperature. Electrical stimulation of the anterior nuclei causes panting, sweating, and vasodilatation, all the mechanisms which play a part in heat loss and are parasympathetic in action. Destruction of this area abolishes these somatic and autonomic reactions when the animal is exposed to a raised environmental temperature. The descending pathways from this rostrally placed heat responsive center pass caudally through the lateral hypothalamic areas and may be interrupted by lesions of the caudal hypothalamus. Damage to this automatic mechanism presumably results in failure to adjust to overproduction of heat energy by the animal itself, and could be looked at seriously as a cause of fever in certain seizure disorders in humans, fever of unknown cause, or even the concept of so-called psychosomatic fever.

Bilateral lesions in the ventromedial nuclei cause hyperphagia resulting in obesity; lateral hypothalamic lesions produce anorexia. The evidence of the presence of "glucoreceptors" in the ventromedial satiety center by injecting gold thioglucose into rats, producing hyperphagia, is of great interest. These facts raise important questions in attempting to manage changes in "food-drive" in man, for it is clear that abnormalities of the hypothalamus override the so-called "hunger contractions" of the stomach, which are equally clearly related to sensations of hunger Certainly, the concept of a simple reflex arc between the stomach and hypothalamus can be defined and the mechanism is mediated through afferent and efferent autonomic impulses. The hypothalamic relation to thirst is well recognized also.

Destruction of the posterior hypothalamus in a cat abolishes the behavioural patterns of estrus, and the transection of the brain stem immediately rostral to the thalamus causes the remarkable reaction known as "sham rage." Trivial stimuli cause this vicious reaction in the experimentally treated animal, and can be evoked in the conscious animal by electrical stimulation of the posterolateral hypothalamus. It is considered that the neocortex may lower the threshold of rage reactions and that the amygdala and limbic cortex exert inhibitory effects on the hypothalamic rage reaction, but the associations vary in different species and are not clearly defined. Hypothalamic lesions and head injury in man have been known to cause sham rage syndrome.

It must be concluded that the limbic system has a fundamental role in automatic regulations and may involve the total concept of "intelligence" as well as reflex reactions. That the cerebral cortex has a large part to play in autonomic function is shown by the results of stimulating prefrontal areas in monkeys. The connections are with the hypothalamus and brain stem. Thus, stimulation of the cortex referred to as area 13 produces changes in heartrate, blood pressure, and breathing. Stimulation of the central end of vagus fibers from the lungs produces activity in this area, and no other area, of the neocortex. Stimulation of area 8 affects motility and secretory activity of the alimentory canal.

CHEMICAL TRANSMISSION

The preganglionic fibers of both the parasympathetic and the sympathetic systems are cholinergic or liberate acetylcholine. Postganglionic fibers in the parasympathetic system are cholinergic, whereas those in the sympathetic system are adrenergic, or release noradrenaline. The cholinergic nature of the eccrine sweat glands has been mentioned. The actions of acetylcholine are:

1) direct peripheral vasodilation in the arteriolar and capillary system,
2) "muscarinic" action which refers to its effect upon parasympathetically innervated structures,[5]
3) "nicotine" action in reference to its stimulatory effect on all autonomic ganglia. Nicotine has the same action in small doses but inhibits the ganglion in large doses. It is not necessary to detail the physiologic response of the viscera to acetylcholine, but certain important features may be underlined to appreciate certain pathophysiologic phenomena considered later.

If acetylcholine is injected into a cat in doses less than 0.01 ug, it lowers the blood pressure by its peripheral effect on blood vessels. This dilator action is abolished by atropine. Larger doses produce slowing and decreased contraction of the heart, which results in considerable fall in blood pressure due to a vagus effect. After injections of atropine, large doses of acetylcholine produce a marked rise in blood pressure and cardiac acceleration due to stimulation of the sympathetic ganglia, and adrenalin is discharged. This action is enhanced after destruction of the medulla and spinal cord. It slows, weakens or arrests the isolated perfused heart. If it is injected into human skin there is total vasodilatation, sweating, and stimulation of pain receptors. Its actions on the central nervous system are excitatory or inhibitory according to the experimental conditions. It is rapidly hydrolyzed in alkaline solution at room temperature to form choline, and this instability partly explains the transient nature of its action. Cholinesterase accelerates its destruction and this can be influenced by drugs that inhibit the action of this enzyme.

Adrenalin, formed biochemically from tyrosine, affects all sympathetically innervated structures and has an action similar to that produced by sympathetic stimulation. Noradrenaline, its immediate precursor, acts similarly but is more potent in elevating blood pressure and less potent in relaxing smooth muscle. There are other differences between noradrenaline and its methylated derivative, adrenalin, but it may be said broadly that they are essentially the neurotransmitters which together are responsible for the mediation of sympathetic response. The physiologic effect of the normal system is the key to understanding the pathophysiology of an abnormal system and is to be considered under the heading of dysautonomia. It is clear that the sympathetic system is the "fight-or-flight" mechanism and is obviously of vital importance to survival.

The parasympathetic mechanism might be regarded as the "rest-and-be-thankful" system. In the first case the organism will be directed to integrate its entire activity to escaping from a threatening situation. At this stage of crisis, there is no room for eating, and appetite is turned off. There is no room for total sexual activity, defecation or micturition, and the metabolic system must be turned into a strictly self-supporting mechanism that mobilizes fuel and empties the storage depots in order to provide it. Above all, it is essential that proper fuel in the form of glucose is provided to the central nervous system, which is the control center for organizing the whole systematized reaction. It is useful to return to the concept of "total" sexual activity, because the review of physiologic activity of autonomia reveals that penile erection is under parasympathetic control, but ejaculation appears to be governed by sympathetic activity. Thus, the act of procreation clearly demands a balance in the system and raises the question of when the "switch" occurs from one system to the other. It is presumably governed by the "input" from the sensory apparatus which eventually mediates orgasm as the crescendo of sensation reaches its climax. It would be surprising if the recuperation activities of the organism were not part of the parasympathetic response, and therefore it would be expected that the necessary changes in intermediary metabolism would be brought about by stimulus from this system. Although there is no direct evidence for this at the present time, there is certainly evidence for endocrine influence, and this in turn may well be under strict control through the activating compounds synthesized by the hypothalamus, the connecting link between the two systems.

We shall return later to the meaning of autonomic "balance" and its fundamental importance in preventing "ease" becoming "disease." The concept has long been recognized by philosophy and is embodied in the phrase "to keep body and soul together," or by more primitive and simplistic codes such as "keep the bowels open and trust in the Lord." Thus, philosophy recognizes that the health of man is partly a spiritual or mental phenomenon which has to be welded to purely physical or structural dynamics. It is suggested that a thorough knowledge of autonomic function may be used to interpret clinically observed changes which represent an imbalance which may then lead to structural abnormality termed "organic" as it refers to the target organ or organs. The effects of nutrition upon various neurotransmitters are now better understood ' and new concepts are developing in perceiving how human behavioural characteristics relate to the quantity and quality of food. This may be a phenomenon affecting individuals or

perhaps ethnic groups where food rituals are part of religious or historical inheritance. It may well be a basic feature of future therapy, particularly in disorders of the nervous system.

Chapter 2

FAMILIAL DYSAUTONOMIA AND RELATED SYNDROMES

Many examples of autonomic dysfunction have been reported. As isolated cases they add little to our knowledge of their etiology and do not give any clear picture of how common such cases are. In this chapter some of the literature is reviewed to clarify what is meant by the term dysautonomia, and the relation with sudden death is examined. The different syndromes that could arise from selective malfunction can easily be imagined, and understanding each would involve detailed knowledge of catecholamine and acetylcholine chemistry as well as an ability to keep in mind the normal physiology.

The best example of dysautonomia is that referred to as familial dysautonomia [1], an inherited condition which is limited primarily to Ashkenazic Jews. The primary lesion in this disease is not yet clarified, and in considering it as a model it is important to remember that the nervous system is not intact because of the unknown effect of this abnormal genetic mechanism. A relatively recent review outlined the symptomatology and the general consensus of opinion regarding the pathophysiology. [2] Riley noted that failure of general body growth appears to be a regular feature despite normal growth hormone. The absence of fungiform papillae and taste buds on the tongue is considered to be related to the trophic failure of autonomic denervation. There are probably a number of reasons why the mortality is high in this disease, but unusual susceptibility to infection is well documented and not easily related to autonomic failure, unless it is recognized that it is part of the general system to coordinate defense mechanisms throughout the body.

A cardinal symptom is excessive sweating, especially on the head during sleep, and although sweat gland activity (apart from the apocrine glands) is sympathetically innervated, the terminal synapse is cholinergic. This is contrasted with failure to produce tears, which is also a cholinergic function and suggests that the lesion may be related to the central control of the system rather than to the synthesis of the peripheral neurotransmitter. Difficulty in feeding, choking, and defective swallowing are coupled with a failure to thrive. An affected infant exhibits vasomotor instability by frequently breaking out in a transient morbilliform rash when eating or excited, a phenomenon seen in many otherwise normal but "nervous" people. Indifference to pain and absence of deep tendon reflexes, anorexia, inappropriate emotional responses, failure to grow, and severe prostrating episodes of vomiting are characteristic phenomena that might be explained by failure in the brain stem and reticular system, although other brain mechanisms could also be involved. These symptoms are similar to those of Leigh's subacute necrotizing encephalomyelopathy (SNE),[3] a disease in which the pathology is clearly delineated in brain stem and upper cord.

Severe and progressive scoliosis occurs frequently in dysautonomic children and the known relation of recurrent pneumonia, poor muscular coordination, abnormal temperature control, and an inappropriate response to hypoxia and hypercapnea is mindful of a family that was described by Rowley et al.[4] and studied in detail by others.[5] This case was described in terms of "familial growth retardation and renal aminoaciduria," and both scoliosis and sudden death were mentioned in family members. It will be necessary to return to some of these features when considering cases where autonomic dysfunction is clearly present. Riley's excellent discussion of familial dysautonomia made it clear that there is "diffuse involvement of the total nervous system function," and that there are defective responses in both adrenergic and cholinergic systems. But the observed reactions are open to pathophysiologic interpretation and some of them are mentioned merely as clinical manifestations of known dysautonomia. Riley cites high blood pressure in response to excitement, failure of hypotension to stimulate tachycardia, and excessive hypertension induced by norepinephrine infusion, as abnormal adrenergic responses. Supersensitivity to infused methacholine resulting in a drop in arterial pressure,

sweating, tear production, and increased bowel activity are related to an abnormally sensitive cholinergic response, and reference is made also to disturbances in catecholamine metabolsim.

PRIMARY HYPOVENTILATION SYNDROME (Ondine's Curse)

Although clinical nomenclature may be inexact when the true biochemical lesion is unknown, it is noteworthy that similar abnormal catecholamine chemistry has been observed both in dysautonomia [6] and in SNE,[7] again reflecting the essentially central nature of the lesion in both diseases. Of particular interest in familial dysautonomia is the work that has been done in respiratory control, for it throws light on the phenomena that gives rise to sudden death. Filler and associates[8] stated that pathophysiology in familial dysautonomia indicates a parasympathetic insufficiency. They found a decreased sensitivity of the respiratory center to CO_2 in the disease and were able to produce serious hypoxic symptoms in three patients by decreasing the concentration of inspired oxygen. They noted that the blood was ineffectively ventilated as indicated by a sharp drop in O_2 saturation and unchanged P_ACO_2. This insensitivity and the known association of recurrent pulmonary infection is characteristic of the condition known as Ondine's Curse. This condition receives its name from a mythological character who cursed her lover by abolishing all the automatic functions of his body. He died during sleep because "he forgot to breathe" and the name was applied to a disease which behaves in this dramatic way.[9] It is illustrated by an adolescent patient known to us whose complete inability to regulate automatic respiration was triggered by infection. The paralysis, requiring a respirator for weeks or months at a time, was associated with insensitivity to inspired CO_2 and O_2, extremely severe scoliosis, short stature, and cor pulmonale, similar to the patient reported by Rowley et al.[4] and required permanent tracheostomy. Born of a first cousin marriage, she had two brothers who died suddenly after simple infections and she had renal aminoaciduria like Rowley's patient. It is noteworthy that Ondine's curse has been related to SNE,[10] also a condition in which automatic respiration is severely compromised.[3]

RADIOLOGIC SIGNS OF DYSAUTONOMIA

Grunebaum [11] drew attention to the roentgenographic findings in familial dysautonomia which included bowel and urinary bladder distension and atony of the ureters. He observed atelectasis, interstitial pneumonia with hyperinflation, and thickened bronchial walls. An 18-year old dysautonomic patient, described by this author, died of respiratory insufficiency and right ventricular failure. Autopsy revealed diffuse fibrosis of the lungs, bronchiectasis, and cor pulmonale. Distended bowel loops, abnormalities of esophageal peristalsis and pylorospasm were described. One patient had atony of the entire bowel, and atony of bladder and ureter were detected roentgenographically. Of some interest was the description of other seemingly unrelated roentgenographic observations. Retarded bone age, coxa valga, scoliosis, and soft tissue swellings around the knees or ankle joints were regarded as the result of muscular imbalance and sensory disturbance, but could just as easily be ascribed to changes in blood supply or atrophic changes from denervation. All these phenomena might be explained by cholinergic inability to oppose or balance the adrenergic system.

PROTEAN NATURE OF DYSAUTONOMIA

One of the five original patients described by Riley et al.[1] illustrated well the protean nature of dysautonomia, including nocturnal death. This patient remained under surveillance by other investigators from the age of six years until her mysterious death at age 31 years.[12] Recurrent vomiting, acrocyanosis, cold hands, blotchy areas of cyanosis and erythema, symptoms which were absent during sleep, would be most readily apparent on awakening in the morning, or during excitement, and diminish as the day progressed. Developmental milestones were delayed and fecal soiling persisted to age four years. She vomited five or six times a day and this was provoked by nervousness. Nervousness, emotional lability, and temper outbursts made schooling a problem. At least one episode of apparent bowel obstruction

cleared spontaneously. An electroencephalogram was abnormal. It is to be noted that this case was interpreted as sympathetic overactivity. Cholinergic underactivity was not considered. When she was 26 years old "compulsive vomiting" occurred every morning and she still suffered profuse nocturnal sweating, both of which were exacerbated by emotional excitement, and she "appeared tense." Slurring of speech, ataxia, failure to perceive the sensation of coldness, mild tremor, and absent tendon reflexes illustrated her central neurologic defect. Her recognition of her own nervousness caused her to try to overcome this by forcing herself to social activity. In recognizing the many faceted symptoms of dysautonomia it was important that she had abdominal pains severe enough to study by roentgenography, the results of which were negative. Sexual conflicts were described in this patient, a complicated function involving the psyche, limbic system, and peripheral autonomic system. Her death during sleep was totally unexpected, and acute pulmonary congestion and acute congestion of liver and spleen were considered to be due to acute cardiac failure or dysautonomic function. This patient had a female sibling who died of "pneumonia" at age 2½ years; this child had always been considered weak and ailing. Interestingly, she had suffered from "asthma, cold hands and drooling," suggesting that she may have had some dysautonomic function also.

INCOMPLETE DYSAUTONOMIA

The phenomena which have been reviewed must be extremely common if we are to judge from our personal experience. Though such cases may be seen by experienced clinicians, laboratory data are either noncontributory in understanding or not detected by usual methods and usually classified as functional. Riley and Moore[13] described an 8-year-old non-Jewish boy with malabsorption syndrome, imperfect bladder control, ichthyotic skin, recurrent skin infection, and indifference to pain. A history of pneumonia and a "rattly chest" for several months during infancy and deliberate "tongue chewing" were observations which we have recognized in similar cases. They described the features considered to be against the diagnosis of familial dysautonomia in this patient, and reviewed the case of another child whose neonatal period was marked by indirect jaundice. Constant irritability, acute gastroenteritis, numerous upper respiratory infections, retarded development, hypotonia, indifference to pain which disappeared spontaneously, and an absence of overflow tears gave rise to a consideration of the diagnosis of familial dysautonomia, but again the syndrome was incomplete.

In 1975 two adult males were reported with a syndrome of pandysautonomia.[14] One was a 37-year-old man whose illness began suddenly with upper abdominal pain, diarrhea, and a sensation of heat and flushing in the abdomen and extremities. Dilated unreactive pupils, blurred vision, loss of consciousness, headache, insomnia, nocturnal polyuria, impotence, difficulty in micturition, and diarrhea were accompanied by low serum concentrations of sodium and chloride, an increase in serum potassium, and stomach hypoacidity. This man demonstrated piloerection after 0.1% epinephrine. Only mentioned tangentially and not discussed at all was the fact that this patient showed signs of malnutrition, although no diet history was given. The second case, a 43-year-old man, suffered fatigue and low back pain, blurred vision, dry mouth, vomiting, anorexia, impotence, loss of consciousness and was "undernourished." Both patients benefitted from the use of fluorinated hydrocortisone. No attempt to improve nutrition was described.

DYSAUTONOMIA IN ASSOCIATION WITH OTHER DISEASE

Dysautonomic responses were reported in five diabetic subjects by demonstration of abnormal cardiovascular reflexes,[15] and insulinopenia has been demonstrated in familial dysautonomia.[16] Perhaps in some cases diabetes mellitus starts with dysautonomic function which results in ineffective stimulus for insulin release from the pancreas. Peripheral neuropathy may then be the cause of abnormal carbohydrate metabolism rather than a sequel to insulin deficiency. If this were true, adequate therapy by control of carbohydrate ingestion and insulin would not affect the primary neuropathy. Insulin dependency would be expected when atrophic changes had developed in the Islets of Langerhans as a result of a period of

denervation as has been suggested as the cause of absent fungiform papillae in familial dysautonomia.[2]

Rubin and associates[17] were among several investigators to point out autonomic abnormality in cystic fibrosis. They suggested that the generalized pathophysiology of the exocrine glands in the disease was related to autonomic innervation and used pupillary reactivity to test the hypothesis. They deliberately chose a "nonglandular" organ for testing to ascertain whether autonomic function was changed in organs other than those which are directly concerned in the disease process. They concluded that patients with cystic fibrosis whom they tested were "deficient in the quantity of adrenergic mediator" as measured by a defective pupillary response in the eye. Two of these investigators showed that patients with cystic fibrosis demonstrated increased sensitivity to stimulation of the parotid glands after administration of methacholine chloride.[18]

Farber claimed experimental production of cystic fibrosis in cats by injecting pilocarpine and noted that one of the striking features of the experiment was the severe degree of malnutrition exhibited by the animals.[19] Roberts [20] published a strong plea in favor of the hypothesis that the disease was a result of prolonged chronic cholinergic stimulation. Whether the disease is caused solely by such disturbed neurologic function or is only part of the picture is unknown and untested, but it certainly introduces the clinician to an idea which is usually foreign to him. That a process within the lung and other organs might really be conditioned by the brain or part of the nervous system is not easy to contemplate with our present ideology of disease, which is considered to be "organic" or "psychological." That a mental state could equally well be a disturbance of the autonomic system is also an unusual concept, but it has been recognized that functionally psychotic adults and autistic children have a clearly defined peripheral dysfunction in this system.[21] A discussion of psychosis as a "disordered response to stress" was also published by the same author[22] who found abnormal pupillary responses in patients. He suggested a lack of "balance" between adrenergic and cholinergic mechanisms.

Modern support has come out strongly in favor of this concept in the etiology of cystic fibrosis by the finding that cells from patients with the disease synthesize more cyclic AMP than normal cells when stimulated with isoproterenol.[23] Exciting vistas have been opened up also by the discovery that calcium, in cooperation with the calcium binding protein calmodulin, can alter cyclic AMP concentrations in the emerging knowledge of biologic activation within the cell.[24] This may now produce a new and completely different approach to therapy of cystic fibrosis, since cells from patients with the disease have been found to have increased calmodulin concentrations.[25] A recent article reported the case of an obese boy with hyperphagia, whose respiratory mechanism was defective.[26] The liver in this patient was enlarged and filled with lipid, thought to be related to the obesity. It is possible that this finding was a result of disordered energy metabolism in a manner similar to that seen in the liver in diabetes. Since it has already been pointed out that central mechanisms may be primary in diabetes,[15] it is pertinent to ask whether the liver pathology was primary in a patient with evidence of central nervous system defect, whether it may have been a biochemical defect affecting cell membrane function in both liver cells and brain cells at the same time, or even whether it might have been produced because of central failure in maintaining the normal coordination of whole body metabolism. The discovery of a genetic mechanism in cystic fibrosis has clarified the mechanisms involved but has, as yet, not helped in treatment. The clinical problems remain.

AUTONOMIC AND ENDOCRINE RESPONSE TO STRESS

Some evidence exists that dysautonomia is an important part of many different diseases, and numerous investigators have reported this association without showing that it is directly causative. Selye has attempted to show that many diseases are related to stress and has certainly proved the phenomenon in experimental animals.[27] Perhaps his study of the integrated endocrine relationships was only part of the picture and indeed Selye repeatedly drew attention to the role of the autonomic

system. Everyone is conversant with symptoms related to the sypathetic response to almost any stress in daily life. Pallor, sweating, tachycardia, and feelings of rage, anger, fear and shivering are just as well recognized by the athlete as the student about to take an exam. Therefore, the physical or "organic" reactions are predictable if such an unbalanced state of affairs should exist chronically. It is not too difficult to associate the blanching pallor of the face with a change in the arteriolar blood supply, but it is a reaction which might as easily apply to the kidney or the colon. Thus, a genetic defect or an acquired hypoxia in the hypothalamus or the reticular system might easily be the true etiology of the organ system disease which follows.

These well-known symptoms of "fight-or-flight" must be considered to be related to survival and preparation of any animal, including man, for the action required. The tension engendered is designed for short-term explosive action, and mobilization of energy reserves is mandatory. Thus oxygen and glucose are required for oxidative metabolism and the non-caloric catalysts of this process are "used up" faster. Since the whole system is rearranged through neuroendocrine activity it might be important to recognize the distinctive physiology as a source of sequential pathophysiology, perhaps nowhere epitomized better than in the well known changes in the bowel. Peristalsis is stopped and sphincters are closed. Adrenergic neurotransmission constricts the arterioles and oxidative metabolism is decreased. If this reaction were to persist on a chronic long term basis the resulting hypoxia of tissue would result ultimately in a fall in concentration of ATP and possibly be followed by cell death and destruction. If parasympathetic stimulus were minimized in Meissner's plexus, it would produce a tissue distribution of hypoxia different from that of Auerbach's plexus and a hypothesis could be derived to explain the essential underlying difference between mucosal ulcerative colitis and transmural colitis. The overall hypothesis suggests that a functional imbalance of the neuroendocrine system is induced by a chronic state of preparation for action which is never consummated. The entire system is geared to produce maximum escape activity on a long term basis and results in a vast waste of cellular energy.

We cannot ignore this mechanism in the civilized state, for we deny our biologic origin at our peril. It is therefore seemingly absurd that we cannot recognize a state of chronic anxiety without a proper degree of emphasis on the physical characteristics which include all the well-known features of the fight-or-flight response. Most physicians accept a “functional” condition as “psychological”, and it is difficult to pass conceptually from there to a state of organic disease. This is basically because we have never really considered the body and the mind as a machine unit which has to obey natural laws of energy utilization just like any man made machine. Biochemistry therefore cannot be reserved for the study of rare and exotic disorders. It must be used and applied in considering common symptoms such as headache and fatigue, where the organism is intact. Symptoms may really be signals perceived by the brain which direct attention to the organ member which is having difficulties. To ablate the symptom without knowing why the signal was originated is equivalent to destroying an important telegram without reading it first. If a given organ is required to work unusually hard, it will use energy in the process and may run into a state of chemical starvation which would include the deficiency of either fuel, oxygen, or catalyst.

This concept has given rise to the notion that many poorly understood aspects of human disease are brought about by the most basic phenomenon of life, a failure to meet an essential energy budget. The symptomatology which gives rise to the functional state of "loss of ease" is potentially the first stage of a progressive condition which finally leads to cellular damage. The symptomatology at this stage may well be a result of the amount of stimulation resulting from environmental factors which may be defined as "stress" and the total ability of the organism to meet the threat appropriately and control it. An invading organism is met by an organized response which involves an increased rate of metabolism. Fever, increased numbers of white cells and vascular changes which we call inflammation, are well-known examples of this response. If such an invasion is not met by this response, we know that the organism is in a state of low resistance and will quickly succumb to the infection.

By using the model of familial dysautonomia it is possible to see that dysautonomic function is a remarkably common phenomenon. We have attempted to obtain ways and means of studying this effect by the use of some relatively simple laboratory tools which will be discussed later.

THE SYNDROME OF FUNCTIONAL DYSAUTONOMIA

Close observation of a large number of patients reveals that dysautonomic symptoms are frequently seen in many conditions. Whether they reveal the underlying cause of the disease, or at least provide clues, would be of great importance. Tables 1-5 list a group of conditions in which dysautonomic function has been described. This list is probably not complete, but serves as an example of what has been observed by others, either in individual and isolated case reports, or as an auxiliary factor known to be associated with diseases deemed to be due to causes which are considered unrelated to autonomic activity.

TABLE 1
Diseases in which autonomic dysfunction has been described

1. Familial Dysautonomia.'
2. Leigh's Disease.[3]
3. Sudden Infant Death Syndrome.[28]
4. Diabetes Mellitus.[29]
5. Psychosis.[21 22]
6. Cystic Fibrosis.[17]
7. Shy-drager Syndrome.[30]
8. Primary Orthostatic Hypotension.[31]
9. Bronchogenic Carcinoma.[32]
10. Wernicke Disease.[33]
11. Primary Systemic Amyloidosis.[34]
12. Acute Pandysautonomia.[14 35 36 37]
13. Adie's Syndrome.[38]
14. Post Traumatic Cephalalgia.[39]

TABLE 2
Functional grouping of abnormal findings in familial dysautonomia

1. Apparent Efferent Nerve Dysfunction
    - Lack of tearing
    - Poor muscular coordination
    - Defective esophageal peristalsis
    - Partially denervated muscle
    - Abnormal response of pupil to topical methacholine
2. Apparent Afferent Nerve Dysfunction
    - Defect in taste, occasionally in smell
    - Relative indifference to pain
    - Defect in proprioception
    - Lack of flare and pain response to intradermal histamine
3. Lack of Appropriate Reflex Response to Varying Stimuli
    - Absent deep tendon reflexes
    - Inappropriate temperature control
    - Postural hypotension
    - Lack of ventilatory response to hypoxia and hypercapnia
    - Lack of tachycardia in response to methacholine induced hypotension
    - Tachycardia and excessive hypertension in response to norepinephrine
    - Lack of epinephrine liberation in response to hypoglycemia
4. Other
    - Normal cranial nerve nuclei
    - Absent fungiform papillae (? inappropriate embryonic innervation)
    - Inconstant CNS pathologic changes
    - ? Abnormal distribution of pressor amine metabolites in urine
    - Tongue Chewing (?)

TABLE 3
Additional Less Common Findings in Familial Dysautonomia [12]

1. Autonomic
    - Peripheral vascular disturbances
    - Hypertension with excitement
    - Erythematous skin blotching after eating or excitement
    - Cold hands and feet
    - Excessive sweating
    - Disturbed swallowing
    - Diarrhea or constipation
    - Drooling beyond the usual age
    - Periodic vomiting
2. Voluntary CNS
    - Poor motor coordination
    - Scoliosis; other orthopedic conditions
    - Dysarthria
    - Convulsions
    - Abnormal EEG
3. Sensory Disturbances
    - Dysesrhesia (bizarre response to painful stimuli)
4. Psychologic
    - Apparent reduction of intellectual capacity
    - Breath-holding in infancy
    - Emotional lability
5. Other
    - Corneal ulceration
    - Frequent pulmonary infections
    - Growth retardation
    - Allergic manifestations
    - Sudden death Insulinopenia [16]

TABLE 4 Roentgenological Signs in Familial Dysautonomia [11]

1. Pulmonary
    - "aspiration" pneumonia
    - atelectasis
    - peribronchitis
    - bronchiectasis
2. Abdominal
    - bowel loop distension
    - air fluid levels
    - atony
3. Esophagus
    - lower and upper sphincter spasm
    - hypomotility
    - atony
4. Urinary tract
    - ureteric atony
    - dye remaining in bladder after voiding

TABLE 5 Symptoms and Signs in Adults with Pandysautonomia [14 35 36 37]

Postural hypotension	Fixed heart rate
Absent sweating	Dry mucous membranes
Unreactive pupils	Decreased bowel motility
Hypotonic bladder	Diabetes
Increased CSF protein	Alternating constipation and diarrhea
Unexplained ileus	Dizziness
Uncontrolled shivering	Loss of Consciousness
Photophobia	Vasomoter paralysis
Deep tendon reflexes only with reinforcement	Poor heat tolerance
Impotence	Hyponatremia
Fatigue	Hypochloremia
Lumbago	Hyperkalemia
Pain in jaw	Hypoacidity
Anorexia	Weight Loss
Vomiting	Oval pupils
Hypersensitive effector responses to neurotransmitters	

FUNCTIONAL DYSAUTONOMIA; CLINICAL PRESENTATION

Most of our patients have been children or adolescents and selected case reports are presented in Chapter 5. A small number of adult patients have also been examined. Dysautonomic features vary considerably and would readily be equated with "anxiety state, neurosis, functional disease or hysteria." We believe that these symptoms are merely a means of signalling an energy crisis in mobilizing the metabolic response required to meet environmental stress. If, for example, fever is a normal component of a computerized defense organization against invading organisms, then "fever of unknown cause" may be an inappropriate internal response generated by a signal to the brain, which is not related to any such infectious invasion. In terms of our normal perception of the cause of fever, it would automatically give rise to a search for infection that may be in truth nonexistent. Such a concept embraces the notion that the brain is a computer which reacts to input data without necessarily interpreting the correct reason for the incoming signals. It would permit us to accept "psychosomatic fever" as a clinical possibility without thinking that the patient "put it on voluntarily." Indeed, one of the radical changes that must be made in such an ideological context is that there is a distinct difference between psychosomatic disease ("loss of ease") and malingering. Therefore, our interest has been generated by accepting that if the patient expresses a given symptom — pain for example — there must be a mechanism in terms of neurological and biological transmission. The idea of malingering has unfortunately been projected to many genuinely sick patients, and this is reflected by such expressions as "the doctor said that it was all in my head." In a sense this is true, since the brain is receiving distress signals which throw no light on the site of somatic reference by clinical examination. Because of a need for concrete evidence such as redness, or swelling, or other outward sign, the physician may deem the situation to be "functional" and explain it to the patient as "it is your nerves." If enough knowledge of the cellular system in a localized area were available, it would probably be found that a state equivalent to cellular hypoxia was giving rise to the distress signals. Obviously, the symptom can be relieved by "reassurance" since this would alleviate some of the input data and may be an explanation for the so-called "placebo effect." By the same token, the patient's lack of acceptance might be expected to cause more pain and discomfort through the generation of anger or fear, which only subserves further expenditure of energy.

In pediatric practice the young patient's symptoms may be turned into a vicious circle by the natural anxiety of the parent. The concern generates fear and becomes a stress factor in itself. Overprotection of a child is the most stressful influence that he can meet. Every physician knows that he makes his patient worse when he displays his own anxiety, and the "bedside manner" is a careful cultivation of personality to

project an air of competence and skill which enables the patient to accept that he is in good hands. An acute and relatively trivial illness in a child may quickly be extinguished when appropriate and efficient concern, without anxiety, is expressed, and assuming that the child's defense mechanisms are intact and efficient. It is also possible to see why proper nutrition is required, since the development of an energy consuming and widespread metabolic response requires appropriate fuel.

Using known symptoms of dysautonomic function, as already considered, we have recognized many patients we believe to be representative of a condition which we have called functional dysautonomia.[40] In many instances the environmental or family stress factors are only exceeded by the enormity of the diet.[41] Much of the stress is easily perceived at the parental level and usually remains as the most important factor to be manipulated, where possible. Headache, fatigue, abdominal pain, and fevers of unknown causes are commonly associated with chronic or recurrent nasal congestion, all symptoms which are extremely common in any physician's office and are attributed to various causes. A popular explanation for nasal congestion and other upper respiratory symptoms is allergy. The small, overprotected child is relatively infantilized, pernickety, unhappy and excessively irritable, sleeps restlessly at night and has nocturnal symptoms which include frequent awakening, sometimes with a start, night terrors, sleep talking, somnambulism, restlessness during sleep, and sweating, particularly on the scalp and forehead. Enuresis is also common. Older children and adolescents have similar symptoms and exhibit this pattern at night, but can also describe their unpleasant and frequently repetitive dreams. This was epitomized by an adolescent girl with extreme anxiety who dreamed repeatedly that she was being chased into a coffin and the lid was then screwed down upon her. She would awaken with a scream, and described the accompanying sensation of suffocation. This could be interpreted as an unusual degree of nocturnal brain hypo-oxidation firing a neocortical distress signal experienced as a vivid sense of suffocation. It should be noted, however, that if this were to be a correct interpretation it would have the benefit of logic, since it would serve to awaken the patient from a dangerous state of hypo-oxidation and thus act as a survival reflex.

Functional dysautonomia patients have other symptoms. Diarrhea, often intermittent, may alternate with constipation. The stools may be extremely large and bulky, frequently causing blockage of the toilet. This may be associated with encopresis. An enhanced gastrocolic reflex is sometimes experienced and gives rise to postprandial abdominal pain relieved by a bowel movement.

Characteristic physical signs give much information during the examination. A small child exhibits unusual fear or anger which may not become as obvious until he is placed in the supine position. This appears to be an extremely threatening position for small infants, possibly because of the "attack vulnerability" automatically perceived. Attempts to roll into the prone position, angry screaming and extreme sweating occur. All physical contact is resisted and the examiner's hand will constantly be pushed away. We have referred to this aspect of the clinical examination as the "touch-me-not" syndrome. Compulsive gagging will occasionally occur as the tongue depressor approaches the mouth and before any touch contact has been made.

The older child and adolescent show anger and frustration by such small indications as eyes raised to the ceiling or little frustrated movements of the hands or fingers. Piloerection is extremely common and is pathognomonic of sympathetic overdrive. The adolescent who complains bitterly of the cold, even on a warm day, will usually demonstrate vascular changes, particularly in the feet and lower legs. Such patients are often unable to go swimming, even in the heat of the summer, for they are unable to get warm and will sit in the sun with cyanotic lips and fingernails, teeth chattering, and shivering. There may be mottled vasculanty and even peripheral acrocyanosis, cold clammy skin, and poor capillary refill following blanching by digital pressure. The pulse may be rapid, or slow, overactive, and the pulse pressure high. Systolic and/or diastolic lability is observed, and there may be a dramatic change in the tones to pistol shot intensity at the phase II change, and a diastolic tone which is audible to zero pressure. The femoral artery can frequently be heard by auscultation over the inguinal ligament; the heart may also be markedly hyperactive,

and there may be an apical flow murmur suggestive of minimal mitral regurgitation. The patellar reflexes are frequently absent, but can be elicited by the expediency of reinforcement, a phenomenon associated with dysautonomic function already described. On the other hand, perhaps dependent upon the nature of the imbalance, the patellar reflex is sometimes unpredictable, hyperactive, "hung up" or double. Dermographia can be a useful indicator. Light stroking of the skin of the leg, particularly on the anteromedial surface, will elicit blanching which may be slow appearing and remain for a long period. This is either not seen at all or seen only lightly and transiently in the normal individual and is an excellent means of observing the therapeutic responsiveness of the patient.

Another example of the dysautonomic function is that referred to and described in the textbook of physiology as "hexamethonium man." The face is flushed, the skin warm and dermographia particularly well marked. Circumoral pallor contrasts with the flushed cheeks and is a facsimile of streptococcal flush as well as that seen characteristically in some children after atropine injection. To complete the appearance, the tongue may have a "streptococcal" appearance. It has a light coating and prominent papillae which show bright red through the coating, thus giving the tongue the superficial appearance known as strawberry tongue. With this appearance, the blood pressure may be hypotonic rather than hypertonic and the pulse pressure quite small. If the patchy morbilliform chest rash appears in such an individual it would be very easy indeed to make a diagnosis of scarlatina, although this rash is characteristically seen in patients with familial dysautonomia and appears sometimes after the patient eats or becomes "nervous." Since the rash is merely a manifestation of spotty vascular patterning, it is not too unrealistic to suggest that it is the same effect in both conditions.

The evidence favors the concept that "functional dysautonomia" is very much part of a given disease process and can be related to three rather obvious aspects. The inheritance of the individual represents a chance combination of unique characteristics which may be likened to specifications in a machine, the result of eons of natural experiment. Though the principle of structure remain the same, the differences are infinite and, thus far, genetic characteristics are not amenable to any form of medical interference other than palliative. The second component is the environment, which is automatically hostile to the organism. Assailed by bacteria, viruses, fungi, chemical toxins, barometric and other weather changes, man and all members of the animal kingdom have been equipped with various adaptations as a defense against this array of "stress factors." Survival reflexes in man are represented by the interrelated aspects of neuroendocrine response and are most vividly seen in the well-known "fight-or-flight" physiology. A failure to meet the stress adequately may well be portrayed by functional dysautonomia. The third component, and perhaps the only one over which man has any control, is the fuel that is provided for activation of the biologic processes and nutrition emerges for its very obvious contribution.

The syndrome of functional dysautonomia is illustrated quite well by a briefcase report of three families. They reveal a familial nature though it is obvious that the symptoms in themselves differ. The pathophysiological feature which the patients have in common appears to be in the response which they make to stress. It is not very surprising that we draw the conclusion that the patient is developing psychosomatic symptoms, which in some ill-defined way enable him/her to "hide away in terms of a physical illness which prevents the usual involvement in day to day activities." The denial of reality seems to be the cornerstone of such an explanation and implies a collapse of the patient's ability to cope. In essence, this is, of course, quite true and society "allows" physical illness but is still somewhat wary of a mental one.

The point at issue appears to be a most important one. The brain signals the body organs through the neuroendocrine system which is directed by the hypothalamus, — the computer. A carefully modulated signal gives rise to an appropriate response, but if the autonomic and endocrine systems are out of phase, dysautonomic symptoms would be expected. The symptoms illustrated in the two families may be compared with those listed in the earlier part of this chapter, and which have been published in cases of familial dysautonomia and pandysautonomia.

Thus there is nothing very revolutionary about the concept of dysautonomia, although it appears to be more common than individual case reports would suggest. For example, abdominal epilepsy was entertained at one time as an appropriate diagnosis, even though it was always rejected by many physicians. Essentially, the patient complains of paroxysmal abdominal pain, often with borborygmi and sometimes in association with a bowel movement or a sensation of imminent bowel movement without any result. Surely this can be pictured as a parasympathetic signal causing contraction and peristalsis. The fact that it occurs paroxysmally seems to be very similar to neuronal discharge referred to as epilepsy. Why it occurs at any particular moment is as unclear as it is in epilepsy. Unless the cause of the pain can be observed at the time that it occurs, it will never be proved, since it is a functional event.

Family I. M.D., a white male, was first seen at the age of six months with diarrhea, fever, and abdominal pain. A similar event reportedly occurred at age seven weeks and intermittent episodes of unexplained diarrhea occurred once a week. A milk-free diet was prescribed and stools became normal. One week later he had intermittent episodes of paroxysmal abdominal pain, screaming and repeated bowel movements.

At the age of 5 years he returned with a 2-year history of repeated episodes of hypopyrexia, as low as 95°F. A personality change was noted before each episode, and he would become more withdrawn. A typical attack started after a deep sleep in the early evening, during which time it was difficult or impossible to awaken him. He would then scream, sit up with widely dilated pupils, widespread piloerection, cyanosis of lips and extremely shallow slow breathing. His mother had observed that the pupils would not constrict, even in bright light. He would be totally unreactive to communication and appear to be blind. Enuresis would occur during the episode and in the morning he would have no recollection of the event. These typical night terrors occurred in clusters of two or three nights and were often followed by fever for several days, each cycle recurring every few months.

At the time of a physical examination a complex clinical presentation was observed while the patient was asleep. Widespread piloerection, bradycardia, virtually 100% abdominal respiration with no chest movement, a blood pressure of 76/20 mmHg and a brief episode of ovoid pupil in one eye were observed. Deep patellar knee reflexes were either unobtainable or would occur unpredictably with slow relaxation and he would exhibit an irritating cough on partial arousal without awakening. Facial pallor was marked and there was divergent strabismus and slow wandering movement of the eyes.

The pupils became pinpoint in size during the period of observation. Red cell transketolase activity (TKA) was 69.8 mU/L/min (normal 42.1 - 86.1) and the thiamine pyrophosphate percentage uptake or effect (TPPE) was 27.7% (normal 0 - 17.4%).

P.D., the 7-year-old sister of M.D., was examined because of a lifelong history of paroxysmal abdominal pain. Birth history revealed that her mother was toxemic in pregnancy and there had been some neonatal jaundice requiring phototherapy. Early development was normal. At the age of six weeks she had an acute episode of gastroenteritis and was chronically debilitated for a month. Following this she had chronic nasal congestion and repeated episodes of asthmatic bronchitis, mostly in the winter months. Paroxysms of abdominal pain started with apparent colic in the first year and had continued. Repeated vomiting occurred, and since the age of 4½ years she had been enuretic at night and sleep sweating was noted. She would frequently get up at night for a bowel movement. Stools were large and sometimes blocked the toilet. Abdominal pains occurred up to two or three times a day, lasted about half an hour, caused her to cry sometimes, and occasional loud borborygmi were heard. She would become pale and her skin clammy and mottled in appearance. She frequently had a headache. She described a rapid heart rate during the attack. There had been recent onset of night terrors and sleep walking. Examination was normal except for marked dermographia in the lower extremities and sluggish deep patellar tendon reflexes, which became normal with reinforcement. The family history is seen in Figure 1.

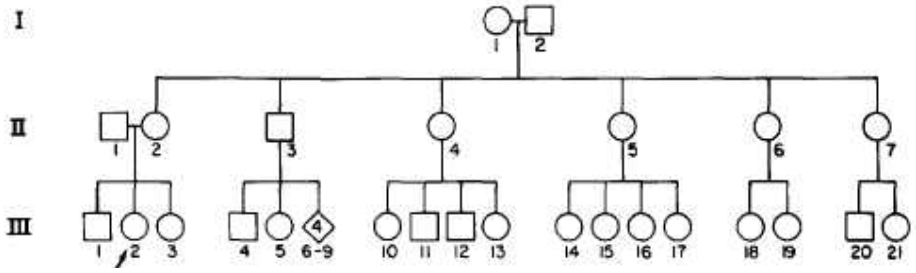


FIGURE 1

1_2	Diabetes, Atherosclerosis, Lung Cancer
11_2	Arthritis, Raynaud's Disease, Syncope
11_3	Hyperactivity
11_4	Abdominal Cancer, Paroxysmal Abdominal Pain, Syncope
$11_{5\,6\,7}$	Hyperactivity, Abdominal and Chest Pain
111_1	M.D. Case 1
111_2	Proband, P.D. Case 2
111_3	Night Terrors, Enuresis, Bruxism
111_4	Hyperactivity, Dyslexia
111_{10}	Hyperactivity, "School Problem"
111_{11}	Learning Disability, Dyslexia
111_{12}	Behavior Problem
111	Hyperactivity
111_{20}	Recurrent Bronchitis
111_{21}	Chronic Nasal Congestion, Rhinorrhea

Impression

In our present disease model, it is extremely difficult to see the two children as having similar functional events except on a purely psychological level of explanation. The functional nature is not in the least disputed. The mechanism is considered to be automatic and biologic, and is regarded as a disordered response to stress. The abnormal thiamin pyrophosphate uptake effect (TPPE} in the first child is of interest. This particular laboratory test is discussed in detail in the next chapter, but it has been shown that an accelerated uptake of TPP by red cells is clearly indicative of deficiency of vitamin B1(thiamin) in the cells being tested. Our experience indicates that this test has far-reaching implications, and that it is by no means a specific indicator of nutritional deficiency. In a patient with trisomy 21 and sleep apnea, in another patient with Prader Willi syndrome dying of cor pulmonale, and a boy who had an epileptic fit in a swimming pool and suffered prolonged hypoxia of the brain, we have seen a similar effect upon this laboratory test. It may be an excellent indicator of hypoxic oxidative stress, and this function may be more important than merely its nutritional implications.

The first child in this family had good evidence of a dysautonomic effect, particularly during sleep. The most obvious feature was general piloerection, which is physiologic proof of sympathetic activity. Widely dilated pupils and sweating are also sympathetic. On the other hand, pinpoint pupils represent evidence of parasympathetic activity, and suggest that the balance between the two systems is distorted or perhaps labile, so that there is a lack of a coordinated normal physiologic response.

Paroxysmal abdominal pain with borborygmi suggests overactive peristalsis, and this can be seen as evidence of an uncoordinated parasympathetic dominance, or overshoot. The family history certainly does not indicate a specific familial disease unless the underlying mechanism is considered in terms of appropriate biochemistry and its relationship with the autonomic and endocrine responses engendered by stress.

Family 2. D.M., 14 years and 9 months old, complained of "dizzy spells." He was a white male who was considered well until three weeks previously, when he suddenly experienced extreme fatigue while playing basketball. He was found to have pyrexia of 101°F, received an injection of penicillin, and was apparently well the next day. During the past year he had experienced minor episodes of dizziness on

standing up and, in a recent episode, had "blacked out" completely, hitting his head as he fell. It was noticed that there was some wandering of the eyes and slight tremor of the hands while he was unconscious. He admitted to ingestion of 36 ounces of cola and one quart of iced tea a day, a one-half gallon of ice cream a week, and massive supplementation of most of his food with tomato ketchup. He had occasional cardiac palpitations, and complained of pain in the chest at intervals.

On examination he was seen to be wearing tinted spectacles, and there was marked conjunctival injection. He admitted to photophobia. The heart rate was 60 bpm, the blood pressure 90/60 mmHg, and the femoral pulse easily audible by auscultation. Deep patellar reflexes were hard to elicit, but were brisk with reinforcement, and there was marked dermographia of the lower extremities. He was told to change his diet drastically, removing all the high calorie carbohydrate foods and beverages.

One year later he reported again, because of recurrence of dizziness, and admitted that he had reverted to his former dietary habits. During the year he had gained 6.4 kg in weight and 6.2 cm in height. The heart rate was 52 bpm, with mild sinus arrhythmia, and deep patellar tendon reflexes were normal. Dermographia was present. A supplement of thiamine was given in a dose of 150 mg/day, and he was again cautioned and diet instruction was given by a qualified dietician.

D.M.M., sister of D.M., was 12 years, 4 months old. She was seen in June 1981 because of an attack of numbness in the legs and general sweating. On a cool evening, while watching a ballgame, she had sudden onset of abdominal pain and profuse sweating. It was noted that she became pale, and the episode lasted about half an hour. Subsequently, there were three or four similar attacks, and at least one of them was associated with numbness in the legs. She was described as irritable, "mean — she wants to snap at you with every little thing," and she also complained of chronic fatigue. She would return from school and go to bed, although she also had insomnia. She had chronic nasal congestion, and her menstrual periods were associated with severe cramping. She admitted to consuming 32 ounces of cola and 32 ounces of iced tea every day.

On examination, her heart rate was 68 bpm, blood pressure 134/40 mmHg, with both systolic and diastolic lability. In discussing the situation with her mother, it was noticed that the mother had obvious cyanosis of the feet and hands. She observed that her heart frequently "missed a beat" and that she had had these symptoms for years.

Impression

There seems little doubt that there was at least an element of heritability in this family, and that the symptoms that they had in common were basically dysautonomic in character. The passing out spells were typical of vasovagal attacks, probably related to postural hypotension. Photophobia was noted as a chronic symptom as in pandysautonomia. The girl's symptoms would certainly be classified as nervous in origin, and a diagnosis of conversion reaction would be applied. The sweating was a typical sympathetic phenomenon, and she had a moderately wide pulse pressure and lability of both the systolic and diastolic components. These symptoms are seen in beri beri, the prototype of dysautonomia in the early stages of the disease.. The mother had some of the elements of increased sympathetic tone giving her Raynaud's phenomenon, and there was apparently an associated cardiac autonomic effect as well.

It is not suggested that diet alone was the cause of this situation, but it has an important bearing on the familial or genetically determined sympathetic dominance that appeared to be common to all three family members. The rapid growth and development of adolescence may also represent a problem of supply and demand as far as nutrients are concerned in the general well-being of the individual.

Family 3. M.F. was a 10-year-old girl who had sprained her ankle two years previously. It was followed by swelling of the joint and great pain, which appeared to be out of proportion to the degree of injury. Subsequently, she experienced a series of quite trivial injuries, each of which caused swelling and pain. Plaster casts were applied on six different occasions over the two-year period. She developed

coldness of both feet and hands, and mottled vascularity of the legs which was worse in the injured one. On examination she had a mild systolic click and systolic murmur due to mitral valve prolapse, and there was gliosis of the temporal side of both optic discs. Both legs were extremely cold to the touch, mottled in appearance, and there was marked epicritic painful sensation on stroking the skin over the repeatedly injured foot. The mother volunteered that she, herself, had suffered from a form of polyneuritis for years.

Impression

This was typical of reflex sympathetic dystrophy which is well-documented in the adult medical literature, but relatively recently in the pediatric equivalent. It did not explain coldness and dysautonomic function in the uninjured leg or the mitral valve prolapse, which is known to be associated in some subjects with autonomic dysfunction. This association is considered later in this work.

An ophthalmologist was asked to give an opinion on the optic gliosis. He said that, though this was normal, it was unusual in a myopic eye — which was the state of affairs in this patient. It is unknown whether the mother's symptoms were related to those of the child, but it suggested that there was a familial element. Perhaps the injuries represented repeated physical stresses that caused an abnormal autonomic response because of an inherited component. In this case there was nothing to suggest a role from the diet.

SUDDEN DEATH

The syndrome of sudden infant death remains partially unsolved. Its existence has been recognized in all parts of the world, and the failure to find an obvious cause of death at autopsy has remained a puzzling feature. This in itself has suggested that an unbalanced pathophysiologic state is responsible. There are almost as many theories to explain the syndrome as there are investigators.[42] At a series of workshops, planned by the National Institute of Child Health and Human Development, infection and immunity, behavioural considerations, neurophysiologic factors, epidemiology, and pathology were discussed without reaching a definite conclusion as to etiology,[43] although recent studies have pointed increasingly toward the autonomic system as the origin of the process which leads to sudden death.[28 44] The question arises as to how the infant at risk is identified, and how such deaths can be prevented. There are some important statistics which have been recognized from a collection of public health information

1. Peak incidence's between one and four months of age
2. Greater incidence in males than females
3. Greater incidence with low socioeconomic status.
4. Low birth weight.
5. Cold weather months predilection with peak incidence in late winter and early spring.
6. Death between midnight and 6.00 a.m.

The results of a great deal of work have now been reported on the clinical presentation and pathology to be able to point increasingly to the relation between brain stem, reticular activating system, and cardiopulmonary function that implicates the mechanism within the autonomic system. Steinschneidet[28] was one of the first investigators to report on studies during sleep in infancy, and he described some of the characteristics of the infant at risk for sudden death. His studies revealed alterations in frequency, variability and character of respirations during sleep, and a decrease in the responsiveness of the respiratory centers to alterations in CO_2 concentration. In five cases he reported the infants at risk had frequent episodes of sleep apnea, some associated with cyanosis and severe enough in some instances to require resuscitation. Two of the five infants subsequently died. Other investigators have also related the syndrome to poor autonomic control, and their findings suggested a brain stem disorder.[44] Naeye[45] described a 38-year-old patient whose death was attributed to the respiratory center associated with abnormalities in the pulmonary vascular bed. Clinical features included general muscular weakness, tachycardia and cardiomegaly with pulmonary hypertension. Laboratory studies revealed a blood glucose of 198 mg/dl, increased CO_2, hypochloremia, hyperkalemia

and elevation of spinal fluid pressure. Death followed recurrent hematemesis and irreversible laryngospasm. The brain was reported to be unremarkable on gross examination, but many areas showed vascular congestion and neuronal degeneration. Hemodynamic features of this case were related to chronic arterial oxygen desaturation and explained the pulmonary hypertension, hypertrophy of pulmonary arterial smooth muscle, and dilatation of the pulmonary arterial bed related to polycythemia. It is particularly important to draw attention to the fact that Asian influenza virus was recovered from the lungs of this patient if "stress" factors are to be considered, and "there was some resemblance to lesions in certain metabolic and nutritional disorders such as Wernicke's encephalopathy, but other evidence of such disturbances was lacking." No nutritional history was recorded. The same investigator reported similar pulmonary arterial abnormalities in sudden infant death syndrome and related them to chronic recurrent hypoxemia in these infants.[46] Known chronic hypoxemia in infancy causes the retention of a large proportion of the brown fat cells that are normally replaced by white fat cells after birth. Such infants also have an abnormal retention of extramedullary hematopoiesis, abnormalities which were found in many victims of the sudden infant death syndrome.[47]

It may be possible to substitute "hypo-oxidative metabolism" for hypoxemia. This would then remove the stigma of failure to detect adequate oxygenation of arterial blood flowing to the brain. It would embrace a need to look at all possible aspects of oxidative metabolism, including the necessary vitamin and mineral catalysts and the ability of cells to utilize oxygen adequately. Recent evidence has suggested a very distinct possibility that defective phosphorylation may be one of the common denominaters in the pathophysiology. Davis, et al.[48] have reported high concentrations of thiamine in infants dying of crib death and have suggested (personal communication) that this represents accumulation of an inactive form of the vitamin. Our own experience [49] [50] has suggested that this may lead to a therapeutic approach in some of the infants with threatened SIDS. Similar thinking led Read [51] to suggest aberrant thiamine neurochemistry as a possible cause in some patients dying of SIDS. It should also be pointed out that a recent article [52] which refuted this concept as an important factor used red cell transketolase activity (TKA) as the criterion. The authors reported normal thiamine pyrophosphate uptake effect, (TPPE); but of perhaps greater importance, this study tells nothing about the state of thiamine triphosphate (TTP) in the brain, and it may be this component which fits better into the hypothesis.

Our experience suggests that an infant at risk for SIDS can be identified with one or more symptoms of autonomic dysfunction, including varying severity of apnea, choking, vomiting, gasping, extreme pallor, muscular hypotonia, bradycardia, tachycardia, excessive pharyngeal mucus, or defective body temperature control. The history from parents has been confirmed in some cases by admission of the infant to the hospital and cardiorespiratory monitoring around the clock. In one instance a three-month old female infant had a history of gasping, vomiting, pallor, muscular weakness and tachycardia. There was a family history of sudden death in three siblings and a first cousin. Autopsy in all four infants revealed acute pulmonary and systemic passive congestion, intra-alveolar hemorrhage, focal hyaline membrane formation, petechial hemorrhages of pleura and pericardium, extramedullary hematopoiesis, acute swelling of oligodendroglia with karyorrhexis and astrocystosis, varying in degree of severity between the four. Urine from the symptomatic infant was examined for urinary monoamines by Doctor Harold Mars of Case Western Reserve University at the time of initial admission at the age of five months. No treatment was given, but the patient remained attached to a night-time cardiorespiratory monitor unit until it was considered that she had matured beyond the period of considered risk. Table 6 shows the changes in urinary biogenic amines which occurred spontaneously in a period of only two months. Note the increase in DOPA, decrease in dopamine, reduced concentrations of serotonin, and 5-hydroxyindoleacetic acid and normal concentration of 5-hydroxytryptophan. The conversion of dopa to dopamine and 5-HTP to serotonin are catalyzed by the pyridoxine dependent enzyme, L-aromatic amino acid decarboxylase and these results suggested a temporary obstruction in this enzyme system. Similar changes were described in familial dysautonomia,[6] and Leigh's disease.[7] It is not yet possible

to state that sudden infant death can be due to unbalanced or unilateral action of the autonomic system. However, there is some evidence for this, as illustrated by the case of a six-week-old male infant referred with repeated episodes of apnea, pallor, and muscular weakness. His mother had a tubal ligation after her delivery and had received succinylcholine for anesthetic purposes. On recovering consciousness, she was completely paralyzed and apneic for six hours. Pseudocholine esterase deficiency could not be detected in her blood or in that of her infant. Perhaps her symptoms were related to another factor interfering with normal acetylcholine function, and the infant might have inherited this factor from her.

TABLE 6

	Controls ng/mg creatine			3 months	5 months
DOPA	236.5	±	106.1	2,370	219.2
Dopamine	1,199	±	46.6	415	950.5
Norepinephrine	84.4	±	32.3	81.9	43.4
Epinephrine	47.6	±	21.0	41.0	27.1
HVA	13,500	±	6,500	12,500	1,090
VMA	13,500	±	14,200	1,620	—
Serotonin	510	±	157	133.8	—
5-HTP	2,138	±	1,633	3,600	2,690
5-HIAA	7,220	±	3,350	3,760	10,500

Urinary biogenic amines from a female infant with threatened SIDS at three months, when symptomatic, and again at five months, when asymptomatic. The values are expressed in ng/mg creatine.

PROLONGED Q-T SYNDROME

The prolonged Q-T syndrome was mentioned in Chapter 1. There are some important facts to be learned about the autonomic system from a study of this syndrome. Schwartz and Malliani [53] referred to two different syndromes, the Romano-Ward type, in which they found T-wave alternans present in thirteen of twenty-eight cases, and the Jervell-Lange-Nielsen syndrome, which is the same except that congenital deafness is also present. Both syndromes are characterized by a prolonged Q-T interval and syncopal attacks due to ventricular fibrillation following emotional or physical stress. Both conditions have a high mortality rate and contribute to sudden death in children. These authors also reported their observation of T-wave alternans during stress in their patients, and they wondered whether this was confirmation of the relation of the syndrome with sympathetic nervous activity. They noted that stimulation of the left stellate ganglion prolonged the Q-T interval in dogs, and reported a diminished incidence of syncopal attacks in an affected child by the use of a beta blocking agent, and their disappearance after partial left sympathectomy. They experimented with cats, and produced alteration of the T-wave by electrical stimulation of one or both stellate ganglia. Of perhaps the greatest interest was the fact that unilateral stimulation was successful only when applied to the left stellate ganglion. When both were stimulated simultaneously, the alteration could be produced only when the stimulation was more intense on the left side. They concluded from their experiments that sympathetic stimulation can elicit a prolongation of the Q-T interval and T-wave alternation.

Fraser and Froggatt [54] suggested that this syndrome might be responsible for some sudden infant deaths, and discussed two unexplained deaths in the neonatal period in sibships of nine cases of the Jervell-Lange-Nielsen type where the evidence is in favor of autosomal recessive inheritance. This concept is not inconsistent with our knowledge of the physiology of early infancy and its unusual relationship with sudden death. A state of electrical right axis deviation is exchanged for left axis deviation, which is considered to be related to the change from a dependent to independent circulation. It would be rational to contemplate the not unreasonable hypothesis that such changes might be either caused by, or related to, concomitant changes in autonomic balance and its ultimate effect on cardiovascular and

respiratory reflexes. If there were such a period of instability, the normal responses to stress, such as a viral infection, would be temporarily jeopardized by dysautonomic reflexes. It would then be easier to explain why the premature infant is more susceptible to sudden death as a result of immaturity in the system.

IMMATURITY OF BRAIN STEM

Apnea is also a common problem in the low birth weight infant, and recent work has shown that this can be modified considerably by the simple expediency of cutaneous stimulation.[55] This suggests that autonomic respiration is, to some extent, dependent upon appropriate sensory input, or that perhaps an immature and poorly functioning central mechanism can be stimulated to activity by sensory stimulus. It would seem to be well established that the limbic system of man is a complicated computer. Like man made computers, it would also seem to be necessary that "input" be considered a mandatory part of the responsiveness of the total system.

We are well aware that infants do not thrive if they are deprived of emotional input, and perhaps even worse in the development of man as an independent creature, that this input appears to have a modifying effect throughout life. The normal infant uses the most sensitive part of his sensory apparatus, namely the mouth and the lips, to learn about his environment. The information is stored and committed to memory as he builds his "guidance system." The child who learns to walk on a tight-rope or play the piano, frequently becomes a child prodigy. The child who is physically abused is so deeply affected that he will repeat the abuse to his own child, even as he is "consciously" aware of his own abuse. The contemplation of such well known phenomena by a physician, school teacher, or social worker must surely give rise to the question of the computer effect in establishing even higher mental function, as well as developing the more primitive reflexes of physical survival.

Man as a species must develop responses to stress which must be learned and exercised repeatedly to survive. Familial dysautonomia represents a defect which frequently leads to failure to survive because of a defective response in the reflex system. This appears to be a well established model, but we have seen how disturbances of the autonomic response are also recognized in other conditions which are apparently quite diverse in origin.

Since SIDS seems to be a maturation problem involving temporary lack of response of the autonomic reflex system, any therapy that is found to be beneficial to autonomic activity might be considered for testing its efficacy in an infant whose symptomatology defines him as being at risk for nocturnal death. In the next chapter, we shall see how the identification of a thiamine responsive encephalopathy led to a consideration of the biochemical features of a stress response in the neuroendocrine system, and the role which this vitamin plays. In Chapter 5, a number of case reports will demonstrate the potential use of thiamine hydrochloride and its fat soluble disulfide derivative in the treatment of autonomic dysfunction.

Sudden death in dogs was seen from ventricular fibrillation in a small percentage of experiments after coronary occlusion. When followed by a hypothalamic signal, the death rate increased to nearly 90%.[56] As noted in Chapter 1, Engel [57] has reported an interesting series of sudden deaths which seem to be related to stressful situations such as the receipt of a telegram. This also suggests that a sudden surge of sympathetic activity can be dangerous under certain circumstances. From this it may be postulated that human beings can indeed be "frightened to death" and perhaps such a phenomenon might be related to marginal energy metabolism, which is inadequate to supply the heart with high energy phosphate bonds to meet the "call to action." Thus dysautonomia may be the clinical exposure of a marginal state and its recognition vitally important in predicting the possibility of disease or sudden death. An example of this will be provided in Chapter 5, where illustrative case reports are discussed. Perhaps there really is a need for a new medical model [58] since there are many flaws in our present concepts, particularly in regard to the artificial division which exists between "mental" and "physical" disease characteristics.

FURTHER EVIDENCE OF FAMILIAL FACTORS IN EXPRESSION OF AUTONOMIC DYSFUNCTION

Evidence has been presented that sudden death may occur as a result of — or in association with — autonomic dysfunction. There appears to be interrelated constitutional and environmental factors always present, and it is suggested that the actual event of death is a fortuitous situation when such an interrelationship provides maximum disadvantage to survival. This is probably seen most easily in infancy, where structural and biochemical maturation are incomplete, suggesting an obvious explanation for the well known epidemiology of sudden death in this age group (SIDS).

To further illustrate that functional dysautonomia may well be a key to understanding this kind of death, and that constitutional or familial factors appear to be involved, case histories of seven families are presented briefly. In five of the families, there were six infants brought for examination to determine whether they were at risk for SIDS. In each case there had been at least one infant in the family who had been found dead in the crib. Though the criteria for accepting such an event as an example of SIDS are poorly defined, nevertheless a sudden unexplained infancy death is always a dramatic event, and in each of the cases reported here the history was that of finding a previously healthy infant dead in the crib. Each was seven months of age or less, with the exception of a few for whom the age was unknown. None had been under immediate treatment for any symptoms preceding the discovery.

CASE REPORTS

Case 1. A two-month-old female infant was delivered by cesarean section at full term, because of pregnancy toxemia and hypertension. The mother had smoked one pack of cigarettes a day throughout pregnancy. The infant had been asymptomatic, and physical examination was normal except for clinically judged poor neck tone. A homegoing infant apnea alarm was prescribed, and three days later the apnea alarm sounded twice at night. The infant was found breathing normally on each occasion. The electrodes were attached appropriately, and the monitor functioning normally. The pedigree is shown in Figure 2.

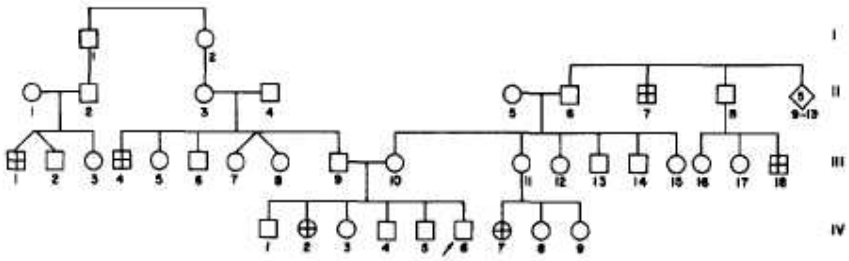


FIGURE 2

II.$_7$ "Crib Death" Age 7 Months: Found Dead in Morning
III.$_1$ "Crib Death" Age 4 Months: Found Dead in Morning
III.$_3$ Case 1
III.$_4$ Congenital Heart Disease: Died at Age 7 Months
III.$_{18}$ Acute Leukemia: Died at Age 8 Years
IV.$_2$ Found Dead In Morning Age 11 Months. Premature Birth, Multiple Respiratory Infections. Pneumonia at Age 9 Months. Autopsy Showed Pneumonia and Pleural Effusion
IV.$_5$ Down's Syndrome
IV.$_6$ Proband: Case 2
IV.$_7$ Found Dead in Crib at Age 3 Months. Autopsy Showed Pneumonia

Pedigree cases 1 and 2

Case2. A three-week-old male infant, related to the infant in case 1 (fig.2) was delivered at the thirty-sixth week of pregnancy by cesarean section because of hemmorrhage from placenta previa. The Apgar score was 2 at five minutes, and 6 at ten minutes. He required resuscitation and eleven days of intensive care, including continuous oxygen for seven days. Physical exam was normal, with the exception of clinically judged poor neck tone and limb tone. A homegoing infant apnea alarm was prescribed. During the following week the apnea alarm sounded four times, and on each occasion the infant was found apneic. Physical stimulation restored normal respiration. At age three months he had four or five explosive, green colored, watery stools, and developed fever, cough and bronchial wheezing, for which he had been admitted to a hospital. After hospital discharge, the bradycardia alarm sounded repeatedly during a twenty-four hour period, and the mother had confirmed the heart rate of less than eighty bpm by palpatation of the carotid pulse. She reported that the fingernails and lips were bluish in color during this twenty-four hour period.

Case 3. A two-week-old asymptomatic female infant was brought for the question of SIDS risk. The mother had smoked half a pack of cigarettes a day through pregnancy. She had lost two previous infants from sudden death, each one by a different father. There was a family history of eight male maternal relatives with unknown slowly progressive neuro muscular disorder (fig.3). The two infancy deaths were also males. The mother reported that she had observed tachypnea and periodic short apneas in the infant during sleep. Physical examination revealed mild acrocyanosis and clinically judged poor neck tone. An infant apnea monitor was prescribed. At the age of two months the apnea alarm sounded, and the infant was found apneic. After physical stimulation she gasped and resumed normal respiration. This was the only event reported.

Case 4. A four week old female with a family history of autopsy supported SIDS (fig.4) was delivered at full term by cesarean section. During pregnancy the mother smoked half a pack of cigarettes a day. She had passed some renal calculi.

The infant reportedly had choked occasionally during sleep and appeared to be unduly sensitive to noise, demonstrating frequent sleep starting. Physical examination was normal, with the exception of clinically judged poor neck tone and some diffuse mottling of the skin. At the age of three months, the infant apnea alarm sounded three or four times in a ten day period, and one apnea to cyanosis had been observed while she was awake.

Case 5. A five-week-old asymptomatic male infant was brought for examination because of a family history of two sudden infancy deaths (fig.5). The mother reported that she, herself, would awaken at night with difficulty in breathing and a sense of suffocation. This had been diagnosed elsewhere as sleep apnea. After trial labor, the infant was delivered by cesarean section. Physical examination was normal, but neck tone was judged to be poor in the flexors. An infant alarm was prescribed, though the father was opposed. At the age of two months, the apnea alarm sounded and the infant was found apneic and limp. Physical stimulation restored normal respiration. The incident convinced the father of the wisdom of using the monitor, since he believed that the event might have been lethal.

Case 6. A one-month-old infant was brought for examination because of familial unexplained infancy death. The mother had gestational diabetes mellitus, and there was a family history of this condition (fig.6). The infant had been noted to wheeze occasionally during feeding, and experienced unusual nasal congestion and irritability. Physical examination was normal. An apnea alarm was prescribed but no events were reported.

Case 7. The proband, an eleven-year-old girl, had a history of headaches, recurrent abdominal pain, unexplained fever, and dizziness. After an upper respiratory infection she experienced a morbilliform rash on the neck and chest, protracted vomiting, difficulty in breathing, choking and cyanosis, which had been treated in an emergency room with administration of oxygen. In this large family (fig.7) the symbols with crosses represent deaths in nine infants who had been found dead in the crib. In each case the death had been completely unexpected, but details of age and circumstances were not available.

Case 8. The proband in this family (fig.8) required extensive resuscitation at birth. Throughout childhood she experienced recurrent fatigue, periorbital edema,

unexplained fever, profuse nocturnal sweating, cold intolerance and extreme irritability. The mother was not aware of her family history until she made enquiries. She found that she was related to her husband, and that there were three infants who had typical histories of crib death. Sudden death had occurred in one seven-year-old child recovering from measles and III3 had been pronounced dead following an apparent heart attack, but had revived spontaneously.

DISCUSSION

This clinical experience is not open to any kind of statistical analysis. But with infinite variability of biological expression, statistics have a limited role at best, and may on occasion be misleading. In these families there does appear to be a series of patterns, and their interpretation may be of utmost importance in our approach to the frustrating problem of SIDS. In the first place, if the death is from abnormal function, it is not likely to leave in its wake any evidence of gross structural damage, and we find this to be the case in autopsy studies of SIDS victims.

In five families there were six infants with either minimal or no symptoms, a phenomenon with which every physician who deals with SIDS has become painfully aware. It is impossible to state whether any one of the episodes which came to light through the alarm system would have been lethal. Some would probably not have been discovered at all. But incidents of greater or lesser severity did occur in five of the six infants who were considered to be at risk from an historical and clinical standpoint.

It has become fairly obvious that pregnancy factors are of utmost importance in predicting risk — perhaps the most notorious of all being smoking, which recorded as a possible factor in three of these case histories. In four of the six cases, the mother had been delivered by cesarean section, but this may have been a reflection of the mothers' health and therefore have indirect importance. In one case the section was performed because of toxemia, in another for placenta previa and in the third case the mother had passed renal calculi and had a urinary tract infection.

Within the seven families there were twenty-six infants who had died unexpectedly, and for whom there was no adequate explanation. Only eight autopsies were known to have been performed, and in six cases the death had been attributed to SIDS. In two infants in one family (fig.2) autopsy had revealed the presence of pneumonia, although neither of these infants had had symptoms recognizable to the mother. Riley and Moore [13] reported sudden pulmonary edema associated with sudden death in a patient with familial dysautonomia, but were unable to decide whether it was related to the autonomic dysfunction or not.

Some evidence of heredity factors appears to emerge from these case histories. In each of two families (fig.3, 6) there were deaths in infants by two different fathers respectively, and in one (fig.3) there was a history of progressive neuromuscular disease. In our present preoccupation with Mendelian inheritance, this might be considered as an entirely different and unrelated disorder. However, in a biochemical sense the deaths in the infants might well have been due to a defect in cholinergic neurotransmission, which could also explain the neuromuscular condition. In case 6 (fig.6) there was a strong family history of diabetes mellitus, and the proband's mother was a gestational diabetic. The potential relationship between diabetes and dysautonomia has already been discussed.[29] In case 5 (fig.5) the proband's mother was reported to have experienced sleep apnea, and evidence exists that some parents of SIDS victims have reduced ventilatory responsiveness to hypercapnia, and reduced compensatory response to added resistive respiratory loads as compared with parents of healthy infants.[59]

A remarkable incidence of disease is demonstrated in the family of case 4 (fig.4) and there were two autopsy certified SIDS victims. Again, on Mendelian lines, this is meaningless, but there may well have been constitutional factors of which we are presently unaware and which yet may make sense out of this kind of family history.

The Proband in cases 7 (fig.7) and 8 (fig.8) had symptoms which included unexplained fever, pulmonary abnormalities, irritable personality, excessive sweating, a morbilliform rash on the chest, vomiting, unusual fatigue, abdominal pain, headache and cold intolerance — all of which have been described in familial

and other forms of dysautonomia.[2 14 36] Centrally mediated abnormal autonomic reflexes have been described in infants who later succumb to SIDS.[28 44]

These brief case histories suggest that sudden death appears in some families in greater than expected incidence. It is by no means clear whether this indicates constitutional factors in common, or whether it suggests environmental or nutritional associations. The two families in whom the probands demonstrated autonomic dysfunction are of interest, since in neither case were the probands' mothers aware of sudden death in family members. In case 6, the mother was asked to make enquiries of her relatives, and she was very surprised to find such a high incidence of nine infant deaths. In the other case (case 7) the mother was ignorant of family history details. She was also surprised to find that her marriage was consanguinous and that there was an incidence of infants dying unexpectedly in the crib.

Further examples of unusual family histories are described in Chapter 5. The cases reported here are in order to illustrate the diversity of autonomic dysfunction, and to show that it might be a key phenomenon in sudden death.

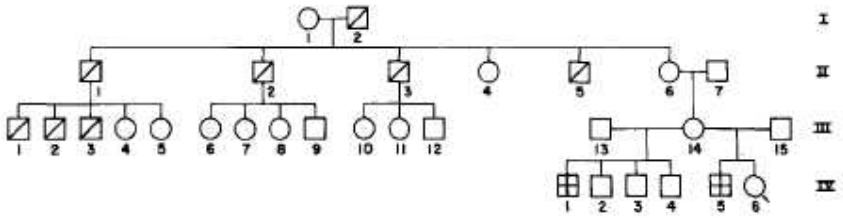


FIGURE 3

⊠	Males affected by a slowly progressive neuromuscular disease beginning in the lower extremities.
IV_1	Found dead in crib in morning, age 5 months: Asymptomatic
IV_5	Found dead in crib in morning, age 3 1/2 months: Asymptomatic
IV_6	Proband

Pedigree case 3

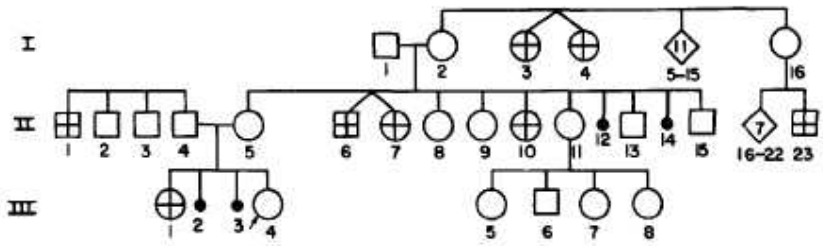


FIGURE 4

I.$_2$ Hypertension. Recurrent "Hypoglycemic Coma"
I.$_{3\ 4}$ Twins, died in infancy. "Blue Babies"
I.$_{16}$ Epilepsy; Under psychiatric treatment
II.$_1$ SIDS age 4 months: Autopsy
II.$_5$ Recurrent Urinary Tract Infections: Renal Calculi
II.$_6$ Stillbirth
II.$_7$ Died in infancy. "Blue Baby"
II.$_8$ Lupus Arthritis
II.$_9$ "Multiple Sclerosis and Hodgkin's Disease"
II.$_{10}$ Died, age 2 days. "Blue Baby"
II.$_{23}$ SIDS age 6 months: Autopsy
III. SIDS age 4 months: Autopsy
III.$_4$ Proband
III.$_6$ Epilepsy; "Ketotic Hypoglycemia"
III.$_7$ Behaviour Disorder
III$_8$ Severe "Allergic" Symptoms

Pedigree case 4

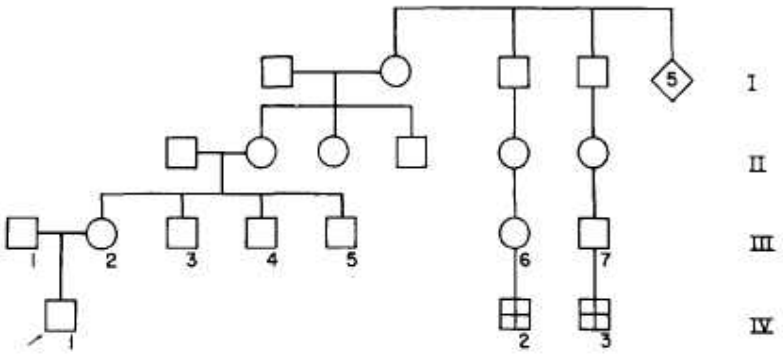


FIGURE 5

III.$_2$ "Stress Related Sleep Apnea"
IV.$_1$ Proband
IV.$_2$ Historically Typical Crib Death at Age 2 Months
IV.$_3$ Autopsy Proved SIDS at Age 5 Months

Pedigree case 5

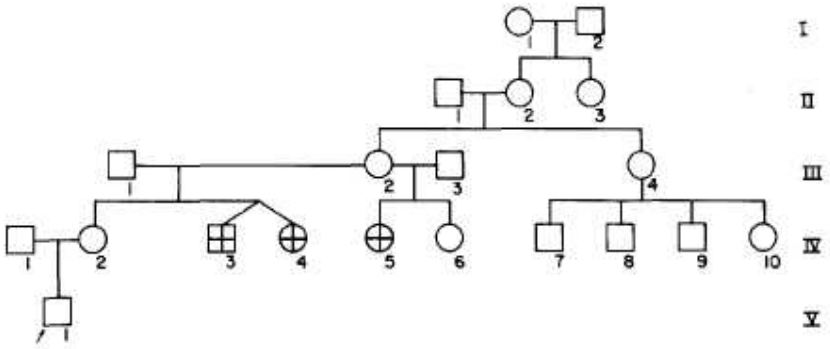


FIGURE 6

$I._2$	Diabetes Mellitus
$II._2$	Diabetes Mellitus
$IV._2$	Gestational Diabetes
$IV._3$	SIDS Age 7 Months: Autopsy
$IV._4$	SIDS Age 9 Months: Autopsy
$IV._5$	SIDS Age 3 months: No Autopsy
$IV._6$	LBW Infant 2.3 kg. Hyaline Membrane Disease
$V._1$	Proband

Pedigree case 6

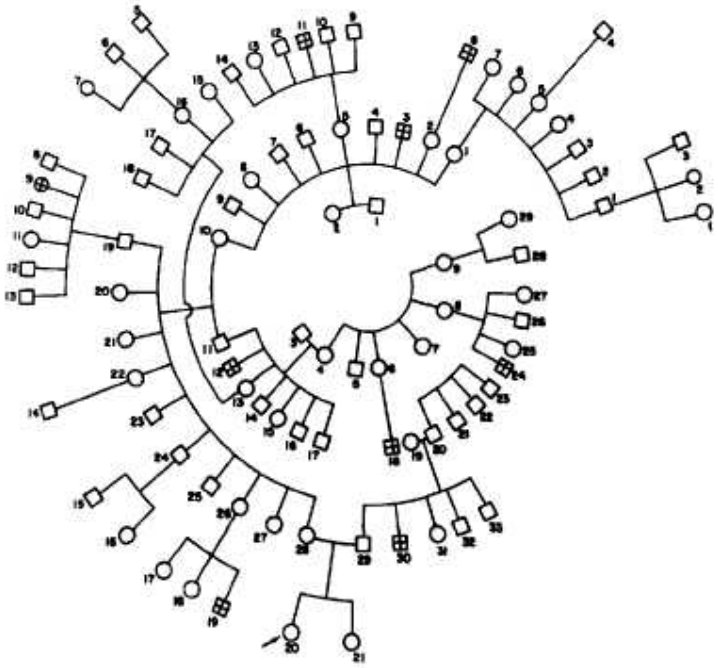


FIGURE 7

In this large family there were many diseases claimed by the mother of the proband. These included hypertension, cancer, diabetes, mental retardation and cardiomyopathy of unknown cause. There was a surprising incidence of sudden infantile deaths in the first year of life. In each case, the child had been found dead in the crib in the morning, without any adequate explanation. In the pedigree, these individuals are the ones marked with a cross. The exact ages could not be ascertained in every case.

$II._3$	Death at 2 months
$II._{12}$	Death at 2 months
$II._{18}$	Death at 6 months
$II._{24}$	Death in first year
$III._8$	Death at 6 weeks
$III._{11}$	Death in first year
$III._{30}$	Death in first year
$IV._9$	Death in first year
$IV._{19}$	Death in first year
$IV._{20}$	Proband: Dysautonomic Symptoms

Pedigree of case 7

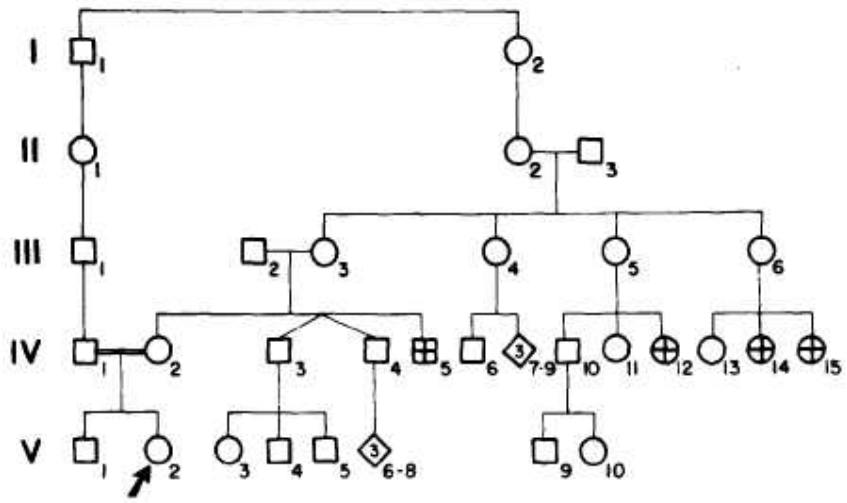


FIGURE 8

III.$_3$ "Heart Attack" age 28; chestpain, hyperpyrexia; considered dead but recovered. Suffers confusion, headaches ? neuropathy

IV.$_5$ Sudden death after measles, age 7

IV.$_6$ Hemiplegia, cerebral palsy, no speech

IV.$_{12}$ Crib Death age 4 months.

IV.$_{14}$ Crib Death ? age

IV.$_{15}$ Crib Death ? age

V.$_2$ Proband

V.$_5$ Premature; RDS; recurrent pneumonia, intractable vomiting, abdominal pain, lethargy, short stature

V.$_9$ Brain Tumor - blind

Pedigree case 8

Chapter 3

THIAMINE, AUTONOMIC FUNCTION AND STRESS

INTRODUCTION

Knowledge concerning the role of vitamins and minerals in mammalian metabolism is still incomplete. Vitamins are catalysts and their absence from the diet will cause deficiency disease. These deficiency diseases are considered to be related only to severely malnourished individuals and, despite a nutritional survey in America,[1] are frequently not even considered as a possible cause of symptoms in affluent societies. Vitamin dependency is thought of as a rare phenomenon, and is the only kind of vitamin related disease which is generally considered to justify vitamin supplementation of diet. An effort will be made to demonstrate that this concept is only true in part, and that a great deal can be done by building up clinical experience with the ways in which vitamins and other nutrients work together. Before proceeding with the clinical background, it is useful to remind the reader of certain parts of biochemistry which represent the foundation of cellular metabolism.

TRANSAMINATION

Nitrogen balance is the key to growth, metabolic stability, and eventual physical decline. A child must be in a state of positive balance to grow and develop, and part of this is achieved by the transfer of nitrogen from transamination. It is dependent upon the presence of transaminases which require a variable organization of cofactors and physical environment for their normal function. Most alpha amino acids have their amino group removed as the first stage of their metabolic breakdown. The amino group is transaminated to a keto acid which thereby becomes an amino acid. A keto acid may be further broken down by a decarboxylating enzyme to become an organic acid which is then oxidized in a series of steps, or it may become reaminated to form the original parent amino acid. Thus nitrogen is transferred and cellular protein synthesized or dietary protein used as fuel. The mechanism of transamination in brain involves glutamic and aspartic acids as the two almost exclusively involved amino acids in this process.[2] Both play other important roles. Glutamic acid is used, for example, to synthesize gamma amino butyric acid, a neurotransmitter which has an anticonvulsive action,[3] and is essential to the activation of choline acetylase,[4] as well as having an important effect on cation metabolism.[5] Aspartic acid is important in the elimination of free ammonia and in the ornithine urea cycle.[3] It would be anticipated that a deletion of either of these amino acids in brain would have serious consequences.

TRANSMETHYLATION

The one carbon pool represents a group of compounds capable of transferring a methyl group to another compound and thus adding an additional carbon atom. Methionine is the most important methyl donor. Oxidative metabolism synthesizes ATP which is required to form S-adenosyl methionine (SAM) from methionine, and energy is therefore used. The labile methyl group is then passed on to a number of receptor compounds and homocysteine is formed. Homocysteine may be transulfurated or remethylated back to methionine to complete the cycle. This remethylated step, like the formation of choline from ethanolamine, requires folate as methyl donor and is also one of the two enzymatic steps dependent upon vitamin B_{12}. Formation of choline is an important methylation reaction in the endogenous synthesis of choline, although diet is the main source of this metabolite which is central in phospholipid synthesis and the formation of acetyl choline. Although choline deficiency in man seldom, if ever, occurs, the effects seen in experimental animals are well known.[6]

THIAMINE METABOLISM

History

Beriberi, now known to be importantly related to thiamine deficiency, was known as a disease to the Chinese as early as 2600 BC. It is still highly relevant in the world where rice is a staple of diet. In 1875 a Japanese navy medical officer named Takaki came to the conclusion that the condition had a dietary cause. He obtained permission to perform experiments, and in 1882 the "Riujo" — a training ship bearing 276 men — made a voyage of 272 days. On its return to Japan there were 169 cases of beriberi and 25 deaths had occurred. Takaki then sent another training ship on a similar voyage. The daily ration of rice was the same as on the previous voyage, but vegetables, fish and meat were increased. After a voyage of 287 days, only 14 men had beriberi and these victims had not consumed their full allowance of the new ration.

In 1897 Eijkman noted that certain fowls developed polyneuritis due to deficiency of something obtainable from rice polishings, and in 1911 Funk prepared some crystals from rice bran which cured pigeons of the polyneuritis that developed after feeding on polished rice. The vitamin was eventually synthesized[7] and this led to the classic experiments of Peters.[8] The physiologic activity of the vitamin is of such critical importance, that it is as well to remind ourselves of the discovery that Peters reported. He stated that "with 100 mg. of brain and 3 c.cm of Ringer phosphate solution, no certain difference between the respiration of normal and avitaminous pigeon's brain has been observed. But with glucose present, there was no doubt that cellular respiration was decreased in the vitamin deprive brains, especially in the lower parts of the brain." This was the first experimental exposure of the relationship between glucose and thiamine. Peters called this effect the "catatorulin reaction," and it is a phenomenon which is vital to remember in our understanding of the needs for the vitamin in human nutrition.

PHYSIOLOGICALLY ACTIVE FORMS OF THIAMINE

Thiamine occurs in mammalian systems in at least four forms, — the free and three phosphorylated compounds. Some evidence exists for a methylated thiamine which has a role in releasing acetyl choline into synaptosomes.[9 10]

The presence in mammalian cells of free thiamine and thiamine monophosphate (TMP), respectively the precursor and the dephosphorylation product of active coenzyme, can be understood in relation to the well known activity of thiamine pyrophosphate (TPP). Whether TMP does or does not have a physiologic role other than that of a phosphate receptor is unknown.

Thiamine Pyrophosphate (TPP)

The process of oxidative decarboxylation is a complicated reaction. For oxidation of pyruvate, three enzymes and five coenzymes are necessary, the whole complex being known as pyruvic dehydrogenase. Its integrated activity is regulated by ATP concentration. First a hydroxyethyl derivative of the thiazole ring of TPP is formed. The hydroxyethyl group is transferred to one of the sulfur atoms of the cyclic disulfide group in lipoic acid. This is covalently bound to dihydrolipoyl transacetylase, the second enzyme in the complex. Lipoic acid is reduced to its dithiol form, the acetyl group is enzymatically transferred to the thiol group of Co A, forming acetylCoA which leaves the complex in its free form. Dihydrolipoyl dehydrogenase, which contains the reducible coenzyme FAD, reoxidizes dihydrolipyl transacetylase to its disulfide form, and FAD acts as a hydrogen receptor. The reduced FAD (FADH2) is reoxidized by NAD + , regenerating FAD and forming NADH. The dehydrogenase complex which catalyzes the formation of branched chain keto acids from leucine, isoleucine, and valine has a structure similar to that of pyruvic dehydrogenase.

Thiamine pyrophosphate serves as coenzyme in a number of enzyme systems, involving conversion of alpha keto acids to acyloins, aldehydes, carboxylic acids, acyl phosphates and formates. It is also cofactor in the transketolase enzyme which occurs twice in the hexose monophosphate shunt. Since this pathway is present in erythrocytes, measurement of transketolase activity in these cells is a useful

laboratory test for TPP. The functions of the hexose monophosphate shunt, also called the pentose phosphate cycle, are to provide pentose phosphate for nucleotide synthesis and to supply reduced NADP for synthetic pathways that include steroid hydroxylation and fatty acid synthesis. The proportion of glucose metabolized by this route is high in lactating mammary gland, adrenal cortex, leukocytes and erythrocytes, and thiamine pyrophosphate must thereby play a critical role in these metabolic processes. Another important enzyme for which TPP is the cofactor is alpha ketoglutarate dehydrogenase. Glyoxilic acid oxidase reportedly requires TPP also.[12]

This cofactor thus takes a central role in the mechanisms involving oxidation, particularly glucose. Since there is no known storage for it in the body, it obviously must be supplied continuously in the diet. To assume that a minimum daily requirement is sufficient for all fluctuations of metabolic response is dangerous, and quite unnecessary, since there is no information to indicate that a modest excess is harmful. As glucose is the only fuel that the central nervous system normally uses, lack of thiamine would be expected to interfere with its function. Since the response to any form of stress must result in accelerated activity in the central control of adaptive mechanisms, the need for thiamine rises in proportion to the rate of glucose utilization.

Thiamine Triphosphate (TTP)

Considerable experimental support exists for the involvement of thiamine compounds in the central nervous system[13] and TTP appears to play a vital role which is independent of the cofactor function of TPP. Its formation from TPP is catalyzed by thiamine pyrophosphate-adenosine triphosphate phosphoryltransferase in the presence of magnesium. Its exact place in cellular metabolism remains somewhat of a mystery, but evidence is in favor of its action being related to excitable membrane.[14]

The first indication that thiamine had an effect on nervous excitation was demonstrated by Minz[15] and was further explored by von Muralt.[16] Cooper and associates have investigated the role of the vitamin in nervous tissue, and Cooper and Pincus[13] reviewed the subject. About 80% of thiamine in nervous tissue is TPP. About 5-15% is in the form of TTP, and the remainder is free thiamine and TMP. Thiamine triphosphatase, diphosphatase and monophosphatase catalyze the respective hydrolysis reactions from TTP to free thiamine. All require magnesium.

Physiologic Actions of Thiamine

The original observations of Minz[15] concerning the release of thiamine into the medium after electrical stimulation of a nerve have been confirmed by other investigators.[17 18 19] This release coincides with a shift of the thiamine phosphate esters to a more dephosphorylated form.[13] A similar release occurs after the use of a variety of neuroactive agents [19 20] so it appears that any condition which results in a change in ion movements dephosphorylates the vitamin and permits its efflux. However, interpretation of this phenomenon is not presently possible.

Of some obvious importance, experimental evidence points to the presence of a saturable thiamine transport system which may be located in the choroid plexus.[21] Entry of thiamine into brain via this system would presumably be compromised if prolonged thiamine deficiency had resulted in deterioration of energy metabolism in this mechanism, and might lead to a vicious cycle and increasing neurological effect. However, since the early work which demonstrated the cofactor importance of TPP, repeated efforts have failed to show any deterioration of pyruvate dehydrogenase, alpha ketoglutarate dehydrogenase or transketolase in nervous tissue of thiamine deficient animals.[22 23 24 25] Hence the mechanism of thiamine deficiency in producing the characteristic reversible functional changes is still not well understood.

Although thiamine is required in only minute amounts for normal biochemical activities, it is relatively poorly absorbed when given as a supplement of water soluble thiamine hydrochloride, and pharmacologic doses must be increased greatly over the actual physiologic needs. This dose is very wide and the margin of safety is enormous. Doses of lG/Kg produced a marked fall in blood pressure in dogs.[26] The

ganglion blocking activity of thiamine has been attributed to the quaternary ammonium similar to the effect of tetraethylammonium bromide.[26 27]

CLINICAL THIAMINE DEFICIENCY

Thiamine derivatives that are better absorbed and provide higher blood and tissue concentrations than thiamine hydrochloride (THCl) have been considered to be improved forms of the vitamin, for use in nutritional deficiency. Their advantage over THCl in postulated vitamin dependent disorders may be an important role, and there may be still another use in developing pharmacologic applications in several diseases for which therapy is still inadequate, toxic, or both.

As the role of the vitamin in biochemical processes is further elucidated, the therapeutic applicability of the newer alkyl derivatives of thiamine can be explored objectively. They are more likely to be of clinical value when metabolic or histologic abnormalities resemble those of athiaminosis, but where there is a metabolic derangement rather than a simple nutritional deficiency. Even in beriberi, the classical clinical prototype of thiamine deficiency, large doses of the vitamin are required for long periods,[28] although it is often mistakenly accepted that the disease is readily reversible with small doses that are considered to fill physiologic need. Large doses have been given clinical trial where evidence exists for impaired absorption, utilization, or dependency. Severe thiamine deficiency may be found in old people,[29 30 31] alcoholism,[32 33 34 35] and children with gastroenteritis.[36] Therapeutic attempts with THCl have demonstrated inconsistent and unpredictable responses. The use of thiamine alone may result in lack of therapeutic effect since its absorption and biochemical activation[37] are critical factors. Essential nutrients work together in complicated biochemical relationships.[38 39]

This chapter emphasizes the clinical conditions of thiamine deficiency or dependency, and explores the possibility of developing therapeutic approaches to neurologic and cardiac disease with similar characteristics. Biochemical abnormalities similar to athiaminosis suggest defective carbohydrate metabolism in some diseases of the heart, nervous system and some hepatic disorders. Covered extensively in the veterinary literature, but virtually ignored in human disease, is the role of thiamine inhibitors which lead to a variety of athiaminotic syndromes. Attention is drawn to those human disorders which have already been reported to respond to large doses of thiamine, and may be considered to be examples of thiamine dependency.

CLINICAL CONDITIONS RELATED TO THIAMINE METABOLISM

1. Nutritional Deficiency
2. Thiamine Dependency Disorders
3. Thiamine Inhibitors
4. Conditions Resembling Athiaminosis

NUTRITIONAL DEFICIENCY

Thiamine deficiency, like other similar nutritional disorders, is considered to be rare or non existent in developed countries. It is still widely prevalent in underdeveloped societies, particularly where rice is staple. It is well established that beriberi is closely associated with ingestion of high calorie foods, particularly carbohydrate. Platt,[40] an early investigator, strongly suspected that beriberi death was frequently a centrally mediated phenomenon, although heart failure was then considered to be the dominant cause. He noted that a regular feature of chronic beriberi was creatinuria, which slowly disappeared with bed rest, even before synthetic thiamine became available. He observed that Wemicke disease was seldom, if ever, seen in beriberi and that the state of glucose metabolism influenced the response to thiamine therapy. Patients with hypoglycemia did not respond, whereas those with hyperglycemia sometimes responded and those with normoglycemia always responded quickly.

A number of features in beriberi are important and need emphasis:

1. It predominantly involves the cardiovascular and nervous systems, — the autonomic system in particular.[41]

2. Symptoms vary with age and method of inducing the deficiency. The disease is especially acute and lethal in infancy.[41]

3. The clinical spectrum is widely protean in nature.[41]

4. Marginal deficiency can exist for long periods, even years, but an acute crisis can be precipitated by stress, including pregnancy, surgery, injury, or febrile illness.[40] This is particularly important in identifying the disease in well developed societies where marginal malnutrition exists[1] — often without clinical recognition.

Beriberi is one of the classic nutritional deficiency disorders, and it is possible that it may not be recognized today, even in its complete expression. Two brothers were reported with unknown cardiomyopathy.[42] The symptoms and physical signs were those of cardiac beriberi, though beriberi was not evidently considered in the differential diagnosis. Wolf and associates[43] reported two cases of Shoshin beriberi in 1960, and they suggested that the disease was not uncommon in the United States, although it was rarely diagnosed. Cardiac beriberi was reported in two cases in 1971,[44] both of which could easily have been treated as heart failure of unknown cause. The rooted opinion that the disease has been stamped out in all its forms creates a danger of misdiagnosis.

Adolescents and children in the United States may develop psychologic and somatic symptoms related to diet,[45] [46] and dietary correction, together with supplements of water soluble vitamins, was shown to result in correction of red cell transketolase.[46] The authors suggested that the intake of naked calories might increase vitamin needs drastically, and thiamine metabolism is particularly related to carbohydrate metabolism. Refined sugar and many varieties of sweets have become virtually an addictive trend in America. The experiments of Peters, using pigeon brain brei,[8] showed that there was no difference in respiratory rate of athiaminotic brain cells compared with thiamine sufficient cells **until glucose was added.**

Experimental thiamine deficiency in human subjects[47] caused typically nervous symptoms. Depression, parasthesiae, weakness, dizziness, backache, muscle pain, palpitations, precordial distress on exertion (pseudoangina), insomnia, anorexia, nausea, vomiting, weight loss, hypotension, bradycardia at rest and tachycardia with sinus arrhythmia on exertion occurred after severe deprivation for several weeks. Moderate prolonged thiamine deficiency, without caloric restriction, resulted in emotional instability, mood changes, lack of cooperation, fearfulness with agitation, and many somatic symptoms. These were the same symptoms reported in a group of young Americans whose red cell transketolase studies plainly indicated thiamine deficiency.[46] Wernicke disease has been reported as a complication of intravenous hyperalimentation.[48] In another similar report[49] the patient had developed Wernicke's encephalopathy, in spite of the fact that she had received 25 mg of thiamine a day in the intravenous fluid. This suggested that the vitamin was either still insufficient, or was not biologically activated.

It is not the purpose here to discuss the clinical characterestics of beriberi in full. Suffice it to say that the disease produces functional changes, particularly in the autonomic system, which make it the prototype of dysautonomia.[50] In many respects the autonomic neuropathy seen in diabetes[51] [52] is similar to that in beriberi, and insulinopenia, observed in familial dysautonomia,[53] suggests the possibility of a primary central mechanism in diabetes. The fact that carbohydrate metabolism is affected in both beriberi and diabetes also suggests the possibility of exploring further the role of thiamine in diabetes.

Animal Experiments

Animal experiments have thrown some light on the effects of dietary thiamine deprivation. The usual clinical effects in rats are fairly well known, involving anorexia, gradually increasing weakness, weight loss and death. Some workers have observed muricidal behaviour [54] and persistent penile erection,[55] suggesting that aggressive functional variations might occur, perhaps in reference to the proportion of other nutrients in the diet. Skelton [56] reported the general adaptation syndrome [57] in rats experimentally deprived of thiamine, and suggested that the vitamin had a bearing on stress resistance. The effects of non-specific stress were studied in dogs[58] by inducing shock from hemorrhage. Thiamine fortified animals withstood bleeding

better than the controls, and copious intestinal hemorrhage, which occurred in controls, was not observed in those receiving thiamine.

Methylglyoxal has been reported in urine from thiamine deficient rats.[59 60] Glyoxalases, enzymes which are ubiquitous in many animal and plant tissues,[61] synthesize D-lactate from methylglyoxal and this may represent an atavistic pathway, activated by prolonged anaerobic metabolism. Liang[62] reported glyoxilic aciduria in athiaminotic rats, suggesting that this represented abnormal glycine metabolism. Creatinuria suggested failure to absorb creatine into body tissues or to trap it as creatine phosphate.[63] Iwata and associates [64 65 66] found higher tissue concentrations of catecholamines and depressed activity of monoamine oxidase in thiamine deficient rats. Ochoa [67] showed that anaerobic conditions resulted in destruction of cocarboxylase. It is possible that thiamine deficiency might set up a vicious cycle, resulting in further destruction of TPP when anaerobic metabolism has been induced.

THIAMINE DEPENDENCY

Defects in TPP

1. Pyruvic dehydrogenase

Several cases of pyruvic dehydrogenase complex deficiency have been reported.[68 69 70] The clinical presentation of a 6-year-old boy with intermittent cerebellar ataxia[70] is considered here in greater detail, since it illustrates the way in which environmental stresses affect the body when energy metabolism is compromised.

There were two boys in this family, both of whom showed malfunction of pyruvic dehyrogenase in fibroblast tissue culture cells.[71] It appeared to be the decarboxylating mechanism that was at fault (Table 1), and although this did not respond to thiamine *in vitro,* both boys were clinically improved when they supplemented their diet with thiamine hydrochloride. The older boy, J.V., was studied in detail, at the age of six years. Whenever he had an infection, a head injury, or inoculation, he was prone to experience a self limiting episode of cerebellar ataxia, involving loss of balance, slurred speech and disorientation, and he would also have frightening delusions. The late winter and early spring were, and have remained, particularly "stressful" times, and to this day he will double or triple the daily dose of thiamine at these times when he begins to notice symptoms of "infection." The daily preventive dose of THCl is 600 mg.

TABLE 1

Pyruvic Decarboxylase m moles/g protein/30 min

Controls	1.23	−	3.45
Patient's father	1.2	±	0.22
Patient's mother	0.85	±	0.05
Patient's brother	0.39	±	0.24
Patient	0.28	±	0.09

Concentrations of pyruvic decarboxylase activity in fibroblast tissue culture cells obtained from child with recurrent episodes of cerebellar ataxia. Assays performed by J.P. Blass.

The episode that was reported lasted a week. Each morning the ataxia and neurologic signs were improved, but deteriorated during the day, so that he was unable to walk by evening. After several days he began gradually to improve, though no treatment was given and he was not receiving any vitamin supplement. Each one of these multiple attacks appeared to leave his general condition and neurologic health a little worse. He was having difficulties in school, had visuomotor incoordination and had early signs of optic atrophy. They were typical of recurrent episodes of childhood beriberi, which is more acute and fulminating than adult forms of the disease. Studies revealed the following data:

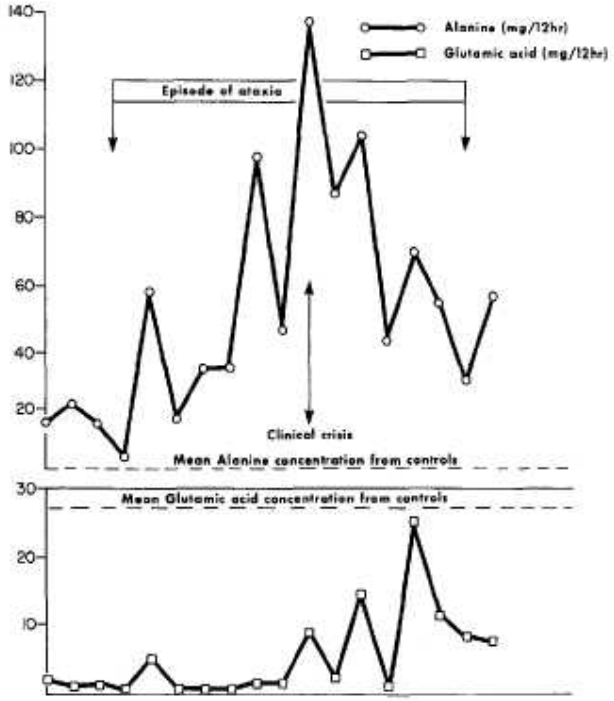
1. Urine, in day and night twelve hour consecutive collections revealed large amounts of alanine, pyruvate and alpha keto glutarate. These concentrations were much greater during the day than the night.[70] Urinary concentrations of glutamic acid and aspartic acid were consistently low until the patient began to improve clinically. This is shown in figures 1 and 2. It was also striking that the glutamic and aspartic acid concentrations rose by day and fell by night during the phase of clinical recovery, coinciding with the diurnal oscillation demonstrated by alanine in the figures. This was more obvious for glutamate than aspartate.

2. Urine was examined by Dr J.R. Cooper of Yale Medical School, who found that urine contained a substance which he has reported to inhibit the formation of TTP in the brain.[72]

3. Low activity of the decarboxylating component of pyruvic dehydrogenase. For these reasons he was given an experimental trial with massive doses of thiamine hydrochloride. Repeated examination of urine revealed much lower concentrations of alanine and pyruvate. His clinical improvement was matched by increased ability to perform a Bender Gestalt. This test, performed in March, and again in the following December, showed marked improvement, as shown in figures 3 and 4.

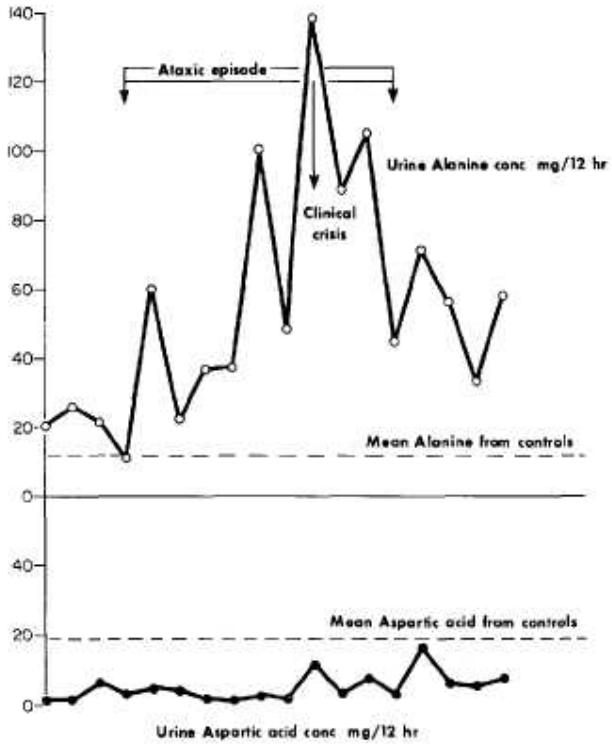
FIGURE 1

ION EXCHANGE URINE AMINO ACIDS



Alternating day and night 12-hour concentrations of alanine and glutamic acid in urine of child during ataxic episode caused by partially defective decarboxylation of pyruvate. Higher values are those of day specimens and lower ones of night specimens.

FIGURE 2



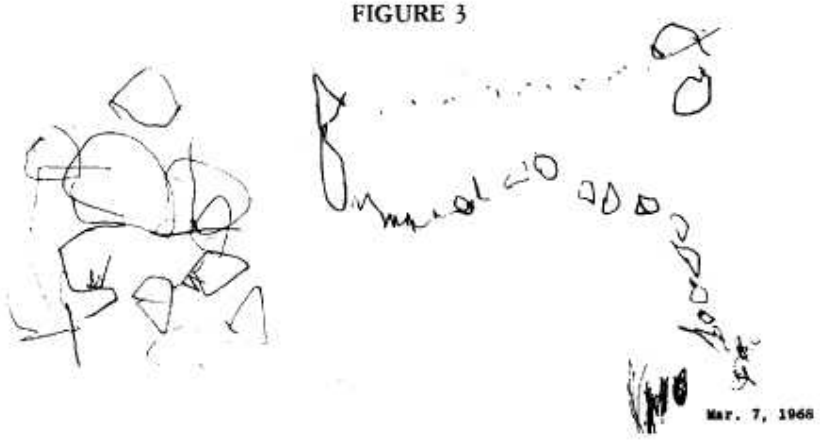
Alternating day and night 12-hour concentrations of alanine and asparate in same urines as represented in Figure 1. Oscillation of higher and lower night concentrations of aspartate began at the time of clinical climax.

Since that time, this boy's health has been remarkably stable. There have been no more episodes of ataxia and he graduated successfully from high school. All evidence of optic atrophy disappeared. He recognizes subjective changes in his own reaction to infections such as colds or "flu." He describes these as "funny feelings" or "nervousness," and he finds that he can abolish such symptoms by temporarily increasing the dose of thiamine supplement.

Another illustration of this boy's inability to react to environmental stress was demonstrated early in his treatment program. He entered an air conditioned store from a 90°F outside temperature. He became unconscious and began asthmatic wheezing. He had never previously experienced asthma. The same thing happened in the family car when the air conditioning was turned on. His brother, who has the same defect, has only experienced one minor episode of ataxia. In adolescence he suffered a relatively minor head injury which caused him to become unconscious, again attesting to the fact that his ability to meet stress was compromised.

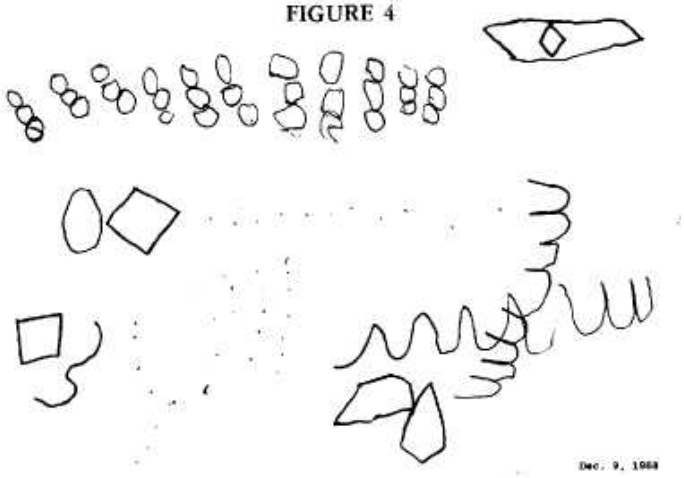
Unfortunately, contact with this family has been lost and little is known of the fate of J.V. It is known that his brother succumbed to a drowning incident but the details are unknown. A previous incident of unconsciousness had been precipitated by a fall, involving a head injury that would not normally be expected to result in a period of unconsciousness.

FIGURE 3



Bender Gestalt performed by child with pyruvic decarboxylase deficiency after recovery from ataxic episode.

FIGURE 4



Bender Gestalt performed by same child after nine months of continuous therapy with 600 mg/day thiamine hydrochloride.

This case history represents an uncommon condition, to be sure. But an acquired biochemical effect may be induced relatively easily by nutritional depletion of vital cofactors and masquerade as "encephalitis" unless the mechanisms by which adaptation occurs are kept in mind. Since most physicians do not believe that such deficiencies can occur in well developed societies, then the diagnosis of acute beriberi, or other nutritional depletion disease, is unlikely to be contemplated.

A good example of such energy depletion might be suggested by exercise induced asthma, and the author has recognized several other incidents where the reaction of the patient appears to be that generally ascribed to infection. If no evidence of bacterial cause is discerned, it is usually assumed that a virus is the cause, whereas it is suggested here that such clinical presentations may be due to a brain directed response to a relatively trivial stress insult of a non infectious variety.

Attempts were made to identify the biochemical mechanisms which had resulted in this devastating disease, which could be largely prevented by so simple means. Several possibilities existed, including those which have been considered in

reference to thiamine deficient metabolism. In this case, however, there were several facts that considerably complicated the issues, and their possible interpretation.

1. There was evidence of depletion in the mechanism of pyruvic dehydrogenase, the entry of pyruvate to the citric acid cycle.

2. Evidence existed for a possible defect in the synthesis of brain dependent TTP. Study of one episode revealed a series of biochemical changes which were so closely related that coincidence was unlikely. Hence it could be hypothesized that blocked entry of pyruvate to the citric acid cycle had resulted in abnormal accumulation of pyruvate. This resulted in an acceleration of transamination with consequently increased synthesis of alanine, alpha keto glutarate and oxaloacetate. Glutamate and aspartate are the principle participants in all brain transamination reactions, and perhaps part of the mechanism was due to their being siphoned away from their normal role in nitrogen balance. This could explain the low concentrations of urinary glutamate and aspartate in the early stage of the ataxic episode, and their "circadian" rise in the later stages, during clinical recovery.

Initially it was considered that the daytime increases in concentrations of the urinary metabolites were related to diet. However, the presence in urine of the TTP inhibitory substance suggests another possibility. Absence or insufficiency of this vital factor in the regulation of nerve function may have resulted in abnormal control of circadian rhythm. A similar situation is seen later in this work in discussion of the fluctuations seen in urinary creatine and creatinine that were identified in a child with learning disability.

In order to support this hypothesis, it was recognized that there should be a coincidental depletion in brain glutamate. Hence experiments were begun on rats by Mr. D. Sigmund, then a premedical student, working in our laboratory. Because of time and other limitations, only a small number of animals were used. As thiamine deficiency was induced by use of a thiamine deficient diet, it was found that there was, indeed, a highly significant statistically tested difference in brain glutamate content of thiamine deficient rats compared with controls (Table 2).

Because of this it was suggested that administration of glutamate to thiamine deficient rats might protect them from the biochemical effects of deficiency. In further experiments it was found that weight gain in deficient, glutamine supplemented animals was better than in deficient rats without supplemental glutamine. On the other hand, weight gain in control rats receiving a normal diet was better than in rats on a similar diet who were glutamine supplemented (Figure 5).

TABLE 2

RAT #	BRAIN WEIGHT (Grams)	GLUTAMINE CONTENT µm/ml
1 TD	1.226	0.4
C	1.283	1.5
2 TD	1.335	0.51
C	1.291	1.8
3 TD	1.322	<0.1
C	1.288	1.0
4 TD	1.233	<0.1
C	1.337	1.5
5 TD	1.314	<0.1
C	1.323	1.62
6 TD	1.408	0.4
C	1.377	1.52
7 TD	1.245	<0.1
C	1.396	2.25
8 TD	1.287	0.25
C	1.301	1.8
9 TD	1.357	<0.1

NUMBER	MEAN GLUTAMINE CONTENT (µm/ml)
8 Controls	1.62 ± .355
9 TD	0.17 ± .215
	p <.001

Decrease in brain glutamine of rats during progressive thiamine depletion.

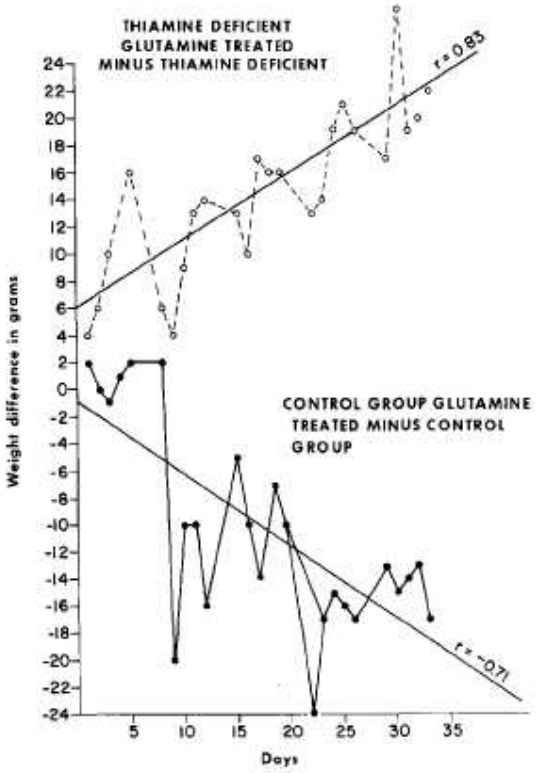
Thus it seemed that glutamine provided some metabolic protection to thiamine deficient rats, but appeared to be a disadvantage to rats receiving a normal diet. Glutamine depletion in thiamine deficiency animal experiments by other investigators might have been the cause of the decreased brain gamma amino-butyric acid concentrations that they found.[73]

2. Other defects in TPP

Intermittent maple syrup urine disease (branched chain ketoaciduria) has been reported to occur following repeated infections[74] and is thiamine dependent in some cases.[75 76] This is to be expected since the branched chain decarboxylase is TPP dependent. In one instance of apparently classic presentation of maple syrup urine disease in an infant, the substance which inhibits formation of TTP was detected in a urine specimen (Lonsdale, D: Unpublished observation). Adequate therapeutic approach with thiamine was not attempted.

A mentally retarded child with hyperuricuria was reported. Profound acidosis and increased concentrations of urinary uric acid in early infancy were repeatedly detected.

FIGURE 5



Regression curves showing difference in weight gain of thiamine depleted, glutamine supplemented rats. Average daily weight gain in thiamine depleted, glutamine supplemented rats was better than weight gain in thiamine deficient animals not receiving glutamine (upper curve). Weight gain in rats receiving normal diet with a similar supplement of glutamine was slower than animals receiving normal diet without glutamine (lower curve).

Blood uric acid was found to be elevated on only one or two occasions. Compulsive lip biting, as seen in the Lesch Nyhan syndrome, was so severe that teeth had to be removed to relieve the constant trauma. Concentration of red cell hypoxanthine-guanine phosphoribosyl transferase (HPRT), the enzyme deficiency responsible for causing Lesch Nyhan syndrome, was normal. Accumulation of pyruvate in serum after intravenous glucose suggested defective entry of pyruvate to the citric acid cycle, and she responded metabolically to administration of thiamine supplementation. Hyperuricuria, which disappeared after thiamine, was thought to be due to a compensatory activity of the hexose monophosphate shunt, inducing de novo biosynthesis through activation of phosphoribosyl-pyrophosphate degradation.[78] It is of interest that one of the thiamine responsive cases of maple syrup urine disease had unexplained hyperuricacidemia.[76] A logical explanation might be proposed, that defective phosphorylation of thiamine was responsible for an effect in the branched chain decarboxylase and pyruvic dehydrogenase at the same time. Hence, overproduction of uric acid could have been a metabolic phenomenon similar to that seen in the child with compulsive lip biting.

OTHER REPORTED THIAMINE DEPENDENCIES

Thiamine responsive hypoglycemia has been reported in a child.[79] Curiously, the metabolic block was in pyruvic carboxylase, which is biotin dependent. The authors attempted to explain this by pointing out evidence that the concentration of acetyl CoA, produced by activity of pyruvic dehydrogenase, has a stimulating effect on the activity of pyruvic carboxylase. This is logical, since the combination of

oxaloacetate and acetyl CoA is the first step in entry of citrate to the citric acid cycle. Hence it was assumed that this was a thiamine dependent stimulation of carboxylase by this indirect method. It is possible that biotin supplementation might have been as effective. It is helpful to point out that phosphoenolpyruvate to pyruvate is a unidirectional step. Therefore, alanine is transaminated to pyruvate which must then be carboxylated to oxaloacetate and converted to phosphoenol pyruvate by carboxykinase, in order to enter the Embden Meyerhof pathway to gluconeogenesis. This is the so-called anaplerotic form of gluconeogenesis. The case of a middle aged woman was partially reported.[50] Gross edema, foot and wrist drop, ophthalmoplegia and recurrect episodes of unconsciousness were not recognized as beriberi until she suffered a severe incident of life-threatening apnea, requiring tracheostomy. Red cell transketolase activity was low, and urine contained large amounts of pyruvate and other keto acids. Thiamine supplementation resulted in slow neurological recovery, which was accompanied by a progressive anemia. Ethanolamine was found in large concentrations in urine and, since this is the receiver of the labile methyl group from folate in endogenous synthesis of choline, it was hypothesized that ethanolamine wastage occurred as a result of folate deficiency. Serum folate was found to be abnormally low, and a supplement of folate was provided. A rapid reticulocyte response and correction of the anemia gave evidence that this was a correct interpretation. It was of some interest that the anemia was not megaloblastic in character. After two years of folate and thiamine therapy she developed vitamin B_{12} deficiency, resulting in recurrence of severe neurologic symptoms, which were treated successfully with injections of cyancobalamin. After the first of these injections she developed fever and myositis, which lasted for several days before her general improvement commenced — a phenomenon which is not uncommonly seen when commencing nutrient therapy. Her neurologic state was considered to be partially induced, and her recovery retarded, by a chronic addiction to cigarettes. This case illustrates quite well some of the biochemical relationships between vitamins.

A patient with sensorineural deafness, diabetes, hyperaminoacidura and megaloblastic anemia was reported.[80] It was discovered that the anemia was responsive to thiamine, although this vitamin has no documented hematopoietic action. Hypersegmentation of granulocytes had suggested folate deficiency, but megaloblastosis and anemia did not respond to either B_{12} or folate. Diversification of biochemical actions may be illustrated by analogy, though proof of mechanisms may be elusive. For example, several patients have been described with deficiency of methionine activating enzyme.[81] This enzyme catalyzes synthesis of S-adenosyl methionine (SAM) and requires ATP. It is a vital link in the important process of transmethylation, which increases the length of carbon chains. Also, SAM has a negative feedback effect on 5,10 N methylene-tetrahydrofolate reductase, which methylates active folate. Deficiency of SAM results in continued activity of this enzyme, and causes it to catalyze increased amounts of methylated (inactive) folate. This then "piles up" at the B_{12} dependent step, where the labile methyl group is transferred back from inactive folate to methionine. This step is catalyzed by 5-N methyltetrahydrofolate methytransferase. When folate is demethylated it becomes "active" in its cofactor functions. This mechanism has been suggested from experimental studies.[82] [83]

It is hypothesized that such a mechanism is capable of explaining a high serum folate concentration in the presence of hypersegmented neutrophils, as was observed in one of the children with methionine activating enzyme deficiency.[81] Possible substrate inhibition of the B_{12} dependent step results in lack of active, and accumulation of inactive, folate. In the case of thiamine responsive megaloblastic anemia, it may have been a relative shortage of ATP which resulted in inefficient SAM production, thus giving rise to loss of folate activity. It would have been interesting to see if folinic acid administration could have corrected the megaloblastic anemia, for an attempt to correct it with inactive folate would have been equally unsuccessful, if this hypothesis is correct.

Another case report is of interest,[84] since the two children described had recurrent febrile lymphadenopathy, a clinical entity which is extremely common. One of the two unrelated boys was found to have abnormal red cell transketolase

activity (TKA), typical of TPP deficiency. The other, though TKA was normal, was found to excrete the substance which is associated with inhibition of TTP synthesis. Elevation of serum folate and B_{12} concentrations fell, and clinical remission occurred when this child received thiamine hydrochloride supplementation. When the vitamin was discontinued, another episode of fever, lymphadenopathy, and extreme irritability occurred several weeks later. Central nervous system implication was indicated by recurrence of night terrors. One episode of sleep walking was accompanied by spontaneous urinary incontinence. Serum concentrations of folate and B_{12} were again increased, and thiamine supplementation was restarted. Within a few days the lymphadenopathy resolved and the serum concentrations of folate and B_{12} became normal. This child continued to take thiamine in the same dose and remained completely well until about a year later, when nocturnal symptoms began again. A high potency multivitamin and mineral complex was prescribed and symptoms rapidly resolved.

These cases deserve to be explained in biochemical terms, even though speculative. It is suggested that the mechanism is as follows. Both children were allowed unlimited sweets, including juice, carbonated beverages and candy, time honored "treats." Lymphadenopathy was well documented as one of the poorly understood effects seen in beriberi. One of the boys had a high pulse pressure with a diastolic pressure of zero, and a femoral pulse audible by auscultation. Both of these findings are seen in beriberi in which autonomic neuropathy is typical. The fever and lymphadenopathy were considered to represent a centrally initiated "defense" response, which may or may not have been caused by viral or other infection. The nocturnal disturbances were additional evidence of central nervous system irritation, triggered by either increased sensitivity of the nervous system, or perhaps representing an alarm signal derived from depreciated oxidative metabolism in brain stem. This explanation is tentatively supported by the presence of TTP inhibitory substance, suggesting that brain was marginally deficient in TTP. The mechanism in the other child may have been similar, since TTP is synthesized from TPP. Alternatively, there may have been a defect in phosphorylation of the vitamin, resulting in the loss of both TPP and TTP.

It is a logical assumption that these reactions in both children were exact imitations of how the body reacts to the assault of an infecting organism. Irrespective of whether such an organism was or was not the initiating etiologic cause, the clinical manifestations would invariably be perceived as those of infection under most observational circumstances. Hence, the use of an antibiotic would be the usual therapy chosen, as indeed it had been repeatedly in both cases before these investigations had been performed.

The fact that a vitamin was preventive appears superficially to be completely illogical according to our present perception of the disease. In fact, the supersensitive brain may be capable of reacting to virtually any "stressor" from environment, in much the same way as the boy with intermittent ataxia when he entered the air conditioned room. In dealing with the human machine, in its environment, it is essential that we attempt to discern the nature of the defense, rather than assume that some unseen, undetected organism is responsible.

Finally, a few words should be said about recurrence of symptoms in one of these children, in whom corrective therapy was reestablished by providing a multivitamin. Vitamins each have their specific actions in a vast biochemical ecology which is much like the food chain in nature. Each step is dependent upon the presence of one or more of the members of this nutritional team. It is this which creates major problems in reaching a better understanding of vitamin therapy. The double blind study, using a single agent, is impossible since virtually any study will prove to be either negative, or revealing no statistical significance. Also, it is probably true that different conditions respond to the same vitamin or vitamins, because they will prove to have similar biochemical etiology. Finally, there is the important phenomenon of interaction as has long been known for the relationship between folate and B

DEFECTS IN THIAMINE TRIPHOSPHATE (TTP)

The only condition that has been shown to be related to deficiency of TTP is Leigh's subacute necrotizing encephalomyelopathy.[85] Cooper and associates[72] have reported the association of this condition with a factor that inhibits the formation of TTP in the brain. The disease causes severe autonomic disturbances[86] and the histopathology is similar to, but not identical with that seen in Wernicke disease, also associated with autonomic symptomatology.[87] Hence thiamine, possibly as TTP, has a vital role in function of the brain, and the lower brain in particular where automatic functional organization is regulated. Ondine's Curse, also known as primary hypoventilation syndrome[88] is due to life-threatening breakdown in the regulation of automatic respiration, and has been described with subacute necrotizing encephalomyelopathy (SNE).[89]

Conditions which may be related to TTP

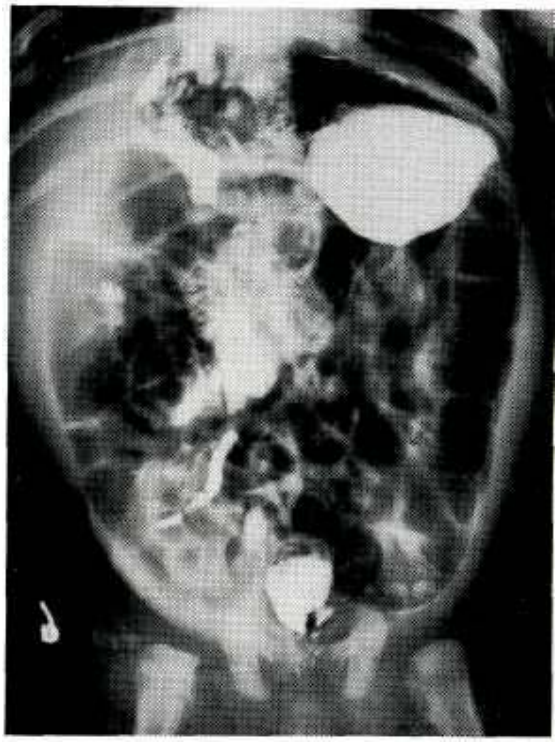
There is much evidence that Sudden Infant Death Syndrome (SIDS) may be caused, at least in some cases, by abnormal thiamine metabolism, as already mentioned. The classic clinical presentation of infantile beriberi is identical with the well documented facts observed in SIDS, and the epidemiology in both conditions has great similarity.[90] Many older texts contain descriptions of infantile beriberi, and these are worth reviewing briefly. Sudden death is one of the most startling features of the condition, and it occurs more commonly with male infants, mostly at night when they are asleep, and more commonly in late winter or early spring. It is unusual before the age of one month and after the age of six months, and autopsy findings are trivial. An important parallel between the two conditions is that the death is frequently preceeded by a cold which appears to be inconsequential, and is usually ignored until it is remembered by the parents after the event has occurred.

Recent studies have been reported [91] which appear to contradict the hypothesis that SIDS might be related to thiamine deficiency. The victims studied were found to have marked elevations in serum thiamine concentration. However, the concentrations were so strikingly abnormal that they strongly suggest an abnormality in biologic use of the vitamin, such as failure to phosphorylate. It seems unlikely that this discovery indicates an excessive intake of thiamine. Using the clinical parallelism between thiamine deficient beriberi and SIDS, Lonsdale suggested a thiamine related mechanism for the modern scourge of SIDS.[50] This investigator reported cessation of recurrent apnea in a small group of infants classified as examples of threatened SIDS, after treatment with large doses of thiamine.[92] Disappearance of life-threatening apnea has been reported in four infants treated with synthetic thiamine tetrahydrofurfuryl disulfide. [93] To support the therapeutic value of this approach, the four infants showed improvement in abnormal brain stem evoked potential tests. Transketolase activity was abnormal in only one of the infants, and one other had TTP inhibitory substance in urine. Another infant with Ondine's Curse has been reported only briefly.[94] Since his case report is unusual, and he responded to supplemental thiamine, it is described more fully here.

This male infant was referred to the author at the age of six weeks. Since shortly after birth he had experienced many episodes of paroxysmal choking, coughing, apnea and cyanosis. Many of them required resuscitation. There had also been recurrent explosive diarrhea and abdominal distension (Figure 6). The liver was clinically enlarged. A clinical diagnosis of tracheo esophageal fistula could not be substantiated, even at exploratory surgery.

Electroencephalographic study revealed shifting, bizarre electrical patterns. Bradycardia alternated with tachycardia; bradypnea alternated with tachypnea. A hemolytic component was demonstrated by increase in plasma hemoglobin to 12.4 mg./DL (normal 1–5 mg./DL(, serum haptoglobin reduction to 10 mg./DL (normal 30–200 mg./DL) and a reticular count of 11.3%. Anisocytes, macrocytes, poikilocytes, target cells and spherocytes were present. There was no anemia, so bone marrow production kept up with the hemolytic destruction.

FIGURE 6



Plain roentgenogram of abdomen of six week old infant who suffered numerous cardiorespiratory arrests, excreted SNE factor in urine, and responded symptomatically to large supplements of thiamine hydrochloride.

A completely unexpected finding was that urine contained TTP inhibitory substance, and because of this he was given a supplement of 150 mg. per day of thiamine hydrochloride. Symptoms, which had been recurring repeatedly throughout the investigation, gradually subsided and ceased. After one year of continued supplementation, it was withdrawn. Wheezing and coughing rapidly developed and the supplement was restored, again with remission. The same thing happened a year later, and it was then decided to maintain thiamine indefinitely. This patient subsequently developed some learning disability and hyperactivity. Both parents had revealed presence of SNE inhibitory substance in their urine, but in smaller concentration in each than in the urine of their child, suggesting a carrier state. The mother developed symptoms a few years later that were diagnosed by another physician as multiple sclerosis.

Red cell TKA has been studied in a small group of SIDS victims and found to be normal.[95] This suggests that the causes of the syndrome are multiple, and it is always possible that the etiology may be due to a defect in TTP in some cases, which would not be detected by TKA since this only reflects biologic activity of TPP. The case just described does not correlate with the classical descriptions of thiamine deficiency in any form, although it is most likely to be an abnormality in brainstem activity due to defective TTP metabolism. The author has found a very close relationship with thiamine responsiveness and the presence of SNE inhibitory substance in urine. In another case a boy with Down's syndrome had an abrupt change in personality following an illness. His mother had symptoms which were being treated as multiple sclerosis. Both mother and child had the SNE inhibitory substance in their urines.

Reflex sympathetic dystrophy,[96] already discussed in a previous chapter, may be responsive to therapeutic thiamine. It is a syndrome which represents a classic example of unusual sympathetic dominance in a limb after trauma. The trauma itself

may be relatively trivial, and the ensuing neurologic sequelae appear to be disproportionate in severity. The condition is sometimes mistaken with connective tissue disorder, neoplasm or phlebitis and is occasionally considered to be a conversion reaction."

An adolescent male received a whiplash injury to the cervical spine. He gradually developed increasing pain, numbness and parasthesiae in the left wrist, then the right. There was numbness in one wrist, the associated thumb and index finger. He later developed glove anesthesia in both forearms and insensitivity to pinprick. He experienced constant neck pain and headaches. Repeated roentgenology of the cervical spine and myelography did not reveal any evidence of structural defect, and one year after the accident he still had symptoms. On examination both hands and forearms were cyanotic and cold to the touch. The femoral artery was easily audible by auscultation in the inguinal area, and the blood pressure was 150/30 mm Hg. and was labile. Gross white fingernail spots were seen, suggesting serious nutritional deficiency.[98] Diet history revealed an excess of sweets and cola. No treatment was given other than dietary instruction, and supplementation with a high potency vitamin and mineral mix. General health began to improve and all neurologic symptoms had disappeared in two months. Both forearms were normal in color. Although red cell TKA was never outside normal range, it increased from 54.4 to 65.6 mU/L/min. Thiamine pyrophosphate percentage effect (TPPE) decreased from 11.4 to 1.0% Thus the trend of this test indicated thiamine response, only by comparison before and after treatment. The symptoms suggested that the trauma acted as a stress insult which triggered the neurologic symptoms mindful of beriberi. Since a peripheral neuropathy was the presenting feature, it is possible that TTP was the important component.

NATURALLY OCCURRING THIAMINE INHIBITORS

Drinking tea and chewing tea leaves is known to reduce biologic effectiveness of dietary thiamine, due to an unidentified inhibitory mechanism." Chewing betel nut and consumption of raw fish results in athiaminosis. [100]

Two enzymes have been identified which attack and destroy thiamine; thiaminase I (thiamine: base 2- methyl-4 aminopyrimidine-5- methenyl transferase. EC 2.5.1.2) and thiaminase II (thiamine hydrolase. EC 3.6.99.2). Fujita[101] demonstrated that thiamine could be formed in the presence of thiaminase I if a base exchanged pyrimidine derivative and the thiazole moiety of thiamine were present. This suggests that an ecologic role of the enzyme is in synthesis of the vitamin, but the equilibrium of the reaction favors destruction of the intact molecule rather than its synthesis. Thiaminase I is found in raw fish, including shell fish, ferns, and other plants, and is produced by a number of bacteria. Fujita[101] studied its possible role in human nutrition, and described "thiaminase disease" with an incidence of 3% in an urban Japanese population. Diagnosis was established by screening feces and ascertaining the degree of destruction of thiamine *in vitro,* at pH 5.6 and 37° centigrade in two hours. Many, but not all, of the subjects found to have fecal thiaminase were experiencing symptoms, which improved after oral thiamine supplementation. Some subjects were placed on a thiamine deficient diet and developed athiaminosis symptoms earlier than the control subjects on a similar diet, but without thiaminase in their feces.

Both enzymes split thiamine at the methylene bridge, but thiaminase I, by a base exchange reaction, causes the base to become linked to the pyrimidine moiety. This newly formed molecule then becomes a thiamine analog inhibitor, which prevents the host animal from using dietary thiamine.[101] Bacillus thiaminolyticus, an aerobe found in human colon, and clostridium thiaminolyticum, an aerobe found in small intestine, produces thiaminase I. Aerobic bacillus aneurinolyticus is found in colon and produces thiaminase II. All three species produce spores. Clostridium thiaminolyticum is a subgenus of clostridium sporogenes, [102] the organism which has been associated with bilateral cortical necrosis (polioencephalomalacia) in cattle and sheep.[103] Thiaminase I has been found to be activated by nicotinic acid and its amide, forming an analog identified as N-(2'methyl-4'aminopyrimidyl- (5') methyl-3-carboxypyridinium) chloride hydrochloride. [104] A relatively simple assay has been

established for the detection of thiaminase in animals that could be adapted to human studies.[195]

Bilateral cortical necrosis may be a model for considering the etiology of some human brain disease, which is presently not identifiable in biochemical terms. For example, the disease has been induced experimentally by exposing a calf to amprolium,[106] a known thiamine analog inhibitor. This substance is used as a coccidiostat in chicken feed,[107] and though its concentration is considered to have no bearing on human nutrition, nevertheless the chickens are produced for human consumption and might result in disease under unusual circumstances. It is also possible that an overwhelming infection of human bowel with clostridium sporogenes might generate neurologic symptoms if thiaminase were found to be produced by the infecting organism.

ALLITHIAMINE AND ITS SYNTHETIC DERIVATIVES

Allithiamine is formed in garlic bulbs, and other plants of the allium species, by the conjugation of allicin with thiamine to form (2' methyl-4'- amino-pyrimidyl-(5') methylformamino-5-hydroxy-2-pentenyl - (3) allyl disulfide.[108] Allicin is produced by the action of alliinase on alliin during grinding of fresh bulbs of garlic. A number of allithiamine derivatives have been synthesized by substituting the S-alkyl radicals by different alkyl groups, forming methyl, ethyl and propyl-allithiamine. The propyl derivative, also known as thiamine propyl disulfide (TPD) was tested extensively and reported by Fujiwara.[108] A later synthetic, thiamine tetrahydrofurfuryl disulfide (TTFD) has almost completely replaced the earlier compounds since it appears to have the same biologic activity, but does not result in a pungent garlic odor from the patient. The laboratory and clinical testing of TPD and TTFD has received little attention in the West.

The biologic activity of TPD was found to be significantly greater than that of thiamine hydrochloride (THCl). It is absorbed more readily and urinary thiamine increases markedly.[108] Rabbits were injected with ^{35}s-labeled TPD, the label being attached to the sulfur atom in the prosthetic group that is left outside the cell when the disulfide bond fractures at the cell membrane Radioactivity was found in serum, and none of the blood cells, indicating that the prosthetic mercaptan remains outside the cell. Pretreatment of mice with TPD partially protected them from the lethal effect of cyanide and other toxic agents.[108] It stimulated intestinal peristalsis when infused into a denervated segment of dog jejunum, indicating cholinergic stimulation.[108] This cholinergic activity has been supported by experiments in TTFD treatment of DBA/J2 inbred mice, since it was shown to delay the natural remission of audiogenically stimulated seizures that occur in the weanlings of this strain.[109] Evidence has been reported that audiogenic seizures in rodents are produced by increased cholinergic activity.[110] Acetyl choline synthesis is known to be closely associated with thiamine[111 112 113 114 115] and methyl thiamine may be required for its release into the synaptosome.[9 10]

Toxicity studies with TTFD show its pharmacologic safety.[116 117] The metabolites excreted in rat urine after TTFD are methysulfonyl and methylsulfinyl derivatives, together with inorganic sulfate. [118] Metabolites from the ^{35}S mercaptan moiety have been identified as a sulfoxide, a sulfone, and a lactone. [119 120 121 122 123] They are excreted quickly, and do not have any discerned toxicity. Pharmacologic studies with TPD and TTFD were performed in isolated guinea pig atria at concentrations of 10^{-5}g/ml. and demonstrated a negative chronotropic and positive inotropic effect. [124] They appear to produce a beneficial effect in pulmonary stenosis [125] and experimentally induced cardiac hypoxia in animals [126 127] Administration of TPD decreased loss of myocardial transaminase in infarcted dog heart and EKG changes were less marked than in controls.[128] Alloxan treated diabetic rats obtained improvement in sciatic nerve function when treated with TTFD.[129]

Thiamine has a ganglion blocking action in excessively large doses, probably due to the quaternary ammonium as in tetraethylammonium bromide. [130 131 132] Doses of lg/Kg lowered blood pressure in dogs.[26] This effect is largely lost in the alkyldisulfides, since the quaternary ammonium is absent in the disulfide configuration.

Clinical Studies

Allithiamine derivatives have been tested in the treatment of musculoskeletal disorder[136] and is reportedly superior to thiamine hydrochloride (THCL) in the treatment of alcoholics with neurologic complications.[136] It has produced clinical remission in Leigh's disease,[133] though some of the patients become resistant to its pharmacologic effects, for unknown reasons.[137] An attempt to identify antibodies to the drug was unsuccessful.[138] Four infants with repeated life threatening apnea and abnormal brainstem evoked potential tests, obtained clinical remission with TTFD.[93] A number of Japanese institutions collaborated in TTFD treatment of 285 patients with neuromuscular pain.[139] Clinical improvement was reported in many of these patients.

Abnormal TKA in psychiatric patients[140 141 142] may be primary or secondary to poor nutrition, but several patients experienced marked clinical improvement after thiamine supplementation, and TTFD might be a more powerful therapeutic agent if absorption mechanisms are compromised.

Because of our experience with dysautonomic function and a report in the literature[143] concerning the relationship of adrenergic mechanisms in hypertension, we wondered whether TTFD might have an effect on blood pressure in spontaneously hypertensive rats. The experiment was designed as an attempt to ascertain whether TTFD could be shown to have a biologic action which was measurable, and whether it would support the ancient belief that garlic had a beneficial effect on human hypertension.

THE EFFECT OF TTFD ON BLOOD PRESSURE IN SPONTANEOUSLY HYPERTENSIVE RATS (SHR)

Thirty age-matched male rats of the Kyoto spontaneously hypertensive strain (SHR) were housed in individual stainless steel cages. Their weights respectively were between 130 and 223 grams. There were 5 deaths early in the experiment, thought to be due to overheating of the animals before taking the tail blood pressure. Two of these deaths occurred in the randomly selected treatment group, and 3 in the control group. The experiment was subsequently completed with 13 in the treated group and 12 in the control group. The dose of TTFD was calculated by assessing the average approximate 24 hour intake of water per rat and adding an aqueous colorless solution of TTFD to the drinking cup of each rat in the treated group. Taste did not seem to influence the intake of water by treated animals compared with controls.

Body weight and blood pressure were recorded twice a week by a technician who was unaware of which rats were receiving TTFD. After a warming period in a heating box, pressures were recorded by the tail cuff method at approximately the same time of day. The same technician performed all necessary procedures throughout the experiment. After an initial period of adjustment, the blood pressure of all animals appeared to be relatively stable and the experiment was commenced.

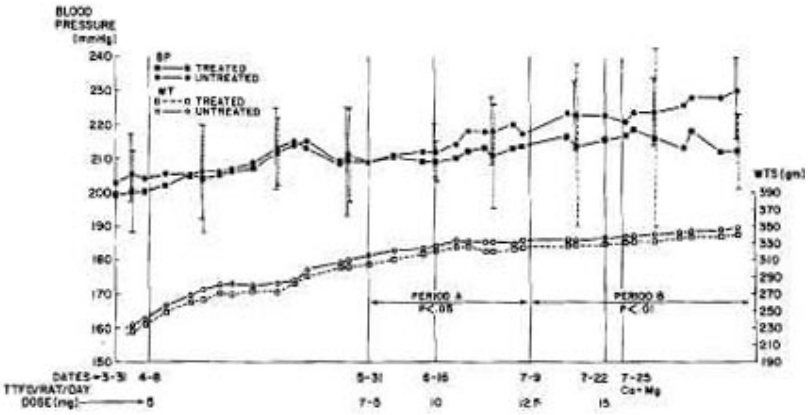
An initial dose of 5 mg. of TTFD a day was given from April 8th. to May 31st. It was then increased to 7.5 mg. Thereafter the dose was increased at intervals. On June 16th. it was raised to 10 mg., to 12.5 mg. on July 9th. and 15 mg. on July 22nd. From July 22nd. to August 11th. both groups were given a supplement of 3 mg. of calcium carbonate and 1.5 mg. of magnesium oxide each. These supplements were also added to drinking cups. The entire experiment covered a period of four months.

RESULTS

The mean blood pressure of each group of rats is shown in figure 7. Blood pressure of a single rat whose response appeared to be definite (Fig 8) are contrasted with one who was treated but did not respond (Fig 9) and an untreated control (Fig 10). All twenty-five records were reviewed blindly and individually, without knowing which group each animal represented. The correct assessment was made in twenty-one. Of the four records which were assessed incorrectly, three were from TTFD supplemented animals that had blood pressure similar to the controls. One record from a rat in the control group appeared to be similar to that seen in a TTFD responsive animal.

Of the thirteen TTFD supplemented rats, five showed a response which appeared to be definite, and the records were similar to that seen in Figure 8. Blood pressures in these responders were much the same at the end of the experiment as at the beginning, whereas controls and non responders showed a rise of approximately 20 to 25 mm. Hg. Some TTFD supplemented animals who failed to show a definite response revealed greater lability in their week to week pressures, but this was too variable to use as a distinguishing feature.

FIGURE 7



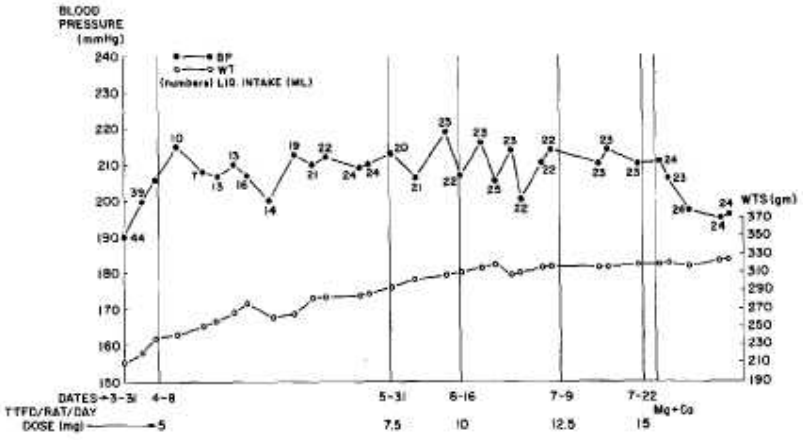
Mean blood pressure of TTFD treated SHR rats compared with untreated controls.

Statistical Analysis

There was no difference in mean blood pressure readings between the 2 groups through April and May. On May 31st. the dose increases began and 2 subsequent periods were analyzed separately: period A from May 31st. to July 7th., and period B from July 12th. to August 22nd. In both of these time periods, using a repeated measures analysis, there was a statistically significant difference between the two groups. For period A the P value was < .05 and for period B < .01 Although the two sample histograms overlapped, the sample means were clearly different, particularly when compared with readings before May 31st. This difference was maintained throughout the duration of each time period. Consequently, in terms of average response differences, there was statistical significance

between the groups. Each bar represents the mean blood pressure for the group, plus or minus two srandard deviations. It is felt that this is an honest portrayal in view of the amount of blood pressure lability noted in individual animals.

FIGURE 8



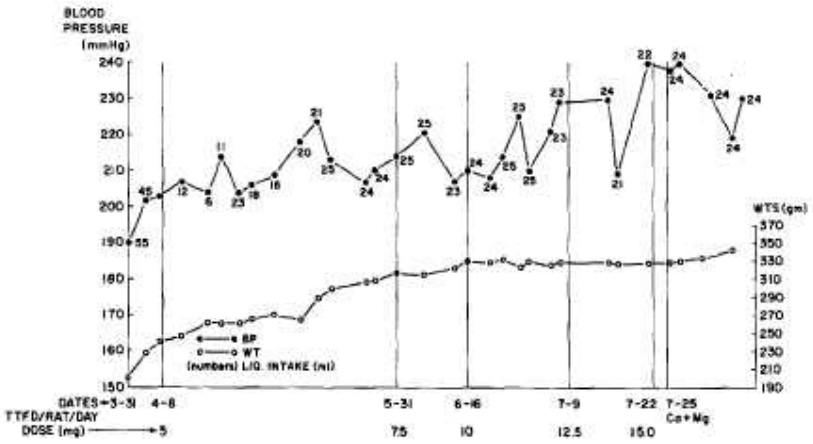
Record of blood pressures obtained in a single SHR rat t eated with TTFD.

This record was typical of only 5 of 13 treated animals that provided a clear response to the experimental use of the compound.

DISCUSSION

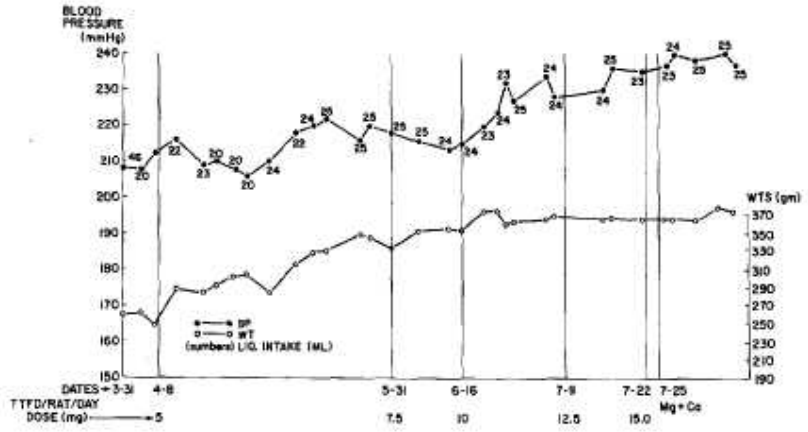
The results suggest that TTFD does have a biologic effect on blood pressure in some of these genetically abnormal rats. This effect appears to be either time or dose related, and might be a mixture of both variables. The mechanism is conjectural, but might be hypothesized from what is known about the action of TTFD. As already discussed, it is known to have thiamine activity and will readily and efficiently restore normal function in experimentally induced thiamine deficient animals. It is most unlikely that SHR animals have a conventional thiamine dependent mechanism causing the hypertension, and this would suggest that TTFD effect is due to factors other than simple replacement of a thiamine deficiency.

FIGURE 9



Record of blood pressures obtained in a single SHR rat treated with TTFD who failed to show a response. Note the unusual lability in the week to week pressure.

FIGURE 10



Typical tracing of blood pressures obtained in an untreated control SHR rat. Lability in the pressures recorded week to week is not as great as in those shown in a treated non-responder (Fig. 9).

It has been suggested that the hypertensive mechanism in SHR is adrenergic in nature,[143] and this would support the evidence that TTFD is cholinergic in action. It was shown that it had a biologic effect on audiogenically seizure prone mice weanlings of the DBA/J2 strain[109] and this was also thought to be cholinergic in nature. It is therefore hypothesized that the antihypertensive effect of TTFD in this

rat experiment was due to its stimulation of cholinergic action to a point where it produced a homeostatic balance against the genetically determined adrenergic dominance.

It seems clear that there is good reason to study the pharmacologic effects of TTFD further. It is well established as a useful therapeutic agent in Japan and in other parts of the world. No toxic effects have been observed in the treatment of human subjects or in animals.

BIOCHEMISTRY OF NEUROTRANSMISSION

The physiology of autonomic transmission was touched upon in Chapter 1. The biochemistry is vital to an understanding of the part played by nutrition in endogenous synthesis of neurotransmitters. Acetyl choline is common to both the autonomic and voluntary nervous systems. Choline, derived mainly from the diet, is also synthesized from ethanolamine by transmethylation. It is used for synthesis of phospholipids, vital to both cell membrane stability and surfactant function. Choline acetylase performs the function of acetylating choline, the acetyl group being derived from acetyl CoA which is formed by the oxidation of pyruvic acid. Acetyl choline then passes to the nerve terminal where it is packaged and released into the synaptosome.

It is important to understand the function of this neurotransmitter: it is an adaptation of the synaptosome that enables the electric eel to form a battery capable of delivering 500 volts of static electricity, and acetyl choline is the neurotransmitter involved.[144] It is evidently a mechanism for energy transduction since it converts chemical into electrical energy. Bhagat and Lockett[145] found acetyl choline synthesis to be impaired in thiamine deficient rats, and concluded that this was caused by deficiency of acetyl CoA. Nagler and associates[6] induced fatty livers and bilateral hemorrhagic cortical necrosis of kidney in choline deficient weanling rats. They reported that the concentration of acetyl choline decreased 20-36% in small intestine, 32-36% in brain, and 50-75% in kidney. Terminal arteries supplying the microcirculatory system in mesentery were found to be hypersensitive to epinephrine which produced vasospasm and led to ischemic damage.

The adrenergic mechanisms were reviewed by Frohman and Stachura[146] who discussed the actions of dopamine, norepinephrine, and serotonin. These are the neurotransmitters that have been most studied in this system, but there are probably many more. Tyrosine is the amino acid from which DOPA, dopamine, norepinephrine and their metabolites are derived. Serotonin is formed from tryptophan, and Fernstrom and Wurtman[147] have drawn attention to the importance of carbohydrate in inducing its synthesis and release from the Raphe nuclei in brain stem. This mechanism appears to be of great nutritional importance and provides an explanation for the growing concept that a large concentration of sugar in the diet causes the release of neurotransmitters and corresponding nervous activity. In a number of instances, we have seen very obvious clinical benefit in hyperactive children by a drastic reduction of their inordinate consumption of carbohydrate foods. In a typical example, hyperactivity in an elementary school child was so much improved by eliminating sweets, that the mother spontaneously did the same with the sister who was equally responsive. A high school student consumed 90 gallons of a well known carbonated beverage in two months. Syncopal attacks ceased after its withdrawal.

It seems to be clear that nutrition, by its effect on neurotransmitter synthesis, has a marked effect on human behaviour. Selye[57] showed that adaptability is goverened by central neurological control in experimental animals. His work demonstrated that failure of this mechanism was caused by a combination of physical stress application and malnutrition. He developed evidence that biochemical changes throughout the general adaptation syndrome were secondary events and concluded that many human diseases were due to adaptive failure. It seemed, therefore, that detailed comparison of this syndrome with the catastrophic effects of the thiamine deficiency might be helpful.

METABOLIC AND CLINICAL PHENOMENA OF THE GENERAL ADAPTATION SYNDROME COMPARED WITH EFFECTS OF THIAMINE DEFICIENCY

Selye's work with animals defined the neuroendocrine response to stress, which he designated as the general and local adaptation syndromes. The general syndrome was defined as "the sum of all the nonspecific system reactions of the body which ensue upon long continued exposure to stress." The alarm reaction, stage of resistance, and stage of exhaustion divide the syndrome into three more or less distinct stages. Adaptation energy was defined as "the ability of the organism to acquire resistance to stress." This concept introduces a vitally important factor which may be insufficiently considered in the etiology of disease, the recognition of dynamic biological changes with reference to the stage of development of the syndrome. Some of these changes were so similar to those observed in various stages of thiamine deficiency that Skelton[56] set out to explore the similarity. He was able to show that a thiamine deficient diet in rats reproduced the classical histopathologic pattern of the general adaptation syndrome.

Attempts were made to protect animals by pretreating with thiamine before inducing the syndrome with the usual trauma. Further study was abandoned when these attempts failed. In the text which follows, comparisons between the biochemistry and histopathology of thiamine deficiency (TD) and the general adaptation syndrome (GAS) will be derived from two standards of reference unless otherwise stated.[57 148]

Although the original work on GAS goes back to mid 20th century , the encompassing paper by Selye, to which reference has been made repeatedly, remains a classic and nothing of a similar nature has been repeated, to our knowledge. Selye has written much more about "stress" since that time, but his early experiments investigated the various biochemical responses of animals in exquisite detail. Not the least important of his teachings was the dynamic changes that he discovered in such ordinary biochemistry involving blood sugar, cholesterol and other metabolites, and his studies of nitrogen balance as represented in urine present us with a wealth of detail that cannot be ignored. For example, in order to use blood sugar as a test for the state of glucose metabolism, the investigator would have to know which stage of the syndrome the animal was in at the time. It would only be by collecting a "profile" of blood and urine metabolites and looking at them together that an interpretation could be made by extrapolating backwards from Selye's studies. Similarly, it can be seen that if thiamine defective metabolism has anything to do with the stress response, it would be expected that the test subject might have a normal, high, or low blood glucose and still have the disease in various stages of development of treatment.

The second reference used is an English translation of a detailed work by the "Vitamin B Research Committee of Japan." Much of the early work on beriberi was conducted by Japanese investigators, where the historical associations with rice ingestion are as important as those of the English in the discovery of a cause and treatment for scurvy. The accumulated knowledge of this committee is provided in thirteen comprehensive chapters covering clinical, pathological and therapeutic details about thiamine. Some very important details are also provided with respect to a large number of synthetic derivatives of the vitamin which have been developed and tested in Japan.

Perhaps the best known example of metabolic change in GAS is that of blood glucose. It rises immediately following exposure to alarming stimuli and then falls before rising again during the stages of resistance. After adrenalectomy or hypophysectomy, prolonged hypoglycemia results from mild alarm stimuli and neglible hyperglycemia follows. Platt[40] recognized that hypoglycemic beriberi victims did not recover, hyperglycemic subjects sometimes recovered, and normoglycemic patients always recovered when treated with thiamine, suggesting that the blood glucose registered the degree of seventy and the stage of the disease. Similarly, serum chlorides decreased during the alarm reaction, rose above normal levels in resistance, and fell again in exhaustion. Geraci[149] observed hypoelectrolytemia as a stage of disease in seals who had been made thiamine deficient by giving them thiaminase containing raw fish. This appeared to be a

prelude to death. The investigator suspected that this was due to failure of the sodium pump in its vital role in cell membrane physiology. Hypokalemia is a well known phenomenon in beriberi. [150]

Selye evaluated the differences in reaction between adapted and unadapted animals. Moderate cold, solar radiation, and muscular exercise evolved intense adaptive responses and marked alarm reactions, but hyperglycemia, tachycardia, and leucocytosis might be the only observations made in a well adapted animal. Similar stimuli were invariably initiating factors in the presentation of an individual patient's first episode of beriberi, which often occurs in the early summer during a spell of hot, sunny weather. In bygone days, when the disease was seen in epidemic proportions, it affected the hard working laborer much more readily than the sedentary worker. Selye also recognized that continued exposure to stress would finally break down the adaptive mechanism of a fully inured animal, and this suggested that adaptation used up, and finally exhausted, the energy required for meeting the adaptive response. Tachycardia, sweating, peripheral vasoconstriction, and stupor, characteristic phenomena in animals in the shock phase of GAS, are equally characteristic of beriberi in man. Blood glucose, pyruvate, and lactic acid rise following exposure to mechanical trauma in non-adapted animals. These metabolic changes can be seen in poorly adapted humans, following injury or surgery, and are also the metabolic characteristics of beriberi.

Lipid deposits were observed in the liver of animals during the alarm reaction. Serum cholesterol decreases in man after strenuous exercise, X-ray treatment, and in infants described by Selye as "toxic." Fatty degeneration, "nutmeg" liver and decreased concentrations of cholesterol and lecithin, together with increased concentrations of fatty acids, occur in beriberi victims. Ketonuria is observed in both conditions. Changes in nitrogen balance have been described in both GAS and TD. Selye reported that nitrogen balance was markedly negative in the alarm reaction, and urinary creatine was increased. An increase in nonprotein nitrogen was detected in blood, and it was noted that such an increase in both nonprotein nitrogen and uric acid have been observed in man after excessive muscular exercise. Selye also suggested that creatinuria, observed in acute conditions in man, was a phenomenon equivalent to the alarm reaction in animals. Platt[40] reported that 90% of cases of beriberi in adult males were of the mild and subacute form, and subjects excreted an excess of urinary creatine. Creatinuria in these patients gradually disappeared with proper nutrition and rest, without supplements of thiamine.

PATHOLOGIC ANATOMY

Both GAS and beriberi are conditions that exhibit metabolic and histopathologic changes that depend on their degree of severity. Some comparisons can be made, and there is evidence to suggest that there is a similarity between them that cannot easily be ignored.

Adrenal Gland

The cholesterol content of the adrenal cortex rapidly decreased in the stage of alarm. Cortical hypertrophy was seen in the stage of resistance. Decreased cortical hypertrophy was seen in the stage of exhaustion. Decreased cortical lipids occurred in beriberi, but both cortical and medullary hypertrophy have been reported. Certain inbred strains of mice are audiogenically seizure prone, and postpubertal males rapidly deplete their adrenal glands of lipid after a stressful event. It has been suggested that this is related to genetic mechanisms governing their stress response and their ability to learn avoidance of painful stimuli.[151] Reference to this is made here since adrenal lipid depletion in males of the DBA/J2 strain is clearly related to their stress response. Orchidectomy in males is known to reduce this lipid depletion effect, making their stress response biochemically similar to that in the female. This is an illustration of the potential differences that may occur in animals as a result of endocrine and sex modification.

Pancreas

Islets of Langerhans became more visible in GAS and sometimes formed "giant islets" by union of several islets. Hypertrophy of islets has been reported in

infantile beriberi. Acute involution of the pancreatic tissue was seen during the alarm reaction. Cells discharged zymogen granules, causing decrease in the size of the organ, and occasionally necrosis occurred. The pancreas also becomes smaller in beriberi, and atrophy of parenchymal cells, together with proliferation of connective tissue, occurs. Zymogen granules are known to be discharged following vagal stimulation or after choline administration.

Hypophysis

Degranulation of eosinophils and nuclear pyknosis were described by Selye in GAS. The borderline between the anterior and posterior lobes was blurred by basophilic invasion, but such changes were inconstant. The gland is reported to be frequently enlarged and congested in beriberi. Localized cellular infiltration has been described in the intermediate lobe.

Blood

Neutrophilic leukocytosis with relative lymphopenia was reported in the shock phase of GAS. Leukopenia would occur initially if the reaction was severe and the animals succumbed without showing any stage of resistance when this persisted. Eosinophilia frequently followed the neutrophilic stage. Red cells increased in number, especially in the shock phase, but could be preceded by a transient decrease, often accompanied by an increase in circulating reticulocytes. In experimental TD in man, red blood cells may decrease in number and may be accompanied by reticulocytosis. Lymphocytosis, neutropenia, and eosinophilia have also been seen in various stages of beriberi, and leukocytosis is reported in Shöshin, the most severe form of the disease.

Although an explanation for these observations can only be postulated, it is suggested that both conditions reveal the organism's stress response, and that energy metabolism is the common denominator. Selye recognized that his experimental animals became exhausted under prolonged stress, and constantly referred to the fact that "some form of energy" was used up. With our modern knowledge of oxidative metabolism, it is easy to hypothesize that an adaptive crisis might place the "energy producing capacity" of the organism under severe strain. Since thiamine is a vital part of this metabolic machinery, it may well be that oxidative capacity is the essential clue to explaining the similarity between the two conditions. In one case, the symptoms accrue from rapid utilization of energy, whereas defective production is the cause in the other. Thus, the loss of red blood cells might occur as a result of failure in the sodium pump, with resulting hemolysis and a subsequent reticulocyte response.

Autonomic System

Selye did not study the autonomic system in detail, although he fully recognized that autonomic transmission was an important part of an animal's responsiveness to stress. This system was examined carefully by Japanese investigators. When beriberi cadavers were autopsied within fourteen hours of death, typical constriction of peripheral arterioles was seen, suggesting that cholinergic drive had been lacking. Capillary dilatation was observed in cerebrum, but no observed changes were recognized in the pons and medulla, including cellular swelling, eccentric nuclear displacement, vacuolization and chromatolysis of Nissl substance. This was particularly marked in the nucleus solitarius, cuneatus and ambiguus, as well as the nuclei of the 9th, 10th, 11th and 12th cranial nerves.

Severe changes were seen in anterior horn cells in the lumbar and sacral level and were much less severe in the cervical and thoracic regions, consistent with the distribution of the craniosacral outflow of the parasympathetic system and its greater susceptibility to damage. Severe involutional changes were noted in large preganglionic medullated fibers, not in post ganglionic small nonmedullated fibers. Ganglion cells exhibited degenerative changes.

Perhaps these changes were linked to TTP in its specific role within neuronal membranes, but whatever the mechanisms may be, it does suggest a reason for the highly labile state of the autonomic system in the beriberi patient. Because autonomic dysfunction is considered to be a commonly overlooked cause of

symptoms in modern man, it is important to outline the symptomatology of classic beriberi as a model for further consideration of such dysfunction.

SYMPTOMS AND SIGNS OF BERIBERI

Certain salient features of the disease will be outlined here. Many classical works are readily available for further reference, but we believe that a consideration of some of these symptoms will alert the reader to some of the characteristic symptoms of functional disease in modern man.

Autonomic Dysfunction

From the Japanese studies, the cardiovascular system reflected best the lability of autonomic activity in beriberi, although the myocardium was also affected. Injection of epinephrine often caused an exaggerated response in the patient, resulting in tachycardia, hypertension, palpitations, substernal pain or oppression, nausea, abdominal pain and vomiting. Sometimes a paradoxical reaction resulted in bradycardia and hypotension. Injection of 0.1% atropine sometimes caused paradoxical bradycardia. Pilocarpine injection frequently caused an unusually strong parasympathetic response, and Aschner's reflex was particularly easy to elicit during convalescence. This reflex, elicited by pressure on the eyeball was common in early cases of the disease.

In the early stage there was vagotonia, demonstrated by bradycardia, low diastolic pressure, and changes in body temperature. Sympathetic tone was seen in later stages, and this was exemplified by tachycardia, intensified heart sounds, and increased metabolic rate. Unpredictable changes in gastric secretion were considered to be related to differences in autonomic activity. In some patients, there was a high concentration of free hydrochloric acid in the stomach, whereas in others it was low. The treatment response from thiamine was curious, and illustrates the dynamic aspects of the disease. Those with low concentrations of HCl developed high concentrations initially, before becoming normoacidic. Those subjects with high concentrations developed initial low concentrations before achieving normoacidity. Prolonged transit time in the bowel, constipation, and ileus were commonly seen in Riley Day syndrome, as has already been described in Chapter 2. This was clearly an effect of parasympathetic failure, and it is interesting that meteorism or intestinal bloating was particularly notable in the infantile form of the disease. Infantile beriberi was frequently accompanied by blepharoptosis and was regarded as an important physical sign related to cholinergic failure, as it is in the recognition of myasthenia gravis, with which beriberi may easily be confused.

Recent work has added further evidence that thiamine has a regulatory function in autonomic activity. In twenty-one cases of adult beriberi, electrocardiographic tracings revealed prolongation of the Q-T interval and inversion of T waves in eight patients.[28] These are the electrocardiographic changes reported by Schwartz and Malliani[152] in the lethal syndrome discussed in Chapter 2. It is worth emphasizing again that death in this syndrome is not uncommonly associated with sudden excitement, underlining the role of stress. There is ample evidence that dysautonomic function is associated with sudden death, and this has been discussed in SIDS, SNE and Riley Day syndrome.

The most relevant symptoms of thiamine deficiency at the present time are those which might easily be called neurotic or "functional." Headache, lassitude, anorexia, insomnia, excessive sweating, nausea, vomiting, abdominal pain, and personality changes may be associated with typical "stocking and glove" analgesia and "funnel vision" symptoms that are usually attributed to “hysteria”. Such early changes can be observed in beriberi and may remain for many years without advancing to the more severe symptoms and signs that characterize the disease. In earlier times, when beriberi was common, it caused a great deal of industrial absenteeism. Optic neuritis, peripheral neuritis, changes in size and shape of the pupil, and retinal changes were seen in the later stages, and it is unlikely that such observations in a patient today would raise beriberi as part of the differential diagnosis.

Calories and Thiamine

The term "naked" or "empty" calories is used to refer to food which has no vitamin or mineral content to recommend it. Since thiamine metabolism is closely tied to oxidation of carbohydrate, it is relevant to consider the wisdom of much refined sugar in the modern American diet. Anorexia was an almost universal symptom of beriberi and it cleared quickly after thiamine supplementation. Animals become hypophagic in experimentally induced thiamine deficiency. This suggests that there is a centrally mediated protective reflex that prevents further ingestion of calories. In 1976 the Japanese newspaper Nihom Keizi Shimbun reported a "strange disease" in southern Japan. Patients had complained of edema of the lower extremities, palpitations and numbness. Polyneuritis, hypotension, and other physical signs were observed. In a series of more than one hundred cases, the diagnosis had been made of "unknown virus," mononucleosis, and "unknown disease." The patients were all adolescents living in the suburbs and were all from affluent families. Like adolescents in America and other highly industrialized societies, they were congregating at the soda fountain and consuming large amounts of carbohydrate, which included highly flavored imported carbonated beverages. Their disease was recognized as beriberi, and the newspaper commented that although 23,000 patients died annually from the disease in the first quarter of this century in Japan, it was thought that the condition had disappeared in relationship to improved nutrition. This is a clear reminder that nutrition involves balance, and a well satisfied stomach is no indication of the nutritional value of the diet in complete terms. Since carbohydrate in the multitudinous and tempting forms in which it is consumed today is virtually an end in itself, it is advisable to pause for a moment and consider whether such dietary indiscretion is a frequent cause of morbidity, generally considered to be psychologic in origin. Even rudimentary clinical observation cannot miss the clear association of hyperactivity and sugar in many children today. Also considered by some investigators to cause hyperactivity are food coloring substances, found predominantly in refined carbohydrate foods.

To illustrate this principle, there is a neurologic disease known as Cuban molasses disease, which occurs in cattle that consume high concentrations of molasses in their food.[153] It can be relieved or prevented by merely adding a higher percentage of fiber in the form of grass to the feed lots. This suggests that fiber is a most important nutritional component that has its effect in regulating or modifying carbohydrate absorption.

The enormous emphasis on refined carbohydrate foods of the modern world may have behavioural effects which have far reaching consequences. Since aggressive personality changes are so often induced, it may be that there is a strong connection with the accelerating incidence of violence. Perhaps the critical knowledge required is the ratio of ingested calories to oxidative capacity of brain cells. A thorough examination of the clinical expressions of thiamine dependent metabolism in the central nervous system appears to provide extremely important clues to behavioural characteristics of man.

Chapter 4

BIOCHEMICAL STUDIES IN FUNCTIONAL DYSAUTONOMIA

Symptoms and physical signs of functional dysautonomia have been outlined, and the condition has been compared with that described in animals by Selye after non-specific stress factors have been applied. It is not very surprising, therefore, that many biochemical changes described by Selye are probably to be seen in human patients since stress, in many forms, must play an increasingly important part in the process of "technological survival." Thiamine deficiency produces functional dysautonomia, but is not unique in this respect. It may be thought of as a model of bioenergy deficit which may be copied by deficiency of other nutritional factors or an internal derangement of enzyme biochemistry, occurring perhaps because of genetic abnormality — as illustrated by a patient whose case was discussed in the last chapter. This will be further illustrated in the next chapter.

DYNAMIC STATE OF BIOCHEMISTRY

Many observers have difficulty perceiving that biochemical reactions are in a continuously dynamic state. Blood and urine metabolites change in concentration constantly, and together they reflect total function of the organism. By the same token, the changes presumably reflect the stage of evolution of a disease, and a given metabolite may be low, normal, or increased in the same disease, in the same patient, at different times. Not infrequently a clinical diagnosis is based upon laboratory observations without sufficiently considering these factors. An example may be cited in beriberi.

Platt[1], already named as one of the early investigators of this disease, was aware of many features that he could not understand, although there is no doubt that his observations were keen and accurate. He was among the first to use crystalline thiamine after it had been synthesized, and he reported several important phenomena which illustrate the point. He gave a patient with beriberi 5 mg of thiamine. The patient stopped breathing and epinephrine was injected. The blood pyruvate first increased dramatically, and then fell without further treatment. As outlined in a previous chapter, Platt reported blood glucose in relationship to the predictability of recovery after administration of thiamine, and noted the disappearance of excessive creatinuria that occurred when the victims of the disease were rested in hospital. Thus the stage of the disease might be judged by combinations of values derived by measuring urine and blood metabolites.

Laboratory assessment of patients with functional dysautonomia may be more credible when these facts are taken into consideration. Obviously, if a given metabolite is slowly changing from low to high concentration it may be measured at a time when it is normal. The use of a nutritional or "orthomolecular" approach in patients proves, however, frequently to be purely empirical because of incomplete knowledge. An awareness of theoretical biochemistry is helpful in perceiving, for example, how transamination, transmethylation, and transulfuration relate to the process of oxidative metabolism since it provides perspective in basic understanding of how cellular function creates and uses energy. The bioenergy process will be considered in greater detail in Chapter 6.

Urine has been found to be useful in reflecting changes in nitrogen excretion more than blood. The nature of the changes is not at present completely understood, but they appear to be relatively non-specific. Correlation with clinical characteristics has occasionally revealed a phenomenon which has become an important part of the therapeutic approach. This effect we have termed "paradox." Put simply, the patient's symptoms may become very much worse initially, before they begin to improve. The period of paradox can last for a variable time of days to months, and appears to be related to chronicity and severity. It is distressing to the patient or his relatives, may cause him to abandon therapy, and must be explained to him in some detail before

treatment is instituted. On the other hand, we have learned that it is often a favorable sign that later success will be achieved, and the family can be reassured that it is worth pursuing. It can give rise to real problems of management as, for example, when the patient reaches a stage where he refuses to take the vitamins or minerals prescribed; this is observed quite frequently in "psychiatric" problems. The biochemical changes in urine will be illustrated in the next chapter, when individual case histories are described. This preliminary discussion prefaces the description of biochemical studies, since it is necessary to recognize that the facts are not absolute in themselves. They are dynamic changes and invariably relative to each other and to the stage of disease or therapy.

LABORATORY STUDIES

1. Urine Amino Acids
2. Urinary Keto Acids
3. *Red Cell Transketolase*
4. Serum Folate and B_{12}
5. Urine Creatine, and Uric Acid

Urine Amino Acids

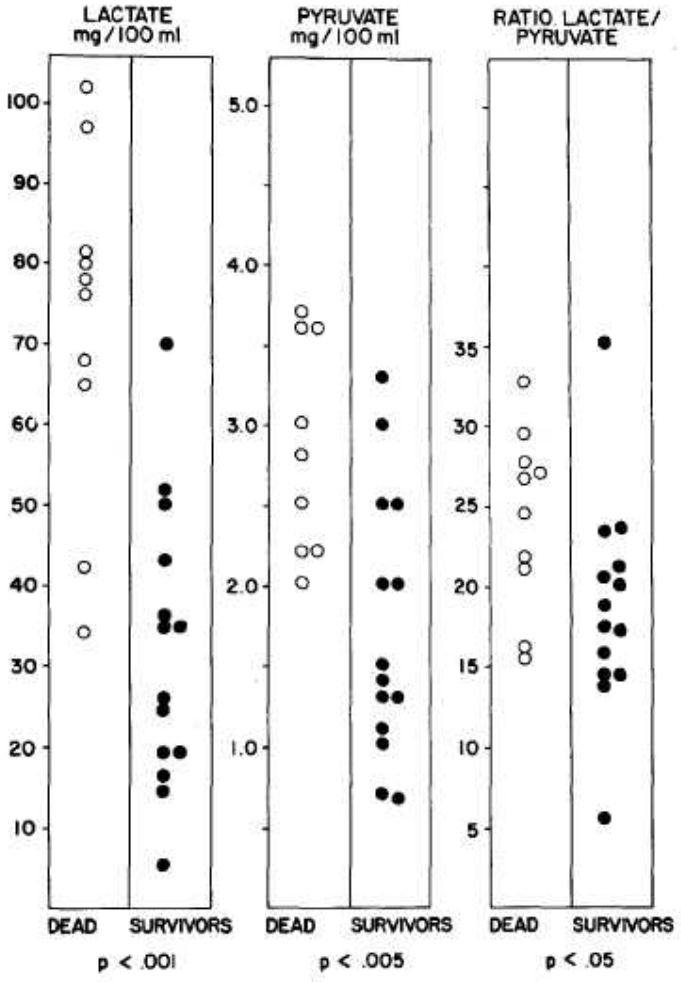
Our laboratory has been performing amino acid screening for many years using standard methods[2 3 4] and a wide experience of a number of inborn errors of metabolism has been acquired.[5 6 7 8 9] As already discussed in the last chapter, one case in particular stimulated further interest in energy metabolism and its relationship with vitamins.[10] Since then, whenever possible, a 24-hour urine is collected from a patient under study, but it is divided into a 12-hour day and a 12-hour night specimen. The idea, as a routine, was derived from the case of the child with intermittent cerebellar ataxia already described in a previous chapter, when it was discovered that the patient had gross differences in urinary excretion of pyruvate, alpha keto glutarate, and some amino acids by day as compared with night. Although the night and day differences in urinary pyruvate and alpha keto gluarate diet were initially thought to be associated with diet, it is now considered possible that they are the effect of disturbed circadian rhythm. Healthy children, receiving a similar diet, did not demonstrate such wide differences in their urinary concentrations of these metabolites.[11] Urinary amino acid concentrations in the case cited revealed day and night differences for alanine, glutamic acid and aspartic acid, as already discussed. Generally speaking, there appears to be some relationship between the nutritional state as a whole and urinary amino acid concentrations. We have observed gross changes in urinary amino acid chromatograms from treated phenylketonuria (PKU) patients, for example. In some instances it is corrected by increasing the phenylalanine intake after finding the serum phenylalanine to be too low. In other cases the serum chromatogram may become normal after increasing the calories through carbohydrate or phenylalanine-low formula.

In attempting to assess patients who might be metabolically abnormal and responsive to nutritional therapy, it has been found that some of them excrete unusually low concentrations of urinary amino acids (oligoaminoaciduria). After therapy begins, the pattern may change to hyperaminoaciduria, possibly at the same time as clinical paradox, as described above, becomes evident. Subsequently, the urinary concentrations become normal. The changes are seemingly non-specific, and may reflect only the degree of nitrogen excretion occurring, since the profile increases or decreases as a whole. The phenomenon may possibly be likened to the pattern of hydrocarbons in the exhaust pipe from an internal combustion engine, reflecting the efficiency of the engine. Obviously it is considerably complicated by factors which may be primarily genetic, or secondarily acquired, such as renal tubular absorption. For example, renal tubular hyperaminoaciduria in galactosemia clears when a galactose free diet is provided to the patient. On the other hand, it may well be that urinary amino acid relationships may be much more important than this relatively simplistic suggestion. Perhaps by studying a disease where there is some evidence of defective energy metabolism some clues might be found. There have been some attempts to do this in Reye's syndrome, a condition in which mitochondrial changes have suggested an abnormality of this nature.[12] A change in

the ratio of branched chain to aromatic amino acids has been reported in the disease[13] and increased concentrations of homovanillic acid have suggested a relationship between brain catecholamines and cerebral ischemia.[14]

In a group of patients with Reye's syndrome under the care of Dr. M.W. Levinsohn of Rainbow Babies and Children's Hospital, Cleveland, urine was examined for amino acids and total keto acids. Blood was examined for concentrations of ammonia, pyruvic and lactic acids. In Figures 1 and 2, these concentrations are compared in the patients who died with those who survived. The ratio of glycine to alanine was lower in urines from both groups of Reye's syndrome patients than in healthy controls, and there were statistically significant differences between non survivors and those who survived, for serum lactate, pyruvate and ammonia as well as keto acids. There were twenty-four patients in all, but not all of them had urine collections completed, and this explains the discrepancy in the number of evaluations as shown. The absolute concentrations of both glycine

FIGURE 1

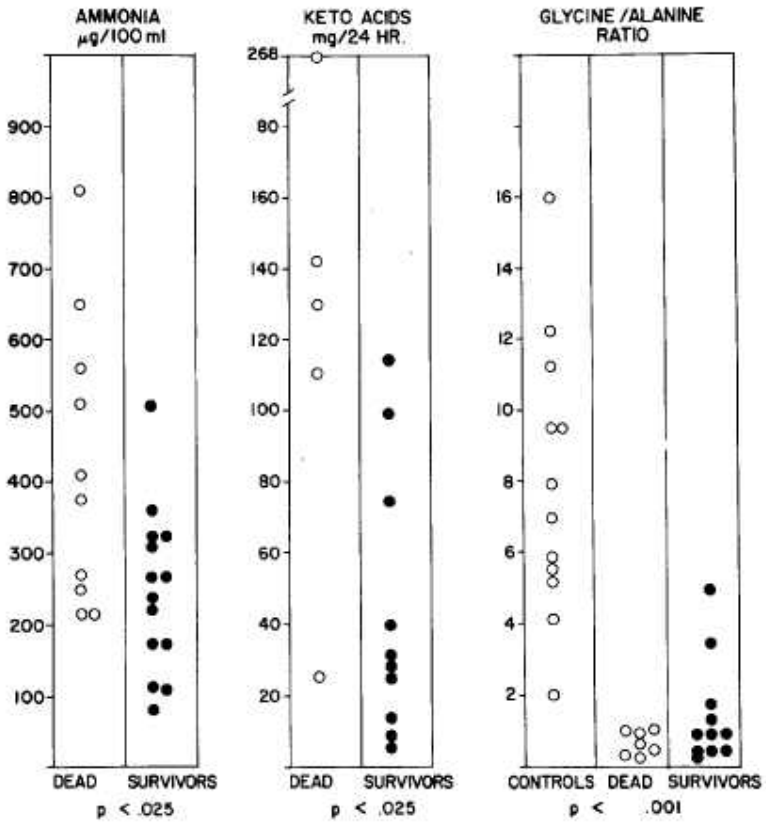


Serum lactate, pyruvate and lactate/pyruvate ratio from 10 children dying from Reye's syndrome compared with 14 survivors. There was evidence of hypoxic tissue state which was more severe in the patients who died, compared with the survivors.

and alanine in urine were usually much increased in these patients, but lower glycine to alanine ratio suggests that the alanine increase was disproportionately greater than that of glycine, indicating that there was a greater alanine production, or renal loss,

in Reye's syndrome urines than in urines from healthy individuals. This was irrespective of whether concentrations of glycine and alanine were in their normal or abnormal individual ranges respectively. Normally, pyruvate, lactate and alanine are in equilibrium and a defect in pyruvate metabolism results in a proportional increase in the concentrations of all three substances in the plasma.[16] Since lactate can be metabolized only by conversion back to pyruvate — and this occurs especially readily in aerobic tissue, such as heart and kidney — the rise in alanine concentration supports the interpretation of hypoxic tissue in Reye's syndrome.

FIGURE 2



Serum ammonia, urinary total keto acids and glycine/alanine ratio from patients dying of Reye's syndrome. The 2 survivors with the highest glycine/alanine ratio were the mildest and least affected children of the 11 children tested.

TABLE 1

Description of Variables Overall by any group

Variable	N	Mean*	Standard Deviation	Minimum-Maximum
Glycine	163	236	233	16 - 1245
Normal	65	86	58	
Threatened SIDS	72	371	228	
Reye's	26	238	291	
Alanine	164	108	262	4 - 2696
Normal	65	17	9	
Threatened SIDS	73	96	50	
Reye's	26	371	587	
Histidine	153	192	223	7 - 1222
Normal	65	61	41	
Threatened SIDS	73	259	193	
Reye's	15	432	421	
1-methyl histidine	147	32	55	0 - 336
Normal	64	48	68	
Threatened SIDS	66	25	43	
Reye's	17	6	15	
3-methyl histidine	151	39	41	0 - 391
Normal	65	36	27	
Threatened SIDS	70	40	50	
Reye's	16	49	44	
Glycine/Alanine	163	4.5	3.0	0.3 - 20
Normal	65	5.5	2.4	
Threatened SIDS	72	4.3	2.8	
Reye's	26	2.3	.5	
Histidine/Alanine	153	3.4	2.7	0.1 - 27.6
Normal	65	3.9	1.6	
Threatened SIDS	73	2.9	1.6	
Reye's	15	3.2	6.9)	

* units = mg/gr creatinine

Means, standard deviations, minimum and maximum values for 5 amino acids in urine of adult healthy subjects compared with those in a group of threatened SIDS infants and a group of children with Reye's syndrome

Urinary Glycine/Alanine, and Histidine/Alanine Ratios In Normal Adults, Threatened SIDS, and Reye's Syndrome

In observing urinary amino acid profiles obtained from ion exchange analysis for many years, we were repeatedly impressed by the relationship that appeared to exist between glycine and alanine. As discussed earlier, this became particularly noticeable in amino acid analyses of urine from patients with Reye's syndrome. Some rather simple experiments were performed with thiamine deficient rats. In most instances there was a sharp early decline in the concentrations of the majority of the urinary amino acids, with the exception of alanine, which increased steadily. Therefore, the ratio of a given amino acid to alanine at the beginning of the experiment was high, but rapidly decreased and remained low throughout the remainder. This phenomenon was not observed when thiamine deficient food was force fed to rats by means of intragastric intubation, although the ultimate death of the animals was induced more quickly and was associated with petechial hemorrhages in many organs. This supported the concept that the effects of thiamine deficiency were related to whether there was an associated caloric excess or deficiency.

After observing the glycine/alanine ratio in Reye's syndrome patients, the results were compared with those obtained from healthy adults and with a group of infants whose symptoms suggested that they were at risk for SIDS. Attempts to obtain urines from healthy age matched infants failed for lack of suitable subjects, but it is considered worth while to present the results obtained by comparison of

histidine to alanine in addition to glycine, since there were statistically significant differences between the two relatively homogenous populations and healthy adults.

Urines from sixty-five normal adults, seventy-three infants with threatened SIDS, and twenty-six Reye's syndrome were assayed for amino acid concentrations by automatic amino acid analysis. Four amino acids were chosen for comparison with alanine; glycine, histidine, 1-methyl histidine and 3-methyl histidine. Means, standard deviations, minimum and maximum values are displayed in Table 1. The distribution of sexes is shown in Table 2. Only the ratio of histidine to alanine and that of glycine to alanine showed any statistically significant differences in the three groups of subjects.

TABLE 2

Frequency of Males and Females by Group

Sex	Normal	Threatened SIDS	Reye's
Male	25	36	9
Female	40	35	8
	65	71	17
Unknown	0	2	9
TOTAL	65	73	26

Sex distribution in 3 groups, normal healthy adults, threatened SIDS and Reye's syndrome

When looking at the distribution of these variables for each group, it appeared that the distributions were abnormal for the Reye's syndrome patients. There were extreme values or outliers that differed from the main body of data. Because of this a non-parametric technique was used to ascertain whether the groups differed in terms of the two ratios (Table 3). The Mann-Whitney test that was used compares the rank of values rather than the absolute values in themselves. It therefore tests whether the values in one group differ in general from those of another group. In each case, for both ratios, the groups differed significantly from each other ($\infty = .05$). Figures 3 and 4 display the histograms for the 2 ratios as seen in the 3 groups of urine.

TABLE 3

Group Comparison (Mann-Whitney Test)

	Normal versus Threatened SIDS				
	Sample Size		Medians		
Variables	Normal	Threatened SIDS	Normal	Threatened SIDS	P-value
Glycine/Alanine	65	72	5.3	3.5	0.0002
Histidine/Alanine	65	73	3.8	2.6	0.0002

	Normal versus Reye's Syndrome				
	Sample Size		Medians		
Variables	Normal	Reye's	Normal	Reye's	P-value
Glycine/Alanine	65	26	5.3	1.0	<0.0001
Histidine/Alanine	65	15	3.8	1.2	0.0001

	Threatened SIDS versus Reye's Syndrome				
	Sample Size		Medians		
Variables	Threatened SIDS	Reye's	Threatened SIDS	Reye's	P-value
Glycine/Alanine	72	26	3.5	1.0	<0.0001
Histidine/Alanine	73	15	2.6	1.2	0.004

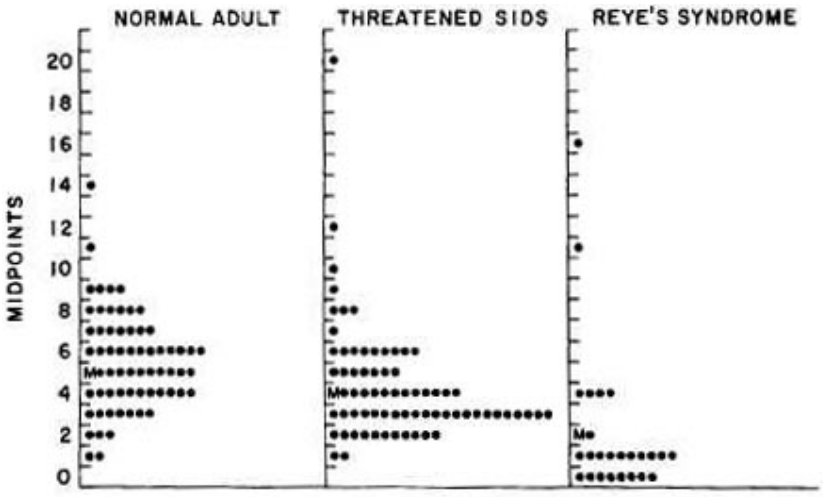
Statistical analysis of glycine/alanine and histidine/alanine ratios in 65 healthy adults, 73 threatened SIDS infants and 26 Reye's syndrome patients, using the Mann-Whitney test.

COMMENT

As already mentioned, there is an extremely wide variation in normal ranges of amino acids in urine. The nutritional state can produce tremendous differences and the experiments with thiamine deficient rats suggest that the effect on urinary amino acids is as much related to caloric starvation as a direct effect of vitamin deficiency. It is also consistent with the creatine and creatinine changes that were seen under similar conditions. Hence it is apparent that little can be gained by measuring these nitrogenous metabolites in urine for their absolute concentrations.

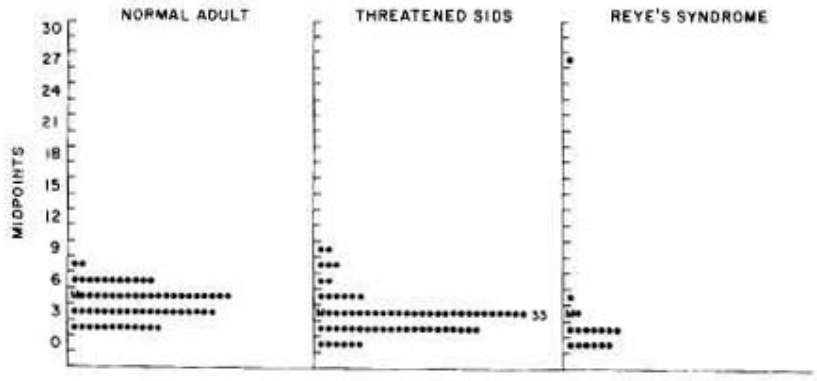
The question is, therefore, whether there is any value in comparing one amino acid with another in the form of a ratio. Since alanine is an important amino acid in the mechanism of anaplerotic gluconeogenesis, it might well be that its concentration differs substantially from those of other amino acids in urine, and that this is reflected in ratios as suggested here. However, it is admitted that the observations presented have no known explanation at present. A great deal more information is required if such a technique is to be of any value in interpreting a dynamic state of metabolism. Now that Reye's syndrome is known to be associated with aspirin ingestion if viral disease in children, there would appear to be at least a template upon which further research in this might be conducted.

FIGURE 3



Histograms of glycine/alanine ratios in urine of normal adults, threatened SIDS, and Reye's syndrome.

FIGURE 4



Histograms of histidine/alanine ratios in urine of normal adults, threatened SIDS, and Reye's syndrome

Although a unique pattern of hyperaminoacidemia has been reported in Reye's syndrome and appears to be valuable as a prognostic tool,[17] it does not appear to be specific to this one disease.[18] However, in this particular case the amino acid pattern similar to Reye's syndrome was from a patient with ornithine transcarbamylase deficiency[18] and this enzyme dysfunction has also been reported in Reye's syndrome.[19] Thus the amino acid pattern might be expected to vary in terms of the biochemical dysfunction which may be found to be more common to more than one disease, rather than a pattern which may be expected to be diagnostic of a finite disease entity as it is presently perceived.

It is apparent that the primary defect in Reye's syndrome is a breakdown of the normal mechanisms for energy production or utilization, and that the various enzyme defects described in the disease have this mechanism in common. Thus we might perceive changes which reflect a kaleidoscope of aberrant function with this as the root cause.

Urinary Keto Acids

Urinary keto acid concentrations, like amino acids, have not proved to be very helpful in determining the exact nature of metabolic abnormality in most cases. The method used was originally reported to be the determination of pyruvic acid [20] but it is not specific, and will recognize the presence of other organic acids. Two dimensional paper chromatography reveals the presence of pyruvic acid and alpha keto glutarate [21] and each has a distinctive color reaction if the paper is dipped in sodium hydroxide, followed by diazotized sulfanilic acid. In selected cases, therefore, it has been possible to observe semiquantitative determinations of these two metabolites. Night to day differences were noted in pyruvate and alpha keto glutarate in a case of pyruvic decarboxylase deficiency as discussed,[10] but these differences have not been seen to the same degree in other patients who have responded to a nutritional approach. Technological problems remain in detecting and quantitating urinary organic acids routinely, and there must be many such compounds awaiting identification. By such identification it is possible that new dimensions might be added to the therapeutic approach. It is now much easier to measure organic acids in a number of commercial laboratories.

Red Cell Tranketolase

Quantitation of red cell tranketolase is a useful method of determining deficiency of thiamine pyrophosphate (TPP).[22] [23] The enzyme occurs twice in the hexose monophosphate shunt and its activity is dependent upon TPP as co-factor. In performing this study, transketolase activity (TKA) is first determined by measuring the amount of sedoheptulose-7-phosphate produced per unit of time *in vitro.* The second part of the test is carried out by incubating lysed red blood cells with substrate in the presence of TPP. Increase in TKA after addition of the co-factor is regarded as an index of acceleration and correlates well with early clinical manifestations of TPP deficiency. This is then referred to as the TPP percentage effect (TPP% or TPPE). The method used was that described by Massod and associates.[25] The range of TKA as reported by these investigators was 42.1 to 86.1 mU/L/min and the TPPE 0-17.4%. If the activity of the enzyme is satisfied with the existing concentration of TPP in the patient's red cells, there will be no acceleration of activity when TPP is added and the TPPE will be zero. The higher the TPPE, the greater the need for TPP and thus the more deficient the red cells. The normal range in control subjects agreed with those published by Massod and associates. There were seventy-three apparently healthy persons, ranging in age from three years to sixty-eight years. The range of TKA was 44.5 to 87.6 mU/L/min with a mean of 63.54 ± 13.06 (SD). The TPP percentage effect ranged from 0 to 15.4%, mean 4.42 ±4.47 (SD). The commonest abnormal result is a high TPPE, and this appears to be the clearest sign of TPP deficiency, for it correlates extremely well with the patient's clinical improvement after thiamine supplement to the diet was provided. In most instances TKA, though initially in the normal range even in thiamine deficient cells, will rise also as the TPPE decreases, often to zero. In some instances TKA is below the normal range also, and is usually considered to be a reflection of a greater degree of deficiency or chronicity in the patient. Using this test[25] forty-two physically

healthy non-alcoholic psychiatric in-patients were evaluated. Sixteen (38%) of them showed evidence of thiamine deficiency. Five patients had received thiamine-containing vitamins for a period of from two to forty-seven days before the test was performed, suggesting that poor nutrition may not fully account for the observed thiamine deficiency. It may well be that some individuals absorb thiamine poorly, or have a genetically determined abnormal transketolase apoenzyme which is not responsive to co-factor therapy.[26]

Some differences of opinion exist in the literature as to the clearest and most expected effect of TPP deficiency on transketolase function. Markannen and Kalliomaki used a method of measuring transketolase which differs from the modification used in our laboratory. These authors used the assay to study a variety of clinical conditions in sixty-seven hospital patients.[27] They concluded that TKA was a better indicator of TPP deficiency than TPPE, which they considered to be unreliable. On the other hand, Geraci[28] found that TPPE was an accurate and reliable method of detecting TPP deficiency in experiments with seals. In these animals, thiamine deficiency was produced by feeding them raw fish, known to contain the anti-thiamine enzyme thiaminase I (E.C. 2.5.1.2),[29] and was a deliberate attempt to study the mechanism by which seals survive this effect from their natural diet. Apart from a possible genetically determined abnormality in transketolase and the effect produced by deficiency of its cofactor, another curious phenomenon had been reported. Markannen and associates[27] observed supernormal TKA in patients with Addisonian pernicious anemia. Wells and co-authors[30] also observed this, and they studied patients with megaloblastic anemia. They found supernormal TKA in those patients whose anemia was caused by deficiency of vitamin B_{12}, but this was not elevated in the Addisonian anemia associated with folate deficiency. Hornabrook and Marks[31] found raised blood pyruvate concentrations in patients with megaloblastic anemia and neuropathy due to vitamin B_{12} deficiency. Blood pyruvate was restored to normal by administering thiamine. They noted that many red cell enzymes have been reported to be abnormal in patients with megaloblastic anemia, and Markannen and co-author pointed out that many of these enzymes were in the anaerobic pathway and were increased in activity in this anemia. It is noteworthy that a patient has been reported whose megaloblastic anemia was found, by exclusion experiments, to be responsive only to thiamine.[32] Since there is, at present, no known direct hematopoietic activity recognized as related to thiamine, it must be concluded that this was an indirect effect. It might be suggested, for example, that the real biochemical lesion in this particular patient was in oxidative metabolism, and that this had its effect on transmethylation by causing a deficiency of ATP. It is to be emphasized, however, from these confusing and conflicting reports, that the biochemical activities of vitamins are closely related and highly dependent upon each other for the ultimate conduct of normal cellular function. The abnormalities observed may arise from a chain reaction due to the dependency of one function upon another, or from multifactorial deficiency in the diet. It is clear from this and from our own work that much more has to be learned about the use of transketolase in evaluating clinical conditions. If, for example, the work of Govier and Greig[33] was correct in showing that hemorrhagic shock destroys or inactivates cocarboxylase, it might be expected that activity of the enzyme would be altered in patients in a state of post traumatic conditions. It would certainly be an oversimplification to assume that the kind of deficiency state being discussed here was an effect of dietary deprivation in terms of presently accepted nutritional standards. A question of far greater significance is whether the nutritional standards of a modern, civilized culture are adequate to meet the true functional requirements of a population that is living under increasingly stressful circumstances, and whether "stress" is capable of inducing an "effective" deficiency by excessive use of the vitamin or its dephosphorylation.

Possible Clinical Use of Transketolase

In using transketolase activity as a clinical tool, we have learned to think in terms of the variety of possibilities upon which it may shed light. Although co-factor status is the key issue, it is by no means always clear whether it indicates deficiency of specific co-factor, depleted activity for some other reason, or a secondary effect

from deficiency of magnesium. It is also obvious that caloric excesses, particularly of carbohydrate, place a demand upon the system which creates a relative deficiency of thiamine and other non-caloric nutrients and may produce symptoms as though the co-factor deficiency itself were absolute. This is perhaps the greatest danger of the modern diet, which contains a high percentage of empty calories — particularly for the young. This is illustrated by the patient reported by Lonsdale.[34] She died after a prolonged course of hyperalimentation, and autopsy revealed early changes of Wernicke encephalopathy in spite of the fact that the patient received extremely large daily doses of thiamine by minimum daily requirement standards. It cannot be assumed that a co-factor is present in sufficient quantity merely on the basis of published standards. Absorption, activation, rate of oxidation, cell membrane function (e.g. choline and phospholipid chemistry), caloric intake and both physical and mental activity are all very much related to needs.

Finally, it must be noted that TKA and TPPE are totally unaffected by deficiency of thiamine triphosphate (TTP). A patient with a TTP deficient form of Leigh's disease would be expected to have normal activity of transketolase. This may well explain why we have seen patients who respond to thiamine when TKA and TPPE are normal, and some case reports in the next chapter will illustrate this further. At present there is no known way of assessing deficiency of TTP, except by finding the inhibition factor already discussed at length in a previous chapter.

Serum Folate and B_{12}

There is reason to believe that both of these can be helpful in shedding light on the integration of oxidative metabolism in reference to transmethylation. To illustrate this important relationship we wish to repeat and reemphasize some biochemical observations in several cases already discussed in the previous chapter. It began by experience with a remarkable patient, whose case is partially published.[35] A middle-aged woman had suffered for five years from a condition which was progressive. She had had an episode of vitamin B_1 responsive polyneurietis fifteen years previously. Gross edema, episodes of unconsciousness, opthalmoplegia. wrist and foot drop, culminating in a sudden cessation of central respiratory control and prolonged apnea which required tracheostomy. Low TKA and increased concentrations of urinary pyruvic acid confirmed a diagnosis of "wet" beriberi, and thiamine hydrochloride was started. Return of consciousness, loss of edema and recovery of neurological deficits demonstrated her slow recovery. She began to develop a progressive anemia which caused a rapid fall in hemoglobin concentration, and which suggested internal bleeding. This could not be demonstrated by thorough search. Urine was evaluated by amino acid chromatography, and a large amount of ethanolamine was found. It will be remembered from previous discussion regarding transmethylation that ethanolamine is a recipient of a methyl group from folate in the endogenous synthesis of choline. If the transmethylation was not proceeding normally, it was then thought possible that ethanolamine might be found in excess in urine, indicating a possible defect in the process of endogenous synthesis of choline. Without choline this patient could not synthesize acetyl choline, and acetyl choline release may be related to thiamine as already reviewed. This patient had not received any oral nutrition for a month. It seemed that this might be the essential clue to her paralysis, and suggested that further study of transmethylation was indicated. Since she had been vitamin B_1 deficient, it seemed reasonable to consider the possibility of folate deficiency, and serum folate was accordingly studied. It was found to be 3.2 ng/ml, (n = 4–18 ng/ml) in the deficiency range. When folate was added to her diet, there was a rapid reticulocyte response and reconstitution of hemoglobin. A combination of large doses of thiamine and folate was continued. Lower extremity paralysis improved slightly, so that she was able to move her legs but unable to bear weight, and an attempt to withdraw thiamine later resulted in immediate compromise of bladder control. One year later she developed nausea, vomiting, diarrhea, and extreme fatigue, and was observed to have developed mottled melanin pigmentation of the forearms, due to vitamin B_{12} deficiency — similar to that reported by Gilliam and Cox.[36] At that time, vitamin B_{12} assay was not available in our laboratory. A dose of 100 μg of vitamin B_{12} was followed by several days of fever, malaise, and muscular pains about the shoulders and upper back. Following this, her well-being

returned, and a weekly dose of vitamin B_{12} was maintained for several years without further complication and with some clinical improvement in lower extremity weakness. An interesting phenomenon was observed during that time. Her entirely grey hair has been partially replaced by hair which is pigmented with the same color that she had before her long illness. It raises speculation as to whether her partial reconstitution represented a complicated interaction representative of an overall improved activity in cellular respiration. This case illustrates the important relationships between these three vital co-factors, and suggested that further study would be needed to attempt to elucidate them.

Suggested Relationship Between Oxidation and Transmethylation

Further experience with the concept occurred when an infant in the Ohio state screening program was identified as one who had persistent hypermethioninemia. She was referred to Doctor Gaull in New York for study, and was found to have deficient activity of methionine activating enzyme.[37] A serum folate concentration of greater than 30 ng/ml (normal 4–18 ng/ml) was reported, but hypersegmentation of polymorphonuclear leucocytes suggested chronic folate deficiency in its active as opposed to its methylated form. Since S-adenosyl methionine, the product of methionine activating enzyme, acts as a negative feedback on methylene tetrahydrofolate reductase, the enzyme which methylates folate, its low concentration or absence might fail to inhibit the reductase, and cause an accumulation of methylated folate at the rate limiting vitamin B_{12} dependent 5-methyltetrahydrofolate-homocysteine transmethylase which transfers the methyl group from folate to methionine. Theoretically this could occur because of B_{12} deficiency as well,[38] or it may reflect B_{12} inactivation. In any case, it became apparent that a high serum folate assayed by the bacterial inhibition method could indicate that normal transmethylation mechanisms were compromised. A third case drew attention to the fact that abnormal thiamine metabolism appeared to result in increase in both folate and vitamin B_{12} serum concentrations, although the mechanism is by no means apparent. Although reported elsewhere,[39] the case is briefly reviewed here, the proposed mechanism having been mentioned in Chapter 3. A seven-year-old boy had repeated attacks of fever over a two year period. They were associated with unusual irritability as well as night terrors and sleep walking, which is suggestive of a nocturnal hypoxic state. Although he had some changes in glucose metabolism, characterized by a flat glucose tolerance curve and accumulation of pyruvate and lactate four hours after epinephrine, transketolase activity and TPPE were normal. It was known from a previous hospital evaluation elsewhere that high concentrations of serum folate and B_{12} had been detected, but the reason for performing this assay in the first place was unknown. Searching further for evidence of abnormal energy metabolism, urine sent to Doctor Cooper at Yale University was reported to be strongly positive for the SNE inhibitory substance. Serum folate was 29 ng/ml (normal 4–18 ng/ml) and vitamin B_{12} by radio-immunoassay 1050 pg/ml (normal 160-900 pg/ml). During two months of high dose thiamine supplement he remained well, the longest period in two years. Serum folate was 12.6 ng/ml, B_{12} 7.40 pg/ml. Thiamine was discontinued and acute onset of fever, cervical lymphadenopathy, irritability and abnormal sleep symptoms recurred three weeks later. Serum folate had increased again to greater than 30 ng/ml and B_{12} to 1250 pg/ml, and thiamine was restarted in a dose similar to that given previously. Rapid improvement in general well-being and disappearance of fever and lymphadenopathy were observed. Five days later the serum folate was 23.4 ng/ml and B_{12} 840 pg/ml.

Although the mechanism is far from obvious in this instance, some deductions can be made:

(a) The patient had no clinical symptoms mindful of those associated with Leigh's disease, and has not developed any since the experiment was performed.

(b) Fever and lymphadenopathy were not infectious in origin, and biopsy of a lymph node on two occasions revealed only reactive hypertrophy.

(c) Symptoms disappeared after thiamine supplementation.

(d) Serum folate and B_{12} increased when he had symptoms and decreased when he improved clinically. It seemed possible that these abnormal results, irrespective of their interpretation, might be providing important information about the host response.

A two-and-a-half-year-old child was examined by an opthalmologust regarding poor visual acuity. The lenses in both eyes were dislocated and the child was referred for metabolic evaluation. Hyperactivity and poor attention span suggested that the active underlying condition might be homocystinuria,[40] but urine was negative by the nitroprusside test, and no homocystine could be identified. Amino acid analysis of urine revealed that there was some increase in histidine. An oral dose of L-methionine (100 mg/kg of body weight) was given to the child, and plasma and urine amino acid analysis performed sequentially over 24 hours. Plasma methionine increased moderately and had returned to normal within 24 hours, indicating no obstruction in normal methionine metabolism. Urine revealed the presence of the mixed disulfides of cysteine and homocysteine, also interpreted as a normal response. The child was then referred to Doctor Gaull for further study, and he was unable to detect any abnormally hypoactive state of any of the enzymes in transmethylation and transulfuration which have been reported previously in cases of homocystinuria.[41] Serum folate was greater than 30 ng/ml and B_{12} 1450 pg/ml. Red cell TKA was 29.7 mU/L/min (normal 42.1-86.1 mU/L/min) and TPPE 32.3% (normal 0-17.4%). The TKA and TPPE clearly indicated that the child's red cells were deficient in the co-factor TPP, and it is tempting to speculate that the raised serum levels of folate and B_{12} were secondary to the slow rate of oxidative metabolism that might be predicted under these circumstances resulting in a partial deficiency of ATP. The interesting suggestion has been raised that homocystinuria might be brought about by an abnormal state of oxidative metabolism.[42] It is not unreasonable to think of this in much the same way as a mechanic might regard defective mechanisms in an automobile. Oxidative metabolism, or the process of burning fuel, represents the engine, whereas the energy consuming processes of transmethylation represent transmission.

Although these important biochemincal relationships are obviously poorly understood, the situation might be summarized as follows:

(a) Serum concentration of folate can apparently be increased when cells show evidence of "active" folate deficiency as indicated by poly-morphonuclear hypersegmentation. This suggests that the biologic deficiency is brought about by accumulation of methylated folate. The active form of the vitamin is formed when the labile methyl group is transferred to methionine.

(b) Deficiency of dietary protein might result in lack of sufficient concentration of methionine to receive the labile methyl group, thus causing accumulation of methylated folate and possibly B_{12}.

(c) Defective synthesis of S-adenosyl methionine may give rise to accumulation of methylated folate which is overproduced because of failure in the negative feedback loop regulating activity of the methylene tetrahydrofolate reductase. This might occur because of a genetic defect of methionine activating enzyme, or by inability for some reason to use ATP in converting methionine to S-adenosyl methionine.

(d) Transmethylation is a complicated vital mechanism performing "energy transmission" and is dependent upon oxidative metabolism, and hence an adequate provision of ATP. The integration of folate and B_{12} in remethylation of methionine is a vital part of the internal "balance" which must be maintained for this function to proceed normally.

(e) For the reasons enumerated, the process depends upon proper nutrition since many of the ingredients are essential nutrients.

Urine Creatine, Creatinine and Uric Acid

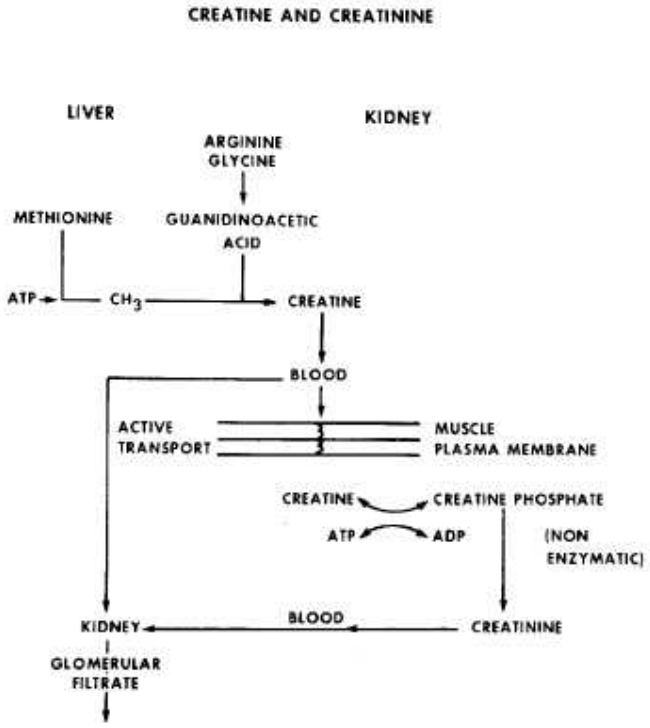
A singular need in evaluating nutritional and biochemical adequacy is a relatively simple method by which energy metabolism might be measured easily in patients. If such a tool were readily available and could be used repetitively for

monitoring therapeutic progress it would have to be non-invasive, and it would be more valuable if a standard clinical laboratory were able to perform the studies. Such a concept is roughly similar to that which is used by an engineer in evaluating the running qualities of highly complicated machinery. An analogy might be considered in the use of an ammeter in the automobile. There is no such thing as a "normal" position for the needle in this instrument. The central line marks the division between a charging and a discharging state of the battery. This analogy seemingly has little to do with the complicated machinery of the human body, or, perhaps in more finite terms, a single cell. But it is the cumulative action of all the cells in the body that represents the total energy metabolism of the organism and, therefore, it should be possible to monitor collective cellular metabolism in some way similar to that used by the engineer.

We have attempted to use the unique biochemical relationship of creatine to creatinine in the body as a means of obtaining this kind of general information. Creatine is synthesized in liver and kidney when the amidine group of arginine is transferred to the nitrogen of glycine to form ornithine and guanidinoacetic acid. Methylation then proceeds, first by the reaction of methionine and ATP in the presence of activating enzyme to form S-adenosyl methionine, which then transfers the methyl group to guanidinoacetic acid by the action of guanidinoacetate methylpherase to form creatine and S-adenosyl homocysteine. The formation of creatine therefore requires ATP, which is essentially a test of oxidative metabolism, and is also dependent upon the presence of methionine and the rate of formation of S-adenosyl methionine.[43]

The methyl group of creatine is not labile, and its nitrogen is not used as a source of protein synthesis. Creatine may therefore be considered to be an end product of metabolism of glycine, arginine and methione. Creatine is then carried in the blood and 95 % is subsequently found in muscle. The remaining 5 % is located in brain and testes.[44] There is evidence for an active transport across the muscle cell plasma membrane, and it is then phosphorylated to form phosphocreatine by the reaction creatine + ATP = phosphocreatine and ADP. This reversible reaction is the means for provision of ATP as required at the contractile site in muscle, and equilibrium of the reaction is influenced by the concentration of magnesium ions. Recent work suggests that creatine, generated during muscular activity, may play a role in energy production through a regulatory feedback mechanism.[45] Formation of creatinine appears to be almost exclusively from phosphocreatine,[43] is non-enzymatic, and in normal health represents the final product of creatine metabolism

FIGURE 5



Synthesis, transport and utilization of creatine and its excretory relationship with creatinine.

since it is found in large concentration in the urine, as compared with only very small amounts of creatine. By examining urinary concentrations of creatine and creatinine it becomes possible, therefore, to derive information about a number of metabolic and physiologic states. A high concentration of both creatine and creatinine in normal ratio would indicate a fast metabolic turnover as compared with low concentrations which would indicate the opposite. High urinary concentrations of creatine with relatively low creatinine might indicate several possibilities:

(a) Overproduction of creatine in liver and kidney which overwhelms the plasma membrane transport system or its "trapping" to form phosphocreatine in the muscle cell. This mechanism, according to Fitch,[44] has not been reported.

(b) Loss of creatine from muscle cells because of abnormal leakage through plasma membrane. Though this is the mechanism proposed in muscle dystrophy, Fitch[44] has produced evidence that it is a membrane absorption or "trapping" defect in this disease.

(c) Renal loss because of a defect in tubular absorption mechanisms.

Because of our previous clinical experience in identifying a patient with defective pyruvate decarboxylation, it is our usual practice to obtain a 24 hour urine in a day and night 12 hour collection in order to ascertain whether there are any differences. It is often surprising to see radical changes between the two, which suggests that this form of nitrogenous excretion is also affected by circadian rhythm. Though concentrations vary grossly from patient to patient and also in repeated studies on the same patient, the ratio of creatine to creatinine remains remarkably constant in healthy children, and a variation in this ratio may be quite a useful indicator of metabolic inefficiency of the absorption mechanism and hence be interpreted as providing indirect evidence of cell membrane activity. If the test is repeated in a patient under treatment, he can act as his own control. In some cases the ratio of creatine to creatinine can be plotted as a graph and the trend of the ratio easily portrayed. Creatinuria has been observed in large number of disease states, including muscular dystrophy,[44] dermatomyositis,[46] and beriberi[1]—to mention but a

few. It is regarded as non-specific, which is why it may be examined with a view to ascertaining the mechanism. As described, the biochemistry is relatively simple, and it is by taking advantage of these metabolic limitations that it promises to be useful in providing information about the basic lesion which may be common to a number of diseases. In children, creatinuria is regarded as physiologic, and since we know that metabolism is faster in childhood, it is of possible value in calibrating the rate of that metabolism in the normal versus abnormal state. Clark and associates[47] published normal values many years ago, and little or no work has been done since in using this information to study disease. The ratio of creatine to creatinine in urine of children is higher, but gradually diminishes to adult proportions at the age of approximately eighteen years. The range for both creatine and creatinine is wide, but the ratio appears to be fairly constant in normal health, according to Clark et al. The ratio in the first two years is frequently greater than 1.0, but decreases to less than 0.1 in the adult. We have studied the urine by measuring both metabolites in a 12-hour day and a 12-hour night collection, presenting the data as total control concentration of each, the ratio, and the concentration per unit of body weight.

Table 4 shows data from eighteen healthy children between 2 and 13 years of age. Although the concentrations were very wide in range, the mean creatine to creatinine ratios were similar in the day and night specimens, suggesting that proportions of each were maintained relative to each other. Thus, the synthesis of creatine can be expected to lead to a proportionate loss of excreted creatinine Perhaps this is why Selye found creatinuria in animals when he applied environmental stress. He was simply observing the animals' metabolic response organized to meet the stress, as an internal combustion engine must accelerate in a lower gear in order to meet the "stress" of causing the automobile to climb a hill. Selye did not compare creatine with creatinine in the urine of his stressed animals, so he considered it as part of the general increase in urinary nitrogen that he reported. It is hypothesized, therefore, than an increased ratio of creatine to creatinine gives nonspecific but potentially important information about the formation of phosphocreatine in the process of energy metabolism.

TABLE 4

	CREATINE mg.			CREATININE mg.			RATIO CREATINE/CREATININE			URIC ACID		
	Day	Night	Total	Day	Night	Total	Day	Night	Total	Day	Night	Total
Range	9-117	10-216	19-253	97-450	109-768	423-1026	.03- ..53	. 02-.50	. 03-..48	40-400	28-720	68-932
Mean	53.2	61.8	114.7	294.1	344.6	641.7	..2 0	. 20	.2 0	200..9	207..9	40 8..8
	± 30.6	± 53.1	± 72.2	± 125.9	± 188.8	± 257.6	±. 13	± .16	± .15 ±	97.5	± 162.1	± 210.3
		N = 18			N = 18			N = 18			N = 16	
mg/kg per 24 hours	4.39 ± 3.03			21.17 ± 6.58						13.32 ± 7.85		

Day (12 hour), night (12 hour) and 24 hours concentrations of urinary creatine, creatinine and uric acid from 18 healthy children from 2 to 13 years of age. There were 11 males and 7 females and each subject was receiving an uncontrolled selective diet, and was in a state of normal activity during the collection.

Some studies in animals have given a great deal of insight into mechanisms which cause creatinuria. In the interpretation of these mechanisms, its comparison with the concentration of creatine seems to be all important, since the process of absorption is a vital link. Very little creatinine is formed directly from creatine. It is formed by a non-enzymatic process from phosphocreatine, the compound which provides the storehouse in muscle from which ATP is formed.[43] By circumstantial evidence it is possible to suggest the hypothesis that a high creatine/creatinine ratio is a function of abnormal membrane physiology. It has been shown that at least part of the mechanism of hyperthyroid induced creatinuria is due to depression of creatine incorporation into muscle.[48]

Carter et al[49] showed that calorie deprived hyperthyroid rats had a 2-4 fold greater increase in creatine excretion compared to fully fed hyperthyroid animals with comparable circulating thyroid hormone levels, and these investigators concluded that excess thyroid hormone appears to cause muscle damage by a mechanism other than mobilization of muscle protein. In another study of thyroid-

induced creatinuria in rat[50] the animals were injected with T_3 and oxygen consumption began to increase 12 hours later, until it reached a peak at 48 hours, decreasing to pre-injection level at 96 hours. Urinary creatine excretion increased, reached a maximum at 34-48 hours and fell to pre-injection concentration at 72-82 hours, whereas urinary creatinine decreased during the same time period. These investigators claimed that their results suggested increased creatine loss from skeletal muscle in addition to decreased creatine uptake, and that there was no evidence of increased hepatic synthesis of creatine to explain the results.

Maley and Lardy[51] showed a lower P:O ratio in thyrotoxic rat mitochondria as compared with controls, whereas thyroidectomized animals revealed a lower rate of respiration. A greater degree of acceleration of respiration occurred after dinitrophenol in the hyperthyroid animals, and they suggested that thyroid hormone also uncouples oxidative phosphorylation, although they were unable to determine the site of the uncoupling reaction. Tapley[52] showed that the effect of various added substances, including thyroxine, was to cause swelling of isolated rat liver mitochondria. It was also found that the extent of swelling was highly dependent upon the nutritional state of the animal, initial state of mitochondria and presence or absence of active cellular respiration and phosphorylation . Tapley and Cooper[53] suggested that the uncoupling effect of thyroxine was an indirect one by altering permeability of the mitochondrial membrane. An old study[54] reported swollen vesiculated mitochondria in thiamine deficient rats, and observation of creatinuria in beriberi has already been discussed. It is tempting to suggest that one role of thiamine may be that of providing a vital energization of cell membrane, and that this loss of energy occurring in thiamine deficiency has a part to play in producing creatinuria.

We believe that further evaluation of the relatively simple measurement of urinary creatine and creatinine may provide a reasonable laboratory tool for further study of energy metabolism. As will be illustrated later, it seems to be particularly valuable in indicating a therapautic response in a patient whose urine is shown to reveal quite marked changes in creatine to creatinine ratio as the clinical symptoms improve.

Uric acid is the end point of de novo purine biosynthesis and degradation. This is produced in excess in the Lesch Nyhan syndrome, due to a defect in hypoxanthine guanine phosphoribosyl transferase, which governs the reconversion of the purines hypoxanthine and guanine to their respective nucleotides.[55] It is produced in excess sometimes in the urine of patients with leukemia,[56] and children with glycogen storage disease also excrete uric acid in excess.[57] Since uric acid is produced by activation of the biochemical pathway beginning with phosphorybosyl pyrophosphate, which is formed by activation of the hexose monophosphate shunt, it has been suggested that hyperuricemia in glycogen storage disease is brought about by this mechanism.[58] This is not the only cause for hyperuricemia. There is evidence that there is renal tubular competition between lactic acid and uric acid, and other mechanisms have been suggested.[56]

In some cases we have found that with therapy there are distinct changes in urinary uric acid in some individuals, and this will also be illustrated in case histories A severely retarded child was found to have organic acidosis and compulsive lip biting caused by self mutilation. Hypcruricuria was found repeatedly, although the blood uric acid was only occasionally increased in concentration. Abnormal carbohydrate metabolism and lactic acid increases suggested the use of thiamine, since TPP stands astride the entry of pyruvate into the citric acid cycle. This resulted in modification of the lactic and uric acidosis, although little or no clinical improvement was observed, possibly because there was already long term organic damage to the central nervous system.[11] It does not throw too much light on the mechanism of self mutilation, which has been almost specifically associated with the Lesch Nyhan syndrome. Perhaps it in some way represents an excessive synthesis of purines rather than an overproduction of uric acid itself which is the end point of the synthetic pathway. There is no evidence to date that limiting uric acid production in Lesch Nyhan syndrome modifies self mutilation, and yet attention is drawn here to compulsive lip biting in two separate conditions in which there is overproduction of uric acid from separate causes. Michener studied some of Lesch Nyhan patients and

found that uric acid concentrations in urine were considerably in excess of 19 mg/ke/24 hours.[59]

Although it is not possible to detect the nature of biochemical effect, urine uric acid evaluation is illustrated by the case of a 7-year-old boy who showed evidence of a learning disability in first grade, and testing by a psychologist reportedly revealed abnormal sensory integrative function." He was irritable, restless and exhibited impulsive motor activity, distractibility and poor attention span. He began having minor seizures He would suddenly drop what he was carrying and remain in a trance like state for a few moments, and this was interpreted as absence seizures. The EEG revealed paroxysmal bursts of 4-5 per second spike and wave discharges lasting up to 4 seconds, without clinical symptoms. TKA and TPPE were normal and all other conventional studies were of no help. Trials with a number of anticonvulsants seemed only to make matters worse and failed to prevent the seizures. Urine studies revealed a C/CR ratio of greater than 1.0 and this was considered to be abnormal by published standards.[47] He was admitted to hospital, and after a control period of 48 hours he was given thiamine tetrahydrofurfuryl disulfidc (TTFD), 150 mg/day in divided doses on empirical trial. Urine was collected in 12 hours day and night consecutive periods throughout. Results are seen in Figures 6 through 10.

Creatine concentrations fell from 16 to 2.4 mg/kg/24 hours and uric acid decreased from 25.2 to 12.3 mg/kg/24 hours in a 3 week period of treatment The figures demonstrate the slow continuous decrease in creatine and uric acid, whereas there was a tendency for creatinine to increase or remain constant. The striking phenomenon in each of the figures is the alternating lower (night) and higher (day) concentrations of all three metabolites. Absence spells ceased and he appeared to be doing better at school bur he was, unfortunately, lost to follow-up, so that nothing more can be said other than the fact that he represents a treatment modality that needs further explanation and study.

FIGURE 6

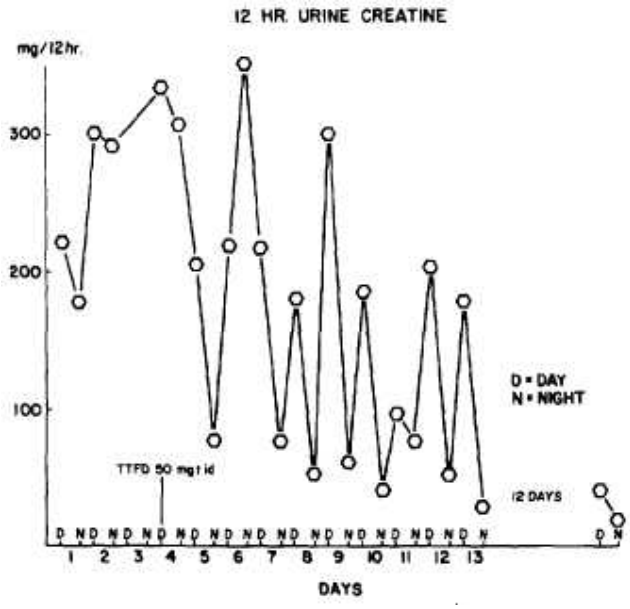


FIGURE 7

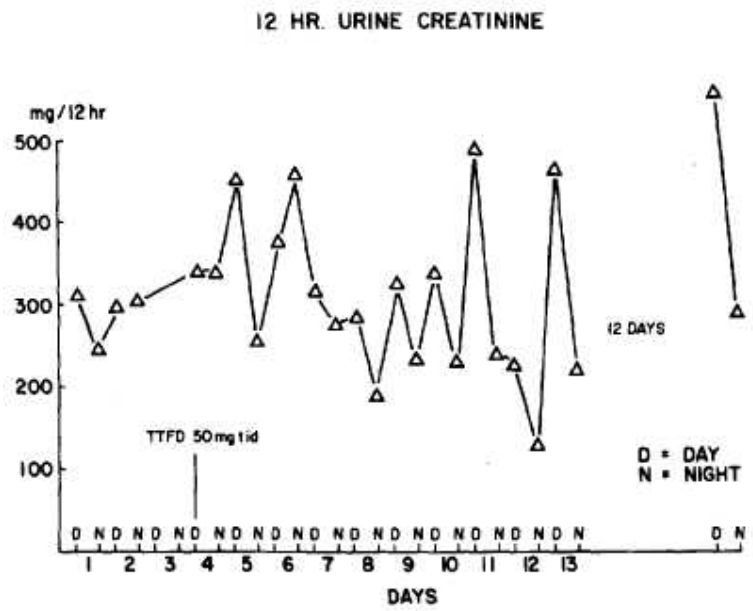


FIGURE 8

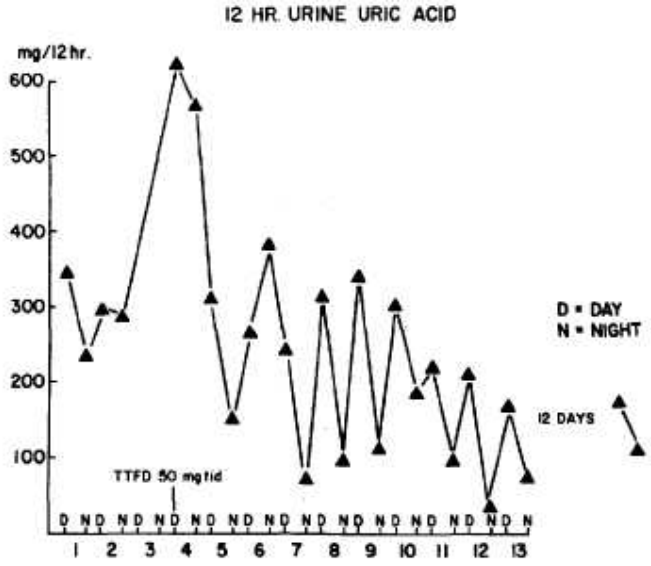
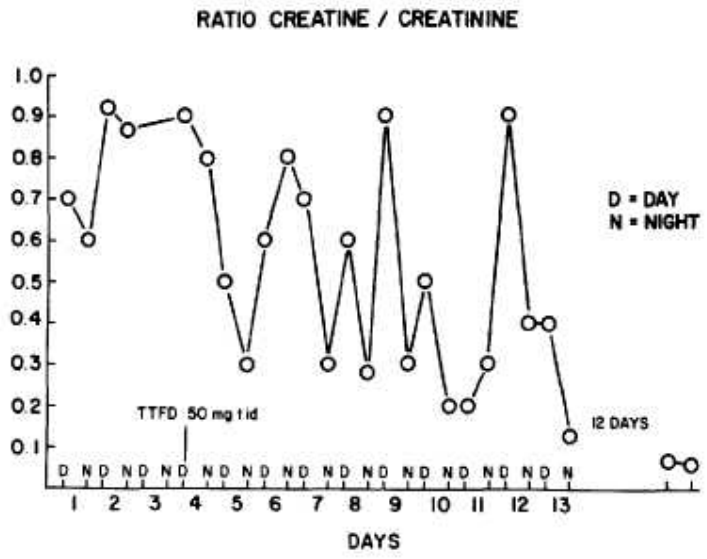
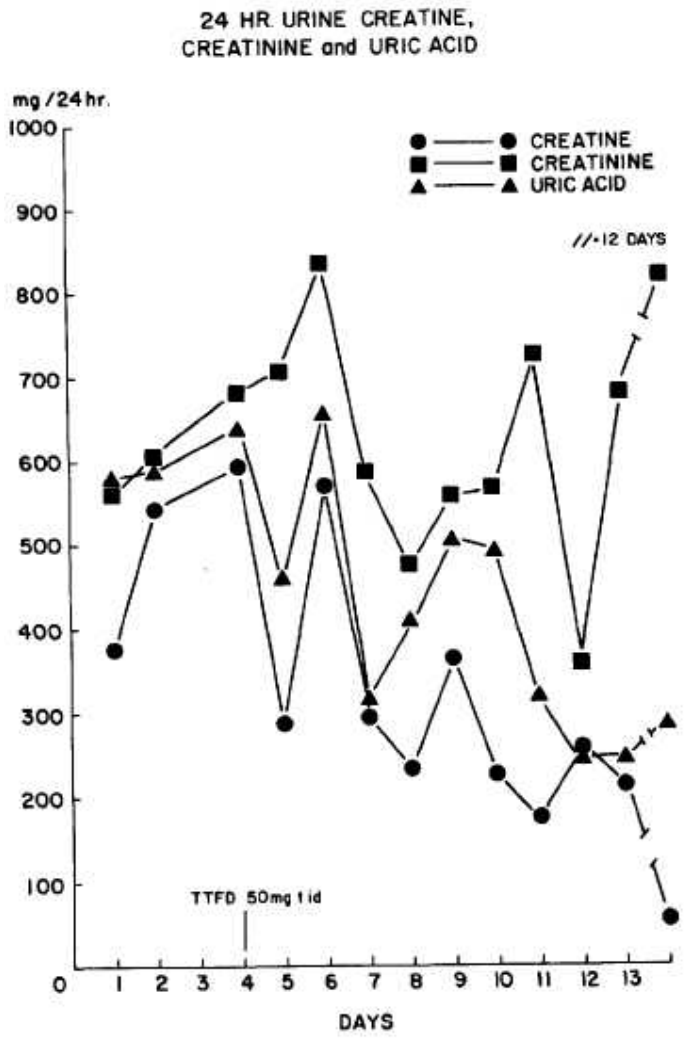


FIGURE 9



Figures 6 through 9
Day (12 hour) and night (12 hour) creatine, creatinine and uric acid concentrations in urine of a 7-year-old boy during treatment with thiamine tetrahydrofurfuryl disulfide (TTFD).

FIGURE 10



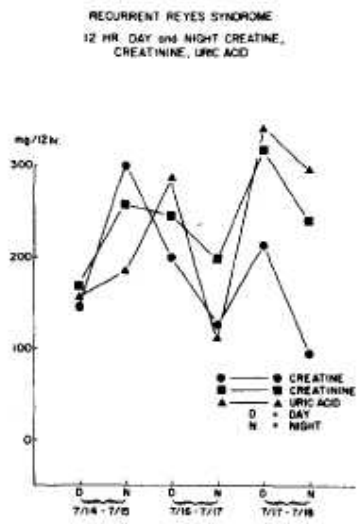
Creatine, creatinine and uric acid concentrations per 24 hour urine of a 7-year-old boy during treatment with TTFD.

In another situation a 10-year-old boy was seen who had experienced more than 30 episodes of a condition which was remarkably like the course of Reye's syndrome, but with repeated spontaneous recovery. No one had any concept of what this recurrent disease represented, but he subsequently died during one of them and, unfortunately, a totally inadequate autopsy was performed, so that no answer was ever obtained. A brother of this child had died from a similar condition, and another sibling had experienced rheumatoid arthritis which remitted spontaneously. Two such episodes in this patient were studied, one over a period of 3 days and another over a 9-day period. One of these (Figure 11) revealed a falling urinary concentration of creatine and rising creatinine. The recovery was spontaneous and totally untreated. During the second episode (Figure 12) he received a supplement of 150 mg TTFD a day in divided doses. The same phenomenon was observed; the creatine and uric acid fell, and creatinine remained relatively steady. Since this child's disease was capable of spontaneous recovery, it becomes virtually impossible to ascertain whether TTFD had any therapeutic effect. Nevertheless, the study revealed the day/night difference in the metabolites, indicating the possible role of circadian rhythm and clues to energy deficiency, perhaps in membrane physiology.

Another patient, a girl of ten years, had repeated episodes of symptoms which might be classified as cyclic vomiting. Three or four times a year she would have an attack of pernicious vomiting that would last several days, and which invariably caused her admission to a hospital. On recovery, she would develop a voracious appetite for several days, and experience repeated spontaneous epistaxis. Urine creatine to creatinine ratio during an attack was greater than 1.0 (Figure 13), and TFFD was started in a dose of 150 mg/day. She had no further attacks, and the ratio of creatine to creatinine and their urinary concentrations — plus that of uric acid — are shown. Again, the evidence is mostly circumstantial. No one could say that the urine changes were proof that the supplement had been responsible, but the complete absence of further episodes of vomiting was dramatic, and appeared to be authentic.

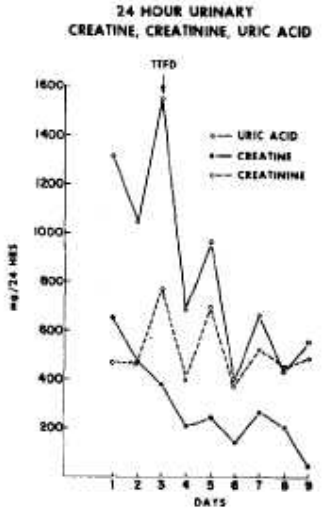
This kind of disease can only be perceived if it is regarded as inherently biochemical in nature, involving an appropriate supply of energy to the cells. The symptoms, and even the clinical and laboratory findings, are likely to blur so that mental, physical, functional and organic factors become related as part of a complex multicellular relationship. If one were to be strictly mechanistic, it would represent "the function of a complicated machine" in which there is only chemistry and electricity to consider. This is somewhat offensive to our present concept of human activity and behaviour, but may be a shift in concept that enables us to treat diseases at a functional level, rather than to await the destructive processes that can be seen under the microscope. This would be in keeping with an emerging idea of preventive medicine.

FIGURE 11



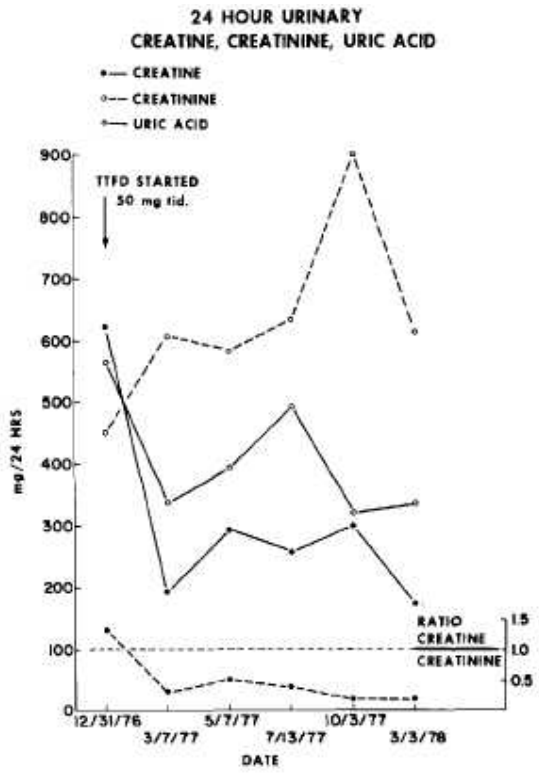
Day (12 hour) and night (12 hour) creatine, creatinine and uric acid concentrations in urine of a 10-year-old boy during an illness resembling Reye's syndrome which resolved spontaneously.

FIGURE 12



Creatine, creatinine and uric acid concentrations per 24 hours in urine from the same patient as Figure 11, in a subsequent episode of illness resembling Reye's syndrome. On this occasion he was treated with TTFD 150 mg/c

FIGURE 13



Creatine, creatinine and uric acid concentrations per 24 hours, and creatine/creatinine ratios in urine of a 10-year old girl under treatment with TTFD for cyclic vomiting.

URINARY CREATINE AND CREATININE IN THIAMINE DEFICIENT RATS

High creatine/creatinine ratios have been observed in urine from thiamine deficient rats[60] and the mechanisms remain obscure. For this reason, an experiment was devised to attempt to ascertain whether the effect might be related directly to the vitamin deficiency or to the secondary caloric starvation resulting from the anorexia. Age matched male albino Sprague Dawley rats, weighing between 200 and 260 grams, were housed in stainless steel metabolic cages with floor mesh and food cup containers designed to keep food droppings to a minimum and avoid contamination of urine collections. The diet used for all the experimental animals was relatively high in carbohydrate, low in protein, fat and non-nutritive fiber. The control diet contained all necessary vitamins, including thiamine, whereas the test diet was identical with the exception of no thiamine (Thiamine deficient diet; catalog number TD 7497. Salt mix; catalog number 170911. Control diet, catalog number 74296, calculated to supply 22 mg of thiamine HCl per kg of diet. Both diets supplied by Teklad Test Diets, Madison Wisconsin, 53711).

The animals were divided into 3 groups as follows:

1. Group I controls; received *ad libitum* control diet.
2 . Group II (TD) received *ad libitum* thiamine deficient test diet.
3 . Group III (CD) received the control diet, but pair fed to Group II.

The amount of food ingested by group II animals was calculated from the uneaten residue in food cups and averaged. That amount of control diet was rationed to each of the Group III animals. Consequently, the TD animals became anorexic, and were lethargic and ill. The group III CD animals remained vigorous but ravenously hungry. Urine was collected periodically from each of the rats throughout the experiment. Each collection was for 48 hours, in order to obtain sufficient urine for creatine and creatinine concentrations to be analyzed. Each of the TD rats received a single injection of l mg of thiamine hydrochloride on the 37th day of the experiment, when the clinical effects of the deficiency were acute and had resulted in a number of unpredicted deaths, and the experiment was continued. The appetite and vigor of the treated rats was rapidly restored after thiamine, and the ration of food to Group III animals increased concomitantly. It was, therefore, possible to observe the effects on both groups of animals that were calorically starved by two different methods. One group was severely ill, whereas the other remained vigorous and active. Inadvertent death occurred in 5 of the TD animals, and 3 were sacrificed to measure erythrocyte TKA in order to prove that thiamine deficiency was present (Table 5). Some of the TD rats developed chromodacryorrhea, and muzzle washings from two of these affected animals revealed an increased concentration of porphyrins (Table 6), as compared with controls.

TABLE 5

TKA mU/L/min	
Group I	78.3
	59.5
	75.2
Group II	10.2
	10.7
Group III	65.0
	75.8
	86.8

Red cell transketolase activity (TKA) in representative rats from all three experimental groups sacrificed on 36th day of TD diet given to Group II animals.

TABLE 6

	Control Rats		TD Rats	
Uroporphyrin (µg/ml)	.005	.005	1.115	.116
Coproporphyrin (µg/ml)	.008	.000	.605	.043
Protoporphyrin (µg/ml)	.015	.024	2.820	.272

Concentrations of porphyrins in muzzle washings of two TD rats with chromodacryorrhea as compared with two healthy controls.

The results are presented in Tab le 7 and Figures 14 through 17 and a number of observations can be made. Table 7 shows the difference that occurred in food intake in TD rats compared with controls. By the 23rd day there was marked hypophagia, but after the TD rats received thiamine on the 37th day their clinical improvement was accompanied by an increase in the amount of food ingested. The weight loss and gain of the two experimental groups was clearly related, as would be expected (Figure 14). There was a clear-cut rise in the creatine/creatinine ratio in the TD group by the 30th day, but a significant rise was not seen in the CD group for another week (Figures 15, 17). Creatine concentrations decreased rapidly in both groups after thiamine was administered.

Statistical analysis using group by trials interaction term, indicated a highly significant differential effect ($p < .001$) in weight loss, which was more rapid in the TD animals. On day 23 there was a statistically significant difference in C/CR between controls and TD, but not between controls and CD, or between CD and TD rats ($p \leq .025$). On day 30 the C/CR difference was seen between controls and TD, between TD and CD, but no difference between controls and CD ($p \leq .05$)(Figure 17).

TABLE 7

Experimental Days	-6	-2	+7	+16	+23	+30	+36	+44	+56	+66	+73
Group 1 (control)	6.2 ± 1.1	5.0 ± 1.6	4.9 ±0.9	5.4 ±0.6	4.8 ±0.6	5.1 ±0.7	5.0 ±0.6	4.2 ±0.6	4.7 ±0.7	4.2 ± 1.0	4.2 ±0.7
n =	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(12)	(12)	(12)	(12)
Group II (TD)	7.2 ±2.0	6.8 ±1.6	5.3 ±0.9	5.0 ±1.0	2.2 ±1.9	2.8 ±0.8	2.6 ±1.0	6.3 ±1.5	3.9 ±1.1	5.2 ±1.6	5.0 ±1.0
n =	(15)	(15)	(15)	(15)	(15)	(15)	(13)	(7)	(7)	(7)	(5)
Group III (CD)	5.8 ±2.8	6.0 ±0.8	4.4 ±0.4	4.7 ±0.4	1.8 ±0.1	2.3 ±0.1	1.3 ±0.1	5.6 ±0.6	3.4 ±0.5	3.4 ±0.2	3.3 ±0.2
n =	(14)	(14)	(14)	(14)	(14)	(14)	(14)	(9)	(9)	(8)	(8)
TD vs CD	N.S	N.S.	p<.005	N.S.	N.S.	N.S.	p<.001	N.S.	N.S.	p<.01	p<.001
TD vs Control	N.S.	p<.005	N.S.	N.S.	p<.001	p<.001	p<.001		N.S.	N.S.	N.S.

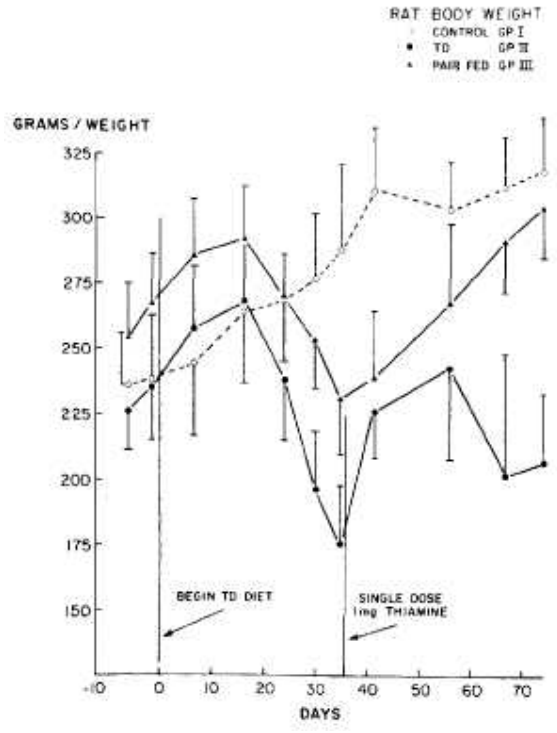
n = Number of animals

Mean weight (grams ± S.D.) of food consumed by each group of rats. Thiamine deficient diet began at day zero and 1 mg of thiamine was injected into each TD rat on day 37.

There is no valid explanation for the fall in creatinine concentrations that occurred in all three groups in the first 23 days of the experiment (Figure 16). There was no evidence that urine supplied to the laboratory was in insufficient supply, or that the analysis itself was faulty — since it was done in a carefully standardized clinical laboratory. Deterioration of the sample was possible, but unlikely, since all were hand carried to the laboratory by the technician who was caring for the animals. It was hypothesized that this might have represented a decrease in metabolic rate in all animals, since they were observed to be much more excitable initially and then

they became calmer as they acclimated. However, the period of interest was from the 20th experimental day until thiamine was given to the TD animals.

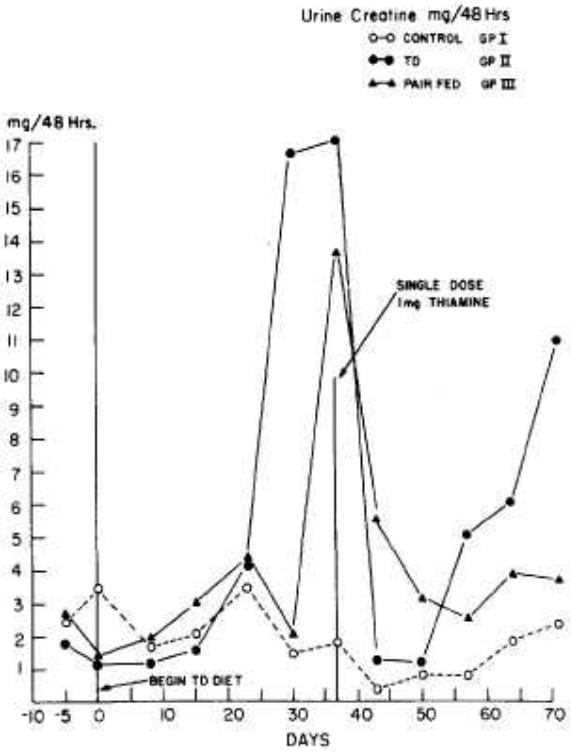
FIGURE 14



Body weights of progressively thiamine deficient (TD) rats compared with calorically deprived (CD) pair fed and *ad lib* fed controls receiving the same diet as CD with thiamine added.

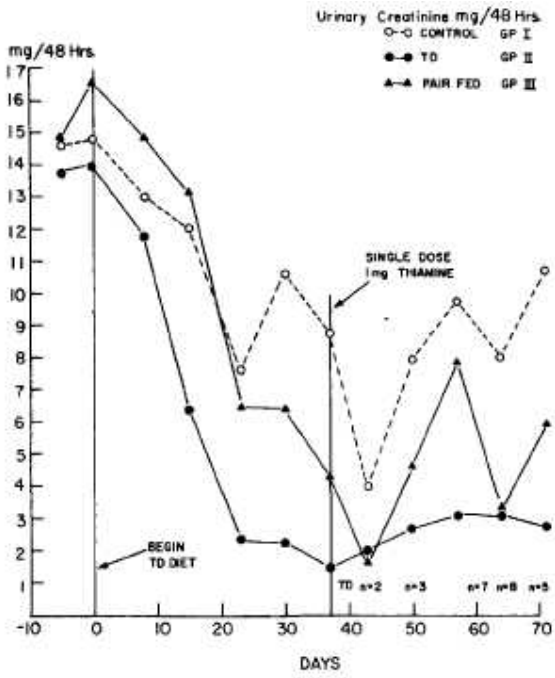
The deductions that can be made are relatively simple. There was apparently a difference in degree of creatinuria, and it occurred earlier in the TD animals compared with the CD. This result is mindful of those that were seen when thyroxine was given to rats. The degree of creatinuria was greater in calorically starved T_3 injected animals, suggesting that the two effects were additive. In our experiment there was a suggestion that thiamine induced starvation produced a greater effect than starvation induced solely by caloric deprivarion. However, the reason still remains obscure, and it can only be hypothesized that there was some effect on cell membrane function to support the circumstantial evidence that thiamine may have some effect on cell membrane physiology. A brief comment on the observed chromodacryorrhea is in order. It occurred only in the TD animals, although it has been described as a result of pantothenic acid deficiency[61] and is particularly seen in older animals.[62] It is not known why rats secrete porphyrins from the Harderian gland under these circumstances. It may be that it is a stress related phenomenon since it is seen commonly in pneumonia and old age. It would not be the first time that thiamine deficiency has been invoked as a missing biochemical factor which is capable of resulting in the general adaptation syndrome.[63] It may be no coincidence that the production of chromodacryorrhea from deficiency of pantothenic acid has been reported,[61] since pantothenic acid is vital to the formation of acetyl CoA in entry of pyruvate to the citric acid cycle, and therefore is as vital to energy producing pathways as thiamine. Our experiment suggested that creatinuria, nonspecific in identifying disease patterns as it appears to be, may be useful in studying various forms of net energy loss and that this could be the reason why creatinuria was reported by Selye in reference to his detailed studies of animal response to mechanically induced stress.

FIGURE 15



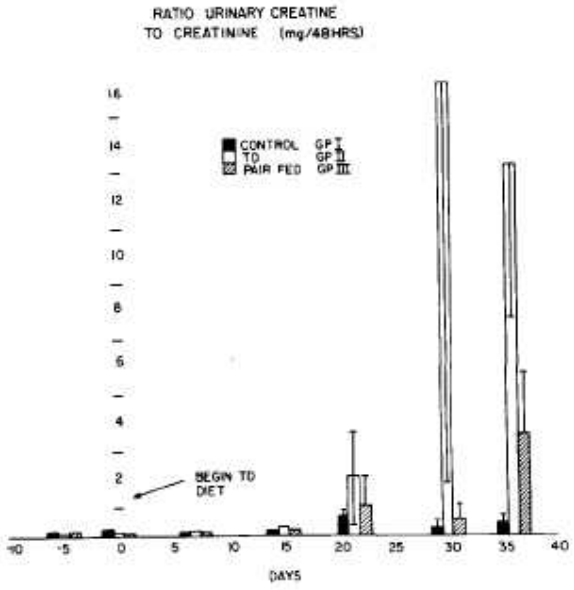
Creatine concentrations in urine of TD versus CD ratscompared with controls during induction ofthiamine deficiency in TD animals.

FIGURE 16



Creatinine concentrations in urine of TD versus CD rats
compared with controls during induction of thiamine deficiency in TD animals.

FIGURE 17



Ratios of urine creatine to creatinine (C/CR) in TD versus CD rats compared with controls during induction of thiamine deficiency in TD animals. Vertical bars on days 23,30 and 36 indicate one standard deviation of the mean

SERIAL STUDIES OF URINARY CREATINE AND CREATININE IN TWENTY-EIGHT PATIENTS

It has been suggested that creatine and creatinine in the urine might be used in demonstrating a biochemical phenomenon which correlates with clinical improvement. Table 8 lists a group of 28 patients whose urines were examined repeatedly in this manner. Two of them were children with Reye's syndrome, whose treatment was under the care of another physician. Urine was examined on admission to an intensive care unit and again on recovery. Neither of them received nutritional supplements. The other 26 patients represented a completely heterogenous group with widely different diagnosis, whose treatment varied and all of whom received nutritional supplements. They did not follow a protocol study, and the only thing they had in common was their observed clinical improvement. Ages within the group varied from 3 months to 54 years, and their period of surveillance was from 8 days up to 2 years.

Although serial collections of urine were made repeatedly throughout surveillance, in most cases the initial and final studies are the only ones displayed. In many instances there was an initial increase in creatine that was proportionately greater than that of creatinine, so the creatine/creatinine ratio (C/CR) increased, sometimes dramatically. Since the time periods were so variable, and in most instances the subjects were children, the 24 hour urinary creatine and creatinine concentrations are expressed as mg. per Kg. body weight. With so many variables and lack of homogeneity it is felt that the results presented can be said to show a trend rather than a proof, for in most cases there was a noticeable decrease in C/CR. In some patients the response was very slow, and the eventual fall in C/CR appeared to correlate with an improved clinical condition. This explains why there were widely different periods of surveillance and treatment attempted on an individual basis.

In 5 cases the C/CR was higher or changed very little, and these require some discussion.

Case 1. This 3-month-old infant was anomalous in appearance and a chromosomal defect was considered to be likely. Chromosome analysis proved to be normal. Urinary amino acid analysis revealed an increase in glycine. Red cell transketolase activity (TKA) 47.75 mU/L/min (normal 42.1 - 86.1) and the TPP percentage uptake (TPPE) was 24.9%. This was a clear indication of TPP deficiency, and for this reason she was treated with thiamine hydrochloride in a dose of 150 mg per day in divided doses. One month later the parents noticed increased alertness. The transketolase activity was 54.89 mU/L/min and TPP percentage uptake had decreased to 10.8%. A high potency multivitamin was started, and one year later there had been a slow, steady improvement. The transketolase activity was 129 mU/L/min and the TPP percentage uptake was zero. Urinary creatine increased from 3.6 to 13.6 mg. per Kg. body weight per 24 hours as creatine increased from 10 to 19.1 mg/Kg/24 hr. This suggested that there was an overall increase in metabolism, although there may have been a continued problem in absorbing creatine into muscle cells or storing it as phosphocreatine. At the age of 5 years she had continued to demonstrate severe temper tantrums and show signs of learning disability, but was normal in appearance. The mother kept noticing that her personality would improve as she slowly but surely increased her daily dose of thiamine. This eventually rose to the astonishing dose of 7 grams a day of a water soluble thiamine salt. She graduated from high school and had participated in the marching band. She subsequently died at the age of 27 years after an infection that led to toxic shock syndrome.

Case 3. This 15-year-old girl had anorexia ncrvosa. In the first 3 months of vitamin therapy the urinary creatine increased from 1.96 to 22.3 mg/kg/24 hr and creatinine decreased from 24.2 to 15 mg/kg/24 hr, reflecting a C/CR of 1.5. At this time TKA was 74.8 mU and TPPE 16.7%. She was treated with TTFD and in 2 weeks the C/CR decreased to 0.17. The TKA decreased to 57.8 ml) and TPPE to 0. These observations suggested that there was a surge of metabolic activity, but there continued to be defective processing of creatine. There was unequivocal improvement in the clinical condition, but she was receiving psychiatric treatment in addition.

Case 12. A 22-month-old girl was the younger sister of a retarded child whose urine C/CR was persistently high on repeated testing. When the younger child developed severe diarrhea and vomiting, followed by seizure, the history was viewed in terms of possible metabolic abnormality. Red cell TKA was 65.9 mU/L/min and TPPE 18.2%. She was treated with large doses of thiamine hydrochloride. When seen again 2 months later the C/CR was 0.48. Red cell TKA was 42.09 mU and TPPE 0. Since she was then well, the vitamin supplement was discontinued. She was seen again 4 months later and C/CR had increased to 1.2. It is suggested that this represented an unstable state which created susceptibility to sudden onset of disease. It was strongly suspected that an inherited factor, such as a defect in cell membrane function, was present in the two children, and that it had affected the older sister more severely. This also suggests that the C/CR cannot be used as an unequivocal test of a disease state, and would obviously depend upon the state of nutrition as well as the degree of environmental stress.

Case 19. This 6-year-old boy had functional dysautonomia. After beginning THCL, the urinary creatine increased from 0.4 to 8.3 mg/kg/24 hr, while creatinine increased from 2.4 to 22.8 mg/kg/24hr in one month. The C/CR increased from 0.17 to 0.36. In the following 2 months, urinary creatine decreased to 4.1 and creatinine only to 18.1 mg/kg/24 hr. Thus there was a symmetrical increase in both urinary creatine and creatinine, followed by a relative decrease in creatine. It is suggested that this would be consistent with a period of "paradox" when metabolism increased, but there remained a temporary abnormality in processing creatine. As this mechanism improved, so the C/CR decreased.

Case 23. A 17-year-old boy had experienced marked personality change as a result of street drug abuse, and he was chemically dependent. During 3 months of vitamin supplementation, red cell TKA increased from 39.7 to 87.9 mU and TPPE decreased from 25.2 to 6.3%. At the same time there was a dramatic symmetrical

decrease in both urinary creatine and creatinine, so that the C/CR remained the same. His subsequent history revealed that these biochemical changes did not appear to be indicative of clinical improvement. After attempted suicide, he was admitted to a residential remedial clinic dealing with adolescent drug abuse.

Several patients whose urinary C/CR decreased concomitantly with evidence of clinical improvement need to be discussed,

Case 8. A 19-year-old male asked for nutritional therapy for his proven Becker dystrophy. During a blind crossover study with placebo identical to the genuine TTFD tablets, there was no change in C/CR and no clinical improvement. He was then treated with authentic TTFD, together with alpha tocopherol, ascorbic acid and a high potency multivitamin. After 4 months there was a decrease in the C/CR. It was interesting that the day 12 hour ratio was consistently 1.0 throughout the TTFD trial and decreased to 0.34 afterwards. During the treatment, the patient was unsure whether he experienced any clinical improvement and discontinued further attendance. Since Becker dystrophy is a relatively mild form of the disease it is possible that these observations present a clue which would be worth following in other cases. The results in this case are consistent with partial healing of muscle plasma membrane or improved trapping of phosphocreatine as has already been discussed earlier. More prolonged treatment may well have been beneficial.

Case 17. A 6-year-old boy had severe life threatening croup and his three siblings had an identical history. Red cell TKA was 46.39 mU and TPPE 23.7% which strongly suggested a need for thiamine supplementation. No further attacks of croup occurred, but after a year of continued thiamine supplementation, the vitamin was discontinued. Within three weeks he was readmitted to hospital with croup. Red cell TKA was 47.1 mU and TPPE 18.3% before thiamine was restored. Interestingly, the main change in C/CR was by day, for this was 0.9 in March 1977 and .08 in February 1978, although there was a small increase from 0.35 to 0.49 in the night C/CR in the same time period. This may have been a clue to the attacks of croup which occurred invariably at night, as is so common in recurrent croup.

Several children were treated for functional dysautonomia. One of these (case 20) was a 5-year-old boy with night terrors. During pregnancy, his mother had toxemia. At birth the child had respiratory distress and jaundice, requiring phototherapy. Severe vomiting and diarrhea caused dehydration which required hospital admission. He was experiencing night terrors, during which his mother had observed cyanosis, piloerection, shallow respiration, enuresis, hypothermia and widely dilated pupils unresponsive to light. Urinary homovanillic acid was 13.8 ug/mg creatinine (normal 2-5 years = 0.5-13.5). Red cell TKA was 69.8 mU and TPPE 27.2%. Clinical improvement correlated with decreased urinary creatinine and a decrease in the C/CR after thiamione therapy.

Symptoms in an 8-year-old boy (case 21) included hyperactivity and night terrors. Red cell TKA was 97.3 and TPPE 19.5%. After four months with thiamine supplementation there was a marked improvement in personality. Red cell TKA was 88.2 mU and TPPE 1.5%. Note (Table 8) that there was a marked increase in both urinary creatine and creatinine. The C/CR remained much the same.

There were two patients with cyclic vomiting (cases 15 and 16) with a remarkably similar history. One of them, case 15, was only partially responsive to THCL and her case is considered later in reference to her treatment with TTFD. In both cases an episode of vomiting was followed by a voracious appetite and repeated epistaxis during recovery. In case 16, the red cell TKA increased from 64.9 to 86.3 mU and TPPE decreased from 19.9 to 3.0% in eight months of continuous treatment with THCL. Note the marked decrease in urinary creatine while creatinine increased. The C/CR decreased from 0.55 to 0.11. At the age of 17 years this girl had remained well and had experienced no further episodes of vomiting.

Two other patients represent important therapeutic principles. The 5-year-old girl in case 2 had been born prematurely, with a birth weight of 0.5 kg. Respiratory distress, irregular heart rate, jaundice, apnea and failure to gain weight were initial problems, and there was chronic, intractable diarrhea and apnea for the first six months of life. There was slight developmental delay and she had a continued history of colds, earaches, asthma, recurrent pneumonia, fatigue, croup, night terrors, excessive nocturnal sweating and tachycardia. She was well under the third

percentile in height and weight. Red cell TKA was 85.7 ml) and TPPE 19.9%. After six months treatment with THCL and a high potency multivitamin, urinary creatine decreased and creatinine increased. General health and personality improved.

By all standards of medical experience, such a child has always been a problem of management, and many are treated with continuous anitbiotic therapy. Frequently there are no laboratory studies to suggest an immune defect. The red cell TKA was a clue, possibly to persistent low grade hypoxia or subnormal oxidation. The urinary studies supported what was unequivocal clinical evidence of her improved well being.

Case 14. A 6-month-old Puerto Rican child had infantile myoclonus. His EEG showed hypsarrhythmia. He was treated only with pyridoxine, 150 mg/day. He quickly became seizure free, and two months later the EEG was normal. However, he had four or five green colored liquid stools a day and had begun to refuse feedings. Thiamine was started in a dose of 150 mg/day and pyridoxine continued. Diarrhea ceased and appetite returned. A few months later, both vitamins were discontinued and he remained well.

This illustrates a phenomenon that has been previously discussed in relation to SNE. There appears to be a synergistic therapeutic effect when large doses of thiamine and pyridoxine are given together, each revealing possible functional abnormalities in the patient when administered singly. This case also suggests that infantile myoclonus may, in some cases, be vitamin dependent without there being any clue other than a response to clinical trial. Atryptophan load in this child had not revealed any increase in urinary xanthurenic acid, a test which is often positive in deficiency of pyridoxine.

Finally, it is perhaps important to emphasize again that two children in this series were treated for Reye's syndrome, and there was a rapid decrease in the C/CR, in one case dramatic. This certainly suggests that the megavitamin therapy given in the other patients was not carrying out a specific curative effect. It is suggested that the C/CR can be used as a metabolic indicator and may have most value in revealing biochemical and physiologic improvement in chronic cases where nutritional therapy might be attempted on an empirical trial basis. The changes in the C/CR listed in Table 8 were subjected to statistical analysis, using the 2-tailed Student t test. This revealed $t = 2.04$, significant at 5 % confidence limits. Thus, while recognizing the tremendous variables in the study, it can be said that the figures do show changes that are less than random, and supports the claim that use of such a very simple study may be worthwhile.

TABLE 8

Case	Sex	Age	Clinical Diagnosis	Treatment	Time Span	Mg/Kg Body Weight Creatine		Creatinine		C/CR	Ratio	mU/L/min TKA		percent TPPE	
						1	2	1	2	1	2	1	2	1	2
1	F	3M	Failure to thrive	THCL MV	1 Yr.	3.6	13.6	10.0	19.1	.37	.7	47.7	129.0	25.0	0
2	F	5Yr	Failure to thrive	THCL MV	6 m.	16.4	10.5	19.2	68.5	.85	.15				
3	F	15Yr	Anorexia nervosa	THCL MV TTFD	9 m.	1.96	2.4	24.2	28.6	.08	.16	74.8	57.8	16.7	0
4	M	12Yr	Anorexia nervosa	TTFD MV	2 m.	0.2	0.9	3.6	17.8	.06	.05				
5	M	10Yr	Psychosis	B 6	4 m.	4.6	7.3	14.2	61.7	.32	.12				
6	M	54Yr	Diabetic neuropathy	TTFD MV	1 Yr.	2.6	0.8	14.4	11.1	.18	.07				
7	F	6Yr	Optic neuritis	TTFD	18 m.	13.3	12.8	16.4	17.0	.8	.75				
8	M	19Yr	Becker dystrophy	TTFD MV C. E.	1 Yr.	15.4	4.2	19.3	9.2	.8	.34				
9	F	4Yr	Kawasaki disease	MV	1 m.	12.0	8.1	16.0	36.9	.75	.22				
10	F	5Yr	Organic brain	TTFD	7 m.	12.3	17.3	11.1	21.1	1.1	.89				
11	M	16Yr	Organic brain	TTFD MV	9 m.	3.1	2.7	7.8	13.7	.38	.2				
12	F	22M	Seizure disorder	THCL	6 m.	1.7	10.1	10.2	8.4	.16	1.2	65.9	42.11	18.2	0
13	M	7Yr	Seizure disorder	TTFD	2 m.	27.3	2.4	23.1	35.1	1.18	.065				
14	M	6M	Hypsarrhythmia	THCL B6	2 m.	14.7	.89	12.3	2.3	1.2	.39				
15	F	7Yr	Cyclic vomiting	TTFD MV	15 m.	19.4	4.8	14.1	17.2	1.3	.3				
16	F	13Yr	Cyclic vomiting	THCL	8 m.	8.1	2.1	14.7	19.0	.55	.11	64.9	86.3	19.9	3.0
17	M	6Yr	Recurrent croup	THCL	1 Yr.	8.0	4.5	13.4	15.7	.59	.28	46.5	47.1	23.7	18.3
18	F	4Yr	Functional dysautonomia	TTFD MV	2 yr.	20.0	15.5	17.8	25.7	1.12	.6				
19	M	6Yr	Functional dysautonomia	THCL	3 m.	0.4	4.1	2.4	18.1	.17	.23				
20	M	5Yr	Functional dysautonomia	THCL	3 m.	15.0	10.3	19.0	17.1	.77	.6				
21	M	8Yr	Functional dysautonomia	THCL	4 m.	1.0	5.6	2.2	14.1	.45	.4	97.3	88.2	19.5	1.5

TABLE 8 continued

Case	Sex	Age	Clinical Diagnosis	Treatment	Time Span	Mg/Kg Body Weight Creatine		Creatinine		C/CR	Ratio	mU/L/min TKA		percent TPPE	
22	F	10Yr	Functional dysautonomia	THCL MV	2 yr.	3.7	4.3	9.1	21.5	.3	.2				
23	M	17Yr	Drug dependency	THCL MV	3 m.	2.7	0.2	26.3	2.0	.10	.11	39.7	87.9	25.2	6.5
24	F	9Yr	Sleep apnea	THCL	1 m.	4.8	2.0	14.1	15.7	.34	.13				
25	M	40Yr	Sleep apnea	THCL	3 m.	4.9	2.0	23.9	23.2	.2	.09				
26	M	8Yr	Sleep disturbance	THCL	2 m.	17.5	5.8	22.7	17.6	.77	.33				
27	F	8Yr	Reye's syndrome	---	2 m.	4.8	5.0	12.4	26.7	.39	.19				
28	F	7Yr	Reye's syndrome	---	8 days	15.8	3.4	6.9	21.1	2.3	.16				

Urinary creatine and creatinine (mg./Kg/24 hours), creatine/creatinine ratio, red cells transketolase, and thiamine pyrophosphate percentage uptake in twenty-eight patients. Twenty-six were treated with large doses of vitamins for variable time periods. The number 1 refers to the results obtained at the first examination and the number 2 refers to the results obtained from the last examination on completion of surveillance. Note that cases 27 and 28 were patients with Reye's Syndrome who did not receive any vitamin supplement.

THCL = thiamine hydrochloride
MV = high potency multivitamin
TTFD = thiamine tetrahydro furfuryl disulfide
TKA = red cell transketolase activity
TPPE = thiamine pyrophosphate percentage uptake
C/CR = creatine to creatinine ratio

Chapter 5

ILLUSTRATIVE CASE REPORTS

The foregoing chapters have considered the function of the normal autonomic system, and have reviewed some of the literature which described the clinical pattern of autonomic dysfunction. No proof exists at the present time as to whether autonomic dysfunction is the forerunner of a given disease entity or merely an associated phenomenon. We have seen that it occurs, however, in many seemingly totally unrelated disease states, and it would seem to be rational to attempt to elucidate this further. It is interesting history that Selye started his investigations because of a very simple and rather obvious fact. As a medical student he noticed and was impressed by the fact that a series of individuals with various diseases, who were presented to his class, all looked alike. In short, they all looked "sick or ill." Much like Newton, who questioned the reason for the falling apple, Selye asked himself why this appearance should be similar, and what the mechanism behind it could be. It was this that led him to start his great work on “stress” and his concept of diseases of adaptation. It would not be too far fetched to substitute “diseases of maladaptation” since the hypothalamic/endocrine/autonomic axis is the basaic means by which we adapt to our environment. Man has occasionally made giant steps in understanding by taking such simple and direct common observations and examining them, rather than merely accepting them as unexplained facts of life.

In the following case reports, the reader will be frequently ready to dismiss the case as "neurotic." He will be more than ready to ascribe benefit to the placebo effect, and to draw attention to the fact that many human conditions are responsive to the power of suggestion. This is not denied; it is the mechanism that is questioned. In what way does the mind influence the physical characteristics of the organism? Psychosomatic symptoms must not be confused with malingering. Case reports have been chosen to illustrate three principles:

I. Nutrition
II. Stress
III. Genetics

It is obvious that the three entities will overlap. Since it is doubtful whether any one of them ever operates without an element of the other two, and perhaps each case illustrates only a greater emphasis on one of them.

CASE REPORTS

1. Nutrition

Case 1

A 2-year-old white male child was referred because of episode's of pallor, diaphoresis, and cyanosis. Birth history, neonatal and early development were normal. Mucous rhinorrhea from the fifth day of life was attributed to "milk allergy." At nine months he developed a series of infections and tympanic aeration tubes were placed. At eleven months of age he had repeated episodes of diarrhea. At fifteen months a nocturnal episode of crying was followed by a seizure and labile blood pressure and an increase in urinary catecholamines was reported elsewhere as the only abnormality. Diarrhea ceased at eighteen months and urinary catecholamines were reported to be only equivocally increased. At age 20 months he was found in his crib early one morning pale, lethargic, with cyanotic lips and nails, and he recovered spontaneously. At age 22 months similar episodes began to occur regularly, usually when awakening from an afternoon nap. Pallor, lethargy, diaphoresis and cyanosis were repeatedly observed. Urinary catecholamine increases and labile blood pressure were reported, and there was frequently bronchial wheezing and tachycardia. Following sedation for electroencephalography he became pale, lethargic, and exhibited patchy cyanotic mottling of the skin. Extreme activity was accompanied by an enormous appetite, estimated to be greater than his

older brother, aged five years. Family history revealed one case each of diabetes in the paternal and maternal family, respectively. On examination the child was in the 75th percentile for height and weight and looked well. Blood pressure was 100/80 and there was cardiac sinus arrhythmia. Urinary amino and keto acid profiles were normal. Fasting serum pyruvate was 2.0 mg/100 ml four hours after epinephrine. Concomitant blood sugar was 85 mg/100ml fasting, 129 mg/100ml at thirty minutes, and 90 mg/100ml four hours after epinephrine. Thiamine hydrochloride was begun in a dose of 150 mg per day. He was asymptomatic three months later. Weight had increased by 0.7 kg and height by 3.1 cm, revealing a slight acceleration on the growth grid. The biogenic amines are shown in Table 1. It was not possible to correlate clinical symptoms with urinary catecholamines in any of the specimens. Changes in concentrations appeared to be spontaneous. Perhaps day-to-day fluctuations were more important than sporadic sampling.

Impression

This case represented a fluctuating state of autonomic activity, and might therefore be called functional dysautonomia. Symptoms were similar to those seen in threatened SIDS, but occurred at a later age. The exact role of thiamine was difficult to assess since urinary biogenic amine concentrations fluctuated spontaneously, but symptoms recurred subsequently when attempts were made to discontinue thiamine. The relationship between catecholamine concentrations and thiamine deficiency is reported in animal studies.[1] Complete remission in all symptoms occurred while he was receiving the vitamin supplement, suggesting that he was dependent upon it during a period of accelerated growth. It is uncertain whether the child's problem can be classified strictly as "nutritional" since there may well be underlying genetic factors that are not understood. It is of interest that most of the episodes described were related to the state of sleep.

TABLE 1

	ug/mg Creatinine	6/6/75	6/10/75	7/14/75	8/26/75	3/5/76	5/15/76
Norepinephrine	0.0	0.09	0.04	0.06	0.04	–.–	0.05
Epinephrine	0.02	0.02	0.02	0.0	0.02	–.–	0.02
VMA	12.06	18.42	15.50	11.41	13.43	10.30	9.57
Normecanephrine	0.36	0.89	0.64	0.48	0.20	0.65	–.–
Metanephrine	0.26	0.34	0.25	0.30	0.29	0.44	–.–
Dopamine	0.54	1.38	0.83	0.66	0.84	0.99	0.60
Dopa	0.07	0	0	0	0	0	0
Creatine (mg/ml)	–.–	0.43	0.32	0.58	0.35	0.47	0.84

Urinary biogenic amines — Case 1.

There might be an interesting parallel in this case with the "allergy fatigue syndrome "[2] which is related to specific sensitivity to food. It is sufficiently similar to postulate that the symptoms in both are due to an excessive sensitivity of a reflex arc which produces autonomic activity, resulting in mucous secretion as one of the effects. If this were true, it would be critically important to know what circumstances might be responsible for the increased neuronal sensitivity. The clinical response to thiamine suggests a modifying effect, whether the condition is termed "allergy" or any other currently popular explanation. If milk, for example, were the factor that initiated a reflex, it would be relieved by removing milk from the diet, or by modifying the reflex that it initiated.

Case 2

A 5-year-old white male was seen and examined because of recurrent urticaria. Withdrawal of eggs, chocolate, aspirin and the use of either antihistamine or steroid had no effect. A search for stool parasites was negative. Nutritional history revealed that he consumed an average of one candy bar and 32 ounces of a popular carbonated beverage every day. He was enuretic, overactive and constantly thirsty or

hungry. He exhibited choreiform and tic-like activity which occurred throughout the examination. With hands extended, he demonstrated the hypotonic positioning frequently seen in children with Sydenham's chorea. Dietary excess of carbohydrate was withdrawn and a high protein diet offered. Thiamine hydrochloride in a dose of 150 mg per day was started. Urticaria and hyperactivity disappeared, and because of the obvious and marked improvement, the child's 9-year-old sister had her excessive carbohydrate withdrawn. As a result, her longstanding insomnia was relieved.

Impression

The rapid reversal of symptoms in both children was testimony to their dysfunctional nature. Appearance of giant urticaria was presumably related to unusual release of histamine or other similar mechanism, and overactivity and "overflow" movement due to excessive neurotransmission. The withdrawal of excessive carbohydrate resulted in major therapeutic benefit, a phenomenon that is becoming a relatively common observation by those who have been increasingly concerned about the effects of diet, particularly in children. Testing this therapeutically is absolutely safe, since no drugs are involved, and the worst that can happen is that no effect is observed. For reasons already discussed, the use of thiamine appears to be logical, the only real issue being the dose used here. However, we have seen no ill effects, even when treating infants.

Case 3

A 15-year-old Caucasian youth was examined because of anorexia, fatigue, epigastric pain and weight loss. Birth history and development were normal, and he was obtaining average grades in school. After three weeks of participation in football practice he noticed unusual fatigue and anorexia. Taking food was followed by nausea, and fatigue forced him to bed early, often without anything to eat. He had constant rhinorrhea, cough, hoarseness and was nervous and irritable, exhibiting constant "knuckle cracking," loss of impulse control, and restlessness during sleep. An episode of "flu" consisting of fever, rhinorrhea, cough, nausea, sore throat and anorexia was followed by severe fatigue, nausea and frequent temporal headaches. A month later he experienced unusual fatigue, cramping abdominal pain and nausea after running, and he began to lose weight. Similar symptoms occurred on awakening in the morning and he began to miss school. After a weight loss of fifteen pounds he was admitted to a hospital. Examination showed an enlargement of axillary lymph nodes and the parents were told that "a blood test suggested liver damage."

Nutritional history revealed that he practically subsisted on cookies and potato chips, and he was described as a "constant nibbler." He consumed two gallons of milk and one gallon of carbonated beverage a week. On examination he was found to be well built and muscular. Heart rate was 60 per minute with a grade I systolic murmur audible at the cardiac apex. Femoral pulse was easily audible by auscultation over the inguinal ligament and blood pressure 130 systolic, with a phase change at 50, and a diastolic disappearance at 20 mmHg. Both systolic and diastolic components were labile.

Laboratory studies were normal, including red cell TKA and TPPE. Glucose tolerance revealed a fasting blood glucose of 74 mg/100 ml, 72 at one hour, 80 at two hours, 66 at three hours and 66 mg/l00ml at four hours. This "flat" curve was shown to be artefactual. When the tolerance was repeated, blood sugars were measured every 10 minutes. An adequate increase in blood sugar occurred, and it had returned to the fasting concentration within half an hour. This indicated an accelerated metabolic response to glucose. He was treated only with a multivitamin, and given diet instruction. One month later he still complained of some fatigue, but nausea, abdominal pain and headache had disappeared. Examination was normal and blood pressure 120/60 with no lability. Contact was made by telephone six months later, and he had remained well and had indulged in normal sport activity.

Impression

This young man represents a very common symptomology in American adolescents, which arises from an inordinate consumption of high calorie "junk"

food or empty calories. The stress of athletic activity precipitated symptoms, and the response to proper nutrition, together with an adequate vitamin supplement, showed that the symptoms were due to high calorie malnutrition. The “flat” glucose tolerance, seen since in other patients represents a maladaptive response induced by the dominantly simple carbohydrate diet.

Case 4

A 7-year-old white male child was referred for investigation of night terrors. He was the second of three children, with a normal birth history. Neonatal and early development were normal, although he did not talk in sentences until after the age of 2 years. He was in second grade and obtained average grades, but was receiving remedial reading. At the age of ten months he was hyperactive, and this increased with age until it became necessary to attempt to modify it with medication. Night terrors and somnambulism began at the age of 6½ years and had recurred weekly, usually with profuse sweating and frequently with urinary incontinence. He had no recollection of the event. Sleep was restless; he snored and would awaken two or three times a night even when no terrors occurred. No sleep apnea had been noted. Fever had been detected after a night terror and occurred occasionally with right hemicranial cephalalgia. He was indulged liberally with candy and soft drinks. Nasal congestion and mouth breathing persisted in spite of removal of tonsils and adenoids, and he experienced epistaxes, polydipsia, and frequent micturition. A school psychologist reported short attention span, poor perceptual multiskills, impulsiveness and poor memory, although testing was in the high range of normal intelligence. Examination revealed transient dermographia and labile patellar reflexes with occasional double or "hung up" responses. Blood pressure was 114/20. Laboratory studies showed increased serum concentrations of SGOT and LDH. Alkaline phosphatase was 200 mU/ml, due to rapid growth (normal adult 30 to 85) and cholesterol 125 mg/100ml (normal 150 to 300). There was a family history of migraine headaches in the mother and paternal grandmother, and diabetes was present on both sides of the family. The child was treated with a supplement of 150 mg per day of thiamine hydrochloride and instructed in a high protein, low carbohydrate diet. He was examined again two months later. There had been no further night terrors and he was less hyperactive. Examination was normal.

Impression

The clues to this child's problem were present in his sleep pattern, which included restlessness, snoring, and night terrors. Other functional disturbance was reflected in headaches, overactivity and mild learning disability — all of which disappeared quickly after appropriate dietary principles were followed, together with a supplement of thiamine. The laboratory studies were non-specific but abnormal. Acute cephalalgia has been described in children as a result of abnormal sympathetic activity following trauma.[3] There was no history of trauma in this case, but paroxysmal cephalalgia was believed to be vascular in origin and its disappearance after vitamin administration suggested dysautonomic etiology.

Case 5

A 19-month-old white boy had repeated fevers of unknown cause. Birth history and development were normal. The child's mother had been operated upon for ovarian tube ligation without her two-month pregnancy having been recognized at the time of surgery. Delivery was spontaneous when she was one month overdue by her date, and the birth weight was 4 kg. At the age of 2 weeks he had his first episode of nocturnal wheezing. There was nocturnal sweating and tachycardia. Nasal congestion and wheezing had been treated repeatedly with antihistamine. At the age of 2 months he began to have episodes when he would be found to be hot to the touch at night. These were interpreted as "ear infections" which were treated with different antibiotics with little or no benefit. At the age of 11 months he awoke from a nap with a fever of 106°F. He was admitted to hospital, but no cause was found. Similar recurrent febrile episodes of this nature followed. Hyperactvitity, irritability, nocturnal restlessness, starting out of sleep, night terrors, and sweating occurred, particularly with the fever. Non-specific leg pain, headaches and breathholding to

cyanosis occurred by day, particularly when he was febrile. Anorexia was indulged by providing *ad libitum* candy, ice cream and soft drinks. Family history revealed a number of individuals who had been affected by a combination of diabetes and cancer, as well as several reported to have pernicious anemia. On examination, height and weight were in the 25th and 97th percentile respectively. He was hyperactive and irritable. Deep tendon reflexes were overactive. The SMA automated profile was normal, except for a slight elevation of LDH. Excretion of urinary creatine, creatinine and uric acid is displayed in Table 2. Dietary advice was given, and the child began thiamine hydrochloride 150 mg per day. He was examined again two months later. He had had no fever, was restful during sleep, less nervous and more compliant. Profuse sweating and tachycardia had disappeared. Appetite had improved, and his mother volunteered that this was the best health that he had enjoyed in a year.

TABLE 2

	Day 12 Hours	Night 12 Hours	24 Hours
Creatine (mg)	46	27	73
Creatinine (mg)	52	54	106
Creatine/Creatinine	0.9	0.5	0.7
Body Weight = 13..2 Kg			
Creatine (mg/Kg/24 hrs)	5.5		
Creatinine (mg/Kg/24 hrs)	8.0		

Impression.

Symptoms in a 19 month old child that included unnexplained recurrent fever, night sweating, tachycardia, nasal congestion, hyperactivity, restless sleep, night terrors, leg pains, headaches, and breath holding, were obviously very disturbing to the family. It is surprising that his diet included 16 oz of cola per day. Response to diet correction and thiamine supplement were dramatic. Note the decrease in night creatine as comparedwith day, with a corresponding fall in the C/Cr ratio.

The symptoms were functional and would conventionally be most easily attributed to maternal anxiety and management, particularly since the mother had undergone surgery during her pregnancy. Dietary correction resulted in their complete disappearance. Family history suggested the possibility that there were genetic factors. In three family members there was a combination of cancer and diabetes. Both diabetes and cancer have been linked with autonomic dysfunction.[4 5] Two cases similar to this have been reported[6] and the biochemical abnormalities discussed. Viewed as a perturbation of the normal response to stressful stimulus, this case makes therapeutic sense, although it does not fit the present disease model. That may well be because the model is partly incorrect.

Case 6

A black female, aged 11½ years was seen with the complaint of swollen fingers. She was the youngest of three children, and at birth her mother underwent trial labor. Her birth weight was 3.1 kg and she was described as "severely bruised." Her early development was normal and she was receiving average grades in an appropriate class for her age. Swollen fingers had been chronically and intermittently present for two months, and she complained of aching and stiffness in the morning, and this improved as the day wore on. She became relatively easily fatigued and complained of transient pains in various muscles and would occasionally have a headache, accompanied by "dizziness" and "lightheadedness." Her legs ached after running, her moods changed very quickly, and she had sudden flares of temper. Apart from a blood pressure of 116/70 (expeted norm 90/60), her examination was normal and her symptoms were considered to be functional in nature.

During the next few years she was treated for eczematous dermatitis of unknown etiology, with varying degrees of success. At the age of 16 years, she was examined because of unusual fatigue, pain in the abdomen and diarrhea. About 3 months previously she had started to return from school with extreme fatigue, and she would go immediately to bed, sometimes without, or after an indifferent, supper.

The dermatitis had flared particularly on the palms and soles; her fatigue had gradually worsened, and she had frequent left temporal and frontal headaches. Recurrent pain in the right hypochondrium had been intermittently present for two or three years. More recently she had developed severe diarrhea, abdominal distension and constant loud audible bowel sounds. Diet history revealed that her daily intake of "empty calories" was large, including at least one pack of potato chips, 16 ounces of carbonated beverages, 16 ounces of chocolate milk, 4 to 6 cups of tea containing 1 to 2 teaspoonsful of sugar, 1 to 2 cups of black coffee and *ad libitum* cookies. In a week she consumed at least half a gallon of ice cream and six chocolate bars. Sleep was restless and accompanied by night sweating, and her menses were heavy and accompanied by cramping and nausea. She had occasional stabbing chest pains. On examination there was striking conjunctival suffusion, and her tongue was shiny and smooth — except for prominent filiform papillae. The blood pressure was 110/60 and there was absence of knee reflexes, which could be elicited only after reinforcement. The palms and soles were covered with rough, dry, scaling dermatitis. Without further investigation she was referred to a dietician for proper dietary instruction and she began a supplement of 150 mg/day of thiamine hydrochloride. Two months later her appetite was normal and headaches, joint pain, abdominal pain and fatigue had disappeared. Her weight had increased by 3.3 kg. She looked well and the conjunctival suffusion had disappeared. She still had an absence of knee jerks without reinforcement, normal ankle jerks, and her blood pressure was 116/50. The dermatitis had improved.

Impression

The early symptoms of swollen fingers and gelling were those generally considered to occur in early arthritis. The later symptoms could easily have been those of chronic infection or early connective tissue disorder. These symptoms slowly improved when appropriate diet was begun. The underlying principles are not new. They are as old as modern nutrition itself, and the relationship between common symptoms in adolescence and ingestion of large amounts of high calorie food is related in many cases. Symptoms like these must raise the question of the incidence of marginal malnutrition in an industrialized and affluent society. It is quite easy to accept some of the present personality characteristics of children and adolescents as normal since they are so widespread. It must be pointed out, however, that malnutrition abuse is also widespread and little or no medical attention has been paid to it as a potential source of disease. The symptoms of functional dysautonomia are readily discerned.

2. STRESS

Case 1

A Caucasian girl aged 8½ years was examined because of dysphagia and a persistently dry mouth. She was the youngest of four children and birth history and early development were normal. She was in third grade and receiving 100% A grades. About one year previously she developed a curious habit of pulling away sharply anything that came into contact with her neck. She complained that such contact seemed to choke her. The habit would disappear and reappear spontaneously. She had several episodes of febrile illness with sore throat but otherwise remained well. About one month previously she began to complain that she was unable to swallow her food, although she could manage liquids. Her father pressed her to eat everything, but she would begin to cry and her father would then excuse her. She was examined by an ear, nose and throat specialist who told her parents that the child's mouth was dry "like that of an old lady." Fruit juices and liquid diet were encouraged but no alleviation ensued. She was considered to be a vigorous and active child. Although there was no change in personality, she was described as extremely nervous. Appetite had always been capricious and, because of their perpetual anxiety about her well-being, her parents constantly encouraged her to eat. She consumed two or three candy bars a day, and was also allowed potato chips, suckers, and packaged snacks *ad libitum.* She drank two glasses a day of a highly concentrated vitamin C containing synthetic canned beverage. The parents remarked

about her constant pallor, which had made them concerned about the possibility of leukemia. Family history revealed that a maternal uncle had multiple sclerosis. Examination revealed a child in the 10th percentile for height and weight, with extreme facial pallor. The blood pressure was 110/60 but labile, and the deep tendon reflexes accentuated and occasionally double or "hung-up." Without further study the child was considered to represent a strong clinical profile of sympathetic dominance. The parents were counselled to discontinue their anxious drive to force her to eat and to withdraw her excess of carbohydrate. Thiamine hydrochloride was started in a dose of 150 mg per day. One month later her appetite had improved and the dryness of the mouth had disappeared. She was less nervous and irritable, but she complained of brief episodes of periumbilical pain. She had gained 0.3 kg in weight, had color in her cheeks, and the patellar reflexes were normal.

Impression

The good intelligence and natural drive in this child had been coupled with excessive parental anxiety, and was sufficient to put her into a state of anxiety tension. This reflected itself in predictable sympathetic dominance which caused constant dryness of the mouth and tic-like activity. Anorexia was naturally linked and worsened by her parents' efforts to get her to eat. Therapy was directed towards alleviating parental anxiety, although the carbohydrate intake was considered to be partly responsible. The rapid reappearance of normal function clearly delineated the fact that a dysfunctional state existed and was easily reversible. It is suggested that the state of "anxiety tension" was chronic fight-or-flight pathophysiology.

Case 2

A 5-year-old Caucasian male was examined because of recurrent vomiting. The birth history and development were normal. Subsequent history revealed that there had been an episode of "severe dehydration" at the age of two years, and he was in a hospital for nine days. At age three years he began to complain frequently of aches and pains in the legs, would cry a great deal, and frequently refused to walk. Swelling of the feet and ankles prevented him from wearing shoes, and a serpiginous rash led to a diagnosis of rheumatic fever. He received injections of penicillin for the next six months. The swelling improved, but he continued to complain of pain in the left knee. Active streptococcal infection was never confirmed. Subsequently he began to experience recurrent episodes of vomiting, which created a repetitive pattern. He would awaken in the morning feeling ill, would ask for a drink, but would immediately vomit. Repeated vomiting continued for the next twelve hours. Body temperature would rise to 102° to 104°F, and occasionally there would be an episode of becoming ' 'rigid and stiff for a few minutes." He resented being touched and would scream. The attack would end with "exhaustion."

The family physician had prescribed prednisone because of the painful knee, but he had discontinued it because of nocturnal symptoms attributed to the drug. The child had experienced night terrors, talking of violence in his sleep, and on one occasion crying out that he was unable to move because he was pinned down by a wild animal. At least one myoclonic seizure had occurred before the onset of a vomiting episode. Personality was normal by day and nocturnal symptoms decreased after prednisone was withdrawn, although spontaneous jerking of the leg was noted during sleep, a phenomenon that the child's mother also experienced. Although the child snored, there was no apnea. There was a history of frequent awakening from sleep and recurrent fever of unknown cause in infancy. Tachycardia had been noted with vomiting attacks, and his appetite was capricious and unpredictable.

Examination revealed an intelligent boy with no unusual physical findings other than extreme variability in knee jerks and very sensitive dermographia. Family history disclosed that a brother had had two seizure-like episodes during early childhood, and there were a number of diabetic relatives of both sides. One maternal aunt had disturbed ideation and was under psychiatric care, as was the maternal grandmother. The electroencephalogram revealed overall high amplitude and poor regulation but no paroxysmal discharges. Glucose tolerance showed a fasting blood glucose of 70 mg/100ml, 117 mg/100ml at ten minutes, 106 mg/100ml at one hour, 59 mg/100ml at three hours, and 78 mg/100ml at four hours. Lactic acid

dehydrogenase was 280 mU/ml (normal 100 to 225) and SGOT 57 mU/ml (normal 17 to 40). Thiamine hydrochloride 150 mg per day was begun. Although he experienced one or two mild episodes of vomiting within the subsequent month, he was asymptomatic six months later.

Impression

The dysautonomic element of "cyclic vomiting" in this case is represented by tachycardia, cephalalgia, fever and vomiting. Jumping leg syndrome, night terrors, infancy sleep disturbance and an incident which may have been sleep paralysis all suggest that sleep rhythms in this child were abnormal, and the episodes of stiffness and epicritical pain recall perplexing clinical characteristics of "stiff man syndrome" which is related to brainstem dysfunction.[7] The recurrent dream of being held down by a wild animal strongly suggests an association with sleep paralysis, a phenomenon that occurs during REM sleep .Although there was no overt history of unusual abnormal family stress, this child was behaving as though there were clear-cut emotional factors. He was considered to be unusually susceptible to normal daily stresses, and there were genetic components suggested by the family history. Diet probably played a part, but it was not unusual for the age of the child.

Case 3

A Caucasian boy, aged 9½ years, was examined for an unusually severe herpangina infection. Since infancy he had been seen repeatedly for unexplained fevers, colds, vomiting, myringitis and "habit cough." Episodes were usually accompanied by extreme irritability and anorexia, and they were invariably assumed to be viral in nature, since no bacterial cause could be demonstrated. The onset of herpangina was marked by fever, earache, irritable personality and anorexia. Bright red hyperemia of the palms of the hands frequently alternated with their being pale and cold. After a short course of oral penicillin, a multivitamin preparation was started. He was seen three months later, and his weight had increased by 1.8 kg and his height by 5 cm. His general health, activity and personality were much improved.

Impression

This case is not impressive by itself, but will be considered in relationship to the case report of his sister and in the light of family relationships.

Case 4

The 4½-year-old sister of Case 3 was first seen for routine pediatric care at the age of one week. Throughout the next few years her history was similar to that of her brother. Unexplained fever, cough, pharyngitis, diarrhea and croup had been treated as viral infections. She had an unusually severe episode of cough, croup and fever of two days' duration and treated symptomatically, but she returned two weeks later because of persistence of fever and cough. There was an intermittent pruritic rash and she complained of feeling cold and shivery. She developed pains behind the knees and in the elbows, a fever of 103°F, anorexia and abdominal pain. Her palms and soles were pruritic. On examination she was pale and acutely ill. *Alae nasi* dilatation was seen occasionally, and her respirations were 40/min. Palms and soles were erythematous and edematous. She had lost 0.9 kg body weight in two weeks. Radial pulse was labile, thready, and 160/min. She had pronounced sinus arrhythmia and a blood pressure of 140/80. Urticarial lesions were randomly situated on the trunk, her course was acutely febrile and laboratory studies showed mild, persistent acetonuria without glycosuria. Serum fibrinogen was 1,050 mg/100ml and glycoproteins 229 mg/100ml (normal 110 to 155 mg/100ml). The sedimentation rate was increased and c-reactive protein 6 + positive. Cold agglutinins were present to a titer of 1:128 and electrocardiographic examination revealed non-specific myocardial changes. Chest roentgenogram revealed consolidation of the anteromedial segment of the left lower lobe, and a diffuse interstitial infiltrate in the right lower lobe. Urinary amino acid profile was abnormal by paper chromatography and by ion exchange analysis.

A presumptive diagnosis of mycoplasma pneumoniae was made. A multivitamin was begun, and the patient was discharged from the hospital afebrile

and asymptomatic one week after admission. Two weeks later there were no unusual physical signs. Blood pressure was 120/40. Serum fibrinogen concentration was 320 mg/100ml and glycoproteins 123 mg/ 100ml. Her sedimentation rate was normal and her weight had increased by 0.7 kg. Two months later examination revealed increased heart activity. The radial pulse was full with marked sinus arrhythmia and the blood pressure was 114/0. The femoral pulse was audible by auscultation. The multivitamin was discontinued. Three weeks later the child's appetite abruptly decreased and she became irritable, started to yawn repeatedly and developed a fever of 102°F. She complained of neck and head pain, abdominal pain and unusual thirst. On examination the radial pulse was full and 124 per minute. The cardiac impulse was forceful and visible, and the femoral pulse was audible by auscultation. The blood pressure was 130 systolic with a distinct phase change at 60 mmHg and was still clearly audible at zero. The TKA was 66.69 mU/L/min and TPPE 22.1%. Thiamine hydrochloride 150 mg/day was begun. Two weeks later the patient's weight had increased and the the cardiac rate was 88 per minute. The pulse was less bounding and heart activity had diminished. Blood pressure was 116/60/30. Three months later her weight had increased by 1 kg and she was asymptomatic. She had experienced one episode of "24-hour flu," another of nocturnal vomiting, and some brief episodes of croup. Her general health had remained otherwise good, and she had experienced less fatigue and her appetite was improved. Pulse rate was 80 per minute and cardiac activity within normal limits.

Impression

The similarity in the history of these siblings is more impressive than their separate courses. The father was a biochemist who expected near perfection of his children, and he had been rigid in enforcing discipline, school performance, and general compliance. This had caused severe family tensions. Repeated episodes of phenomena interpreted as viral or bacterial in etiology may have been due to abnormal host response. The symptoms of cough, fever, vomiting, diarrhea, abdominal pain and croup are perceived as derailed stress responses, and unequivocal evidence of thiamine pyrophosphate deficiency was obtained by TPPE in the red cells of one of the children. Both children had been allowed *ad libitum* intake of carbohydrate, which may have been contributory. Erythroderma of palms and soles and myocardial changes have been reported in mucocutaneous lymph node syndrome.[8] Although the presumptive diagnosis of mycoplasma was made on the basis of positive cold agglutination, perhaps the symptomatology represented an altered host response, which in turn was identified with a temporary defect in energy metabolism required to meet the stress of the infection.

Case 5

A Caucasian girl aged 7¾ had a history of recurrent lymphadenopathy and fever for five months. The first episode was followed several weeks later by malaise and fatigue, repeated vomiting of coffee ground material, fever to 104°F, and chronic fatigue. She was brought for examination because of yet another episode of fever and cervical lymphadenopathy. She had a history of restlessness during sleep, sleep talking, and somnambulism, breathing during sleep was rapid and shallow, and she snored loudly. She was ingesting a significant amount of carbohydrate foods by preference. She complained of frequent fleeting abdominal pain, bloating, and abdominal distension. Examination revealed a pleasant child with flushed cheeks, circumoral pallor, and prominent filiform papillae on the tongue. The heart was overactive and the rate 150 per minute. Blood pressure was 110/70 with lability and the femoral pulse audible by auscultation over the inguinal ligament. Deep tendon knee reflexes were erratic. Urinary amino acid analysis revealed an increase in 1-methyl histidine only. Roentgenography showed an increased adenoidal mass and audiogram demonstrated a mild conductive hearing loss. A few beta hemolytic streptococci were cultured from the throat for which she had received a course of oral penicillin. Thiamine hydrochloride 150 mg per day was given orally. Snoring, sleep restlessness, shallow respiration and nasal congestion disappeared. General well-being increased. On examination she looked well. The heart rate was 128, blood pressure 100/60 without lability, and the audible femoral pulse and dermographia

had disappeared. Adenoidectomy was performed and laboratory tests before and after thiamine supplementation are shown in Table 3.

TABLE 3

STUDY	MAY 6	MAY 26	NORMAL
Serum Vitamin B_{12}	1220 pg/ml	1050 pg/ml	160-900)
Folate	14.8 ng/ml	> 30 ng/ml	(4-18)
Transketolase	36.07 mU/L/min	39.05 mU/L/min	(42.1-86.1)
TPP % Uptake	34.38%	0%	(0-17.4%)

Serum concentrations of vitamin B_{12} and folate; red cell TKA and TPPE before and after treatment with thiamine hydrochloride (Case 5)

Impression

It is unlikely that improvements n oted were due only to penicillin. The elevated TPPE was a clear demonstration of thiamine pyrophosphate deficiency, and clinical improvement correlated with its return to normal, although the baseline activity of TKA was much the same. The reason for a fall in serum vitamin B_{12} and an increase in folate represented in the Table is unknown. Lymphadenopathy, vomiting, fever, fatigue, abdominal pain, meteorism, constipation, tachycardia, labile blood pressure, and audible femoral pulse are all characteristics of beriberi, and there is reason to believe that this was the reason that her symptoms were responsive to a supplementation of thiamine. Although diet may have been the sole cause because — since there was demonstrable TPP deficiency — TKA did not change after thiamine supplementation. Blass [9] has reported genetic changes in transketolase. This case is presented as a possible example of an abnormal host response to stress. The role of the streptococcus is not clear but the clinical appearance of flushed cheeks, circumoral pallor and "strawberry tongue" is time honored as characteristic of streptococcal infection which may have represented the attacking stressor. Perhaps insufficient attention is given to the symptoms in terms of the organization and nature of the host response and its deviations. The use of vitamins may well be an advantage, irrespective of the etiology of the "stress."

Case 6

A Caucasian girl, aged 6 years, was examined because of episodes of severe intractable vomiting beginning at the age of nine months and recurring from two to eight times a year. Each attack occurred in three stages. An upper respiratory infection was followed in two or three days by vomiting and abdominal cramps lasting four or five days, and frequently resulting in dehydration requiring intravenous fluids. The third stage was characterized by a rapid change to a sense of well-being, cessation of vomiting, a ravenous or voracious appetite and repeated epistaxis, usually accompanied by pallor and edema of the face and eyelids. There were associated headaches, tachycardia and sweating. There were no unusual physical findings. Routine urinalysis revealed 3 + acetone, no sugar and no albumin. An epinephrine stress test showed a fasting blood glucose of 75 mg/100ml, 125 mg/100ml in one-half hour and 78 mg/100ml at two hours. An intravenous glucose tolerance showed a fasting concentration of 78 mg/100ml, 40 mg/100ml after half an hour, 70 mg/100ml at one hour, 80 mg/100ml at two hours and 76 mg/100ml at four hours. This study was repeated with more frequent analyses. The fasting concentration was 87 mg/100ml, 190 mg/100ml at ten minutes, 150 mg/100ml at twenty minutes, 138 mg/100ml at thirty minutes, 108 mg/100ml at forty minutes, 91 mg/100ml at fifty minutes and 87 mg/100ml at one hour. An attempt to prevent attacks was made by the administration of thiamine hydrochloride, 150 mg per day, but in the next ten months there were four further episodes, two of which required hospital admission. One occurred following chickenpox, the other three after colds. Each was associated with extremely irritable behaviour, and nocturnal enuresis began after the most recent episode began. There was constant general sweating. On examination, she was pale and conjunctivae suffused. Body weight had increased by 5.5 kg in ten months. Heart rate was 100 per minute and sinus arrhythmia marked. Blood pressure was 100/50 with systolic lability. Pupils reacted poorly to light and

there was striking dermographia. Thiamine hydrochloride was increased to 300 mg per day and a multivitamin added. One month later a typical episode started with an upper respiratory infection, followed by diarrhea, abdominal cramping, irritability, headache, tachycardia and vomiting. On examination she was pale and looked ill. Cardiac rate was 128 and the blood pressure 114/80 with systolic lability. Serum vitamin B_{12} was 1170 pg/ml (normal 160 to 900) and folate greater than 30 ng/ml (normal 4 to 18). Urinary creatine, creatinine and uric acid were measured. Initially a total of 622 mg of creatine per 24 hours and 451 mg of creatinine yielded a creatine/creatinine ratio of 1.3. Total creatinine excretion was 14.1 mg/kg/24 hours, and uric acid excretion 17.6 mg/kg/24 hours. As the vomiting subsided she experienced one brief epistaxis. After informed consent she was begun on thiamine tetrahydrofurfuryl disulfide, 150 mg per day, and was seen again in three months. Although she had some nasal congestion and a few episodes of epistaxis accompanied by facial edema, there had been no further episodes of vomiting. Examination was normal and the blood pressure 90/50 with no lability. Urinary creatine had dropped to 193 mg/24 hours and creatinine increased to 608 mg/24 hours, yielding a ratio of 0.32. Total creatinine excretion had risen to 18.7 mg/kg/24 hours and uric acid had fallen to 10.5 mg/kg/24 hours. After two years of continuous therapy there were no further episodes of vomiting, and she remained well.

Impression

Cyclic vomiting is also referred to as abdominal migraine and abdominal epilepsy. there are a number of questions raised by the course of this child's recurrent illness and her response to fat soluble, but not water soluble, thiamine. A distinct personality change occurred at the onset of any one of her individual attacks. Acute irritability and facial pallor invariably heralded an episode of intractable and prolonged vomiting. Individual attacks terminated with voracious appetite accompanied by repeated epistaxis. Perhaps the most important clue to her intermittent disease was well marked creatinuria. The ratio of creatine to creatinine in the urine was much closer to normal after the use of TTFD. Although the mechanism is unknown, it is possible that the inherent biochemical relationship involves the energy dependent transport system of creatine across the cell membrane or its trapping in the cell as phosphocreatine.[10] The relationship between thiamine, caloric deprivation and creatinuria was reviewed in the last chapter.

Case 7

An eighteen-month-old white girl was admitted to hospital in a coma. Four days before, she had begun a 48 hour episode of repeated vomiting. During the subsequent night she was restless, vomited several times in her sleep and experienced a *grand mal* seizure in the morning. She became unconscious and was admitted to a community hospital. Increases in concentrations of SGOT, and LDH were noted, and the blood ammonia was 1000 mcgs/DL. A diagnosis of Reye's syndrome was made and she was referred for further care.

Coma was assessed at stage three, and there was Kussmaul respiration with grunting, tightly clenched jaw and random movements of extremities. There was minimal response to pain and pupils reacted sluggishly to light. Coma deepened rapidly, and she became unresponsive to pain. Chest roentgenogram revealed a light mid lobe infiltrate. Blood ammonia was 856 mcg/DL. An arteriovenous fistula was placed in the left arm and a ventriculostomy tube inserted for monitoring intracerebral pressure. A two volume exchange transfusion was performed, without any observed change in the clinical condition. Curare was administered and an automatic respirator set up. On the following day blood ammonia was 50 mcg/DL and partial thromboplastin time 74 seconds (control 37 seconds). The SGOT was 400 mU/ml, LDH 500 mU/ml and CPK 600 mU/ml. A second exchange transfusion was performed, during which repeated seizures were observed, involving the right arm and face, vertical nystagmus and blinking. Decadron, 10 mg, and 6 units of insulin were administered. The EEG showed absense of alpha rhythm and high voltage diffuse slow wave activity. Corneal, gag and pupillary reflexes were present. There was a down beat nystagmus; mouthing and flailing limb movements occurred. Intraventricular pressure was 40-45 mm Hg.

On the following day her clinical condition was interpreted by a neurologist to be "at the brainstem level." Pupils became fixed and dilated and a decerebrate posturing was seen, although spontaneous respirations occurred, independent of the respirator. She was judged to be in a terminal state and the respirator was withdrawn. She began to hyperventilate spontaneously. Serum cholesterol was 152 mg/DL and triglycerides 180 mg/DL.

One week after admission there was no change in her condition. She was deeply comatose and all treatment, other than normal life support, was withdrawn. After informed consent by the parents, TTFD in a dose of 100 mg was given by nasogastric tube every four hours, and she received 150 mg by intravenous injection — a total of 750 mg per 24 hours. After 24 hours of treatment the lip vermilion was bright red, compared with previous duskiness, and there was flushing of the cheeks. Two days later there was some response to pain and, after three days of treatment, there was spontaneous movement of the limbs and diminished hypertonicity. Pupils responded to light and she had a cough reflex. There was some bruxism and lip smacking. The intratracheal tube was removed.

After one week, intravenous TTFD was discontinued and the oral dose decreased to 300 mg a day. After nine days from the beginning of treatment there was a widespread exanthem of small superficial bullous lesions containing clear fluid. The medication was stopped, the lesions gradually disappeared and TTFD was then resumed in a dose of 150 mg a day. On the fifteenth day the patient was in a state of so called *coma vigilum.* Eye contact could be established and she responded to sounds, but was not conscious. Subsequently, she began to take jello from a spoon and showed primitive crying responses. The right pupil was seen to be larger than the left. Head control increased, although general muscular hypotonicity remained. On the twenty-first day she was able to chew and could support her own weight with help. Serum cholesterol had risen to 363 mg/DL and the triglycerides decreased to 134 mg/DL. Gross motor function on the Denver scale was seven months, and a personal social scale of ten months. She began to walk with her hand held and self feeding and speech gradually improved. She was discharged from hospital one month after TTFD was begun. Medication was continued in the same dose, and three months later she was clinically well, though muscular tone was diminished. Serum cholesterol was 221 mg/DL and triglycerides 169 mg/DL.

In subsequent follow up, muscular tone gradually improved, but never became normal. At the age of eight years she began to experience a seizure disorder, each seizure lasting about thirty seconds, and more likely to occur after she had been reprimanded. She had repeated kindergarten and was in first grade, able to read and do arithmetic. The EEG revealed slow spike and wave complexes.

Impression

This child was treated in 1975, and explains why the conventional treatment of exchange transfusion and use of insulin and glucose are reported. These methods have now been mostly abandoned. There is still no metabolic treatment for this devastating disease, although better methods of life support are now used and the mortality consequently less. It is also well recognized that Reye's syndrome can spontaneously improve, sometimes even in very severe cases. This makes any treatment modality very hard to assess, as is the case with any disease capable of remitting spontaneously. However, it would be lacking common sense if we fail to apply a non invasive, absolutely safe measure, if there are clues that it has a beneficial effect, irrespective of hard core proof, especially in a disease as devastating as this. No claim is made, here, that this child's life was saved, but the change from a seemingly hopeless state to one of relative normality was impressive, and this medication's effectiveness might be explored further. It was not used by us in other cases of Reye's syndrome for a variety of reasons, including lack of opportunity.

Since thiamine, and perhaps even more, its sulfide derivative (TTFD) both appear to have a therapeutic effect in conditions where energy metabolism is endangered, it seemed logical to attempt to use TTFD in this case, where "terminal care only" had been ordered. It would be very easy to give the medication to every

other case in a series of patients, all of whom would otherwise receive the present care given in this disease.

It is tempting to suggest that the mechanism in Reye's syndrome involves a breakdown in cell membrane physiology, and that systematic research into vitamin and mineral replacement might yield a method of relatively easy medical therapy.

In relationship to stress, it may be relevant in this case that the mother later admitted to excessive punishment, and that she volunteered the statement that it came near to being child abuse in her opinion. It is not inconceivable that a combination of excessive stress and nutritional deficiency creates a pathophysiological state that renders the child highly susceptible to a virus infection. The disease might then be seen as a "derailed stress response" where a computerized attempt is made to meet the stress, and breaks down because the increase in metabolism becomes "the last straw."

It has already been pointed out that stress such as infection sometimes uncovers a genetically determined metabolic disease like diabetes or maple syrup urine disease, causing it to express itself clinically for the first time. The best that can be said is that well chosen nutrients can be expected to improve the natural resources of the body, rather than acting against it.

Another factor may also be worth a comment. The cholesterol was initially lower than the triglyceride concentration. Selye observed a fall in serum cholesterol in his stressed animals, and considered that it was a response to stress. It must be emphasized that his experiments were always performed on an animal after a significant period of complete starvation. It might even be pertinent to consider whether a reduced cholesterol is really a normal or an abnormal stress response. Later in the period of surveillance of this child, it was reported by the parents that seizures were more likely to occur when she was reprimanded. In other words, non specific stress appeared to be more likely to expose a constitutional or biochemical weakness. This may well have been the legacy of the acute event occurring six years previously, or perhaps the constitutional weakness of the child in the first place.

This case is considered to be further circumstantial evidence of the vital but variable integration of environmental stress, genetic or constitutional weakness, and nutrition as a source of fuel for the energy required by the defense mechanisms.

A rider must be added to this case history that is now thirty years old. Reye’s syndrome is now known to be due to aspirin given to a young child with a viral disease and it is now rare. It does not alter the fact that these children died from brainstem failure and there are other conditions of a smilar nature where TTFD could be life saving. Thiamine deficiency has an important effect on brainstssesm physiology, particularly in young children.

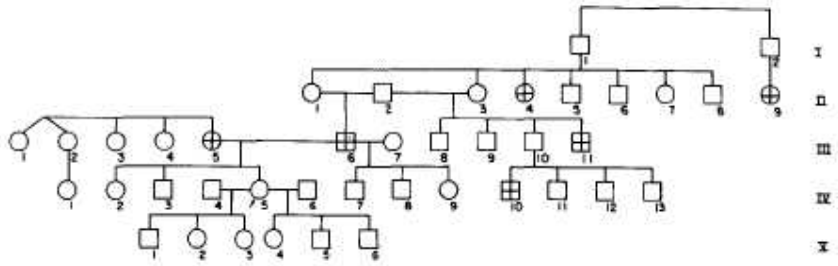
3. Genetics

Case 1

A thirty-six-year-old housewife complained of cardiac irregularity. Birth history was normal. She had "whooping cough" at the age of four years and at five years an illness characterized by a morbilliform rash on the upper trunk and face, associated with high fever and photophobia. At the age of twelve years she experienced inappropriate emotional responses, recurrent diplopia, constant lacrimation with sneezing, and photophobia. Subsequently she began to have increased academic difficulties in school. At the age of twenty-six years her first pregnancy terminated prematurely. The second was followed by a bleeding duodenal ulcer and the third by thrombo-phlebitis. Following dental local anesthesia with epinephrine in 1974, she had respiratory distress, irregular heart rate and hypertension for several hours. Repeated episodes of cardiac palpitations, fatigue, heat and cold intolerance, anorexia and weight loss followed. There was an episode of hemoptysis and respiratory distress and on another occasion she awakened at night with palpitations and asthma. Cardiac irregularity was treated with digitalis. A series of dental abcesses were accompanied by postural hypotension, anorexia,

lassitude, weakness and recurrent cardiac arrhythmia. Other symptoms included ichthyosiform patches of skin on the elbows and knees, epigastric pain, constipation, dysphagia, hoarseness or aphonia, insomnia and unwarranted fear. On the current admission to hospital examination revealed a pale, haggard woman with obvious weight loss, cold cyanotic extremities, pitting edema of the feet, and calf tenderness. Blood pressure varied from 194/50 to 144/88 and the pulse rate increased from 100 supine to 150 when standing. A heart murmur was due to mitral valve prolapse. A 24-hour urine revealed an increase in the total keto acid content and 196 mg of 1-methyl histidine per gram of creatinine (normal less than 108). After beginning a multivitamin supplement she experienced tachycardia, followed by bradycardia and cardiac irregularity. After commencing a supplement of thiamine hydrochloride, she had temporary insomnia but there followed a rapid improvement in general well-being and resolution of symptoms. Figure 1 shows the pedigree of this family. There was an unusual incidence of sudden death in family members, without the mechanism being known.

FIGURE 1



II_3	Rheumatoid Arthritis	IV_1	"Hypoglycemia"
II_4	Sudden Death, Age 17 Years	V_2	Cardiac Irregularity
II_5	Diabetes Mellitus	IV_5	Propositus; Autonomic Dysfunction
II_9	Sudden Death, Age 8 Years	IV_{10}	Sudden Nocturnal Death; Age 18 Years
III_1	Hypertension, Diverticulitis, Cardiac Infarction, Age 48 Years	IV_{11}	Bladder Syncope
III_3	Diverticulitis; Cardiac Arrhythmia	V_1	Infantile Apnea
III_5	Colitis; Sudden Syncopal Death, Age 63	V_2	Premie; Died RDS
III_6	Rheumatoid Arthritis, Sudden Death, Age 63	V_3	L.B.W.; Died RDS
III_9	"Night Suffocation" Attacks	V_4	Cardiac Arrhythmia
III_{11}	Sudden Unexpected Death at Age 18 Months	V_5	Cardiac Arrhythmia

⊗ ⊕ Sudden Unexpected Death

Pedigree of the patient in Case 1.
Note the unusual incidence of unexplained sudden death

Impression

The clinical characteristics are consistent with a diagnosis of an incomplete form of familial dysautonomia, as discussed by Riley et al.[17] A marked improvement occurred in the index patient after the diet was supplemented with moderate doses of thiamine and a multivitamin. Mitral valve prolapse has recently been reported in association with autonomic dysfunction.[11]

Case 2

A sixteen-year-old girl was examined because of a sudden unexpected death in two siblings. She had no overt symptoms except for insomnia, and gave a history of an excessive number of streptococcaal throat infections. Her appetite was poor but she indulged in frequent snacking between meals. On examination, the only abnormal findings were absence of knee jerks, unless consciously reinforced, and slowly developing dermographia. There was also poor capillary circulation in the lower extremities, which felt cold to the touch. Blood pressure was 110/70. Echocardiogram revealed mild mitral valve prolapse. No EKG abnormalitites were observed either before or after exercise. A glucose tolerance revealed a fasting blood sugar of 80 mg/DL, 79 at one hour, 75, 86 and 62 mg DL at successive hours. When the tolerance was repeated, the fasting concentration was *66* mg/DL, but at five minutes it rose to 201, 164 at fifteen minutes, 132 at thirty minutes, 80 at forty-five minutes and 65 mg/DL at 60 minutes. This demonstrated that the original glucose tolerance was not "flat" at all, but that the rise in blood sugar had been missed within the first hour. After a standard injection of epinephrine, there was no mobilization of glucose. The fasting concentration on two separate occasions was 68 mg/DL, and 72 mg/DL. At half an hour the blood sugars were 75 and 72 mg/DL respectively. At four hours they were 63 and 67 mg/DL respectively. Lactic acid concentrations were also measured during this tolerance. Fasting concentrations were 0.6 and 0.9 mEq/L. At five hours the concentration was 2.9 mEq/L in the first, and 5.7 mEq/L at six hours in the second.

The patient was advised to begin graduated exercise, to discontinue smoking and to obviate all refined carbohydrate from the diet. A supplement of thiamine hydrochloride 150 mg a day was prescribed. When examined again, forty-two days later, the patient stated that her feet were less cold and her appetite had returned. She had gained 3.6 Kg. in body weight, looked well, and deep tendon patellar reflexes were normally reactive. Dermographia was mild. A telephone call nine months later revealed that her personality was improved and that she was well.

The family history revealed an unusual account of death in two siblings. A twelve-year-old sister had taken part in a practice swim meet and, after attempting to swim two laps of the pool, she suddenly stopped swimming at the turn. When pulled from the pool, she was found to be dead. Autopsy revealed "myocarditis," and there was no water aspiration into the lung. The only complaint that she had made on the day of her death was of some cramping abdominal pain. On a subsequent occasion a fifteen-year-old brother, apparently in good health, had climbed a rope in the gymnasium. While resting, he suddenly experienced cardio-respiratory arrest, and was thought to be dead on arrival at the hospital. Rescuscitation was partly successful, but a hemiplegia remained and speech was impaired. Gradual recovery progressed, and feedings were begun with glucose in solution. He was suddenly seized with severe cramping abdominal pain, had eleven blood stained bowel movements and expired. Autopsy was reported to the mother to reveal only "myocarditis," and no obvious cause for the gastro-intestinal bleeding.

Impression

The history of unusual sudden death in these two siblings, and a report of myocarditis in each, suggests that there were genetically determined factors in common. Lown and associates [12] have shown that a hypothalamic stimulus in dogs with electrically unstable myocardium developed ventricular fibrillation more easily than dogs whose myocardia were hypoxic, but had not received the hypothalamic stimulus. The patient had symptoms of sympathetic dystrophy[13] and she and both siblings were fond of high calorie carbohydrate foods in preference to a well-balanced diet. Since it appears to be hypothalamic stimulus that induces ventricular fibrillation in dog studies, it is suggested that this was the mechanism here, induced by the response during physical stress. It does not reveal why the myocardium was diseased in the two siblings, but perhaps the combination of poor diet and genetic predisposition was the key.

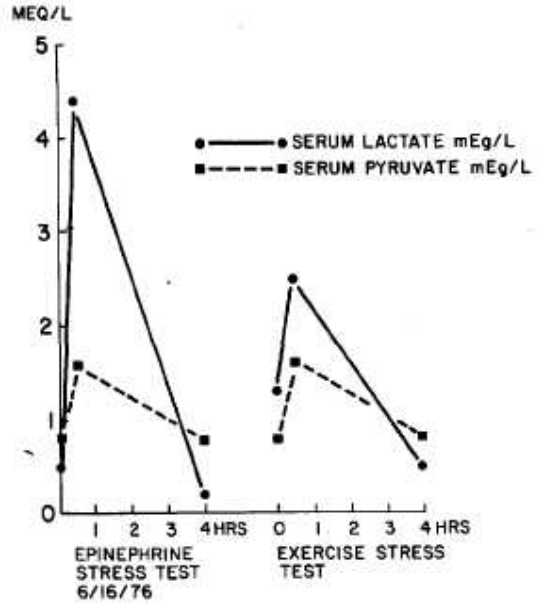
Case 3

A ten-year-old girl complained of headaches and blacking out spells. The mother took medication for "nerves" during pregnancy and the infant was held back at the time of delivery. There was a neonatal history of excessive pharyngeal mucus and cyanosis for a few hours. In the first few weeks after birth there was repeated vomiting. She sat up at nine months, walked at eighteen months, and began words at two years. She was in the fourth grade, but had been held back in the first grade and was performing second and third grade work. Following an episode of pneumonia at the age of eight months, she experienced prolonged nocturnal insomnia. She was hyperkinetic, disruptive, perseverative and annoying at home and at school, and all attempts to modify behaviour with medication had, in fact, aggravated it. The mother had noticed absence spells and the teacher reported daydreaming. She began to have daily headaches associated with paroxysmal abdominal pain, and the left pupil was observed to be larger than the right. Following a cold, her breathing pattern would become abnormal. She would repeatedly hold her breath in inspiration, particularly during sleep, which was restless, with repeated jerking movements and which would occur during the day, whereas she would remain active and awake at night. Diurnal enuresis further suggested her psychologic abnormality. Family history revealed that a first cousin stopped breathing at the age of eight months, and was found dead in the crib in the morning. Autopsy revealed no obvious cause. A maternal second cousin was retarded.

On examination the patient had a pleasant disposition and was of average build. The left pupil was larger than the right but reacted normally to light. Deep tendon reflexes were mostly symmetrical, but the patellar and ankle reflexes on the left were more marked than on the right. Otherwise, the physical examination was normal. An electroencephalogram revealed diminished sleep spindling from the left frontal area as compared with the right, and this was partly corrected by giving a bolus of 5 mg of diazepam intravenously. Imipramine hydrochloride, 25 mg three times a day, had a beneficial effect. Headaches, hyperactivity, and personality improved and she slept better. Her mother gradually withdrew this medication and the child seemed well until eighteen months later when unusual attacks began. During such an episode it was noticed that the left pupil would dilate, and excessive sweating would be seen on the left side of her body, which also became flushed. By contrast, the right half of the body would become pale, and there was no sweating. Following this she noted a hemicranial headache, usually on the left, accompanied by nausea and epigastric pain occurring as often as two or three times a day, each lasting for up to two hours. Her appetite was usually good, although she suffered from constipation and repeated, unexplained abdominal distension. Occasional apnea during sleep had been observed. Exercise would cause undue dyspnea and sometimes precipitated an episode of headache. Her menses were frequent, heavy, lasted nine to ten days and were associated with cramping pain. Frequent tachycardia occurred, particularly with her vasomotor episodes. She was easily upset or irritated and experienced sudden nocturnal awakening. Further family history revealed that the child's mother had frequent headaches, palpitations, ankle edema and blurred vision. She had two sisters who had each delivered a stillborn child, and her parents were both hypertensive. Examination revealed a profound dermographia on light stroking of the skin of the legs. Many conventional neurologic studies in hospital, including computerized skull tomography, were negative and a central space occupying lesion was ruled out. A number of metabolic studies were performed. Lactate and pyruvate increased after epinephrine and after exercise, but returned to fasting concentrations at four hours (Figure 2). The conventional glucose tolerance revealed a "flat" curve, but this was shown to be quite different when the blood samples were drawn every ten minutes in the first hour (Figure 3). Infusion of norepinephrine caused asymmetrical elevation of blood pressure which was notably greater in the systolic component, widening the pulse pressure, and more marked in the left arm (Figure 4). An increase in systolic pressure from 110 to 200 is considerably greater than observed in normal subjects under similar circumstances, although the bradycardia which occurred in this patient is considered to be a normal

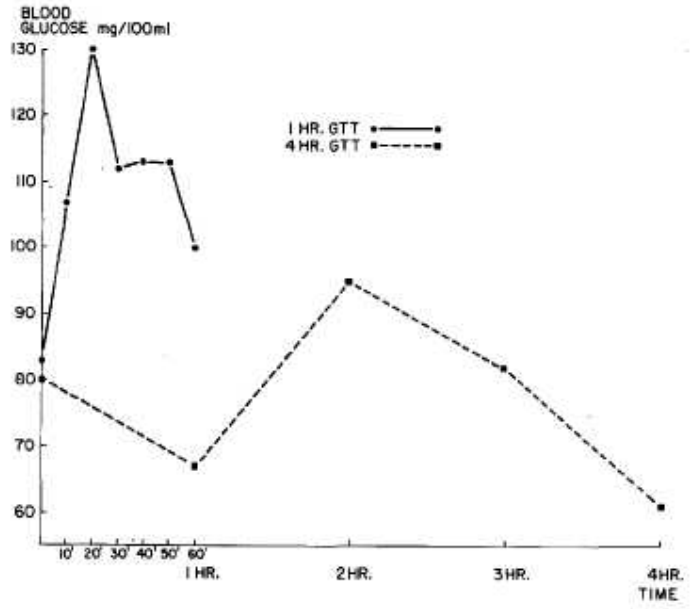
response.[14] During epinephrine infusion she experienced nausea, abdominal pain and headache. The left pupil became widely dilated without any observed effect on the right pupil. Sweat test by pilocarpine iontophoresis yielded 138 mg of sweat from the left forearm and 17 mg from the right forearm in the same test period. She began a supplement of thiamine hydrochloride with a multivitamin and was examined again after two months. Some of the previous unilateral flushing episodes had occurred, but black outs had ceased. Sweating, headaches and abdominal pain were modified and the pupils were more symmetrical. She was studied again a year later. An infusion of norepinephrine showed that the pulse pressure response in the two arms was symmetrical. There was no pupillary asymmetry induced by the infusion, and she did not experience the previous symptoms (Figure 5).

FIGURE 2



Serum lactate and pyruvate showing elevation after epinephrine injection and after exercise. Both returned to the baseline concentration within four hours.

FIGURE 3



Standard four hour glucose tolerance curve contrasted with blood glucose concentrations measured every ten minutes for one hour after a similar dose of glucose.

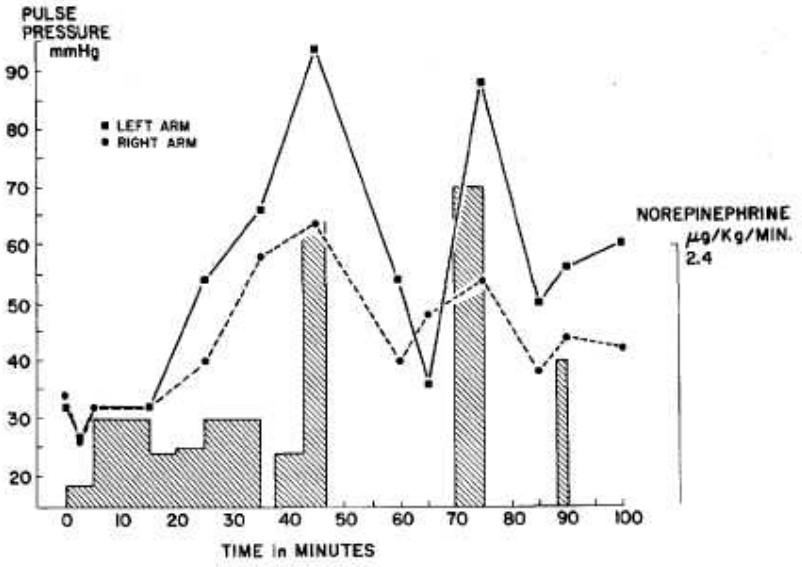
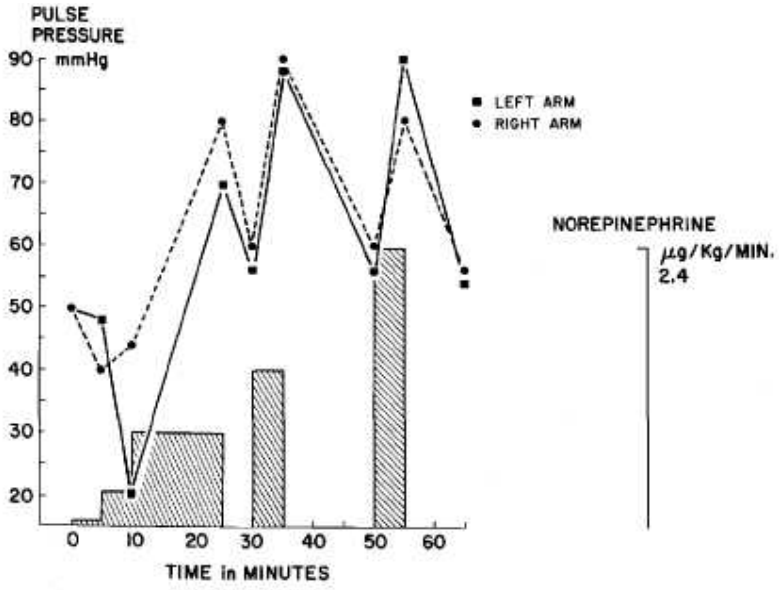


FIGURE 4

Case 3

Pulse pressure in the right and left arms measured simultaneously during intravenous administration of norepinephrine.
Impression

FIGURE 5



Case 3

Pulse pressures in the right and left arms measured simultaneously during intravenous administration of norepinephrine after one year of continuous administration of thiamine hydrochloride supplement.

Impression

This patient showed unequivocal evidence of functional dysautonomia, which is unusual because it was asymmetrical. The association of unusual breathing patterns, asymmetrical sleep spindling, sleep apnea, hyperactivity, and learning problems suggest that it was central in character. No prolongation of Q-T interval or T wave changes were seen in electrocardiographic tracings before or after exercise. The situation on the right side of the body in our patient appeared to be normal, although underactive. The production of sweat stimulated by pilocarpine iontophoresis was asymmetric on the two sides and was consistent on the left with the response seen in familial dysautonomia.[15] This patient demonstrated sensitivity to norepinephrine, which was even more remarkable because of the asymmetry. It is consistent with autonomic control being bilateral in the brain. She represents a syndrome that is not complete enough to suggest familial dysautonomia.

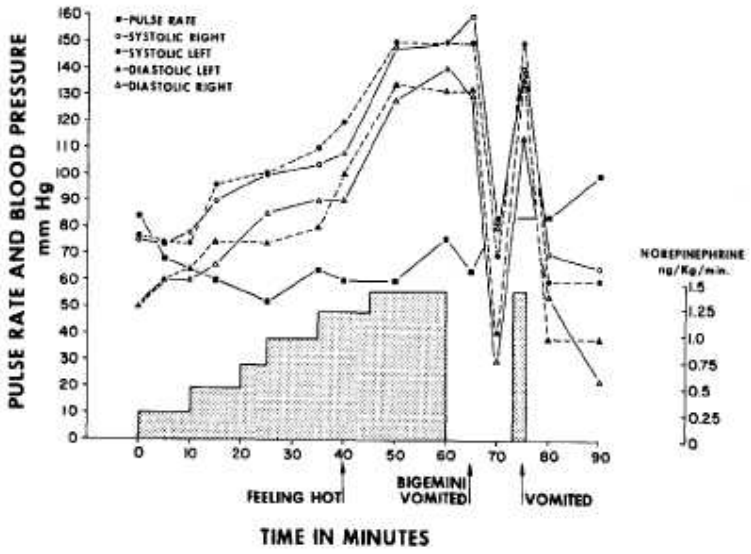
Case 4

A Caucasian boy was first examined at the age of five months because of recurrent episodes of cough and fever. Birth history was normal except for onset of premature labor at thirty-five weeks of gestation. Symptoms at birth described as "breathing trouble" were treated by placing him in an incubator. Jaundice on the second day was treated with light therapy. After release from the nursery, he sucked from the bottle poorly, and at the age of six weeks fever and cough developed and he refused feedings. A white blood cell count of 39,000 was found, but its cause remained unclear. Cough was mainly nocturnal and he choked on liquids. He was irritable, cried constantly, was recurrently constipated and frequently febrile. Apart from excessive oral pharyngeal mucus, examination was normal. Further study revealed a persistent right aortic arch, a fibrous remnant of the left aortic arch which formed a constrictive vascular ring anterior to the trachea and esophagus, and a retroesophageal left subclavian artery. The esophagus below the constriction was found to be dilated and unusually muscular, evidently a post stenotic dilation, but with muscular hypertrophy. The anterior fibrous cord was cut and the immediate separation of the two ends revealed its constrictive nature.

Following this, the infant did well until the age of ten months, when he began persistent vomiting after every feeding. Finger sucking and regurgitation suggested rumination, but marked muscular hypotonia and refusal to chew foods suggested that there might be some developmental delay. An esophagogram with contrast revealed persistent narrowing of the esophagus at the level of the previous constriction, but it appeared to be a functional phenomenon, as vomiting ceased in the hospital. He was next seen at the age of four and a half years, and interim history revealed that he had not been able to sit up on his own until twelve months and that he first walked at twenty months. Toilet training was started at two and a half years and the course had been marked by persistent nocturnal enuresis, alternating diarrhea and constipation, repeated episodes of unexplained abdominal pain and intermittent fever. On examination he was observed to be overactive and the left pupil was 4 mm in diameter, whereas the right was 2 mm in diameter. Both pupils reacted to light. No further contact was sought until he returned at the age of six because of unusual behaviour and a speech defect. The kindergarten teacher complained of overactivity and disruptive behaviour and a speech defect. The child experienced difficulty in getting to sleep at night, was restless and enuretic. He consumed a large amount of sugar, taking it with a spoon from the sugar bowl.

Examination revealed a pale, thin, chronically ill child. The skin was dry and there was well marked piloerection. The left pupil was half as big again as the right pupil and both reacted slowly but symmetrically to light. The left pupil was a little irregular in outline and unusual hippus was observed. Blood pressure was 86/30 with systolic and diastolic lability. Nasal obstruction resulted in mouth breathing. Glucose tolerance revealed a fasting glucose of 78 mg/100ml, 200 mg/100ml at one hour, 127 mg/100ml at two hours, 69 mg/100ml at three hours, 84 mg/100ml at four hours, and 77 mg/100ml at five hours. Chromatography of mixed hydrazones was normal and amino acid analysis of urine by ion exchange showed an increase in histidine to 338 mg/gram of creatine (normal 12 to 187). Norepinephrine infusion (Figure 6) caused a symmetrical rise in both the systolic and diastolic components of blood pressure which rose from 76/50 to 160/130. As blood pressure increased there was bradycardia which was followed at the end of the infusion with mild tachycardia. The child became extremely restless and tearful as the infusion was increased in dose and he vomited on the two occasions that reached maximum rise in blood pressure. Elevation was sensitive to norepinephrine infusion when the maximum dose was given for the second time for only a few minutes and fell rapidly after the drug infusion was discontinued.

FIGURE 6



Norepinephrine infusion in a 4 '/2-year-old boy, showing rise in blood pressure and rapid fall after infusion was discontinued. Note the observation of bigeminal pulse and vomiting that occurred at maximum infusion rate.

Impression

This case cannot be explained entirely on the basis of the surgically relieved vascular ring. The appearance of functional symptoms was accompanied by clinical evidence of abnormal dysautonomic activity. It is unknown whether the structural abnormalities were related or not, although it has been suggested that the mechanism of familial dysautonomia is related to the lack of trophic factor in nerve growth, which may have some effect on maintaining healthy cells that are innervated.[16] Smith and Dancis[14] showed that cases of familial dysautonomia were pathologically sensitive to norepinephrine infusion, and the case of this child suggests that he represented an incomplete form of dysautonomia.[17]

Case 5

An eighteen-month-old white male infant was examined because of failure to thrive, hypophagia, nocturnal breathing difficulty and vomiting. The birth weight was 4.1 kg. There was no history of maternal mellituria. He sat at six months, was beginning to walk, and saying a few words. At the age of six weeks he began to have "raspy" breathing and repeated vomiting. There was unusual pallor, respiratory congestion and irritability. At the age of eight months he had pneumonia, and at eleven months tracheobronchitis. At thirteen months serous otitis caused his hospital admission for placement of aeration tubes, but infection precluded surgery which was then postponed until he was fifteen months old. On hospital admission for this procedure, his night breathing was severely embarrassed, and he was described as gasping for air, snoring loudly, and breathing as though he had croup. After discharge, his mother observed nocturnal breathing problems of major proportions. Loud snoring would be suddenly interrupted by awakening, frequently with a scream, only to repeat the cycle. Sleep was restless, would last for seventeen to eighteen hours, and was supplemented by frequent naps during the afternoon. Vomiting of "coffee-ground" material was observed and he was fatigued, irritable, and hypophagic. He drank sweetened fruit juices sporadically, which resulted in frequent choking, and he had excessive oral mucus, coughing and excessive sweating. On examination he was hyperirritable, pale and well under the third percentile in weight and height. Loose folds of skin and poor subcutaneous fat

suggested chronic dehydration, and inspiratory stridor was heard occasionally during sleep. The heart rate was 176 per minute with marked sinus arrhythmia and the blood pressure was 120/0 with a 20 mm fluctuation at systole in the phases of respiration. Deep tendon reflexes were unpredictable, varying from unobtainable to 1+. Electrocardiography revealed left and right ventricular hypertrophy, although chest roentgenography did not reveal any observed cardiac enlargement. Red cell TKA was 91.38 mU/L/min and TPPE 6.93%. Serum folic acid was 20.0 ng/ml and vitamin B_{12}1100 pg/ml. Monitoring of arterial oxygen saturation by night using ear oximetry revealed that oxygen saturation was as low as 72% at night, and invariably lower than those of a similar aged normal child monitored simultaneously. The blood hemoglobin was 6.8 gm/100ml and the serum iron concentration 2 mcg/100ml with a normal iron binding capacity. There was moderate enlargement of the adenoids and adenoidectomy was followed by troublesome persistent laryngospasm. Snoring cycles continued in spite of surgery and after informed consent by the parent TTFD, 150 mg per day, and a multivitamin preparation begun. When seen one month later the child had gained weight and nocturnal snoring and personality were improved. Sleep was no longer disturbed and there was no undue sweating.

Impression

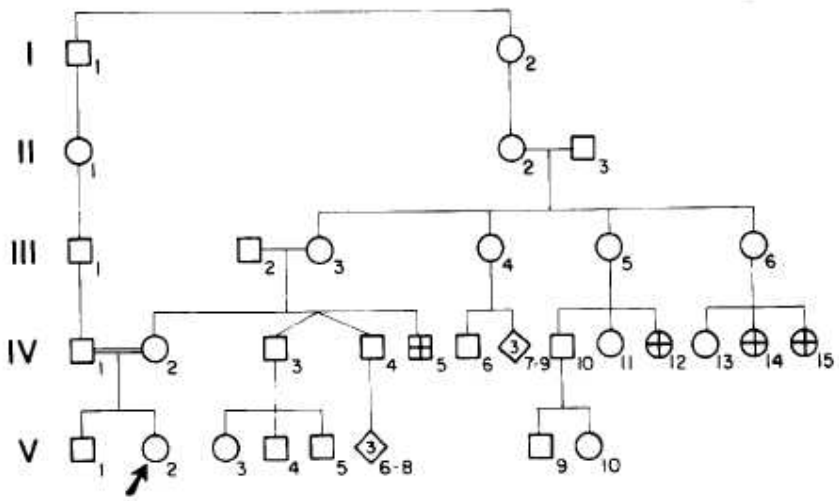
This chronically ill child suffered from the increasingly recognized disorder of sleep apnea,[18] a relatively common problem in adults. Studies in the sleep laboratory have shown that there is a mixture of airway obstruction and central disturbance which combines to present a potentially dangerous situation. Nocturnal hypoxia appeared to be a physiological phenomenon but the dangerous degree of hypoxia in patients with sleep apnea appears to fail in stimulating reticular activity. Adenoidectomy did not abolish snoring or his sleep restlessness, and TFFD was used empirically, hoping to catalyze an increased uptake of oxygen in both red cells and in brain. This child improved spectacularly, but the clinical observations could not be sustained by laboratory tests, though his ultimate recovery was a surprise to all observers.

Case 6

A Caucasian female, aged 7 $^{10}/_{12}$ years, was examined because of recurrent fever, weight loss and fatigue. Her mother's pregnancy had been normal except for a kidney infection and labor one month premature. Artifical respiration was required for the infant at birth but subsequent development was normal. Throughout infancy and early childhood she had many episodes of upper respiratory infection and diarrhea. About one month after one of these episodes she paid a visit to the dentist from whom she experienced unusual bruising, although manipulations were gentle. She continued to feel and look ill with fatigue, anorexia, lassitude, facial edema, and unusual infrequency of urination. Examination was negative and the symptoms considered by many other observers to befunctionally psychological in nature. At the age of nine she returned because of fever and cough. Chest roentgenography revealed a left lower lobe infiltrate and a small pleural effusion, both of which cleared spontaneously one week later. However, this was associated with night sweating, fatigue, thirst, anorexia, irritability, pallor and excessive sleep. Family history revealed four crib deaths and consanguinity (Figure 7). Red cell TKA was 88.02 mU/L/min and TPPE was 16.5%. Thiamine 150 mg a day and a multivitamin were started, and one month later she was symptomatically improved. Irritability decreased, appetite improved, and excessive sweating diminished. Occasional swelling and erythroderma of knees, urticarial wheals, mildly labile blood pressure and audible femoral tones on auscultation over the femoral artery continued. She gained 1 kg in body weight. She remained partially cold intolerant and easily became cyanotic when in cold surroundings. Swimming on a hot day caused her to experience uncontrollable shivering and great difficulty in getting warm. This was followed subsequently by hypersomnia, repeated epistaxis, anorexia and abdominal pain. On examination she was pale and there was a small amount of periorbital edema and tachycardia. She was apathetic and unresponsive. The feet were ice cold and dusky, with poor capillary circulation and slowly reactive dermographia. Blood pressure was 100/30 and labile. Femoral tones were audible in the inguinal area.

Psychologic assessment revealed considerable family stress, and counselling resulted in some improvement. When last examined at the age of nine and a half years she was asymptomatic.

FIGURE 7



Case 6

III_3	"Heart Attack" age 28, chest pain, hyperpyrexia; considered dead but recovered. Suffers confusion, headaches ? neuropathy
IV_5	Sudden death after measles, age 7
IV_6	Hemiplagia, cerebral palsy, no speech
IV_{12}	Crib Death, age 4 months
IV_{14}	Crib Death ? age
IV_{15}	Crib Death ? age
V_2	Proband
V_5	Premature; RDS; recurrent pneumonia, intractable vomiting, abdominal pain, lethargy, short stature
V_6	Brain tumor — blind

Note the unusual incidence of sudden death in this family. Though not proven, the three infants were suspected of being examples of sudden death syndrome from the typical histories of being found dead in the crib in the morning. Mother of the proband did not know that she was previously related to her husband.

Impression

This case suggested that the emotional environment represented a potent source of stress in a child whose unstable neuroendocrine system was possibly genetically determined. Diet may have been been an additional factor. It is not known why the crib deaths occurred, but it appeared to be an unusual incidence in a family. The incidence of consanguinity also suggested the possibility of genetic influences. There were a number of symptoms and physical signs which indicated autonomic dysfunction. The discovery of four crib deaths in the immediate family and consanguinity was made by the proband's mother only after enquiry, and was a surprise to her. Since there is documentation of autonomic dysfunction in crib death [19] it may be pertinent to consider that the behaviour of the autonomic system was the common and possibly genetically determined factor in this family.

Case 7

A Caucasian girl, aged 8¼ years, was examined because of severe photophobia, clouding of the cornea, loss of weight and a constant rash. Birth history and early development were normal. At the age of eighteen months she had suppurative parotitis, after which she had recurrent photophobia, clouding of the cornea and persistent piloerection. Photophobia gradually became constant and was accompanied by nasal congestion. She kept her eyes covered and would play outside only at night. Sudden rapid loss of weight would occur, but would be rapidly restored. Acetone was frequently detected in her breath. Appetite was normal but she had polydypsia, recurrent tachycardia and periorbital edema recurred at intervals. She had a past history of recurrent fever with headache and profuse sweating, and she had complained of tinnitus and deafness. Examination revealed a pale, thin child who sat with her head, which was covered by a blanket, between her knees. This position had been adopted ostensibly to protect her eyes from light. Only with difficulty was she persuaded to lie down on the examining couch, and she easily and quickly returned to a position which protected her eyes. Blepharospasm was acute, and any attempt to open her eyes by the examiner caused lid eversion and tearing, accompanied by sneezing and nasal discharge. There was edema of the eyelids and face, and acetone was easily detectable in her breath. There was asymptomatic myringitis on the right. Her skin was dry to touch and there was widespread piloerection. Deep tendon reflexes were normal. Blood pressure was 100/60 and the heart rate 140 per minute. Glucose tolerance revealed a fasting blood glucose of 302 mg/100ml, 372 at one hour, 414 at two hours, 354 at three hours and 308 mg/100ml at four hours. Insulin was started and within forty-eight hours the fall in blood sugar concentration was accompanied by disappearance of piloerection. Her skin became warm and smooth to the touch. Although she was occasionally able to open her eyes, she spent most of the time with her eyes buried in a pillow. Ophthalmologic examination under anesthesia revealed clouded edematous cornea with microcysts and bilateral cataracts. There was pigment disbursion in the retinal periphery and bilateral "salt and pepper" maculopathy with maintenance of foveal reflex.

TABLE 4

AMINO ACID	NORMAL mg/G creatine	6/23	7/23	7/30	9/10	11/11
Taurine	188-779	300	203	51	99	21
Aspartic	13- 95	34	32	18	25	7
Threonine	15- 81	640	505	174	133	132
Serine	31-186	569	397	228	205	202
Asparagine	TR-171	60	0	26	0	0
Glutamic Acid	13- 90	289	334	67	TR	60
Glutamine	54-540	766	0	225	237	172
Adipic Acid	TR- 43	278	26	TR	38	16
Glycine	50-326	595	566	349	325	321
Glycine/Alanine Ratio		3.6	1.8	2.1	1.5	1.8
Alanine	15- 78	163	315	166	209	178
Citrulline	0	31	9	0	0	0
Beta Amino Isobutyric Acid	2-10	52	0	0	0	0
Valine	TR- 22	360	40	21	43	23
Cystine	TR- 18	50	43	19	12	12
Methionine	TR- 18	5	15	10	13	TR
Isoleucine	TR- 19	53	13	5	19	7
Leucine	TR- 51	123	35	12	20	18
Tyrosine	TR- 65	277	127	56	80	52
Phenylalanine	TR- 33	84	33	24	28	19
Ethanolamine			Present			
Lysine	24-570	544	450	138	70	92
Histidine	12-178	798	681	420	538	277
I M Histidine	TR-108	106	22	10	TR	TR
3 M Histidine	TR- 93	TR	18	12	56	TR

TR = Trace

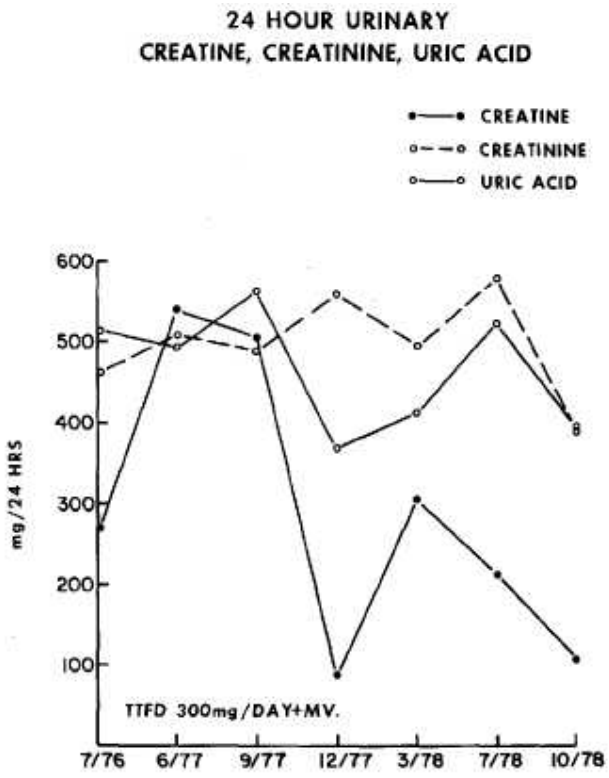
Case 7

Urinary Amino Acid Analysis. Initially 15 of 21 amino acids were increased in concentration. Only 4 of 20 amino acids were increased five months later, after continuous administration of TTFD and a high potency multivitamin. .

A 24-hour urine collection showed 463 mg of creatine and 370 mg of creatinine, yielding a creatine to creatinine ratio of 1.3. Uric acid was 592 mg/24 hours, yielding a uric acid to creatinine ratio of 1.6. Serum pyruvic acid was 0.8 mg/100ml fasting, rose to 1.6 mg/100ml one half hour after epinephrine, and returned to 0.8 mg/100ml at four hours. Fasting serum lactate was 0.8 mEq/L, 1.5 mEq/L one half hour after epinephrine, and 1.2 mEq/L four hours after. Sweat test by iontophoresis was normal, and screening test for mucopolysaccharides negative.

Electrocardiographic examination revealed sinus tachycardia and myocardial changes. Special audiometry revealed moderate to severe high frequency hearing loss. Amino acid chromatography by both paper and ion exchange analysis were grossly abnormal (Table 4). She was treated with TTFD 300 mg per day and a multivitamin. Creatine, creatinine and uric acid excretions in urine were measured periodically and are shown in Figure 8. Nine weeks later the blepharospasm had improved and the child's body weight had increased by 4 kg. Examination revealed persistent pallor, tachycardia and labile blood pressure. There was no improvement in visual acuity. Two months later she was normally active, and although there was no improvement in visual acuity or physical findings in the eyes, the blepharospasm was considerably improved and body weight had again increased by 1,5 kg. Tachycardia was still prominent. Blood pressure was 90/56 and heart rate 120 per minute. Photophobia, deafness and abnormal eye findings have persisted. Although lost to follow up, it was learned later that a calcified mass had been seen on X-ray some years after the clinical episode described here.

FIGURE 8



Case 7

Twenty-four hour concentrations of urinary creatine, creatinine and uric acid over more than two years of continuous treatment. Note that creatinine and uric acid remained relatively constant, whereas the creatine decreased. This would obviously result in a fall of the creatine to creatinine ratio, irrespective of the absolute concentrations of either. Thiamine disulfide treatment was accompanied by the administration of a high potency multivitamin (MV).

Impression

Deafness, recurrent fever, profuse diaphoresis and bizarre behaviour appeared to be centrencephalic in origin. Acute Reflex Blepharospasm is reported as psychopathological but occurs after strokes occasionally, and was clearly organic in nature in this child.[20] Diabetes appeared to be a late manifestation of her disease since neuropathy was already present when diabetes was found, and this appeared therefore not to be the primary causative factor. Evidence favored abnormal metabolism in brain rather than pancreas or other affected organs. Disappearance of piloerection after insulin was begun indicated that sympathetic activity was diminished, strongly suggesting a central effect. The significance or the treatment of a reported calcified tumor in the brain at a later date remained unknown. The case is reported here because of the remarkable improvement that occurred in symptomatology by her exposure to thiamine tetrahydrofurfuryl disulfide (TTFD).

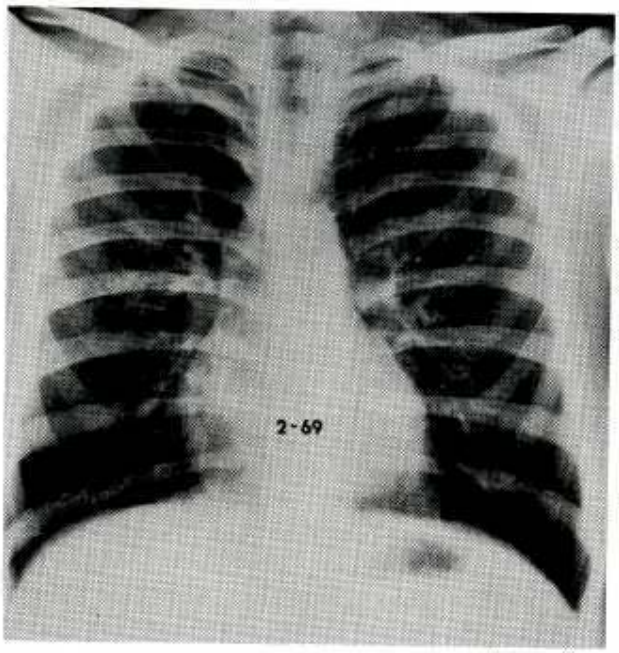
Case 8

A six-year-old white male was examined because of poor motor coordination. At birth the maternal liquor had been meconium stained. His birth weight was 2.5 kg. Spontaneous respirations were delayed and cyanosis was noted initially. Throughout the neonatal period he was irritable; he sat up at ten months, walked at twenty-two months and talked indistinctly at two years. Hyperactivity, short attention span, sound sensitivity and periodic asthmatic wheezing became apparent in early childhood. Family history revealed that the paternal grandmother was diabetic. On examination, the child overreacted to all stimuli. Echolalia and

hyperactive deep tendon reflexes were observed, and psychological examination revealed an IQ of 73 on the Stanford-Binet Form LM.

At age twelve years the patient was examined again because of coughing and coffee-ground vomiting. Interim history disclosed similar episodes for the previous two years and for which no cause had been determined. Melena and hematemesis were reported in one of these. On examination his pulse was 100 and blood pressure 140/90. There was a grade II systolic murmur at the pulmonic base. There was a striking lack of body hair, a morbilliform rash on the anterior chest and some well-marked dermographia. No ulceration of the bowel could be detected by roentgenography. Some increase in ground-glass clotting time was revealed, but it was not studied further, and glucose tolerance showed a fasting concentration of 114 mg/100ml, 170 at one hour and 150 mg/100 at two hours. There was no glycosuria. The EEG was non-specifically abnormal. Chest roentgenogram revealed a normal heart shadow (Figure 9).

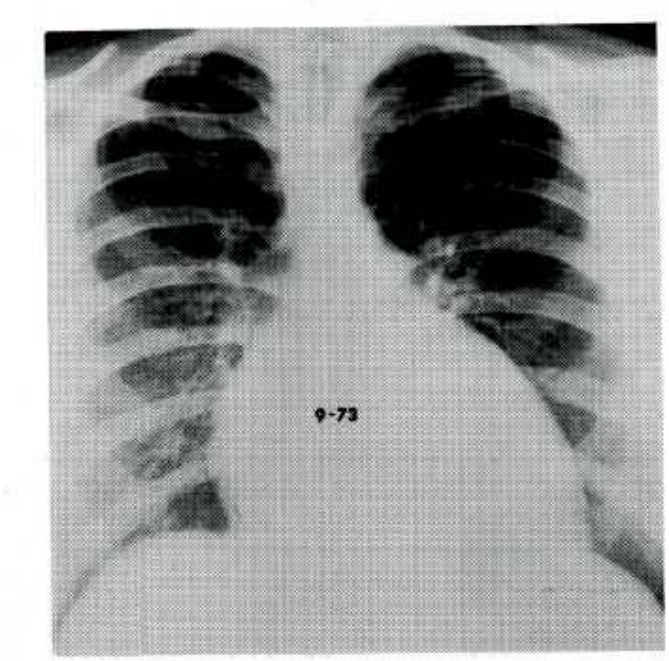
FIGURE 9



February 1969, normal PA chest (Case 8)

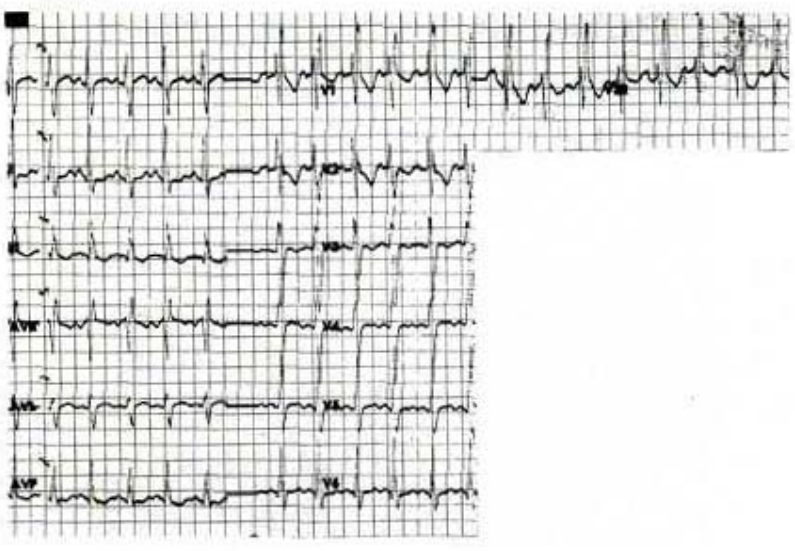
At sixteen years of age he was admitted to a hospital with a transient right hemiplegia. Two weeks previously he had had a severe episode of anorexia, lethargy, diarrhea, vomiting, abdominal pain and cardiac palpitations. Ten days later, recovery seemed complete and a family picnic took him into mountainous terrain. He complained of malaise, and while sitting at a table in hot sunshine he suddenly complained of feeling dizzy and tried to stand up. Slurred speech, oculogyria and ataxia were described. Weakness in the right arm and leg were accompanied by left facial weakness and drooling. During transmission to hospital in an air-conditioned car, the hemiplegia disappeared within twenty minutes. While in hospital he was febrile and developed generalized giant urticaria. An enlarged heart was revealed by roentgenography. He was discharged home after three days but complained of a severe "pinching" in the chest, and so the parents brought him for further examination to Cleveland Clinic. On examination he was acutely ill and orthopneic. There was intermittent dilatation of *alae nasi* and a repetititve dry cough. Respirations were 40 and pulse 140 per minute with many dropped beats. Auscultation of the heart revealed muffled heart sounds and gallop rhythm. Roentgenography revealed cardiomegaly (Figure 10).

FIGURE 10



September 1973, PA chest now demonstrating generalized cardiomegaly
(Case 8)

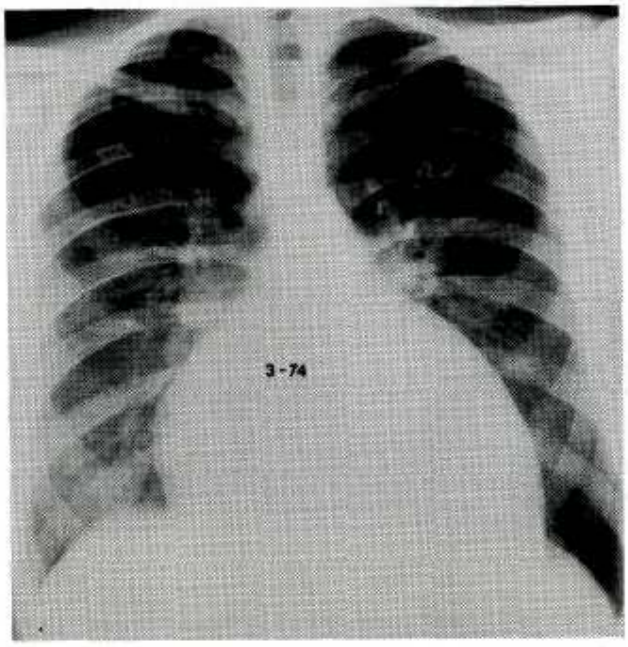
FIGURE 11



This electrocardiogram is representative of the many recorded between September, 1973 and September, 1974. Sinus rhythm is present with prolonged intraventricular conduction (0.14 sec). The pattern is that of right bundle branch block. Very pronounced electrical alternans of both QRS and T wave complexes is present. The P-R interval does not show alteration. The intrinsicoid deflection in lead V6 is prolonged to 0.05 sec. indicating left ventricular hypertrophy or delayed activation of the free wall of the left ventricle. Case 8 (interpretation: courtesy Dr. R.C. Lewis)

Although the etiology of the acute illness may have been viral in nature, the association of cardiac enlargement and the neurological history was considered to be mindful of classical beriberi. He was given 100 mg of thiamine hydrochloride by intramuscular injection together with digitalis and a diuretic. On the following day respirations were 36 per minute and the pulse 100 to 130 per minute and regular. He looked better. Improvement was accompanied by diuresis. During the next few days he improved steadily and was discharged from hospital. He returned two weeks later with the main complaint of recurrent acute "pinching" chest pain. He had experienced increased sweating and orthopnea. He was apprehensive, wheezing, and pitting edema was observed over sacrum and ankles. The fingernail beds were cyanotic. Electrocardiography revealed myocardial changes (Figure 11). During the next few months there were repeated admissions to hospital. He complained increasingly of a "thumping" epigastric pain, nausea, vomiting, intermittent diarrhea, sweating and it was apparant that his cardiac condition was slowly progressive. Hypokalemia was frequent and potassium supplements were given. In spite of an improved appetite, he lost 7 kg in weight. He continued to experience premature auricular contractions and the pulse was bigeminal. After six months there was rapid clinical deterioration. Recurrent episodes of chest and epigastric pain, vomiting, diarrhea, constant sweating and irritating cough were accompanied by increasing heart size (Figure 12). Gallop rhythm, hepatomegaly, peripheral cyanosis and edema testified to the cardiac status. The constant state of anxiety and sensitivity to sound prevailed. Hemoglobin concentration was 17.2 gm/100ml and hypokalemia was persistent. All relevant laboratory studies are shown in Tables 2-4. Viral studies were negative.

FIGURE 12



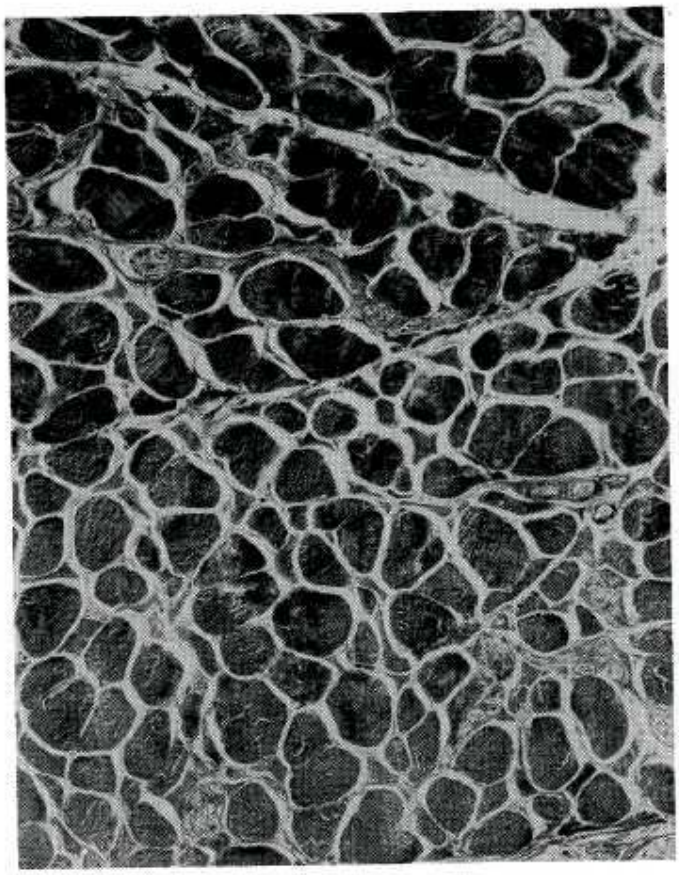
March 1974, PA chest demonstrating further cardiac enlargement, small right-sided pleural effusion and prominence of pulmonary vasculature.
(Case 8)

FIGURE 13

Right biceps muscle biopsy: small group and perifascicular muscle fiber atrophy (paraffin, H & E, original magnification X64.)
(Case 8)

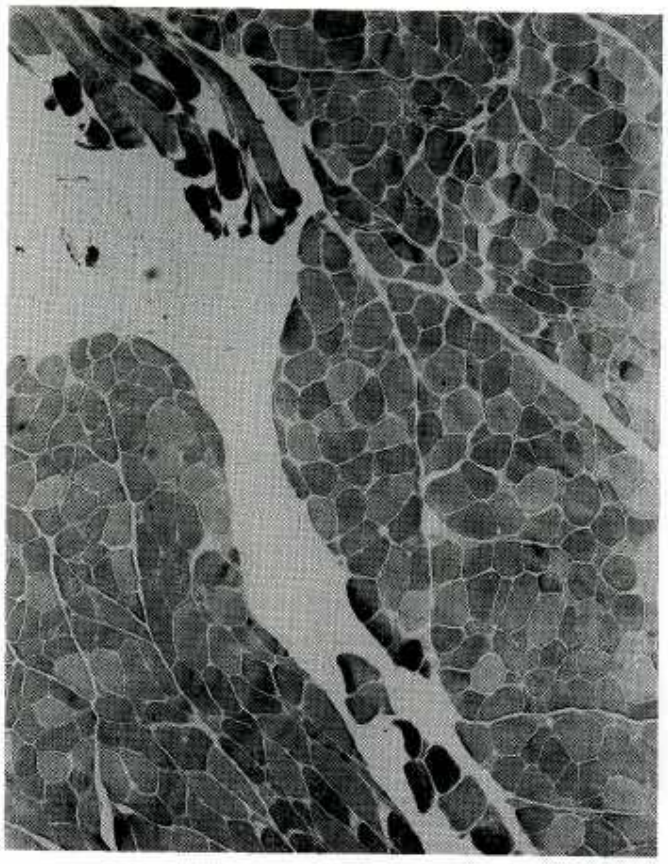
Within a month the patient's condition was critical again. He had massive carotid pulsation in the neck, audible sounds by auscultation of the femoral artery in the inguinal region, and pounding of the chest wall. Dyspnea and extreme restlessness of the patient were typical of the Shoshin form of beriberi. The parents gave informed consent for the use of TTFD, and the drug was started in a dose of 150 mg a day. His general condition rapidly improved. Carotid pulsations ceased and there was no dyspnea or restlessness within several days. Diuresis occurred and there was a striking loss of weight. This therapeutic response suggested that the disease had a metabolic etiology, related to thiamine metabolism. Electromyography showed diffuse muscle irritability, or active denervation in almost every muscle in the lower extremity, much more abundant in the *vastus lateralis* and in two proximal upper extremity muscles. The changes suggested a combination of chronic neurogenic and upper motor neuron abnormality, although there were spotty changes in a few lower extremity muscles which appeared to be those of myopathy. A muscle biopsy from the right biceps showed a group (denervation) atrophy. There was some decrease in the number of fibers in the intramuscular nerves and increased connective tissue, indicating a neuromyopathic cause (Figures 13-17). There were no pathologic changes in the retina.

FIGURE 14



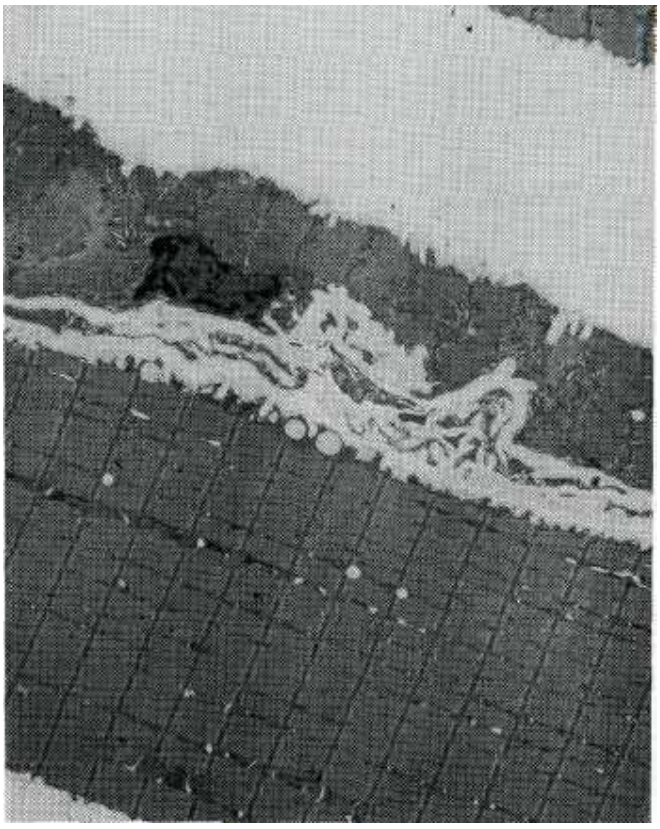
Right biceps muscle biopsy: small group and single muscle fiber atrophy. Intramuscular nerve twigs show increased endoneurial connective tissue (paraffin, H & E, original magnification XI60.)
(Case 8)

FIGURE 15



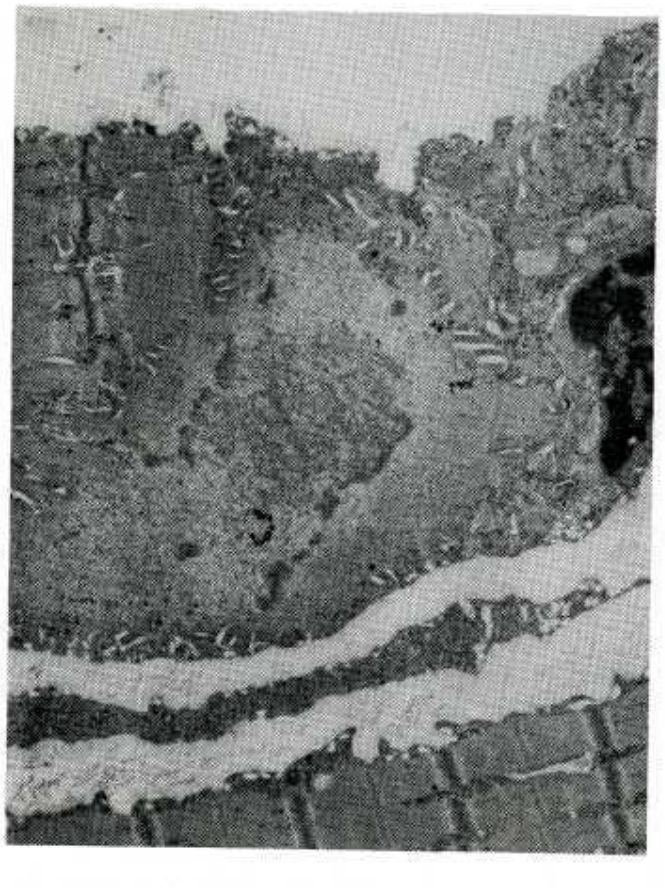
Right biceps muscle biopsy: glycolytic enzyme histochemistry. Note that the small angular fibers are both Type I and Type II (frozen section, phosphorylase.)
(Case 8)

FIGURE 16



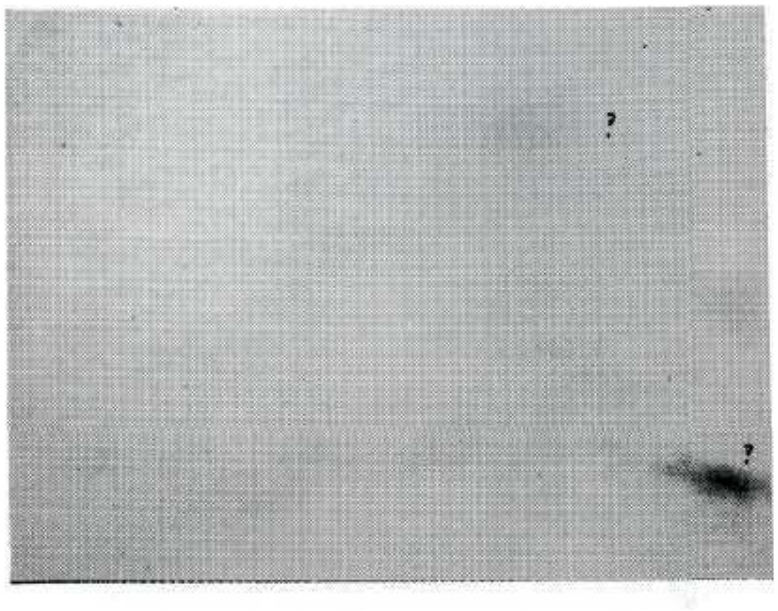
Right biceps muscle biopsy: longitudinal section of two myofibers. The atrophic fiber above shows mild dilatation of the SR-T system and a cytoplasmic body (left upper margin). The fiber below is small and relatively normal (original magnification X 7, 850).
(Case 8)

FIGURE 17



Right biceps muscle biopsy: high magnification of cytoplasmic body showing its apparent origin from Z-band streaming and disorganized myofilaments (original magnification X20, 200).
All muscle biopsy interpretations courtesy Dr. M. Steinberg
(Case 8)

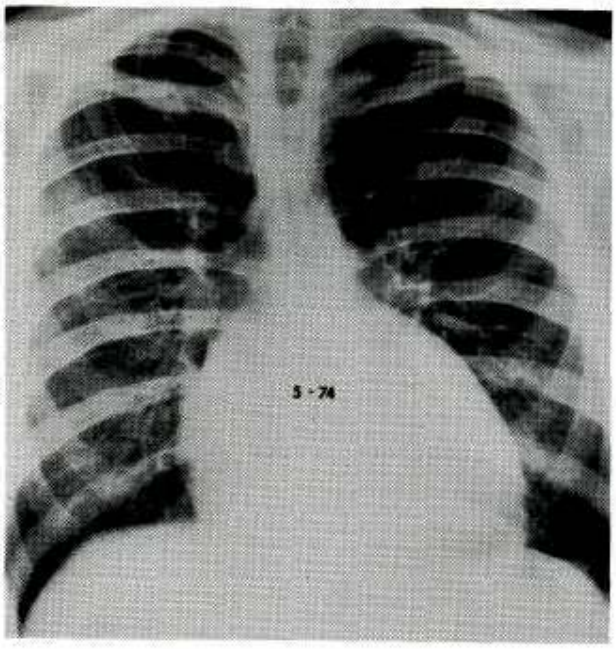
FIGURE 18



Urinary amino acid chromatogram, July 1974. Center of chromatogram normally shows a large cluster of amino acids which were in very low concentration in this specimen. Spot in the bottom right corner of photograph is close to the position of taurine, but elution and ion exchange chromatography revealed its acidic nature; it did not conform to the position of taurine. Another faint, unknown spot is seen above this, and the spot in the upper zone indicated by a question mark was later found to be caused by a breakdown product of the antibiotic Ampicillin (Case 8)

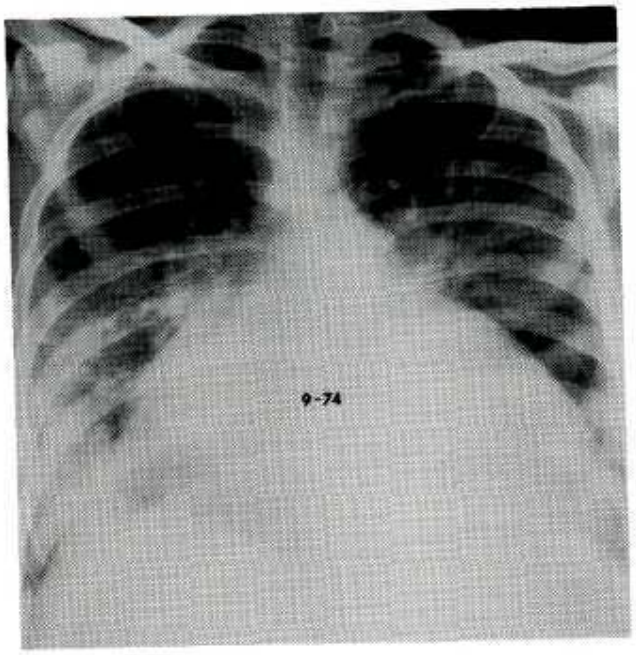
One week later he had another episode of abdominal pain and nausea, accompanied by intense anxiety, and TTFD was increased to 450 mg per day. All symptoms disappeared and after three more weeks he claimed that he felt better than he had for several years. Figure 19 shows the appearance of heart by roentgenogram which revealed some reduction in overall size. The laboratory studies shown in Table 5 were much improved. In the next two months his weight increased by 2.7 kg and there was some visible increase in muscle tissue, but blood pressure remained labile. *Pulsus alternans* and cardiac gallop rhythm reappeared intermittently. He began to have renewed episodes of "thumping" epigastric pain associated with a sense of nervousness. Respiratory and cardiac rate steadily increased and he was readmitted to hospital six months after beginning TTFD. Examination revealed acute distress, cyanotic lips, hyperdynamic precordium, carotid pulsation, sweating, dyspnea, hepatomegaly, and edema resistant to all therapeutic measures. Cardiac size by roentgenography had increased (Figure 20). A 24-hour urine revealed 900 mg of creatine per 24 hours and 700 mg of creatinine per 24 hours — a ratio of 1.3. He expired two weeks after readmission to hospital. Autopsy was refused.

FIGURE 19



May, 1974, PA chest demonstrating decrease in cardiac size and less vascular engorgement, two months after commencing TTFD.
(Case 8)

Figure 20



September, 1974, portable AP supine chest demonstrating massive cardiomegaly and pulmonary edema
(Case 8)

Impression

There was a history of probable hypoxic birth. The infant was irritable, cried endlessly and was unusually sensitive to sound. Neurologic, psychologic, and cardiac disease were associated with episodes of vomiting, diarrhea, acute abdominal pain, and bowel hemorrhage of unknown cause. Throughout life he had never been normal. His sensitivity to sound was remarkable, particularly in the final stages of his disease, when the exploding of a firecracker caused extreme palpitations, sweating and unusual fear. Hemoglobin concentration and physical signs of hypoxia suggested that there were endogenous attempts unsuccessfully to adapt to the physical environment encountered on a high mountain. This may have been important in reference to the seizure like episode that occurred in mountainous terrain on a hot day. Repeated episodes of vomiting, diarrhea, and abdominal pain suggested abnormal "fight-or-flight" reactions and may have been due to centrencephalic causes. This is similar to the clinical course of Leigh's disease, already discussed in detail, in which the histopathology is similar to Wernicke's encephalopathy. His temporary response to TTFD is also similar to that seen in Leigh's disease in which "resistance" develops, and symptoms and signs of the disease reappear.[21] In the pre-terminal stage there was marked creatinuria, also suggestive of beriberi. Urinary creatinine concentration was 200 mg less than that of creatine resulting in a high ratio of creatine to creatinine. If hypooxidative metabolic function of brain could have been proved, it might have provided an adequate etiology. No SNE inhibitory substance was found in urine. Autopsy might have given further information. The late clinical course was typical of the peracute form of beriberi known as Shoshin.

TABLE 5

RESULTS OF LABORATORY TESTS — CASE 8

Date	Test	Result	Normal Range
Age 12 years			
2/11/69	Ground glass clot time	145, 145, 150 sec	90-130 sec
2/12/69	Glucose tolerance		
	Fasting blood sugar	114 mg/100ml	60-105 mg/100ml
	1 hour blood sugar	170 mg/100ml	
	2 hour blood sugar	154 mg/100ml	
9/8/73	SGOT	64 U	<40 U
	SGPT	80 U	0-40 U Karmen Units
	LDH	150 U	30-120 U
Age 16 years			
11/8/73	Serum potassium	3.8 mEq/liter	4-5.6 mEq/liter
12/8/73	Serum uric acid	10 mg/100ml	2.5-8 mg/100ml
12/4/73	Serum potassium	2.9 mEq/liter	4-5.6 mEq/liter
3/11/74	CPK	1090 mU/ml	28-145 mU/ml
	LDH	370 mU/ml	100-225 mU/ml
	SGOT	106 mU/ml	7-40 mU/ml
3/11/74	Arterial O_2 tension	64 mmHg	90 mmHg
	Arterial O_2 saturation	96%	>95%
	Serum lactate	84 mg/100ml	3-12 mg/100ml
	Serum pyruvate	0.4 mg/100ml	0.3-0.7 mg/100ml
3/21/74	Urine pyruvate	Night 7.6 mg/12 hr Day 8.6 mg/12 hr	<5 mg/12 hr
	Urine alpha keto-glutarate	1.6 mg/100 ml	<2.5 mg/100 ml
3/24/74	Serum CO_2	28.5 mEq/liter	22/27 mEq/liter
	Serum chloride	<90 mEq/liter	95-195 mEq/liter
	Serum sodium	125 mEq/liter	130-150 mEq/liter
	Serum potassium	4.3 mEq/liter	4-5.6 mEq/liter
	Serum BUN	30 mg/100ml	10-20 mg/100ml
3/25/74	Serum carotene	25 µg/100ml	50/250 µg/100ml
3/28/74		TTFD STARTED	
4/5/74	CPK	80 mU/ml	28-145 mU/ml
7/10/74	SGOT	15 mU/ml	<40 mU/ml
	LDH	215 mU/ml	100-225 mU/ml
	CPK	150 mU/ml	28-145 mU/ml
9/12/74	Urine pyruvate	Night 9.0 mg/12 hr Day 9.2 mg/12 hr	<5 mg/12 hr
	Urine alpha keto-glutarate	0.7 mg/100ml	<2.5 mg/100ml
9/13/74	RBC transketolase	71 mU/L/min	42.1-86.1 mU/L/min
	TTP uptake *(in vitro)*	10.8%	0-17.4%
	SGOT	70 mU/ml	7-40 mU/ml
	CPK	390 mU/ml	23-145 mU/ml
	LDH	380 mU/ml	100-225 mU/ml
9/18/74	A.M. plasma cortisol	407.7 µg/100ml	6-26 µg/100ml
	Urine creatine	900 mg/24 hr	0-50 mg/24 hr
	Urine creatinine	700 mg/24 hr	1060-1590 mg/24 hr
9/18/74	Capillary blood gasses		
	Ph	7.5	7.35-7.45
	CO_2 content	35 mEq/liter	23-27 mEq/liter
	CO_2 tension	36.2 mmHg	34-46 mmHg
	O_2 tension	46 mmHg	85-95 mmHg
	O_2 saturation	90%	90%-98%

Results of all relevant laboratory tests performed during the treatment administered to the patient in Case 8

Case 9

A black girl aged 8¼ years had a four year history of increasingly severe asthma, and many episodes of bronchitis. Skin testing revealed multiple sensitivities. The episodes of asthma increased in severity and began to occur nightly. An attack would begin in the late evening, become worse during the night, and gradually subside throughout the following day. Occasionally there was associated fever and at least one of these had been accompanied by a headache, intractable vomiting and sweating. Family history revealed that the maternal grandmother had chronic asthma and liver disease of unknown cause. Examination of lungs revealed audible high-pitched expiratory wheezing, evanescent scattered expiratory sybilant rhonchi and crepitant rales by auscultation. There was widespread piloerection on the trunk. Chest roentgenogram showed no organic changes and immunoglobulins were in the normal range. Serum alpha-1 antitrypsin assay revealed a concentration of 394 meg/ml (0 to 400 mcg/ml = homozygous range of deficiency). Symptomatic therapy was continued as required and a clinical trial with 150 mg of thiamine hydrochloride begun. During the next five months she experienced only two mild attacks of asthma, and her weight had increased by *6.4* kg. The lungs were clear by auscultation and serum alpha-1 antitrypsin assay revealed a concentration of 1786 mcg/ml, an increase of more than four times the former concentration.

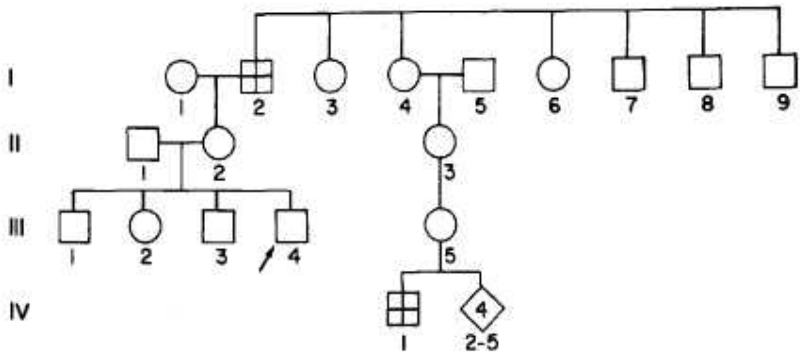
Impression

It is difficult to prove a cause and effect relationship here, but the symptomatic improvement was obvious and physical examination normal after thiamine supplementation. The change in serum antitryptic activity, performed in the same laboratory, was striking although no suggestion is made for the mechanism by which this test gave such radically different results. It is possible that the clinical improvement was brought about by modification of overly sensitive autonomic reflex pathways, improved oxidative metabolism or membrane function.

Case 11

A six-year-old Caucasian boy was admitted to hospital with severe croup. Similar attacks had been occurring five or six times a year since the age of one year, and during the winter months only. Each began between 2:00 a.m. and 4:00 a.m., and they were characterized by difficulty in respiration, tachycardia, barking cough, typical croup, and sometimes accompanied by repeated vomiting. His poor appetite had caused great maternal anxiety, resulting in attempts to feed him. He had frequent temper tantrums, slept restlessly, and frequently talked in his sleep. Previous history revealed that he had an illness at the age of four years characterized by rash and low grade fever for two weeks, which terminated by desquamation of hands and feet. On examination there was intercostal retraction, inspiratory wheezing, and stridor. The epiglottis was inflamed and petechial hemorrhages were seen on the face. Rapid resolution followed symptomatic therapy, and he was examined again two weeks later. He was pale and rough ichthyosiform skin below the knees was noted. Knee reflexes were difficult to obtain without reinforcement. Red cell TKA was 46.49 mU/L/min and TPPE 23.6%. Table 6 shows urinary concentrations of creatine, creatinine, and uric acid. In the next two months he experienced two further attacks of nocturnal croup. Blood pressure was 100/0 and much "overflow" movement of a choreiform nature was seen. After one month's trial with thiamine hydrochloride, his general health was improved. He had a normal appetite, was sleeping restfully, and had no more croup. The supplement was continued and one year later he had remained completely well with no further episodes of croup. Thiamine supplement was discontinued and another episode of croup occurred three weeks later, requiring admission to hospital.

FIGURE 21



I – 2	Died: amyotrophic lateral sclerosis
I – 4	Diabetes
I – 5	Diabetes
II – 3	Breast cancer
IV – 1	Died: crib death
III – 1,2,3,4	Recurrent croup

Pedigree - Case 10

TABLE 6

	Day		Night		Total	
	3/30/77	2/16/78	3/30/77	2/16/78	3/30/77	2/16/78
Creatine	117	16	57	87	174	103
Creatinine	130	184	162	175	292	359
Creatine/creatinine	0.9	.08	0.35	.49	0.59	.28
Uric acid	213	48	103	145	316	193
Body Weight (kg)					21.8	24.5
Creatine: mg/kg/24 hr					7.98	4.5
Creatinine: mg/kg/24 hr					13.4	15.7
Uric acid: g/kg/24 hr					14.5	8.4

Creatine, creatinine and uric acid in urine before and after thiamine supplementation. Note the decrease in creatine and uric acid per unit body weight, whereas the concentration of creatinine increases. Case 10

Impression

The main points of clinical interest in this patient and his family are not immediately obvious. Night time croup is a common pediatric complaint, but this child had many such episodes as did his sister and two brothers. The complaint of the mother was "why have *all my* children had repeated episodes of croup? Could it be hereditary?" The nocturnal onset is not unusual. Each was accompanied by symptoms which could be autonomic in nature, tachycardia and vomiting being the most obvious. Poor appetite, surrounded by maternal anxiety, temper tantrums and sleep characteristics would support a concept of "sympathetic dominance." His illness at the age of four years suggested Kawasaki Disease[8] which might have been a maladaptive response to stress. Red cell TKA and TPPE were classical for TPP deficiency, and his clinical well being was strikingly improved after vitamin supplementation. The mother called one year later and requested advice on its continuation. She was told that it was probably no longer necessary. It was very striking that he had a recurrence of croup three weeks later, mindful of the patient with febrile lymphadenopathy described by Lonsdale.[6] The pedigree (Figure 21) revealed that the grandfather died with amyotrophic lateral sclerosis, a condition which has been reported to be treated with partial success by TTFD, calcium and magnesium.[22,23]

Whether the crib death (IV_1) and diabetes[14 15] have any genetic relationship with the proband's family is conjectural. It is worth considering that the genetic link in common between family members was simply in the organization of cell membrane efficiency and energy metabolism. The possibility exists that this unique biochemical "fingerprinting" could be preventively managed by dietary supplement if a means could be made available for detecting the specific needs. Was the transketolase abnormality in this pro-band a major clue to these genetically determined needs? There was no manifest evidence of dietary indiscretion.

The biochemical changes in urinary creatine and creatinine (Table 6) were interesting. Though the 24 hour creatine and uric acid decreased and the creatinine increased, this change was not represented in the night time 12 hour urine. It has already been pointed out in the previous chapter that creatinuria was an important biochemical observation in beriberi, and perhaps that disease represents a model for ' 'slow oxidation."

Case 11

AFR was first examined at the age of 38 years because of extreme dyspnea and inability to function. Symptoms had been increasingly severe for eleven years and were exacerbated by air pollution. He had smoked cigarettes for fourteen years but had given this up for one year. Pulmonary function studies showed evidence of chronic obstructive emphysema. The STIC and Pi phenotype were characteristic of the homozygous state of Alphe 1 AT deficiency. He was the father of four children, cases 12 through 15.

Case 12

MTR was the oldest of four siblings and was brought for STIC and Pi phenotyping at the age of 17½ years because of the father's condition. Both were typical for the carrier state for Alpha 1 AT deficiency. She complained of excessive fatigue and an increased sleep requirement. Past history revealed that she had been born prematurely with a birth weight of 2.1 kg. General health had been good until the age of sixteen when there was marked increase in her sleep requirement from an average of seven to eight hours a night to ten to twelve hours, and she usually awakened with a sense of fatigue. The mother noted that she would return from school looking extremely tired and she would retire to bed. She had recurrent abdominal pain above the right iliac crest. Menses were irregular and associated with cramps. She experienced unusual intolerance to cold.

On examination she was pale. There was widespread hypertrichosis and the left breast was visibly smaller than the right. The pulse was regular at 52 BPN. Deep tendon patellar reflexes were unobtainable without reinforcement and there was moderate dermographia on light stroking of the skin of the legs. Red cell TKA was low and TPPE increased. Because of this she received a supplement of thiamine, but ingested it irregularly. Three months later TKA had increased and TPPE was in the normal range. She noticed less fatigue and felt better. She volunteered the fact that she appeared to have more energy and less fatigue when she was taking the supplement regularly.

Case 13

RAR was first examined at the age of 15 $^{10}/_{12}$ years. She was brought, also, for STIC and Pi phenotyping which were characteristic of the heterozygous state for Alpha 1 AT deficiency. Past history revealed that at the age of three years she had had several episodes of syncope, each associated with a slight injury, a hot environment or inoculation. At the age of fourteen years she began to have recurrent headaches and spells of dizziness when she described herself as "nearly blacking out." Apart from the irregular menses, there were no other symptoms. Red cell TKA was normal. At the age of sixteen years she consulted again because of near fainting episodes, insomnia, tachycardia and intermittently swollen right ankle. Physical examination was normal. She exhibited profound dermographia on light stroking of the legs.

Case 14

JMR was 9 years of age when first examined because of a rather dramatic change in personality. Past history revealed that both early development and school performance had been normal. On a visit to a dentist he complained of abdominal pain and extreme fear. The dental examination had to be cut short because of his total lack of cooperation, which his parents felt was quite out of character. After this incident, he became increasingly worried by trivialities. Two months later he had an illness involving vomiting and diarrhea for three days, followed by rather abrupt change in personality. His parents felt that before this incident he had been more self-assured and confident but he became hesitant and cried easily. There were repeated episodes of periumbilical pain and he became persistently anorexic in contrast to his former appetite, which had been excellent. After relatively mild exercise he was heard to gasp for air, and this also occurred during sleep. During sleep he also sweated profusely and exhibited extreme restlessness, occasionally awakening and entering his parents' room. He was reported to consume a considerable amount of candy and sweet beverages. Because of abnormal transketolase activity, he received a clinical trial using a supplement of thiamine hydrochloride in a dose of 150 mg per day. Two months later he was greatly improved, regaining his former personality traits. Craving for sweets had diminished and his normal appetite had returned. Unpleasant dreams and occasional night terrors still occurred. Profuse nocturnal sweating had decreased. After an initial weight loss of 0.3 kg, he gained 2.5 kg in the next two months and appeared to be in good health. The red cell TKA was normal.

Three years after this, he witnessed a serious accident to a friend and a similar change in personality occurred. Although there was some increase in TPPE, it was still in the acceptably normal range. Physical examination was normal. His mother reported that he was always better in his general health and behaviour when he was receiving a regular supplement of the vitamin.

Case 15

JAR was first examined by an allergist at the age of two years because of atopic dermatitis which was particularly sensitive to peanuts, chocolate and eggs. He had recurrent episodes of febrile asthmatic bronchitis which were responsive to epinephrine.

At the age of 10 $^{7}/_{12}$ years he complained of extreme fatigue, sleeping as long as 12 hours. He complained of irritation of the eyes, nasal congestion, intermittent cough and nocturnal wheezing. He had demonstrated a recent tendency to crave chocolate and iced tea. Although red cell TKA was normal, it was still considered to be worth providing him with a thiamine supplement because of the improvement that occurred in his brother. When seen again four months later, his general health was excellent. Fatigue had disappeared and he had not experienced any more asthmatic wheezing.

TABLE 7

Case	Family Member	STIC	Pi Phenotype		TKA	TPPE
12	A.F.R.	0.2	ZZ		70.3	0%
13	M.T.R.	0.99	MZ	(7/80)	48.8	30.7%
				(10/80)	70.3	0%
				(1/81)	85.9	7.5%
14	R.A.R.	0.89	MZ		65.3	3.0%
15	J.M.R.	0.98	MZ	(7/76)	64.4	23.7%
				(11/76)	72.2	0.5%
				(9/79)	76.1	11.9%
16	J.A.R.	0.95	MZ		57.1	11.2%

Results of STIC, Pi Phenotyping, red cell transketolase activity (TKA) and thiamine pyrophosphate percentage uptake (TPPE) on cases 11-15
STIC - Serum trypsin inhibitory capacity (N = 1.2-5.0 mg/ml)
Pi phenotype - Serum crossed immunoelectrophoretic pattern for alpha-1-antitrypsin phenotype
Normal = MM Heterozygous = MZ Homozygous = ZZ
Normal TKA = 42.1-86.1 mu/L/min. Normal TPPE = 0-17.4%
Determination of STIC and Pi Phenotype performed by Dr. Rynbrandt, at St. Luke's Hospital, Cleveland, Ohio.

Impression

The father in this family was homozygously affected for the phenotype ZZ, alpha-1-anti trypsin deficiency, related to his severe pulmonary disease. His four children were heterozygously affected since their Pi and STIC test results were compatible with the MZ phenotype (Table 7).

By the use of red cell transketolase studies, two of the four children were shown to be deficient in TPP and appeared to respond symptomatically to supplementation with thiamine hydrochloride. This abnormality apparently could not be linked directly with the genetic trait since the father (AFR) had the clinical manifestations of the ZZ phenotype, but whose transketolase activity was normal. Two of the sibs with abnormal transketolase activity were shown to have normal TPPE and increased TKA after thiamine supplementation and their symptoms coincidentally improved. One of the siblings (JAR) had symptoms which were generally similar to those of MTR and JMR, but TKA and TPPE were in the normal range.

The important question, which cannot be answered, is whether the transketolase observations were merely coincidental or whether it indicated a biochemical partial defect in phosphorylation of thiamine. The symptomatic response in JAR suggests this possibility, though the abnormality in his case may have been in formation of theiamin trophosphate (TTP) by phosphorylation of TPP. This would not be detected by transketolase.

Perhaps the genetic abnormality which was so clearly expressed in this family placed a physiological burden which made them more susceptible to normal environmental stress. If this concept is extended, the logical interpretation would state that the only defense against this would be in recognition of a unique nutritional need and that this need would be more valuable when any such stress was applied. If so, then functional changes in personality might be seen only under certain circumstances and not during others, depending upon (1) individual variation within family members, (2) degree of stress imposed and (3) quality of nutrition.

Case 16

An eight-year-old white girl was first examined for juvenile rheumatoid arthritis, a diagnosis made elsewhere. She had been born prematurely with a birth weight of 1.6 kg. Early development was normal and she was receiving high scholastic grades.

Six months previously her right knee became swollen and stiff. Fluid was aspirated and she received an intraarticular injection of corticosteroid. Laboratory tests showed no systemic effects and culture of the synovial fluid was sterile. Three months later the same knee became swollen and the joint was reported to be warm to the touch and tender. Laboratory tests were again reportedly negative. Appropriate doses of acetylsalicylic acid were started, which she was unable to tolerate because of nausea.

Other symptoms reported were constantly cold hands, recurrent abdominal pain with nausea, easy fatigue and pallor. Stiffness in the joint was more marked in the morning. Her sleep requirement was noticeably increased compared with her two siblings, and she was described as persistently irritable and bad tempered.

On examination, she was normal for height and weight and looked pale. Filiform papillae on the tongue were prominent. The heart rate was 140 bpm and blood pressure 120/66 mmHg. Both legs were mildly cyanotic and the feet cold to the touch. Dermographic stimulation produced obvious blanching which was more marked on the right leg. The right knee was swollen with some patellar tap elicited and the circumference of the left thigh was measurably greater than that of the right.

A qualified dietician reported that her nutrient intake was adequate and she was counselled. Two weeks later she developed some swelling in the left knee. Examination revealed facial flush with circumoral pallor, overactive heart, audible femoral pulse by auscultation, unpredictable deep patellar knee reflexes varying from nonreactive to double in nature and mild cyanosis of the feet and hands together with well-marked hippus of the pupils. Laboratory studies (Table 7) revealed an abnormal TPP effect in red cell TKA, elevation of serum B_{12} and moderately increased ratio of creatine to creatinine in urine.

After informed consent of both the child and her parents, TTFD, 150 mg per day, and a comprehensive high potency multivitamin were started. Two months later it was reported that there was no change in her knees but that her disposition was improved. Body weight had increased by lkg. Recurrent cyanosis and coldness of the feet were still present. The right knee was swollen and there was about 5 ° of flexion deformity. No patellar tap could be elicited.

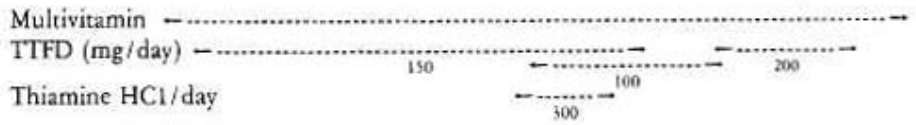
Three months later she reported the disappearance of pain and stiffness and her activity included running and riding a bicycle. After seven months she reported full physical activity without pain or stiffness and great improvement in personality. She looked well. There was a mild livid mottling of the skin in the legs. Blood pressure was 100/60 mmHg and heart rate was normal. Thigh circumference was greater on the left, but no deformity or swelling was detectable in either knee. Red cell TKA had increased and TPPE had fallen to 1.8%. The dose of TTFD was decreased to 100 mg per day.

In the next few months it was revealed that there had been some stresses within the family, although their nature was not discussed and eight months after decreasing the dose of TTFD there was found to be some synovial effusion and swelling in the left knee. Urinary ratio of creatine to creatinine had again increased. The dose of TTFD was increased to 200 mg/day. Four months later TTFD was replaced by thiamine hydrochloride, 300 mg per day. General health was good and she was asymptomatic. At the age of twelve years when last examined, she was completely well and free from symptoms.

TABLE 8

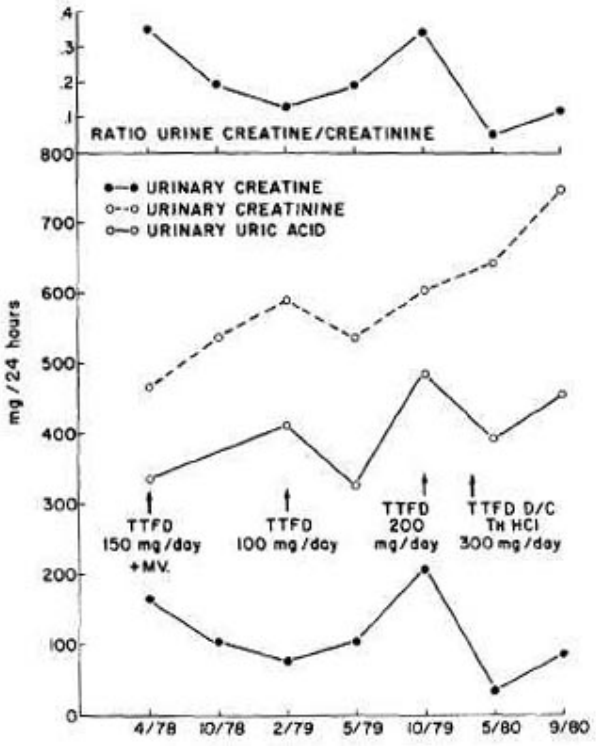
DATE		4/78	7/78	10/78	2/79	5/79	10/79	5/80	9/80
Day	Creatine (c)	85		56	41	62	85	11	50
	Creatinine (CR)	187		266	305	296	206	319	320
	Ratio (C/CR)	45		.21	.13	.20	.41	.03	.16
	Uric Acid (UA)	163		218	247	209	210	218	265
Night	Creatine	79		48	37	43	125	25	38
	Creatinine	281		272	285	242	400	325	429
	Ratio (C/CR)	.28		.18	.12	.18	.31	.08	.09
	Uric Acid	173		170	165	120	275	175	192
Total	Creatine	164		104	78	105	210	36	88
	Creatinine	468		538	590	538	606	644	749
	Ratio (C/CR)	.35		.19	.13	.19	.35	.05	.12
	Uric Acid	336		388	412	329	485	393	457
TKA									
(N = 42.1-86.1 mu/L/min)		58.2	67.8	83.9		114.2	99.3		
TPPE (N = 0-17.4)		22.7	19.9	2.2		10.5	8.8		
Folate (N = 4-18 mg/ml)		7.8	21.6	14.8		22	22		
†B_{12} (N= 170-700 pg/ml)		1450	1150	1810		940	1790		

† with cobalamin analogues removed



Day, night and total concentrations of urinary creatine, creatinine and uric acid throughout treatment period. Note also the steady increase in the activity of red cell transketolase, although the TPPE increased again after a brief decrease. Case 16

FIGURE 22



Graphs showing 24 hour urinary concentrations of creatine, creatinine and uric acid, and the ratio of creatine to creatinine. Note the sharp rise in creatine and uric acid in October, 1979, and their subsequent decrease after increased dose of TTFD. Creatinine gradually increased throughout the entire treatment period, although this would also be influenced by increasing age of the patient.

Case 16

Impression

The graph (Figure 22) shows the consistent fall in the urinary ratio of creatine to creatinine and Table 8 shows the changes in laboratory studies that were performed repeatedly. There was a temporary rise in the creatine to creatinine ratio in October, 1979, which was coincident with a recurrence of symptoms.

There are a number of questions that arise from this case. In spite of normal conventional laboratory studies, could this child really have rheumatoid arthritis? Each physician who had examined her had stated this to be the diagnosis. A diagnosis of reflex sympathetic dystrophy was suggested by the obvious vascular changes that were observed. In spite of the lack of history of trauma, this seemed to be appropriate. Can this condition be a precursor to the fixed pathological changes of fully developed rheumatoid arthritis?

Was the irritability and poor disposition in this child directly related to the state of sympathetic dominance, or was it secondary? Are we justified in assuming that the undisputed personality changes seen in this condition are merely because the child does not feel well? Can the blood pressure and the overactive heart be equated with sympathetic dominance, or are they the nonspecific effects of an illness as we usually have assumed? The serial changes in TPPE were slow and this suggested that it was a biochemical phenomenon which was adjusting, for it certainly was not a simple dietary insufficiency. The urinary studies are virtually valueless, taken by themselves, but the changes that occurred serially do seem to conform to the clinical changes that were observed and may be a very simple way of monitoring the

metabolic response, suggesting improved transport of creatine across the plasma membrane or its trapping as phosphocreatine within the cell.

The changes seen in folate and B_{12} may be purely random or related to the administration of vitamins. We have already seen, however, that these values can be related to metabolic changes which are poorly understood and are by no means a simple reflection of dietary intake.

Finally, it must be recognized that this treatment was possible in this child because the parents themselves had sought a nutritional approach and were disenchanted with the treatment that had been offered previously. They were told that they had a choice, at all times, of changing to the care of a rheumatologist. Much more study is required in ascertaining whether such an approach is valid for other similar cases. It also seems quite important to take into consideration the fact that family stresses may have played a part in causing a temporary exacerabation of symptoms. The course of the condition is consistent with the viewpoint that the initial stage of the child's disease was functional in nature, and that her ability to cope with it depended on whether she could muster sufficient cellular energy to meet the threat.

The reason for the increase in urinary uric acid is unknown. We have seen this increase in a number of patients under similar circumstances. It is possible that it reflects activation of the hexose monophosphate shunt and an increase in purine synthesis. This patient is merely an example of a pattern seen in other cases.

Chapter 6

ENERGY METABOLISM IN A NEW PERSPECTIVE OF DISEASE IN MAN

One of the well known phenomena which invariably confounds a medical study involving a new treatment is the placebo effect. The fact is that suggestion operates mechanisms within the patient that relieve him of his symptoms. It seems to be a vitally important aspect of human disease to understand its mechanism, since it might be a step towards encouraging it therapeutically. Every physician has consciously or unconsciously exercised the effect which is sometimes referred to as a bedside manner. It is a simple fact that the power of the physician is increased in proportion to the stature he holds within the community and the respect that he commands from his patient. This seems to be only distantly related to the drugs, medicines or techniques that are used, and many stories abound concerning this. A very successful treatment for warts was used in England at one time. In a small town the patient, going to a certain drugstore to purchase a wart cure, would be asked to sign his name in a book and was charged sixpence. No other exchange took place, but the "cure rate" was high. In another instance a popular practitioner kept a large bag of sodium bicarbonate in the cellar. Every patient received this simple compound, irrespective of his complaint or diagnosis. It must have been the personality of the physician that commanded his undoubted success and his widespread popularity. The reverse of this has been considered to be the malignant mechanism of "voodoo death" [1] which is well documented in Africa. Norman Cousins became a modern champion of the "mind-over-matter" approach to disease.[2] It is interesting that little attention has been given to the fact that he used extremely large doses of vitamin C in addition to his method of inducing "cure" laughter. This can hardly be ignored if we attempt to look seriously at why the crippling disease from which he is reported to have suffered went into remission.

Modern medicine is appropriately preoccupied with the belief that proof of efficacy is an inherent part of authentic therapeutic response. It builds mechanisms into experiments with new medications which attempt to compensate for the placebo effect, and recognizes well the fallacy of attributing effects to a biochemical or physiological mechanism induced by a drug. Perhaps a look at the underlying mechanism of the placebo effect itself may be a therapeutic advance in its own right. Could it, for instance, explain the documented miracles at Lourdes? Might it explain some of the spontaneous remissions that occur in cancer? We propose, here, to argue that the feasibility is acceptable, but that it demands a change in outlook and perspective in the causation of disease. Observation of patients over many years teaches us that the vitally important "faith factor" has been damaged in the present era of scientific medicine. It is often impossible to reassure a sick person, with or without a battery of tests. We are fully aware of the present popularity of doctor shopping, when the patient is seeking a person with unusual brilliance who will have new insight into the physical symptoms. The patient has perhaps been repeatedly, and correctly, told that his symptoms represent a "conversion reaction." This implication projected is invariably accusative, since we have no scientific model. Reassurance is impossible, since the patient is deeply suspicious of the physician's explanation. The method by which we frequently attempt to prove our explanation is by means of a series of technologically complicated tests, each of which is applied to the system in question in order to eliminate the underlying organic disease, and hence arrive at a point of total reassurance. This is frequently successful, if expensive, but all too often the patient's peace of mind is short lived. A break through symptom occurs and the patient is alerted once again to the fallibility of the physician's knowledge. He becomes obsessed with the idea that the appropriate test was not ordered and his worry becomes the firing point once again of his

psychosomatic symptoms. By providing the modern physician with "feet of clay" society has deprived itself of a valuable health asset, in its own right.

There is little value, however, in bemoaning this state of affairs, since we are "stuck with it." The sophisticated modern patient, able to read about his disease from many different sources, is able to question the authentic ignorance of the physician who, in days of yore, was never to be doubted. The proverb that claims that "a little knowledge is a dangerous thing" reminds us that this is a well known human failing. It is only to be expected that the physician will practice more and more defensively, whereas his patient becomes gradually more militant and demanding. The mainstay of the following argument and discussion is that the firing point of the symptoms is the self concern and constantly active worry of the patient, which can be regarded as the stress factor. Anything that can appropriately inhibit this will be therapeutic. The most recent answer in medicine is the development of the tranquilizer, and pharmacotherapy in the treatment of psychotic disorders has changed the face of psychiatry. It is to be recognized, however, that this approach has not solved the problem of a virtual epidemic of psychiatric disorders that have sprung up in modern industrial societies.

Another point that must be taken into account in the discussion is why modern pharmacotherapy is partially effective. We know, in point of fact, that these drugs have either an enhancing or inhibiting effect on neurotransmitter release and it is therefore inherently part of the therapeutic response that we change the net effect of central nervous system balance. Since the effect is dose responsive and highly specific in action, it becomes a trial and error experiment in each to know what the ultimate clinical response will be. Is it the ablation of a given neurotransmitter which produces the observed response, or is it the positive effect of the opposing neurotransmitter? In the first instance the response is a negative one, since the effect of the metabolite is removed. In the second, it is a positive response, albeit in the opposite direction — since it is produced by the effective enhancement of another chemical. In perspective it must therefore be argued that the true net effect is a balance between the two. Then why was there a lack of physiologic balance in the first place? Does this mean that there is unusual strength in one, weakness in the other, or a combination of the two? Could therapy be found to enhance, stimulate, or otherwise activate the weak side of the system? A given pharmacologic agent does this on occasion by protecting the physiologic effect of a neurotransmitter, perhaps the best known example being in the various drugs that facilitate the activity of acetyl choline, such as pilocarpine. The opposite is the use of atropine. Our discussion will attempt to focus on the means by which physiologic enhancement of a weak system might be achieved, if it can be recognized,

Another part of the discussion which must be addressed is in relation to the physical and mental well-being of healthy humans. An attempt will be made to show that these two cannot be separated and that it is possibly the lack of functional balance that is forerunner to organic disease and its eventual visibility in terms of structural change in the cells. It is suggested that the initial response to any stimulus, whether it be noxious or not, is a fundamental reflex organization which is continuous throughout life. Like Selye, it is restated that this adaptive continuum might well be the key to further understanding of the relationship between the mental and physical states of man.

INTRODUCTION

A perspective on disease is proposed that treats the brain and psyche as part of the soma, only recognizing that the corporate body of the organism represents a composite of specialized organs. The brain, operating in a fashion similar to that in a computer, coordinates all function, including energy metabolism, in a continuously active response to environment and dictated by the unique genetic specifications of each individual. This mechanism requires continuous input of sensory data, data processing and executive response. The normal response to the fluctuating state of environment is automatically made through a balanced and appropriate defense conducted through the autonomic and endocrine systems and that abnormal or unbalanced responses of this mechanism represents the basic cause of a disease process.

DEFINITIONS

Stress

In further discussions, stress is used in order to define the forces that act upon any organism, and is not used in discussing the organism's response. Under these circumstances it is proposed that environmental temperature, barometric change, chemical poison, infection or circumstances of life situation represent different forms of stress and are all met by the same response of the organism. Normal response of the organism is universally the same for the species and dictated by adaptation, evolutional development, and genetically determined sophistication. It is simplified to consider the dual control of two basic systems which govern energy expenditure.

Energy Expenditure

The fight-or-flight response is a well recognized emergency mechanism that provides a rapidly organized physical and mental state that offers maximum chance for survival. Although many transmitters are involved, the organization of the response is through the sympathetic autonomic and endocrine systems respectively, and coordinated through the hypothalamus. In further discussion this will be referred to as Sympathetic (with a capital S). The opposing or balancing mechanism, ignoring anatomical distribution but recognizing its physiologic function, is referred to as Parasympathetic (with a capital P).

Energy Conservation

The state of the organism on completion of survival activity is regarded as a state of recuperation and implies that energy stores will be conserved. It may be possible that this activity takes place most rapidly during sleep which would explain disappearance of natural fatigue, which normally leads to sleep.

Control

The hypothalamus has been considered to govern Parasympathetic activity in its anterior half and Sympathetic activity posteriorly, from an overall functional point of view. It is well known that autonomic function is influenced by many areas of the higher brain and limbic system. In further discussion this control will be referred to as Hypothalamic (with a capital H) in order to simplify, irrespective of the recognized effect of other brain areas.

Stress Response

This is defined as the physiological and predictable response of the organism and is considered to be normal. It represents a continually fluctuating state, governed by Hypothalamic control, which is stimulated by a continuous and lifetime stream of sensory input. For the most part this remains automatic and below the level of consciousness, operating during sleep and during the awake state under the influence of circadian rhythm.

Neurotransmission

This is considered to be either Sympathetic or Parasympathetic and makes no attempt otherwise to identify the chemical substance released from the nerve ending. These compounds are the chemical messengers that cause the organ system to become active, and are therefore part of the normal stress response. In spite of this oversimplification, it is necessary to emphasize again that acetyl choline is the neurotransmitter common to both components of the autonomic system.

Adenosine Triphosphate

Cells rely exclusively on the presence of ATP or other high energy phosphate bonds for their function and activity. All energy regeneration systems are directed toward adequate provision of these compounds which might be likened to the storage of potential energy as, for example, in a taut bow string. Energy expenditure is required in order to accumulate ATP which is similar to the simpler action of pulling the bow string to a position of tautness.

Disease

The most obvious condition to consider first is the response to infection, which can be local or general, and is considered to be a normal response.

Local Infection (Local stress) This was seen by Selye as a local adaptation syndrome and is operated by well known homeostatic mechanisms. An invasion of tissue by an attacking organism brings into play local defense mechanisms and a pustule represents the death of the defending cells. If this "beach head" is extended because of the virulence of the infectious invader or because of relative weakness of defense, there must be a plan of defense which must be coordinated through central mechanisms.

General Infection (Generalized stress) Selye referred to this as the general adaptation syndrome and defined the phases by which animals coordinate their defense. Thus, fever, leukocytosis and the loss of feeling of well being might be seen as a normal defense, to be basically assisted by any therapeutic means. Perhaps the sensation of "feeling ill" serves its purpose by forcing a patient to accept physical rest. Fever might be an attempt to rob the organism of its virulence by changing its temperature environment, and perhaps it is therapeutically wrong to reduce the fever and make the patient feel better artificially by means of medication other than one which kills the invading infection. Antibiotics have created a therapeutic revolution, but what else can be done for the patient? Is an antipyretic drug an advantage or disadvantage? Does the return of a sense of relative well being cause the patient to defy the principle of rest?

Abnormal Response to Infection

Hypoactive Response It has long been known that a patient who develops no leukocytosis and no body temperature elevation in the presence of infection is in great danger of being totally overcome, and dying. It is seen in the poorly nourished individual with tuberculosis who develops staphylococcal pneumonia. Evidence of the "brain effect" can be seen by the patient "picking at thin air" or at the bedclothes, as he gazes — unseeing — at the ceiling. Before antibiotics were available these patients invariably died, and autopsy revealed abscesses and widespread infection in all organs. The question occurs as to whether the defense mechanisms were poorly organized in the first place. The total lack of any response suggests that the patient was unable to mount any form of coordinated resistance. This effect may therefore be essentially neurologic.

Hyperactive Response If fever is a normal response to infection, and since we know that it is centrencephalically controlled, perhaps it is the result of an exaggerated signal to the brain. Infection by a foreign microorganism is merely a form of stress, but another form of stress attack, such as an injury for example, might generate the same response if the “conductor of the orchestra” is hyper-responsive. The possibility of “psychosomatic” fever would then have to be considered in a patient with a continuously stressful life situation. Such an abnormal stress response is visualized when high calorie intake malnutrition is a way of life for the patient. It would be difficult to accept this with present concepts of psychogenic versus organic disease, but if it were true it could be extended to consider that leukocytosis might be possible under similar circumstances. It is suggested that such a phenomenon represents a hyperactive stage in Hypothalamic control. Selye's experiments certainly showed that leukocytosis was a familiar stress response in his experimental animals.

Genetic Deletion Any stressful input resulting in increased general responsiveness would be expected to affect the entire patient. The executive signals engendered by Hypothalamic control would go to all parts. Thus, in a patient with defective genetically determined phenylalanine hydroxylase, for example, the metabolic response would cause an increase in concentration of serum phenylalanine, a well known phenomenon in phenylketonuria abd other inborn errors of metabolism. If any form of stress could do this, it would sometimes be difficult to assess whether the patient really had an infection or not.

Unbalanced Response Normal defense is considered to be mediated through a reflex combination of Sympathetic and Parasympathetic balance with the required

system dominating according to necessity. It is possible to consider that such a system might be warped either temporarily or permanently so that there might exist a state of Parasympathetic or Sympathetic dominance activated under stress conditions.

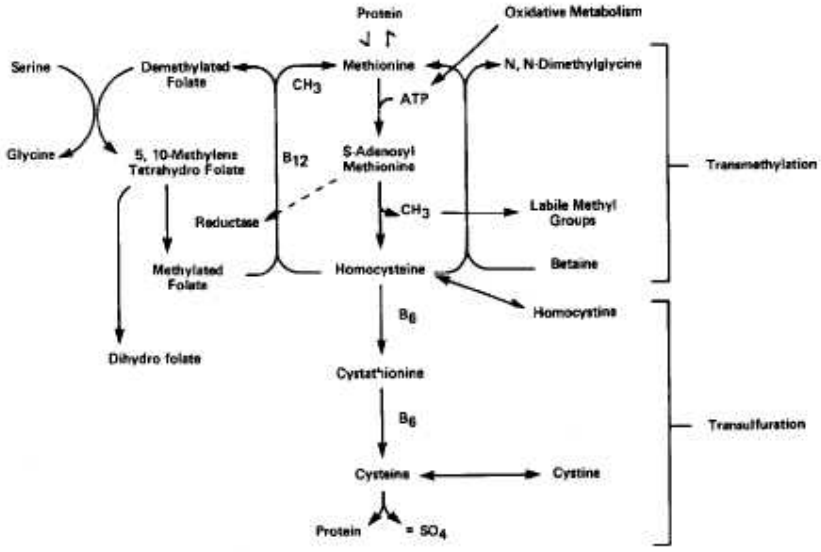
Sympathetic dominance:
(a) Normal Parasympathetic, increased Sympathetic.
(b) Inferior Parasympathetic, normal Sympathetic.
Parasympathetic dominance:
(a) Normal Sympathetic, increased Parasympathetic.
(b) Inferior Sympathetic, normal Parasympathetic.

It is suggested that the balance of this system dictates the nature of the response, and this concept might be examined for evidence of its possibility. Previous chapters have dealt with some of the evidence since these four combinations can be stated to be dysautonomic in nature, and it has been noted that a significant number of diseases have been recognizably associated with autonomic dysfunction. It is suggested that the autonomic dysfunction is an inherent part of the disease, and not merely an associated factor.

HEALTH VERSUS DISEASE

It is suggested that normal health is maintained by homeostatic balance between two systems. The Sympathetic response is intended and maintained as a survival reflex. The well known symptoms of fight-or-flight give a temporary strength to the organism which provides a template for excellence, whether it be escaping physically from an attack, running a race, or preparing for a state of high mental concentration such as taking part in a play. The mechanism is designed for relatively short term use, and brief examination of its symptoms reveal that it is energy consuming. The state of physical and mental activity is high and other reflexes, such as sexual desire or hunger, are overruled until the emergency has been dealt with. However, it is not just Sympathetic activity that speeds the heart; it is partly a reduction of vagal tone and therefore Parasympathetic function is part of the total response to stress. Although there are known to be many neurotransmitters, we have seen that the synthesis of those whose functions are partly understood is highly dependent upon the nutritional state. Tyrosine gives rise to a large array of Sympathetic transmitters and methylation is an important part of the synthesis. Like any machine the organism requires fuel, and energy storage is in the form of high energy phosphate bonds which are then used to drive the transmission. An example of this is the demethylation and remethylation of methione. The formation of S adenosyl methionine requires ATP and this provides methyl groups that are used in the vital process of transmethylation. Homocysteine is partly remethylated to methionine and partly broken down by the transulfuration pathways. The remethylation mechanism, which relies heavily on the regeneration of methyl groups from folate, can be likened to a mechanical cogwheel which "meshes" with the folate pathway (Figure 1). Transulfuration can be likened to an exhaust pipe. Both transmethylation and transulfuration are dependent upon the process of oxidative phosphorylation which provides ATP. We have also seen how acetyl choline, representing all aspects of autonomic activity, is also heavily dependent upon nutrition. This important compound induces a transmembrane potential across the post synaptic membrane and is a necessary part of any muscle action. Hence, if sympathetic activity predominates and signals tachycardia, cholinergic activity is just as important for normal heart muscle contraction and its deficiency might result in an abnormal cardiac response.

FIGURE 1



Simplified diagram to suggest a mechanism by which oxidative metabolism relates with transmethylation and transulfuration. Formation of S-adenosyl methionine from methionine requires ATP and results in the formation of labile methyl groups for addition of one carbon atom as required. Concentration of S-adenosyl methionine controls the activity of the reductase enzyme which catalyzes formation of methylated folate. Thus, a deficiency of S-adenosylmethionine (e.g. lack of ATP, insufficient methionine etc.) would result in increased activity of reductase and "piling up" of methylated folate at the step which transfers the methyl group from folate back to methionine and leads to formation of "active" folate. A high serum concentration of "inactive" or methylated folate might thus be associated with a deficiencyof "active" folate and produce an apparent paradox of hypersegmented polymorphonudear cells in blood. In the simplest terms, this machinery might be likened to mechanical cogwheelswhich "mesh" with each other in the transmission mechanism. This explains why a patient can have homocystinuria from inactive remethylation of homocysteine to methionine (low methionine) or the same amino acid in urine from a block of transulfuration. In this diagram the enzymes have been left out but the vitamin cofactors are shown in order to emphasize that nutrition, as well as biochemical activation, enters into the very complicated reactions which are required for normal "running" of the cellular system. It is theoretically possible to have the "engine" running too fast or too slow as was suggested by Lejeune.[23] (See Text)

It is now possible to suggest why stress is beneficial, providing the organism is healthy and is mechanically able to respond. Any speaker knows that the characteristic sensation of uneasiness and abdominal “butterflies” is an important preparation which dissipates in the speech giving process. It is the secret of any successful public presentation. Since fever, leukocytosis and tachycardia are normal defensive responses to invasion by infection, this expected reaction is not truly a disease. It is its failure that is pathological. But perhaps it is exactly the same mechanism that operates under any attack, whether it be environmental, chemical or even "psychological." The whole concept of psychologic stress is dependent upon the individual's perception of a given situation, and it raises many questions about the physical symptoms that arise as a result. Could there be psychosomatic increase in body temperature and white cell count, as has already been suggested? The pathologic disease process is envisioned as a state of abnormal balance which is produced and maintained, resulting in a state of either Sympathetic or Parasympathetic dominance. This may be induced temporarily by diet, or permanently as part of a genetically determined inherited constitution. It may, in some cases, be in a state of lability between the two.

SYMPATHETIC DOMINANCE

This implies that a person under any form of stress will respond with a strong Sympathetic balance of autonomic and endocrine activity. It would not be possible to tell whether such an individual had an unusually strong Sympathetic or weak Parasympathetic system, since it would be the dominance of one over the other that dictated the nature of the response. It is known that hypothalamic stimulus (that is, stimulus of the hypothalamus itself) in an appropriate location in cats will give rise to a fierce reaction called "sham rage." The phenomenon has been described in man in relation to a hypothalamic tumor. In normal health such a person might be unusually aggressive, hostile, and hot tempered. He would be expected to be a good soldier under battle conditions and a man of action. If the circumstances of life in such an individual were to keep him in a state of stress, he would be expected to react in a way which would emphasize the Sympathetic component, and there would be an unusually rapid use of energy — hence ATP stores might be depleted. This depletion would affect the organ or organ systems involved in the action and it would be relatively easy to explain a consequent pathophysiologic reaction as a sequel. Suppose that this hypothetical person has business worries that keep him in a state of anxiety. He would experience chronically stimulated fight-or-flight physiology. The loss of appetite, pallor, unusual sweating, tachycardia and a state of nervous tension would be the physical symptoms of this. The normal reflexes would cause paralysis of peristalsis of bowel and closure of sphincters so that vague digestive symptoms might arise. His ability to sustain such a rugged abuse of his energy providing systems would depend very much on his ability to carry out the oxidative processes fast enough to keep up with the abuse, and he would then maintain a normal state of physical health in spite of the stress. If, however, his system used more energy than could be restored to meet demand, he would be expected to deplete stores of ATP in cells where minimum nutrient and oxidative mechanisms were operating. For example, the Sympathetic influence which would act upon the alimentary system might result in a depleted delivery of oxygen because of arteriolar spasm. The decline in ATP under these circumstances[3] might ultimately result in cellular death and the formation of an ulcer. Thus the organic disease would, in fact, be the result of a chronically sustained and unbalanced state of the stress response. A potentially more serious apparent dominance of the Sympathetic response may, in reality, be a depletion of Parasympathetic action, perhaps leaving a normal but unbalanced Sympathetic system. We have seen that autonomic activity is a balanced response of both adrenergic and cholinergic, and a failure of the cholinergic component might be damaging to both the autonomic outflow tracts and result in a primary isolated endocrine response.

Suppose, for example, that the colon was the organ most victimized by stress; lack of parasympathetic action might cause a different distribution of effect if Meissner's plexus was more affected than Auerbach's. This might supply at least a primary etiology for the difference between ulcerative colitis and Crohn's disease, even if it does not explain why one person might develop one of them and someone else develop the other under similar circumstances. There are obviously genetic, familial, or constitutional factors that play a part in much the same way as a specific weakness might be exposed in one model of a man made machine — such as an automobile — versus another. If the inherent mechanism of adrenergic dominance were found to be really a failure of acetyl choline dependent transmission, it is worth emphasizing once more that the effect would be throughout the entire autonomic system, since the first relay is cholinergic in both sympathetic and parasympathetic components. The dominance would then presumably be governed by the nature of the endocrine response and represent release of catecholamines, adrenalin, and any other hormone that might be involved in a stress response. It is known, for instance, that the DBA/J2 strain of male mouse has a stress response which is different from that of the female. There is a rapid evacuation of lipids from the adrenal gland which is not seen in the female, but this effect can be removed after orchidectomy.[4] This implies that the secretions from the testicle play an important part in release of adrenal lipids in this strain of mouse. It also suggests that there are inherently different stress responses which are sex governed in these animals that may well be similar in other species.

PARASYMPATHETIC DOMINANCE

It would not be possible to tell whether Parasympathetic dominance were due to a strong Hypothalamic drive, weak Sympathetic drive, strong autonomic (cholinergic) response, or a weakness within the sympathetic (adrenergic) nervous or endocrine system. There is some evidence that this net dominance can occur. Until the abnormal gene in this disease was discovered cystic fibrosis appeared to be an excellent model. It has already been pointed out that this disease has long been associated with autonomic dysfunction.[5] Pupillary responses in affected individuals are surprisingly similar to those that have been reported in psychosis[6] but the ultimate connection with the genetically determined cause of the disease is unclear. Farber[7] produced pancreatic lesions in normal kittens by repeated injections of pilocarpine. The lesions were similar to those seen in human cystic fibrosis. Another investigator[8] also suggested autonomic influence in relation to causation in this disease. More recent work has supported this approach, since fibroblast tissue culture cells from patients with cystic fibrosis have been found to have higher concentrations of 3'5'-cyclic AMP[9] than cells from normal subjects. This implies that there is increased autonomic transmission, but does not verify whether it is primary or secondary. It can now be assumed that it is the abnormal cellular response to the reception of signals from the autonomic system where the fault lies.

CONCLUSION

If the hypothesis is examined closely and tested for the implications of disease, it is seen that the basic root of any disease could well be derived from three phenomena.

1. Genetics: This is viewed as inborn specifications derived from forebears and governed by an infinite number of permutations and combinations which create a unique individual. Certain design modalities emerge that may enable us to classify certain individuals within broad groups of similarity. Such similarities may vary sufficiently within a family structure that a given member may respond to an inherent constitutional weakness differently from another family member. The model allows for Mendelian inheritance as a cause of genetically determined disease, but does not accept that this is the sole form of inheritance in man. Rather, it is considered that in most instances the weakness within a given family is a constitutional one brought about by a composite of gene action, rather than the sole influence of a single gene.

Since this was written, we now have much more knowledge. The genome has been unraveled and it has resulted in the discovery of genes that cause many diseases. But the new science of epigenetics has shown us that our genes are susceptible to changes caused by malnutrition and poor lifestyle and this may well be more important therapeutically than attempts to replace the faulty gene. I have seen the clinical course of children with cystic fibrosis much improved by the addition of nutritional supplements to their daily diet.

2. Environment: This is seen as "the life journey" and represents a potential for lesser or greater degree of stress. Any one of the multiple environmental factors, whether it be infection, chemical, natural day-to-day weather conditions or social circumstances, represent the forces that act upon, and are themselves independent of, the individual upon whom they act. Thus stress is considered to be a characteristic of the environment itself.

3. Nutrition: This is the fuel that provides the organized system with its raw materials. Very important questions have arisen as to whether the fuel can alter the functions of the machine and whether it truly differs from the effect of drugs, which are often considered to be highly specific. Recent work has shown that we are far from understanding the long term implications of this, particularly with reference to our desire to maintain health rather than treat disease. For example, the work of Fernstrom and Wurtman[10] has shown that nutrition does indeed signal the brain, and the neurotransmission can be altered by nutrition.[11] Even the role of vitamin deficiency is clouded, since experimental work has shown the extraordinary diversity of response that can be seen, and we have not come to fully realize the implications of endogenous biochemical mechanisms in activating the ingested vitamins. Perhaps

not surprisingly, there appears to be a fundamental relationship between the nature of the fuel and the capacity of the organism to oxidize it. But the results are not always predictable. For example, thiamine deficiency in rats may produce muricidal behaviour [12] or may be associated with permanent penile erection,[13] not usually considered to be classic symptoms of this deficiency. Iwata and associates [14] reported results of animal experiments in relation to raised tissue catecholamine levels in thiamine deficient rats. It would certainly seem to be reasonably proven that an excess of carbohydrate can produce functional changes in man, but whether this applies to everyone is unknown, and it may well be shown that constitutional characteristics represent decisive factors in the nature of this response. That all three factors — genetics, environment and diet — have to be considered at all times is illustrated by the following case.

A seven-year-old boy received a head injury, causing a depressed skull fracture. After surgical treatment and recovery he returned to school. The school nurse insisted that he report to her every two weeks for tests of his vision, because she considered the possibility of blindness after such an injury. At the time of the injury his vision was classified as excellent, and it remained so for 2½ months, when a marked change was observed. He was referred to an opthalmologist who found mature cataracts in both eyes. Subsequent studies revealed that this child had approximately 50% of a normal concentration of the enzyme galactokinase. This deficiency, when complete, results in cataracts. Beutler[15] has reported that it is hard to relate cataracts to galactokinase deficiency if the cataracts are not found under the age of two years, and so this deficiency might easily be regarded as coincidental for this particular boy. Before he entered hospital for eye surgery it was revealed that he was a very hyperactive child and that his diet contained an extraordinary amount of high calorie carbohydrate foods, candy, chocolate and soft drinks. It also included milk. His mother was counselled to withdraw milk and the simple carbohydrate excesses and to pay particular attention to balanced nutrition. One month later the child was admitted to hospital for surgery and the admitting physician recorded that hyperactivity had disappeared. It is very tempting to postulate that this child would not have developed cataracts at all if the three interlocking characteristics had not been present together. It is necessary to point out that the injury, representing environment and the stress factor, could not be avoided by planning. The carrier state of galactokinase deficiency was genetically determined and could not have been suspected by itself. This also could not be controlled. On the other hand, the hyperactivity in this case was evidently exacerbated or caused by the nature of the diet and was abolished or improved by careful consideration of the fuel. This is consistent with animal experiments[16] which showed that it was easy to cause cataracts in rats by giving them an excess of galactose. It was just as easy to prevent the cataracts by providing the animals with improved nutritional intake through addition of an array of vitamins, even though the same concentration of galactose was administered. Finally, once the cataracts had formed after feeding galactose, they could not be treated by giving the animals the high . vitamin intake.

It seems that the message in this case is abundantly clear. Prevention is indeed better than cure, and the case of this child illustrates the importance that must be given to the science of nutrition. In point of fact, if the three aspects of the condition to which the allusion is made were all necessary to the formation of cataracts, the only one that was controllable was that of diet, and it is suggested that a great deal more emphasis should be given to nutrition in its potential disease role. It is not apparently sufficient to assume that there is a standard of nutrition for all people in terms merely of the combination of protein, fat, carbohydrate, vitamins and trace elements. Each person has a unique background and is a unique individual. It is certainly true that the average balanced diet is appropriate, and nutritional science has come a long way. Concern may come from diet excesses and how they apply to the metabolic machinery of a given individual who fits into either Sympathetic or Parasympathetic dominance. Evidence seems to be very strong that Sympathetic dominance is encouraged by a lot of sweet foods with a poor vitamin intake, particularly thiamine. Lonsdale and Shamberger[17] published the cases of twenty individuals who had functional symptoms. Transketolase determination showed that they were thiamine deficient, and large doses of the vitamin appeared to abolish their

symptoms, restore their sense of well being and, in those who were retested, the transketolase studies became normal. If one examines their symptoms closely, there was a persistent theme of personality change. They were hostile, aggressive, anxious, jumpy, irritable and easily upset. Physical symptoms were those which are found in dysautonomic conditions and strongly suggested chronic fight-or-flight activity and therefore Sympathetic. Not all of them were ingesting an excess of carbohydrate foods, but it was a common theme. Attempts to illustrate this phenomenon were made in Chapter 5, when the case histories were related to nutrition, genetics or stress. It was clear that there was an overlap between these three interrelated causes.

Is there evidence that nutrition can have any effect on Parasympathetic dominance? Pfeiffer and associates[18] found that a single large dose of a choline precursor had no affect on rats. If smaller doses were given repeatedly, they found that they could induce audiogenic seizures in the experimental animals. They suggested that this was because excessive cholinergic activity was being induced.

TESTING THE MODEL

Perhaps the placebo effect, to which reference was made earlier, is induced by focussing the net effect of energy metabolism and its efficient utilization through an appropriate balance of autonomic and endocrine activity. In this case, faith healing would be explained, since any mechanism that caused this action would be effective as long as the neuronal and cellular mechanisms were intact. It would not be effective if part of the mechanism were deleted as, for example, because of a Mendelian gene defect. If metabolic activity is stimulated in phenylketonuria, the serum phenylalanine increases because the machinery is interrupted at the level of the phenylalanine hydroxylase. Dietary approach in this condition must be aimed at providing only that amount of phenylalanine that can be processed by the defective enzyme and attempting to eliminate or control those stress factors that can be avoided. It provides a complex and intricate problem of nutritional science if the serum phenylalanine in a patient with phenylketonuria can be increased by means of non nutritional factors.

The hypothesis could explain why a patient whose hypertension was due to Sympathetic dominance would develop a higher blood pressure just on the basis of suggestion provided by the approach of a physician with a sphygmomanometer. It would also explain the amelioration of a number of psychosomatic conditions from the techniques of biofeedback, transcendental meditation, hypnosis and other semiphilosophic therapies which undoubtedly work in many individuals.

In one of his popular books on veterinary medicine in the Yorkshire Dales, Heriot described the case of a young bull who developed a neurologic disease due to a hair ball in the abomasum. A simple explanation might be that the continuous sensory input from the obstruction gave rise to a barrage of reflexes which exhausted local energy stores resulting in functional neuronal failure reversible by removing the sensory input. This suggestion is potentially valid since removal of the hair ball stopped the severe neurologic abnormalities and cured the patient. It is remarkable how often such observations are made in human disease without conventionally being able to make the slightest connection between them. It has been suggested that our present disease model is out dated [19] and that it is necessary to describe a model which invariably links the physical and mental aspects together. A few tentative examples might be quoted from experience and from the literature.

An adolescent girl began to have episodes described as hypnogogic seizures. She would cry out, stare and bang her head against the wall. Frequently she could be ' 'talked out of it." Her history revealed that she had a number of neonatal and early infancy symptoms which affected bulbar mechanisms and a cystic mass was detected in the *posterior fossa.* She was expected to die since it was considered inoperable, but spontaneous remission of symptoms occurred and she then remained well until the advent of seizures in adolescence. Since there were severe family stresses, a diagnosis of psychiatric disease was made and she was admitted to a psychiatric locked ward. Urine studies revealed massive ketoaciduria and it was thought that her condition was metabolic in origin. A partial remission was observed when she was treated with fat soluble thiamine which was given empirically and experimentally because of the ketoaciduria. The ketoaciduria disappeared and the symptoms

improved. The parents, understandably, rebelled against a psychiatric diagnosis, but this label remained until further studies identified that the cystic mass was still present in the *posterior fossa.* Its removal by surgery abolished all symptoms.

A ten-year-old boy was examined because of a short history of sudden unpredictable vomiting which was thought to be psychosomatic since there were no neurologic signs. Closer inspection revealed that one pupil was slightly larger than the other, suggesting autonomic dysfunction and urine was found to contain a large amount of keto acids. Further studies revealed a tumor in the *posterior fossa* which was completely removed at surgery. Ketoaciduria had disappeared only forty-eight hours after surgery.

The question that arisess in these two examples is, which come first, the tumor or the metabolic change? In the second case, the disappearance of ketoaciduria within forty-eight hours of surgery strongly suggests that it was the result of the presence of the tumor, and therefore secondary. What is so striking, however, in these two patients is the confusion between mental and physical in our disease model. The fact is that neither of them was a true mental case. Both had lesions whose presence caused massive changes in bodily function which were reflected by presence of ketoaciduria, considered usually to be primarily metabolic in origin. They were indeed metabolic in origin, but due to a cause which would generally seem to be far removed from the biochemistry lab.

Urticariapigmentosa is a condition usually involving only the skin, but occasionally will become a generalized systemic condition when many organs are involved in mast cell infiltration. A case of systemic mastocytosis was reported in a sixteen-year-old boy whose life long diarrhea was successfully treated with disodium cromoglycate.[20] The interest here lies in the fact that this drug is considered to act by inhibiting the release of mediators of the allergic reactions[21] and it represented an intelligent therapeutic use of the drug. It is worth looking at some of the aspects of this case. A significant number of drugs had been prescribed to the mother during pregnancy, and she had experienced an illness described as "flu." The patient had the mastocytosis at birth, and vomiting and diarrhea were associated with chronic failure to thrive and developmental delay. The drug interrupted the bodily responses induced by some humoral or even central nervous initiating mechanisms. What then was the true cause of the disease — the neurologic stimulus, abnormal cellular response to the stimulus, or the cellular infiltration itself?

In yet another case report of general mastocytosis in a sixty-one-year-old woman,[22] she had undergone exploratory laparotomy at the age of fifty-six years, and during surgery was given intravenous alcohol. It was reported that violent peristaltic movements of both the small intestine and the colon were observed. No reason was provided by the authors for giving the alcohol, which was presumably experimental, and which had demonstrated an unusually active parasympathetic response. In the discussion it was emphasized that this subject had the "entire symptom complex without evidence of histaminuria. Histidine loading produced neither symptoms nor the pronounced histaminuria noted in other patients with mast cell disease." The underlying cause of the condition is not apparent. Could there have been either a central or peripheral mechanism which was capable of triggering off autonomic signals much too readily? The cellular system of the soma would then be unduly sensitive to any kind of signal arising centrally as a result of input, whether this were environmental stress, "psychologic" or dietetic as was depicted in her sensitivity to alcohol.

Our experience with one case of *urticaria pigmentosa* illustrates the principle that is emphasized here. A six-month-old infant was referred with brown spots on the skin and an enlarged liver. He was chronically sick and lay in his crib initially with little response to nurses or other hospital personnel. While making arrangements for a liver biopsy to identify what was thought to be generalized mastocytosis, a strange series of events occurred. The liver size rapidly diminished until it was barely palpable, the brown spots of *urticartia pigmentosa* almost completely faded, and the infant became responsive and began sitting up spontaneously. All this occurred within a week. The mother was informed that *urticaria pigmentosa* is usually restricted to infancy and, since it often disappears spontaneously, is thought of as a

condition of relatively slow maturation. One week after discharge from the hospital, the mother brought the infant back because the brown spots had increasingly returned and the liver was again enlarged. He was certainly not as ill as he had been on the first occasion and the mother was again instructed that she should await natural events. This caused her to become angry, and during the ensuing discussion it was observed that there was evidence of latent psychosis. A letter was sent to the referring physician advising him that child abuse was a definite possibility in the subsequent case record of this child. Three weeks later the infant was taken to a hospital emergency room and came under the care of the primary physician, who found a skull fracture in the patient. Heeding the warning of possible child abuse, he referred the mother to a psychiatrist, who reported that she was a normally concerned parent with no evidence of underlying psychosis. A few weeks later, the child was found asphyxiated by drowning in a bath, and the mother was charged with neglect.

The physical details in this case are obvious, but their interpretation is of importance in attempting to understand further the ' 'human story." No physician today would contemplate the possibility of *urticaria pigmentosa* being psychosomatic in origin, since there is no existing model to explain it satisfactorily. It requires only an adjustment in perspective to provide an explanation which is capable of putting the facts together. There was no doubt that this patient had a form of mastocytosis, since the skin was abnormal. He had a clinically abnormal enlarged liver, though the reason for this can only be surmised. Both of these abnormalities rapidly disappeared when the infant was placed in a relatively non-stressful situation with benign surrogate parent care, and just as rapidly began to reappear when he was placed in an atmosphere which later proved to be abusive. It might be assumed that the infant's response to stress accelerated the abnormal somatic state, and that the combination of the underlying slow maturation or cellular defect and the increased reactivity of the nervous system represented varying degrees of the disease severity. In this instance, since we do not know the basic mechanism in mastocytosis, the only possibility of therapeutic control was identification and removal of the factors which caused the stress. This may have "allowed" the final resolution of the disease under conditions of natural repair. It is immediately apparent that such a situation cannot be proven by any known means of scientific study. If correct, it is a solution that must be arrived at by close observation of the facts and meticulous attention to the details. No statistics could be applied and the whole case can be described as "anecdotal" at the best. New ways must be devised to study such an important situation, for no double blind clinical trial is possible when the number of variables and chance associations are considered.

Perhaps such a tranquillizing effect is induced by faith, placebo, or any modality which causes the patient to redirect the reflexes that are engendered by the fear of uncertainty and ignorance. It is well known that the antidote to fear is knowledge. For example, we no longer fear evil spirits or black magic because we have developed our knowledge sufficiently. But voodoo and belief in evil spirits still exists in many parts of the world, and both are still producing the time honored effects which are so well known.

To further illustrate the concept of mind over matter, the writer had a personal experience with three middle-aged unrelated patients who had chronic cancer phobia. Their fear of cancer was unrelenting and many examinations carried out over several years, each being quite negative. All three subsequently died of cancer, the ultimate condition that they feared. Did these individuals "think" themselves into developing cancer?

HYPOMETABOLIC VERSUS HYPERMETABOLIC

Energy metabolism is seldom considered to be an important part of a disease process by the clinician. It is usually taken for granted that energy will always be available to an organ and almost no consideration is given to the rate of utilization of high energy phosphate bonds or how the stores are replaced. It is a simple fact that energy can only be created by using energy. Rolling a stone up a hill stores its potential energy which is changed to kinetic energy as it rolls down. A man will use the energy of his arm to pull back a bow string. Energy expenditure takes place in cells to synthesize ATP. The process depends mostly upon the citric acid cycle,

which provides the electron transfer chain with NADH. The coupling process which synthesizes ATP in the inner mitochondrial membrane depends upon the mechanical efficiency of the membrane itself. The storage of ATP in the form of creatine phosphate is its main source for muscle control. Thus an organ "called to action" through nervous impulses initiates ATP utilization. It is hypothesized that the sensation of fatigue, whether it be localized to a single muscle, limb or generalized is through an input signal to the brain that indicates exhaustion of energy stores. Its survival value is that it "warns" the brain through a code which demands rest. It therefore subserves the whole organism, since the centrencephalic organization causes the system to rest either partially or totally. This is the proposal that was made by Selye, who suggested that disease was caused by a failure to adapt to a new situation brought about by stress. The advances in biochemistry made it possible to see how the "energy of adaptation" proposed by Selye is provided by the normal mechanism of oxidative phosphorylation, formation of ATP and its expenditure in driving cellular mechanisms. It is suggested that an individual whose oxidative process is slow for any of multiple reasons is a hypometabolic subject, as Lejeune[23] proposed for Down's syndrome. Lejeune pointed out that patients with Down's syndrome had normal adrenergic but weak cholinergic responses, and compared the syndrome with homocystinuria — which he suggested was a hypermetabolic state. It is not illogical to consider that homocystinuria occurs when the transmethylation or transulfuration mechanisms are overwhelmed, perhaps by a fast oxidative drive. Such a condition is considered only in relationship to a specific enzyme defect on pure Mendelian lines, and perhaps this is indeed the only way that homocystine may actually appear as an abnormal product of metabolism, and therefore perhaps a marker of "oxidative overflow." The really important aspect may well be how fast and overactive overall sulfur metabolism is in such an individual. Folate responsive schizophrenia has been reported[24] and this is consistent with the hypothesis that the devious behaviour in such an individual might be derived from an overwhelmed transmethylation mechanism, resulting in abnormal neurotransmitter metabolism.

It is suggested that overall physical and mental well being represents an equation between the rate at which energy can be produced and the rate at which it is expended. An intelligent individual uses energy faster than one who is less well endowed. Energy production depends on a number of consecutive biochemical links, each one of which would have the same net effect if it broke down. If oxidative metabolism was slow, there would be slow production of high energy phosphate bonds. But also, a fast rate of metabolism would depend upon a proper alignment of the coupling mechanisms to produce ATP. If uncoupling took place from damage to the inner mitochondrial membrane, for example, there would be rapid conversion of oxygen to water and increased heat production. Such a physiologic situation is seen in the thermogenic effect of uncoupled metabolism in brown fat[25] which is known to be responsive to sympathetic stimulation. One can easily perceive the value of such a mechanism in maintaining normal body habitus. Excess calories can be "burned off" simply by applying a sympathetic signal to brown fat. Interestingly, recent evidence[26] has suggested that obese subjects fail to engender this normal response when injected intravenously with norepinephrine and thus they lose a significant mechanism for balancing their energy equation. Since "depression" might be considered to be a failure of normal neurotransmission it would provide a theoretical link between obesity and the well known personality changes usually associated with it. It would even provide a theoretical basis for explaining the close association between obesity, diabetes and hypertension. We have already pointed out previously that there is autonomic neuropathy in diabetes, and that insulinopenia is seen in familial dysautonomia.

If this concept be true, it demands considerable practical knowledge of the biochemical relationships for a physician to interpret pathophysiologic mechanisms. It no longer becomes necessary to remember that a given symptom might occur in a given disease, but only how the symptom arises. For example, it would not be necessary to remember that gastroesophageal reflux is associated with the syndrome of sudden infant death — among other conditions. One could reason that the association in a particular case depended upon failure of parasympathetic action on the esophageal peristalsis, since the esophagus has no sympathetic innervation. By

the same token, the erythematous rash seen on the neck and chest in "nervous" people can be visualized as the same rash which occurs in familial dysautonomia. It was pointed out that this rash occurred in familial dysautonomia after eating and when the patient is emotionally excited. Eating requires integrated autonomic reflex action and emotional stimulus results in reflex neurotransmission. It is deductive reasoning that suggests that the rash represents a spotty vascular response involving dilatation of some skin vessels and failure to dilate in others.

It is much harder to project organ disease as a long term result of functional dysautonomic neurotransmission but an example of this might be given from our own experience. A forty-year-old woman was in hospital for months with a combination of vomiting and psychiatric symptoms. Studies, carried out extensively and repeatedly, showed that her entire bowel was atonic but that each sphincter that was visualized was in spasm. Her liver biopsy revealed extensive fatty infiltration. This kind of fatty infiltration is regarded as non-specific but it is also seen in experimental choline deficiency.[27] Since choline is derived from the diet, she could have been nutritionally deprived. If other nutritional elements were missing, for example folate, she would be unable to transmethylate endogenous ethanolamine to form choline. She would then be unable to synthesize acetyl choline and her bowel would be under unilateral Sympathetic action. Physiologically, we know that adrenergic neurotransmission will cause decreased peristaltic action and closure of sphincters, which was the chronic state of her bowel. Unfortunately no link was perceived between hepatic fatty infiltration and the condition of the bowel, so the total medical condition was beyond interpretation by our present medical model. Of equal importance, this patient's erratic and hostile personality made her a psychiatric case and much of her problem was regarded as psychosomatic in terms of the conventional model. Her physician considered that her attitude of mind acted against her own interests. If we see this individual according to our projected model, we can immediately make sense of it. It is obvious that her "mental" state could not be dissociated from her "physical" state, and that each was a part of a disease that was understandably biologic in nature. The irony in this case was that the physician in charge of the patient thought that this explanation was nothing more than imaginative and no further effort was made in this direction. He probelme remained unsolved.

A young man was incarcerated in a psychiatric locked ward. He had Crohn's disease and psychosis, although the two conditions alternated. When the "mental" component was successfully treated the bowel symptoms increased. When the "physical" aspect of his condition was treated and improved, psychotic symptoms returned. Surely both conditions were merely complemental to each other, since they may well have been produced by the same basic cause affecting different aspects of the complete physiologic system.

We have already discussed the emerging role of nutrition in neurotransmission, and it would seem that greater consideration must be given to all its aspects in both the prevention and treatment of disease in man. If we are able to accelerate or decelerate metabolic function by appropriate mixing of caloric and non-caloric nutrients, and if the recipe produces valid effects on the "balance" of neurotransmission, then we must concentrate on a number of related factors:

1. The physiologic balance of neurotransmission within a genetically determined individual.
2. Further information on how diet has its effect on that balance.
3. The application of broad nutritional principles to suit the genetically determined characteristics of either Sympathetic or Parasympathetic dominance on a "preventive" basis.
4. The application of highly specific principles of vitamins, minerals, and caloric intake in order to apply correction when a long term chronic state of abnormal neurotransmission has been in effect for some period of time.

This overall concept suggests that appropriate nutrition is the only means we have to attempt to prevent disease. It goes without saying that avoidance of toxic chemicals is the other preventive that we can use, but in a world that depends so much upon industry, that is virtually impossible. It also seems that the weakness of the human lies in his voracious appetite for addictive substance over which he

apparently loses control, and these are apparently harmful in much the same way. It suggests also that all is not lost if the disease process is underway, and that healing regeneration can occur if the pathophysiology can be "coerced" back into a state of normal balance. Using vitamins or other nutrients in larger than physiologic dose converts them from being purely nutrients to becoming drugs, since they are then being used to change the "balance" of neurotransmission.

On the other hand it is also important to consider that such nutrients might be used at an excessive rate, as has been suggested as a case of vitamin C deficiency in Australian aboriginal children,[28] or that biochemical deactivation might occur, as has been suggested for thiamine in some victims of sudden infant death.[29] Indeed, there are many different ways in which "effective" deficiency may occur. It would seem that any disease process can be considered only in the light of genetics, environment and nutrition, as we have tried to demonstrate.

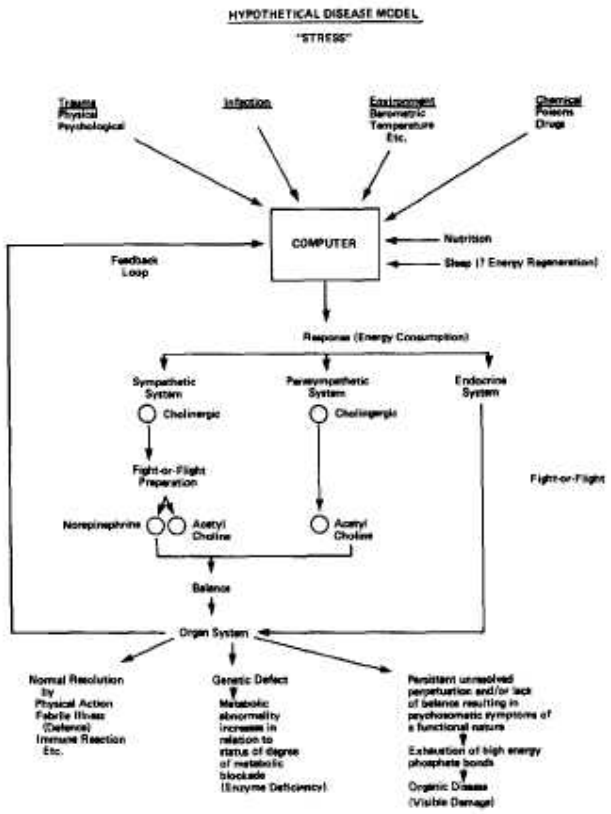
An adolescent girl gave a history of being well until three years before she presented with typical anorexia nervosa. Her symptoms began after an abdominal injury when she developed vascular changes in the legs and arthritis in several joints. Later she developed Crohn's disease, Reynaud's disease and then the personality change and loss of weight of anorexia nervosa. Her heart rate was 48 per minute and her skin was dry and cold. Capillary skin circulation in the legs was poor and she complained of feeling cold all the time. There is no medical model for connecting her inflammatory joint disease with her bowel disease, except that we know that this relationship is common in Crohn's disease. But it is not possible to connect this aspect of her condition with anorexia nervosa, and so she appears to have two diseases. Using the proposed model, it is possible to put it together to make one disease process. We know that reflex sympathetic dystrophy[30] occurs after injury and that this condition starts with sympathetically dominant activity, which may be followed by painful swelling of joints and even lead to bone changes, including Sudeck's atrophy.[31] The reflex mechanisms then begin to effect the bowel vasculature and the patient develops Crohn's disease. The complex associations of neurotransmission lead to chronic loss of appetite, characteristic personality changes, and profound weight loss as the patient becomes progressively more hypometabolic.

It is suggested that this patient makes an excellent example of the interpretation of the proposed hypothesis. It is true that she was under family stress of a psychologic nature and she was subjected to unforseen physical stress which may have created an overload in her response mechanisms, so we certainly can perceive the stress element. Her constitution, genetically determined, provides her with certain energy limitations which have to be protected by appropriate nutrition. The vicious cycle is completed by the advent of anorexia, considered to be part of the Sympathetic mechanism. This, in turn, leads to nausea at the sight of food and she will get most of her survival calories from liquids which, because of their carbohydrate nature, cause more Sympathetic activity. It is of considerable importance that the only controllable condition is nutrition. Her disease, starting as an autonomic response to stress, has gradually led her to a condition that endangers her life and that has all the elements of "organic" as well as "psychiatric" effect.

Recently mitral valve prolapse was linked with dysautonomia,[32] and this condition has been designated the cardiac disease of the decade, since it has been reported that it occurs in about 10% of the U.S. population.[33] It is fascinating to read the important information which is to be found in these two papers, one delivered in the austere tones of the medical scientist writing for his medical colleagues, the other one more freely presented for nonmedical readers. In the second paper the author noted that the condition had often been endured by patients after a diagnosis of neurosis had been made, in spite of the fact that some of them died suddenly, suffered documented heart attacks, or were admitted to coronary care units with severe chest pain "almost indistinguishable from the pain of severe coronary artery disease." He noted also that his own research suggested very strongly that there was failure of the "central computer" located in the mid brain, which acts as if it is unable to interpret the incoming messages accurately nor able to modulate or control the activity of the sympathetic and parasympathetic systems within an appropriate balance."

The same author and his associates described the technicalities of their research in the former paper[30] and several interesting comments were made which are compellingly supportive of some of the ideas in this monograph. They listed a number of clinical abnormalities in these patients which included easy fatigability, asthenia, reduced effort tolerance, vasomotor instability, inappropriate heart response during general anesthesia, and excessive bradycardia.

FIGURE 2



This representation of a hypothetical disease model is an extension of that proposed by Selye. The main difference is that it considers the metabolic machinery in terms of energy utilization and regeneration, suggesting that this equation is not necessarily one that is automatically balanced. Modern knowledge of oxidative metabolism and its transmission through the mechanisms of transmethylation, transamination and transulfuration is used to replace the "energy bank" proposed by Selye

Changes in the electrocardiogram included S-T segment depression during sub-maximal treadmill testing, despite demonstrated normal coronary artenograms and normal thallium 201 uptake by the myocardium. The defects in autonomic reflexes reported are similar to those discussed in Chapter 2 and emphasize again the widespread association of autonomic dysfunction with human disease. The symptoms are also those described in the various forms of beriberi, the prototype for autonomic dysfunction. These phenomena were discussed in Chapter 3 when beriberi was compared and contrasted with manifestations of the general adaptation syndrome resulting in animals from experimental stress.

It is suggested that these multiple examples of autonomic dysfunction arise from the combination of the 20th century stress (civilization) and a serious propensity towards overeating particularly an excess of refined (i.e. lacking in fiber)

carbohydrate, coupled with a marked lack of daily exercise. If this is true, it is not surprising to find 10% of the U.S. population affected by mitral valve prolapse syndrome, and it might well be that the coming decades will reveal a steady increase in heart disease, diabetes and other severe handicaps, including idiopathic syncope and personality changes, unless this trend can be perceived and checked.

This unifying concept, summarized in Figure 2, is badly needed in our search for the true nature of disease which so frequently seems to be a function related to civilization It seeks to relate together known perspectives and, like the blind men and the elephant identifies what may well be the elephant, recognizing also that the elements that represent the various parts are equally true. Seen by themselves they create a partial truth which is insufficient to the whole concept.

PRE MENSTRUAL TENSION SYNDROME (PMTS)

It is suggested that this model provides a very reasonable explanation for a syndrome that is extremely common, and that appears to be virtually infinitely complicated and complex. The Hypothalamus, being viewed as the centrally located computer, regulates body rhythms. The two most notable are circadian rhythm, which regulates the cycle alternating day/night physiology, and the 28 day menstrual cycle.

The menstrual cycle, in a healthy woman, is a fairly regular 28 day rotation, governed by a biological time clock. Whether this time clock is influenced by outside stimulus is unknown. For example, it might be that the powerful gravitational pull of the moon could be an influence, since the cycle is similarly timed. Virtually nothing is known about the effects of natural environmental rhythms upon humans, but there are many examples in animals and it is not unreasonable to deduce that the unconscious response of the Hypothalamus is regulated by something of this nature.

Women with PMTS develop alarming symptoms before a menstrual cycle and these are conventionally considered as psychogenic in origin. The symptoms vary from severe depression (cholinergic?) to extreme irritability and aggressiveness (adrenergic?). This may be associated with changes in breasts, varying from tenderness to formation of cysts or mastitis. This is endocrine in nature. During the menstrual flow there are often severe cramps and, since the nerve supply to the uterus is known, this must be Sympathetic in character (note the capital letter). The craving for food, usually chocolate or something sweet, which occurs premenstrually, can be viewed as an adaptive mechanism in the hypothalamus (note there is no capital letter) and is similar to that seen in pregnancy.

During the cycle, an array of neurologic or functional symptoms include exquisite fatigue, changes in sleep patterns, postural hypotension, poor cold tolerance, coldness in the extremities, parasthesiae, urinary frequency, urinary tract infection, abdominal pain, vaginal yeast infection, pseudoangina, a sense of suffocation, nasal congestion, cardiac palpitations, excessive sweating and piloerection. Marked extremes in the appetite may be experienced and there may be diarrhea or constipation. Such individuals are maladapted to their environment and cannot handle the metabolic stresses associated with menstruation.

The key to understanding this syndrome lies in recognizing lack of Hypothalamic coordination. The frequency of yeast infection is related to this, since yeast is a predator that is able to detect the biochemical changes which are to its advantage and disadvantageous to the host. Many such women with this syndrome show a peculiar effect upon the tongue, produced by the tongue being thrust forward onto the back of the lower teeth. This causes the edges of the tongue to be indented by depressions made by the teeth, possibly resulting from the unconscious tongue thrust. It may be associated with the geographic tongue, or an increase in reddened appearance of the filiform papillae. Many women also suffer from temporo mandibular joint syndrome.

It is suggested that the mechanism of PMTS is causally related to inefficient oxidative metabolism in Hypothalamic control, and that this explains the multiplicity of dysautonomic and endocrine symptoms. Since the brain is extremely sensitive to oxygen deprivation, or to put it into a more accurate perspective, oxidative metabolism, it is easy to see how PMTS is caused by a combination of malnutrition and increased environmental stress. Treatment with drugs occasionally helps to

suppress the symptoms, but only an effective approach to nutritional resources is therapeutic. In many patients the birth control pill appears to be a potent causative factor and this may also be because of the effect of hormones on receptor sites in the brain.

Mitral valve prolapse is not uncommon in this syndrome, and the associated dysautonomia can be profound. The author has observed a patient with the syndrome whose pulse rate doubled immediately on standing upright, and she experienced severe postural hypotension. She was virtually crippled, and yet she had been discharged from the hospital with the explanation that "nothing was found wrong." As has been repeatedly emphasized, changes in function can be severe without there being any evidence of organic disease, and clinical observation is the easiest and least expensive way of making the diagnosis. A relatively recent and rapidly emerging state of scientific understanding has focused on the generation of free oxygen radicals. The excessive formation of oxygen in this form is considered to be mechanically destructive in the cell, but perhaps another hypothesis might be added. If the oxygen in this form is not available to the cell in oxidative phosphorylation, the energy efficiency might be proportionately affected, resulting in the loss of cellular function. Increased rate of cellular death might then result in accumulation of organic debris which stimulates yeast growth, since the ecological objective of yeast is to recycle organic matter.

This syndrome makes it clear that the basic reason for the dysfuntion is central in origin, and has a definable biochemical cause. Furthermore, many physicians know that it is responsive to applied nutritional therapy, since they have seen clear cut clinical benefit repeatedly. It is no longer sufficient to offer these patients one of the many tranquillizers available, and hormonal treatment appears only to create further problems, since hormones have their own effect in the hypothalamus. If the role of nutrition can be perceived appropriately as the source of both fuel and ignition, it is relatively easy to make the transition in concept and the idea of treating a complicated syndrome by such a simple means appears less bizarre.

CONCLUSION

Throughout this monogram, thiamine and its therapeutic derivatives have been on center stage. It is not intended to imply that thiamine is the only nutriment being used therapeutically by the author or by any other preventive physician. On the other hand, the experience of the author has slowly accumulated an absolute conviction that many of the common diseases in advanced society are caused by failures of adaptation, exactly as was proclaimed by Selye. In the last analysis, we are getting to grips with the the complicated mechanisms of redox, the ability to convert fuel to energy. In other words, the optimum efficiency of utilization of oxygen must be the one factor that would enable us to judge whether a human body is working up to top capacity.

Since thiamine is a catalyst that is linked to citric acid cycle function as well as its possible role in cell membranes — and hence its potential regulation of electron transfer in producing ATP — it certainly stands astride the fundamental mechanisms of energy metabolism. However, a number of examples have been provided in attempting to show that this vitamin is closely related to all other vitamin and mineral functions in their catalytic role.

It is suggested that traditionally diagnosed "functional" or "neurotic" manifestations are merely the reactions of a brain which is chronically starved of oxidative metabolism. In a sense, it can be viewed as a biochemical distortion which is epitomized by the early behavioural changes in both beriberi and experimental thiamine deficiency, even though there are definite differences between the two conditions. It must alter medical perspective towards psychosomatic disease. We must begin to realise that our traditional approaches may be catastrophically wrong and that there is no artificial separation of mental from physical. The psychiatrist, like the internist, may have to stop being concerned about the descriptive diagnosis and begin to probe the total individual for determining the biochemical lesion.

The very interesting observation that a given nutriment can be used in the treatment of 250 different conditions does not imply that the symptomatic representation is always due to the same biochemical lesion. For example, a patient

with rheumatoid arthritis may have the same biochemical cause which, in another individual, results in depression. Therefore both would be treated in the same way in that instance. By the same token, three patients with the same disease, diagnosed in descriptive terms, may have three different biochemical causes. Hence, each may have to be treated by applying differently selected nutritional therapy. Even cancer has moved into scientific thought as possibly nutritionally caused disease, and there seems to be little doubt that the science of nutrition is on the eve of a massive renaissance.

In order to come even close to understanding the basic nature of the disease process, a physician requires a very broad base of understanding in the mechanics of the machine that he is servicing. His handmaiden must therefore be biochemistry, and how it relates to the synthesis of neurotransmitters. For example, the esophagus has only a parasympathetic supply and we can assume that the autonomic neurotransmitter to that organ is unequivocally cholinergic. Knowing that sympathetic action in the heart is different, according to which sympathetic chain delivers the signal, helps us to understand the peculiarities that are represented in the prolonged Q-T syndrome. Most of all, it provides a basic view of the relationship between mental and physical, since all controls are central and the body is merely the target. However, the brain is also part of that total body and is activated by the same neurotransmitters. Hence, behaviour is a composite of brain/body interplay.

We have much to learn, but it is abundantly obvious to all who have begun to practice the developing art of preventive medicine that nutritional understanding is beginning to revolutionize medicine in a manner which is similar to the dramatic discovery of penicillin.

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