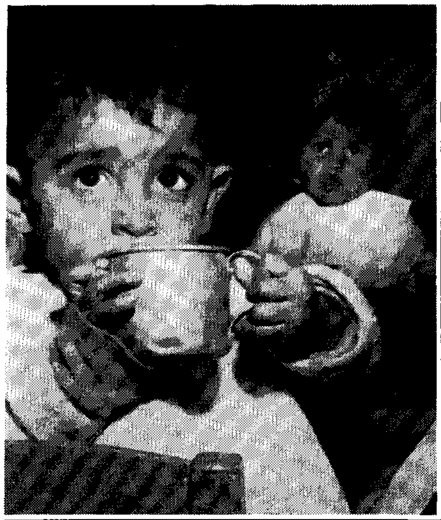

SIGNIFICANCE OF THE VITAMINS IN HUMAN NUTRITION

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Vitamins have become large volume articles of commerce since their discovery 40 years ago. In many ways they are better known popularly than scientifically. Only now is research involving the most complicated aspects of biochemistry uncovering the physiological basis of their action in the human diet

A VITAMIN IS COMMONLY DEFINED as an organic compound required in trace amounts as a component of the diet for normal health and well-being. Depending upon one's nationality or alma mater, one of the following recent or contemporary investigations is usually credited with discovering the existence of vitamins: Hopkins (England), Lunin (Germany), Hart (Wisconsin), Osborne and Mendel (Connecticut, Yale), Eijkman and Grijns (Dutch East Indies), or McCollum (Wisconsin). Each group in its own way showed that a diet composed of purified protein, carbohydrate, fat, and minerals is not sufficient to sustain the well-being of animals when consumed in amounts that satisfy their caloric requirements. Others have noted even earlier that the consumption of green vegetables or citrus fruits would cure scurvy. By 1804 a regular issue of lemon juice was made compulsory in the British navy. If desired, one may push the discovery of the vitamins back into ancient history and say that vitamins were known to the Chinese who, in the preparation of certain items of food, allowed grains to sprout before use, thus increasing measurably their content of what is now known as vitamin C.

When it became apparent to some of the early pioneers in vitamin research that more than one active dietary material is concerned in promoting the well-being of laboratory animals, a nomenclature became necessary. Early papers refer to "fat-soluble vitamine A," "water-soluble vitamine B," and "water-soluble vitamine C." The solubility characteristic was soon dropped from the name. Actually the word vitamine was coined by Casimir Funk who was working with vitamin B. He recognized it to be a base (amine) necessary for life. Soon the final "e" was dropped. While the word vitamin is an attractive one for describing these new dietary essentials it is incongruous to the extent that most of the vitamins are acids rather than bases. A number do not even contain nitrogen. Despite this objection, the word (as well as the subject) is here to stay.

When the list of known vitamins had increased to six (vitamins A, B, C, D, E, and F), the subject of nomenclature became complicated by the realization that vitamin B as known at that time was a group of factors rather than an entity. Perhaps because of the confused state of vitamin research at that time someone began using the term vitamin B complex to describe this group of factors. The term "B vitamins" was applied to the water-soluble dietary essentials present in yeast, wheat germ, protein-free milk, etc. They are frequently considered together as a group because: (a) they are ordinarily found together, (b) their distribution is more universal, being found with only one or two exceptions in every living cell. For a time the English and European investigators chose to assign new letters to these separate factors while American investigators chose to assign subscripts to each new factor: vitamin G and vitamin B_2, for example, are identical. Soon there were widespread lapses from any system, but in America there has been some tendency to stick with the subscript system. Reference to the label on any polyvitamin preparation will indicate the presence of vitamin B_2, vitamin B_6, and vitamin B_{12}.

One may reasonably ask what happened to vitamin B_3, B_4, B_5, B_7, B_8, B_9, B_{10}, and B_{11}? These designations were assigned to describe the curative agents responsible for overcoming various ill-defined conditions in experimental animals. In most cases, they were never followed up and remain together with some others as a monument to the overexuberance of biochemists. The hopeless nomenclature, in a sense, is unfortunate since it has served to confuse the general public and has hampered the intelligent use of vitamin preparations.

Vitamin Deficiencies

From the historical point of view a vitamin is considered as a factor whose presence in the diet prevents the occurrence of a specific "deficiency syndrome." Vitamin B_1 (thiamin) prevents or cures beriberi in humans and the counterpart in animals. Vitamin A prevents or cures xerophthalmia. Twenty to 30 years ago the student of nutrition learned a list of vitamins and the specific diseases which a particular deficiency elicited in much the same way that a bacteriologist learned a list of microorganisms and the specific disease that each could cause. However, it has gradually become apparent that, with few exceptions, no vitamin is concerned solely with a particular tissue or a particular disease.

The condition attributable to the deficiency of a given vitamin represents the weakest link in a whole chain of reactions and interrelationships. For example, night blindness and xerophthalmia result not from the fact that the eyes require vitamin A while the other tissues do not, but because the eyes are most susceptible to a dietary deficiency, perhaps because their requirements compared to other tissues is particularly high. There has been a gradual shift away from relating a particular vitamin to a particular disease but to emphasize instead the particular chemical reaction(s) in which each vitamin is concerned, realizing, as will be elaborated more in detail, that all cells are much alike in their metabolism.

Actually, it is known that many of the vitamins do not function as such in metabolism but act instead as prosthetic groups or "sites of action" of much larger compounds termed coenzymes. These coenzymes are usually found associated in combination with specific proteins. Table I attempts to summarize this information. The interrelationship of vitamins and enzymes is becoming clearer as more is learned about each field. A number of recent reviews have been concerned in more detail with vitamins whose functions have been elucidated in terms of *chemical reactions*. It is interesting to note that quite a bit is known about the function of some of the relative newcomers, for example folic acid or folinic acid. However, little if anything really is known about the function of some of the vitamins that were discovered, isolated, and synthesized early, for example, vitamin A. Of all the vitamins, least is known about the real function of vitamin C, yet vitamin C was the first to be obtained in the pure crystalline state. That isolation was a milestone in vitamin research since it established that the vitamin concept is essentially sound and that the dietary restriction of a *single specific chemical identity in trace amounts* can lead to disease. As a matter of fact, thiamin was isolated earlier by Jansen and by Windaus but uncertainty about its composition and biological activity delayed acceptance of the premise that a vitamin can be a single chemically pure compound.

Complex Relationships

In the course of vitamin research it became apparent to clinical investigators that an uncomplicated dietary deficiency (a particular disease as a result of failure to consume a particular vitamin) does not ordinarily occur. An individual consuming a self-selected diet deficient in thiamin is consuming a diet deficient in a number of other factors as well. This is so because with few exceptions, vitamins, particularly those of the B group, generally occur together. For example, liver, heart, and kidney are rich sources of many vitamins while polished rice is a poor source. As a result, if a patient suffering from beriberi were treated with thiamin the beriberi might be cleared up but he might then come down with pellagra. The administration of thiamin and nicotinic acid might not even then produce a well individual. Considerable emphasis was therefore placed on the administration of "complete" vitamin mixtures. While the wisdom of giving a "complete" vitamin mixture to one with a history of dietary deficiency or with evidence of an increased requirement is not questioned, the logic behind such treatment is somewhat different. A person on a diet deficient in a number of factors is "just getting by." With the administration of a particular vitamin, one restriction is overcome and metabolism perhaps increases a bit. This requires the presence of increased amounts of the factor concerned with the next "weakest link" and a second deficiency ensues. Well being can result only when all dietary essentials are present simultaneously. Actually the consumption of a particular vitamin does not induce a deficiency of a second. It merely unmasks the already existing requirement for the second.

This is not intended to imply that there are no metabolic interrelationships between the vitamins. The facts of the matter are quite the contrary. A striking example of such a relationship is illustrated in the biosynthesis of coenzyme A (see Figure 1). Coenzyme A is present in all cells. Some species of living things synthesize it from relatively simple compounds available to them. Other species including the higher animals, and probably man, are restricted in their synthetic ability and require that at least the pantothenic acid moiety be present in the diet. With the raw materials available either by synthesis or from the diet it is known that a number of vitamins (in the form of their appropriate coenzymes) are required to assemble the coenzyme A molecule. This is an illustration of the "all or none" or "a chain is only as strong as its weakest link" principle in nutrition which says that all dietary essentials must be present at the same time for optimal effect. Although the diagram does not show it, if one were to trace the diagram back far enough one would come to steps that involve coenzyme A for their operation. Thus, vicious circles are entirely possible in vitamin metabolism where the presence of a given vitamin in appropriate form is required for the utilization of itself. With respect to vitamins, all living things "lift themselves with their own bootstraps."

Benefits Derived from a Study of the Vitamins

A substantial amount of money, time, energy, and thought has been devoted

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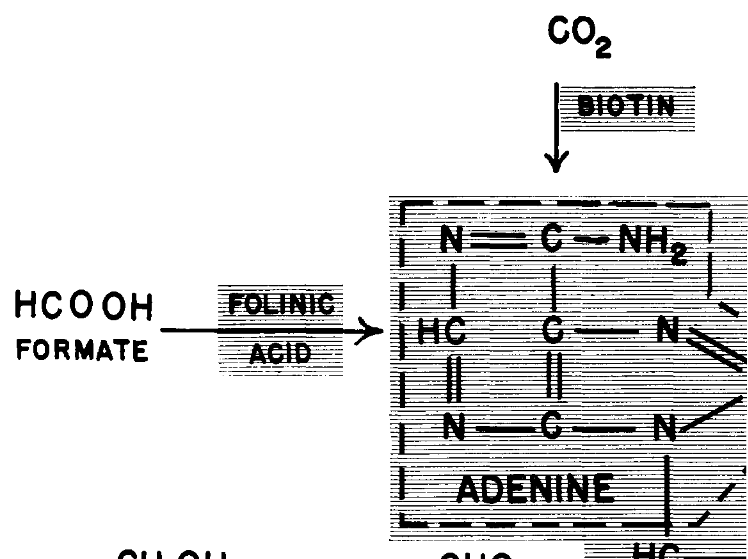
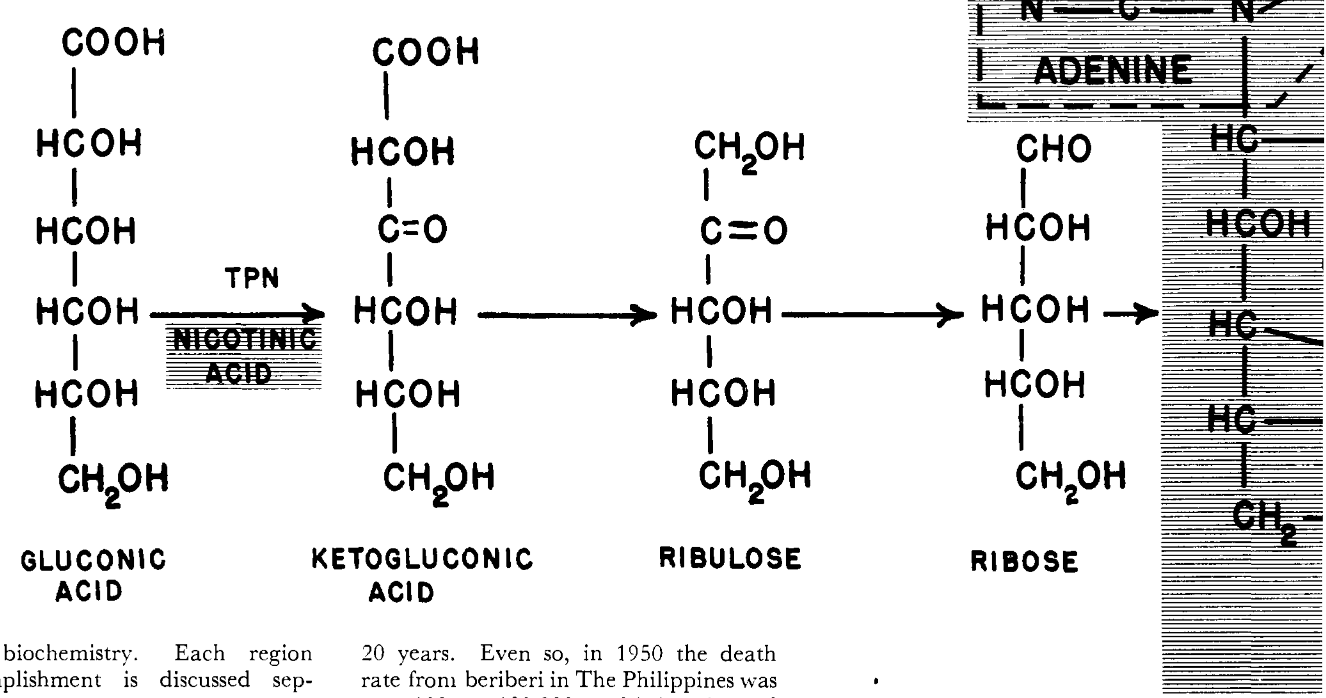
to study of the vitamins. Table II summarizes some of the scientific milestones in this research. One may ask in all seriousness, what has all this effort accomplished? The following separate accomplishments stand out: (a) the general health and well being of man and animals has been measurably improved, (b) an "antimetabolite concept" has developed which has permitted the design of a number of compounds useful in the treatment of disease, and (c) the general fund of knowledge has been enriched especially in the field of comparative biochemistry. Each region of accomplishment is discussed separately.





Vitamins and the General Health

Even the untrained observer can detect that over the past several decades the general health of the population in this country has markedly improved. A number of factors have contributed to this general improvement in health; included are a higher standard of living, development and use of the antibacterial and other biological and chemotherapeutic agents, and improvements in the nutritional status of the population. It is difficult to assess the relative significance of any single factor and it is appreciated that all are in a sense interrelated. A higher standard of living carries with it an implication of improvement in the quality of food consumed.

Where it has been possible to make needed changes in the diet of an isolated group, the results have been spectacular. For example, it has been known for approximately 40 years that beriberi results from eating a restricted diet composed largely of polished rice. Foodstuffs known to cure the condition were recognized almost that long ago, and synthetic thiamin has been available for 20 years. Even so, in 1950 the death rate from beriberi in The Philippines was over 100 per 100,000, and it is estimated that the morbidity rate is at least 100 times the mortality rate.

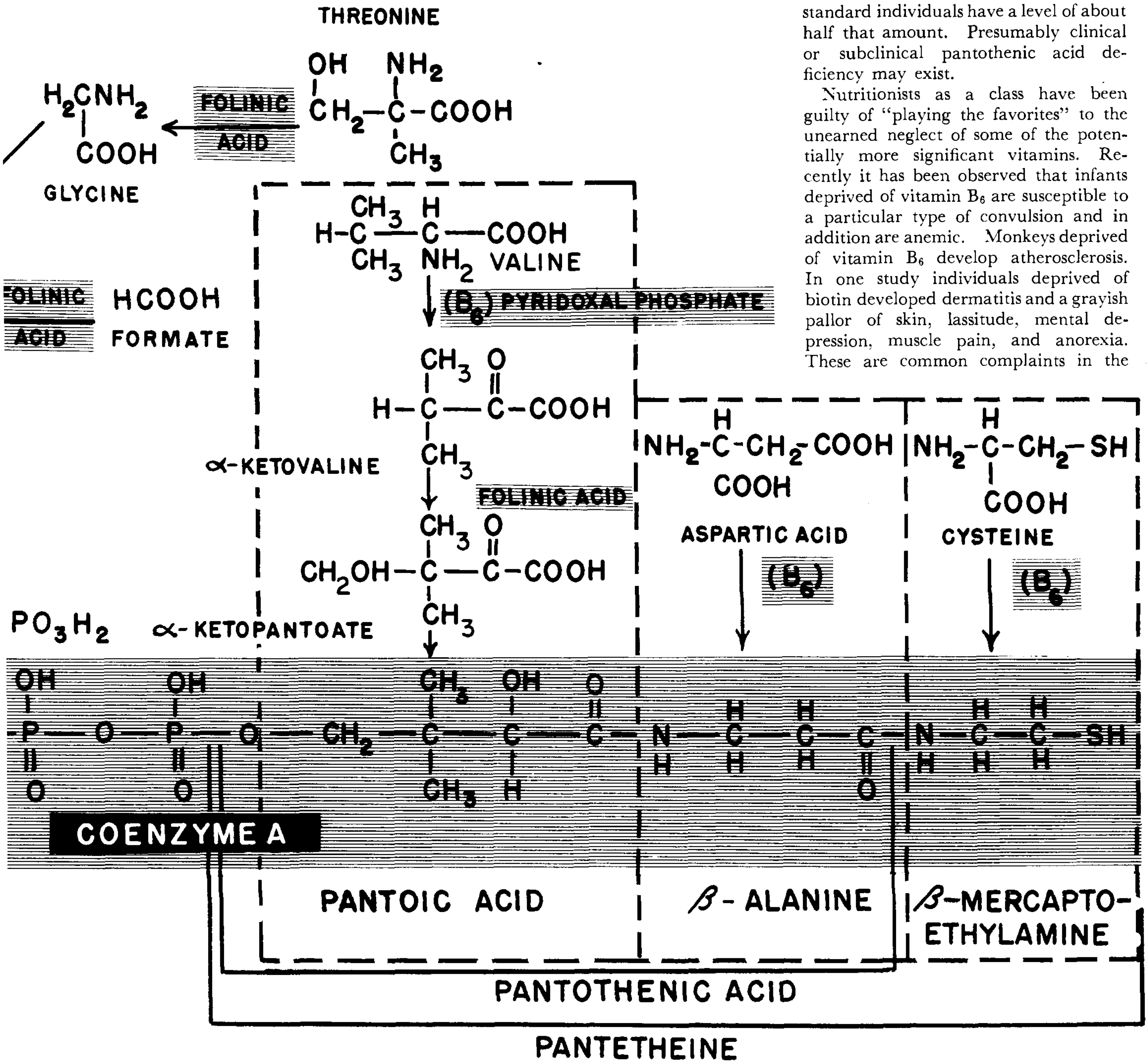
In 1948 a trial of enriched (thiamin, niacin, and iron) rice was started on the peninsula of Bataan, The Philippines. In the two-year period immediately prior to the enrichment program the beriberi mortality rate in the particular experimental area was 263 per 100,000. In the first two-year period following initiation of the enrichment program the death rate fell to 28 per 100,000. Indeed, for many months no deaths from beriberi occurred.

So conclusive were the beneficial effects that smuggling of the enriched rice into adjacent areas became a problem complicating the control statistics. This reduction in death rate could be accomplished at an estimated increase in the cost of the rice of only about 1 to 2%. Despite the ratio of the benefits involved to the increased cost of the rice, it is believed that wherever free competition between enriched and unenriched rice is permitted, enriched rice will be driven out.

Nutrition Deficiency Decreasing

The facts of nutrition have been so well applied in the U. S. that the search for frank evidences of nutritional deficiencies, except in certain defined segments of the population, has become unrewarding. Since such frank evidences of nutritional deficiencies have all but disappeared, nutritionists are presently more concerned now about: (a) borderline or subclinical avitaminoses of the various vitamins whose significance in the nutrition of humans has been established, and (b) the possible existence of deficiencies of those newer factors whose essentiality for humans has not been established but is implied since they are required by animals.

To detect the existence of subclinical or borderline vitamin deficiency, a number of microchemical and microbiological tests have been developed for investigating with a particular vitamin the resting blood or other tissue level, its existence in the urine, or the response of the body with respect to blood and urine levels to a given "load" dose. As a result of such studies it has been established that normal well-fed individuals have a fasting blood level of vitamin C of 0.7 milligram per 100 milliliters or



higher. Those on a poor diet have less. Thus the blood level in an individual gives an indication of his status with respect to vitamin C.

Normal well-fed individuals excrete in the urine about 0.5 milligram of riboflavin per day. Poorly fed individuals excrete 0.1 milligram or less per day. Obviously if John Doe excretes only 0.05 milligram his dietary intake of riboflavin may be considered suboptimal and in all probability he may be in need of increased amounts of riboflavin. The development of such micro tests has now developed to the point that with a few drops of finger-tip blood (actually only 0.1 milliliter) one can determine the status of an individual with respect to vitamin A, carotene, thiamin, riboflavin, vitamin C, diphosphopyridine nucleotide, hemoglobin, iron, serum protein, and phosphatase.

Nutrition's "Stepchildren"

Human dietary requirements and deficiencies of vitamins which have been established as essential for animals are now under investigation. The role of these factors in human nutrition is still unknown. These vitamins have been termed the "stepchildren" of nutrition by György and include pantothenic acid, vitamin B_6, and biotin. It has been known for 10 years that "normal" individuals have a plasma level of pantothenic acid of the order of 20 micrograms per 100 milliliters and that substandard individuals have a level of about half that amount. Presumably clinical or subclinical pantothenic acid deficiency may exist.

Nutritionists as a class have been guilty of "playing the favorites" to the unearned neglect of some of the potentially more significant vitamins. Recently it has been observed that infants deprived of vitamin B_6 are susceptible to a particular type of convulsion and in addition are anemic. Monkeys deprived of vitamin B_6 develop atherosclerosis. In one study individuals deprived of biotin developed dermatitis and a grayish pallor of skin, lassitude, mental depression, muscle pain, and anorexia. These are common complaints in the general population. It may be expected that we will hear more of the utility of the less well-known vitamins in the future.

Vitamins and the Antimetabolite Concept

All studies bearing on the point have indicated that vitamins are extremely specific structurally. With a few minor exceptions structural alteration of a vitamin in even a relatively minor way is associated with loss of biological activity. If nicotinic acid is catalytically reduced to nipecotic acid it is no longer a vitamin. If the carbon of the ureido ring of biotin is removed with barium hydroxide it becomes just another organic compound. Of great

Table I. Functional Forms of the Vitamins

Vitamin	*Functional Forms*	*Reaction Concerned*
Riboflavin (B_2, G)	Riboflavin phosphate, flavin adenine dinucleotide	Numerous oxidative and reductive reactions
Nicotinic Acid (Niacin)	Diphosphopyridine nucleotide, triphosphopyridine nucleotide	Numerous reversible dehydrogenation reactions
Vitamin B_6	Pyridoxal phosphate, pyridoxamine phosphate	Activation of α-carbon atoms leading to racemization, transamination, reversible aldol condensation, α, β addition and elimination reaction
Pantothenic Acid	Coenzyme A	Transfer of acyl groups (R—COOH)
Thiamine (B_1)	(a) Cocarboxylase (thiamine pyrophosphate) (b) Lipothiamide pyrophosphate	(a) Nonoxidative decarboxylation (b) Oxidative decarboxylation
Folic acid	Folinic acid (Leuconostoc citrovorum factor)	Utilization of formate (one carbon transfer)
Biotin	Biotin (or biocytin) protein derivative (biotoprotein)	Utilization of carbon dioxide (one carbon transfer) Protein synthesis, deamination

significance are certain compounds that may be derived from the vitamins by various structural modifications which, instead of yielding inert compounds, yield what are termed antimetabolites. An antimetabolite is defined as a compound similar in structure to one involved (catalytically or structurally) in metabolism and which competes with the essential compound in such a way as to prevent its function.

The situation may be likened to a lock and key. If a vitamin is imagined as a key notched and grooved to fit a particular lock it will be appreciated that the lock can function only when the correct key is employed. An antivitamin that functions by competitive interference, then, may be described as a key with similar grooves but different notches. It may enter the lock but cannot turn the bolt. Furthermore, its presence in the lock prevents the correct key from functioning. In another instance an antivitamin may be likened to a group of spectators observing a construction project. The spectators, although accomplishing no useful work, frequently may get in the way and obstruct operations. The potency of a compound as an inhibitor is given by a ratio of the amount of antivitamin to the amount of vitamin necessary to prevent a given metabolic step.

There are a number of naturally occurring antimetabolites, for example dicoumarol (antivitamin K), or actithiazic acid (antibiotin). Others have been synthesized deliberately in the laboratory. The sulfonamides, for example, are antimetabolites of *p*-aminobenzoic acid (PABA), a precursor of folic acid. They are considered to function by hindering PABA so that bacteria cannot synthesize folic acid at an optimum rate. Man and higher animals require their folic acid preformed and so are not affected (below toxic levels) by sulfonamides. A summary of a few of the more interesting vitamin antimetabolites is given in Table III. Some of the more important antimetabolites are modifications of structural components rather than of metabolic catalysts and include such compounds as azaguanine, azaserine, thioadenine, compounds that are finding utility in experimental tumor chemotherapy.

One may confidently expect that in the future additional antimetabolites will be synthesized with even greater promise for the treatment of disease.

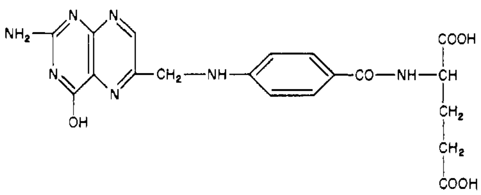
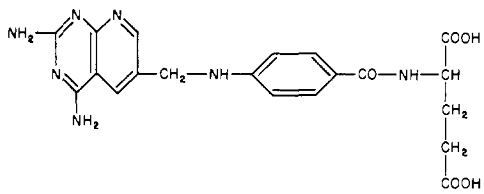
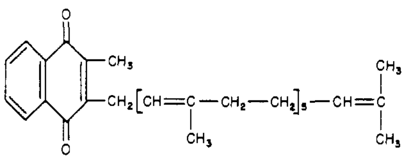
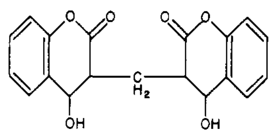
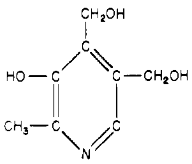
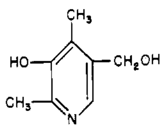
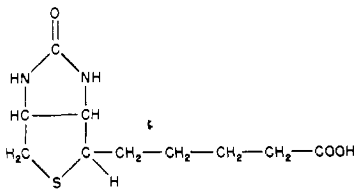
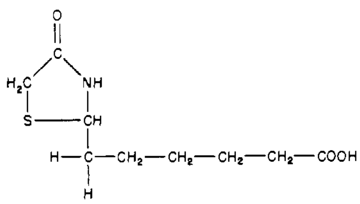
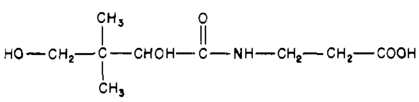
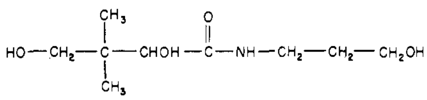
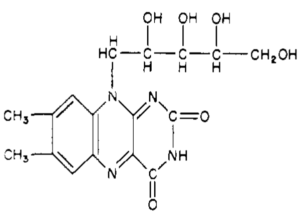
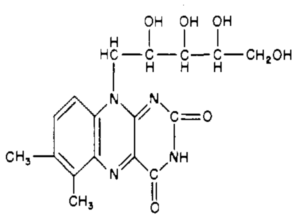
Vitamins and Comparative Biochemistry

The idea is prevalent among many biologists that life originated on this planet by a fortuitous accumulation of inorganic compounds which reacted with each other under the influence of

Table II. Some Milestones in Vitamin Research

Date	Achievement	Responsible Group
1897	Production and cure of experimental beriberi by dietary changes	Eijkman
1906	First clear statement of vitamin concept	Hopkins
1919	Rickets cured in children with ultraviolet light	Huldschinsky
1925	Antirachitic activation of foods	Hess
1926	Isolation of thiamine (vitamin B_1)	Jansen and Donath
1927	The "cure" of pernicious anemia with oral liver	Minot and Murphy
1931	Structure of vitamin A determined	Karrer, Morf, and Schopp
1932	Isolation of vitamin C	Waugh and King
1933	Isolation and identification of vitamin B_2 (G) as riboflavin (lactoflavin)	Kuhn, György-and Wagner-Jaureg
1935	Isolation of biotin	Kögl
1936	Structure of thiamine (vitamin B_1) elucidated and synthesis achieved	Williams and Cline; Andersag and Westphal
1937	Cure of blacktongue in dogs and pellagra in humans with nicotinic acid	Elvehjem, Madden, Strong, and Woolley; Spies
1937	Isolation of vitamin A	Holmes and Corbet
1937	Synthesis of vitamin A	Kuhn and Morris
1938	Isolation of pyridoxine (vitamin B_6) and structure elucidated	Kuhn and Wendt; Lepkovsky; Keresztesy and Stevens; György; Ichiba and Michi
1938	Structure of α-tocopherol (vitamin E) elucidated and synthesis achieved	Fernholz; Karrer, Fritzsche, Ringier, and Salomon
1939	Synthesis of pyridoxine	Harris and Folkers; Kuhn *et al.;* Morii and Makino
1940	Structure of pantothenic acid elucidated and synthesis achieved	Williams and Major
1942	Structure of biotin determined	du Vigneaud
1943	Isolation of folic acid	Eight authors from the Parke-Davis Laboratories
1944	Synthesis of biotin	Harris, Wolf, Mozingo, and Folkers
1944	Synthesis of pyridoxal and pyridoxamine	Harris, Heyl, and Folkers
1946	Structure of folic acid elucidated and synthesis achieved	Sixteen authors from the Lederle Laboratories and American Cyanamid Company
1948	Isolation of vitamin B_{12}	Rickes, Brink, Koniuszy, Wood, and Folkers
1951	Isolation of lipoic acid (protogen, thioctic acid)	Reed, DeBusk, Gunsalus, and Hornberger

Table III. Some Important Vitamin Antimetabolites

Vitamin	*Antimetabolite*	*Use*
 FOLIC ACID	 AMINOPTERIN	Treatment of leukemia and other neoplastic diseases
 VITAMIN K	 DICOUMAROL	Treatment of coronary thrombosis and other conditions where an anti-coagulant *in vivo* is required
 PYRIDOXINE	 DESOXYPYRIDOXINE	Treatment of certain experimental tumors in animals
 BIOTIN	 ACTITHIAZIC ACID	Inhibition of mycobacteria *in vitro* only
 PANTOTHENIC ACID	 PANTOTHENYL ALCOHOL	Inhibition of oral lactobacilli
 RIBOFLAVIN	 ISORIBOFLAVIN	Treatment of certain experimental tumors in animals

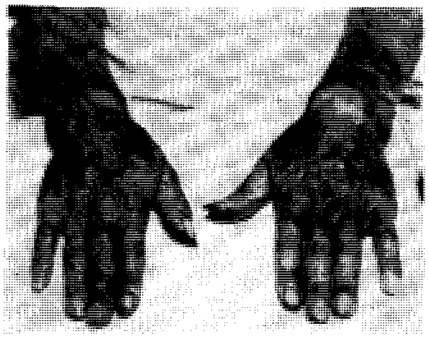
some physical phenomenon, light, cosmic rays, or other influence, to produce larger and larger molecules which gradually acquired the properties attributable to living things. The autotrophic bacteria, some species of which obtain their energy from the oxidation of sulfur and their protoplasmic constituents ultimately from inorganic compounds, are frequently cited as examples of these primitive forms. However, with the development of microbiological methods for the determination of the vitamins it has been possible to assay autotrophic bacteria and it has been found that these so-called primitive forms have a complete supply of vitamins. These results are now interpreted to mean that the really essential reactions of cellular metabolism are much the same in all species, being carried out under the same coenzymes.

Autotrophic bacteria then emerge not as lowly species but as perhaps better chemists than our own cells in that they can perform chemical reactions which our cells have "forgotten" how to do. Their vitamins are "home made" while those of man must be obtained in expensive foods or from even more expensive polyvitamin preparations. Autotrophic bacteria or other "primitive forms" are what they are because some living thing at some time learned to tap a source of energy that was otherwise going to waste and thereby obtained for itself some selective advantage.

It seems that dependence upon a dietary source of vitamins is one of the penalties higher species, including man, paid for specialization.

A corollary to this growing recognition that living things are similar in essential metabolism is an appreciation that anything learned about the metabolism of lower things will sooner or later have an application to man. Thus, a number of microbiologists are looking for bacterial growth factors not so much with the idea in mind of growing better bacteria but of ultimately finding factors which are similarly required by higher species under various dietary conditions. Indeed pantothenic acid, biotin, folic acid, vitamin B_{12}, nicotinic acid, to name only a few, were discovered as bacterial vitamins before their role or usefulness in the nutrition of higher species was fully established.

The essential nature of certain vitamins for various bacteria forms the basis for microbiological methods for determining many of the vitamins. There are no known chemical tests for determining pantothenic acid, biotin, or folic acid. In other instances where chemical or animal assays are available, microbiological methods of assay frequently are superior. It is safe to say that we know what we do about the biochemistry of the B vitamins and about their role in metabolism primarily because of the



Enflamed and crusty skin characteristic of pellagra. This B vitamin deficiency disease has almost disappeared from the U. S.

Tissue edema, a characteristic of Kwashiorkor. This is one of the most widespread nutritional diseases of tropical and subtropical climates. The active components of high protein sources which alleviate this condition have not yet been identified

availability of such sensitive, precise, and even simple methods of assay. It is tempting to speculate what could be accomplished in the field of the fat-soluble vitamins or even in the unrelated field of the hormones if corresponding methods of microbiological assay were available.

The Future of the Vitamins

Someone with a whimsical sense once predicted that there are 26 vitamins, one for each letter of the alphabet. The use of letters combined with subscripts has played havoc with this prognostication. With the discovery, isolation, and elucidation of each new vitamin the opinion is usually expressed by some that this is the last one. The advent of vitamin B_{12}, a compound with remarkable significance in human and animal nutrition, postponed these thoughts for a time but they are again being expounded by some. A few random thoughts may be cited to indicate that the last of the vitamins is not yet at hand.

No single species of higher animal has been grown normally and carried through a number of generations on a synthetic diet—at least not as an organic chemist understands the term. While such a feat would have considerable academic interest, a complete knowledge of the vitamin requirements of the chick, for example, so that this species could be grown at an optimal rate on certain low-cost feeds would have added practical significance.

A disease of small children called Kwashiorkor described as one of the most widespread nutritional disorders in tropical and subtropical areas presents a challenge to nutritionists. The condition is characterized by retarded growth in the late breast-feeding, weaning, and postweaning ages; alteration in skin and hair pigmentation; edema, fatty infiltration, cellular necrosis, or fibrosis of the liver; and a high mortality rate (30 to 90%) when untreated. Mental apathy, anemia, and a variety of dermatoses and gastro-intestinal disorders are commonly associated with but are not essential components of this syndrome. It is known that supplementing the disease-producing diet (largely plantains, cassava, and tubers) with milk, meat, fish, or beans brings about relief. The active components of such supplements is unknown. There is considerable acceptance among workers in the field that the active ingredient is a vitamin or other minor component of the diet. The elucidation of this factor so that it could be made available to those afflicted would be an achievement, to put it mildly.

Ulcers of some portion of the digestive tract is a disease that affects many individuals the world over. It is estimated that there are 8,460,000 patients in the United States who will be under treatment this year for peptic ulcer. Of this number, one-fourth, or two million, will be new cases under treatment for the first time. Over six million cases will represent those diagnosed in prior years but still under treatment. The extent to which we fail to treat all gastric ulcer patients is indicated by the result of autopsies, indicating that from 10 to 12% of the entire population had ulcers some time during their lifetime. While ulcers are commonly considered to be of neurological origin, Cheney has reported that the condition may be produced experimentally in animals and cured or prevented by certain unheated dietary supplements presumably because of a preventive factor or vitamin that they contain. The factor is claimed to be especially prevalent in raw cabbage and has been designated as vitamin U. The curative effects of raw cabbage extracts are now under study in human patients. If preliminary favorable results can be confirmed and extended *ad consequentiam*, then one more disease will join the growing list now recognized to be of nutritional etiology and curable with the appropriate dietary component.