Vitamins of the B Complex

GRACE A. GOLDSMITH

AN investigation of beriberi in the late 19th century started the chain of events that led to the discovery of vitamins. Beriberi had long been a common and a serious disease in parts of the world where polished rice was the staple food.

Christiaan Eijkman, a Dutch surgeon, was carrying out studies on fowls in a military hospital in Java in the 1890's. To save money, he fed them scraps—mostly polished rice—from the patients' meals. The fowls unexpectedly developed a bad nerve ailment, which resulted in paralysis.

Somewhat later the director of the hospital withheld permission to use the scraps, and Dr. Eijkman had to buy natural or undermilled rice for the chickens he used in his experiments. The ailing birds improved after they began eating the natural rice.

Dr. Eijkman then began a series of experiments that led to the first clear concept of disease due to nutritional deficiency. He fed polished white rice to pigeons, chickens, and ducks. They developed the paralysis he had observed previously, and they recovered when he fed them natural rice. Birds fed whole rice remained well.

He noted that the disease that resulted from a polished rice diet in birds resembled beriberi in man.

He believed that rice contained too much starch, which poisoned nerve cells, and that the outer layers, removed from the grain in milling, were an antidote. His report was published in Dutch, and some time elapsed before it was known generally.

G. Grijns, another Dutch physician, interpreted Dr. Eijkman's findings in a different way. He concluded in 1901 that beriberi in birds or man was due to a deficiency or absence of an essential nutrient from the diet.

From then on, chemists in many countries tried to concentrate the substance in rice that prevented beriberi in order to obtain it in pure form. Among them was Casimir Funk, of the Lister Institute, London, who coined the term "vitamine" and applied it to the antiberiberi substance.

B. C. P. Jansen and W. P. Donath in Holland in 1926 isolated the antiberiberi vitamin, and in the 1930's

Robert R. Williams and his associates determined its structure and synthesized it.

Thus men discovered the cause and cure of beriberi, which nevertheless remains a serious disease today in countries in which overpolished and overmilled rice is a staple in the diet.

During the first stages of separating and identifying vitamins, the designation "water-soluble B" was given by Dr. Elmer V. McCollum and Marguerite Davis to the concentrates that cured beriberi. Vitamin B at that time was thought to be a single substance. Later research showed that it consists of a number of substances that differ widely in chemical structure but have much the same natural distribution in foods.

Of the 11 substances in the vitamin B complex that now are available in pure form, five are components of one or more coenzymes—thiamine, riboflavin, niacin, pyridoxine, and pantothenic acid. Coenzymes are catalysts that have important and often related functions in the biochemical processes by means of which nutrients are used for energy and for building up or maintaining the cells and tissues of the body.

Two of the B vitamins, folic acid and vitamin B_{12}, have antianemic properties and presumably exert their function in a similar way—that is, as coenzymes.

These seven vitamins are essential in human nutrition and must be included in the daily diet.

Of the other four members of the B complex, choline is important in human nutrition but is probably not an essential dietary constituent because the body can form it from other compounds.

Very likely biotin is required by man, but it is furnished by bacterial synthesis in the intestinal tract as well as by food.

Inositol and p-aminobenzoic acid, other members of the B complex, have not been shown to be essential in human nutrition.

A LACK OF VITAMINS of the B complex is one of the forms of malnutrition that often occur throughout the world. Because of the similar distribution of the B vitamins in foods, a deficiency of several factors is observed oftener than a deficiency of a single substance. The interrelationship of many of these vitamins in life processes means that signs of deficiency often are similar when the diet lacks any one of several factors.

Many physiologic and pathologic stresses influence the need for the B vitamins. Larger amounts are needed during growth and in pregnancy and lactation than in maintenance of health in adult life. The requirement may be increased by diseases that elevate metabolism and by conditions associated with poor absorption, improper utilization, or increased excretion. Administration of antibiotics may lead to vitamin deficiency in some circumstances; in others, antibiotics spare vitamin requirements.

THIAMINE, or vitamin B_1, also known as the antineuritic or antiberiberi vitamin, is a water-soluble compound. It is readily broken down by heat in neutral or alkaline solutions. Its solubility and the ease with which it is destroyed are important, because overcooking food and discarding the water in which the food is cooked may cause large amounts of the vitamin to be lost.

Thiamine is present in many natural foods but is abundant in few. Lean pork is one of the best sources. Dry beans and peas, certain of the organ meats, and some nuts furnish sizable amounts. Whole wheat and enriched cereals and bread are dependable sources. They can contribute valuable amounts to the diet. The small amounts provided by other foods, such as milk, eggs, other meat, fruit, and vegetables, add up and represent a worthwhile contribution to the diet.

The thiamine requirement is related to caloric intake. The minimum need is approximately 0.20 to 0.23 milligram per 1,000 Calories. This requirement is based on experiments in which

thiamine in the diet is restricted, on studies of diets of population groups, and on estimates of the amounts excreted in the urine of people having known intakes of thiamine.

The requirement of infants in relation to Calories appears to be comparable to that of the adult. Human milk supplies an average of 0.21 milligram per 1,000 Calories. We have evidence that the ratio of carbohydrate to fat in the diet influences the requirement.

The recommended dietary allowance for thiamine is 0.5 milligram per 1,000 Calories. When an adult's diet furnishes fewer than 2,000 Calories a day, the thiamine allowance should not be less than 1 milligram daily. This allowance provides a large factor of safety above the minimum need and seems desirable because requirements vary among individuals and because stores of thiamine in the body are not large and may be exhausted readily in diseases associated with an increase in metabolism.

Bacteria in the intestines may synthesize some thiamine, but the amount available to the human body to supplement the dietary supply seems to be small.

Thiamine is absorbed readily from the intestinal tract. It is excreted in the urine in amounts that reflect the amount taken in and the amounts stored in tissues. Measurement of the urinary excretion of thiamine after giving a small dose of thiamine is useful in determining whether body stores are adequate or deficient.

Thiamine functions in the body as a coenzyme, which is called cocarboxylase. It acts as a catalyst in one of the chemical reactions by which glucose (sugar) is broken down in the tissues to supply energy. These reactions proceed stepwise, and cocarboxylase acts at an intermediate stage when a substance known as pyruvic acid has been formed.

In thiamine deficiency, pyruvic acid accumulates in the blood and tissues and there is a change in the ratio of this acid to lactic acid. These metabolic changes are magnified by administration of glucose and by exercise and form the basis of a diagnostic test for thiamine deficiency. The concentration of glucose, lactic acid, and pyruvic acid in blood is determined after the administration of glucose and a standard amount of exercise. Results are expressed as a "carbohydrate index," which increases in thiamine deficiency.

Thiamine deficiency has been produced experimentally in people. Effects of a moderate shortage of thiamine include fatigability; apathy; loss of appetite; nausea; such psychic and personality disturbances as moodiness, irritability, and depression; a sensation of numbness in the legs; and abnormalities of the electrocardiogram.

Advanced deficiency of thiamine, or beriberi, is characterized by peripheral neuritis, heart disease, and edema. Peripheral neuritis is a disease of the nerves of the extremities; usually both legs are affected and sometimes the arms as well. The symptoms include loss of sensation, muscle weakness, and paralysis.

A deficiency of thiamine can also cause damage to the brain, which may be manifested by confusion, delirium, and paralysis of the muscles that move the eyeballs. This condition is called Wernicke's syndrome.

RIBOFLAVIN, formerly known as vitamin B_2 or G, is a water-soluble, yellow pigment. It is widely distributed in foods of plant and animal origin. It is stable to heat, especially in acid solutions, but it is destroyed on exposure to light.

Among the best sources of riboflavin are milk and variety meats, like liver, heart, and kidney. Other lean meat, cheese, eggs, and many of the leafy, green vegetables also furnish valuable amounts. Whole-grain and enriched cereals and bread, in the amounts in which they are eaten in this country, contribute important amounts of riboflavin to the diet.

Pasteurizing and drying milk do not lower its riboflavin content very

much, but exposure to sunlight destroys large amounts of the vitamin.

The minimal daily requirement of riboflavin is about 0.6 to 0.7 milligram for adults and 0.4 to 0.5 milligram for infants. Considerable evidence indicates that an intake of 1.1 to 1.6 milligrams daily will provide adequate body stores.

The need for riboflavin does not seem to be related to caloric consumption but may be related to body weight. Both riboflavin and protein requirements are increased by similar conditions, such as growth, pregnancy, and lactation. Riboflavin allowances accordingly are computed from the protein allowances; a factor of 0.025 is used. Recommendations for men and women are 1.8 and 1.5 milligrams daily, respectively.

The recommended intake during the second half of pregnancy is 2 milligrams. During lactation it is 2.5 milligrams. The allowance for infants is 0.5 to 0.8 milligram daily.

Chemical research on riboflavin started in 1879, but its function and importance in nutrition were not understood fully until the 1930's. Otto Warburg and W. Christian of Germany in 1932 studied a yellow enzyme in yeast and were able to split it into a protein and a pigment (flavin).

Later research disclosed riboflavin to be an essential human nutrient, which is combined with protein in the body to form a number of important enzymes. These flavoproteins function in the respiration of tissue and act closely with enzymes containing niacin, another B vitamin. Some flavoproteins are known as oxidases since they catalyze the oxidation of various chemical substances.

The functional association of riboflavin and niacin-containing enzymes helps to explain the similarity of certain findings in deficiency of these two vitamins.

Deficiency of either may result in soreness and redness of the tongue and lips, atrophy of papillae on the surface of the tongue, and cracks at the angles of the mouth. In riboflavin deficiency, dermatitis of the greasy type often involves the scrotum and may affect the face and ears. Another finding is injection of the blood vessels of the eye and growth of the vessels into the cornea, which normally does not contain these vessels.

In animals, too little riboflavin during pregnancy may result in abnormalities in the embryo or in abortion. We do not know whether any congenital defects in man may be due to an inadequate supply of riboflavin in the mother.

Chemical tests are available for estimating the adequacy of riboflavin nutrition. The amount excreted in the urine can be measured and tends to reflect dietary supply and body stores. One feature of riboflavin metabolism can markedly influence the test, however. Riboflavin is excreted when protein of the body is being broken down; it is retained when protein is being accumulated. Thus, in acute starvation, uncontrolled diabetes mellitus, and other conditions associated with negative nitrogen balance, excretion in the urine does not reflect body stores.

The concentration of riboflavin in red blood cells is under investigation as a measure of adequacy of riboflavin intake. This test may prove useful in determining nutritional status.

NIACIN, the pellagra-preventing vitamin, was discovered after long search. Its elusiveness may be explained partly by a recent finding that one of the amino acids, tryptophan, is a precursor of niacin.

Pellagra was known to be associated with a poor, monotonous diet high in corn, since the disease was first described in the 18th century by Gaspar Casal in Spain and Francesco Frapoli in Italy. Theories regarding the cause of pellagra were many. For years, the disease was believed to be due to a toxic or infectious substance in spoiled corn. Early in the present century, Casimir Funk suggested that

pellagra was due to vitamin deficiency. Investigators in Egypt held that the disease was related to lack of an essential amino acid, probably tryptophan. The investigations of Joseph Goldberger, beginning about 1914, demonstrated that pellagra is due to a nutritional deficiency.

Conrad Elvehjem and his associates at the University of Wisconsin in 1937 discovered that niacin (nicotinic acid) cured blacktongue in dogs, a condition previously recognized as similar to pellagra in human beings. Shortly thereafter niacin was shown to be effective in the prevention and treatment of pellagra.

The whole story was not yet complete, however. Diets in parts of the world in which pellagra was rare contained less niacin than did diets in areas in which pellagra was common. Furthermore, some foods such as milk are low in niacin but they effectively prevent pellagra. These discrepancies were cleared up after the discovery by Willard Krehl and his associates in the University of Wisconsin in 1945 that either tryptophan or niacin could counteract a retarded growth in rats produced by diets high in corn. Tryptophan has been shown since then to be a precursor of niacin in many animal species, and the steps by which this amino acid is converted to niacin have been determined.

We found that administration of tryptophan to people was followed by an increased urinary excretion of niacin derivatives and that tryptophan was effective in the treatment of pellagra. Similar findings were reported by other investigators. The efficacy of tryptophan as a precursor of niacin was studied in our laboratory in the Tulane University School of Medicine and by Max K. Horwitt and his associates. Approximately 60 milligrams of dietary tryptophan furnish 1 milligram of niacin, although there is wide variation in this conversion ratio among individuals.

Most foods that are high in animal protein are also high in tryptophan. Gelatin is an exception; it has almost no tryptophan. Lean meat and poultry are good sources of both tryptophan and niacin.

Among plant sources, peanuts are outstanding in niacin and are also among the best sources of tryptophan. Other plants that are good sources of both nutrients include beans, peas, other legumes, most nuts, and several whole-grain or enriched cereal products. Corn and rice are low in tryptophan. Oatmeal is low in niacin.

The requirement of niacin can be determined only in terms of both niacin and tryptophan intake. Our studies and those of Dr. Horwitt indicate that the minimum amount of niacin that will prevent pellagra in adults is about 9 milligrams daily. This includes the niacin formed from tryptophan, if we assume that 60 milligrams of tryptophan are equivalent to 1 milligram of niacin. The term "niacin equivalent" is useful for expressing this total potential niacin value of the diet.

Calculation of the niacin equivalent of the diets used by Dr. Goldberger, which resulted in pellagra, gives a figure of 12 milligrams. These diets were higher in Calories than those used by me and by Dr. Horwitt, and the niacin requirement appears to be related to caloric intake and to body weight.

Dr. Horwitt suggested a minimum need of 4.4 milligrams of niacin equivalent for each 1,000 Calories furnished by the diet.

We found the minimum requirement in relation to body weight to be slightly more than 0.10 milligram of niacin per kilogram when the diet furnished 200 milligrams of tryptophan.

Dr. Emmett Holt's studies and the calculation of the niacin equivalent received by breast-fed infants suggest that the requirement of infants is about 5 milligrams daily, if the conversion of tryptophan to niacin is comparable to that in adults.

Recommended dietary allowances

for niacin expressed as niacin equivalents are 17 to 21 milligrams for adults and 6 to 7 milligrams for infants. These amounts are 50 percent higher than the minimum need, calculated on the basis of caloric intake or body weight, whichever is the greater amount. The many uncertainties make this large factor of safety seem desirable.

Niacin functions in the body as a component of two coenzymes, diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN), in tissue respiration and glycolysis (the process by which sugar is broken down to produce energy). Niacinamide was found to be part of these coenzymes before its nutritional importance was discovered. They work in close association with enzymes that contain riboflavin.

Niacin deficiency is characterized by dermatitis, particularly of areas of skin which are exposed to light or injury; inflammation of mucous membranes, including the entire gastrointestinal tract, which results in a red, swollen, sore tongue and mouth, diarrhea, and rectal irritation; and psychic changes, such as irritability, anxiety, depression, and (in advanced pellagra) delirium, hallucinations, confusion, disorientation, and stupor.

In severe deficiency, hydrochloric acid may be absent from the gastric juice. The excretion of niacin metabolites in the urine falls to low levels. An excretion of less than 2 milligrams in 24 hours is typical of pellagra.

A deficiency of riboflavin often accompanies a deficiency of niacin. Thiamine deficiency may also be present at times.

VITAMIN B_6 consists of a group of three closely related substances, pyridoxine, pyridoxal, and pyridoxamine. They are widely distributed in foods and are present in both free and bound form.

The best sources of vitamin B_6 are muscle meats, liver, vegetables, and whole-grain cereals. The bran from the cereal grains has especially large amounts. Few foods can be classed as poor sources of this vitamin.

The exact requirement of vitamin B_6 has not been determined. Probably 1 to 2 milligrams daily should be enough for an adult, an amount readily provided by the average diet in the United States.

The need of infants can be supplied by milk, which contains 100 micrograms per liter.

In animals, vitamin B_6 requirement is increased by methionine (an amino acid), protein, and sucrose (cane sugar) and apparently is reduced by choline, essential fatty acids, biotin, and pantothenic acid. In the rat, vitamin B_6 is synthesized by intestinal organisms, and some of this seems to be available for metabolic needs. We do not know whether these findings apply to people.

Vitamin B_6 occurs in tissues predominantly as the phosphates of pyridoxal or pyridoxamine.

Pyridoxal phosphate functions as a coenzyme in a number of chemical reactions involving amino acids. This explains the increased need of the vitamin when diets are high in protein.

Enzymes containing vitamin B_6 are important in many reactions that provide material for the citric acid cycle, a metabolic pathway that furnishes energy for the body.

Vitamin B_6 has a role in the conversion of tryptophan to niacin derivatives. This function forms the basis of a test for deficiency of vitamin B_6. When a large amount of tryptophan is administered to deficient animals or man, xanthurenic acid is excreted in the urine in abnormal quantities. Vitamin B_6 may also function in the metabolism of essential fatty acids.

A deficiency of vitamin B_6 due solely to dietary inadequacy has not been observed in adults.

Deficiency has been reported in infants who received a liquid milk formula in which much of the vitamin B_6 was destroyed unknowingly in processing. The infants developed irritability, muscular twitchings, and con-

vulsive seizures. If vitamin B_6 is not supplied in adequate amounts, infants cease gaining weight and may develop anemia.

Experimental deficiency in adults has been produced by the administration of a pyridoxine antagonist, desoxypyridoxine. Symptoms included irritability, depression, and sleepiness. Other findings were a seborrheic (greasy) type of dermatitis, skin lesions that resembled pellagra, soreness of the tongue and lips, conjunctivitis, and peripheral neuritis. These abnormalities resemble those seen in deficiency of riboflavin, niacin, and thiamine and attest the close metabolic relationship of these vitamins of the B complex.

Vitamin B_6 metabolism may be altered during pregnancy, and the requirement may be increased. Pregnant women excrete abnormally large amounts of xanthurenic acid after the administration of tryptophan. There is also an abnormal response to administration of alanine, an amino acid. Blood urea nitrogen remains high for more than 12 hours. Similar findings have been observed in animals deficient in vitamin B_6.

Pyridoxine has been shown to prevent or alleviate the peripheral neuritis that may develop when isoniazid, an antituberculosis medication, is administered.

PANTOTHENIC ACID is needed by man and many species of animals.

It is widely distributed in foods. Liver and eggs, particularly good sources, contain 100–200 micrograms per gram. Broccoli, cauliflower, lean beef, skim milk, white potatoes and sweetpotatoes, tomatoes, and molasses are quite high in pantothenic acid.

The human requirement is unknown but is probably not above 5 milligrams daily.

Pantothenic acid has a vital role in metabolic processes as it is a constituent of coenzyme A. This coenzyme is required for acetylation, one of the essential chemical reactions of the body. An important compound, active acetate, is actually the acetylated coenzyme that reacts in numerous ways.

Coenzyme A occupies a central position in metabolism. It functions in the formation and breakdown of fatty acids and in the entry of fat and carbohydrate into the citric acid cycle, a series of chemical reactions that provide energy for the organism. Coenzyme A functions in the synthesis of the porphyrin part of the hemoglobin molecule and in the formation of sterols (such as cholesterol) and steroid hormones (formed by the adrenal and sex glands).

The symptoms of a deficiency of pantothenic acid in animals are more diverse than are observed for most other vitamins, perhaps because of the fundamental importance of coenzyme A in metabolism and the many reactions in which it participates.

A deficiency disease due to lack of pantothenic acid has not been observed in man. Diets may never be sufficiently low in this vitamin to produce deficiency.

William Bean and his associates at the State University of Iowa attempted to induce deficiency by administering a pantothenic acid antagonist, omega-methyl-pantothenic acid, to volunteer subjects who were receiving a diet devoid of pantothenic acid.

(A vitamin antagonist is a substance so similar in structure to the vitamin that the body accepts it in place of the vitamin, but the antagonist is unable to perform the functions of the true vitamin.)

Numerous physical and biochemical disturbances resulted. The subjects became quarrelsome, sullen, and petulant. Some of them developed pains and disturbances of sensation in the arms and legs. Others noted loss of appetite, indigestion, and nausea. Fainting attacks were common. The pulse tended to be unduly rapid. There seemed to be an increase in susceptibility to infection. Laboratory tests showed many abnormal findings related to the numerous functions of pantothenic acid in the chemical reactions of the body.

A deficiency of pantothenic acid may be responsible for the "burning foot syndrome," which is encountered in places where other B complex deficiencies are common. This condition has been reported to respond to doses of pantothenic acid.

Other studies indicate that pantothenic acid may influence the reaction of human subjects to stress.

THE FOLIC ACID group of vitamins are essential for many animal species. They are necessary for the formation of blood cells in man.

Members of this group include folacin (or pteroylglutamic acid), pteroyltriglutamic acid, pteroylheptaglutamic acid, and folinic acid or citrovorum factor, a derivative of folic acid that occurs in natural materials in both free and combined form.

Information is meager concerning the amounts of folacin and folinic acid compounds in foods and their biological availability. Enzymes that can break down conjugated pteroylglutamates (combined forms of folic acid) to folacin occur in many animal tissues. In several natural products, these enzymes or conjugases are accompanied by an inhibitor. This inhibitor appears to influence the availability of the combined forms of folacin to human subjects. These findings illustrate the difficulties involved in estimating the folacin that is available from foods and in determining the human need for it.

The best sources include liver, dry beans, lentils, cowpeas, asparagus, broccoli, spinach, and collards. Other good sources include kidney, peanuts, filberts, walnuts, immature or young lima beans, cabbage, sweet corn, chard, turnip greens, lettuce, beet greens, and whole-wheat products.

Intestinal bacteria synthesize folacin. This source may be important in man, because experimental deficiency has not been induced by diets low in folacin. The dietary requirement of folacin is not known, but available evidence suggests that approximately 0.1 to 0.2 milligram daily may suffice.

Much has been learned about the function of folacin and its derivatives, although their exact metabolic role has not been delineated. It seems likely that a derivative of folinic acid is the functioning form of the vitamin and that this derivative combines with a protein and functions as a coenzyme. Folacin participates in the formation by the body of complex chemical compounds known as purines and pyrimidines that are utilized in the building up of nucleoproteins—that is, proteins that are found in the nucleus of every cell.

The essentiality of folacin for hematopoiesis (the manufacture of blood cells) in man presumably resides in its function in the formation of purines and pyrimidines.

Folic acid stimulates the formation of blood cells in certain anemias, which are characterized by oversized red cells and the accumulation in the bone marrow of immature red blood cells, called megaloblasts. The bone marrow is the organ that manufactures blood cells. It cannot complete the process in the absence of folic acid. Vitamin B_{12} also is needed for the formation of blood cells and is effective in the treatment of many anemias.

The exact biochemical interrelationships of these two vitamins in metabolism have not been clarified. Vitamin B_{12}, like folacin, seems necessary for the formation of nucleoproteins.

Two human anemias appear to be due primarily to folacin deficiency—macrocytic anemia of pregnancy and megaloblastic anemia of infancy. These anemias occasionally respond to treatment with vitamin B_{12}.

Sprue and nutritional macrocytic anemia often improve when either folacin or vitamin B_{12} is administered. Sprue is a disease in which absorption of food from the intestinal tract is seriously impaired, and the stools contain large amounts of fat. Folacin may improve absorption in this condition.

In pernicious anemia, treatment with folacin may bring the blood status

to normal, but relapse occurs. Damage to the spinal cord and peripheral nerves, which is a common finding in pernicious anemia, is neither prevented nor alleviated.

The mechanism by which deficiency of folacin develops is not clear. The deficiency may be of dietary origin in some instances but not in others. Defective absorption may explain deficiency at times.

Macrocytic anemia of pregnancy may be related to an increased folacin requirement that is not met by the diet. Folacin has a role in the reproductive process in animals.

The syndrome of folacin deficiency in man is exemplified best by the symptoms that develop when large amounts of a folic acid antagonist such as aminopterin are administered. Manifestations include glossitis (a sore, red, smooth tongue), diarrhea, gastrointestinal lesions, and anemia. Similar findings occur in sprue and nutritional macrocytic anemia; they often revert to normal with folacin therapy.

Folacin is functionally related to ascorbic acid. Megaloblastic anemia of infancy occurs in infants receiving diets deficient in ascorbic acid. It can be prevented by ascorbic acid but responds to treatment only with folacin or folinic acid.

Folacin is related to the metabolism of the amino acid tyrosine, and so is ascorbic acid. An abnormal excretion of tyrosine metabolites in the urine occurs in infants who lack ascorbic acid. Administration of ascorbic acid or large doses of folacin relieve the abnormality.

VITAMIN B_{12}, like many other members of the B complex, is not a single substance but consists of several closely related compounds with similar activity. The term "cobalamin" is applied to this group of substances because they contain cobalt. Vitamin B_{12} is cyanocobalamin, named for the cyanide ion in the molecule. Other compounds are hydroxycobalamin and nitritocobalamin.

The search for vitamin B_{12}, which is the antipernicious anemia factor of liver, forms an interesting chapter in medical investigation. Pernicious anemia was an incurable disease until 1926, when George R. Minot and William P. Murphy, of Boston, showed that feeding whole liver was effective therapy. William Castle and his associates at Harvard demonstrated that mixtures of beef muscle and normal gastric juice would also induce remission in pernicious anemia. Beef muscle alone and beef muscle and the gastric juice of a patient with pernicious anemia were ineffectual.

Castle postulated that a substance in gastric juice (intrinsic factor) combined with a substance in food (extrinsic factor) to form the antipernicious anemia factor of liver. Intrinsic factor was absent from the gastric juice of patients who had pernicious anemia.

As each new B vitamin was discovered, it was tested for antipernicious anemia activity. Folic acid at first was thought to be the active principle of liver, as it caused improvement in the blood picture in pernicious anemia.

Later study indicated that folic acid would not maintain normal blood status and failed to influence the neurologic changes that occur in this disease. A serious handicap in the search for the antipernicious anemia factor was the need to test all materials in human subjects who had pernicious anemia in relapse. No animal developed a comparable disease.

Mary Shorb, of the University of Maryland, in 1947 found that liver extract contained a growth factor that was required by a micro-organism, *Lactobacillus lactis* Dorner. Using this microbiological assay, Edward L. Rickes and his associates, at Rahway, N.J., isolated B_{12} in 1948.

Lester Smith, in England, at about the same time isolated the vitamin by procedures designed to obtain in pure form the red pigment that gave color to active preparations of liver.

Vitamin B_{12} was shown to be effective in the treatment of pernicious anemia by Randolph West, of Columbia University, and others.

Subsequently it was discovered that vitamin B_{12} is not only the antipernicious anemia factor of liver but also the extrinsic factor of food.

Intrinsic factor of gastric juice appears to be necessary for the absorption of vitamin B_{12}, but the mechanism of action has not been determined.

Intrinsic factor may have other functions as well. We have found that intrinsic factor will increase the binding of vitamin B_{12} by proteins in tissues and in human serum.

Vitamin B_{12} is found in animal protein foods. The best sources are liver and kidney. Other sources are muscle meats, milk, cheese, fish, and eggs. As far as we know, fruit and vegetables do not furnish any vitamin B_{12}.

The dietary requirement for the vitamin is unknown. A normal diet is estimated to contain 8 to 15 micrograms. The daily administration by injection of 1 microgram will induce remission in pernicious anemia. The normal adult presumably needs to absorb an amount no larger than this.

The biological availability of vitamin B_{12} in the diet has not been determined.

Much remains to be learned about the specific functions of vitamin B_{12} in bodily processes. It appears to be involved in the synthesis of nucleoproteins through participation in the metabolism of purines and pyrimidines. The close relationship to folic acid in stimulating blood regeneration has been discussed. The specific role of this vitamin in the metabolism of nerve tissue has not been determined.

Vitamin B_{12} is essential for the growth of animals. It may have a growth-promoting effect in man in certain conditions of diet and nutrition.

Pernicious anemia is the most important human disease that is due to too little vitamin B_{12}. The deficiency is not due to dietary inadequacy but to failure of absorption of the vitamin from the intestinal tract in the absence of intrinsic factor from the gastric juice.

Pernicious anemia is characterized by degenerative lesions in the spinal cord and peripheral nerves as well as by macrocytic (large cell) anemia.

The concentration of vitamin B_{12} in blood is extremely low. Failure of absorption of vitamin B_{12} can be demonstrated by administration of Co^{60} vitamin B_{12}—that is, vitamin B_{12} containing radioactive cobalt. If intrinsic factor is given with Co^{60} vitamin B_{12}, absorption is increased to normal.

Macrocytic anemia that follows surgical removal of the stomach is due to failure of absorption of vitamin B_{12}, as in pernicious anemia. Sprue may be associated with a deficiency of vitamin B_{12}, as are some other syndromes due to intestinal malabsorption. In these situations, there is failure of absorption of vitamin B_{12}, even when intrinsic factor is administered with the vitamin.

A deficiency of vitamin B_{12} due to dietary inadequacy is rare. Only two cases of severe macrocytic anemia on this basis have been reported. A small percentage of persons who subsist for years on a strict vegetarian diet, however, have been found to develop other signs of vitamin B_{12} deficiency. Soreness of the mouth and tongue, numbness and tingling of the hands, pains in the back, and (in one instance) combined degeneration of the spinal cord have been observed. Levels of vitamin B_{12} in the blood are lower than normal in vegetarians.

CHOLINE is not a vitamin in the strict sense. It is classified usually as a member of the vitamin B complex. It is an essential nutrient in that methyl groups (part of the choline molecule) must be included in the diet. The amino acid methionine (in protein) and betaine are other dietary sources of methyl groups. It seems likely that choline and methionine are not completely interchangeable as sources of methyl in all species.

A dietary requirement for choline cannot be given, since the compound can be manufactured in the body and

the need for choline depends also on other sources of methyl groups. The average diet contains 250 to 600 milligrams of choline.

Foods that supply large amounts of choline are liver, kidney, brain, muscle meats, nuts, beans, peas, and skim milk. Moderate amounts exist in cereals and a number of vegetables.

Choline functions in the body as a source of labile methyl groups and in the formation of phospholipids, a class of fatty substances found in all body tissues.

The most important phospholipids are lecithin, cephalin, and sphingomyelin. These compounds are found especially in nerve tissue. Lecithin and cephalin are present in egg yolks. Choline is a component of the compound acetylcholine, which functions in the transmission of nerve impulses across neuromuscular junctions.

Labile methyl groups are used in the synthesis of creatine, N^1-methylnicotinamide (an excretion product of niacin) and probably other vital substances, such as epinephrine, the hormone of the adrenal medulla. Methyl groups have a lipotropic function—that is, they prevent the accumulation of fat in the liver.

Choline deficiency leads to many abnormal findings in various animal species, among them hemorrhagic lesions in the kidney.

Incomplete evidence suggests that choline may have an influence on fatty infiltration of the liver in man. Choline, methionine, vitamin B_{12}, and folic acid are interrelated in the prevention of fatty livers in animals under certain dietary conditions.

BIOTIN is needed in animal nutrition and presumably is essential for man. It is present in many foods and is synthesized by the intestinal bacteria. The urinary excretion of biotin in humans at times is greater than the intake.

Liver, milk, meat, nuts, egg yolk, most vegetables, and a number of fruits (bananas, grapefruit, tomatoes, watermelon, and strawberries) contain significant amounts of biotin.

It seems unlikely that a dietary deficiency of biotin occurs in human beings. The requirement has not been determined.

Biotin seems to be an essential component of a coenzyme in carbon dioxide fixation, an important reaction in intermediary metabolism. Considerable data suggest that one manifestation of this role of biotin is a requirement for purine synthesis. Biotin is the anti-egg-white injury factor. Raw egg white contains the protein, avidin, which combines with biotin to prevent its absorption.

Virgil Sydenstricker and associates at the University of Georgia produced experimental deficiency of biotin in people by feeding large amounts of raw egg white. Manifestations included a dry, scaly dermatitis and changes in the color of the skin. Nervous symptoms, tongue lesions, and abnormalities in the electrocardiogram were noted—findings similar to those produced by deficiency of other vitamins of the B complex.

GRACE A. GOLDSMITH, M.D., *is professor of medicine in the Tulane University School of Medicine, New Orleans. She also is consultant physician, Charity Hospital of Louisiana, New Orleans; chairman, Food and Nutrition Board, National Academy of Sciences-National Research Council; and member of the Council on Foods and Nutrition of the American Medical Association.*

If all that we know about nutrition were applied to modern society, the result would be an enormous improvement in public health, at least equal to that which resulted when the germ theory of infectious disease was made the basis of public health and medical work.—FRANK G. BOUDREAU, M.D.

We know that a lot of people who are regarded as poor prospects for jobs need food. They are set down in personnel records as lazy and dumb. What is really wrong with them is that they are hungry.—PAUL V. MCNUTT.