the remaining protein is not so easily removed. At this time, the rate of gluconeogenesis decreases to one third to one fifth its previous rate, and the rate of depletion of protein becomes greatly decreased. The lessened availability of glucose then initiates a series of events that leads to excessive fat utilization and conversion of some of the fat breakdown products to ketone bodies, producing the state of *ketosis,* which is discussed in Chapter 68. The ketone bodies, like glucose, can cross the blood-brain barrier and can be used by the brain cells for energy. Therefore, about two thirds of the brain's energy is now derived from these ketone bodies, principally from beta-hydroxybutyrate. This sequence of events leads to at least partial preservation of the protein stores of the body.

There finally comes a time when the fat stores are almost depleted, and the only remaining source of energy is protein. At that time, the protein stores once again enter a stage of rapid depletion. Because proteins are also essential for the maintenance of cellular function, death ordinarily ensues when the proteins of the body have been depleted to about half their normal level.

Vitamin Deficiencies in Starvation. The stores of some of the vitamins, especially the water-soluble vitamins—the vitamin B group and vitamin C—do not last long during starvation. Consequently, after a week or more of starvation, mild vitamin deficiencies usually begin to appear, and after several weeks, severe vitamin deficiencies can occur. These deficiencies can add to the debility that leads to death.

Vitamins

Daily Requirements of Vitamins. A vitamin is an organic compound needed in small quantities for normal metabolism that cannot be manufactured in the cells of the body. Lack of vitamins in the diet can cause important metabolic deficits. Table 71–3 lists the amounts of important vitamins required daily by the average person. These requirements vary considerably, depending on such factors as body size, rate of growth, amount of exercise, and pregnancy.

Storage of Vitamins in the Body. Vitamins are stored to a slight extent in all cells. Some vitamins are stored to a major extent in the liver. For instance, the quantity of vitamin A stored in the liver may be sufficient to maintain a person for 5 to 10 months without any intake of vitamin A. The quantity of vitamin D stored in the liver is usually sufficient to maintain a person for 2 to 4 months without any additional intake of vitamin D.

The storage of most water-soluble vitamins is relatively slight. This applies especially to most vitamin B compounds. When a person's diet is deficient in vitamin B compounds, clinical symptoms of the deficiency can sometimes be recognized within a few days (except for vitamin B_{12}, which can last in the liver in a bound form for a year or longer). Absence of vitamin C, another water-soluble vitamin, can cause symptoms within a few weeks and can cause death from scurvy in 20 to 30 weeks.

Table 71–3

Required Daily Amounts of Vitamins

Vitamin	Amount
A	5000 IU
Thiamine	1.5 mg
Riboflavin	1.8 mg
Niacin	20 mg
Ascorbic acid	45 mg
D	400 IU
E	15 IU
K	70 μg
Folic acid	0.4 mg
B_{12}	3 μg
Pyridoxine	2 mg
Pantothenic acid	Unknown

Vitamin A

Vitamin A occurs in animal tissues as *retinol.* This vitamin does not occur in foods of vegetable origin, but *provitamins* for the formation of vitamin A do occur in abundance in many vegetable foods. These are the yellow and red *carotenoid pigments,* which, because their chemical structures are similar to that of vitamin A, can be changed into vitamin A in the liver.

Vitamin A Deficiency Causes "Night Blindness" and Abnormal Epithelial Cell Growth. One basic function of vitamin A is its use in the formation of the retinal pigments of the eye, which is discussed in Chapter 50. Vitamin A is needed to form the visual pigments and, therefore, to prevent night blindness.

Vitamin A is also necessary for normal growth of most cells of the body and especially for normal growth and proliferation of the different types of epithelial cells. When vitamin A is lacking, the epithelial structures of the body tend to become stratified and keratinized. Vitamin A deficiency manifests itself by (1) scaliness of the skin and sometimes acne; (2) failure of growth of young animals, including cessation of skeletal growth; (3) failure of reproduction, associated especially with atrophy of the germinal epithelium of the testes and sometimes with interruption of the female sexual cycle; and (4) keratinization of the cornea, with resultant corneal opacity and blindness.

In vitamin A deficiency, the damaged epithelial structures often become infected, for example, the conjunctivae of the eyes, the linings of the urinary tract, and the respiratory passages. Vitamin A has been called an "anti-infection" vitamin.

Thiamine (Vitamin B_1)

Thiamine operates in the metabolic systems of the body principally as *thiamine pyrophosphate;* this compound functions as a *cocarboxylase,* operating mainly in conjunction with a protein decarboxylase for decarboxylation of pyruvic acid and other α-keto acids, as discussed in Chapter 67.

Thiamine deficiency *(beriberi)* causes decreased utilization of pyruvic acid and some amino acids by the tissues, but increased utilization of fats. Thus, thiamine is specifically needed for the final metabolism of carbohydrates and many amino acids. The decreased utilization of these nutrients is responsible for many debilities associated with thiamine deficiency.

Thiamine Deficiency Causes Lesions of the Central and Peripheral Nervous Systems. The central nervous system normally depends almost entirely on the metabolism of carbohydrates for its energy. In thiamine deficiency, the utilization of glucose by nervous tissue may be decreased 50 to 60 per cent and is replaced by the utilization of ketone bodies derived from fat metabolism. The neuronal cells of the central nervous system frequently show chromatolysis and swelling during thiamine deficiency, changes that are characteristic of neuronal cells with poor nutrition. These changes can disrupt communication in many portions of the central nervous system.

Thiamine deficiency can cause *degeneration of myelin sheaths* of nerve fibers in both the peripheral nerves and the central nervous system. Lesions in the peripheral nerves frequently cause them to become extremely irritable, resulting in "polyneuritis," characterized by pain radiating along the course of one or many peripheral nerves. Also, fiber tracts in the cord can degenerate to such an extent that *paralysis* occasionally results; even in the absence of paralysis, the muscles atrophy, resulting in severe weakness.

Thiamine Deficiency Weakens the Heart and Causes Peripheral Vasodilation. A person with severe thiamine deficiency eventually develops *cardiac failure* because of weakened cardiac muscle. Further, the venous return of blood to the heart may be increased to as much as two times normal. This occurs because thiamine deficiency causes *peripheral vasodilation* throughout the circulatory system, presumably as a result of decreased release of metabolic energy in the tissues, leading to local vascular dilation. The cardiac effects of thiamine deficiency are due partly to high blood flow into the heart and partly to primary weakness of the cardiac muscle. *Peripheral edema* and *ascites* also occur to a major extent in some people with thiamine deficiency, mainly because of cardiac failure.

Thiamine Deficiency Causes Gastrointestinal Tract Disturbances. Among the gastrointestinal symptoms of thiamine deficiency are indigestion, severe constipation, anorexia, gastric atony, and hypochlorhydria. All these effects presumably result from failure of the smooth muscle and glands of the gastrointestinal tract to derive sufficient energy from carbohydrate metabolism.

The overall picture of thiamine deficiency, including polyneuritis, cardiovascular symptoms, and gastrointestinal disorders, is frequently referred to as beriberi—especially when the cardiovascular symptoms predominate.

Niacin

Niacin, also called *nicotinic acid,* functions in the body as coenzymes in the form of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are hydrogen acceptors; they combine with hydrogen atoms as they are removed from food substrates by many types of dehydrogenases. The typical operation of both these coenzymes is presented in Chapter 67. When a deficiency of niacin exists, the normal rate of dehydrogenation cannot be maintained; therefore, oxidative delivery of energy from the foodstuffs to the functioning elements of all cells cannot occur at normal rates.

In the early stages of niacin deficiency, simple physiologic changes such as muscle weakness and poor glandular secretion may occur, but in severe niacin deficiency, actual tissue death ensues. Pathological lesions appear in many parts of the central nervous system, and permanent dementia or many types of psychoses may result. Also, the skin develops a cracked, pigmented scaliness in areas that are exposed to mechanical irritation or sun irradiation; thus, it appears that in persons with niacin deficiency, the skin is unable to repair irritative damage.

Niacin deficiency causes intense irritation and inflammation of the mucous membranes of the mouth and other portions of the gastrointestinal tract, resulting in many digestive abnormalities that can lead to widespread gastrointestinal hemorrhage in severe cases. It is possible that this results from generalized depression of metabolism in the gastrointestinal epithelium and failure of appropriate epithelial repair.

The clinical entity called *pellagra* and the canine disease called *black tongue* are caused mainly by niacin deficiency. Pellagra is greatly exacerbated in people on a corn diet, because corn is deficient in the amino acid tryptophan, which can be converted in limited quantities to niacin in the body.

Riboflavin (Vitamin B_2)

Riboflavin normally combines in the tissues with phosphoric acid to form two coenzymes, *flavin mononucleotide (FMN)* and *flavin adenine dinucleotide (FAD).* They operate as hydrogen carriers in important oxidative systems of the mitochondria. NAD, operating in association with specific dehydrogenases, usually accepts hydrogen removed from various food substrates and then passes the hydrogen to FMN or FAD; finally, the hydrogen is released as an ion into the mitochondrial matrix to become oxidized by oxygen (described in Chapter 67).

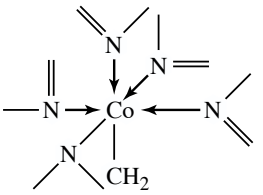
Deficiency of riboflavin in experimental animals causes severe dermatitis, vomiting, diarrhea, muscle spasticity that finally becomes muscle weakness, coma and decline in body temperature, and then death. Thus, severe riboflavin deficiency can cause many of the same effects as a lack of niacin in the diet; presumably, the debilities that result in each instance are due to generally depressed oxidative processes within the cells.

In the human being, there are no known cases of riboflavin deficiency severe enough to cause the marked debilities noted in experimental animals, but mild riboflavin deficiency is probably common. Such deficiency causes digestive disturbances, burning sensations of the skin and eyes, cracking at the corners of the mouth, headaches, mental depression, forgetfulness, and so on.

Although the manifestations of riboflavin deficiency are usually relatively mild, this deficiency frequently occurs in association with deficiency of thiamine, niacin, or both. Many deficiency syndromes, including *pellagra, beriberi, sprue,* and *kwashiorkor,* are probably due to a combined deficiency of a number of vitamins, as well as other aspects of malnutrition.

Vitamin B_{12}

Several *cobalamin* compounds that possess the common prosthetic group shown next exhibit so-called vitamin B_{12} activity.



Note that this prosthetic group contains cobalt, which has bonds similar to those of iron in the hemoglobin molecule. It is likely that the cobalt atom functions in much the same way that the iron atom functions to combine reversibly with other substances.

Vitamin B_{12} Deficiency Causes Pernicious Anemia. Vitamin B_{12} performs several metabolic functions, acting as a hydrogen acceptor coenzyme. Its most important function is to act as a coenzyme for reducing ribonucleotides to deoxyribonucleotides, a step that is necessary in the replication of genes. This could explain the major functions of vitamin B_{12}: (1) promotion of growth and (2) promotion of red blood cell formation and maturation. This red cell function is described in detail in Chapter 32 in relation to pernicious anemia, a type of anemia caused by failure of red blood cell maturation when vitamin B_{12} is deficient.

Vitamin B_{12} Deficiency Causes Demyelination of the Large Nerve Fibers of the Spinal Cord. The demyelination of nerve fibers in people with vitamin B_{12} deficiency occurs especially in the posterior columns, and occasionally the lateral columns, of the spinal cord. As a result, many people with pernicious anemia have loss of peripheral sensation and, in severe cases, even become paralyzed.

The usual cause of vitamin B_{12} deficiency is not lack of this vitamin in the food but deficiency of formation of *intrinsic factor,* which is normally secreted by the parietal cells of the gastric glands and is essential for absorption of vitamin B_{12} by the ileal mucosa. This is discussed in Chapters 32 and 66.

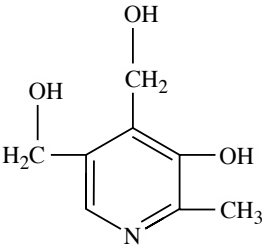
Folic Acid (Pteroylglutamic Acid)

Several pteroylglutamic acids exhibit the "folic acid effect." Folic acid functions as a carrier of hydroxymethyl and formyl groups. *Perhaps its most important use in the body is in the synthesis of purines and thymine, which are required for formation of DNA.* Therefore, folic acid, like vitamin B_{12}, is required for replication of the cellular genes. This may explain one of the most important functions of folic acid—to promote growth. Indeed, when it is absent from the diet, an animal grows very little.

Folic acid is an even more potent growth promoter than vitamin B_{12} and, like vitamin B_{12}, is important for the maturation of red blood cells, as discussed in Chapter 32. However, vitamin B_{12} and folic acid each perform specific and different chemical functions in promoting growth and maturation of red blood cells. One of the significant effects of folic acid deficiency is the development of *macrocytic anemia,* almost identical to that which occurs in pernicious anemia. This often can be treated effectively with folic acid alone.

Pyridoxine (Vitamin B_6)

Pyridoxine exists in the form of *pyridoxal phosphate* in the cells and functions as a coenzyme for many chemical reactions related to amino acid and protein metabolism. *Its most important role is that of coenzyme in the transamination process for the synthesis of amino acids.* As a result, pyridoxine plays many key roles in metabolism, especially protein metabolism. Also, it is believed to act in the transport of some amino acids across cell membranes.



Pyridoxine

Dietary lack of pyridoxine in lower animals can cause dermatitis, decreased rate of growth, development of fatty liver, anemia, and evidence of mental deterioration. Rarely, in children, pyridoxine deficiency has been known to cause seizures, dermatitis, and gastrointestinal disturbances such as nausea and vomiting.

Pantothenic Acid

Pantothenic acid mainly is incorporated in the body into *coenzyme A* (CoA), which has many metabolic roles in the cells. Two of these discussed at length in Chapters 67 and 68 are (1) conversion of decarboxylated pyruvic acid into acetyl-CoA before its entry into the citric acid cycle, and (2) degradation of fatty acid molecules into multiple molecules of acetyl-CoA. *Thus, lack of pantothenic acid can lead to depressed metabolism of both carbohydrates and fats.*

Deficiency of pantothenic acid in lower animals can cause retarded growth, failure of reproduction, graying of the hair, dermatitis, fatty liver, and hemorrhagic adrenocortical necrosis. In the human being, no definite deficiency syndrome has been proved, presumably because of the wide occurrence of this vitamin in almost all foods and because small amounts can probably be synthesized in the body. This does not mean that pantothenic acid is not of value in the metabolic systems of the body; indeed, it is perhaps as necessary as any other vitamin.

Ascorbic Acid (Vitamin C)

Ascorbic Acid Deficiency Weakens Collagen Fibers Throughout the Body. Ascorbic acid is essential for activating the enzyme *prolyl hydroxylase,* which promotes the hydroxylation step in the formation of hydroxyproline, an integral constituent of collagen. Without ascorbic acid, the collagen fibers that are formed in virtually all tissues of the body are defective and weak. Therefore, this vitamin is essential for the growth and strength of the fibers in subcutaneous tissue, cartilage, bone, and teeth.

Ascorbic Acid Deficiency Causes Scurvy. Deficiency of ascorbic acid for 20 to 30 weeks, which occurred frequently during long ship voyages in the past, causes *scurvy.* One of the most important effects of scurvy is *failure of wounds to heal.* This is caused by failure of the cells to deposit collagen fibrils and intercellular cement substances. As a result, healing of a wound may require several months instead of the several days ordinarily necessary.

Lack of ascorbic acid also causes *cessation of bone growth.* The cells of the growing epiphyses continue to proliferate, but no new collagen is laid down between the cells, and the bones fracture easily at the point of growth because of failure to ossify. Also, when an already ossified bone fractures in a person with ascorbic acid deficiency, the osteoblasts cannot form new bone matrix. Consequently, the fractured bone does not heal.

The *blood vessel walls become extremely fragile* in scurvy because of (1) failure of the endothelial cells to be cemented together properly and (2) failure to form the collagen fibrils normally present in vessel walls. The capillaries are especially likely to rupture, and as a result, many small petechial hemorrhages occur throughout the body. The hemorrhages beneath the skin cause purpuric blotches, sometimes over the entire body. To test for ascorbic acid deficiency, one can produce such petechial hemorrhages by inflating a blood pressure cuff over the upper arm; this occludes the venous return of blood, the capillary pressure rises, and red blotches occur on the forearm if the ascorbic acid deficiency is sufficiently severe.

In extreme scurvy, the muscle cells sometimes fragment; lesions of the gums occur, with loosening of the teeth; infections of the mouth develop; and vomiting of blood, bloody stools, and cerebral hemorrhage can all occur. Finally, high fever often develops before death.

Vitamin D

Vitamin D increases calcium absorption from the gastrointestinal tract and helps control calcium deposition in the bone. The mechanism by which vitamin D increases calcium absorption is mainly to promote active transport of calcium through the epithelium of the ileum. In particular, it increases the formation of a calcium-binding protein in the intestinal epithelial cells that aids in calcium absorption. The specific functions of vitamin D in relation to overall body calcium metabolism and bone formation are presented in Chapter 79.

Vitamin E

Several related compounds exhibit so-called vitamin E activity. Only rare instances of proved vitamin E deficiency have occurred in human beings. In experimental animals, lack of vitamin E can cause degeneration of the germinal epithelium in the testis and, therefore, can cause male sterility. Lack of vitamin E can also cause resorption of a fetus after conception in the female. Because of these effects of vitamin E deficiency, vitamin E is sometimes called the "antisterility vitamin." Deficiency of vitamin E prevents normal growth and sometimes causes degeneration of the renal tubular cells and the muscle cells.

Vitamin E is believed to play a protective role in the prevention of oxidation of unsaturated fats. In the absence of vitamin E, the quantity of unsaturated fats in the cells becomes diminished, causing abnormal structure and function of such cellular organelles as the mitochondria, the lysosomes, and even the cell membrane.

Vitamin K

Vitamin K is necessary for the formation by the liver of prothrombin, Factor VII (proconvertin), Factor IX, and Factor X, all of which are important in blood coagulation. Therefore, when vitamin K deficiency occurs, blood clotting is retarded. The function of this vitamin and its relation to some of the anticoagulants, such as dicumarol, are presented in greater detail in Chapter 35.

Several compounds, both natural and synthetic, exhibit vitamin K activity. Because vitamin K is synthesized by bacteria in the colon, it is rare for a person to have a bleeding tendency because of vitamin K deficiency in the diet. However, when the bacteria of the colon are destroyed by the administration of large quantities of antibiotic drugs, vitamin K deficiency occurs rapidly because of the paucity of this compound in the normal diet.

Mineral Metabolism

The functions of many of the minerals, such as sodium, potassium, and chloride, are presented at appropriate points in the text. Only specific functions of minerals not covered elsewhere are mentioned here. The body content of the most important minerals is listed in Table 71–4, and the daily requirements of these are given in Table 71–5.

Magnesium. Magnesium is about one sixth as plentiful in cells as potassium. Magnesium is required as a catalyst for many intracellular enzymatic reactions, particularly those related to carbohydrate metabolism.

The extracellular fluid magnesium concentration is slight, only 1.8 to 2.5 mEq/L. Increased extracellular concentration of magnesium depresses nervous system activity as well as skeletal muscle contraction. This latter effect can be blocked by the administration of calcium. Low magnesium concentration causes increased irritability of the nervous system, peripheral vasodilation,

Table 71–4

Average Content of a 70-Kilogram Man

Constituent	Amount (grams)
Water	41,400
Fat	12,600
Protein	12,600
Carbohydrate	300
Sodium	63
Potassium	150
Calcium	1,160
Magnesium	21
Chloride	85
Phosphorus	670
Sulfur	112
Iron	3
Iodine	0.014

Table 71–5

Average Required Daily Amounts of Minerals for Adults

Mineral	Amount
Sodium	3.0 g
Potassium	1.0 g
Chloride	3.5 g
Calcium	1.2 g
Phosphorus	1.2 g
Iron	18.0 mg
Iodine	150.0 µg
Magnesium	0.4 g
Cobalt	Unknown
Copper	Unknown
Manganese	Unknown
Zinc	15 mg

and cardiac arrhythmias, especially after acute myocardial infarction.

Calcium. Calcium is present in the body mainly in the form of calcium phosphate in the bone. This subject is discussed in detail in Chapter 79, as is the calcium content of extracellular fluid. Excess quantities of calcium ions in extracellular fluid can cause the heart to stop in systole and can act as a mental depressant. At the other extreme, low levels of calcium can cause spontaneous discharge of nerve fibers, resulting in tetany, as discussed in Chapter 79.

Phosphorus. *Phosphate is the major anion of intracellular fluid.* Phosphates have the ability to combine reversibly with many coenzyme systems and with multiple other compounds that are necessary for the operation of metabolic processes. Many important reactions of phosphates have been catalogued at other points in this text, especially in relation to the functions of adenosine triphosphate, adenosine diphosphate, phosphocreatine, and so forth. Also, bone contains a tremendous amount of calcium phosphate, which is discussed in Chapter 79.

Iron. The function of iron in the body, especially in relation to the formation of hemoglobin, is discussed in Chapter 32. *Two thirds of the iron in the body is in the form of hemoglobin,* although smaller quantities are present in other forms, especially in the liver and the bone marrow. Electron carriers containing iron (especially the cytochromes) are present in the mitochondria of all cells of the body and are essential for most of the oxidation that occurs in the cells. Therefore, iron is absolutely essential for both the transport of oxygen to the tissues and the operation of oxidative systems within the tissue cells, without which life would cease within a few seconds.

Important Trace Elements in the Body. A few elements are present in the body in such small quantities that they are called *trace elements.* The amounts of these elements in foods are also usually minute. Yet without any one of them, a specific deficiency syndrome is likely to develop. Three of the most important are iodine, zinc, and fluorine.

Iodine. The best known of the trace elements is iodine. This element is discussed in Chapter 76 in connection with the formation and function of thyroid hormone; as shown in Table 71–4, the entire body contains an average of only 14 milligrams. Iodine is essential for the formation of *thyroxine* and *triiodothyronine,* the two thyroid hormones that are essential for maintenance of normal metabolic rates in all cells of the body.

Zinc. Zinc is an integral part of many enzymes, one of the most important of which is *carbonic anhydrase,* present in especially high concentration in the red blood cells. This enzyme is responsible for rapid combination of carbon dioxide with water in the red blood cells of the peripheral capillary blood and for rapid release of carbon dioxide from the pulmonary capillary blood into the alveoli. Carbonic anhydrase is also present to a major extent in the gastrointestinal mucosa, the tubules of the kidney, and the epithelial cells of many glands of the body. Consequently, zinc in small quantities is essential for the performance of many reactions related to carbon dioxide metabolism.

Zinc is also a component of *lactic dehydrogenase* and is therefore important for the interconversions between pyruvic acid and lactic acid. Finally, zinc is a component of some *peptidases* and is important for the digestion of proteins in the gastrointestinal tract.

Fluorine. Fluorine does not seem to be a necessary element for metabolism, but the presence of a small quantity of fluorine in the body during the period of life when the teeth are being formed subsequently protects against caries. Fluorine does not make the teeth themselves stronger but has a poorly understood effect in suppressing the cariogenic process. It has been suggested that fluorine is deposited in the hydroxyapatite crystals of the tooth enamel and combines with and therefore blocks the functions of various trace metals that are necessary for activation of the bacterial enzymes that cause caries. Therefore, when fluorine is present, the enzymes remain inactive and cause no caries.

Excessive intake of fluorine causes *fluorosis,* which manifests in its mild state by mottled teeth and in its more severe state by enlarged bones. It has been postulated that in this condition, fluorine combines with trace metals in some of the metabolic enzymes, including the phosphatases, so that various metabolic systems become partially inactivated. According to this theory, the mottled teeth and enlarged bones are due to abnormal enzyme systems in the odontoblasts and osteoblasts. Even though the mottled teeth are highly resistant to the development of caries, the structural strength of these teeth may be considerably lessened by the mottling process.

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