

# 68

## Vitamins

*Suzanne Barone*



### DRUG LIST

<b>GENERIC NAME</b>	<b>PAGE</b>	<b>GENERIC NAME</b>	<b>PAGE</b>
Biotin	780	Pyridoxine	780
Cyanocobalamin	780	Retinol	778
Folic acid	780	Riboflavin	779
Nicotinic acid	780	Thiamine	779
Pantothenic acid	780		

Vitamins are a group of unrelated chemical substances that are essential in small amounts for the regulation of normal metabolism, growth, and function of the human body. Not all of the vitamins can be synthesized in the body, and therefore, some vitamins must be obtained from an external source, such as a proper well-balanced diet or dietary supplements.

Vitamins become a pharmacological concern when there is an imbalance in the body's vitamin supply. Deficiency diseases can result from insufficient vitamin ingestion, irregular absorption, or impaired metabolic use of these nutrients. The ingestion or administration of excessive quantities of vitamins, also known as hypervitaminosis, may result in toxicity.

This chapter focuses on the pharmacological and toxicological properties of vitamins.

### **DIETARY REFERENCE STANDARDS**

The Food and Nutrition Board of the Institute of Medicine (IOM) has been developing reference standards for vitamins and other nutrients called Dietary

Reference Intakes (DRIs). In the past, the recommended dietary allowances (RDAs), which are the levels of intake of essential nutrients that are considered to be adequate to meet the known nutritional needs of practically all healthy persons, were the primary reference value for vitamins and other nutrients. The DRIs also include other reference values, such as the estimated average requirement (EAR) and the adequate intake (AI). The RDA, EAR, and AI reference standards define nutritional intake adequacy. Since these recommendations are given for healthy populations in general and not for individuals, special problems, such as premature birth, inherited metabolic disorders, infections, chronic disease, and use of medications, are not covered by the requirements. Separate RDAs have been developed for pregnant and lactating women. Vitamin supplementation may be required by patients with special conditions and for those who do not consume an appropriate diet.

A varied diet containing a wide range of foodstuffs provides adequate intake of vitamins for most people, and supplementing these amounts will have no beneficial effect and may result in the toxicity associated with hypervitaminosis. The DRI also includes the tolerable

upper intake level (UL) of vitamins. The UL is defined as the highest level of intake of a nutrient that will not pose a risk of adverse health effects to most individuals in the general population. The UL is an important reference standard, especially with the current promotion and wide availability of vitamin preparations. A table of the DRIs for vitamins is available on the IOM's web site at <http://www.nationalacademies.org/IOM/IOMHome.nsf/Pages/Ongoing+Studies#FNB>.

## DEFICIENCY DISEASES

Medical personnel who work in affluent areas are unlikely to see large numbers of people with vitamin deficiency diseases. However, certain groups of the population are particularly at risk, such as low-income families and chronically ill patients. The classic symptoms of any vitamin deficiency disease as observed in laboratory animals are often blurred in humans. The clinical picture is often complicated by deficiencies of other vitamins, minerals, calories, and protein and by infections and parasite infestations, which usually accompany longstanding malnutrition. Biochemical, physiological, and behavioral changes can occur in the marginal deficiency state without or before the appearance of more specific symptoms. Since the nonspecificity of these changes makes them difficult to detail, this section focuses on the symptoms associated with individual vitamin deficiency diseases.

## VITAMIN TOXICITY

Toxic effects have been observed when large dosages of some vitamins are ingested. Generally the water-soluble vitamins are less toxic, since excess quantities are usually excreted in the urine. Excessive amounts of fat-soluble vitamins, however, are stored in the body, which makes toxic levels of these vitamins easier to obtain.

## PHYSIOLOGICAL FUNCTION AND DIETARY SOURCES

Vitamins are usually classified as either fat soluble (vitamins A, D, E, and K) or water soluble (vitamins B and C). The fat-soluble vitamins are generally metabolized slowly and are stored in the liver. In contrast, the water-soluble vitamins are rapidly metabolized and are readily excreted in the urine.

### **Fat-Soluble Vitamins** **Vitamin A**

Vitamin A, or retinol, is essential for the proper maintenance of the functional and structural integrity of epithelial cells, and it plays a major role in epithelial dif-

ferentiation. Bone development and growth in children have also been linked to adequate vitamin A intake. Vitamin A, when reduced to the aldehyde 11-*cis*-retinal, combines with opsin to produce the visual pigment rhodopsin. This pigment is present in the rods of the retina and is partly responsible for the process of dark adaptation.

Principal dietary sources of vitamin A are milk fat (cheese and butter) and eggs. Since it is stored in the liver, inclusion of liver in the diet also provides vitamin A. A plant pigment, carotene, is a precursor for vitamin A and is present in highly pigmented vegetables, such as carrots, rutabaga, and red cabbage.

An early sign of hypovitaminosis A is night blindness. This condition is related to the role of vitamin A as the prosthetic group of the visual pigment rhodopsin. The night blindness may progress to *xerophthalmia* (dryness and ulceration of the cornea) and blindness. Other symptoms of vitamin A deficiency include cessation of growth and skin changes due to hyperkeratosis.

Since vitamin A is a fat-soluble vitamin, any disease that results in fat malabsorption and impaired liver storage brings with it the risk of vitamin A deficiency; these conditions include biliary tract disease, pancreatic disease, sprue, and hepatic cirrhosis. One group at great risk are children from low-income families, who are likely to lack fresh vegetables (carotene) and dairy products (vitamin A) in the diet.

*Acute hypervitaminosis A* results in drowsiness, headache, vomiting, papilledema, and a bulging fontanel in infants. The symptoms of chronic toxicity include scaly skin, hair loss, brittle nails, and hepatosplenomegaly. Anorexia, irritability, and swelling of the bones have been seen in children. Retardation of growth also may occur. Liver toxicity has been associated with excessive vitamin A intake. Vitamin A is teratogenic in large amounts, and supplements should not be given during a normal pregnancy. The IOM has reported the UL of vitamin A to be 3,000  $\mu\text{g}/\text{day}$ .

### **Vitamin D**

Vitamin D is the collective term for a group of compounds formed by the action of ultraviolet irradiation on sterols. Cholecalciferol (vitamin D<sub>3</sub>) and calciferol (vitamin D<sub>2</sub>) are formed by irradiation of the provitamins 7-dehydrocholesterol and ergosterol, respectively. The conversion to vitamin D<sub>3</sub> occurs in the skin. The liver is the principal storage site for vitamin D, and it is here that the vitamin is hydroxylated to form 25-hydroxyvitamin D. Additional hydroxylation to form 1,25-dihydroxyvitamin D occurs in the kidney in response to the need for calcium and phosphate. A discussion of the role of vitamin D in calcium homeostasis is provided in Chapter 66.

The principal disorder associated with inadequate vitamin D intake is rickets. The low blood calcium and

phosphate levels that occur during vitamin D deficiency stimulate parathyroid hormone secretion to restore calcium levels (see Chapter 66). In children, this deficiency leads to the formation of soft bones that become deformed easily; in adults, osteomalacia results from the removal of calcium from the bone. Vitamin D deficiency may occur in patients with metabolic disorders, such as hypoparathyroidism and renal osteodystrophy. The requirement for vitamin D is slightly higher in members of darker-pigmented races, since melanin interferes with the irradiation that produces vitamin D<sub>3</sub> in the skin. People with limited exposure to the sun may need to supplement vitamin D intake.

The hypercalcemia resulting from *hypervitaminosis D* is responsible for toxic symptoms such as muscle weakness, bone pain, anorexia, ectopic calcification, hypertension, and cardiac arrhythmias. Toxicity in infants can result in mental and physical retardation, renal failure, and death.

### Vitamin E

Vitamin E is a potent antioxidant that is capable of protecting polyunsaturated fatty acids from oxidative breakdown. This vitamin also functions to enhance vitamin A use. Although several other physiological actions have been suggested, to date no unifying concept exists to explain these actions. Vitamin E ( $\alpha$ -tocopherol) is found in a variety of foodstuffs, the richest sources being plant oils, including wheat germ and rice, and the lipids of green leaves.

Deficiency of vitamin E is characterized by low serum tocopherol levels and a positive hydrogen peroxide hemolysis test. This deficiency is believed to occur in patients with biliary, pancreatic, or intestinal disease that is characterized by excessive steatorrhea. Premature infants with a high intake of fatty acids exhibit a deficiency syndrome characterized by edema, anemia, and low tocopherol levels. This condition is reversed by giving vitamin E.

Prolonged administration of *large dosages of vitamin E* may result in muscle weakness, fatigue, headache, and nausea. This toxicity can be reversed by discontinuing the large-dose supplementation.

### Vitamin K

Vitamin K activity is associated with several quinones, including phylloquinone (vitamin K<sub>1</sub>), menadione (vitamin K<sub>3</sub>), and a variety of menaquinones (vitamin K<sub>2</sub>). These quinones promote the synthesis of proteins that are involved in the coagulation of blood. These proteins include prothrombin, factor VII (proconvertin), factor IX (plasma thromboplastin), and factor X (Stuart factor). A detailed discussion of blood coagulation is found in Chapter 22. The vitamin K quinones are obtained from three major sources. Vitamin K is present in vari-

ous plants, especially green vegetables. The menaquinones that possess vitamin K<sub>2</sub> activity are synthesized by bacteria, particularly gram-positive organisms; the bacteria in the gut of animals produce useful quantities of this vitamin. Vitamin K<sub>3</sub> is a chemically synthesized quinone that possesses the same activity as vitamin K<sub>1</sub>.

Vitamin K deficiency results in increased bleeding time. This hypoprothrombinemia may lead to hemorrhage from the gastrointestinal tract, urinary tract, and nasal mucosa. In normal, healthy adults, deficiency is rare. The two groups at greatest risk are newborn infants and patients receiving anticoagulant therapy; hypoprothrombinemia preexists in these two groups. Any disease that causes the malabsorption of fats may lead to deficiency. Inhibition of the growth of intestinal bacteria from extended antibiotic therapy will result in decreased vitamin K synthesis and possible deficiency.

*Toxicity of vitamin K* has not been well defined. Jaundice may occur in a newborn if large dosages of vitamin K are given to the mother before birth. Although kernicterus may result, this can be prevented by using vitamin K.

## Water-Soluble Vitamins

### The B Vitamins

The B vitamin group is made up of substances that tend to occur together in foods and are given the collective name vitamin B complex. The vitamins of the B group usually have to be converted to an active form, and most of them play a vital role in intracellular metabolism (Table 68.1). The B vitamins are obtained from both meat and vegetable products, except for vitamin B<sub>12</sub>, which occurs only in animal products. The richest source of the B vitamin group is seeds, including the germ of wheat or of rice.

The deficiency diseases associated with the lack of the individual B vitamins are briefly described next.

Severe *thiamine (vitamin B<sub>1</sub>) deficiency* results in beriberi. The symptoms can include growth retardation, muscular weakness, apathy, edema, and heart failure. Neurological symptoms, such as personality changes and mental deterioration, also may be present in severe cases. Because of the role played by thiamine in metabolic processes in all cells, a mild deficiency may occur when energy needs are increased. Since thiamine is widely distributed in food, beriberi is rare except in communities existing on a single staple cereal food. The disease does occur with some frequency in alcoholics, whose poor diet may lead to an inadequate daily intake of thiamine.

*Riboflavin (vitamin B<sub>2</sub>) deficiency* results in local seborrheic dermatitis that may be limited to the face and scrotum. Other symptoms of ariboflavinosis include angular stomatitis, cheilitis, and glossitis. Specific ocular

**TABLE 68.1 The B Vitamins**

Vitamin	Active Form	Role
Thiamine (B <sub>1</sub> )	Thiamine pyrophosphate	Carbohydrate metabolism
Riboflavin (B <sub>2</sub> )	Flavin adenine dinucleotide; flavin mononucleotide	Carbohydrate metabolism
Nicotinic acid (niacin)	Nicotinamide adenine dinucleotide	Dehydrogenation of proteins in cellular respiration
Pyridoxine (B <sub>6</sub> )	Pyridoxal phosphate Pyridoxamine phosphate	Amino acid transformations
Pantothenic acid	Coenzyme A	Transfer of acetyl groups
Cyanocobalamin (B <sub>12</sub> )	—	Nucleic acid synthesis
Biotin	—	Fatty acid synthesis
Folic acid (folacin)	Pteroylglutamic acid-containing coenzymes	Nucleic acid synthesis, protein metabolism

signs include vascularization of the cornea and keratitis. This deficiency usually occurs in association with deficiency of other B complex vitamins.

*Niacin* or *nicotinic acid deficiency* produces the symptoms of pellagra. The clinical picture progresses from an initial phase of general malaise to symptoms including photosensitivity, sore and swollen tongue, gastritis, and diarrhea. Neurological disturbances, depression, and apathy also may occur. Both niacin and the amino acid tryptophan can be converted to diphosphopyridine nucleotide and triphosphopyridine nucleotide. These reactions require the presence of thiamine, riboflavin, and pyridoxine. Therefore, treatment of the symptoms of pellagra should include, in addition to B complex vitamin supplementation, an intake of dietary proteins to provide adequate amounts of tryptophan.

*Pyridoxine (vitamin B<sub>6</sub>) deficiency* symptoms are generally expressed as alterations in the skin, blood, and central nervous system. Symptoms include sensory neuritis, mental depression, and convulsions. Hypochromic, sideroblastic anemia also may result. Since pyridoxine is required for the conversion of tryptophan to diphosphopyridine and triphosphopyridine nucleotides, pellagra-like symptoms can occur with vitamin B<sub>6</sub> deficiency. This deficiency is found most often in conjunction with other B complex deficiencies.

The symptoms of *pantothenic acid deficiency* have not been clinically described. Since pantothenic acid is a ubiquitous vitamin, isolated deficiency is unlikely. However, marginal deficiency may exist in persons with general malnutrition.

Severe *cyanocobalamin (vitamin B<sub>12</sub>) deficiency* results in pernicious anemia that is characterized by megaloblastic anemia and neuropathies. The symptoms of this deficiency can be masked by high intake of folate. Vitamin B<sub>12</sub> is recycled by an effective enterohepatic circulation and thus has a very long half-life. Absorption of vitamin B<sub>12</sub> from the gastrointestinal tract requires the presence of gastric intrinsic factor. This factor binds to the vitamin, forming a complex that

can now be absorbed in the terminal ileum. Lack of this factor results in pernicious anemia. Following a gastrectomy, patients must be given vitamin B<sub>12</sub> parenterally. There is no way to determine how many people have undiagnosed vitamin B<sub>12</sub> deficiency. Since Vitamin B<sub>12</sub> is found in almost all animal products, dietary deficiencies are rare except in some vegan vegetarians who consume no animal products and need to get their vitamin B<sub>12</sub> from a supplement. However, marginal nutritional levels of Vitamin B<sub>12</sub> have been observed in elderly persons, demented patients, AIDS patients, and patients with malignant diseases.

*Biotin deficiency* is characterized by anorexia, nausea, vomiting, glossitis, depression, and dry, scaly dermatitis. Biotin deficiency occurs when *avidin*, a biotin-binding glycoprotein, is present. Avidin, which is found in raw egg whites, binds the biotin, making it nutritionally unavailable.

*Folic acid deficiency* symptoms include megaloblastic anemia, glossitis, diarrhea, and weight loss. The requirement for this vitamin increases during pregnancy and lactation.

The effects of most *vitamin B overdoses* have not been documented, although large dosages of pyridoxine have been reported to cause peripheral neuropathies. Ataxia and numbness of the hands and feet and impairment of the senses of pain, touch, and temperature may result. Excessive niacin intake may result in flushing, pruritus, and gastrointestinal disturbances. These symptoms are due to niacin's ability to cause the release of histamine. Large dosages of niacin can result in hepatic toxicity.

## Vitamin C

Vitamin C (ascorbic acid) is essential for the maintenance of the ground substance that binds cells together and for the formation and maintenance of collagen. The exact biochemical role it plays in these functions is not known, but it may be related to its ability to act as an oxidation–reduction system.

Vitamin C is found in fresh fruit and vegetables. It is very water soluble, is readily destroyed by heat, especially in an alkaline medium, and is rapidly oxidized in air. Fruit and vegetables that have been stored in air, cut or bruised, washed, or cooked may have lost much of their vitamin C content.

The deficiency disease associated with a lack of ascorbic acid is called scurvy. Early symptoms include malaise and follicular hyperkeratosis. Capillary fragility results in hemorrhages, particularly of the gums. Abnormal bone and tooth development can occur in growing children. The body's requirement for vitamin C increases during periods of stress, such as pregnancy and lactation.

*Megavitamin intake of vitamin C* may result in diarrhea due to intestinal irritation. Since ascorbic acid is partially metabolized and excreted as oxalate, renal oxalate stones may form in some patients.

## THERAPEUTIC USES

All of the vitamins are used as specific treatments for their respective deficiency diseases. The dosages required will vary depending on the severity of the disease and the vitamin. Vitamins have also been used like drugs to "treat" diseases. However, unlike drug products, vitamins are not reviewed by the U. S. Food and Drug Administration before formulations appear on the market. Vitamins are considered to be dietary supplements under the Dietary Supplement Health and Education Act (DSHEA). Vitamins and other dietary supplements are not permitted to be marketed as a treatment or cure for a specific disease or condition unless the vitamin is approved as a drug for that purpose. However, under DSHEA, supplement manufacturers may make health claims, such as the link between a food substance and a disease or health-related condition. This may make it difficult for patients to assess the need for vitamin supplementation.

Legitimate clinical research is being conducted with vitamins in many areas including heart disease, ophthalmological disease, neurocognitive function, and dermatological diseases. It is important for physicians to be aware of scientific information that either supports or refutes a role for vitamins in the maintenance of health or in the avoidance of disease.

## Cancer

Vitamin A can suppress many chemically induced tumors in the laboratory. Epidemiological evidence suggests that foods rich in carotenes or vitamin A are associated with a lower risk of cancer. However, the use of vitamin A supplementation is not advised because of the toxicities produced by large amounts of this vitamin.

The antioxidant properties of vitamins C and E can inhibit the formation of some carcinogens. The antioxidant vitamins have been studied as cancer chemopreventive agents for many cancer types, including gastrointestinal and ovarian cancers. However, data are not sufficient to draw conclusions about the vitamins' effects on human cancers.

## Coronary Heart Disease

The role of the antioxidant properties of vitamins C, E, and  $\beta$ -carotene in the prevention of cardiovascular disease has been the focus of several recent studies. Antioxidants reduce the oxidation of low-density lipoproteins, which may play a role in the prevention of atherosclerosis. However, an inverse relationship between the intake or plasma levels of these vitamins and the incidence of coronary heart disease has been found in only a few epidemiological studies. One study showed that antioxidants lowered the level of high-density lipoprotein 2 and interfered with the effects of lipid-altering therapies given at the same time. While many groups recommend a varied diet rich in fruits and vegetables for the prevention of coronary artery disease, empirical data do not exist to recommend antioxidant supplementation for the prevention of coronary disease.

Niacin has been used clinically to lower serum cholesterol levels (see Chapter 23). It is used as adjunctive therapy in patients with hyperlipidemia. It is one of the drugs of first choice for patients who do not respond adequately to diet and weight loss.

## Miscellaneous Uses

Vitamin A and its retinoid analogues have gained popularity in the treatment of acne and other dermatological diseases (see Chapter 41).

Vitamin K supplements are given to neonates until normal intestinal bacteria that are capable of producing the vitamin develop.

Folic acid supplements are given to pregnant women to decrease the risk of neural tube defects such as spina bifida. Prenatal vitamin preparations that contain higher concentrations of folic acid must be dispensed under a health care worker's guidance because high folate intakes can mask the symptoms of pernicious anemia.

A study of the vitamins in neurocognitive diseases such as Alzheimer's disease have not provided sufficient evidence to demonstrate that vitamins play a role in the prevention of these diseases.

Clinical trials have also been conducted to study the effect of the antioxidants on the progression of age-related macular degeneration (AMD) and vision loss. The Age-Related Eye Disease Study Research Group recommends supplements of zinc and antioxidants for adults at risk for developing AMD. However, the group

cautions about unknown long-term effects of high-dose supplementation.

## VITAMIN-DRUG INTERACTIONS

Drug interactions and the adverse effects that can result are a special concern. Although vitamins are not always thought of as being drugs, these nutrients can interact with drugs and result in a variety of effects. Vitamin-drug interactions can produce either a decrease or an increase in the effectiveness of the drug; conversely, the intake of drugs can affect the disposition of vitamins in the body. Many drugs, such as some laxatives and cholestyramine, can produce vitamin malabsorption or fecal nutritional loss, resulting in drug-induced nutrient depletion and hypovitaminosis. Both fat-soluble and water-soluble vitamins can be affected by drug intake.

### Vitamin A

Vitamin A absorption from the small intestine requires dietary fat and pancreatic lipase to break down retinyl esters and bile salts to promote the uptake of retinol and carotene. Drugs, such as mineral oil, neomycin and cholestyramine, that can modify lipid absorption from the gastrointestinal tract can impair vitamin A absorption. The use of oral contraceptives can significantly increase plasma vitamin A levels.

Since alcohol dehydrogenase is required for the conversion of retinol to retinal, excessive and prolonged ethanol ingestion can impair the physiological function of vitamin A. The decreased conversion of retinol to retinal results from competitive use of the enzyme by ethanol. Night blindness may result, since the visual cycle is a retinol-dependent physiological process.

### Vitamin D

Laxatives and agents that bind bile salts inhibit the gastrointestinal absorption of vitamin D. The glucocorticoids in high dosages may interfere with the hepatic metabolism of vitamin D. Prolonged administration of hepatic microsomal enzyme inducers, such as phenobarbital, phenytoin, primidone and glutethimide, can lead to an accelerated degradation of vitamin D<sub>3</sub> to form inactive metabolites. The synthesis of vitamin D<sub>3</sub> can be impaired by physical and chemical barriers to ultraviolet light (e.g., sunscreens).

### Vitamin K

The most common group of drugs that produce vitamin K deficiency are the coumarin anticoagulants. The hypoprothrombinemic effects of dicumarol can be overcome by administration of vitamin K.

### Vitamin C

Oral contraceptives decrease the plasma levels of ascorbic acid. Aspirin also decreases tissue levels of vitamin C. The renal excretion of acidic and basic drugs may be altered when they are coadministered with large doses of vitamin C.

### Vitamin B Complex

Many drugs interact with folate to affect its absorption, antagonize its biochemical activity, or increase its loss from the body. These drugs include ethanol, phenytoin, and oral contraceptives. Salicylates can compete with folic acid for plasma protein binding. Methotrexate, a cytotoxic agent, is a folate antagonist that inhibits the biosynthesis of this coenzyme.

Many drug classes have been shown either to act as vitamin B<sub>6</sub> antagonists or to increase vitamin B<sub>6</sub> turnover. Alcohol decreases the production of pyridoxal phosphate, the coenzyme formed from vitamin B<sub>6</sub>. Hydrazines, such as isoniazid, act as coenzyme inhibitors. Cycloserine, an antitubercular drug, and penicillamine, a chelating agent, inactivate the coenzyme. Steroid hormones, such as those in oral contraceptive preparations, compete with the coenzyme. Pyridoxine can decrease the efficacy of levodopa, an antiparkinsonian drug, by stimulating the decarboxylation of dopa to dopamine in peripheral tissues. Phenobarbital and phenytoin serum levels may be decreased following pyridoxine supplementation.

Four groups of drugs have been shown to affect the absorption of vitamin B<sub>12</sub>. These include the oral hypoglycemic biguanides, colchicine, ethanol, and aminosalicic acid.

Drug-induced niacin deficiency has resulted from the use of isonicotinic acid hydrazide, which interferes with the conversion of niacin from tryptophan. Administration of ethanol or the antimetabolites 6-mercaptopurine and 5-fluorouracil also may lead to niacin deficiency. The uricosuric effects of sulfinpyrazone and probenecid may be inhibited by nicotinic acid.

Drugs that increase intestinal motility or induce diarrhea may decrease riboflavin absorption. Hyperthyroidism and the administration of thyroxine also reduce riboflavin absorption.

Alcoholics may have both decreased intake and decreased absorption of thiamine. Liver disease can prevent the formation of the active coenzyme.

## ANEMIA

Anemia occurs when the hemoglobin concentration of blood is reduced below normal levels. This condition may result from chronic blood loss, abnormal hemolysis, or nutritional deficiency. Many therapeutic agents can induce this change in hemoglobin as an unwanted side effect.

Different classifications of anemia are based in part on the pathophysiological factor inducing the decreased hemoglobin concentration. Anemias due to cell hypoproliferation include aplastic anemia and iron deficiency anemia. Hemolytic anemia results from excessive destruction of red blood cells. Megaloblastic anemia, sideroblastic anemia, and iron deficiency anemia result from an abnormality in the maturation of red blood cells.

### Iron Deficiency Anemia

Iron is a constituent of hemoglobin, and iron deficiency will lead to a decrease in hemoglobin synthesis. Since iron is conserved by the body, deficiency usually results from acute or chronic loss of blood or insufficient iron intake during physiological stress. Infants, children, and premenopausal women require more iron than do men because of the increased demand that occurs during growth, pregnancy, and loss of blood during menstruation. In tropical climates, bleeding due to an infestation by the hookworm parasite is a common cause of iron deficiency.

The symptoms of iron deficiency anemia include fatigue, weakness, shortness of breath, and soreness of the tongue. Therapeutic iron supplementation is used to treat this type of anemia. Oral administration of ferrous salts (generic ferrous sulfate, *Feosol*, *Slo Fe*) is preferred, but parenteral iron (iron dextran, *InfeD*) can be given if oral therapy fails. Toxic reactions occur more frequently after parenteral iron administration. Gastrointestinal disturbances are common following oral dosages.

Antacids may decrease the gastrointestinal absorption of iron. Iron may chelate or decrease the gastroin-

testinal absorption of drugs like levodopa and tetracycline.

### Megaloblastic Anemia

Megaloblastic anemia is characterized by the appearance of large cells in the bone marrow and blood due to defective maturation of hematopoietic cells. Folic acid or vitamin B<sub>12</sub> deficiency will result in this type of anemia. Malabsorption, impaired use, chronic infections, and drugs can lead to folic acid or vitamin B<sub>12</sub> deficiency.

Folic acid or folate salts (*Folvite*) are administered to correct folate-deficient megaloblastic anemia. Vitamin B<sub>12</sub>-deficient patients receive cyanocobalamin supplements. Dosage is very important, since patients with severe megaloblastic anemia may develop hypokalemia and die suddenly if treated intensively with vitamin B<sub>12</sub>. Vitamin B<sub>12</sub> deficiency due to a lack of gastric intrinsic factor results in pernicious anemia. This type of megaloblastic anemia causes neurological damage if it is not treated. Treatment of Vitamin B<sub>12</sub>-deficient megaloblastic anemia with folic acid may improve the symptoms; however, neurological damage may still occur if vitamin B<sub>12</sub> intake is not supplemented. Parenteral injections of vitamin B<sub>12</sub> must be given.

### Sideroblastic Anemia

Sideroblastic anemia is characterized by excessive iron in the cells that cannot be incorporated into porphyrin to form heme. Although it is rare, the most common cause of sideroblastic anemia is alcoholism and pyridoxine deficiency. Pyridoxine is required for the formation of pyridoxal phosphate, a coenzyme in porphyrin synthesis.

## Study QUESTIONS

1. A patient with pancreatic disease complains of difficulty driving at night because of vision problems. Ulceration of the cornea is detected on ophthalmic examination. Which of the following should be recommended?
  - (A) Supplementation with vitamin B complex
  - (B) Supplementation with vitamin A
  - (C) Decreased intake of vitamin A
  - (D) Supplementation of diet with more red meat
  - (E) Decreased vitamin C intake
2. A patient comes into the clinic for a pregnancy test. It is positive. Which of the following should be recommended?
  - (A) A multivitamin without iron
  - (B) A multivitamin with iron
  - (C) A diet rich in carrots
  - (D) No vitamin supplement
  - (E) A vitamin A supplement
3. Capillary fragility, malaise, and abnormal bone and tooth development describe a deficiency of which vitamin?
  - (A) Vitamin A
  - (B) Vitamin B<sub>6</sub>
  - (C) Vitamin C
  - (D) Riboflavin
  - (E) Vitamin E
4. Which vitamin can mask the symptoms of pernicious anemia by alleviating the anemia but not preventing the neurological damage?
  - (A) Vitamin B<sub>12</sub>
  - (B) Niacin
  - (C) Folic acid

- (D) Vitamin C  
(E) Vitamin D
5. An epileptic patient who is taking phenytoin and lamotrigine to control her seizures is in the first month of pregnancy and definitely wants to have the baby. What vitamin supplement would be essential?
- (A) Vitamin B<sub>6</sub>  
(B) Vitamin D  
(C) Vitamin C  
(D) Niacin  
(E) Folic Acid

### ANSWERS

- B.** Supplement with vitamin A. Vitamin A deficiency symptoms include night blindness that can lead to corneal ulceration. This deficiency can occur in patients with impaired liver storage or fat malabsorption. Dairy products, such as milk, are a good source of vitamin A.  $\beta$ -Carotene, a vitamin A precursor, is found in pigmented vegetables, such as carrots. When a deficiency is diagnosed, it is appropriate to treat the patient with a supplement rather than to rely on increased consumption of vitamin A-rich foods. A patient with pancreatic disease and malabsorption syndrome will need parenteral supplementation.
- B.** Pregnancy increases the need for vitamins and iron in general. Folic acid has been shown to decrease the risk of neural tube defects, such as spina bifida. It is important to assess the nutritional status of the patient to determine whether higher levels of folic acid are needed. Vitamin A is a teratogen and should not be given in high doses during pregnancy.
- C.** Early symptoms of vitamin C deficiency, or scurvy, include malaise. Hemorrhages, especially of the gums, may result from capillary fragility.
- C.** The only effective treatment of pernicious anemia is supplementation of vitamin B<sub>12</sub>. It is important to determine whether megaloblastic anemia is from a deficiency of folic acid or vitamin B<sub>12</sub>. Treatment of vitamin B<sub>12</sub>-deficient anemia with folic acid may result in neurological damage if vitamin B<sub>12</sub> is not adequately supplemented.
- E.** Folic acid supplements should be given to all pregnant women. In addition, phenytoin use is associated with lowered folate levels.

### SUPPLEMENTAL READING

- AREDS Report No. 8. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss. *Arch Ophthalmol* 2001;119:1417.
- Combs GF. *The Vitamins: Fundamental Aspects in Nutrition and Health* (2nd ed.). San Diego: Academic, 1998.
- Fleming A. The role of folate in the prevention of neural tube defects: Human and animal studies. *Nutr Rev* 2001;58:S13.
- Gaytan RJ and Prisant LM. Oral nutritional supplements and heart disease: A review. *Am J Ther* 2001;8:255.
- Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B<sub>6</sub>, Folate, Vitamin B<sub>12</sub>, Pantothenic Acid, Biotin, and Choline*. Washington: National Academy, 1998.
- Rosenberg IH. B Vitamins, homocysteine, and neurocognitive function. *Nutr Rev* 2001;59:S69.
- Sarubin A. *The Health Professional's Guide to Popular Dietary Supplements*. Chicago: American Dietetic Association, 2000.
- Willett WC and Stampfer MJ. What vitamins should I be taking, doctor? *N Engl J Med* 2001;345:1819.

### CASE Study Vitamin Deficiency and Alcoholism

A patient has muscular weakness, apathy, and edema in both legs. You schedule a series of tests, including a cardiac stress test. The results of the stress test suggest that the patient is in moderate congestive heart failure. The patient suffered a personal loss last year with the death of a son. Soon after his son's death he began drinking heavily. You suspect that the drinking is responsible for his present condition. Give an analysis of this clinical picture.

**ANSWER:** The symptoms resemble those you remember from medical school for beriberi, but you fail to see the connection. Then a light clicks on. If the patient were consuming most of his calories as alcohol, he may have a nutritional deficiency, a beriberi-like syndrome, as a result of insufficient intake of thiamine. You prescribe a daily vitamin tablet and admonish the patient to cut back on alcohol intake. At the next appointment, the edema is much better and the cardiac stress tests results are normal. He has joined Alcoholics Anonymous and indicates that he is doing better.