Vitamins

28

I. OVERVIEW

Vitamins are chemically unrelated organic compounds that cannot be synthesized in adequate quantities by humans and, therefore, must be supplied by the diet. Nine vitamins (folic acid, cobalamin, ascorbic acid, pyridoxine, thiamine, niacin, riboflavin, biotin, and pantothenic acid) are classified as water-soluble, whereas four vitamins (vitamins A, D, K, and E) are termed fat-soluble (Figure 28.1). Vitamins are required to perform specific cellular functions, for example, many of the water-soluble vitamins are precursors of coenzymes for the enzymes of intermediary metabolism. In contrast to the water-soluble vitamins, only one fat soluble vitamin (vitamin K) has a coenzyme function. These vitamins are released, absorbed, and transported with the fat of the diet. They are not readily excreted in the urine, and significant quantities are stored in the liver and adipose tissue. In fact, consumption of vitamins A and D in excess of the Dietary Reference Intakes (DRIs) can lead to accumulation of toxic quantities of these compounds.

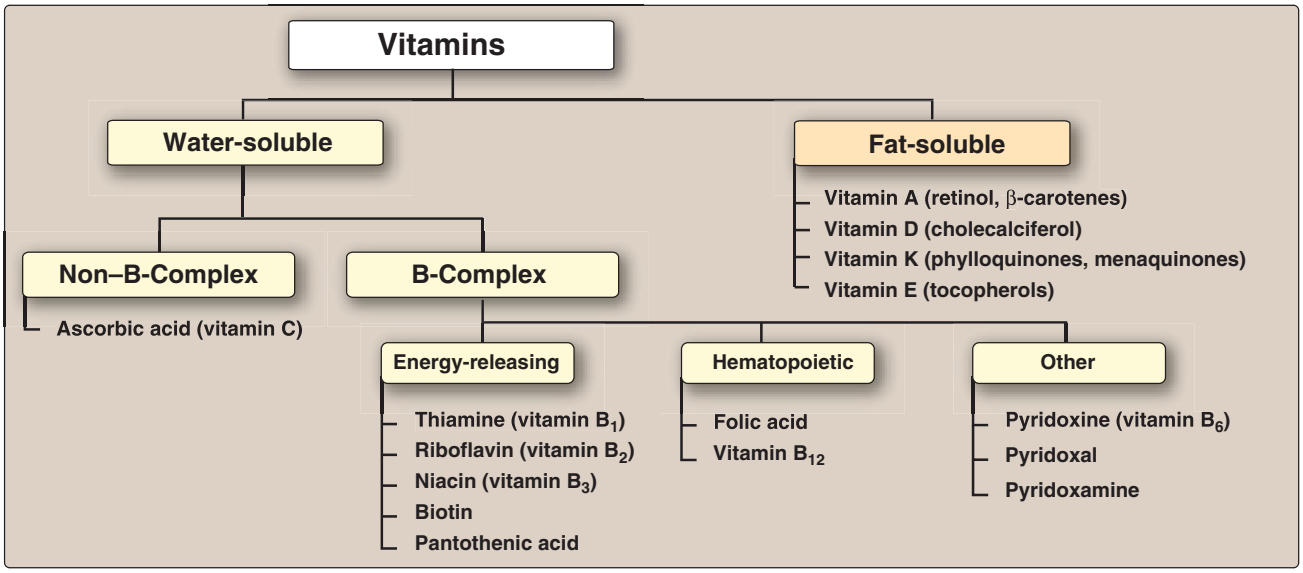

Figure 28.1
Classification of the vitamins.

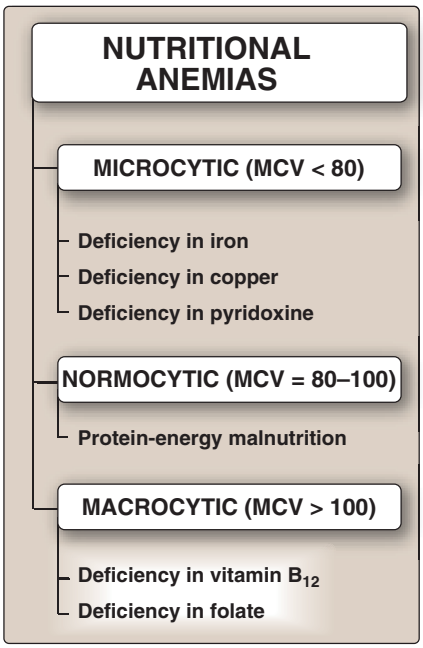

Figure 28.2
Classification of nutritional anemias by cell size. The normal mean corpuscular volume (MCV) for people older than age 18 is between 80 and 100 μm^3. [Note: Microcytic anemia is also seen with lead poisoning.]

II. FOLIC ACID

Folic acid (or folate), which plays a key role in one-carbon metabolism, is essential for the biosynthesis of several compounds. Folic acid deficiency is probably the most common vitamin deficiency in the United States, particularly among pregnant women and alcoholics.

A. Function of folic acid

Tetrahydrofolate (reduced folate) receives one-carbon fragments from donors such as serine, glycine, and histidine and transfers them to intermediates in the synthesis of amino acids, purines, and thymidine monophosphate (TMP)—a pyrimidine found in DNA.

B. Nutritional anemias

Anemia is a condition in which the blood has a lower than normal concentration of hemoglobin, which results in a reduced ability to transport oxygen. Nutritional anemias—those caused by inadequate intake of one or more essential nutrients—can be classified according to the size of the red blood cells or mean corpuscular volume observed in the individual (Figure 28.2). Microcytic anemia, caused by lack of iron, is the most common form of nutritional anemia. The second major category of nutritional anemia, macrocytic, results from a deficiency in folic acid or vitamin B_{12}. [Note: These macrocytic anemias are commonly called megaloblastic because a deficiency of folic acid or vitamin B_{12} causes accumulation of large, immature red cell precursors, known as megaloblasts, in the bone marrow and the blood.]

1. **Folate and anemia:** Inadequate serum levels of folate can be caused by increased demand (for example, pregnancy and lactation), poor absorption caused by pathology of the small intestine, alcoholism, or treatment with drugs that are *dihydrofolate reductase* inhibitors, for example, methotrexate (Figure 28.3). A folate-free diet

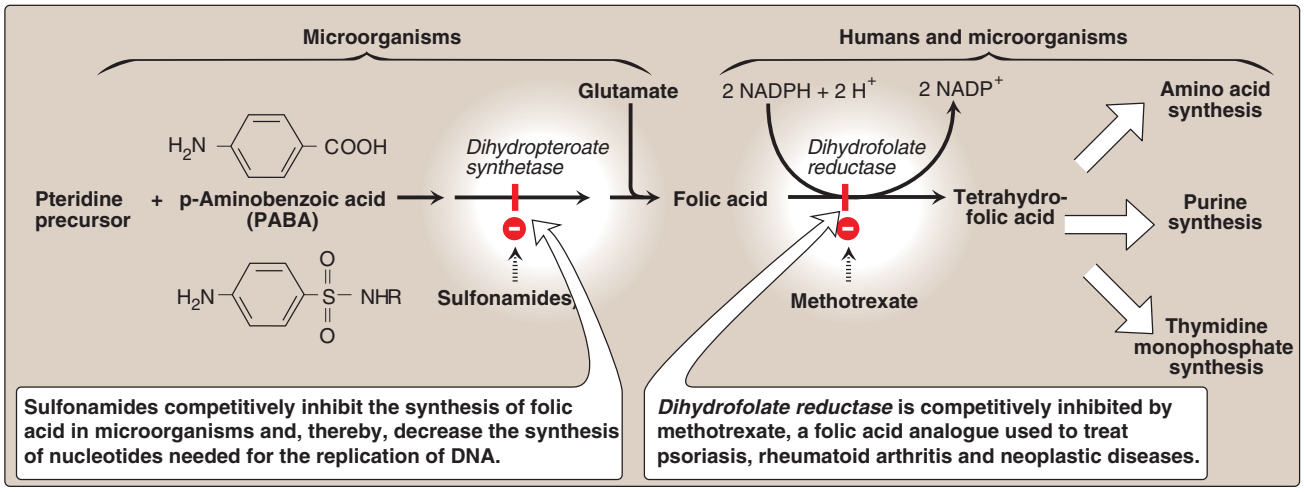

Figure 28.3
Inhibition of tetrahydrofolate synthesis by sulfonamides and methotrexate.

can cause a deficiency within a few weeks. A primary result of folic acid deficiency is megaloblastic anemia (Figure 28.4), caused by diminished synthesis of purines and TMP, which leads to an inability of cells (including red cell precursors) to make DNA and, therefore, they cannot divide. [Note: It is important to evaluate the cause of the megaloblastic anemia prior to instituting therapy, because vitamin B_{12} deficiency indirectly causes symptoms of this disorder (see p. 377).]

2. **Folate and neural tube defects in the fetus:** Spina bifida and anencephaly, the most common neural tube defects, affect approximately 4,000 pregnancies in the United State annually. Folic acid supplementation before conception and during the first trimester has been shown to significantly reduce the defects. Therefore, all women of childbearing age are advised to consume 0.4 mg/day of folic acid to reduce the risk of having a pregnancy affected by neural tube defects. Adequate folate nutrition must occur at the time of conception because critical folate-dependent development occurs in the first weeks of fetal life—at a time when many women are not yet aware of their pregnancy. The U.S. Food and Drug Administration has authorized the addition of folic acid to enriched grain products, resulting in a dietary supplementation of about 0.1 mg/day. It is estimated that this supplementation will allow approximately 50% of all reproductive-aged women to receive 0.4 mg of folate from all sources. However, there is an association of high-dose supplementation with folic acid (>0.8 mg/day) and an increased risk of cancer. Thus, supplementation is not recommended for most middle-aged or older adults.

III. COBALAMIN (VITAMIN B_{12})

Vitamin B_{12} is required in humans for two essential enzymatic reactions: the remethylation of homocysteine to methionine and the isomerization of methylmalonyl coenzyme A (CoA) that is produced during the degradation of some amino acids (isoleucine, valine, threonine, and methionine), and fatty acids with odd numbers of carbon atoms (Figure 28.5). When the vitamin is deficient, unusual fatty acids accumulate and become incorporated into cell membranes, including those of the nervous system. This may account for some of the neurologic manifestations of vitamin B_{12} deficiency.

A. Structure of cobalamin and its coenzyme forms

Cobalamin contains a corrin ring system that differs from the porphyrins in that two of the pyrrole rings are linked directly rather than through a methene bridge. Cobalt is held in the center of the corrin ring by four coordination bonds from the nitrogens of the pyrrole groups. The remaining coordination bonds of the cobalt are with the nitrogen of 5,6-dimethylbenzimidazole and with cyanide in commercial preparations of the vitamin in the form of cyanocobalamin (Figure 28.6). The coenzyme forms of cobalamin are 5'-deoxyadenosylcobalamin, in which cyanide is replaced with 5'-deoxyadenosine (forming an unusual carbon–cobalt bond), and methylcobalamin, in which cyanide is replaced by a methyl group (see Figure 28.6).

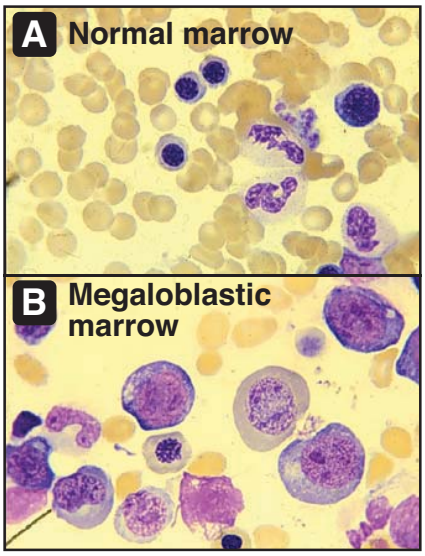

Figure 28.4
Bone marrow histology in normal and folate-deficient individuals.

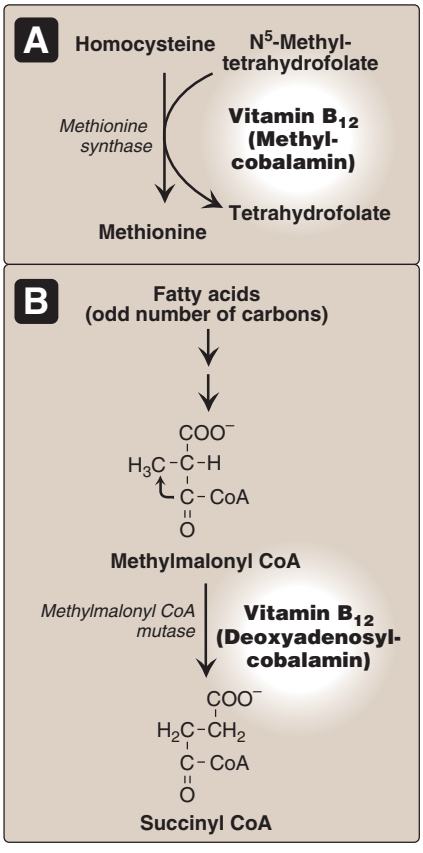

Figure 28.5
Reactions requiring coenzyme forms of vitamin B_{12}.

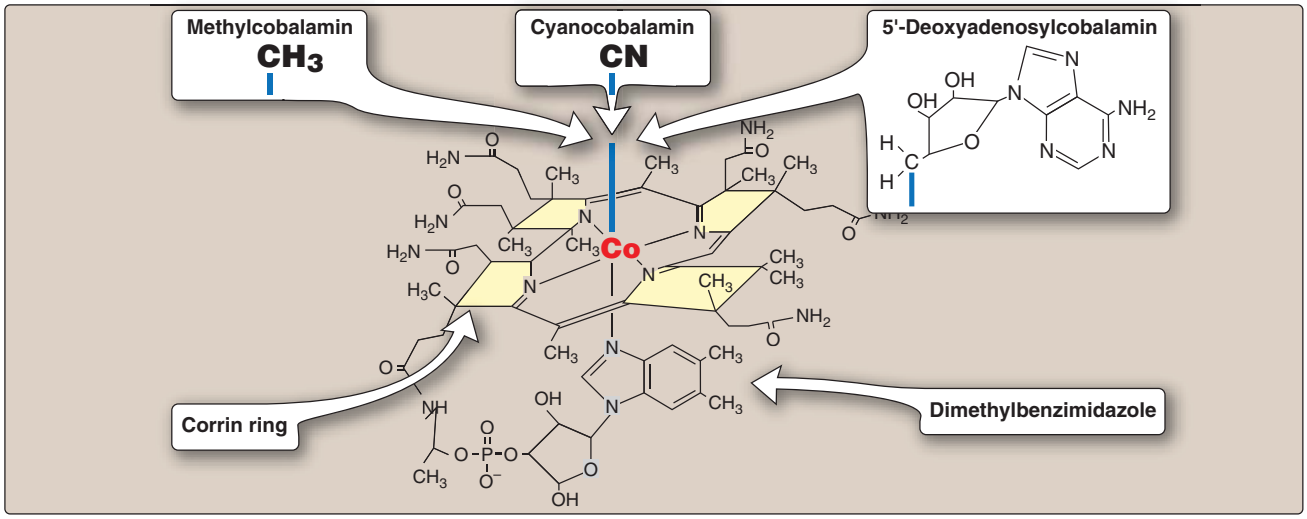

Figure 28.6
Structure of vitamin B_{12} (cyanocobalamin) and its coenzyme forms (methylcobalamin and 5'-deoxyadenosylcobalamin).

B. Distribution of cobalamin

Vitamin B_{12} is synthesized only by microorganisms; it is not present in plants. Animals obtain the vitamin preformed from their natural bacterial flora or by eating foods derived from other animals. Cobalamin is present in appreciable amounts in liver, whole milk, eggs, oysters, fresh shrimp, pork, and chicken.

C. Folate trap hypothesis

The effects of cobalamin deficiency are most pronounced in rapidly dividing cells, such as the erythropoietic tissue of bone marrow and the mucosal cells of the intestine. Such tissues need both the N^5,N^{10}-methylene and N^{10}-formyl forms of tetrahydrofolate for the synthesis of nucleotides required for DNA replication (see pp. 293 and 303). However, in vitamin B_{12} deficiency, the utilization of the N^5-methyl form of tetrahydrofolate in the B_{12}-dependent methylation of homocysteine to methionine is impaired. Because the methylated form cannot be converted directly to other forms of tetrahydrofolate, folate is trapped in the N^5-methyl form, which accumulates. The levels of the other forms decrease. Thus, cobalamin deficiency is hypothesized to lead to a deficiency of the tetrahydrofolate forms needed in purine and TMP synthesis, resulting in the symptoms of megaloblastic anemia.

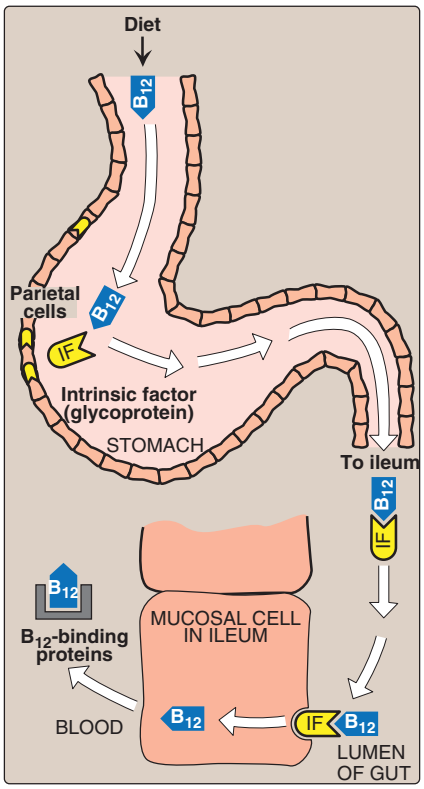

Figure 28.7
Absorption of vitamin B_{12}. IF = intrinsic factor.

D. Clinical indications for vitamin B_{12}

In contrast to other water-soluble vitamins, significant amounts (4–5 mg) of vitamin B_{12} are stored in the body. As a result, it may take several years for the clinical symptoms of B_{12} deficiency to develop in individuals who have had a partial or total gastrectomy (who, therefore, become intrinsic factor-deficient, see p. 377) and can no longer absorb the vitamin.

1. **Pernicious anemia:** Vitamin B_{12} deficiency is rarely a result of an absence of the vitamin in the diet. It is much more common to find

deficiencies in patients who fail to absorb the vitamin from the intestine. Malabsorption of cobalamin in the elderly is most often due to reduced secretion of gastric acid and less efficient absorption of vitamin B_{12} from foods. A severe malabsorption of vitamin B_{12} leads to pernicious anemia. This disease is most commonly a result of an autoimmune destruction of the gastric parietal cells that are responsible for the synthesis of a glycoprotein called intrinsic factor. Normally, vitamin B_{12} obtained from the diet binds to intrinsic factor in the intestine (Figure 28.7). The cobalamin–intrinsic factor complex travels through the gut and eventually binds to specific receptors on the surface of mucosal cells of the ileum. The bound cobalamin is transported into the mucosal cell and, subsequently, into the general circulation, where it is carried by B_{12}-binding proteins. Lack of intrinsic factor prevents the absorption of vitamin B_{12}, resulting in pernicious anemia. Patients with cobalamin deficiency are usually anemic, but later in the development of the disease they show neuropsychiatric symptoms. However, central nervous system (CNS) symptoms may occur in the absence of anemia. The CNS effects are irreversible and occur by mechanisms that appear to be different from those described for megaloblastic anemia. The disease is treated by giving high-dose B_{12} orally, or intramuscular (IM) injection of cyanocobalamin. Therapy must be continued throughout the lives of patients with pernicious anemia. Deficiency of vitamin B_{12} can be measured by the level of methylmalonic acid in blood, which is elevated in individuals with low intake or decreased absorption of the vitamin.

> Folic acid can partially reverse the hematologic abnormalities of B_{12} deficiency and, therefore, can mask a cobalamin deficiency. Thus, therapy of megaloblastic anemia is often initiated with folic acid and vitamin B_{12} until the cause of the anemia can be determined.

IV. ASCORBIC ACID (VITAMIN C)

The active form of vitamin C is ascorbic acid (Figure 28.8). The main function of ascorbate is as a reducing agent in several different reactions. Vitamin C has a well-documented role as a coenzyme in hydroxylation reactions, for example, hydroxylation of prolyl and lysyl residues of collagen (see p. 47). Vitamin C is, therefore, required for the maintenance of normal connective tissue, as well as for wound healing. Vitamin C also facilitates the absorption of dietary iron from the intestine.

A. Deficiency of ascorbic acid

A deficiency of ascorbic acid results in scurvy, a disease characterized by sore and spongy gums, loose teeth, fragile blood vessels, swollen joints, and anemia (Figure 28.9). Many of the deficiency symptoms can be explained by a deficiency in the hydroxylation of collagen, resulting in defective connective tissue.

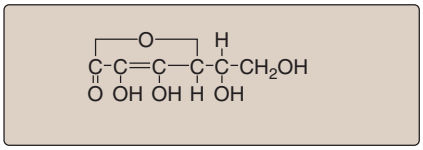

Figure 28.8
Structure of ascorbic acid.

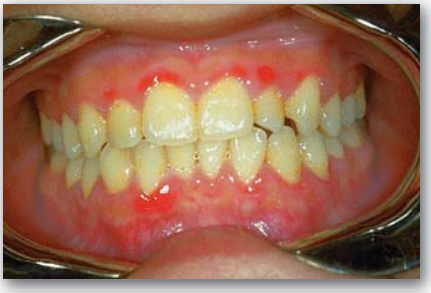

Figure 28.9
Hemorrhage and swollen gums of a patient with scurvy.

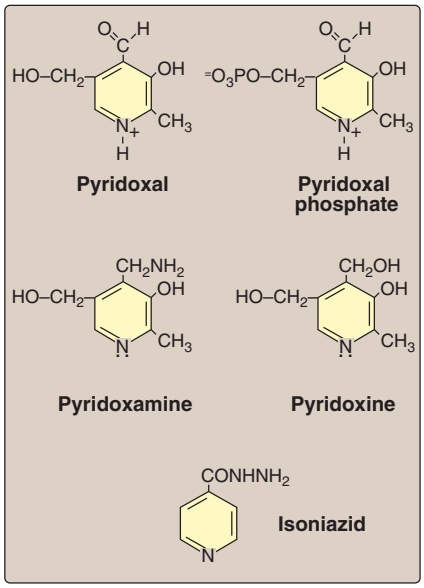

Figure 28.10
Structures of vitamin B_6 and and the antituberculosis drug isoniazid.

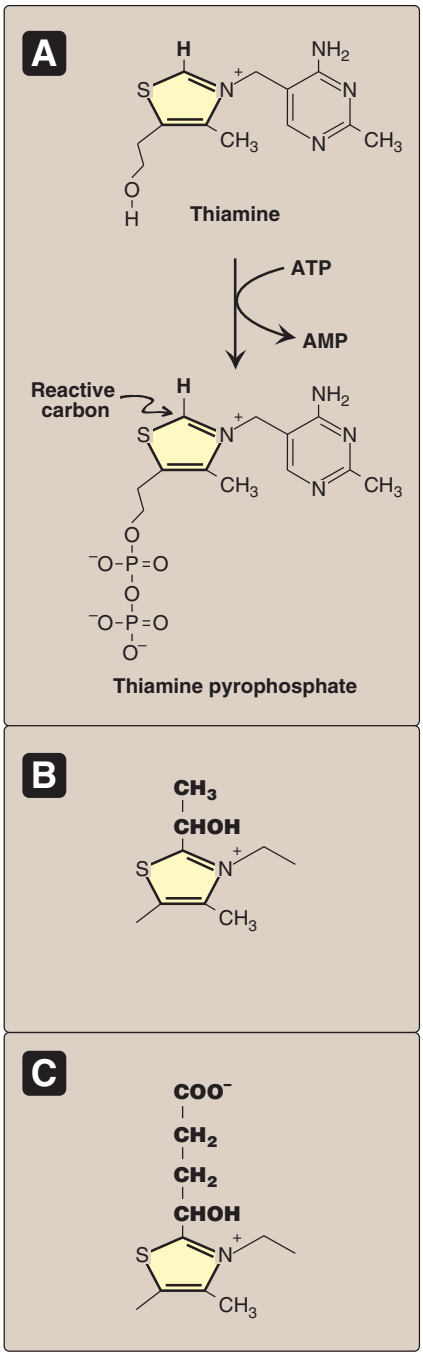

Figure 28.11
A. Structure of thiamine and its coenzyme form, thiamine pyrophosphate. B. Structure of intermediate formed in the reaction catalyzed by *pyruvate dehydrogenase*. C. Structure of intermediate formed in the reaction catalyzed by *α-ketoglutarate dehydrogenase*.

B. Prevention of chronic disease

Vitamin C is one of a group of nutrients that includes vitamin E (see p. 391) and β-carotene (see p. 382), which are known as antioxidants. Consumption of diets rich in these compounds is associated with a decreased incidence of some chronic diseases, such as coronary heart disease and certain cancers. However, clinical trials involving supplementation with the isolated antioxidants have failed to determine any convincing beneficial effects.

V. PYRIDOXINE (VITAMIN B_6)

Vitamin B_6 is a collective term for pyridoxine, pyridoxal, and pyridoxamine, all derivatives of pyridine. They differ only in the nature of the functional group attached to the ring (Figure 28.10). Pyridoxine occurs primarily in plants, whereas pyridoxal and pyridoxamine are found in foods obtained from animals. All three compounds can serve as precursors of the biologically active coenzyme, pyridoxal phosphate. Pyridoxal phosphate functions as a coenzyme for a large number of enzymes, particularly those that catalyze reactions involving amino acids.

Reaction type	Example
Transamination	Oxaloacetate + glutamate $\rightleftarrows$ aspartate + α-ketoglutarate
Deamination	Serine $\rightarrow$ pyruvate + NH_3
Decarboxylation	Histidine $\rightarrow$ histamine + CO_2
Condensation	Glycine + succinyl CoA $\rightarrow$ δ-aminolevulinic acid

A. Clinical indications for pyridoxine:

Isoniazid (isonicotinic acid hydrazide), a drug frequently used to treat tuberculosis, can induce a vitamin B_6 deficiency by forming an inactive derivative with pyridoxal phosphate. Dietary supplementation with B_6 is, thus, an adjunct to isoniazid treatment. Otherwise, dietary deficiencies in pyridoxine are rare but have been observed in newborn infants fed formulas low in B_6, in women taking oral contraceptives, and in alcoholics.

B. Toxicity of pyridoxine

Pyridoxine is the only water-soluble vitamin with significant toxicity. Neurologic symptoms (sensory neuropathy) occur at intakes above 200 mg/day, an amount more than 100 times the RDA. Substantial improvement, but not complete recovery, occurs when the vitamin is discontinued.

VI. THIAMINE (VITAMIN B_1)

Thiamine pyrophosphate is the biologically active form of the vitamin, formed by the transfer of a pyrophosphate group from adenosine triphosphate (ATP) to thiamine (Figure 28.11). Thiamine pyrophosphate serves as a coenzyme in the formation or degradation of α-ketols by *transketo-*

lase (Figure 28.12A), and in the oxidative decarboxylation of α-keto acids (Figure 28.12B).

A. Clinical indications for thiamine

The oxidative decarboxylation of pyruvate and α-ketoglutarate, which plays a key role in energy metabolism of most cells, is particularly important in tissues of the nervous system. In thiamine deficiency, the activity of these two *dehydrogenase*-catalyzed reactions is decreased, resulting in a decreased production of ATP and, thus, impaired cellular function. [Note: Thiamine deficiency is diagnosed by an increase in erythrocyte *transketolase* activity observed on addition of thiamine pyrophosphate.]

1. **Beriberi:** This is a severe thiamine-deficiency syndrome found in areas where polished rice is the major component of the diet. Signs of infantile beriberi include tachycardia, vomiting, convulsions, and, if not treated, death. The deficiency syndrome can have a rapid onset in nursing infants whose mothers are deficient in thiamine. Adult beriberi is characterized by dry skin, irritability, disordered thinking, and progressive paralysis.

2. **Wernicke-Korsakoff syndrome:** In the United States, thiamine deficiency, which is seen primarily in association with chronic alcoholism, is due to dietary insufficiency or impaired intestinal absorption of the vitamin. Some alcoholics develop Wernicke-Korsakoff syndrome—a thiamine deficiency state characterized by apathy, loss of memory, ataxia, and a rhythmic to-and-fro motion of the eyeballs (nystagmus). The neurologic consequences of Wernicke's syndrome are treatable with thiamine supplementation.

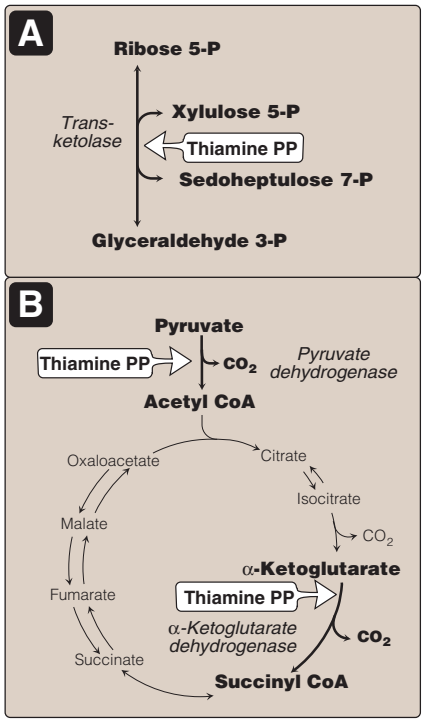

Figure 28.12
Reactions that use thiamine pyrophosphate (TPP) as coenzyme. A. *Transketolase*. B. *Pyruvate dehydrogenase* and *α-ketoglutarate dehydrogenase*. Note that TPP is also used by *branched-chain α-keto acid dehydrogenase*.

VII. NIACIN

Niacin, or nicotinic acid, is a substituted pyridine derivative. The biologically active coenzyme forms are nicotinamide adenine dinucleotide (NAD^+) and its phosphorylated derivative, nicotinamide adenine

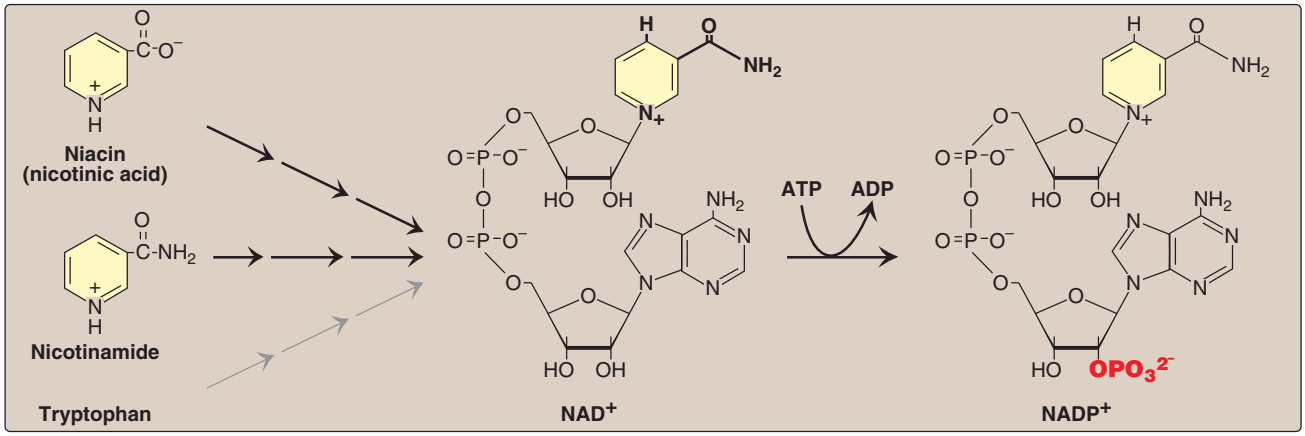

Figure 28.13
Structure and biosynthesis of NAD^+ and $NADP^+$. Note that a metabolite of tryptophan (quinolinate) can also be used in the synthesis of NAD^+.

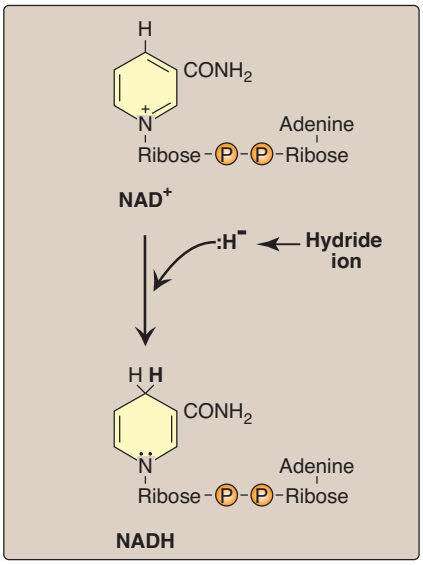

Figure 28.14
Reduction of NAD^+ to NADH.

dinucleotide phosphate ($NADP^+$, Figure 28.13). Nicotinamide, a derivative of nicotinic acid that contains an amide instead of a carboxyl group, also occurs in the diet. Nicotinamide is readily deaminated in the body and, therefore, is nutritionally equivalent to nicotinic acid. NAD^+ and $NADP^+$ serve as coenzymes in oxidation-reduction reactions in which the coenzyme undergoes reduction of the pyridine ring by accepting a hydride ion (hydrogen atom plus one electron, Figure 28.14). The reduced forms of NAD^+ and $NADP^+$ are NADH and NADPH, respectively.

A. Distribution of niacin

Niacin is found in unrefined and enriched grains and cereal, milk, and lean meats, especially liver. [Note: Corn is low in both niacin and tryptophan. Corn-based diets can cause pellagra (see below).]

B. Clinical indications for niacin

1. **Deficiency of niacin:** A deficiency of niacin causes pellagra, a disease involving the skin, gastrointestinal tract, and CNS. The symptoms of pellagra progress through the three Ds: dermatitis, diarrhea, dementia—and, if untreated, death.

2. **Treatment of hyperlipidemia:** Niacin (at doses of 1.5 g/day or 100 times the Recommended Dietary Allowance or RDA) strongly inhibits lipolysis in adipose tissue—the primary producer of circulating free fatty acids. The liver normally uses these circulating fatty acids as a major precursor for triacylglycerol synthesis. Thus, niacin causes a decrease in liver triacylglycerol synthesis, which is required for very-low-density lipoprotein (VLDL, see p. 231) production. Low-density lipoprotein (LDL, the cholesterol-rich lipoprotein) is derived from VLDL in the plasma. Thus, both plasma triacylglycerol (in VLDL) and cholesterol (in VLDL and LDL) are lowered. Therefore, niacin is particularly useful in the treatment of Type IIb hyperlipoproteinemia, in which both VLDL and LDL are elevated. [Note: Niacin raises HDL levels.]

VIII. RIBOFLAVIN (VITAMIN B_2)

The two biologically active forms are flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), formed by the transfer of an adenosine

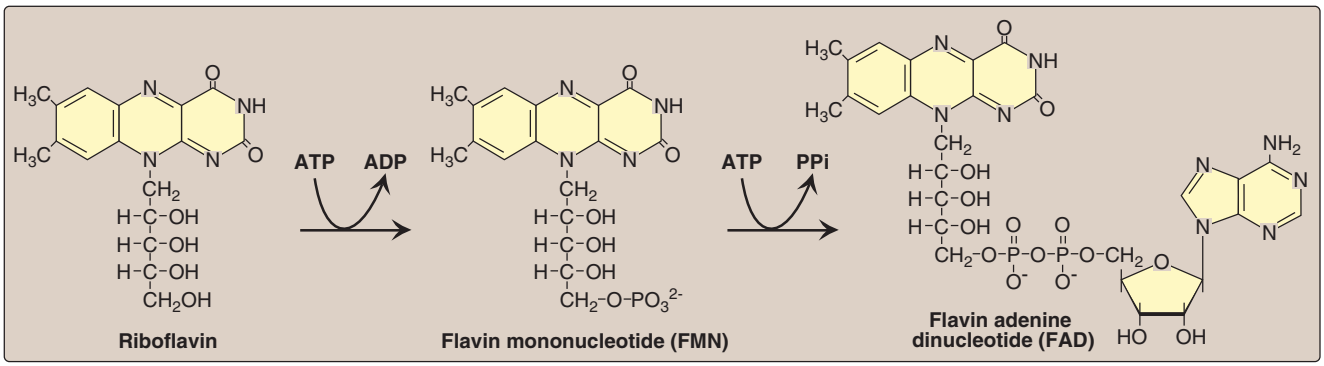

Figure 28.15
Structure and biosynthesis of flavin mononucleotide and flavin adenine dinucleotide.

monophosphate moiety from ATP to FMN (Figure 28.15). FMN and FAD are each capable of reversibly accepting two hydrogen atoms, forming $FMNH_2$ or $FADH_2$. FMN and FAD are bound tightly—sometimes covalently—to flavoenzymes that catalyze the oxidation or reduction of a substrate. Riboflavin deficiency is not associated with a major human disease, although it frequently accompanies other vitamin deficiencies. Deficiency symptoms include dermatitis, cheilosis (fissuring at the corners of the mouth), and glossitis (the tongue appearing smooth and purplish).

IX. BIOTIN

Biotin is a coenzyme in carboxylation reactions, in which it serves as a carrier of activated carbon dioxide (see Figure 10.3, p. 119, for the mechanism of biotin-dependent carboxylations). Biotin is covalently bound to the ε-amino groups of lysine residues in biotin-dependent enzymes (Figure 28.16). Biotin deficiency does not occur naturally because the vitamin is widely distributed in food. Also, a large percentage of the biotin requirement in humans is supplied by intestinal bacteria. However, the addition of raw egg white to the diet as a source of protein induces symptoms of biotin deficiency, namely, dermatitis, glossitis, loss of appetite, and nausea. Raw egg white contains a glycoprotein, avidin, which tightly binds biotin and prevents its absorption from the intestine. With a normal diet, however, it has been estimated that 20 eggs/day would be required to induce a deficiency syndrome. Thus, inclusion of an occasional raw egg in the diet does not lead to biotin deficiency, although eating raw eggs is generally not recommended due to the possibility of salmonella infection.

> Multiple *carboxylase* deficiency results from a defect in the ability to link biotin to *carboxylases* or to remove it from *carboxylases* during their degradation. Treatment is biotin supplementation.

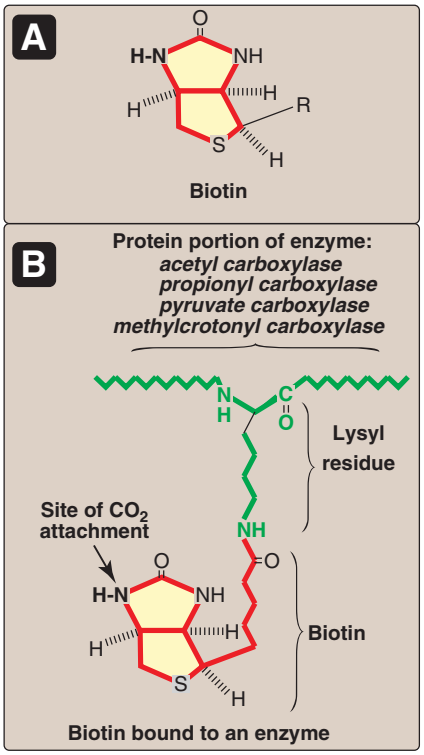

Figure 28.16
A. Structure of biotin. B. Biotin covalently bound to a lysyl residue of a biotin-dependent enzyme.

X. PANTOTHENIC ACID

Pantothenic acid is a component of coenzyme A (CoA), which functions in the transfer of acyl groups (Figure 28.17). CoA contains a thiol group that carries acyl compounds as activated thiol esters. Examples of such structures are succinyl CoA, fatty acyl CoA, and acetyl CoA. Pantothenic acid is also a component of the acyl carrier protein (ACP) domain of *fatty acid synthase* (see p. 184). Eggs, liver, and yeast are the most important sources of pantothenic acid, although the vitamin is widely distributed. Pantothenic acid deficiency is not well characterized in humans, and no RDA has been established.

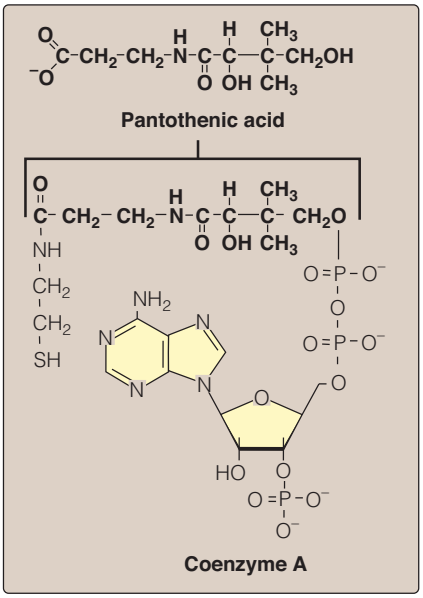

Figure 28.17
Structure of coenzyme A.

XI. VITAMIN A

The retinoids, a family of molecules that are related to retinol (vitamin A), are essential for vision, reproduction, growth, and maintenance of epithelial tissues. Retinoic acid, derived from oxidation of dietary retinol, mediates most of the actions of the retinoids, except for vision, which depends on retinal, the aldehyde derivative of retinol.

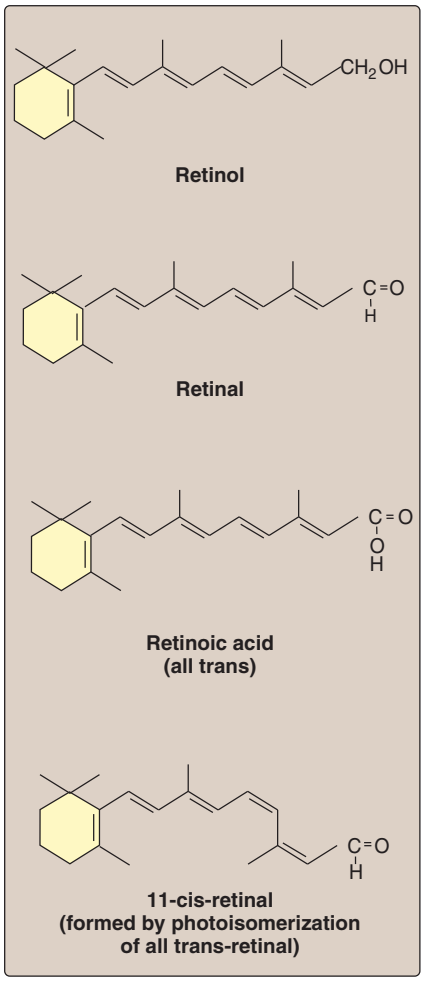

Figure 28.18
Structure of the retinoids.

A. Structure of vitamin A

Vitamin A is often used as a collective term for several related biologically active molecules (Figure 28.18). The term retinoids includes both natural and synthetic forms of vitamin A that may or may not show vitamin A activity.

1. **Retinol:** A primary alcohol containing a β-ionone ring with an unsaturated side chain, retinol is found in animal tissues as a retinyl ester with long-chain fatty acids.

2. **Retinal:** This is the aldehyde derived from the oxidation of retinol. Retinal and retinol can readily be interconverted.

3. **Retinoic acid:** This is the acid derived from the oxidation of retinal. Retinoic acid cannot be reduced in the body, and, therefore, cannot give rise to either retinal or retinol.

4. **β-Carotene:** Plant foods contain β-carotene, which can be oxidatively cleaved in the intestine to yield two molecules of retinal. In humans, the conversion is inefficient, and the vitamin A activity of β-carotene is only about one twelfth that of retinol.

B. Absorption and transport of vitamin A

1. **Transport to the liver:** Retinyl esters present in the diet are hydrolyzed in the intestinal mucosa, releasing retinol and free fatty acids (Figure 28.19). Retinol derived from esters and from the cleavage and reduction of carotenes is re-esterified to long-chain fatty acids in the intestinal mucosa and secreted as a component of chylomicrons into the lymphatic system (see Figure 28.19). Retinyl esters contained in chylomicron remnants are taken up by, and stored in, the liver.

2. **Release from the liver:** When needed, retinol is released from the liver and transported to extrahepatic tissues by the plasma retinol-binding protein (RBP). The retinol–RBP complex attaches to specific receptors on the surface of the cells of peripheral tissues, permitting retinol to enter. Many tissues contain a cellular retinol-binding protein that carries retinol to sites in the nucleus where the vitamin acts in a manner analogous to that of steroid hormones.

C. Mechanism of action of vitamin A

Retinol is oxidized to retinoic acid. Retinoic acid binds with high affinity to specific receptor proteins present in the nucleus of target tissues, such as epithelial cells (Figure 28.20). The activated retinoic acid–receptor complex interacts with nuclear chromatin to regulate retinoid-specific RNA synthesis, resulting in control of the production of specific proteins that mediate several physiologic functions. For example, retinoids control the expression of the gene for keratin in most epithelial tissues of the body. The specific retinoic acid–receptor proteins are part of the superfamily of transcriptional regulators that includes the steroid and thyroid hormones and 1,25-dihydroxycholecalciferol, all of which function in a similar way (see p. 240).

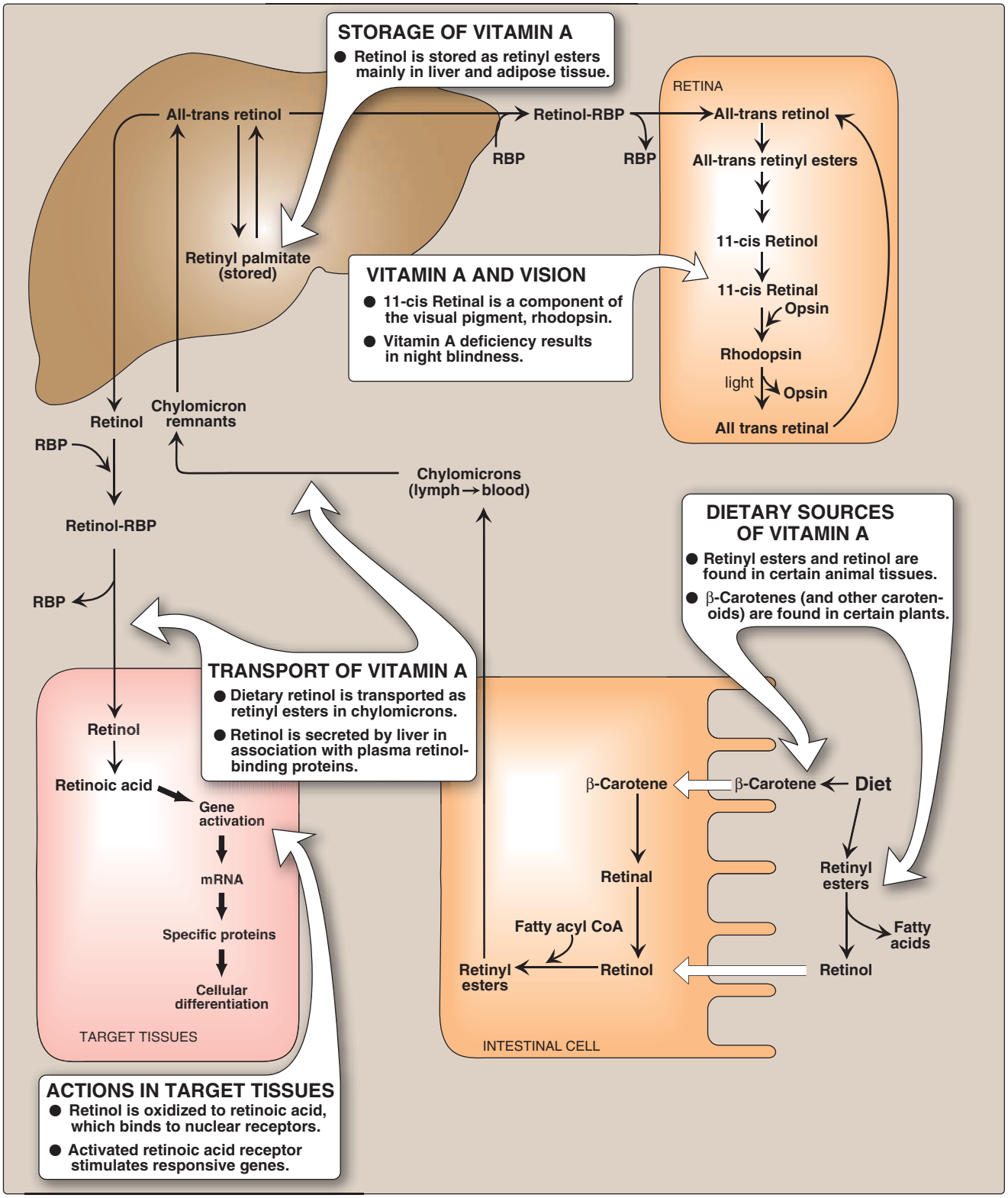

Figure 28.19
Absorption, transport, and storage of vitamin A and its derivatives. RBP = retinol-binding protein.

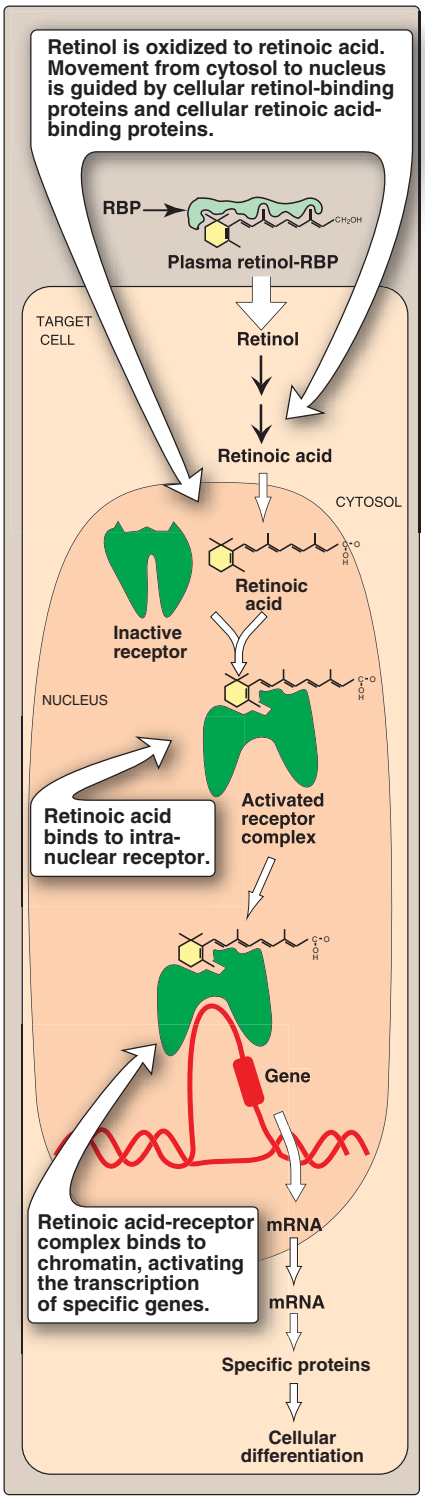

Figure 28.20
Action of retinoids Note: Retinoic acid-receptor complex is a dimer, but is shown as monomer for simplicity. [RBP = retinol-binding protein.]

D. Functions of vitamin A

1. **Visual cycle:** Vitamin A is a component of the visual pigments of rod and cone cells. Rhodopsin, the visual pigment of the rod cells in the retina, consists of 11-cis retinal specifically bound to the protein opsin. When rhodopsin is exposed to light, a series of photochemical isomerizations occurs, which results in the bleaching of the visual pigment and release of all-trans retinal and opsin. This process triggers a nerve impulse that is transmitted by the optic nerve to the brain. Regeneration of rhodopsin requires isomerization of all-trans retinal back to 11-cis retinal. All-trans retinal, after being released from rhodopsin, is reduced to all-trans retinol, esterfied, and isomerized to 11-cis retinol that is oxidized to 11-cis retinal. The latter combines with opsin to form rhodopsin, thus completing the cycle. Similar reactions are responsible for color vision in the cone cells.

2. **Growth:** Vitamin A deficiency results in a decreased growth rate in children. Bone development is also slowed.

3. **Reproduction:** Retinol and retinal are essential for normal reproduction, supporting spermatogenesis in the male and preventing fetal resorption in the female. Retinoic acid is inactive in maintaining reproduction and in the visual cycle, but promotes growth and differentiation of epithelial cells; thus, animals given vitamin A only as retinoic acid from birth are blind and sterile.

4. **Maintenance of epithelial cells:** Vitamin A is essential for normal differentiation of epithelial tissues and mucus secretion.

E. Distribution of vitamin A

Liver, kidney, cream, butter, and egg yolk are good sources of preformed vitamin A. Yellow and dark green vegetables and fruits are good dietary sources of the carotenes, which serve as precursors of vitamin A.

F. Requirement for vitamin A

The RDA for adults is 900 retinol activity equivalents (RAE) for males and 700 RAE for females. In comparison, 1 RAE = 1 mg of retinol, 12 mg of β-carotene, or 24 mg of other carotenoids.

G. Clinical indications

Although chemically related, retinoic acid and retinol have distinctly different therapeutic applications. Retinol and its precursor are used as dietary supplements, whereas various forms of retinoic acid are useful in dermatology.

1. **Dietary deficiency:** Vitamin A, administered as retinol or retinyl esters, is used to treat patients who are deficient in the vitamin (Figure 28.21). Night blindness is one of the earliest signs of vitamin A deficiency. The visual threshold is increased, making it difficult to see in dim light. Prolonged deficiency leads to an irreversible loss in the number of visual cells. Severe vitamin A deficiency leads to xerophthalmia, a pathologic dryness of the conjunctiva and cornea. If untreated, xerophthalmia results in

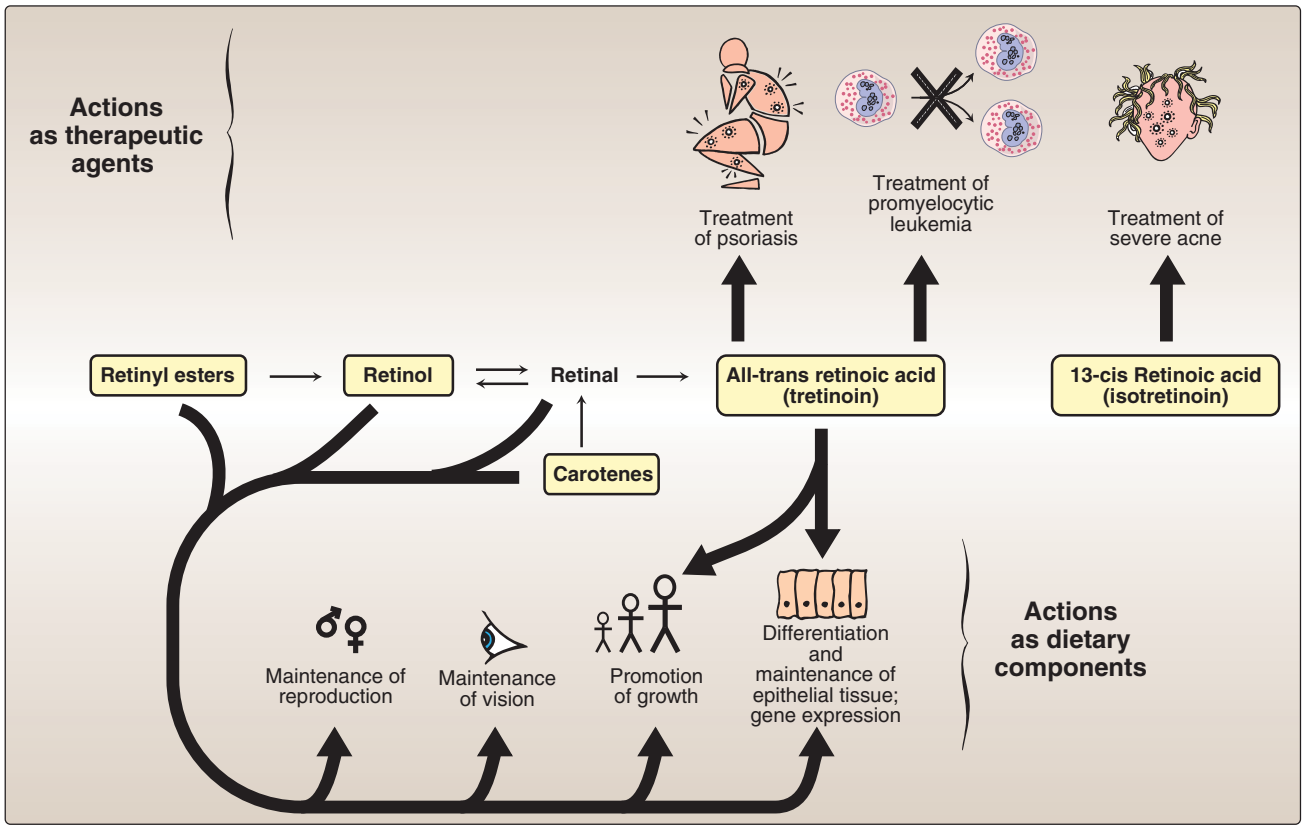

Figure 28.21
Summary of actions of retinoids. Compounds in boxes are available as dietary components or as pharmacologic agents.

corneal ulceration and, ultimately, in blindness because of the formation of opaque scar tissue. The condition is most frequently seen in children in developing tropical countries. Over 500,000 children worldwide are blinded each year by xerophthalmia caused by insufficient vitamin A in the diet.

2. **Acne and psoriasis:** Dermatologic problems such as acne and psoriasis are effectively treated with retinoic acid or its derivatives (see Figure 28.21). Mild cases of acne, Darier disease (keratosis follicularis), and skin aging are treated with topical application of tretinoin (all-trans retinoic acid), as well as benzoyl peroxide and antibiotics. [Note: Tretinoin is too toxic for systemic administration and is confined to topical application.] In patients with severe, recalcitrant, cystic acne unresponsive to conventional therapies, the drug of choice is isotretinoin (13-cis retinoic acid) administered orally. Retinoic acid is also used in the treatment of promyelocytic leukemia.

H. Toxicity of retinoids

1. **Vitamin A:** Excessive intake of vitamin A produces a toxic syndrome called hypervitaminosis A. Amounts exceeding 7.5 mg/day of retinol should be avoided. Early signs of chronic hypervitaminosis A are reflected in the skin, which becomes dry and pru-

ritic (due to a decrease in keratin synthesis), the liver, which becomes enlarged and can become cirrhotic, and in the nervous system, where a rise in intracranial pressure may mimic the symptoms of a brain tumor. Pregnant women particularly should not ingest excessive quantities of vitamin A because of its potential for causing congenital malformations in the developing fetus.

2. **Isotretinoin:** The drug is teratogenic and absolutely contraindicated in women with childbearing potential unless they have severe, disfiguring cystic acne that is unresponsive to standard therapies. Pregnancy must be excluded before initiation of treatment, and adequate birth control must be used. Prolonged treatment with isotretinoin leads to hyperlipidemia and an increase in the LDL/HDL ratio, providing some concern for an increased risk of cardiovascular disease.

XII. VITAMIN D

The D vitamins are a group of sterols that have a hormone-like function. The active molecule, 1,25-dihydroxycholecalciferol (1,25-diOH-D_3), binds to intracellular receptor proteins. The 1,25-diOH-D_3–receptor complex interacts with DNA in the nucleus of target cells in a manner similar to that of vitamin A (see Figure 28.20), and either selectively stimulates gene expression or specifically represses gene transcription. The most prominent actions of 1,25-diOH-D_3 are to regulate the plasma levels of calcium and phosphorus.

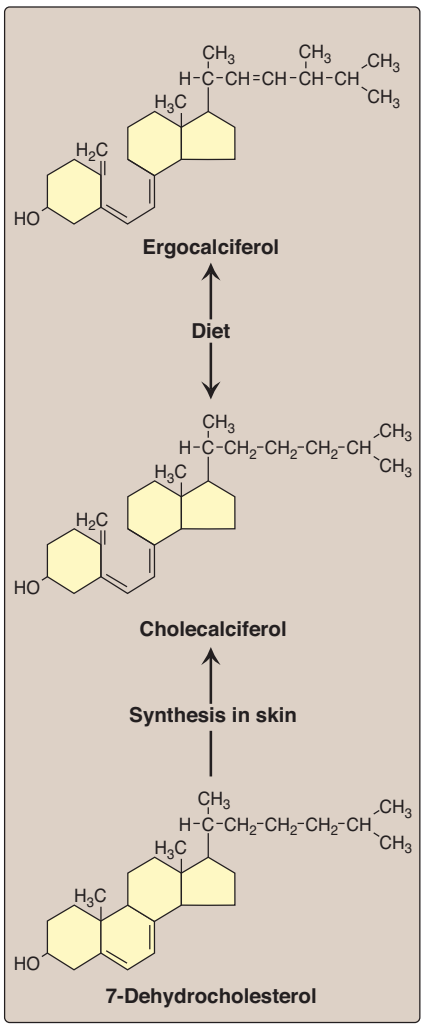

Figure 28.22
Sources of vitamin D.

A. Distribution of vitamin D

1. **Diet:** Ergocalciferol (vitamin D_2), found in plants, and cholecalciferol (vitamin D_3), found in animal tissues, are sources of preformed vitamin D activity (Figure 28.22). Ergocalciferol and cholecalciferol differ chemically only in the presence of an additional double bond and methyl group in the plant sterol.

2. **Endogenous vitamin precursor:** 7-Dehydrocholesterol, an intermediate in cholesterol synthesis, is converted to cholecalciferol in the dermis and epidermis of humans exposed to sunlight. Preformed vitamin D is a dietary requirement only in individuals with limited exposure to sunlight.

B. Metabolism of vitamin D

1. **Formation of 1,25-diOH-D_3:** Vitamins D_2 and D_3 are not biologically active, but are converted in vivo to the active form of the D vitamin by two sequential hydroxylation reactions (Figure 28.23). The first hydroxylation occurs at the 25-position, and is catalyzed by a specific *hydroxylase* in the liver. The product of the reaction, 25-hydroxycholecalciferol (25-OH-D_3, calcidol), is the predominant form of vitamin D in the plasma and the major storage form of the vitamin. 25-OH-D_3 is further hydroxylated at the 1 position by *25-hydroxycholecalciferol 1-hydroxylase* found primarily in the kidney, resulting in the formation of 1,25-diOH-D_3 (calcitriol). [Note: This *hydroxylase*, as well as the liver *25-hydroxylase*, are cytochrome P450 (CYP) proteins (see p. 149).]