Vitamin B_{12} is one of the most complex of the vitamin molecules, containing an atom of cobalt held in a *corrin ring* (similar to that of iron in hemoglobin). The cobalt ion is at the active center of the ring and serves as the site for attachment of alkyl groups during their transfer. The vitamin functions in single-carbon transfers and is intimately related to folate function and interconversions. Vitamin B_{12} is essential for normal lipid and carbohydrate metabolism in energy production and in protein biosynthesis and nucleic acid synthesis.

In contrast to other water-soluble vitamins, absorption of vitamin B_{12} is complex, involving cleavage of the vitamin from dietary protein and binding to a glycoprotein called *intrinsic factor*, which is secreted by the gastric mucosa (parietal cells). The cobalamin–intrinsic factor complex is efficiently absorbed from the distal ileum.

As vitamin B_{12} is absorbed into the portal circulation, it is transported bound to a specific protein, transcobalamin II. Its large stores in the liver also are unusual for a water-soluble vitamin. Efficient enterohepatic circulation normally protects from deficiency for months to years. Dietary sources of the vitamin are animal products only. Strict vegetarians should take a vitamin B_{12} supplement.

Vitamin B_{12} deficiency in children is rare. Early diagnosis and treatment of this disorder in childhood are important because of the danger of irreversible neurologic damage. Most cases in childhood result from a specific defect in absorption (see Table 31-2). Such defects include **congenital pernicious anemia** (absent intrinsic factor), **juvenile pernicious anemia** (autoimmune), and deficiency of transcobalamin II transport. Gastric or intestinal resection and small bowel bacterial overgrowth also cause vitamin B_{12} deficiency. Exclusively breastfed infants ingest adequate vitamin B_{12} unless the mother is a strict vegetarian without supplementation.

Depression of serum vitamin B_{12} and the appearance of hypersegmented neutrophils and macrocytosis (indistinguishable from folate deficiency) are early clinical manifestations of deficiency. Vitamin B_{12} deficiency also causes **neurologic manifestations**, including depression, peripheral neuropathy, posterior spinal column signs, dementia, and eventual coma. The neurologic signs do not occur in folate deficiency, but administration of folate may mask the hematologic signs of vitamin B_{12} deficiency, while the neurologic manifestations progress. Patients with vitamin B_{12} deficiency also have increased urine levels of methylmalonic acid. Most cases of vitamin B_{12} deficiency in infants and children are not of dietary origin and require treatment throughout life. Maintenance therapy consists of repeated monthly intramuscular injections, although a form of vitamin B_{12} is administered intranasally.

FAT-SOLUBLE VITAMINS

Fat-soluble vitamins generally have stores in the body, and dietary deficiencies generally develop more slowly than for water-soluble vitamins. Absorption of fat-soluble vitamins depends on normal fat intake, digestion, and absorption. The complexity of normal fat absorption and the potential for perturbation in many disease states explains the more common occurrence of deficiencies of these vitamins.

Vitamin A

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Hepatomegaly
Hypercalcemia

The basic constituent of the vitamin A group is retinol. Ingested plant carotene or animal tissue retinol esters release retinol after hydrolysis by pancreatic and intestinal enzymes. Chylomicron-transported retinol esters are stored in the liver as retinol palmitate. Retinol is transported from the liver to target tissues by retinol-binding protein, releasing free retinol to the target tissues. The kidney then excretes the retinol-binding protein. Diseases of the kidney diminish excretion of retinol-binding protein, whereas liver parenchymal disease or malnutrition lowers the synthesis of retinol-binding protein. Specific cellular binding proteins facilitate the uptake of retinol by target tissues. In the eye, retinol is metabolized to form **rhodopsin**; the action of light on rhodopsin is the first step of the visual process. Retinol also influences the growth and differentiation of epithelia. The clinical manifestations of vitamin A deficiency in humans appear as a group of ocular signs termed **xerophthalmia.** The earliest symptom is **night blindness**, which is followed by **xerosis** of the conjunctiva and cornea. Untreated, xerophthalmia can result in ulceration, necrosis, keratomalacia, and a permanent corneal scar. Clinical and subclinical vitamin A deficiencies are associated with **immunodeficiency**; increased risk of infection, especially measles; and increased risk of mortality, especially in developing nations. Xerophthalmia and vitamin A deficiency should be urgently treated. Hypervitaminosis A also has serious sequelae, including headaches, pseudotumor cerebri, hepatotoxicity, and teratogenicity.

Vitamin E

Eight naturally occurring compounds have vitamin E activity. The most active of these, α-tocopherol, accounts for 90% of the vitamin E present in human tissues and is commercially available as an acetate or succinate. Vitamin E acts as a biologic **antioxidant** by inhibiting the peroxidation of polyunsaturated fatty acids present in cell membranes. It scavenges free radicals generated by the reduction of molecular oxygen and by the action of oxidative enzymes.

Vitamin E deficiency occurs in children with fat malabsorption secondary to liver disease, untreated celiac disease, cystic fibrosis, and abetalipoproteinemia. In these children, without vitamin E supplementation, a syndrome of progressive **sensory and motor neuropathy** develops; the first sign of deficiency is loss of deep tendon reflexes. Deficient preterm infants at 1 to 2 months of age have hemolytic anemia characterized by an elevated reticulocyte count, an increased sensitivity of the erythrocytes to hemolysis in hydrogen peroxide, peripheral edema, and thrombocytosis. All the abnormalities are corrected after oral, lipid, or water-soluble vitamin E therapy.