The U.S. National Academy of Sciences recently concluded that the majority of North Americans are receiving adequate amounts of vitamin D (RDA = 15 μg/d or 600 IU/d; Chap. 95e). However, for people older than 70 years, the RDA is set at 20 μg/d (800 IU/d). The consumption of fortified or enriched foods as well as suberythemal sun exposure should be encouraged for people at risk for vitamin D deficiency. If adequate intake is impossible, vitamin D supplements should be taken, especially during the winter months. Vitamin D deficiency can be treated by the oral administration of 50,000 IU/week for 6–8 weeks followed by a maintenance dose of 800 IU/d (100 μg/d) from food and supplements once normal plasma levels have been attained. The physiologic effects of vitamin D_2 and vitamin D_3 are identical when these vitamins are ingested over long periods.

Toxicity The upper limit of intake has been set at 4000 IU/d. Contrary to earlier beliefs, acute vitamin D intoxication is rare and usually is caused by the uncontrolled and excessive ingestion of supplements or by faulty food fortification practices. High plasma levels of $1,25(OH)_2$ vitamin D and calcium are central features of toxicity and mandate discontinuation of vitamin D and calcium supplements; in addition, treatment of hypercalcemia may be required.

VITAMIN E

Vitamin E is the collective designation for all stereoisomers of tocopherols and tocotrienols, although only the RR tocopherols meet human requirements. Vitamin E acts as a chain-breaking antioxidant and is an efficient pyroxyl radical scavenger that protects low-density lipoproteins and polyunsaturated fats in membranes from oxidation. A network of other antioxidants (e.g., vitamin C, glutathione) and enzymes maintains vitamin E in a reduced state. Vitamin E also inhibits prostaglandin synthesis and the activities of protein kinase C and phospholipase A_2.

Absorption and Metabolism After absorption, vitamin E is taken up from chylomicrons by the liver, and a hepatic α-tocopherol transport protein mediates intracellular vitamin E transport and incorporation into very low density lipoprotein. The transport protein has a particular affinity for the RRR isomeric form of α-tocopherol; thus, this natural isomer has the most biologic activity.

Requirement Vitamin E is widely distributed in the food supply, with particularly high levels in sunflower oil, safflower oil, and wheat germ oil; γ-tocotrienols are notably present in soybean and corn oils. Vitamin E is also found in meats, nuts, and cereal grains, and small amounts are present in fruits and vegetables. Vitamin E pills containing doses of 50–1000 mg are ingested by ~10% of the U.S. population. The RDA for vitamin E is 15 mg/d (34.9 μmol or 22.5 IU) for all adults. Diets high in polyunsaturated fats may necessitate a slightly higher intake of vitamin E.

Dietary deficiency of vitamin E does not exist. Vitamin E deficiency is seen only in severe and prolonged malabsorptive diseases, such as celiac disease, or after small-intestinal resection or bariatric surgery. Children with cystic fibrosis or prolonged cholestasis may develop vitamin E deficiency characterized by areflexia and hemolytic anemia. Children with abetalipoproteinemia cannot absorb or transport vitamin E and become deficient quite rapidly. A familial form of isolated vitamin E deficiency also exists; it is due to a defect in the α-tocopherol transport protein. Vitamin E deficiency causes axonal degeneration of the large myelinated axons and results in posterior column and spinocerebellar symptoms. Peripheral neuropathy is initially characterized by areflexia, with progression to an ataxic gait, and by decreased vibration and position sensations. Ophthalmoplegia, skeletal myopathy, and pigmented retinopathy may also be features of vitamin E deficiency. A deficiency of either vitamin E or selenium in the host has been shown to increase certain viral mutations and, therefore, virulence. The laboratory diagnosis of vitamin E deficiency is based on low blood levels of α-tocopherol (<5 μg/mL, or <0.8 mg of α-tocopherol per gram of total lipids).

TREATMENT VITAMIN E DEFICIENCY

Symptomatic vitamin E deficiency should be treated with 800–1200 mg of α-tocopherol per day. Patients with abetalipoproteinemia may need as much as 5000–7000 mg/d. Children with symptomatic vitamin E deficiency should be treated orally with water-miscible esters (400 mg/d); alternatively, 2 mg/kg per day may be administered intramuscularly. Vitamin E in high doses may protect against oxygen-induced retrolental fibroplasia and bronchopulmonary dysplasia as well as intraventricular hemorrhage of prematurity. Vitamin E has been suggested to increase sexual performance, treat intermittent claudication, and slow the aging process, but evidence for these properties is lacking. When given in combination with other antioxidants, vitamin E may help prevent macular degeneration. High doses (60–800 mg/d) of vitamin E have been shown in controlled trials to improve parameters of immune function and reduce colds in nursing home residents, but intervention studies using vitamin E to prevent cardiovascular disease or cancer have not shown efficacy, and, at doses >400 mg/d, vitamin E may even increase all-cause mortality rates.

Toxicity All forms of vitamin E are absorbed and could contribute to toxicity; however, the toxicity risk seems to be rather low as long as liver function is normal. High doses of vitamin E (>800 mg/d) may reduce platelet aggregation and interfere with vitamin K metabolism and are therefore contraindicated in patients taking warfarin and antiplatelet agents (such as aspirin or clopidogrel). Nausea, flatulence, and diarrhea have been reported at doses >1 g/d.

VITAMIN K

There are two natural forms of vitamin K: vitamin K_1, also known as *phylloquinone*, from vegetable and animal sources, and vitamin K_2, or *menaquinone*, which is synthesized by bacterial flora and found in hepatic tissue. Phylloquinone can be converted to menaquinone in some organs.

Vitamin K is required for the posttranslational carboxylation of glutamic acid, which is necessary for calcium binding to γ-carboxylated proteins such as prothrombin (factor II); factors VII, IX, and X; protein C; protein S; and proteins found in bone (osteocalcin) and vascular smooth muscle (e.g., matrix Gla protein). However, the importance of vitamin K for bone mineralization and prevention of vascular calcification is not known. Warfarin-type drugs inhibit γ-carboxylation by preventing the conversion of vitamin K to its active hydroquinone form.

Dietary Sources Vitamin K is found in green leafy vegetables such as kale and spinach, and appreciable amounts are also present in margarine and liver. Vitamin K is present in vegetable oils; olive, canola, and soybean oils are particularly rich sources. The average daily intake by Americans is estimated to be ~100 μg/d.

Deficiency The symptoms of vitamin K deficiency are due to hemorrhage; newborns are particularly susceptible because of low fat stores, low breast milk levels of vitamin K, relative sterility of the infantile intestinal tract, liver immaturity, and poor placental transport. Intracranial bleeding as well as gastrointestinal and skin bleeding can occur in vitamin K–deficient infants 1–7 days after birth. Thus, vitamin K (0.5–1 mg IM) is given prophylactically at delivery.

Vitamin K deficiency in adults may be seen in patients with chronic small-intestinal disease (e.g., celiac disease, Crohn's disease), in those with obstructed biliary tracts, or after small-bowel resection. Broad-spectrum antibiotic treatment can precipitate vitamin K deficiency by reducing numbers of gut bacteria, which synthesize menaquinones, and by inhibiting the metabolism of vitamin K. In patients with warfarin therapy, the anti-obesity drug orlistat can lead to international normalized ratio changes due to vitamin K malabsorption. Vitamin K deficiency usually is diagnosed on the basis of an elevated prothrombin time or reduced clotting factors, although vitamin K may also be measured directly by high-pressure liquid chromatography. Vitamin K deficiency