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Vitamin and Trace

Mineral Deficiency

and Excess Vitamins are required constituents of the human diet because they are synthesized inadequately or not at all in the human body. Only small amounts of these substances are needed to carry out essential bio chemical reactions (e.g., by acting as coenzymes or prosthetic groups). Overt vitamin or trace mineral deficiencies are rare in Western coun tries because of a plentiful, varied, and inexpensive food supply; food fortification; and use of supplements. However, multiple nutrient deficiencies may appear together in persons who are chronically ill, alcoholic, on specific medications (see below), or living in poverty. After bariatric surgery, patients are at high risk for multiple nutrient deficiencies. Moreover, subclinical vitamin and trace mineral deficien cies (often designated as “hidden hunger”), as diagnosed by laboratory testing, are quite common in the normal population, especially in the geriatric age group and socioeconomically deprived individuals due to the lack of nutrient-dense foods. Conversely, because of the widespread use of nutrient supplements and food fortification, nutrient toxicities are gaining pathophysiologic and clinical importance. Victims of famine, emergency-affected and displaced populations, refugees, and camp populations are at increased risk for protein-energy malnutrition and classic micronutrient deficiencies (vitamin A, iron, zinc, iodine) as well as for overt deficiencies in thiamine (beriberi), riboflavin, vitamin C (scurvy), and niacin (pellagra). Body stores of vitamins and minerals vary tremendously. For exam ple, stores of vitamins B12 and A are large, and an adult may not become deficient until ≥1 year after beginning to eat a deficient diet. However, folate and thiamine may become depleted within weeks among those eating a deficient diet. Therapeutic modalities can deplete essential TABLE 344-1 Principal Clinical Findings of Vitamin Malnutrition NUTRIENT CLINICAL FINDING Thiamine Beriberi: neuropathy, muscle weakness and wasting, cardiomegaly,

edema, ophthalmoplegia, confabulation Riboflavin Magenta tongue, angular stomatitis, seborrhea, cheilosis, ocular symptoms, corneal vascularization Niacin Pellagra: pigmented rash of sun-exposed areas, bright red tongue, diarrhea, apathy, memory loss, disorientation Vitamin B6 Seborrhea, glossitis, convulsions, neuropathy, depression, confusion, microcytic anemia Folate Megaloblastic anemia, atrophic glossitis, depression,

↑ homocysteine Vitamin B12 Megaloblastic anemia, loss of vibratory and position sense, abnormal gait, dementia, impotence, loss of bladder and bowel control, ↑ homocysteine,

↑ methylmalonic acid Vitamin C Scurvy: petechiae, ecchymosis, coiled hairs, inflamed and bleeding gums, joint effusion, poor wound healing, fatigue Vitamin A Xerophthalmia, night blindness, Bitot's spots, follicular hyperkeratosis, impaired embryonic development, immune dysfunction Vitamin D Rickets: skeletal deformation, rachitic rosary, bowed legs; osteomalacia Vitamin E Peripheral neuropathy, spinocerebellar ataxia, skeletal muscle atrophy, retinopathy Vitamin K Elevated prothrombin time, bleeding <10 µg/d Fat malabsorption, liver disease, antibiotic use

nutrients from the body; for example, hemodialysis or diuretics remove water-soluble vitamins, which must be replaced by supplementation.

Vitamins and trace minerals play several roles in diseases: (1) defi ciencies of vitamins and minerals may be caused by disease states such as malabsorption; (2) either deficiency or excess of vitamins and min erals can cause disease in and of itself (e.g., vitamin A intoxication and liver disease); and (3) vitamins and minerals in high doses may be used as drugs (e.g., niacin for hypercholesterolemia). Since they are covered elsewhere, the hematologic-related vitamins and minerals (Chaps. 102 and 104) either are not considered or are considered only briefly in this chapter, as are the bone-related vitamins and minerals (vitamin D, calcium, phosphorus, magnesium; Chap. 421). VITAMINS See also Table 344-1 and Fig. 344-1. ■ ■THIAMINE (VITAMIN B1) Thiamine was the first B vitamin to be identified and therefore is referred to as vitamin B1. Thiamine functions in the decarboxylation of α-ketoacids (e.g., pyruvate α-ketoglutarate) and branched-chain amino acids and thus is essential for energy generation. In addition, thiamine pyrophosphate acts as a coenzyme for a transketolase reaction that mediates the conversion of hexose and pentose phosphates. It has been postulated that thiamine plays a role in peripheral nerve conduction, although the exact chemical reactions underlying this function are not known. Food Sources The median intake of thiamine in the United States from food alone is ~2 mg/d. Primary food sources for thiamine include yeast, organ meat, pork, legumes, beef, whole grains, and nuts. Milled rice and grains contain little thiamine. Thiamine deficiency is there fore more common in cultures that rely heavily on a milled polished rice-based diet. Certain foods contain antithiamine factors such as heat-labile thiaminases (raw fish, shellfish), which destroy the vitamin, or heat-stable polyhydroxyphenols (tannins; in coffee, tea, Brussels sprouts, or betel nuts), which inactivate the vitamin. Thus, drinking large amounts of tea or coffee could theoretically lower thiamine body stores. CHAPTER 344 Vitamin and Trace Mineral Deficiency and Excess
DIETARY LEVEL PER DAY ASSOCIATED WITH OVERT DEFICIENCY IN ADULTS CONTRIBUTING FACTORS TO DEFICIENCY <0.3 mg/1000 kcal Alcoholism, chronic diuretic use, bariatric surgery, hyperemesis, thiaminases in food <0.4 mg Alcoholism, individuals with poor diets and low intake of milk products <9.0 niacin equivalents Alcoholism, vitamin B6 deficiency, riboflavin deficiency,

tryptophan deficiency <0.2 mg Alcoholism, isoniazid <100 µg/d Alcoholism, sulfasalazine, pyrimethamine, triamterene <1.0 µg/d Gastric atrophy (pernicious anemia), terminal ileal disease, strict vegetarianism, acid-reducing drugs (e.g., H2 blockers), metformin <10 mg/d Smoking, alcoholism <300 µg/d Fat malabsorption, infection, measles, alcoholism, protein-energy malnutrition <2.0 µg/d Aging, lack of sunlight exposure, fat malabsorption, deeply pigmented skin Not described unless underlying contributing factor is present Occurs only with fat malabsorption or genetic abnormalities of vitamin E metabolism/transport

Deficiency Most dietary deficiency of thiamine worldwide is the result of poor dietary intake due to the lack of food or disproportion ate reliance on highly processed staple crops. Food processing removes thiamine, and high-heat or long-duration cooking destroys it. In Western countries, the primary causes of thiamine deficiency are alcohol ism and chronic illnesses such as cancer. Alcohol interferes directly with the absorption of thiamine and with the synthesis of thiamine

Vitamin Thiamine (B1) NH2 CH3 N N N S CH2CH2OH Riboflavin (B2) Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) O N NH O N N Ribityl Niacin Nicotinamide adenine dinucleotide phosphate (NADP) and nicotinamide adenine dinucleotide (NAD) PART 10 Disorders of the Gastrointestinal System O C O + N H Vitamin B6 Pyridoxal phosphate Cofactor for enzymes of amino acid metabolism CH2OH CH2OH HO N Folate Polyglutamate forms of (5, 6, 7, 8) tetrahydrofolate with carbon unit attachments n N H O COOH N C CH O H CH2 N CH2 CH2 H2N N N C CH N H O Vitamin B12 Methylcobalamine Adenosylcobalamin Coenzyme for methionine synthase and CH2CH2CONH2 CONH2 H3C CH2CH2CONH2 CH3 CH2 CH2CH2CONH2 H3C H3C Co+ N N CONH2 N N CH3 CH3 CH2 CH3 NHCOCH2CH2 CH2CH2CONH2 CH3 CH2 CHCH3 N CH3 O– N O CH3 P O O HO O HOCH2 OH Cbl FIGURE 344-1 Structures and principal functions of vitamins associated with human disorders.

pyrophosphate, and it increases urinary excretion. Thiamine should always be replenished when a patient with alcoholism is being refed, as carbohydrate repletion without adequate thiamine can precipitate acute thiamine deficiency with lactic acidosis. Other at-risk popula tions are women with prolonged hyperemesis gravidarum, anorexia (including eating disorders), patients with overall poor nutritional status who are receiving parenteral glucose, patients who have had Active derivative or cofactor form Principal function Thiamine pyrophosphate Coenzyme for cleavage of carbon-carbon bonds; amino acid and carbohydrate metabolism Cofactor for oxidation, reduction reactions, and covalently attached prosthetic groups for some enzymes Coenzymes for oxidation and reduction reactions Coenzyme for one carbon transfer in nucleic acid and amino acid metabolism COOH CH2 CH2 C OH O L-methylmalonyl- CoA mutase

bariatric/metabolic surgery (bariatric Wernicke), and patients receiving chronic diuretic therapy (e.g., in hypertension or systolic heart failure) due to increased urinary thiamine losses. Different drugs (e.g., metfor min, verapamil) could inhibit intestinal thiamine transporters (ThTR2), thereby increasing the risk of deficiency for this vitamin. Maternal thiamine deficiency can lead to infantile beriberi in breast-fed children. Thiamine deficiency could be an underlying factor in motor vehicle accidents and could be overlooked in the setting of head injury. Thiamine deficiency in its early stage is challenging to identify. It causes anorexia and nonspecific symptoms (e.g., irritability, decrease in short-term memory). Prolonged thiamine deficiency causes beriberi, which is classically categorized as wet or dry, although there is consid erable overlap between the two categories. In

either form of beriberi, patients may complain of pain and paresthesia. Wet beriberi presents primarily with cardiovascular symptoms that are due to impaired myo cardial energy metabolism and dysautonomia; it can occur after 3 months of a thiamine-deficient diet. Patients present with an enlarged heart, tachycardia, high-output congestive heart failure, peripheral edema, and peripheral neuritis. Patients with dry beriberi present with a sym metric peripheral neuropathy of the motor and sensory systems, with diminished reflexes. The neuropathy affects the legs most markedly, and patients have difficulty rising from a squatting position. Alcoholic patients with chronic thiamine deficiency also may have central nervous system (CNS) manifestations known as Wernicke's encephalopathy, which consists of horizontal nystagmus, ophthal moplegia (due to weakness of one or more extraocular muscles), cerebellar ataxia, and mental impairment (Chap. 464). When there Vitamin Vitamin C O O C C C C C CH2OH OH OH OH Vitamin A Retinol, retinaldehyde, and retinoic acid Formation of rhodopsin (vision) and glycoproteins (epithelial cell function); also regulates gene transcription (β-Carotene) CH2OH (Retinol) Vitamin D 1,25-Dihydroxyvitamin D Maintenance of blood calcium and phosphorus levels; antiproliferative hormone CH2 OH HO Vitamin E Tocopherols and tocotrienols Antioxidants O CH2[CH2 CH2]3H CH CH2 HO Vitamin K Vitamin K hydroquinone Cofactor for posttranslation carboxylation of many proteins including essential clotting factors O O R FIGURE 344-1 (Continued)

is an additional loss of memory and a confabulatory psychosis, the syndrome is known as Wernicke-Korsakoff syndrome. Despite the typical clinical picture and history, Wernicke-Korsakoff syndrome is underdiagnosed.

The laboratory diagnosis of thiamine deficiency usually is made by a functional enzymatic assay of transketolase activity measured before and after the addition of thiamine pyrophosphate. A >25% stimulation in response to the addition of thiamine pyrophosphate (i.e., an activity coefficient of 1.25) is interpreted as abnormal. Thiamine or the phos phorylated esters of thiamine in serum or blood also can be measured by high-performance liquid chromatography to detect deficiency. TREATMENT Thiamine Deficiency In acute thiamine deficiency with either cardiovascular or neu rologic signs, 200 mg of thiamine three times daily should be given intravenously until there is no further improvement in acute symptoms; oral thiamine (10 mg/d) should subsequently be given until recovery is complete. Cardiovascular and ophthalmoplegic improvement occurs within 24 h. Other manifestations gradually clear, although psychosis in Wernicke-Korsakoff syndrome may be permanent or may persist for several months. Other nutri ent deficiencies should be corrected concomitantly (e.g., magne sium, required for thiamine activation). In view of the widespread, often unrecognized (subclinical) deficiency, a more generous CHAPTER 344 Active derivative or cofactor form Principal function Ascorbic acid and dehydroascorbic acid Participation as a redox ion in many biologic oxidation and hydrogen transfer reactions Vitamin and Trace Mineral Deficiency and Excess
OH CH3

supplementation of this vitamin in the emergency care setting and in all patients with any alcohol use disorder is warranted.

Toxicity Although hypersensitivity/anaphylaxis has been reported after high intravenous doses of thiamine, no adverse effects have been recorded from either food or supplements at high doses. ■ ■RIBOFLAVIN (VITAMIN B2) Riboflavin is important for the metabolism of fat, carbohydrate, and

protein, acting as a respiratory coenzyme and an electron donor in energy production. Enzymes that contain flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN) as prosthetic groups are known as flavoenzymes (e.g., succinic acid dehydrogenase, monoamine oxidase, glutathione reductase). FAD is a cofactor for methyltetrahy drofolate reductase and therefore modulates homocysteine metabo lism. The vitamin also plays a role in drug and steroid metabolism, including detoxification reactions. Although much is known about the chemical and enzymatic reac tions of riboflavin, the clinical manifestations of riboflavin deficiency are nonspecific and are similar to those of other deficiencies of B vita mins. Riboflavin deficiency is manifested principally by lesions of the mucocutaneous surfaces of the mouth and skin. In addition, corneal vascularization, anemia, and personality changes have been described with riboflavin deficiency. Deficiency and Excess Riboflavin deficiency is rare and almost always due to dietary deficiency. Milk, other dairy products, and enriched breads and cereals are the most important dietary sources of riboflavin in the United States, although lean meat, fish, eggs, broccoli, and legumes are also good sources. Riboflavin is extremely sensitive to light, and milk should be stored in containers that protect against photodegradation. Laboratory diagnosis of riboflavin deficiency can be made by determination of red blood cell or urinary riboflavin con centrations or by measurement of erythrocyte glutathione reductase activity, with and without added FAD. Because of the limited capacity of the gastrointestinal tract to absorb riboflavin (~27 mg after one oral dose or meal) as well as the instantaneous urinary excretion, riboflavin toxicity has not been described. PART 10 Disorders of the Gastrointestinal System ■ ■NIACIN (VITAMIN B3) The term niacin refers to nicotinic acid and nicotinamide and their biologically active derivatives. Nicotinic acid and nicotinamide serve as precursors of two coenzymes, nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), which are important in numer ous oxidation and reduction reactions in the body. In addition, NAD and NADP are active in adenine diphosphate–ribose transfer reactions involved in DNA repair and calcium mobilization. Metabolism and Requirements Nicotinic acid and nicotinamide are absorbed well from the stomach and small intestine. The bioavail ability of niacin from beans, milk, meat, and eggs is high; bioavailability from cereal grains is lower. Since flour is enriched with “free” niacin (i.e., the non-coenzyme form), bioavailability is excellent. Median intakes of niacin in the United States considerably exceed the recom mended dietary allowance (RDA). The amino acid tryptophan can be converted to niacin with an efficiency of 60:1 by weight. Thus, the RDA for niacin is expressed in niacin equivalents. A lower-level conversion of tryptophan to niacin occurs in vitamin B6, riboflavin, and/or iron deficiencies, and in the presence of isoniazid. The urinary excretion products of niacin include 2-pyridone and 2-methyl nicotinamide, measurements of which are used in the diagnosis of niacin deficiency. Deficiency Niacin deficiency causes pellagra, which is found mostly among people eating corn-based diets in parts of China, Africa, and India. Pellagra in North America is found mainly among alcohol ics; among patients with congenital defects of intestinal and kidney absorption of tryptophan (Hartnup disease); and among patients with carcinoid syndrome, in which there is increased conversion of trypto phan to serotonin. The antituberculosis drug isoniazid is a structural

analogue of niacin and can precipitate pellagra. This also occurs in the setting of mass scale-up of isoniazid tuberculosis preventive therapy in low-income countries. In the setting of famine or population displace ment, pellagra results from the absolute lack of niacin but also from the deficiency of micronutrients required for the conversion of tryptophan to niacin (e.g., iron, riboflavin, and pyridoxine). The early symptoms of pellagra include loss of appetite, generalized weakness and irritabil ity, abdominal pain, and vomiting. Bright red glossitis then ensues and is

followed by a characteristic skin rash that is pigmented and scaling, particularly in skin areas exposed to sunlight. This rash is known as Casal’s necklace because it forms a ring around the neck; it is seen in advanced cases. Vaginitis and esophagitis also may occur. Diarrhea (due in part to proctitis and in part to malabsorption), depression, seizures, and dementia are also part of the pellagra syndrome. The pri mary manifestations of this syndrome are sometimes referred to as “the four Ds”: dermatitis, diarrhea, and dementia leading to death. Aging is characterized by a decline in cellular NAD+, and it seems plausible that maintaining and/or reestablishing cellular NAD+, might have beneficial effects (e.g., metabolic disorders). TREATMENT Pellagra Treatment of pellagra consists of oral supplementation with 100– 200 mg of nicotinamide or nicotinic acid three times daily for up to 4 weeks. High doses of nicotinic acid (2 g/d in a time-release form) may be used for the treatment of elevated cholesterol and triglyc eride levels and/or low high-density lipoprotein cholesterol levels, but without proven evidence to prevent cardiovascular disease. Nevertheless, nicotinic acid may be useful in patients with statin intolerance or severe hypertriglyceridemia (Chap. 419). Toxicity Prostaglandin-mediated flushing due to binding of the vitamin to a G protein–coupled receptor has been observed at daily nicotinic acid doses as low as 30 mg taken as a supplement or as therapy for dyslipidemia. There is no evidence of toxicity from niacin that is derived from food sources. Flushing always starts in the face and may be accompanied by skin dryness, itching, paresthesia, and headache. Flushing is subject to tachyphylaxis and often improves with time; premedication with aspirin may alleviate these symptoms. Nausea, vomiting, and abdominal pain also occur at similar doses of niacin. Hepatic toxicity is the most serious toxic reaction caused by sustained-release niacin and may present as jaundice with elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. A few cases of fulminant hepatitis requiring liver transplantation have been reported at doses of 3–9 g/d. Other toxic reactions include glucose intolerance, hyperuricemia, macular edema, and macular cysts. The combination of nicotinic acid preparations for dyslipidemia plus 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitors may increase the risk of rhabdomyolysis. The upper limit for daily (nontherapeutic) niacin intake has been set at 35 mg. ■ ■PYRIDOXINE (VITAMIN B6) Vitamin B6 refers to a family of compounds that includes pyridoxine, pyridoxal, pyridoxamine, and their 5′-phosphate derivatives. 5′-Pyridoxal phosphate (PLP) is a cofactor for >100 enzymes involved in amino acid metabolism. Vitamin B6 also is involved in heme and neurotransmitter synthesis and in the metabolism of glycogen, lipids, steroids, sphingoid bases, and several vitamins, including the conversion of tryptophan to niacin. Dietary Sources Plants contain vitamin B6 in the form of pyridox ine, whereas animal tissues contain PLP and pyridoxamine phosphate. The vitamin B6 contained in plants is less bioavailable than that in animal tissues. Rich food sources of vitamin B6 include legumes, nuts, wheat bran, and meat, although it is present in all food groups. Deficiency Symptoms of vitamin B6 deficiency include epithelial changes, as seen frequently with other B vitamin deficiencies. In

addition, severe vitamin B6 deficiency can lead to peripheral neuropa thy, abnormal electroencephalograms, and personality changes that include depression and confusion. In infants, diarrhea, seizures, and anemia have been reported. Microcytic hypochromic anemia is due to diminished hemoglobin synthesis, since the first enzyme involved in heme biosynthesis (aminolevulinate synthase) requires PLP as a cofactor (Chap. 102). In some case reports, platelet dysfunction has been reported. Since vitamin B6 is necessary for the conversion of homocysteine to cystathionine, it is possible that chronic low-grade vitamin B6 deficiency may result in hyperhomocysteinemia, which has been associated with vascular dysfunction and an increased risk

of car diovascular disease; however, so far, there is only limited randomized controlled trial evidence (Chap. 431). Independent of homocysteine, low levels of circulating vitamin B6 have been associated with inflam mation and elevated levels of C-reactive protein. Certain medications, such as isoniazid, l-dopa, penicillamine, and cycloserine, interact with PLP due to a reaction with carbonyl groups. Pyridoxine should be given concurrently with isoniazid to avoid neuropathy. The increased ratio of AST to ALT seen in alcoholic liver disease reflects the relative vitamin B6 dependence of ALT. Vitamin B6 dependency syndromes that require pharmacologic doses of vitamin B6 are rare; they include cystathionine β-synthase deficiency, pyridoxineresponsive (primarily sideroblastic) anemias, and gyrate atrophy with chorioretinal degeneration due to decreased activity of the mitochon drial enzyme ornithine aminotransferase. In these situations, 100–200 mg/d of oral vitamin B6 is required for treatment. Severe nausea and vomiting in pregnancy might respond to pyri doxine combined with doxylamine. High doses of vitamin B6 have been used to treat carpal tunnel syndrome, premenstrual syndrome, schizophrenia, autism, and diabetic neuropathy but have not been found to be effective. The laboratory diagnosis of vitamin B6 deficiency is generally based on low plasma PLP values (<20 nmol/L). Vitamin B6 deficiency is treated with 50 mg/d; higher doses of 100–200 mg/d are given if the deficiency is related to medication use. Vitamin B6 should not be given with l-dopa, since the vitamin interferes with the action of this drug. Toxicity The safe upper limit for vitamin B6 has been set at 100 mg/d, although no adverse effects have been associated with high intakes of vitamin B6 from food sources only. When toxicity occurs, it causes severe sensory neuropathy, leaving patients unable to walk; however, in most cases, this is reversible upon cessation of the high intake. Medi cation safety monitoring suggests a rather high prevalence of vitamin B6–induced neuropathy. Accordingly, long-term high-dose vitamin B6 supplementation should be discouraged. Some cases of photosensitiv ity and dermatitis have been reported. ■ ■FOLATE (VITAMIN B12) See Chap. 104. ■ ■VITAMIN C Both ascorbic acid (only the l-isomer) and its oxidized product dehy droascorbic acid are biologically active. Actions of vitamin C include antioxidant activity, promotion of nonheme iron absorption, carnitine biosynthesis, conversion of dopamine to norepinephrine, tyrosine catabolism, histone and DNA demethylation, and synthesis of many peptide hormones. Vitamin C is also important for connective tissue metabolism and cross-linking (proline hydroxylation), and it is a com ponent of many drug-metabolizing enzyme systems, particularly the mixed-function oxidase systems. Absorption and Dietary Sources Vitamin C is almost com pletely absorbed if <100 mg is administered in a single dose; however, only ≤50% is absorbed at doses >1 g. Enhanced degradation and fecal and urinary excretion of vitamin C occur at higher intake levels. Good dietary sources of vitamin C include citrus fruits, green veg etables (especially broccoli), tomatoes, and potatoes. Consumption of five servings of fruits and vegetables a day provides vitamin C in excess of the RDA of 90 mg/d for men and 75 mg/d for women. In addition, ~40% of the U.S. population consumes vitamin C as a dietary

supplement in which “natural forms” of the vitamin are no more bio available than synthetic forms. Smoking (including “passive” smoking), hemodialysis, pregnancy, lactation, and stress (e.g., infection, trauma) appear to increase vitamin C requirements.

Deficiency Vitamin C deficiency causes scurvy. In the United States, this condition is seen primarily among the poor and the elderly, in alcoholics who consume <10 mg/d of vitamin C, and in young adults who eat severely unbalanced diets. In addition to generalized fatigue, symptoms of scurvy primarily reflect impaired formation of mature connective tissue and include bleeding into the skin

(petechiae, ecchy moses, perifollicular hemorrhages); inflamed and bleeding gums; and manifestations of bleeding into joints, the peritoneal cavity, the pericardium, and the adrenal glands. In children, vitamin C deficiency may cause impaired bone growth. Laboratory diagnosis of vitamin C deficiency is based on low plasma or leukocyte levels. Administration of vitamin C (200 mg/d) improves the symptoms of scurvy within several days. High-dose vitamin C supplementation (e.g., 0.2 g up to several grams per day) may slightly decrease the symp toms and duration of upper respiratory tract infections. Vitamin C sup plementation has also been reported to be useful in Chédiak-Higashi syndrome (Chap. 67) and osteogenesis imperfecta (Chap. 425). Diets high in vitamin C have been claimed to lower the incidence of certain cancers, particularly esophageal and gastric cancers. If proven, this effect may be because vitamin C can prevent the conversion of nitrites and secondary amines to carcinogenic nitrosamines. Emerging evi dence suggests a therapeutic effect of intravenous parenteral (not oral) pharmacologic doses of up to 1 g/kg body weight of ascorbic acid in the treatment of cancers (e.g., metastatic pancreatic, ovarian, glioblastoma, and non-small-cell lung cancers). The mechanism of pharmacologic ascorbate in cancer treatment (as a stand-alone agent or with other therapeutic agents) appears to be pro-oxidative, either synergistic (e.g., gemcitabine, programmed cell death protein 1 [PD-1] inhibitors, radia tion) or additive with other agents. CHAPTER 344 Vitamin and Trace Mineral Deficiency and Excess

Toxicity Taking >2 g of vitamin C in a single dose may result in abdominal pain, diarrhea, and nausea. Since vitamin C may be metabolized to oxalate, it is feared that chronic high-dose vitamin C supplementation could result in an increased prevalence of kidney stones. However, except in patients with preexisting renal disease, this association has not been borne out in several trials. Nevertheless, it is reasonable to advise patients with a history of kidney stones (especially oxalate renal stones) and renal insufficiency not to take large doses of vitamin C. There is also an unproven but possible risk that chronic high doses of vitamin C could promote iron overload and iron toxicity (e.g., in patients with hemochromatosis or thalassemia major). High doses of vitamin C can induce hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, and doses >1 g/d can cause false-negative guaiac reactions and interfere with tests for urinary glucose. High doses may interfere with the activity of certain drugs and diagnostic tests (e.g., false-negative results of guaiac-based fecal occult blood tests). Parenteral high-dose vitamin C in patients with severe infections or sepsis has no beneficial effects and may increase mortality. ■ ■BIOTIN Biotin (also known as vitamin B7 or vitamin H) is a water-soluble vita min that plays a role in gene expression, gluconeogenesis, and fatty acid synthesis and serves as a carbon dioxide (CO_2) carrier on the surface of both cytosolic and mitochondrial carboxylase enzymes. The vitamin also functions in the catabolism of specific amino acids (e.g., leucine) and in gene regulation by histone biotinylation. Excellent food sources of biotin include organ meat such as liver or kidney, soy and other beans, yeast, and egg yolks; however, egg white contains the protein avidin, which strongly binds the vitamin and reduces its bioavailability. Biotin deficiency due to low dietary intake is rare; rather, deficiency is due to inborn errors of metabolism (e.g., biotinidase deficiency). Biotin deficiency has been induced by experimental feeding of egg white diets and by biotin-free parenteral nutrition in patients with short bowels. In adults, biotin deficiency results in mental changes (depression, hallucinations), paresthesia, anorexia, and nausea. A

scaling, seborrheic, and erythematous rash may occur around the eyes, nose, and mouth as well as on the extremities. In infants, biotin defi ciency presents as hypotonia, lethargy, and apathy. In addition, infants may develop alopecia and a characteristic rash that includes the ears. At present,

evidence does not support a therapeutic role of high-dose biotin in multiple sclerosis. The laboratory diagnosis of biotin defi ciency can be established on the basis of a decreased concentration of urinary biotin (or its major metabolites), increased urinary excretion of 3-hydroxyisovaleric acid after a leucine challenge, or decreased activity of biotin-dependent enzymes in lymphocytes (e.g., propionyl-CoA car boxylase). Treatment requires pharmacologic doses of biotin, that is, up to 10 mg/d. No toxicity is known. High-dose biotin supplements could interfere with different immunoassay platforms based on streptavidinbiotin technology (e.g., biotinylated antibodies), resulting in false-positive (e.g., free T4 or T3) or false-negative tests (e.g., thyroid-stimulating hormone, troponin, β-human chorionic gonadotropin pregnancy test).

■ ■PANTOTHENIC ACID (VITAMIN B5) Pantothenic acid is a component of coenzyme A and phosphopante theine, which are involved in fatty acid metabolism and the synthesis of cholesterol, steroid hormones, and all compounds formed from isoprenoid units. In addition, pantothenic acid is involved in the acety lation of proteins. The vitamin is excreted in the urine, and the labora tory diagnosis of deficiency is based on low urinary vitamin levels. The vitamin is ubiquitous in the food supply. Liver, yeast, egg yolks, whole grains, and vegetables are particularly good sources. Human pantothenic acid deficiency has been demonstrated only by experimental feeding of diets low in pantothenic acid or by admin istration of a specific pantothenic acid antagonist. The symptoms of pantothenic acid deficiency are nonspecific and include gastrointes tinal disturbance, depression, muscle cramps, paresthesia, ataxia, and hypoglycemia. Pantothenic acid deficiency is believed to have caused the “burning feet syndrome” seen in prisoners of war during World War II. No toxicity of this vitamin has been reported. PART 10 Disorders of the Gastrointestinal System ■ ■CHOLINE Choline is a precursor for acetylcholine, phospholipids, and betaine. Choline is necessary for the structural integrity of cell membranes, cholinergic neurotransmission, lipid and cholesterol metabolism, methyl-group metabolism, and transmembrane signaling. Recently, a recommended adequate intake was set at 550 mg/d for men and 425 mg/d for women, although certain genetic polymorphisms can increase an individual’s requirement. Choline is thought to be a “con ditionally essential” nutrient in that its de novo synthesis occurs in the liver and results in lesser-than-used amounts only under certain stress conditions (e.g., alcoholic liver disease). The dietary requirement for choline depends on the status of other nutrients involved in methylgroup metabolism (folate, vitamin B12, vitamin B6, and methionine) and thus varies widely. Choline is widely distributed in food (e.g., egg yolks, wheat germ, organ meat, milk) in the form of lecithin (phospha tidylcholine). Choline deficiency has occurred only in experimental conditions or in patients receiving parenteral nutrition devoid of choline and rarely in specific inborn errors of choline metabolism. Deficiency results in fatty liver, elevated aminotransferase levels, and skeletal muscle damage with high creatine phosphokinase values. The diagnosis of choline deficiency is currently based on low plasma levels, although nonspecific conditions (e.g., heavy exercise) may also sup press plasma levels. Toxicity from choline results in hypotension, increased sweating, diarrhea, salivation, and a fishy body odor. The upper limit for choline intake has been set at 3.5 g/d. Because of its ability to lower choles terol and homocysteine levels, choline treatment has been suggested for patients with dementia and patients at high risk of cardiovascular disease. However, the benefits of such treatment have not been firmly documented; recently, signals for an increased cardiovascular risk have been reported. Choline- and betaine-restricted diets are of therapeutic value in trimethylaminuria (“fish odor syndrome”) or in decreasing the production of the gut microbiome-derived trimethylamine N-oxide (TMAO) as a potential cardiovascular risk modulator.

■ ■FLAVONOIDS Flavonoids constitute a large family of polyphenolic phytochemicals that contribute to the aroma, taste, and color of fruits and vegetables. Major groups of dietary flavonoids include anthocyanidins in ber ries; flavanols (catechins) in green tea and chocolate; flavonols (e.g., quercetin) in broccoli, kale, leeks, onions, and the skins of grapes and apples; and isoflavones (e.g., genistein) in legumes. Isoflavones have a low bioavailability and are partially metabolized by the intestinal flora. The dietary intake of flavonoids is highly variable and estimated at 10–400 mg/d; this figure is almost certainly an underestimate attribut able to a lack of information on their concentrations in many foods. Several flavonoids have antioxidant activity and affect cell signaling. From observational epidemiologic studies and limited clinical (human and animal) studies, flavonoids have been postulated to play a role in the prevention of several chronic diseases, including neurodegen erative disease, diabetes, and osteoporosis. The ultimate importance and usefulness of these compounds against human disease have not been consistently demonstrated. Nevertheless, a dietary pattern with high intake of fruits, vegetables, and legumes should be encouraged to assure a higher intake of these and others nonnutritive bioactives. ■ ■VITAMIN A Vitamin A, in the strictest sense, refers to retinol and retinyl esters. However, the oxidized metabolites retinaldehyde and retinoic acid are also biologically active compounds. The term retinoids includes all molecules (including synthetic molecules) that are chemically related to retinol. Retinaldehyde (11-cis) is the form of vitamin A that is required for normal vision, whereas retinoic acid is necessary for normal morphogenesis, growth, and cell differentiation. Retinoic acid does not function directly in vision and, in contrast to retinol, is not involved in reproduction. Vitamin A also plays a role in iron utiliza tion, humoral immunity, T cell–mediated immunity, natural killer cell activity, and phagocytosis. Vitamin A is found in the human food supply in two forms: pre formed as retinyl esters and provitamin A carotenoids. There are >700 carotenoids in nature, ~50 of which can be metabolized to vitamin A. β-Carotene is the most prevalent carotenoid with provitamin A activity in the food supply. In humans, significant fractions of carotenoids are absorbed intact and are stored in liver and fat. It is estimated that in healthy humans ≥12 μg (range, 4–27 μg) of dietary all-trans β-carotene is equivalent to 1 μg of retinol activity, whereas the figure is ≥24 μg for other dietary provitamin A carotenoids (e.g., β-cryptoxanthin, α-carotene). The vitamin A equivalency for a β-carotene supplement in an oily solution is 2:1. Metabolism The liver contains ~90% of the vitamin A reserves in healthy individuals and secretes vitamin A in the form of retinol, which is bound in the circulation to retinol-binding protein. Once binding has occurred, the retinol-binding protein complex interacts with a second protein, transthyretin. This trimolecular complex functions to prevent vitamin A from being filtered by the kidney glomerulus, thus protecting the body against the toxicity of retinol and allowing retinol to be taken up by specific cell-surface receptors that recognize retinolbinding protein. A certain amount of vitamin A enters peripheral cells even if it is not bound to retinol-binding protein. After retinol is inter nalized by the cell, it becomes bound to a series of cellular retinol-binding proteins, which function as sequestering and transporting agents as well as co-ligands for enzymatic reactions. Certain cells also contain retinoic acid–binding proteins, which have sequestering functions but also shuttle retinoic acid to the nucleus and enable its metabolism. Vitamin A metabolites (retinoids) such as retinoic acid are potent regulators of gene transcription through nuclear receptor signaling, thus playing a key role in many cellular and metabolic pathways. Two families of receptors (retinoic acid receptors [RARs] and retinoid X receptors [RXRs]) are active in retinoid-mediated gene transcription. Retinoid receptors regulate transcription by binding as dimeric com plexes to specific DNA sites—the retinoic acid response elements—in target genes (Chap. 389). The receptors can either stimulate or repress gene expression in response to their ligands. RARs bind all-trans

retinoic acid and 9-cis-retinoic acid, whereas RXRs bind only 9-cisretinoic acid. The retinoid receptors play an important role in controlling cell proliferation and differentiation. RXRs dimerize with other nuclear receptors to function as coregulators of genes responsive to retinoids, but also to thyroid hormone and calcitriol. RXR agonists induce insulin sensitivity experimentally, perhaps because RXRs are cofactors for the peroxisome proliferator-activated receptors, which also mediate fatty acid and carbohydrate metabolism and are targets for different drugs including thiazolidinedione drugs (e.g., rosiglitazone and pioglitazone) (Chap. 416). Dietary Sources The retinol activity equivalent (RAE) is used to express the vitamin A value of food: 1 RAE is defined as 1 μg of retinol (0.003491 mmol), 12 μg of β-carotene, and 24 μg of other provitamin A carotenoids. In older literature, vitamin A often was expressed in international units (IUs), with 1 μg of retinol equal to 3.33 IU of retinol and 20 IU of β-carotene. Although these IUs are no longer in scientific use, they can still be found in reports of the food industry and in public health interventions in low-income countries. Liver, fish, and eggs are excellent food sources for preformed vitamin A; vegetable sources of provitamin A carotenoids include dark green and deeply colored fruits and vegetables. Moderate cook ing of vegetables enhances carotenoid release for uptake in the gut. Carotenoid absorption is also aided by some fat in a meal. Exclusive breast-feeding can cover the vitamin A needs of infants if the mother has an adequate vitamin A status and a large enough volume of milk. If the nursing mother has inadequate vitamin A intake or concomitant diseases or her infant was a preterm delivery, breast milk probably will not supply enough vitamin A to prevent deficiency. In developing countries, chronic dietary deficiency is the main cause of vitamin A deficiency and is exacerbated by infection. In early childhood, low vita min A status results from inadequate intakes of animal food sources and edible oils, both of which are expensive, coupled with seasonal unavailability of vegetables and fruits and lack of marketed fortified food products. Factors that interfere with vitamin A metabolism may also affect status or function. For example, concurrent zinc deficiency can interfere with the mobilization of vitamin A from liver stores. Alco hol interferes with the conversion of retinol to retinaldehyde in the eye by competing for alcohol (retinol) dehydrogenase. Drugs that interfere with the absorption of vitamin A include mineral oil, neomycin, and bile acid sequestrants (e.g., cholestyramine). Deficiency Vitamin A deficiency is endemic in areas where diets are chronically poor, especially in southern Asia, sub-Saharan Africa, some parts of Latin America, and the western Pacific, including parts of China. Vitamin A status is usually assessed by measuring serum retinol (normal range, 1.05–3.50 μmol/L [30–100 μg/dL]) or via doseresponse tests or tests of dark adaptation. To assure a correct biochemi cal assessment of vitamin A status, a simultaneous assessment of the inflammatory status is needed (in analogy to the assessment of iron status); not doing so may result in an overestimation of vitamin A deficiency. Correction factors to adjust the measured plasma vitamin A levels to account for the influence of C-reactive protein and α1-acid glycoprotein are available. Stable isotopic or invasive liver biopsy meth ods are available to estimate total-body stores of vitamin A. As judged by deficient serum retinol (<0.70 μmol/L [20 μg/dL]), vitamin A deficiency worldwide is present in 190 million preschool-age children, among whom >5 million have an ocular manifestation of deficiency termed xerophthalmia. This condition includes milder stages of night blindness and conjunctival xerosis (dryness) with Bitot’s spots (white patches of keratinized epithelium appearing on the sclera) that may affect 1–5% of children in deficient populations as well as rare, poten tially blinding corneal ulceration and necrosis. Keratomalacia (soften ing of the cornea) leads to corneal scarring that blinds an estimated quarter of a million children each year and is associated with fatality rates of 4–25%. However, vitamin A deficiency severe enough to cause any clinical stage poses an increased risk of death from diarrhea, dys entery, measles, malaria, or respiratory

disease. This is because vitamin A deficiency can compromise barrier, innate, and acquired immune

defenses to infection. In areas where deficiency is widely prevalent, vitamin A supplementation can markedly reduce the risk of childhood mortality (by 23–34%, on average). About 10% of pregnant women in undernourished settings also develop night blindness (assessed by history) during the latter half of pregnancy; this level of moderate to severe vitamin A deficiency is associated with an increased risk of maternal infection and death. Maternal vitamin A deficiency may also exacerbate already low vitamin A nutrition and associated risks for the newborn. In South Asia, where maternal deficiency is prominent, giving infants a single oral dose (50,000 IU) of vitamin A shortly after birth has reduced infant mortality by ≥10%, whereas in African set tings less affected by maternal vitamin A deficiency, no effect has been noted, revealing differences in risk of deficiency and benefit of supple mentation across regions. However, the World Health Organization does not recommend high-dose supplementation to newborns.

TREATMENT Vitamin A Deficiency Vitamin A is commercially available for treatment and prevention in esterified forms (e.g., acetate, palmitate), which are more stable than other forms. Any stage of xerophthalmia should be treated with 60 mg (or RAE) or 200,000 IU of vitamin A in oily solution, usually contained in a soft-gel capsule. The same dose is repeated 1 and 14 days later. Doses should be reduced by half for patients 6–11 months of age. Mothers with night blindness or Bitot's spots should be given vitamin A orally 3 mg daily for at least 3 months. These regimens are efficacious, and they are far less expensive and more widely available than injectable water-miscible vitamin A. A common approach to prevention is to provide vitamin A supple mentation every 4–6 months to young children 6 months to 5 years of age (both HIV-positive and HIV-negative) in high-risk areas. For prevention, infants 6–11 months of age should receive 30 mg of vitamin A; children 12–59 months of age should receive 60 mg. For reasons that are not clear, although early neonatal vitamin A may reduce infant mortality, vitamin A given between 1 and 5 months of age has not proven effective in improving survival in high-risk settings. CHAPTER 344 Vitamin and Trace Mineral Deficiency and Excess
Uncomplicated vitamin A deficiency is rare in industrialized countries. One high-risk group—extremely low-birth-weight (<1000-g) infants—is likely to be vitamin A deficient and should receive a supplement of 1500 μg (or RAE) three times a week for 4 weeks. Severe measles in any society can lead to secondary vitamin A deficiency. Children hospitalized with measles should receive two 60-mg doses of vitamin A on 2 consecutive days. Vitamin A deficiency most often occurs in patients with malabsorptive dis eases (e.g., celiac sprue, short-bowel syndrome) who have abnormal dark adaptation or symptoms of night blindness without other ocular changes. Typically, such patients are diagnosed in advanced care settings where they are treated for 1 month with 15 mg/d of a water-miscible preparation of vitamin A. This treatment is followed by a lower maintenance dose, with the exact amount determined by monitoring serum retinol. Finding application elsewhere in medicine, retinoic acid is useful in the treatment of promyelocytic leukemia (Chap. 109) and also is used in the treatment of cystic acne because it inhibits keratinization, decreases sebum secretion, and possibly alters the inflammatory reaction (Chap. 60). No specific signs or symptoms result from carotenoid deficiency. It was postulated that β-carotene would be an effective chemopre ventive agent for cancer because numerous epidemiologic studies had shown that diets high in β-carotene were associated with lower incidences of cancers of the respiratory and digestive systems. However, intervention studies in

smokers found that treatment with high doses of β-carotene actually resulted in more lung cancers than did treatment with placebo. Non–provitamin A carotenoids such as lutein and zeaxanthin have been suggested to confer protection against macular degeneration, and one large-scale intervention study did not show a beneficial effect except in those with a low

lutein status. The use of the non–provitamin A carotenoid lycopene to protect against prostate cancer has been proposed. However, the effectiveness of these agents has not been proved by intervention studies, and the mechanisms underlying these purported biologic actions are unknown.

Selective plant-breeding techniques that lead to a higher provi tamin A carotenoid content in staple foods may decrease vitamin A malnutrition in low-income countries. Moreover, a recently devel oped genetically modified food (Golden Rice) had a β-carotene–to– vitamin A conversion ratio of ~3:1 in children. Toxicity The acute toxicity of vitamin A was first noted in Arctic explorers who ate polar bear liver and has also been seen after admin istration of 150 mg to adults or 100 mg to children. Acute toxicity is manifested by increased intracranial pressure, vertigo, diplopia, bulg ing fontanels (in children), seizures, and exfoliative dermatitis; it may result in death. Among children being treated for vitamin A deficiency according to the protocols outlined above, transient bulging of fon tanels occurs in 2% of infants, and transient nausea, vomiting, and headache occur in 5% of preschoolers. Chronic vitamin A intoxication is largely a concern in industrialized countries and has been seen in otherwise healthy adults who ingest 15 mg/d and children who ingest

6 mg/d over a period of several months. Manifestations include dry skin, cheilosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pres sure and papilledema. Liver fibrosis with portal hypertension may also result from chronic vitamin A intoxication. Provision of vitamin A in excess to pregnant women has resulted in spontaneous abortion and in congenital malformations, including craniofacial abnormalities and valvular heart disease. In pregnancy, the daily dose of vitamin A should not exceed 3 mg. Also, topical retinoids should be avoided during pregnancy. Commercially available retinoid derivatives are also toxic, including 13-cis-retinoic acid, which has been associated with birth defects. Thus, contraception should be continued for at least 1 year and possibly longer in women who have taken 13-cis-retinoic acid. PART 10 Disorders of the Gastrointestinal System In malnourished children, vitamin A supplements (30–60 mg), in amounts calculated as a function of age and given in several rounds over 2 years, are considered to amplify nonspecific effects of vaccines. However, for unclear reasons, in one African setting, there has been a negative effect on mortality rates in incompletely vaccinated girls. High doses of supplemental carotenoids do not result in toxic symp toms but should be avoided in smokers due to an increased risk of lung cancer. Very high doses of β-carotene (~200 mg/d) have been used to treat or prevent the skin rashes of erythropoietic protoporphyria. Caro tenemia, which is characterized by a yellowing of the skin (in creases of the palms and soles) but not the sclerae, may follow ingestion of >30 mg of β-carotene daily. Hypothyroid patients are particularly susceptible to the development of carotenemia due to impaired break down of carotene to vitamin A. Reduction of carotenes in the diet results in the disappearance of skin yellowing and carotenemia over a period of 30–60 days. ■ ■VITAMIN D The metabolism of the fat-soluble vitamin D is described in detail in Chap. 421. The biologic effects of this vitamin are mediated by vitamin D receptors, which are found in most tissues; binding with

these receptors potentially expands vitamin D actions to many differ ent cell systems and organs (e.g., immune cells, brain, breast, colon, and prostate) in addition to the classic endocrine effects on calcium and phosphate metabolism and bone health. Vitamin D is thought to be important for maintaining normal function of many nonskeletal tissues such as muscle (including heart muscle), for immune func tion, and for inflammation as well as for cell proliferation and differ entiation. Older studies have shown that vitamin D may be useful as adjunctive treatment for tuberculosis, psoriasis, and multiple sclerosis or for the prevention of certain cancers. Vitamin D insufficiency may increase the risk of type 1 diabetes mellitus, cardiovascular disease (insulin resistance, hypertension, or low-grade inflammation), or brain

dysfunction (e.g., depression). However, the exact physiologic roles of vitamin D in these nonskeletal diseases and the importance of these roles have so far not been clarified. Recent placebo-controlled studies did not show a therapeutic benefit of vitamin D for cancer prevention, control of cardiovascular disease, or risk of type 2 diabetes, depression, tuberculosis infection, or other respiratory infections. Presently, it is not known whether these effects of vitamin D supplements (with or without calcium) might be different according to the baseline status (normal vs severely deficient) of patients. The skin is a major source of vitamin D, which is synthesized upon skin exposure to ultraviolet B radiation (UV-B; wavelength, 290–320 nm). Except for fish, food (unless fortified) contains only limited amounts of vitamin D. Vitamin D2 (ergocalciferol) is obtained from plant sources and is the chemical form found in some supplements. Deficiency Vitamin D status is assessed by measuring serum levels of 25-dihydroxyvitamin D (25[OH] vitamin D); however, there is no consensus on a uniform assay, on optimal serum levels, or on the real benefit of biochemical screening in asymptomatic adults. The optimal level might, in fact, differ according to the targeted disease entity. Epi demiologic and experimental data indicate that a 25(OH) vitamin D level of >20 ng/mL (≥50 nmol/L; to convert ng/mL to nmol/L, multiply by 2.496) is sufficient for good bone health. The latter 25(OH) vitamin D plasma concentration would cover the requirements of 97.5% of the population. Some experts, however, advocate higher serum levels (e.g., >30 ng/mL) for other desirable endpoints of vitamin D action. There is insufficient evidence to recommend combined vitamin D and calcium supplementation as a primary preventive strategy (as opposed to secondary prevention) for reduction of the incidence of fractures in healthy men and premenopausal women. Risk factors for vitamin D deficiency are old age, lack of sun expo sure, dark skin (especially among residents of northern latitudes), fat malabsorption, and obesity; deficiency can also occur after gastric bypass surgery. In addition, in African populations, the prevalence of vitamin D deficiency might be high (especially in women, newborn babies, urban populations, and those living in northern African coun tries). Rickets represents the classic disease of vitamin D deficiency. Signs of deficiency are muscle soreness, weakness, and bone pain. Some of these effects are independent of calcium intake. To prevent glucocorticoid-induced osteoporosis, treatment with calcium (1000– 1200 mg/d) and vitamin D (600–800 IU/d) through diet and/or supple ments in combination with weight-bearing exercise is recommended. The U.S. National Academy of Sciences recently advised that the majority of adult North Americans should receive 600 IU/d of vitamin D (RDA = 15 µg/d or 600 IU/d; Chap. 343). However, for people aged

> “ 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, espe cially during the winter months. Vitamin D deficiency can be treated by oral administration of 50,000 IU/week for 6–8 weeks followed by a maintenance dose of 800 IU/d (20 µg/d) from food and supplements once normal plasma levels have been attained. There is still uncertainty regarding the optimal therapeutic dosage (high vs low) for elderly at risk of falls. The physiologic effects of vitamin D2 and vitamin D3 are similar when these vitamins are ingested over long periods. Toxicity The upper limit of intake has been set at 4000 IU/d. Con trary 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 tocoph erols and tocotrienols, although only the α-tocopherols meet human requirements. Vitamin E acts as a chain-breaking antioxidant and is an efficient peroxyl 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 inhib its prostaglandin synthesis and the activities of protein kinase C and phospholipase A2. 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 incor poration 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 contain ing 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 in developed coun tries but can occur in developing countries due to inadequate intake. Vitamin E deficiency is seen only in severe and prolonged malabsorp tive diseases, such as celiac disease, chronic cholestatic liver disease, or after small-intestinal resection or bariatric surgery. Children with cystic fibrosis or prolonged cholestasis may develop vitamin E defi ciency 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 are flexia, 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 labo ratory 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 d may be administered intra muscularly. Vitamin E in high doses may protect against oxygeninduced 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 convincing evidence for these properties is lacking. When given in combination with other antioxidants, vitamin E may help prevent macular degenera tion. Vitamin E may have favorable therapeutic effects in noncir rhotic nondiabetic patients with nonalcoholic steatohepatitis. 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 and prostate cancer risk (especially in combination with selenium supplements).

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 anti platelet 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 K1, also known as phylloquinone, from vegetable sources, and vitamin K2, or menaqui nones, which are 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 glu tamic acid, which is necessary for calcium binding to γ-carboxylated proteins such as prothrombin (factor II); factors VII, IX, and X; pro tein C; protein S; and proteins found in bone (osteocalcin) and vascu lar smooth muscle (e.g., matrix Gla protein). However, the importance of vitamin K for bone mineralization and prevention of vascular calcifi cation in different patient groups (including chronic kidney disease) is unclear. 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 mar garine 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. CHAPTER 344 Deficiency The symptoms of vitamin K deficiency are due to hem orrhage; 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. Intra cranial 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 and Trace Mineral Deficiency and Excess
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. Broadspectrum 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 antiobesity drug orlistat can lead to changes in international normalized ratio due to vitamin K malabsorption. The assessment of the vitamin K status can be done by measurement of phylloquinone (vitamin K1) concentration in serum (deficiency <0.15 μg/L); the cellular utilization of vitamin K can be assessed by the serum or plasma concentration of undercarboxylated prothrombin (protein induced by vitamin K absence/antagonism [PIVKA-II]). An elevated prothrombin time or activated partial thromboplastin time or reduced clotting factors are useful markers in severe deficiency but are otherwise nonspecific and lack sensitivity. Vitamin K deficiency is treated with a parenteral dose of 10 mg. For patients with chronic mal absorption, 1–2 mg/d should be given orally or 1–2 mg per week can be taken parenterally. Patients with liver disease may have an elevated prothrombin time because of liver cell destruction as well as vitamin K deficiency. If an elevated prothrombin time does not improve during vitamin K therapy, it can be deduced that this abnormality is not the result of vitamin K deficiency. Toxicity Toxicity from dietary phylloquinones and menaquinones has not been described. High doses of vitamin K can impair the actions of oral vitamin K antagonist anticoagulants. MINERALS See also Table 344-2. ■ ■CALCIUM See Chap. 421.

TABLE 344-2 Deficiencies and Toxicities of Metals ELEMENT DEFICIENCY TOXICITY Boron No biologic function determined Developmental defects, male sterility, testicular atrophy 20 mg/d (extrapolated from animal data) Calcium Reduced bone mass, osteoporosis Renal insufficiency (milk-alkali syndrome), nephrolithiasis, impaired iron absorption, thiazide diuretics Copper Anemia, growth retardation, defective keratinization and pigmentation of hair, hypothermia, degenerative changes in aortic elastin, osteopenia, mental deterioration Nausea, vomiting, diarrhea, hepatic failure, tremor, mental deterioration, hemolytic anemia, renal dysfunction Chromium Impaired glucose tolerance Occupational: Renal failure, dermatitis, pulmonary cancer Fluoride ↑ Dental caries Dental and skeletal fluorosis, osteosclerosis 10 mg/d (fluorosis) Iodine Thyroid enlargement, ↓ T4, cretinism Thyroid dysfunction, acne-like eruptions 1100 μg/d (thyroid dysfunction) Iron Muscle abnormalities, koilonychia, pica, anemia, ↓ work performance, impaired cognitive development, premature labor, ↑ perinatal maternal death Gastrointestinal effects (nausea, vomiting, diarrhea, constipation), iron overload with organ damage, acute and chronic systemic toxicity, increased susceptibility to malaria, increased risk association with certain chronic diseases (e.g., diabetes) Manganese Impaired growth and skeletal development, reproduction, lipid and carbohydrate metabolism; upper body rash General: Neurotoxicity, Parkinson-like symptoms Occupational: Encephalitis-like syndrome, Parkinson-like syndrome, psychosis, pneumoconiosis Molybdenum Severe neurologic abnormalities Reproductive and fetal abnormalities 2 mg/d (extrapolated from animal data) Selenium Cardiomyopathy, heart failure, striated muscle degeneration General: Alopecia, nausea, vomiting, abnormal nails, emotional lability, peripheral neuropathy, lassitude, garlic odor to breath, dermatitis Occupational: Lung and nasal carcinomas, liver necrosis, pulmonary inflammation PART 10 Disorders of the Gastrointestinal System Phosphorus Rickets (osteomalacia), proximal muscle weakness, rhabdomyolysis, paresthesia, ataxia, seizure, confusion, heart failure, hemolysis, acidosis Hyperphosphatemia 4000 mg/d Zinc Growth retardation, ↓ taste and smell, alopecia, dermatitis, diarrhea, immune dysfunction, failure to thrive, gonadal atrophy, congenital malformations General: Reduced copper absorption, gastritis, sweating, fever, nausea, vomiting Occupational: Respiratory distress, pulmonary fibrosis ■ ■ZINC Zinc is an integral component of many metalloenzymes in the body; it is involved in the synthesis and stabilization of proteins, DNA, and RNA and plays a structural role in ribosomes and

membranes. Zinc is necessary for the binding of steroid hormone receptors and several other transcription factors to DNA. Zinc is essential for normal sper matogenesis, fetal growth, and embryonic development. Absorption The absorption of zinc from the diet is inhibited by dietary phytate, fiber, oxalate, iron, and copper as well as by certain drugs, including penicillamine, sodium valproate, and ethambutol. Protein-containing foods, i.e., meat, shellfish, nuts, and legumes, are good sources of bioavailable zinc, whereas zinc in grains and legumes is less available for absorption. Grains and legumes contain phytate that binds zinc in the intestine and reduces its availability for absorption. Deficiency Mild zinc deficiency has been described in many dis eases, including diabetes mellitus, HIV/AIDS, cirrhosis, alcoholism, inflammatory bowel disease, malabsorption syndromes, and sickle cell disease. In these diseases, mild chronic zinc deficiency can cause stunted growth in children, decreased taste sensation (hypogeusia), and impaired immune function. Severe chronic zinc deficiency has been described as a cause of hypogonadism and dwarfism in several Middle Eastern countries. In these children, hypopigmented hair is also part of the syndrome. Acrodermatitis enteropathica is a rare autosomal reces sive disorder characterized by abnormalities in zinc absorption. Clinical manifestations include diarrhea, alopecia, muscle wasting, depression, irritability, and a rash involving the extremities, face, and perineum. The rash is characterized by vesicular and pustular crusting with scaling and erythema. Occasional patients with Wilson’s disease have developed zinc deficiency as a consequence of penicillamine therapy (Chap. 427).

TOLERABLE UPPER (DIETARY)

INTAKE LEVEL 2500 mg/d (milk-alkali) 10 mg/d (liver toxicity) Not determined 45 mg/d of elemental iron (gastrointestinal side effects) 11 mg/d (neurotoxicity) 400 µg/d (hair, nail changes) 40 mg/d (impaired copper metabolism) Zinc deficiency is prevalent in many developing countries and usu ally coexists with other micronutrient deficiencies (especially iron defi ciency). Zinc (20 mg/d until recovery) may be an effective adjunctive therapeutic strategy for diarrheal disease and pneumonia in children ≥6 months of age. The diagnosis of zinc deficiency is usually based on a serum zinc level <12 µmol/L (<70 µg/dL). Pregnancy and birth control pills may cause a slight depression in serum zinc levels, and hypoalbuminemia from any cause can result in hypozincemia. In acute stress situations (illness, but also postexercise recovery), zinc may be redistributed from serum into tissues. Zinc deficiency may be treated with 60 mg of elemental zinc taken by mouth twice a day. Zinc gluconate lozenges (13 mg of elemental zinc every 2 h while awake) have been reported to reduce the duration and symptoms of the common cold in adults, but study results are conflicting. Toxicity Acute zinc toxicity after oral ingestion causes nausea, vomiting, and fever. Zinc fumes from welding may also be toxic and cause fever, respiratory distress, excessive salivation, sweating, and headache. Chronic large doses of zinc (ranging from 150 to 450 mg/d) may depress immune function and cause hypochromic anemia as a result of a secondary copper deficiency. Intranasal zinc preparations should be avoided because they may lead to irreversible damage of the nasal mucosa and anosmia. ■ ■COPPER Copper is an integral part of numerous enzyme systems, including amine oxidases, ferroxidase (ceruloplasmin), cytochrome c oxidase, superoxide dismutase, and dopamine hydroxylase. Copper is also a component of ferroprotein, a transport protein involved in the baso lateral transfer of iron during absorption from the enterocyte. As such,

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