vascularization, anemia, and personality changes have been described with riboflavin deficiency.

Deficiency and Excess Riboflavin deficiency almost always is 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 concentrations or by measurement of erythrocyte glutathione reductase activity, with and without added FAD. Because the capacity of the gastrointestinal tract to absorb riboflavin is limited (~20 mg after one oral dose), riboflavin toxicity has not been described.

NIACIN (VITAMIN B_3)

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 numerous 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 bioavailability 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 recommended 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 B_6 and/or riboflavin 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 alcoholics; among patients with congenital defects of intestinal and kidney absorption of tryptophan (Hartnup disease; **Chap. 434e**); and among patients with carcinoid syndrome **(Chap. 113)**, in which there is increased conversion of tryptophan to serotonin. The antituberculosis drug isoniazid is a structural analog of niacin and can precipitate pellagra. In the setting of famine or population displacement, 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 irritability, 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 primary manifestations of this syndrome are sometimes referred to as "the four *D*'s": *d*ermatitis, *d*iarrhea, and *d*ementia leading to *d*eath.

TREATMENT **PELLAGRA**

Treatment of pellagra consists of oral supplementation with 100–200 mg of nicotinamide or nicotinic acid three times daily for 5 days. High doses of nicotinic acid (2 g/d in a time-release form) are used for the treatment of elevated cholesterol and triglyceride levels and/or low high-density lipoprotein cholesterol levels **(Chap. 421)**.

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. Pharmaceutical preparations of nicotinic acid combined with laropiprant, a selective prostaglandin D_2 receptor 1 antagonist, or premedication with aspirin may alleviate these symptoms. Flushing is subject to tachyphylaxis and often improves with time. 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 with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors may increase the risk of rhabdomyolysis. The upper limit for daily niacin intake has been set at 35 mg. However, this upper limit does not pertain to the therapeutic use of niacin.

PYRIDOXINE (VITAMIN B_6)

Vitamin B_6 refers to a family of compounds that includes pyridoxine, pyridoxal, pyridoxamine, and their 5′-phosphate derivatives. 5′-Pyridoxal phosphate (PLP) is a cofactor for more than 100 enzymes involved in amino acid metabolism. Vitamin B_6 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 B_6 in the form of pyridoxine, whereas animal tissues contain PLP and pyridoxamine phosphate. The vitamin B_6 contained in plants is less bioavailable than that in animal tissues. Rich food sources of vitamin B_6 include legumes, nuts, wheat bran, and meat, although it is present in all food groups.

Deficiency Symptoms of vitamin B_6 deficiency include epithelial changes, as seen frequently with other B vitamin deficiencies. In addition, severe vitamin B_6 deficiency can lead to peripheral neuropathy, 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. 126)**. In some case reports, platelet dysfunction has been reported. Since vitamin B_6 is necessary for the conversion of homocysteine to cystathionine, it is possible that chronic low-grade vitamin B_6 deficiency may result in hyperhomocysteinemia and increased risk of cardiovascular disease **(Chaps. 291e and 434e)**. Independent of homocysteine, low levels of circulating vitamin B_6 have been associated with inflammation 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 B_6 dependence of ALT. Vitamin B_6 dependency syndromes that require pharmacologic doses of vitamin B_6 are rare; they include cystathionine β-synthase deficiency, pyridoxine-responsive (primarily sideroblastic) anemias, and gyrate atrophy with chorioretinal degeneration due to decreased activity of the mitochondrial enzyme ornithine aminotransferase. In these situations, 100–200 mg/d of oral vitamin B_6 is required for treatment.

High doses of vitamin B_6 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 B_6 deficiency is generally based on low plasma PLP values (<20 nmol/L). Vitamin B_6 deficiency is treated with 50 mg/d; higher doses of 100–200 mg/d are given if the