currently based on low plasma levels, although nonspecific conditions (e.g., heavy exercise) may also suppress plasma levels.

Toxicity from choline results in hypotension, cholinergic 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 cholesterol 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. Choline- and betaine-restricted diets are of therapeutic value in trimethylaminuria ("fish odor syndrome").

FLAVONOIDS

Flavonoids constitute a large family of polyphenols that contribute to the aroma, taste, and color of fruits and vegetables. Major groups of dietary flavonoids include anthocyanidins in berries; catechins in green tea and chocolate; flavonols (e.g., quercitin) 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 estimated at 10–100 mg/d; this figure is almost certainly an underestimate attributable 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 neurodegenerative disease, diabetes, and osteoporosis. The ultimate importance and usefulness of these compounds against human disease have not been demonstrated.

VITAMIN A

Vitamin A, in the strictest sense, refers to retinol. 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 essential 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 in vision and, in contrast to retinol, is not involved in reproduction. Vitamin A also plays a role in iron utilization, humoral immunity, T cell–mediated immunity, natural killer cell activity, and phagocytosis. Vitamin A is commercially available in esterified forms (e.g., acetate, palmitate), which are more stable than other forms.

There are more than 600 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 ≥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., 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 and secretes vitamin A in the form of retinol, which is bound 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 retinol-binding protein. A certain amount of vitamin A enters peripheral cells even if it is not bound to retinol-binding protein. After retinol is internalized 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.

Retinoic acid is a ligand for certain nuclear receptors that act as transcription factors. 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 complexes to specific DNA sites—the retinoic acid response elements—in target genes (Chap. 400e). 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-*cis*-retinoic acid.

The retinoid receptors play an important role in controlling cell proliferation and differentiation. Retinoic acid is useful in the treatment of promyelocytic leukemia (Chap. 132) and also is used in the treatment of cystic acne because it inhibits keratinization, decreases sebum secretion, and possibly alters the inflammatory reaction (Chap. 71). RXRs dimerize with other nuclear receptors to function as coregulators of genes responsive to retinoids, thyroid hormone, and calcitriol. RXR agonists induce insulin sensitivity experimentally, perhaps because RXRs are cofactors for the peroxisome proliferator-activated receptors, which are targets for thiazolidinedione drugs such as rosiglitazone and troglitazone (Chap. 418).

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 (IU), with 1 μg of retinol equal to 3.33 IU of retinol and 20 IU of β-carotene, but these units are no longer in scientific use.

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 cooking of vegetables enhances carotenoid release for uptake in the gut. Carotenoid absorption is also aided by some fat in a meal. Infants are particularly susceptible to vitamin A deficiency because neither breast nor cow's milk supplies 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 vitamin 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. Concurrent zinc deficiency can interfere with the mobilization of vitamin A from liver stores. Alcohol 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 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 blood-spot retinol or by tests of dark adaptation. Stable isotopic or invasive liver biopsy methods 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 >90 million preschool-age children, among whom >4 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) as well as rare, potentially blinding corneal ulceration and necrosis. *Keratomalacia* (softening of the cornea) leads to corneal scarring that blinds at least a quarter of a million children each year and is associated with fatality rates of 4–25%. However, vitamin A deficiency at any stage poses an increased risk of death from diarrhea, dysentery, measles, malaria, or respiratory disease. 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, and this moderate vitamin A deficiency is associated with an increased risk of maternal infection and death.