As already discussed, vitamin A is a component of rhodopsin and other visual pigments. Not surprisingly, one of the earliest manifestations of vitamin A deficiency is impaired vision, particularly in reduced light *(night blindness)*. Other effects of deficiency are related to the role of vitamin A in maintaining the differentiation of epithelial cells. Persistent deficiency gives rise to *epithelial metaplasia* and *keratinization*. The most devastating changes occur in the eyes and are referred to as *xerophthalmia* (dry eye). First, there is dryness of the conjunctiva (xerosis conjunctivae) as the normal lacrimal and mucus-secreting epithelium is replaced by keratinized epithelium. This is followed by a buildup of keratin debris in small opaque plaques *(Bitot spots)* that progresses to erosion of the roughened corneal surface, softening and destruction of the cornea *(keratomalacia)*, and blindness.

In addition to the ocular epithelium, the epithelium lining the upper respiratory passage and urinary tract also undergoes *squamous metaplasia*. Loss of the mucociliary epithelium of the airways predisposes to secondary pulmonary infections, and desquamation of keratin debris in the urinary tract predisposes to renal and urinary bladder stones. Hyperplasia and *hyperkeratinization of the epidermis* with plugging of the ducts of the adnexal glands may produce follicular or papular dermatosis. Another very serious consequence is immune deficiency, which is responsible for higher mortality rates from common infections such as measles, pneumonia, and infectious diarrhea. In parts of the world where deficiency of vitamin A is prevalent, dietary supplements reduce mortality by 20% to 30%.

***Vitamin A Toxicity.*** Both short- and long-term excesses of vitamin A may produce toxic manifestations, a point of concern because of the megadoses touted by certain sellers of supplements. The consequences of acute hypervitaminosis A were first described by Gerrit de Veer in 1597, a ship's carpenter stranded in the Arctic, who recounted in his diary the serious symptoms that he and other members of the crew developed after eating polar bear liver. With this cautionary tale in mind, the adventurous eater should be aware that acute vitamin A toxicity has also been described in individuals who ingested the livers of whales, sharks, and even tuna.

The symptoms of acute vitamin A toxicity include headache, dizziness, vomiting, stupor, and blurred vision, symptoms that may be confused with those of a brain tumor (*pseudotumor cerebri*). Chronic toxicity is associated with weight loss, anorexia, nausea, vomiting, and bone and joint pain. Retinoic acid stimulates osteoclast production and activity, leading to increased bone resorption and high risk of fractures. Although synthetic retinoids used for the treatment of acne are not associated with these types of conditions, their use in pregnancy should be avoided because of the well-established teratogenic effects of retinoids.

### Vitamin D

**The major function of the fat-soluble vitamin D is the maintenance of adequate plasma levels of calcium and phosphorus to support metabolic functions, bone mineralization, and neuromuscular transmission.** Vitamin D is required for the prevention of bone diseases known as *rickets* (in children whose epiphyses have not already closed), *osteomalacia* (in adults), and *hypocalcemic tetany*. This latter condition is a convulsive state caused by an insufficient extracellular concentration of ionized calcium, which is required for normal neural excitation and the relaxation of muscles. Rickets was nearly endemic in large European cities and poor areas of New York and Boston at the end of the nineteenth century. Although cod liver oil was recognized for its anti-rachitic properties in the early part of that century, it took almost 100 years for it to be accepted by the medical profession as an effective preventive agent (it did not help that cod liver oil consumed in fishing villages in Northern Europe, Scandinavia, and Iceland was a dark, foul-smelling liquid). In addition to its effects on calcium and phosphorus homeostasis, vitamin D has effects in nonskeletal tissues.

***Metabolism of Vitamin D.*** **The major source of vitamin D for humans is its endogenous synthesis from a precursor, 7-dehydrocholesterol, in a photochemical reaction that requires solar or artificial UV light in the range of 290 to 315 nm (UVB radiation).** This reaction results in the synthesis of *cholecalciferol,* known as *vitamin* $D_3$. Herein, the term *vitamin D* is used to refer to this compound. Under usual conditions of sun exposure, about 90% of the required vitamin D is endogenously synthesized the skin. However, individuals with dark skin generally have a lower level of vitamin D production because of melanin pigmentation. Dietary sources, such as deep-sea fish, plants, and grains, contribute the remaining required vitamin D and depend on adequate intestinal fat absorption. In plants, vitamin D is present in a precursor form (ergosterol), which is converted to vitamin D in the body.

The main steps of vitamin D metabolism are summarized as follows):

1. Photochemical synthesis of vitamin D from 7-dehydrocholesterol in the skin and absorption of vitamin D from foods and supplements in the gut
2. Binding of vitamin D from both of these sources to plasma $\alpha_1$-globulin *(D-binding protein or DBP)* and transport into the liver
3. Conversion of vitamin D into 25-hydroxycholecalciferol (25-OH-D) in the liver, through the action of 25-hydroxylases, including CYP27A1 and other CYPs
4. Conversion of 25-OH-D into *1,25-dihydroxyvitamin D,* $[1\alpha,25(OH)_2D_3]$, the most active form of vitamin D, by the enzyme 1α-hydroxylase in the kidney

The production of 1,25-dihydroxyvitamin D in the kidney is regulated by three main mechanisms (Fig. 9-26):

- *Hypocalcemia stimulates secretion of parathyroid hormone (PTH),* which in turn augments the conversion of 25-OH-D into 1,25-dihydroxyvitamin D by activating 1α-hydroxylase
- *Hypophosphatemia directly activates* 1α*-hydroxylase*, increasing the production of 1,25-dihydroxyvitamin D
- *Through a feedback mechanism*, increased levels of 1,25-dihydroxyvitamin D down-regulate its own synthesis through inhibition of 1α-hydroxylase activity

***Functions.*** Like retinoids and steroid hormones, 1,25-dihydroxyvitamin D acts by binding to a high-affinity nuclear receptor (*vitamin D receptor),* which associates with