11-*cis*-retinal, but most is reduced to retinol and lost to the retina, dictating the need for continuous supply.

- *Cell growth and differentiation.* Vitamin A and retinoids play an important role in the orderly differentiation of mucus-secreting epithelium; when a deficiency state exists, the epithelium undergoes *squamous metaplasia,* differentiating into a keratinizing epithelium. Activation of retinoic acid receptors (RARs) by their ligands causes the release of corepressors and the obligatory formation of heterodimers with another retinoid receptor, known as the *retinoic X receptor* (RXR). Both RAR and RXR have three isoforms, α, β, and γ. The RAR/RXR heterodimers bind to retinoic acid response elements located in the regulatory regions of genes that encode receptors for growth factors, tumor suppressor genes, and secreted proteins. Through these effects, retinoids regulate cell growth and differentiation, cell cycle control, and other biologic responses. *All-trans-retinoic acid*, a potent acid derivative of vitamin A, has the highest affinity for RARs compared with other retinoids.
- *Metabolic effects of retinoids.* The retinoic X receptor (RXR), believed to be activated by 9-*cis* retinoic acid, can form heterodimers with other nuclear receptors, such as (as we have seen) nuclear receptors involved in drug metabolism, the peroxisome proliferator-activated receptors (PPARs), and vitamin D receptors. PPARs are key regulators of fatty acid metabolism, including fatty acid oxidation in fat tissue and muscle, adipogenesis, and lipoprotein metabolism. The association between RXR and PPARγ provides an explanation for the metabolic effects of retinoids on adipogenesis.
- *Host resistance to infections.* Vitamin A supplementation can reduce morbidity and mortality from some forms of diarrhea, and in preschool children with measles, supplementation can improve the clinical outcome. The beneficial effect of vitamin A in diarrheal diseases may be related to the maintenance and restoration of the integrity of the epithelium of the gut. The effects of vitamin A on infections also derive in part from its ability to stimulate the immune system, although the mechanisms are not entirely clear. Infections may reduce the bioavailability of vitamin A by inhibiting retinol binding protein synthesis in the liver through the acute-phase response associated with many infections. The drop in hepatic retinol binding protein causes a decrease in circulating retinol, which reduces the tissue availability of vitamin A.

In addition, retinoids, β-carotene, and some related carotenoids function as photoprotective and antioxidant agents.

Retinoids are used clinically for the treatment of skin disorders such as severe acne and certain forms of psoriasis, and also in the treatment of acute promyelocytic leukemia. As discussed in Chapter 7, all-*trans*-retinoic acid induces the differentiation and subsequent apoptosis of acute promyelocytic leukemia cells through its ability to bind to a PML-RARα fusion protein that characterizes this form of cancer. A different isomer, 13-*cis* retinoic acid, has been used with some success in the treatment of childhood neuroblastoma.

Vitamin A Deficiency. Vitamin A deficiency occurs worldwide either as a consequence of general undernutrition or as a secondary deficiency in individuals with conditions that cause malabsorption of fats. In children, stores of vitamin A are depleted by infections, and the absorption of the vitamin is poor in newborn infants. Adult patients with malabsorption syndromes, such as celiac disease, Crohn disease, and colitis, may develop vitamin A deficiency, in conjunction with depletion of other fat-soluble vitamins. Bariatric surgery and, in older persons, continuous use of mineral oil as a laxative may lead to deficiency. The pathologic effects of vitamin A deficiency are summarized in Figure 9-25.

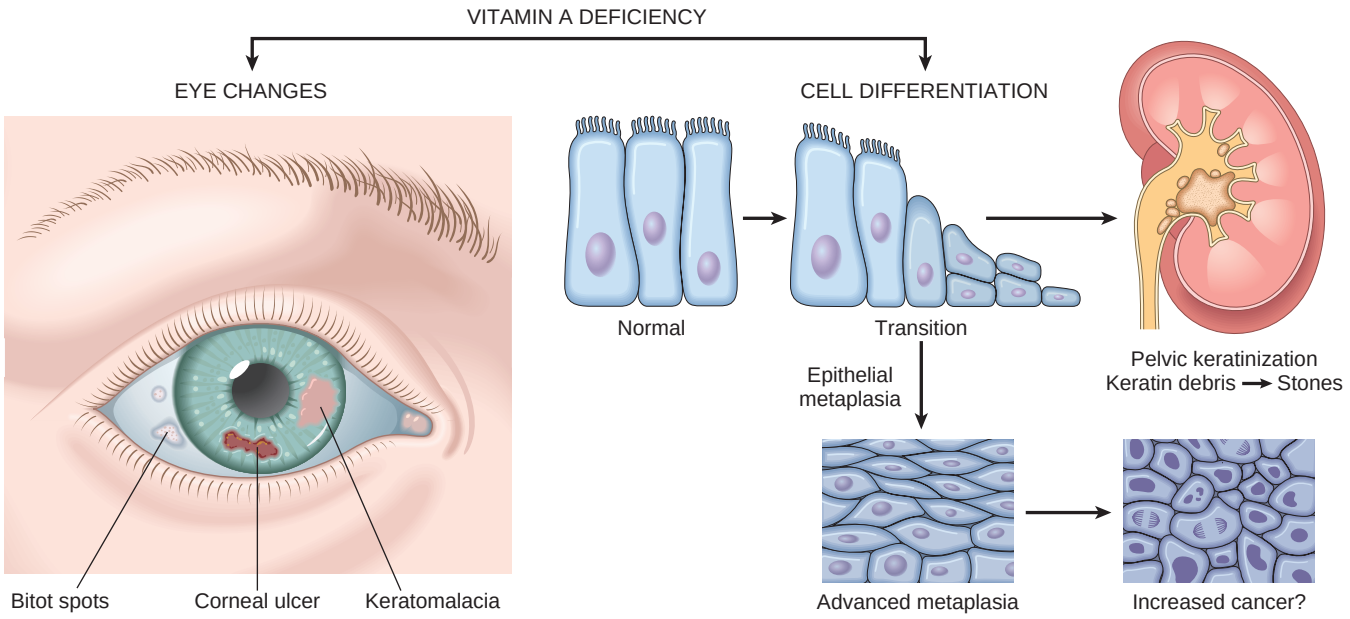

Figure 9-25 Vitamin A deficiency, its major consequences in the eye and in the production of keratinizing metaplasia of specialized epithelial surfaces, and its possible role in epithelial metaplasia. Not depicted are night blindness and immune deficiency.