of eicosanoids in this reaction has been verified by studies showing that nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce it.

Epidermal changes in sunburn include the induction of "sunburn cells," which are keratinocytes undergoing p53-dependent apoptosis as a defense, with elimination of cells that harbor UV-B-induced structural DNA damage.

VITAMIN D SYNTHESIS AND PHOTOCHEMISTRY Cutaneous exposure to UV-B causes photolysis of epidermal 7-dehydrocholesterol, converting it to pre–vitamin D_3, which then undergoes temperature-dependent isomerization to form the stable hormone vitamin D_3. This compound diffuses to the dermal vasculature and circulates to the liver and kidney, where it is converted to the dihydroxylated functional hormone 1,25-dihydroxyvitamin D_3. Vitamin D metabolites from the circulation and those produced in the skin itself can augment epidermal differentiation signaling and inhibit keratinocyte proliferation. These effects are exploited therapeutically in psoriasis with the topical application of synthetic vitamin D analogues. In addition, vitamin D is increasingly thought to have beneficial effects in several other inflammatory conditions, and some evidence suggests that—besides its classic physiologic effects on calcium metabolism and bone homeostasis—it is associated with a reduced risk of various internal malignancies. There is controversy regarding the risk-to-benefit ratio of sun exposure in vitamin D homeostasis. At present, it is important to emphasize that no clear-cut evidence suggests that the use of sunscreens substantially diminishes vitamin D levels. Since aging also substantially decreases the ability of human skin to photocatalytically produce vitamin D_3, the widespread use of sunscreens that filter out UV-B has led to concerns that the elderly might be unduly susceptible to vitamin D deficiency. However, the amount of sunlight needed to produce sufficient vitamin D is small and does not justify the risks of skin cancer and other types of photodamage linked to increased sun exposure or tanning behavior. Nutritional supplementation of vitamin D is a preferable strategy for patients with vitamin D deficiency.

Chronic Effects of Sun Exposure: Nonmalignant The clinical features of photoaging (*dermatoheliosis*) consist of wrinkling, blotchiness, and telangiectasia as well as a roughened, irregular, "weather-beaten" leathery appearance.

UVR is important in the pathogenesis of photoaging in human skin, and ROS are likely involved. The dermis and its connective tissue matrix are major targets for sun-associated chronic damage that manifests as solar elastosis, a massive increase in thickened irregular masses of abnormal-appearing elastic fibers. Collagen fibers are also abnormally clumped in the deeper dermis of sun-damaged skin. The chromophore(s), the action spectra, and the specific biochemical events orchestrating these changes are only partially understood, although more deeply penetrating UV-A seems to be primarily involved. Chronologically aged sun-protected skin and photoaged skin share important molecular features, including connective tissue damage and elevated levels of matrix metalloproteinases (MMPs). MMPs are enzymes involved in the degradation of the extracellular matrix. UV-A induces expression of some MMPs, including MMP-1 and MMP-3, leading to increased collagen breakdown. In addition, UV-A reduces type I procollagen mRNA expression. Thus, chronic UVR alters the structure and function of dermal collagen. On the basis of these observations, it is not surprising that high-dose UV-A phototherapy may have beneficial effects in some patients with localized fibrotic diseases of the skin, such as localized scleroderma.

Chronic Effects of Sun Exposure: Malignant One of the major known consequences of chronic excessive skin exposure to sunlight is nonmelanoma skin cancer. The two most common types of nonmelanoma skin cancer are BCC and SCC (Chap. 105). A model for skin cancer induction involves three major steps: initiation, promotion, and progression. Exposure of human skin to sunlight results in *initiation*, a step by which structural (mutagenic) changes in DNA evoke an irreversible alteration in the target cell (keratinocyte) that begins the tumorigenic process. Exposure to a tumor initiator such as UV-B is believed to be a necessary but not a sufficient step in the malignant process, since initiated skin cells not exposed to tumor promoters generally do not develop tumors. The second stage in tumor development is *promotion*, a multistep process by which chronic exposure to sunlight evokes further changes that culminate in the clonal expansion of initiated cells and cause the development, over many years, of premalignant growths known as *actinic keratoses*, a minority of which may progress to form SCCs. As a result of extensive studies, it seems clear that UV-B is a *complete carcinogen*, meaning that it can act as both a tumor initiator and a tumor promoter. The third and final step in the malignant process is *malignant conversion* of benign precursors into malignant lesions, a process thought to require additional genetic alterations.

On a molecular level, skin carcinogenesis results from the accumulation of gene mutations that cause inactivation of tumor suppressors, activation of oncogenes, or reactivation of cellular signaling pathways that normally are expressed only during epidermal embryologic development. Accumulation of mutations in the tumor-suppressor gene *p53* secondary to UV-induced DNA damage occurs in both SCCs and BCCs and is important in promoting skin carcinogenesis. Indeed, the majority of both human and murine UV-induced skin cancers have characteristic *p53* mutations (C → T and CC → TT transitions). Studies in mice have shown that sunscreens can substantially reduce the frequency of these signature mutations in *p53* and inhibit the induction of tumors.

BCCs also harbor inactivating mutations in the tumor-suppressor gene *patched*, which result in activation of the sonic hedgehog signaling pathway and increased cell proliferation. Thus, these tumors can manifest mutations in tumor suppressors (*p53* and *patched)* or oncogenes (*smoothened)*. New evidence links alterations in the Wnt/β-catenin signaling pathway, which is known to be critical for hair follicle development, to skin cancer as well. Thus interactions between this pathway and the hedgehog signaling pathway appear to be involved in both skin carcinogenesis and embryologic development of the skin and hair follicles.

Clonal analysis in mouse models of BCC revealed that tumor cells arise from long-term resident progenitor cells of the interfollicular epidermis and the upper infundibulum of the hair follicle. These BCC-initiating cells are reprogrammed to resemble embryonic hair follicle progenitors, whose tumor-initiating ability depends on activation of the Wnt/β-catenin signaling pathway.

SCC initiation occurs both in the interfollicular epidermis and in the hair follicle bulge stem cell populations. In mouse models, the combination of mutant K-Ras and p53 is sufficient to induce invasive SCCs from these cell populations.

The transcription factor Myc is important for stem cell maintenance in the skin, and oncogenic activation of Myc has been implicated in the development of BCCs and SCCs. Thus, nonmelanoma skin cancer involves mutations and alterations in multiple genes and pathways that occur as a result of their chronic accumulation driven by exposure to environmental factors such as UVR.

Epidemiologic studies have linked excessive sun exposure to an increased risk of nonmelanoma cancers and melanoma of the skin; the evidence is far more direct for nonmelanoma skin cancers (BCCs and SCCs) than for melanoma. Approximately 80% of nonmelanoma skin cancers develop on sun-exposed body areas, including the face, neck, and hands. Major risk factors include male sex, childhood sun exposures, older age, fair skin, and residence at latitudes relatively close to the equator. Individuals with darker-pigmented skin have a lower risk of skin cancer than do fair-skinned individuals. More than 2 million individuals in the United States develop nonmelanoma skin cancer annually, and the lifetime risk that a fair-skinned individual will develop such a neoplasm is estimated at ~15%. The incidence of nonmelanoma skin cancer in the population is increasing at a rate of 2–3% per year. One potential explanation is the widespread use of indoor tanning. It is estimated that 30 million people tan indoors in the United States annually, including >2 million adolescents.

The relationship of sun exposure to melanoma development is less direct, but strong evidence supports an association. Clear-cut risk