factors include a positive family or personal history of melanoma and multiple dysplastic nevi. Melanomas can occur during adolescence; the implication is that the latent period for tumor growth is shorter than that for nonmelanoma skin cancer. For reasons that are only partially understood, melanomas are among the most rapidly increasing human malignancies (Chap. 105). Epidemiologic studies indicate that indoor tanning is a risk factor for melanoma, which may contribute to the increasing incidence of melanoma formation. Furthermore, epidemiologic studies suggest that life in a sunny climate from birth or early childhood may increase the risk of melanoma development. In general, risk does not correlate with cumulative sun exposure but may be related to the duration and extent of exposure in childhood.

However, in contrast to nonmelanoma skin cancers, melanoma frequently develops in sun-protected skin, and oncogenic mutations in melanoma may also not be UVR-signature mutations; these observations suggest that UVR-independent factors contribute to melanomagenesis. Low MC1R activity leads to production of the red/yellow pheomelanin pigment in individuals with red hair and fair skin, while high MC1R activity results in increased production of the black/brown eumelanin. Experiments in mice suggest that high pheomelanin content in skin (as in individuals with red hair and fair skin) leads to a UVR-independent increase in the risk of melanoma through a mechanism that involves oxidative damage. Thus, both UVR-dependent and UVR-independent factors are likely to contribute to melanoma formation.

Photoimmunology Exposure to solar radiation causes both local immunosuppression (through inhibition of immune responses to antigens applied at the irradiated site) and systemic immunosuppression (through inhibition of immune responses to antigens applied at remote, unirradiated sites). For example, human skin exposure to modest doses of UV-B can deplete the epidermal antigen-presenting cells known as Langerhans cells, thereby reducing the degree of allergic sensitization to application of the potent contact allergen dinitrochlorobenzene at the irradiated skin site.

An example of the systemic immunosuppressive effects of higher doses of UVR is the diminished immunologic response to antigens introduced either epicutaneously or intracutaneously at sites distant from the irradiated site. Various immunomodulatory factors and immune cells have been implicated in UVR-induced systemic immunosuppression, including tumor necrosis factor α, interleukin 4, interleukin 10, *cis*-urocanic acid, and eicosanoids. Experimental evidence suggests that prostaglandin E_2 signaling through prostaglandin E receptor subtype 4 mediates UVR-induced systemic immunosuppression by elevating the number of regulatory T cells, and this effect can be inhibited with NSAIDs.

The major chromophores in the upper epidermis that are known to initiate UV-mediated immunosuppression include DNA, *trans*-urocanic acid, and membrane components. The action spectrum for UV-induced immunosuppression closely mimics the absorption spectrum of DNA. Pyrimidine dimers in Langerhans cells may inhibit antigen presentation. The absorption spectrum of epidermal urocanic acid closely mimics the action spectrum for UV-B-induced immunosuppression. Urocanic acid is a metabolic product of the essential amino acid histidine and accumulates in the upper epidermis through breakdown of the histidine-rich protein filaggrin due to the absence of its catabolizing enzyme in keratinocytes. Urocanic acid is synthesized as a *trans*-isomer, and UV-induced *trans-cis* isomerization of urocanic acid in the stratum corneum drives immunosuppression. *Cis*-urocanic acid may exert its immunosuppressive effects through a variety of mechanisms, including inhibition of antigen presentation by Langerhans cells.

One important consequence of chronic sun exposure and associated immunosuppression is an enhanced risk of skin cancer. In part, UV-B activates regulatory T cells that suppress antitumor immune responses via interleukin 10 expression, whereas, in the absence of high UV-B exposure, epidermal Langerhans cells present tumor-associated antigens and induce protective immunity, thereby inhibiting skin tumorigenesis. UV-induced DNA damage is a major molecular trigger of this immunosuppressive effect.

Perhaps the most graphic demonstration of the role of immunosuppression in enhancing the risk of nonmelanoma skin cancer comes from studies of organ transplant recipients who require lifelong immunosuppressive/antirejection drug regimens. More than 50% of organ transplant recipients develop BCCs and SCCs, and these cancers are the most common types of malignancies arising in these patients. Rates of BCC and SCC increase with the duration and degree of immunosuppression. These patients ideally should be screened prior to organ transplantation, be monitored closely thereafter, and adhere to rigorous photoprotection measures, including the use of sunscreens and protective clothing as well as sun avoidance. Notably, immunosuppressive drugs that target the mTOR pathway, such as sirolimus and everolimus, may reduce the risk of nonmelanoma skin cancer in organ transplant recipients from that associated with the use of calcineurin inhibitors (cyclosporine and tacrolimus), which may contribute to nonmelanoma skin cancer formation not only through their immunosuppressive effects but also through suppression of p53-dependent cancer cell senescence pathways independent of host immunity.

PHOTOSENSITIVITY DISEASES

The diagnosis of photosensitivity requires elicitation of a careful history in order to define the duration of signs and symptoms, the length of time between exposure to sunlight and the development of subjective symptoms, and visible changes in the skin. The age of onset can also be a helpful diagnostic clue; for example, the acute photosensitivity of erythropoietic protoporphyria almost always begins in childhood, whereas the chronic photosensitivity of porphyria cutanea tarda (PCT) typically begins in the fourth and fifth decades of life. A patient's history of exposure to topical and systemic drugs and chemicals may provide important diagnostic clues. Many classes of drugs can cause photosensitivity on the basis of either phototoxicity or photoallergy. Fragrances such as musk ambrette that were previously present in numerous cosmetic products are also potent photosensitizers.

Examination of the skin may offer important clues. Anatomic areas that are naturally protected from direct sunlight, such as the hairy scalp, the upper eyelids, the retroauricular areas, and the infranasal and submental regions, may be spared, whereas exposed areas show characteristic features of the pathologic process. These anatomic localization patterns are often helpful, but not infallible, in making the diagnosis. For example, airborne contact sensitizers that are blown onto the skin may produce dermatitis that can be difficult to distinguish from photosensitivity despite the fact that such material may trigger skin reactivity in areas shielded from direct sunlight.

Many dermatologic conditions may be caused or aggravated by sunlight (Table 75-2). The role of light in evoking these responses may be dependent on genetic abnormalities ranging from well-described defects in DNA repair that occur in xeroderma pigmentosum to the inherited abnormalities in heme synthesis that characterize the porphyrias. The chromophore has been identified in certain photosensitivity diseases, but the energy-absorbing agent remains unknown in the majority.

Polymorphous Light Eruption A common type of photosensitivity disease is *polymorphous light eruption* (PMLE). Many affected individuals never seek medical attention because the condition is often transient, becoming manifest in the spring with initial sun exposure but then subsiding spontaneously with continuing exposure, a phenomenon known as "hardening." The major manifestations of PMLE include (often intensely) pruritic erythematous papules that may coalesce into plaques in a patchy distribution on exposed areas of the trunk and forearms. The face is usually less seriously involved. Whereas the morphologic skin findings remain similar for each patient with subsequent recurrences, significant interindividual variations in skin findings are characteristic (hence the term "polymorphous").

A skin biopsy and phototest procedures in which skin is exposed to multiple erythemal doses of UV-A and UV-B may aid in the diagnosis. The action spectrum for PMLE is usually within these portions of the solar spectrum.

Whereas the treatment of an acute flare of PMLE may require topical or systemic glucocorticoids, approaches to preventing PMLE are