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Current Concepts in Ultraviolet Carcinogenesis (41406)

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The relationship between sunlight and cutaneous malignancy has been recognized for almost a century. Unna (1) is generally credited with first describing this association; others followed shortly thereafter (2, 3). Hyde (3) in 1906, also recognized the role of pigmentation in the relative protection of pigmented races from skin cancer. Findlay, in 1928, was able to induce the production of skin cancer in albino mice with radiation from a quartz mercury vapor lamp (4). He also noted that application of tar to the skin of the mice shortened the exposure time necessary to induce tumors. In recent years substantial progress in understanding the pathophysiology of ultraviolet-induced skin cancer has been made. Furthermore, considerable epidemiologic and experimental evidence linking ultraviolet radiation and cutaneous malignancies has been obtained. The purpose of this review is to summarize these data.

Nonmelanoma Skin Cancer. In the generic sense any malignant tumor of the skin other than melanoma could be included under this heading. The two most common types of nonmelanoma skin cancers in humans and those most related to sun exposure are basal cell carcinoma and squamous cell carcinoma. In this paper "nonmelanoma skin cancer" will refer to those two entities jointly. In mouse models of nonmelanoma skin cancer induced by ultraviolet radiation, fibrosarcomas, and squamous cell carcinomas are most commonly produced.

Epidemiology. The incidence of nonmelanoma skin cancer in the United States was recently estimated to be approximately 400,000 new cases per year (5). Since the treatment of most nonmelanoma skin cancers does not require hospitalization and these types of neoplasms are generally not considered serious problems, the actual incidence is difficult to establish. Current estimates are most likely on the low side due to underreporting of cases.

A great deal of circumstantial evidence associates sun exposure with nonmelanoma skin cancer. Several phenotypic characteristics have been found by investigators to be more common in cancer patients than in controls (6–8). These include light eye color (blue, hazel, gray, green), light hair color, fair complexion, and poor tanning ability. It has also been reported that skin cancer patients have a prolonged duration of delayed erythema (lasting 2 to 3 weeks) after exposure to erythemogenic doses of ultraviolet B (280 to 320 nm) radiation compared with that of controls, independent of skin type (9, 10). [Skin can be classified into several types based on history and physical examination after sunlight exposure: I—always burn, never tan; II—always burn, then slight tan; III—sometimes burn, always tan; IV—never burn, always tan; V—heavily pigmented; VI—blacks (11)]. However, a recent study challenges this observation and indicates that prolonged erythema is characteristic of type I ("never tans") skin (12). Cancer patients have a higher frequency than expected on the basis of chance of having parents with light-colored eyes and ancestry from the British Isles (6, 8). Skin cancer is very rare in the black races (13) presumably because of the photoprotection provided by heavily melanized skin. In Caucasians, the ability to tan was found in one case-control study to be a greater deterrent to nonmelanoma skin cancer than a dark complexion (14). Albinos of highly pigmented races have a

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high incidence of skin cancer on sun-exposed areas of the body (15).

Skin cancer patients have been reported to have had a greater number of hours of outdoor exposure than controls (7, 8) and a recent study showed exposure to sunlight to be the most important risk factor for both basal cell carcinomas and squamous cell carcinomas (14). Interestingly, this study showed that for the same level of cumulative lifetime exposure to sunlight, subjects over 60 years of age were at higher risk for developing tumors than those of younger ages, implying that physiologic aging plays a role in photocarcinogenesis. Skin cancer occurs most commonly on the most exposed body areas (16), also suggesting a relationship to sunlight. Rates of nonmelanoma skin cancer vary inversely with latitude (8, 17, 18); in the United States the rate doubles with each 3°48′ of decreasing latitude (17).

These findings suggest that skin cancer is related to the dose of photons at the basal cell layer with a less effective barrier to photons (less melanin) and increased exposure dose (hours outdoors, decreased latitude, exposed parts of the body) leading to an increased risk of cancers. It is uncertain if patients with a genetically poor melanin barrier also have other heritable features making them more susceptible to skin cancer.

The incidence of skin cancer is higher in geographic areas of greater sunlight exposure and is reported more frequently in summer (19) suggesting that in addition to a long-term cumulative effect on the skin, sunlight may have a more immediate effect and precipitate the appearance of skin cancers. If true, avoidance of sun exposure even in patients already with severely sunlight-damaged skin may be helpful in preventing tumor development. Alternatively, patients preparing for summer activities may examine their skin and find a preexisting tumor.

Nonmelanoma skin cancer is more common in men than in women (17, 18). This may merely reflect differences in occupational sunlight exposure as the rates are similar in the Union of Soviet Socialist Republics where occupations of men and women are more nearly equivalent (17). In addition, men have a higher risk of squamous cell cancer relative to basal cell cancer compared with women (6, 8, 18). This observation might be explained by increased exposure to sunlight by men. Several lines of evidence suggest that squamous cell carcinomas are more closely associated with sun exposure than basal cell carcinomas; one-third of basal cell carcinomas have been found to be in areas relatively well protected from light (17), the ratio of basal cell to squamous cell carcinomas increases with increasing latitude, and the average age of occurence for basal cell carcinomas is younger than that for squamous cell carcinomas (19). This last finding is consistent with the hypothesis that more ultraviolet radiation is required to produce squamous cell carcinomas and/or a longer latency period exists for them compared with basal cell carcinoma.

Mathematical models have been derived from empirical data regarding the incidence of nonmelanoma skin cancer, the age distribution of patients, and the ultraviolet light flux at given geographical locations, that suggest that the risk of nonmelanoma skin cancer is related to the total lifetime exposure to sunlight (20, 21). Furthermore, one model implies that apart from cumulative dose, the skin becomes more susceptible to tumor formation with age (21). This is consistent with the empirical finding noted above and may possibly be due to a natural deterioration of physiologic defenses with age. Some models also suggest that for a given increase in ultraviolet light dosage, a larger percentage increase in the incidence of skin cancer occurs (21).

Pathogenesis. Ultraviolet radiation. The ultraviolet spectrum ranges from 200 to 400 nm. This range has been divided into three parts—UVC (200 to 280 nm), UVB (280 to 320 nm), and UVA (320 to 400 nm). While these divisions are somewhat arbitrary, they do have some biological relevance. UVC radiation is efficient at killing unicellular organisms and is often called "germicidal radiation." However, wavelengths in this region are totally absorbed by the

stratospheric ozone layer (11). UVC and UVB radiation are much more effective at producing erythema in human skin than is UVA radiation (11). However, when the amount of radiation reaching the earth's surface at the different wavelengths of the ultraviolet spectrum is accounted for, the solar erythemal effectiveness curve lies largely in the UVB range (11).

Blum and his associates performed a large series of experiments to quantify the factors that result in the induction of tumors in albino mice (22). They estimated that the effective wavelengths are between 260 and 300 nm. While tumor development time decreases and tumor number increases with increasing ultraviolet radiation dose, the response of the mice is influenced by dose rate, fractionation, rest intervals, and age of the animals at onset of exposure (16, 23). The production of squamous cell carcinomas with UVB radiation has been reproduced many times (24, 25). In mice, when different wavelengths are studied, the effectiveness of UVB radiation in producing tumors appears to be proportional to its erythemal effectiveness (11, 26). UVB radiation is more efficient than UVC at producing tumors (11, 27). UVA radiation may be able to produce tumors in mice at high doses with continuous exposure (27); it is estimated to be 1600 times less carcinogenic than UVB radiation (23). Compared with the daytime solar UVA radiation intensities to which man is exposed, the accumulated daily dose of UVA radiation received by the mice was not unrealistically high (27). However, continuous exposure without a daily dark period, may produce a set of conditions for which no fair comparison can be made to the human situation (27).

Other investigators have found that UV irradiation of hairless mice with 290 to 400 nm radiation (UVB plus UVA) given in nonulcerating erythemogenic doses produces squamous cell carcinomas more rapidly than UVB radiation alone (28). Tumors reportedly arose in as few as 18 days in some animals. This interesting finding awaits confirmation.

The role of DNA. Exposure of human skin to ultraviolet radiation results in immediate changes in the nuclear DNA that can be demonstrated with antibodies specific for DNA altered by ultraviolet radiation (29). Ultraviolet radiation from 254 to 300 nm was effective in producing damaged DNA (30). However, the energy required to damage DNA increased greatly for longer wavelengths with at least four times more energy required at 310 nm than at shorter wavelengths (254 to 300 nm). Recently, production of pyrimidine dimers by ultraviolet radiation (290–360 nm) was demonstrated *in vivo* in human skin (31). The role of DNA damage in the production of some carcinomas by ultraviolet radiation was supported by the discovery that cells from patients with xeroderma pigmentosum, a condition marked by numerous sunlight-related cutaneous malignancies, are defective in their ability to repair ultraviolet damaged DNA (32–36). It is of interest that studies on patients without xeroderma pigmentosum but exhibiting actinic keratoses (a premalignant condition) showed that the DNA repair capacity of their cells was less than that of age-matched controls (37–39).

Evidence that ultraviolet-induced pyrimidine dimers in DNA can give rise to tumors comes from the Amazon molly, *Poecilia formosa,* a small fish that can be grown in clones (40). Thyroid tissue irradiated with 254 nm radiation and transplanted into the abdominal cavity of another fish produces a growth (tumor). However, if the 254 nm radiation is followed by photoreactivating illumination, the percentage of fish yielding tumors is markedly reduced. This suggests that pyrimidine dimers can give rise to tumors, because photoreactivating enzyme monomerizes cyclobutylpyrimidine dimers in DNA. In mouse skin, of wavelengths studied (310, 300, 290, 280, and 260 nm), 290 nm was found to be the most effective, and 310 nm the least effective in producing pyrimidine dimers (41). This correlates with the carcinogenic action spectrum in mice as noted above.

In *in vitro* studies, 254 nm radiation has been shown to transform C3H mouse embryo-derived fibroblasts (42) and human

fibroblasts (43–45). In Syrian hamster embryo cells an action spectrum for ultraviolet radiation-induced transformation of cells was determined (46). It was found to be similar to the action spectrum for cytotoxicity and for pyrimidine dimer formation. Sensitivity of the cells is maximal at 265–270 nm with a rapid decline of sensitivity above 290 nm.

Antioxidants. Feeding antioxidants to mice has been shown to suppress ultraviolet radiation-induced tumor formation (47, 48). Speculation regarding mechanisms of action include the scavenging of free radicals or induction of microsomal mixed function oxidases. Another study showed that antioxidants inhibited the formation of cholesterol-α-oxide in animals (49). Cholesterol-α-oxide, a known carcinogen and a photoproduct of cholesterol, is found in both human and hairless mouse skin on exposure to ultraviolet radiation (50, 51). Despite early enthusiasm, it is most probably not ultimately responsible for ultraviolet-induced carcinogenesis because (51): (i) Peak cutaneous levels are much lower than that required to produce tumors in mice (4 to 16 μg vs 20 mg); (ii) when introduced subcutaneously, only tumors of dermal origin are produced; and (iii) cholesterol-α-oxide levels found in antioxidant-fed animals should be lower than those on a regular diet, but this was not the case. Cholesterol-α-oxide levels in animals on an antioxidant-supplemented diet, while reaching a peak 4 weeks after that of animals on the regular diet, were thereafter consistently higher. Antioxidants nevertheless were effective in suppressing tumor formation.

Physical effects. In animal models, heat (52–54), humidity, and high wind velocity (54) accelerate ultraviolet-induced tumor formation. The mechanisms involved remain speculative. In the case of humidity; increased hydration of the stratum corneum probably allows increased penetration of light due to decreased scatter and reflection (54).

Chemical influences. (*i*) *Carcinogens.* The role of chemical carcinogens in photocarcinogenesis has been examined in animal models. UVA radiation exposure following topical application of 20-methylcholanthrene accelerates papilloma formation initially, but these growths regress with final results showing decreases in papilloma and cancer yield (55). (In this work the light source was unfiltered, thus some UVB was presumably present.) Suggested mechanisms for this inhibition by ultraviolet radiation include enhanced absorption of the chemical with a reduction in carcinogen concentration at skin surface (56) and photooxidation of the chemical leading to decreased carcinogenicity (57–59); the mechanisms involved remain speculative (60). By separating ultraviolet radiation from chemical application temporally, it has been shown that UVB will stimulate cancer formation initiated by 7,12-dimethylbenz[a]anthracene (DMBA) (61, 62). In one study UVB radiation given prior to DMBA application increased tumor yield in mice, whereas irradiation after application decreased tumor yield (63). Promotion of ultraviolet initiated cancers by croton oil (64–66) and 1,3-bis(2-chloroethyl)-1-nitrosourea (60) has also been demonstrated in mice. The relevance of these findings to humans is unclear; while the environment allows opportunity for exposure to numerous chemicals, the concentrations are usually small, and the interactions with ultraviolet radiation in man are unknown.

(*ii*) *Retinoids.* Vitamin A and its analogs comprise the retinoid group of agents that perform a variety of functions. All-*trans*-retinoic acid has been studied both clinically and in animal models for its effects on ultraviolet-induced malignant and premalignant lesions. Actinic keratoses, premalignant sunlight-induced lesions, have been shown to regress in patients treated with topical retinoic acid (67–71). The oral retinoid 13-*cis*-retinoic acid has recently been reported to have been of value in patients with basal cell carcinomas (72).

In animal models retinoic acid applied topically in irritating concentrations (73) and in low nonirritating concentrations have been reported to promote ultraviolet carcinogenesis (74, 75). However, another study found that a nonirritating concentra-

tion inhibited tumor formation (76). The details of these effects are not yet clear and the mechanisms involved are unclear (75, 76). However, it appears that depending on the condition present, retinoic acid can either promote or inhibit ultraviolet carcinogenesis.

(iii) β-Carotene. β-Carotene administration in hairless mice appeared to delay the appearance and decrease the growth rate of squamous cell carcinomas induced by ultraviolet radiation in one study (77). The significance of this finding awaits further study.

Immunologic considerations. Animal studies. In recent years a series of observations has added a new dimension to the understanding of cutaneous malignancies (reviewed in (78, 79). These led to the finding that, at least in certain circumstances, host immunity plays an important role in photocarcinogenesis. It was found that murine ultraviolet-induced fibrosarcomas and squamous cell carcinomas are highly antigenic and regress when transplanted to normal syngeneic mice (80). These tumors are antigenically dissimilar; the regression is immunologically mediated and attributable to T cells (81). These tumors would, however, grow in immunosuppressed mice. Further experiments showed that after removal of ultraviolet-induced tumors, primary hosts were susceptible to challenge with these autochthonous tumors, although most of these were rejected by untreated control mice. These animals are also susceptible to isografts of antigenically dissimilar ultraviolet-induced tumors from another primary host (82). Furthermore, ultraviolet-irradiated non-tumor-bearing mice were also susceptible to challenge with syngeneic ultraviolet-induced tumor; even when doses of ultraviolet radiation (280 to 340 nm) below that necessary to produce tumors were given (81–83) Also, spleen cells in these tumor-challenged mice show no cytotoxicity against the tumor in an *in vitro* microcytotoxicity test (84). However, ultraviolet irradiation does not interfere with second-set rejection of ultraviolet-induced tumors in mice that were specifically immunized before ultraviolet exposure (81), indicating that a specific step in acquiring immunity is most likely affected by ultraviolet radiation.

To try to characterize the mechanisms responsible for these findings, several experiments were done. Normal mice were rendered tumor susceptible by the adoptive transfer of lymphoid cells from either tumor-bearing or non-tumor-bearing, ultraviolet-irradiated donors. This susceptibility could be abolished by pretreatment of the lymphoid cells with anti-θ antibody and complement (85), showing involvement of T cells in the susceptibility induced. In other experiments, lethally x-irradiated mice were reconstituted with lymphoid cells either from normal donors or an ultraviolet-irradiated donors (82). Mice receiving lymphoid cells from normal donors were resistant to tumor challenge; those receiving lymphoid cells from ultraviolet-irradiated donors did not reject the tumor. Mice given equal numbers of lymphoid cells from both categories of donor also did not reject tumors. These experiments suggest that the T cells involved in the induced susceptibility to tumor are suppressor cells.

Numerous tests of immunocompetence in ultraviolet-irradiated mice are normal (86, 87), confirming that these findings are not due to a general immunosuppressive effect of ultraviolet radiation. However, it was found that the ability to sensitize to contact and subcutaneously injected antigens was depressed. The ability to sensitize mice to subcutaneous dinitrochlorobenzene (DNCB) is depressed in the early months of ultraviolet irradiation (86–89). This phenomenon occurs on areas shielded from irradiation. It is transient, disappearing by the third month of UV exposure. Upon removal from the ultraviolet-irradiated host, lymphocytes are able to respond effectively to DNCB. This implies that the deficiency arises in the earlier antigen processing stage of the immune response, and suggests that macrophages rather than lymphocytes were the target in this effect of ultraviolet radiation (88). Studies have shown that splenic antigen presenting cells from ultraviolet-irradiated mice are incapable of presenting contact sensitizing antigens to normal lym-

phocytes in a way that triggers the lymphocytes to respond to the antigen (88, 90). This defective antigen presentation not only prevents the induction of a normal immune response, but also stimulates the production of suppressor lymphocytes that are specific for the "improperly" presented antigen (88, 90). In this regard it is interesting to speculate on the role of the Langerhans cell (an epidermal cell with certain macrophage-type surface markers) in defective presentation of antigens as it is known that ultraviolet radiation affects the membrane characteristics, cytoplasm, and viability of Langerhans cells at doses below that required to damage other epidermal cells (91). In addition, in mice it has been shown that on skin either naturally deficient in Langerhans cells (tail skin) or skin treated with ultraviolet radiation (290–320 nm), an inability to sensitize to topical 2,4-dinitro-1-fluorobenzene (DNFB) is present (92). Furthermore, these animals become specifically unresponsive to the chemical and are unable to become sensitized when DNFB is painted on normal skin 14 days later (92). However, this does not explain the systemic effect noted above. The mechanism by which ultraviolet radiation influences splenic adherent cells and whether it involves Langerhans cells remain speculative.

Defective antigen presentation may explain the presence of suppressor cells in ultraviolet-irradiated animals that prevent the rejection of ultraviolet-induced tumors (88). Following ultraviolet irradiation, new antigens, related in specificity to tumor antigens, presumably appear in the skin. At the same time, the defect in antigen presentation occurs with inappropriate presentation of these new antigens to the lymphoid system. The alteration in antigen presentation would then lead to the production of suppressor cells with specificity for the tumor antigens present on ultraviolet-induced skin cancers (88). No direct proof of a connection between the antigen-presenting defect and ultraviolet-induced tumor suppressor cells currently exists; however, this hypothesis is consistent with the information currently available (88).

Human studies. The role of the immune system in human cutaneous carcinogenesis is suggested by the increased risk of malignancy in patients undergoing immunosuppressive therapies. Skin cancers occur with increased frequency in immunosuppressed patients (93) including basal cell and squamous cell carcinomas (94), and possibly melanoma (95). The overall increased risk of skin cancer in renal transplant patients is 7.1-fold, mostly due to squamous cell carcinomas that are increased 36.4-fold (96). There are also reports of skin cancers occurring rapidly in patients being treated with immunosuppressive chemotherapuetic agents for lymphomas (94, 97).

Both B and T lymphocytes have been isolated from human basal cell and squamous cell carcinomas in numbers comparable to those found in biopsies of delayed hypersensitivity reactions (98, 99). The specificity of the cells or their products has not been determined, and their relevance is unknown. In one study eight of nine patients with squamous cell carcinoma of the skin had at least some immunologic reactivity against their tumor cells by their own serum or peripheral blood lymphocytes (100). However, patients in another study with large (>3 cm) squamous cell carcinomas had defective cell-mediated immunity as measured by intradermal antigen reactivity and DNCB sensitization (101).

These studies provide some suggestion that at least some human skin tumors may be antigenic and that immunosuppression may lead to an increased risk of some skin malignancies. However, definitive evidence for specific immunologic involvement is scant. In addition, most immunosuppressive agents are also mutagens. Therefore, it is difficult to draw definitive conclusions regarding the role of immunosuppression in cutaneous oncogenesis.

Malignant Melanoma. Malignant melanoma is a neoplasm derived from melanocytes. On the basis of histologic and clinical criteria, it can be classified into four types (102–104). Lentigo maligna melanoma is the least common form; it occurs in the elderly on sun-exposed areas and grows

slowly prior to invasion. Superficial spreading melanoma is the most common type, comprising about 70% of all melanomas (Melanoma Clinical Cooperative Group data), and undergoes a lateral growth phase for 1–7 years prior to invasion. Nodular melanoma seems to occur *de novo* as an invasive nodule. The fourth and most recently described type is acrolentiginous melanoma. This rare tumor occurs predominantly on palms, soles, nail beds, and mucous membranes. It is the predominant type in Blacks and Orientals.

Epidemiology. Both the incidence and the death rate from malignant melanoma appear to have been increasing in the past few decades, both inside and outside the United States (105–110). In Norway the age-adjusted incidence of melanoma doubled from 1955 to 1970 (107). In Australia the death rate rose from 8.5 per 100,000 in the years between 1931 to 1940 to 31.9 per 100,000 from 1961 to 1970. One study challenges this apparent increase and suggests that it is artifactual in nature (111); however, this study represents a singular opinion.

Although solar exposure appears to be associated with the incidence of melanoma, the relationship is not as clear as for nonmelanoma skin cancer. The anatomic aggregation of melanomas on maximally sun-exposed areas is not as striking as for nonmelanoma skin cancer, and melanoma is more common among indoor workers compared to outdoor workers (112). These points suggest that another factor or factors other than sunlight may be involved in the genesis of melanoma. (Although, the increased risk of indoor workers might be explained by intermittent, intense exposures to sunlight without benefit of protection from the increased melanization and thickened stratum corneum that occurs with chronic sun exposure.) Also, the acrolentiginous variety of melanoma and the existence of precurser lesions, both familial (113) and nonfamilial (114–116) suggest factors other than sunlight as important etiologic influences.

Several lines of evidence appear to implicate solar radiation in the genesis of melanoma. Epidemiologic studies have shown melanoma patients to possess phenotypic characteristics similar to those patients with nonmelanoma skin cancer; patients in some studies have a greater tendency than controls to have light complexion, light eyes, and blond or red hair (117, 118); the data of one study do not support these findings (119). A latitude effect has been noted such that in the United States, Australia, and Scandinavia, the incidence of melanoma increases with decreasing latitude (14, 107, 120). In the United States the age-adjusted death rate from melanoma in the southern states is two to three times that in the northern states (14, 108). Although the incidence of melanoma in Sweden increases with lower latitude within the country, the overall incidence of melanoma is higher than that of southern Europe. This may be explained by the preponderance of fair skin in northern Europe (120). Melanoma is more common on exposed sites of the body and rarely occurs on "double clothed" (outer clothing plus underwear) areas (121). The subset of lentigo maligna melanoma almost always occurs on exposed sites. Also, melanoma may occur with increased frequency in patients with xeroderma pigmentosum (35).

If solar radiation is a significant etiologic factor, then the increase in incidence of melanoma in recent decades may be due to changes in dress and recreational habits allowing for increased sun exposure (109). A "cohort" effect has been observed with successively later born cohorts of people experiencing higher incidence and higher mortality rates (109). The most striking increases have been on the lower limbs in females, the trunk in men, and the upper limbs in both sexes. It has been suggested that this reflects the tendency of men to go shirtless during work or recreation after World War II, and the replacement in women of opaque stockings by nylons in the 1940s (109).

A mathematical model, that assumes solar ultraviolet radiation to be the primary factor in the etiology of melanoma and is derived from empirical data, suggests that the risk of melanoma might be related to the annual amount of exposure to ultraviolet

radiation rather than to total lifetime exposure (20). If true, brief exposure to high-intensity ultraviolet radiation may be significant for melanoma risk. However, an alternative explanation that would satisfy the model is a change in exposure habits such that young people today are more likely to be exposed to sunlight or some other environmental agent than were young people of previous generations (21). This would be consistent with the "cohort effect" discussed above.

Experimental studies. In 1959 Fitzpatrick and Szabo showed that the melanocyte is a major target of ultraviolet radiation exposure (122). Melanin formation and migration were found to be enhanced by ultraviolet radiation. Good animal models involving ultraviolet radiation in the production of melanoma are lacking. Melanocytic tumors have been produced in hairless mice with 7,12-dimethylbenz(*a*)anthracene (DMBA) and ultraviolet radiation (123). Melanoma-like tumors have been produced in guinea pigs with 7,12-DMBA alone (124), and with 9,10-DMBA alone (125). Other animal models also exist. The relevance of these to human melanoma is unclear. In one study of ultraviolet-induced DNA repair synthesis in peripheral lymphocytes, there was no difference between melanoma patients and controls (126).

Discussion. The epidemiologic evidence linking ultraviolet radiation and skin cancer can hardly be doubted in light of current knowledge. This is especially true of nonmelanoma skin cancer. In the case of melanoma, ultraviolet exposure appears to be at least a contributing factor. Similarly, laboratory evidence for the generation of nonmelanoma skin cancers (fibrosarcomas and squamous cell carcinomas) with ultraviolet radiation in animal models is abundant, but scant for melanoma. The incidence of melanoma appears to have been increasing for several decades. This could reflect increased exposure to sunlight due to changes in recreational and dress habits, but other factors may be responsible.

Ultraviolet radiation-induced immunologic effects on photocarcinogenesis have been shown in animals. This may increase our understanding of cutaneous carcinogenesis.

While nonmelanoma skin cancer is generally not considered to be a serious problem, it can cause considerable morbidity and in some cases mortality. The large number of cases diagnosed each year attests to its public health significance. This, and the evidence linking melanoma with sun exposure, indicates that at the present time it is prudent to advise many patients to limit sun exposure and to use adequate sunscreens.

The links between ultraviolet radiation and skin cancer also have public health policy implications. The stratospheric ozone layer is responsible for filtering out the most biologically active solar ultraviolet radiation. The activity of chlorofluorocarbon propellants and refrigerants in depleting the ozone layer has been well reviewed (127, 128). If the ozone layer is significantly depleted, nonmelanoma skin cancer and possible melanoma rates would increase greatly. Thus, even ignoring the numerous other biologic effects of increased ultraviolet radiation on plant and animal life, possibly even affecting the food chain, a strong case for controlling the emissions of chlorofluorocarbons on an international basis can be made.

Finally, the delineation of some of the mechanisms involved in photocarcinogenesis may have relevance to other systems of carcinogenesis. For example, it is possible that carcinogenesis by other agents may be influenced by immunologic effects.

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1. Unna PG, "The Histopathology of the Diseases of the Skin," p719. WF Clay, Edinburgh 1896.
2. Shield AM, Lancet 1:22, 1899.
3. Hyde JN, Amer J Med Sci 131:1, 1906.
4. Findlay GM, Lancet 2:1070, 1928.
5. Silverberg E, CA-a Cancer J Clin 31:13, 1981.
6. Hall AF, Arch Dermatol Syph 61:589, 1950.
7. Gellin GA, Kopf AW, and Garfinkel L. *in* "Advances in Biology of the Skin" (W. Montagna

and RL Dobson, eds), Vol. 7:p329. Pergamon, Oxford 1966.
8. Urbach F, Rose DB, and Bonnem M. *in* "Environment and Cancer, a Collection of Papers," p355. William & Wilkins, Baltimore 1972.
9. Tanenbaum L, Parrish JA, Haynes HA, Fitzpatrick TB, and Pathak MA. J Invest Dermatol **67**:513, 1976.
10. Klostermann G, Bohnert E, and Jung EG. Arch Dermatol Res **261**:87, 1978 (Abstract).
11. Parrish JA, White HAD, and Pathak MA. *in* "Dermatology in General Medicine" (TB Fitzpatrick, AZ Eisen, K Wolff, IM Freedberg, and KF Austen, eds.), p942. McGraw–Hill, New York 1979.
12. Wilson PD, Kaidbey KH, and Kligman AM. J Invest Dermatol **76**:322, 1981 (Abstract).
13. Fleming ID, Barnawell, JR, Burlison PE, and Rankin JS. Cancer **35**:600, 1975.
14. Vitaliano PP, and Urbach F. Arch Dermatol **116**:454, 1980.
15. Oettle AG. Nat Cancer Inst Monogr **10**:197, 1963.
16. Forbes PD, Davies RE, and Urbach F. J Invest Dermatol **73**:131, 1979.
17. Emmett EA. CRC Crit Rev Toxicol **2**:211, 1973.
18. Scotto J, Kopf AW, and Urbach F. Cancer **34**:1333, 1974.
19. Freeman RG, and Knox JM. Arch Dermatol **101**:403, 1970.
20. Fears TR, Scotto J, and Schneiderman MA. Amer J Epidemiol **105**:420, 1977.
21. Green AES, Findley JB, Klenk KF, Wilson WM, and Mo T. Photochem Photobiol **24**:353, 1976.
22. Blum HF. "Carcinogenesis by Ultraviolet Light" Princeton Univ. Press, Princeton, N.J. 1959.
23. Appendix F. *in* "Protection Against Depletion of Stratospheric Ozone by Chlorofluorocarbons," p325. National Academy of Sciences, Washington, D.C. 1979.
24. Winkelmann RK, Zollman PE, and Baldes EJ. J Invest Dermatol **40**:217, 1963.
25. Epstein JH, and Epstein WL. J Invest Dermatol **41**:463, 1963.
26. Freeman RG. J Nat Cancer Inst **55**:1119, 1975.
27. Urbach F., Epstein JH, and Forbes PD. *in* "Sunlight and Man" TB Fitzpatrick, MA Pathak, LC Harber, M Seiji, and A Kukita. eds.), p259. Univ. of Tokyo Press, Tokyo 1974.
28. Willis I, Menter JM, and Whyte HJ. J Invest Dermatol **76**:404, 1981.
29. Tan EM, and Stoughton RB. J Invest Dermatol **52**:537, 1969.
30. Tan EM, Freeman RG, and Stoughton RB. J Invest Dermatol **55**:439, 1970.
31. Sutherland BM, Harber LC, and Kochevar IE. Cancer Res **40**:3181, 1980.
32. Cleaver JE. Nature (London) **218**:652, 1968.
33. Setlow RB, Regan JD, German J, and Carrier WL. Proc Nat Acad Sci USA **64**:1035, 1969.
34. Epstein JH, Fukuyama K, Read WB, and Epstein WL. Science **168**:1477, 1970.
35. Robbins JH, Kraemer KH, Lutzner MA. Festoff BW, and Coon HG. Ann Int Med **80**:221, 1974.
36. Kraemer KH, Robbins JH, and Coon HG. Clin Res **21**:480, 1973 (Abstract).
37. Lambert B, Ringborg U, and Swanbeck G. J Invest Dermatol **67**:594, 1976.
38. Sbano E, Andreassi L, Fimiani M, Valentino A, and Baiocchi R. Arch Dermatol Res **262**:55, 1978.
39. Abo-Darub JM, Mackie R, and Pitts JD. Bull Cancer **65**:357, 1978.
40. Hart RW, Setlow RB, and Woodhead AD. Proc Nat Acad Sci USA **74**:5574, 1977.
41. Cooke A, and Johnson BE. Biochem Biophys Acta **517**:24, 1978.
42. Chan GL, and Little JB. Nature (London) **264**:442, 1976.
43. McCloskey JA, and Milo G. *in* "In Vitro Transformation of Normal Diploid Human Cells by UV and X-Rays," p110. San Juan, Puerto Rico 1977 (Abstract).
44. Sutherland BM. Nat Cancer Inst Monogr **50**:129, 1978.
45. Sutherland BM, Cimino JS, Delihas N, Shih AG, and Oliver RP. Cancer Res **40**:1934, 1980.
46. Doniger J, Jacobson ED, Krell K, and DiPaolo JA. Proc Nat Acad Sci USA **78**:2378, 1981.
47. Black HS, Chan JT, and Brown GE. Cancer Res **38**:1384, 1978.
48. Black HS, and Chan JT. J Invest Dermatol **65**:412, 1975.
49. Lo W, and Black HS. Nature (London) **246**:489, 1973.
50. Chan JT, and Black HS. Science **186**:1216, 1974.
51. Black HS, and Chan JT. Photochem Photobiol **26**:183, 1977.
52. Freeman RG, and Knox JM. Arch Dermatol **89**:858, 1964.
53. Bain JA, Rusch HP, and Kline BE. Cancer Res **3**:610, 1943.
54. Owens DW, and Knox JM. Nat Cancer Inst Monogr **50**:161, 1978.
55. Clark JH. Cancer Res **24**:207–211, 1964.
56. Morton JJ, Mider GB, Luce-Clausen EM, and Mahoney EB. Cancer Res **11**:559, 1951.
57. Miller EC. Cancer Res **11**:100, 1951.
58. Moodie MM, Reid C, and Wallick CA. Cancer Res **14**:367, 1954.
59. Santamaria L, and Giodano GG. *in* "The

Biologic Effects of Ultraviolet Radiation" (F. Urbach, ed.), p569. Pergamon, Oxford 1969.
60. Epstein JH. Natl Cancer Inst Monogr 50:13, 1978.
61. Epstein JH, and Epstein WL. J Invest Dermatol 39:455, 1962.
62. Epstein JH. J Nat Cancer Inst 34:741, 1965.
63. Stenback F. J Invest Dermatol 64:253, 1975.
64. Epstein JH, and Roth HL. J Invest Dermatol 50:387, 1968.
65. Pound AW. Pathology 2:269, 1970.
66. Stenback F. Eur J Cancer 11:241, 1975.
67. Stuttgen G. Dermatologica 124:65, 1962.
68. Schumacher A, and Stuttenger G. Dtsch Med Wochenschr 40:1547, 1971.
69. Bollag W, and Ott F. Agents Actions 1:172, 1970.
70. Robinson TA, and Kligman AM. Brit J Dermatol 92:703, 1975.
71. Barranco VP, Olson RL, and Everett MA. Cutis 6:681, 1970.
72. Peck GL, Olsen TG, Butkus D, Pandya M, Arnad-Battandier J, Yoder K, and Levis WR. Proc Amer Assoc Cancer Res 20:56, 1979.
73. Epstein JH. Aust J Dermatol 18:57, 1977.
74. Forbes PD, Urbach F, and Davies RE. Cancer Lett 7:85, 1979.
75. Kripke ML, and Glassman HN. J Amer Acad Dermatol 2:439, 1980.
76. Epstein JH. J Invest Dermatol 77:144, 1981.
77. Epstein JH. Photochem Photobiol 25:211, 1977.
78. Kripke ML. Photochem Photobiol 32:837, 1981.
79. Kripke ML. Advan Cancer Res 34:69, 1981.
80. Kripke ML. J Nat Cancer Inst 53:1333, 1974.
81. Fortner GW, and Kripke ML. J Immunol 118:1483, 1977.
82. Kripke ML, and Fisher MS. J Nat Cancer Inst 57:211, 1976.
83. Fisher MS, and Kripke ML. Proc Nat Acad Sci 74:1688, 1977.
84. Daynes RA, Spellman CW, Woodward JG, and Stewart DA. Transplantation 23:343, 1977.
85. Spellman CW, and Daynes RA. Cell Immunol 36:383, 1978.
86. Kripke ML, Lofgreen JS, Beard J, Jessup JM, and Fisher MS. J Nat Cancer Inst 59:1227, 1977.
87. Spellman CW, Woodward JG, and Daynes RA. Transplantion 24:112, 1977.
88. Kripke ML. *in* "Genetic and Environmental Factors in Experimental and Human Cancer" (HV Gelboin, B Macmahon, T Matsushima, T Sugimura, S Takayama, and H Takebe, eds), p103. Japan Sci Soc Press, Tokyo, 1980.
89. Jessup JM, Hanna N, Palazynski E, and Kripke ML. Cell Immunol 38:105, 1978.
90. Green MI, Sy MS, and Kripke ML. Proc Nat Acad Sci USA 76:6591, 1979.
91. Aberer W, Schuler G, Stingl G, Honigsmann H, and Wolf K. J Invest Dermatol 76:202, 1981.
92. Streilein JW, Toews GT, Gilliam JN, and Bergstresser PR. J Invest Dermatol 74:319, 1980.
93. Hoover R, and Fraumeni JF. Lancet 2:7820, 55, 1973.
94. Hill BHR. Aust J Dermatol 17:46, 1976.
95. Greene MH, Young TI, and Clark WH. Lancet 1:1196, 1981.
96. Hoxtell EO, Mandel JS, Murray SS, Schuman LM, and Goltz RW. Arch Dermatol 113:436, 1977.
97. Poleksic S, and Young KY. Cancer 41:12, 1978.
98. Viac J, Bustamante R, and Thivolet J. Brit J Dermatol 97:1, 1977.
99. Bustamante R, Schmitt D, Pillet C, and Thivolet J. J Invest Dermatol 68:346, 1977.
100. Nairn RC, Nind APP, Guli EPG, Muller HK, Rolland JM, and Minty CCJ. Brit Med J 4:701, 1971.
101. Weimar VM, Ceilley RI, and Goeken JA. J Amer Acad Dermatol 2:143, 1980.
102. Clark WH, Jr. *in* "Advances in Biology of the Skin," Vol. VIII, "The Pigmentary System" (W. Montagna, ed.), p154. Pergamon, New York, 1967.
103. Clark WH, Jr, From L, Bernardino EA, and Mihm MC. Cancer Res 29:705, 1969.
104. Reed RJ, *in* "New Concepts in Surgical Pathology of the Skin," p89. Wiley, New York, 1976.
105. Lee JAH, and Carter AP. J Nat Cancer Inst 45:91, 1970.
106. Elwood JM, and Lee JAH. Canad Med Assoc J 110:913, 1974.
107. Magnus K. Cancer 32:1275, 1973.
108. Lee JAH. J Invest Dermatol 59:445, 1973.
109. Elwood JM, and Lee JAH. Semin Oncol 2:149, 1975.
110. Schreiber MM, Bozzo PD, and Moon TE. Arch Dermatol 117:6, 1981.
111. Resseguie LJ, Marks SJ, Winkelmann RK, and Kurland LT. Mayo Clin Proc 52:191, 1977.
112. Human health effects, *in* "Protection Against Depletion of Stratospheric Ozone by Chlorofluorocarbons," p74. National Academy of Sciences, Washington, D.C., 1979.
113. Reimer RR, Clark WH, Jr, Green MH, Ainsworth AM, and Fraumeni JF, Jr. J Amer Med Assoc 239:744, 1978.
114. Reed WB, Becker SW, Sr, Becker SW, Jr, and Nickel WR. Arch Dermatol 91:100, 1965.
115. Kaplan EN. Plast Reconstr Surg 53:421, 1974.
116. Trozak DJ, Rowland WD, and Hu F. Pediatrics 55:191, 1975.
117. Lancaster HO, and Nelson J. Med J Aust, April, 452, 1957.
118. Gellin GA, Kopf, AW, and Garfinkel L. Arch Dermatol 99:43, 1969.
119. Sober AJ, Lew RA, Fitzpatrick TB, and Marvell R. Clin Res 27:536a, 1979 (Abstract).
120. Eklund G, and Malec E. Scand J Plast Reconstr Surg 12:231, 1978.

121. Kopf AW, Bart RS, and Rodriguez-Sains R. J Dermatol Surg Oncol 3:45, 1977.
122. Fitzpatrick TB, and Szabo G. J Invest Dermatol 32:197, 1959.
123. Epstein JH, Epstein WL, and Nakai T. J Nat Cancer Inst 38:19, 1967.
124. Clark WH, Min BH, and Kligman LHL. Cancer Res 36:4079, 1976.
125. Pawlowski A, Haberman HF, and Menon IA. *in* "Pigment Cell" (SN Klaus ed), Vol 5: p120. Karger, Basel, 1979.
126. Ringborg U, Lagerlof B, and Lambert B. J Invest Dermatol 74:72, 1980.
127. Fears TR, Scotto J, and Schneidermann MA. Amer J Public Health 66:461, 1976.
128. Projected changes in stratospheric ozone, *in* "Protection against Depletion of Stratospheric Ozone by Chlorofluorocarbons," p41. National Academy of Sciences, Washington, D.C., 1979.

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