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Aging, Environmental Influences, and Photocarcinogenesis

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Repeated exposure of human skin to solar ultraviolet radiation (UVR) over a period of many years is responsible for the induction of most nonmelanoma skin cancers in man. The tumors are progressively more common in chronologically older people. Is this fact purely a function of adequate dose accumulation and development time, or is tumor expression influenced by "physiological age"? The answer to this question influences risk estimates of the results of atmosphere modification. Data from animal studies indicate that the tumor incidence is affected by dose-delivery factors and not just by the accumulated lifetime dose. In addition, young mice are more prone to tumor induction by a given UVR dose than are older animals. Because the quality and quantity of the stimulus (UVR) can be readily manipulated and accurately described, studies on photocarcinogenesis offer distinct possibilites for untangling some of the interactive variables in the aging process.

Any injury that leaves a physical trace, as all but the most minimal do, increases the vulnerability of older individuals and because injuries of one sort or another are recurring hazards, older individuals, having been exposed to them more of their life, have built up a bigger acturial debt.[1]

Nonmelanoma skin cancer (NMSC) is a classic example of the damage wrought by multiple, cumulative, individually minor injuries to tissue, i.e., by repeated exposure of skin of genetically susceptible individuals to solar ultraviolet radiation (UVR) over a period of many years. Because repeated injury is necessary, the passage of sufficient time is required for effective exposure to UVR; thus NMSC is progressively more common in chronologically older people.

But how does "aged" skin influence the expression of damage? And is the damage accumulated arithmetically and expressed as a function of the total sunlight dose, or is the result influenced by exposure factors such as intensity, seasonal variation, and age at onset of exposure? Without answers to these questions we cannot relate quantitatively the amount of exposure to the tumor response, and without such a dose -response relationship, we cannot rationally predict the consequences of changes in life style or modification of the environment. In order to discuss our current understanding of aging, environmental influences, and photocarcinogenesis, we will examine the available evidence on sunlight exposure and human skin cancer, the epidemologic trends that have been reported, and some studies on laboratory animals designed to provide quantitative data on the sunlight-skin cancer connection.

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Abbreviations:
BCC: basal cell carcinoma
NMSC: nonmelanoma skin cancer
SCC: squamous cell carcinoma
UV: ultraviolet
UVR: ultraviolet radiation

SUNLIGHT AND HUMAN SKIN CANCER

The sun's role in the production of human skin cancers does not lend itself to direct experimentation. Nevertheless, many studies give evidence for causal significance of light energy in the induction of these tumors. Blum [2], Epstein [3], Emmett [4], Urbach et al [5], and Black and Chan [6] have reviewed the main lines of evidence, which are briefly outlined below.

1. Pigmented people, who sunburn less readily that white-skinned people, have much less skin cancer.
2. Among caucasians there appears to be a much greater incidence of skin cancer in those who spend more time outdoors than in those who work predominately indoors.
3. Skin cancer is more common in white-skinned people living in areas where insolation is greater.
4. Genetic diseases resulting in a greater sensitivity of the skin to the effects of solar radiation are associated with marked increases and premature skin cancer development (albinism and xeroderma pigmentosum).
5. Superficial skin cancers occur predominately on the body areas receiving the maximum amounts of solar radiation and where histological changes by chronic light damage are most severe (head, neck, arms, and hands).
6. Skin cancer can be produced readily on the skin of mice and rats with repeated doses of UVR.

These lines of evidence have been derived largely from data on basal and squamous cell carcinomas: there is parallel evidence linking malignant melanoma to sunlight exposure, but with at least 2 differences: (a) malignant melanomas are not as obviously associated with the most frequently exposed areas of the body and (b) there is less evidence to implicate UVR as the causally significant portion of the solar spectrum. This evidence has been interpreted as suggesting that malignant melanoma induction in skin may depend on light interaction with other, as yet unidentified, factors [7, 8].

Skin cancer, like most other forms of cancer, occurs more frequently in older people. However, unlike the rates for other types of cancer, the rates for skin cancer are increasingly significant even in the middle age groups, i.e., in 35- to 54-yr-old persons.

Surveys of the incidence of skin cancer have been performed with varying success in the past [9–14]. Even allowing for the fact that until recently most studies seriously underestimated the actual skin cancer incidence, one finds that the annual incidence appears to have increased in the past several decades. As industrial societies develop, the possibility for exposure of the population to sunlight once again increases since hours of work indoors become fewer, vacations become longer, and opportunities for travel to areas of high insolation become greater. The relationship between disease pattern and life style appears to be more than coincidental.

The magnitude of the effect of several factors is well illustrated in a recent model proposed by Vitaliano [14]. An analysis of the relative risks for NMSC (squamous cell carcinoma [SCC] and basal cell carcinoma [BCC]) shows clearly that a major controlling variable is solar exposure. The influence of UVR exposure is particularly evident in the SCC category. Pale-skinned easily sunburned people with an estimated lifetime sunlight exposure of > 30,000 hr have a 20-fold greater risk of having SCC than a comparable group with < 10,000 hr of

exposure. For BCC, the analogous ratio is about 3:1. These ratios hold true for people in both groups (< 59 yr and > 60 yr).

The remarkable frequency of NMSC is well demonstrated in Fig 1, which shows the prevalance of premalignant solar keratosis and of NMSC in Caboolture, Australia, and in Galway, Ireland. By age 75, 75% of all men and 67% of all women had at least 1 solar keratosis, and 28% of all men and 12% of all women had NMSC in northern Australia (latitude 27° South). Even in Galway (latitude 54° North), 11% of all men and 6% of all women had skin cancer [15].

The best estimate for the present annual incidence of NMSC in the U. S. (in caucasians) is 165/100,000 population [5]. Therefore, at present skin cancer develops in about 300,000 people in the U. S. each year, and about a third to a half of all cancers of all sites arise in the skin.

ENVIRONMENT, ATMOSPHERE, AND SKIN CANCER

The sunlight-skin cancer connection is important because of the possibility that anthropogenic changes in the environment may significantly increase the amount of UVR reaching the earth's surface. Several models for estimating the photobiological impact of the reduced ozone layer have been proposed [16]. Several assumptions, given below, underlie all these models.

1. At least 1 molecular species (e.g., oxides of nitrogen, chlorofluorocarbons) may diffuse into the stratosphere and cause photocatalytic destruction of a significant potion of the ozone layer.

2. A decrease in stratospheric ozone (the primary ultraviolet [UV] absorber) would result in an increase in transmitted UVR shorter than 320 nm (UV-B).

3. An increase in earth-level UV-B would result in an increase in skin cancer in a susceptible human population.

4. The photobiological response of skin would be strictly a function of accumulated radiation dose, independent of the mode of delivery (flux, duration, seasonal variation, rest intervals, etc.) (Fig 2).

What is the magnitude of the potential effect of a reduction in stratospheric ozone on the incidence of skin cancer? One would derive the most straightforward answer by plotting the present known skin cancer incidence against the ozone thickness over the areas where such epidemiologic data have been obtained, by extrapolating from this information, and by making reasonable assumptions about the effects of all factors (in addition to ozone thickness) thought to affect the skin cancer incidence. At least 2 problems are apparent: (a) this method presupposes a knowledge of ozone conditions that, for a variety of technical reasons, is presently nonexistent and (b) the observed increase in skin cancer with decreasing latitude is not due to ozone thickness alone. Other differences include local atmospheric conditions; genetic background of the population; type, length, and kind of outdoor exposure; and conditions of UVR dose delivery. Because some of these variables cannot be resolved with clinical or experimental data from humans, the calculations will be based, at least for the forseeable future, on laboratory animal studies.

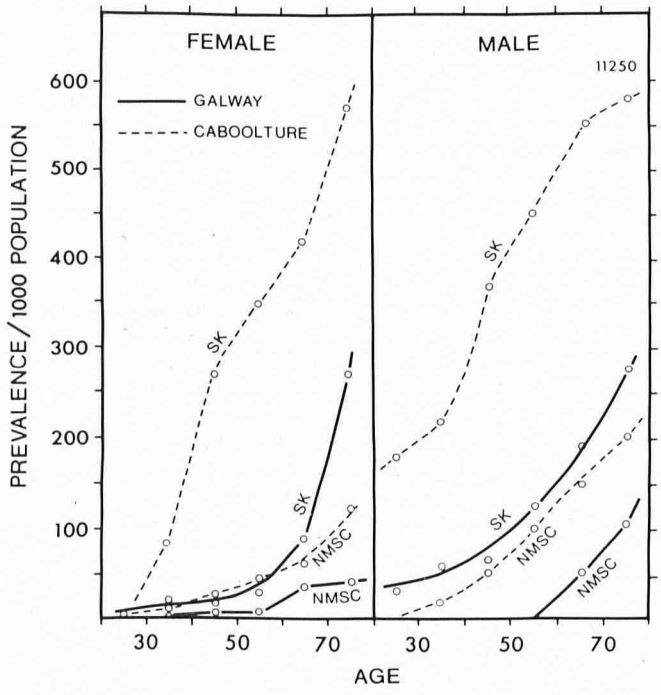

FIG 1. Prevalence of solar keratosis (*SK*) and nonmelanoma skin cancer (*NMSC*) in Caboolture, Queensland, Australia, and Galway, Ireland, Note the steep and parallel slopes of tumor prevalence in Australia and Ireland.

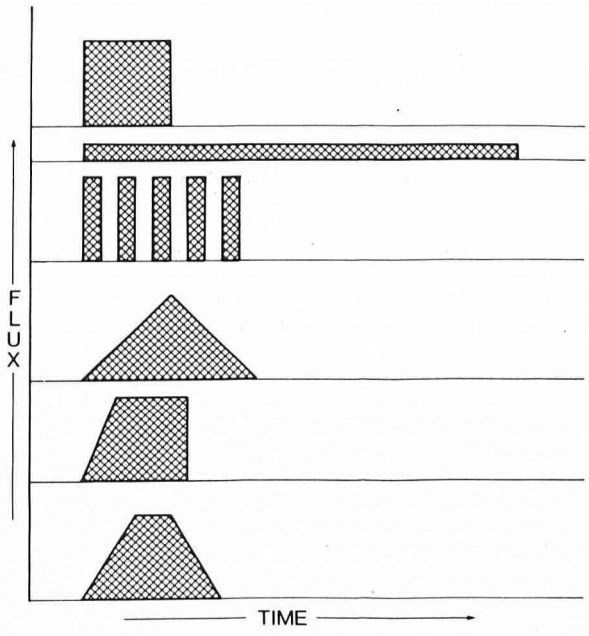

FIG 2. Geometric figures used to illustrate the law of reciprocity. Dose is the product of intensity (flux) times the duration of exposure. Thus, the time required to deliver a specified dose is influenced by whether the flux is constant and whether the exposure is continuous or interrupted. The figures suggest such variables as day-night cycles, lamp warm-up, sunrise, and sunset.

Several complicating factors, such as the uncertainty about the skin-UV action spectra, chemicals in the environment, the influence of the immune system, and DNA damage and repair mechanisms, lie beyond the scope of this paper. In the present context, the pertinent factor is *time*, particularly as it relates to aging and to the cumulative sunlight dose.

EXPERIMENTAL PHOTOCARCINOGENESIS

In mice, tumor development time decreases and tumor multiplicity increases with increasing UVR dose to the skin; some dose-response data appear to fit a log-normal distribution (incidence versus log weeks after beginning of exposure) [2]. However, dose *delivery* is also a matter of concern. Ultraviolet radiation is an efficient carcinogen only when delivered repeatedly. The response is not merely a function of the total (accumulated) dose; it can be influenced by the UVR dose rate (flux), fractionation, rest intervals, and age at the onset of exposure [2]. Currently, such complications are largely ignored in estimates of the predicted human skin cancer incidence.

An important implication of the total-dose assumption is that changes in the UV-B flux would have relatively little effect on the development of tumors in elderly people, who have already

accumulated most of their lifetime doses. This assumption suggests that they would be little affected by ozone changes, and also that little can be done to protect them from further tumor formation. It further suggests that the effects of a change in the ozone level would appear relatively slowly, over many years. There is some reason to question these conclusions: some clinical evidence suggests that the progression of tumors to clinical status is affected by natural solar variations within each year [17], and there is also a clinical impression that the elderly would be benefited by protection from additional UVR exposure. Animal studies suggest that irradiation of preexisting tumors has an effect on their development and aggressiveness that is not simply proportional to the dose required to produce them [2]. As a first approach to this question we performed a dose-response study in which the intermediate total dose level was achieved either by constant intermediate daily doses or by combinations of high and low daily doses (Fig 3). To avoid the special problems of irradiating existing tumors and of the effect of the induction period on the accumulated dose-to-first-tumor, we ceased irradiation prior to the appearance of the first tumor.

Three groups (groups T1, T3, and T5) of 108 hairless mice were irradiated for 1, 2, or 3 hr per day, 5 days per week, for 10 weeks with a xenon long-arc solar simulator with a 1-mm Schott WG320 glass filter [18, 19]. Additional groups were irradiated 1 hr per day for 5 weeks and then 3 hr per day for 5 weeks (group T2), and 3 hr per day for 5 weeks and then 1 hr per day for 5 weeks (group T4). Thus, groups T2, T3, and T4 received the same total 10-week dose. We chose UVR doses that would not chronically irritate the skin. The expected dose response (T1 < T3 < T5) was observed in these experiments (Fig 4). The 3 equivalent lifetime doses indicated that the cumulative effect

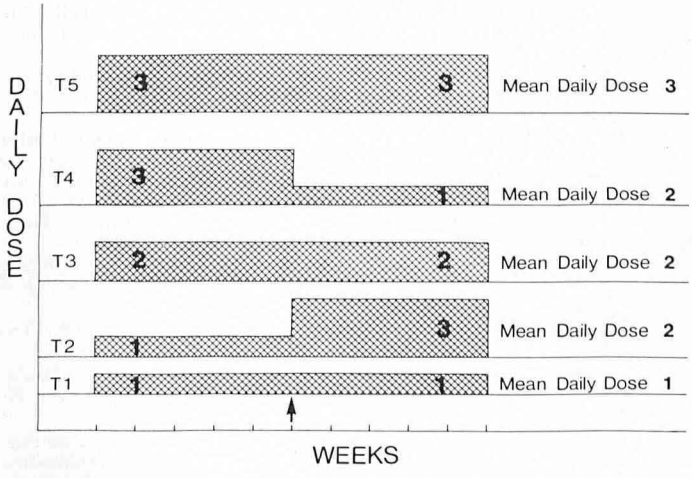

FIG 3. Treatment design for mouse experiments on time-dose reciprocity. Three levels of "lifetime" dose are delivered by variation of the daily dose delivered in 1 or 2 or 3 hr. In addition, the middle "lifetime" dose is delivered in 3 ways: by administration of a constant daily amount, by averaging of the higher-then-lower daily dose, and by averaging of a lower-then-higher daily dose.

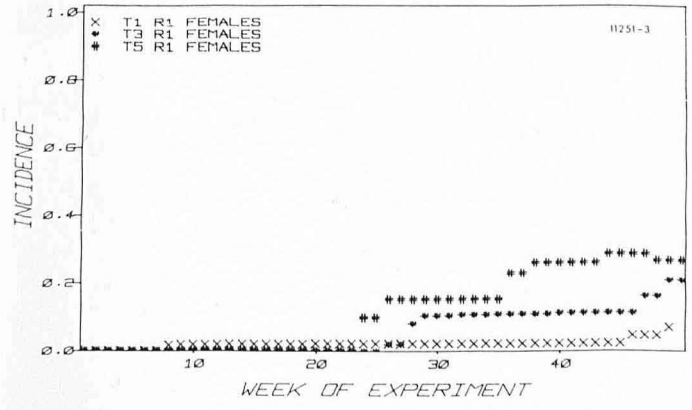

FIG 4. Tumor induction in mice irradiated for 1 or 2 or 3 hr daily; females are shown in the *upper graph*, males *below*.

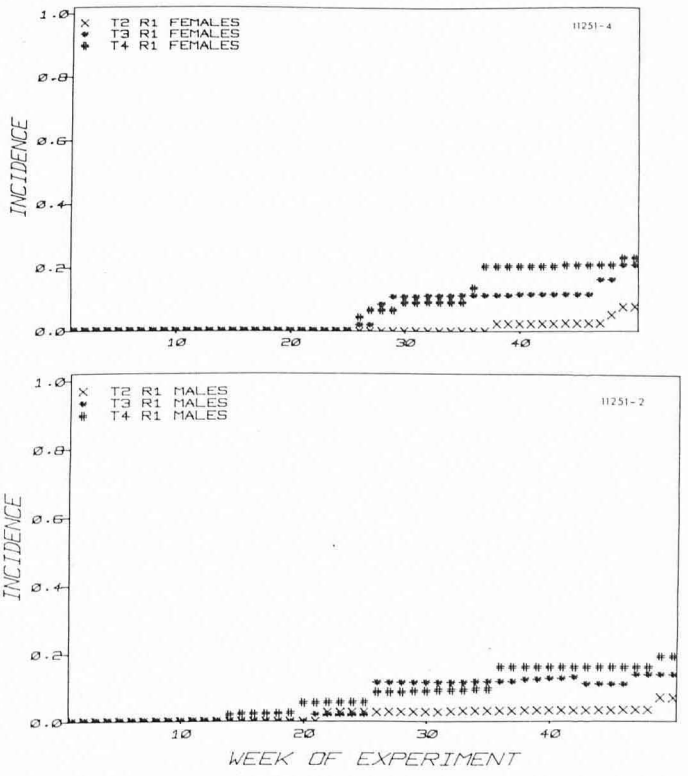

FIG 5. Influence of dose distribution on tumor incidence. The greatest incidence occurred when the early exposures were highest.

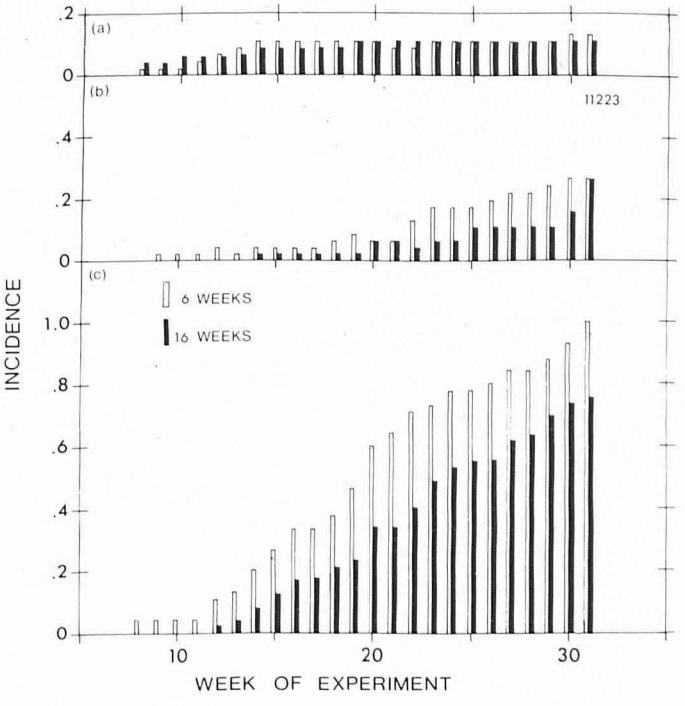

FIG 6. Influence of age on susceptibility to skin tumors induced by ultraviolet irradiation (*UVR*). Animals starting exposure at 16 weeks were less susceptible to UVR carcinogenesis than those starting exposure at 6 weeks. Differences are greatest in the group receiving the highest daily dose (*a* = treatment dose T1, *b* = T3, *c* = T5).

was related to the size of the initial dose (T1 ≃ T2; T3 < T4 < T5) (Fig 5).

This influence of dose distribution could be attributed either to a differential sensitivity to the initial exposures in a series, or to a differential sensitivity to individual doses because of age. Another experiment compared animals starting exposure to UVR at 6 weeks rather than 16 weeks of age. On the basis of their tumor responses, the older animals were less sensitive (Fig 6).

Blum and colleagues reported an analogous finding in their classic studies in which they used a mercury arc lamp to induce tumors on the ears of haired mice [20]. Their experiments, except for one in which the animals were approximately 10 mo old at onset, were carried out on mice 2 to 3 mo of age at the beginning of the study. For the older mice the time to 50% tumor incidence was much greater than for younger animals receiving the same UVR treatment. Blum et al mention the general concept that old mice may be less susceptible to cancer than young mice, but they also point out that the thicker strata cornea of older mice might offer greater initial protection aginst UVR penetration. In both cases, then, the observations are inconsistent with the use of the "cumulative lifetime dose" as a predictor unless dose increments are constant and all individuals are the same age at initial exposure. As LeGrand [21] has implied, it would have been unreasonable to expect that time-dose reciprocity, which is confined to relatively simple physical systems, should be relevant to something as complex and interactive as the process of carcinogenesis.

CONCLUSIONS

Current evidence clearly implicates repeated environmental solar UVR exposure to the genesis of human NMSC. Because many years of repeated exposures are normally required to produce tumors in human skin, the passage of time (i.e., chronological or temporal aging) is a co-variable. The preliminary observations from our animal experiments (and from limited clinical data) strongly suggest that the tumor response reflects 2 distinguishable aspects of aging: (a) the passage of time required by repeated exposure that results in accumulated damage and (b) the biological *effect* correlated with time passage, i.e., "physiological age." The mechanism by which physiological age influences photocarcinogenesis is not clear; it may be based on a structural change (e.g., thickening of the protective statum corneum), a change in the biological properties of tissue (e.g., a reduction in the DNA repair capacity or an alteration in the fibrous protein), a change in the biological properties of the organism (e.g., an alteration in the immune capability), or any of the many other phenomena currently associated with "aging" [22, 23]. The realization that such changes in the biological system can demonstrably affect the process of UVR-induced carcinogenesis, in which at least the quality and quantity of the stimulus (UVR) can be very accurately described and controlled, now makes it possible to design experiments that can truly shed light on the complex features of aging, at least aging of the skin.

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