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THE HISTORICAL ASPECTS OF PHOTOCARCINOGENESIS

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1. ABSTRACT

The concept of photocarcinogenesis is of fairly recent duration. Although cancer of the breast is described in the ancient Greek medical literature, skin cancer is not mentioned even as late as the 18th Century. This is most likely due to the poor survival of humans, 80% of people did not live past 40 years, and only 6% lived longer than 60 years. The first association of skin cancer (face and lip) with outdoor exposure dates to the middle of the 19th Century. About that time it was shown that it was Ultraviolet Radiation (UVR) that could cause skin and eye inflammation. It was not until the 20th Century that competent epidemiologic studies associated human skin cancer with chronic solar exposure, and it was shown that chemicals could augment the effects of UVR exposure. It has only been in the last quarter of a Century that it was found that UVR could cause immunologic changes that allow multiple skin cancers to develop. Advances in molecular biology have begun to show the cellular and molecular events that lead to UVR induced skin carcinogenesis.

2. INTRODUCTION

The high energy, short wavelength portion of the solar electromagnetic spectrum (less than 320nm) is potentially very detrimental to living cells and tissues. A low concentration of Ozone formed in the stratosphere absorbs most of the photons of UVR and thus prevents them from reaching the earth. However, even in the presence of this Ozone layer, which varies in thickness at different latitudes and at different seasons, a biologically significant amount of UVR reaches the surface of the earth.

The major effects on humans of radiation in the UV-B range (280-320 nm) are on the skin and eyes. Acute effects consist of "Sunburn", an inflammatory response of the tissues that may be no more than mild redness or stinging of the eyes, or may develop into the equivalent of second degree (blistering) burns. The acute effects of single overdoses of UV-B are transient, heal without scarring, and in the skin lead to adaptive changes of skin thickening and pigmentation, which afford some degree of protection. The only established positive (*i.e.* beneficial) effect of UV-B is the production of Vitamin D precursors in the skin, which are absorbed into the bloodstream and prevent Rickets, a serious deficiency disease. Most work has been done on the harmful effects of UV-B and relatively little attention has been given to its possible beneficial effects. Repeated UV-B exposure, prolonged over years, can result in chronic degenerative changes in skin, characterized by skin “aging”

and the development of pre-malignant and malignant skin lesions.

Within a relatively short period of time, there have appeared in the scientific literature three concepts that stimulated interest in photocarcinogenesis: One was the concern that human activities could adversely affect the ability of the earth's atmosphere to remove harmful solar UVR by optical filtration (1);

A second was the realization that photocarcinogenesis could be enhanced greatly by a variety of chemical agents (2), A third was the discovery that UVR could affect photocarcinogenesis *via* the immune system (3).

In each case, the concept enriched the field of photobiology, while contributing to an understanding of immediately relevant phenomena.

3. THE ROLE OF LIGHT IN THE PATHOGENESIS OF SKIN CANCER

In 1857 Charcot (4) determined that UVR caused acute erythema and in 1894 Unna (5) proved that pigmentation could be induced by UVR. It soon became apparent that the capability of skin to react to light by pigmenting was most variable, that this variability pertained not only to different races, but also to individuals apparently of similar ancestry. In 1927, Hausser and Vahle (6) showed that the longer UVR wavelengths were more effective for producing pigmentation than the more erythemogenic shorter ones. By then, Bloch (7) had carried out his classical study of the mechanism of melanin formation in human skin, discovered DOPA oxidase and laid the groundwork for the development of histochemistry.

In 1785, Jean Senebier, a Swiss biologist, noted that " Peasants, working much in the open, have paler skin on the covered than the exposed areas, and if exposed for years to sunlight, the skin of the face and hands appears thickened and tanned, while in contrast the covered areas retain their white appearance" (8). The dominant inheritance of freckling was noted by Ehrman (9), an observation which decades later was correlated with a predisposition to skin carcinogenesis.

Changes in the stratum corneum, epidermis and dermis due to chronic light exposure were first associated with UVR exposure by Unna (5). That thickening of the stratum corneum provided some measure of protection against further UVR injury was documented in detail in 1930 by Miescher (11). Eventually a marked degeneration of the elastica and collagen of the skin develops virtually only on the most exposed sites of very heavily sun exposed persons (5,11). The observation that at least one skin cancer, that of the lip, was related to outdoor exposure was made by Enzière (10) who noted that this malignancy was much more common in poor country people, mostly on the lower lip and much more common in men than in women. It mostly occurred in people with long outdoor exposure.

The first detailed studies that skin cancer might be due to prolonged and repeated exposure to sunlight came almost simultaneously from two sources: Unna (5) associated the severe degenerative changes of the exposed areas of skin of sailors with the development of skin cancer. Dubreuilh (12), studying skin diseases in the Bordeaux region of France, observed the frequent incidence of keratoses and skin cancer in the workers in the vineyards, but only occasionally in the city dwellers nearby. He noted that these skin changes occurred only on chronically sunlight exposed skin. On the peasant women, habitually wearing a headscarf like that of widows or the coif of nuns, the ears and lateral cheeks were spared. He concluded that chronic solar exposure was the direct cause of keratoses and skin cancers. These observations were later confirmed by Shield (13), and others, who observed a high incidence of skin cancer among country people in the USA and Australia, where sun exposure is much more intense than in central Europe. Bruusgard (14), in 1926, reported that frequent incidence of skin cancer among sailors was due to a combination of sun exposure and coal tar, to which sailors were heavily exposed in those days.

After Unna (5), Dubreuilh (12) and others had made the clinical association of chronic sunlight exposure with skin cancer, dermatologists debated whether this association is found in all pale-skinned people, or as Haxthausen and Haussman had proposed, only in those carrying a forme-fruste trait of Xeroderma Pigmentosum (15). In 1928, this latter view began to change when Findlay (16) found that daily irradiation of mice with UVR from a mercury arc induced skin cancer. Findlay also observed that when mice are treated with coal tar before irradiation, the time to induce skin cancer was reduced. His findings were soon corroborated by Putschar and Holtz (17). The individual most responsible for calling attention to the causal relation between solar and artificial UVR and skin cancer in man and animals was Roffo (18). He showed that skin cancer could be induced in rats with natural sunlight as well as with mercury arc radiation, and he was the first to carry out a real epidemiological study of skin cancer in man (19). Roffo also carried out the first action spectrum studies of cutaneous photocarcinogenesis when he showed that clear window glass was sufficient to prevent development of skin cancer, and thus set an approximate limit of less than 320nm for effective UVR (19).

In 1941-1945, Blum, Grady and Kirby-Smith at the US National Cancer Institute performed a comprehensive series of experiments on UV carcinogenesis in mice (20). For details of these elegant experiments, Blum's classic work "Carcinogenesis by Ultraviolet Light" should be consulted (21). Blum reported several important observations on tumor induction:

1. A single dose of UVR did not induce tumors in the lifetime of the animal.

2. A useful measure for tumor induction was the " Development Time", *i.e.*, the time lapse between the first UVR dose and the appearance of a tumor of a certain

volume. Within an identically treated population of mice, this was distributed in a consistently regular fashion.

3. Differences in dose, intensity or interval between doses did not alter the shape or the slope of the dose-time relation, but only moved their relative positions on the dose axis.

4. The incidence of skin tumors was well distributed in the mouse population when plotted against the log of the square of the number of doses (21).

5. Reciprocity held until the doses became too small to produce tumors in the lifetime of the animals.

Chemically pure phenanthrene compounds which produced skin cancer in rodents had been isolated in the early 1930's. Findlay had already reported that application of coal tar, followed by UVR increased the probability of skin carcinogenesis and shortened the development time of the tumors. Doniach and Mottram (22) compared the carcinogenic and photodynamic activity of various hydrocarbons, as well as of tar, soot and shale oil, and found strong correlation between these two activities. When experimental studies in animals were performed, however, various investigators found either potentiation or even protection during simultaneous carcinogen and UVR exposure. It was nor until decades later that the explanation for these discrepancies became apparent, namely that not only are the phenanthrenes photodynamically active, but they can be photochemically decomposed to non-carcinogenic photoproducts (23).

4. CELLULAR AND MOLECULAR PHOTOBIOLOGY

Widely varied effects of UVR on many cell types and organisms have been reported over the past 100 years, but this early work failed to appreciate both the need to control the wavelength of the radiation and the importance of the physiologic state of the biologic system before, during and after the irradiation. In 1929, Gates (24) had discovered that the relative effectiveness of different wavelengths in killing bacteria paralleled the absorption spectrum of nucleic acids

4.1. Effects of UVR on DNA

The chemical basis for some of the effects of UVR on nucleic acids did not become evident until late in the 1940's. More recently, the discovery of Beukers and Berents (25) of UVR induced thymine dimers in DNA stimulated an interest in molecular photobiology. We now know that many other types of photo-products besides thymine dimers are formed in the nucleic acids of cells, some of which have been isolated and characterized (26). In several, their biologic importance has also been determined. The molecular mechanism of UVR carcinogenesis was, however, poorly understood until recent results of the effects of UVR on DNA structure and replication became available. It is now established that UV irradiation results in pyrimidine dimer formation in DNA and that both excision repair and photoreactivation repair occur in mammalian cells (27). The observation that cells from a cancer prone skin disease (Xeroderma Pigmentosum) are unable to repair DNA damage resulted in a flurry of activity (28). However, XP variants were soon discovered in which excision repair systems were apparently normal, although patients were cancer prone. In addition to the well documented capability of UVR to induce cancer in the skin of men and mice, Hart and Setlow (29), have shown that fish liver cells, UV irradiated *in vitro* and re-injected into isogenic recipients, give rise to tumors. The tumor induction was dose dependent, and illumination of irradiated cells with visible light before re-injection markedly reduced tumor production. Since fish cells possess photoreactivating enzymes, these data imply that pyrimidine dimers, induced in cellular DNA by UVR are causally related to the development of the tumors. More recently, Ley (30) has shown that pyrimidine dimers are efficiently photoreactivated in the skin of a South American opossum, and that the induction of squamous cell carcinomas and melanomas due to UVR can be prevented by photoreactivating light. This again strongly suggests that pyrimidine dimer production by UVR is, indeed, one very effective pathway for cutaneous photocarcinogenesis. This assumption is also tenable in view of the evidence that DNA damage results in mutagenesis in cells.

4.2. Molecular events in UVR induced skin carcinogenesis

In experimental carcinogenesis, at least three stages are recognized: initiation, promotion and progression. Very recent work has shown that gene expression as well as mutation can be induced by UVR, and that such changes are found in human skin cancers. UVR induced tumors display mutations preferentially in the N-*ras* oncogene, and most of these mutations occur opposite dipyrimidine sequences, thus suggesting that these sites are the targets for UVR induced mutations and transformation. Finally, loss of a putative tumor suppressor function controlling the epidermal differentiation phenotype (*p53*) is associated with tumor progression to highly anaplastic lesions (31). In human tumors, heterozygous mutations in the *p53* gene have been found in 7 of 14 Basal Cell carcinomas (32). 14 of 24 invasive Squamous Cell carcinomas contained mutations in the *p53* suppressor gene, either CC-TT double base change, or mutations exclusively at dipyridine sites (33). Consequently it appears that in all three stages of photocarcinogenesis genomic changes, attributable to UVR can be found.

5. ACTION SPECTRA FOR PHOTOCARCINOGENESIS

In the period of about 40 years after the early experiments, there was little progress in the knowledge of wavelength dependence of photocarcinogenesis. This began to change when in the 1960's a hairless mouse became available for experimental studies (34). How the carcinogenicity of UVR changes with wavelength has been a topical question that has assumed greater importance because of the threat of depletion of the protective stratospheric ozone. Skin cancer has long been known to be induced by UVR (19). Roffo (18) and Funding, Henriques

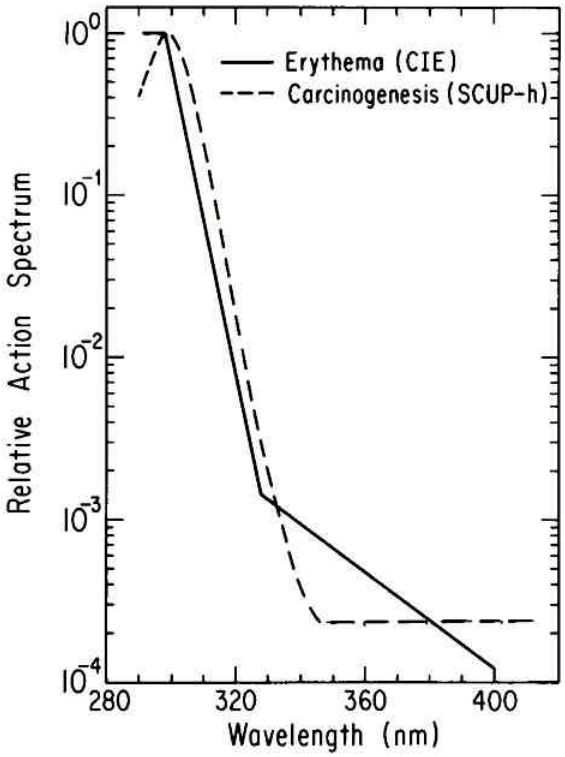

Figure 1. Action spectrum for minimal erythema (solid line) Action spectrum for human photocarcinogenesis calculated from animal data and estimated human skin transmission (dashed line) From (53).

and Reckling (35) showed that apparently wavelengths longer than 320 nm did not produce skin cancer in rats. Using a variety of modern light sources including a reasonable solar simulator, Forbes, Cole and Davies (36) found that an action spectrum for mouse skin edema performed best in their photocarcinogenicity experiments. Recently, sufficient evidence has been found that UVA can induce skin cancer in experimental animals, although it is 1000 times less effective than UVB (37). Thus attempts have been made to extend the carcinogenesis action spectrum into the UVA. The latest skin carcinogenesis action spectrum shows a rapid drop in effectiveness from 295 to 341 nm (by about four logs) and then a fairly flat effectiveness to 390nm**.** The action spectrum parallels the human skin erythema action spectrum in the UVB and in the short UVA, but is well below that in the long wave UVA (38). (Figure 1)

6. INTERACTION OF UVR AND CHEMICALS IN PHOTOCARCINOGENESIS

The evidence is long standing and compelling that chemical agents can modify the carcinogenic effects of light (39). There are several possibilities for such interactions: [1].Chemical carcinogenesis may be modified by UVR – enhanced or reduced (39). [2] Chemically enhanced photocarcinogenesis follows topical or systemic administration of agents that are phototoxic, but not in themselves carcinogenic, and irradiation with UVR in doses not primarily carcinogenic under the conditions of the experiment (40) and [3] Chemical promotion of photocarcinogenesis –enhancement of minimal UVR induced carcinogenesis by application of a non-carcinogenic compound –*i.e.,* Croton Oil (41) or All trans Retinoic Acid. (42). The classic example of chemically enhanced photocarcinogenesis is that induced by Psoralen and UVA. That Psoralens can enhance photocarcinogenesis has been known since 1959 (43). Since 1974, PUVA (Psoralen plus UVA) therapy has been extensively used for the treatment of Psoriasis and other skin diseases. The first report indicating an increased risk for skin cancer in man was published in 1979 (44). Since then it has been shown that there is a small, but real risk for increase of Squamous Cell carcinoma in patients treated with PUVA. Important cofactors are history of arsenic ingestion, ionizing radiation therapy, and severe sunlight damage.

7. PHOTOIMMUNOLOGY

It has long been known that skin cancers, induced in mice by UVR, are highly antigenic (45). This finding raised the question of how the tumors were able to survive in the original host without being destroyed by the immune system. The answer turned out that UVR (primarily in the UVB) alters the host immunity only against UVR induced cancers(46). This inability of UVR irradiated mice to reject the induced cancers results from the presence within host lymphoid tissues of suppressor lymphocytes that prevent the destruction of the developing primary skin cancers. These suppressor cells are induced by exposure to natural and artificial UVB sources and are specific for a common antigen, present on UVR induced tumors, but are generally not found on tumors induced by chemical agents. Studies on the nature and mechanisms of the immunologic alterations brought about by exposure to UVR suggest that induced DNA damage triggers a cascade of events, leading ultimately to a state of antigen specific, systemic T lymphocyte mediated immunosuppression. Key components of this cascade are epidermal cytokines that modulate the immune response (45). In addition to producing cancer suppressor cells, UVR induces antigen specific suppression of delayed–type hypersensitivity, a process that may be important in protecting against some infectious diseases (45). It has been suggested that the photoreceptor for UVR induced immunosuppression is Urocanic Acid, which isomerizes from the naturally occurring *trans* form to the *cis* form upon UV irradiation (46). That immunosuppresssion can increase the risk of skin cancer in humans has been demonstrated by the observation that renal transplant patients, who are seriously immunosuppressed, develop Squamous cell carcinomas, mostly on previously sun exposed sites.

8. SKIN CANCER IN HUMANS

Repeated sunlight exposure, prolonged over many years can result in degenerative changes in human skin, characterized by skin “aging” and the development of pre-malignant and malignant skin lesions. Recent epidemiological research has resulted in the development of a preliminary dose-response relationship of non-

melanoma skin cancer (NMSC) to UVR exposure. Reasonable hypotheses based on tissue culture and animal experiments for the relationship of various wavelength of UVR to NMSC induction have been proposed. Whereas there is still some uncertainty regarding the exact relationships of various segments of the UVR spectrum to carcinogenesis, existing data seem sufficient for developing models that allow for prediction of the probable rise in the incidence of NMSC consequent to an increase in UVR resulting from stratospheric ozone decrease (1).

8.1. Possible effects of stratospheric Ozone decrease

That changes in stratospheric ozone concentration can have an influence on the biologic effects of solar radiation, and the potential magnitude of such effects on the skin, was described first by Latarjet in 1935 (47). It is interesting to note the close resemblance of Latarjet's prophetic studies 66 years ago to the most recent calculations of an international task force (48). Significant, global scale decreases in total stratospheric ozone have occurred over the years 1979-1944, in addition to the major spring decreases over the antarctic continent (48). Current evidence indicates a decline of more than 5% in the winter and spring months, and less than 2% in the summer, mainly between the latitude of 40 and 52 degrees north. The increases of UVB radiation resulting from the stratospheric ozone depletion are likely eventually to result in an increase in skin cancer incidence. On the basis of the most recent skin cancer action spectrum (38), it is estimated that a 1% ozone decrease will eventually increase the incidence of Basal Cell Carcinoma by 2%, that of Squamous Cell Carcinoma by 3.5%, for an overall increase of NMSC by 2.3%. Malignant Melanoma may increase by 0.6%. Depending on the model chosen, a 10% ozone depletion, constant for 20-40 years, could after four decades result in 300,000 to 400,000 additional NMSC and 4500 Malignant Melanomas world-wide (48). However, to date no significant, consistent increase in ground level UVR has been measured near populated areas, at least in the USA (49). This is most likely due to tropospheric absorption of UVR by aerosols, clouds and tropospheric ozone. Thus, the recent increase in Squamous Cell Carcinoma (50) is not likely to be due to an UVR increase, but rather to greater exposure to sunlight of populations for social reasons.

8.2. Epidemiology

It is not possible in a brief review to describe and cite the extensive work on epidemiology of skin cancer that has been reported in the last two decades. There is evidence that the incidence of Basal Cell Carcinoma has been increasing by 3% per year, and that Squamous Cell Carcinoma has shown a three-fold rise in females, and a 2.6 fold rise in males between 1960 and 1986 in the USA (50). Although skin cancer is most often found among people with fair or lightly pigmented skin, not all people with similar skin color, even when equally exposed, develop skin cancer. Recent studies on the ability of patients to develop contact dermatitis, have shown that those whose immune system was impaired by UVR exposure, were the ones who had developed skin cancer (51). The relationship of Malignant Melanoma to UVR exposure is still uncertain, although the existence of latitude gradients and the relation to severe sunburn in childhood makes it very suggestive. Incidence rates of Malignant Melanoma among the white-skinned races through out the world are rising at an alarming rate. From 1974 to 1985 Malignant Melanoma has increased at an average yearly rate of 3-4% per year in the US (50). However, it appears that at least the risk of dying has peaked, it is projected to bend downward by the second decade of the 21st Century (52).

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