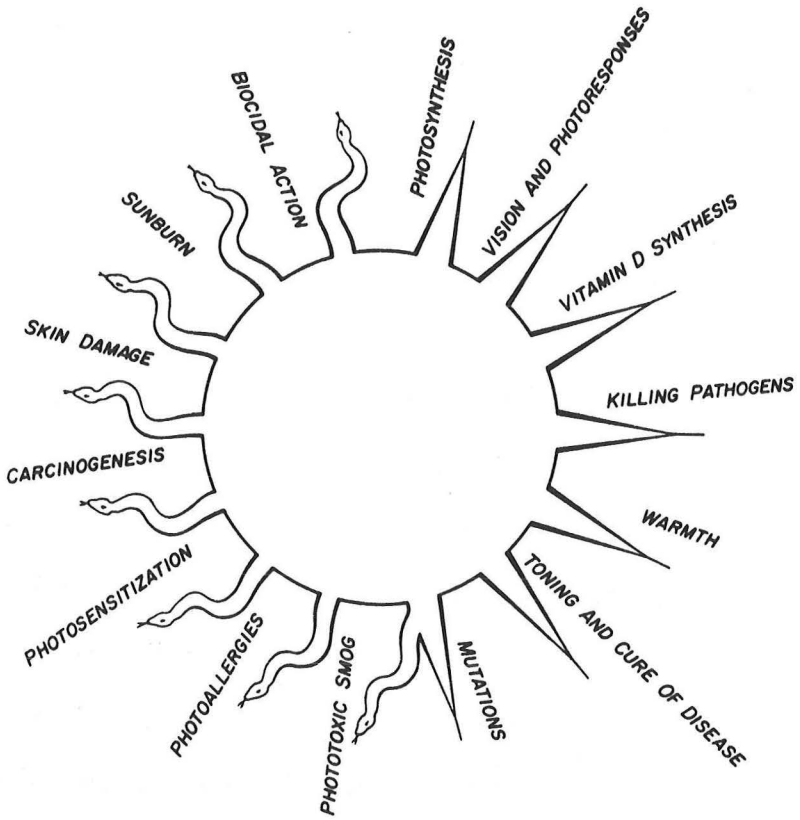
SUNLIGHT AND SKIN CANCER

MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

APRIL 23, 1981

PAUL R. BERGSTRESSER, M.D.



Our sun has two faces-one good and one bad, like Janus, the Roman god who guards the gateway to heaven.

(Giese, 1976)

SUMMARY

Human skin which receives ultraviolet light on a chronic basis from either natural sunlight or from artifical sources will develop degenerative changes. These changes include premature aging and the propensity to develop skin cancer. Since well tanned human skin in today's culture is synonomous with an image of health and beauty and since ultraviolet light is responsible for both tanning and degenerative changes, each patient faces a dilemma which only he can resolve. For those who wish to protect their skin and to retard such changes, simple measures are sufficient. They include: 1) avoiding mid-day sun exposure, 2) wearing protective clothing, 3) using commercially available "sun screens" daily, and 4) never falling into the trap of the "tanning salon".

INTRODUCTION

Skin cancers, which are malignant cancers arising from cell populations within the epidermis, constitute one-third of all human malignancies. Approximately 300,000 new patients with skin cancer are treated in the U.S. each year. From the vantage point of probability, the annual incidence of new nonmelanoma skin cancers in Caucasians living in the U.S. is estimated to be 165/100,000, with the regional incidence in the one epidemiologic study ranging from 124/100,000 in Iowa to 379,100,000 in Texas (Scotto, et al., 1974). Although most skin cancers produce frequent morbidity and infrequent mortality, patients with one type, the malignant melanoma, have a five year survival of about 60%. In 1981, several relatively new issues are of particular relevance to those who practice internal medicine, most especially because they serve as primary care physicians for the majority of patients who acquire skin cancer. For all of these reasons, I have chosen to review selected clinical and experimental observations which give appropriate perspective to our understanding of human skin cancer. This review is subdivided accordingly:

I. Basic Principles

- Cutaneous Structure and Function
- Light as Electromagnetic Radiation
- Special Case of Xeroderma Pigmentosum

II. Ultraviolet Light and Skin

- Acute Effects
- Melanin
- Chronic Effects
- Skin Cancer

III. Therapy of Skin Cancer

IV. Photoprotection

V. Special Problems

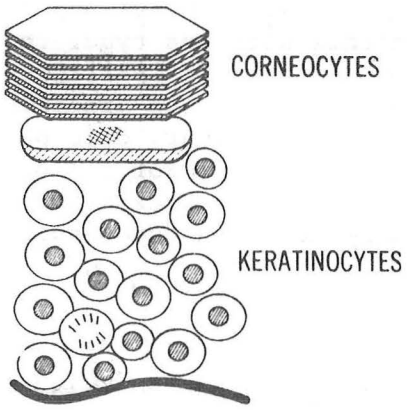
- Psoriasis
- Tanning Salons
- Vitamin D
- Immune System Interactions

I. BASIC PRINCIPLES

CUTANEOUS STRUCTURE AND FUNCTION

The outer surface of skin establishes a barrier between man and his environment, and the specific region or surface in the skin which serves as a barrier to the exchange of small molecules is a unique laminated surface membrane called the stratum corneum. This structure, which measures 10 microns in thickness, is made up of flattened, dead epidermal cells (corneocytes) which are locked together laterally and vertically into a

laminated membrane. Barrier properties of the stratum corneum are similar to that of polyetheylene film which is about 10 microns thick. An important aspect of stratum corneum homeostasis is that individual cells from which it is constituted are replaced continuously, since the individual cells exfoliate from the outer surface. This continued loss is replaced by cells which proliferate and mature in obligate fashion within the underlying viable portion of the epidermis. This process is illustrated in the figure taken from Bergstresser and Taylor (1977).



More than 90% of the cell mass within the epidermis consists of proliferating and maturing keratinocytes. These cells arise from a germinative pool and subsequently undergo a series of maturational steps from which they emerge to become flat, dead, laminated cells of the stratum corneum. For our purposes today, attention must be paid to these epidermal cells as well as the other two major cell populations: melanocytes and Langerhans cells. Keratinocytes constitute a barrier to bacterial and molecular penetration; melanocytes provide the primary basis for ultraviolet light exclusion as well as the primary basis of racial discrimination; and Langerhans cells have been recognized recently as being important in the development of cutaneous contact hypersensitivity and in their contribution to cutaneous immune surveillance.

As alluded to above, the epidermis forms an incomplete barrier to ultraviolet light penetration into the skin. The biologic effect of incomplete penetration will constitute the discussion today. Since some light penetration is required for life, there must be some physiologic feedback system to regulate light penetration. This control system does work in general, but when genetic populations which have acclimatized to one environment move to a different one, or when experiments of nature occur, breakdown of that physiologic system will ensue. Hindus who emigrate to 19th Century London develop rickets; 19th Century British prisoners who are taken to Australia develop cancer.

LIGHT AS ELECTROMAGNETIC RADIATION

The notion that light is of benefit to mankind dates to the earliest records of man's existence and religious worship of the sun and moon, our

two major light-emitting bodies, occurs in numerous primitive societies. Even in our sophisticated 20th Century (Modern) Culture we now recognize with an almost religious fervor that only the direct conversion of the sun's energy to electricity and steam will save us and our energy-dependent economy from backruptcy or blackmail. In addition, many of the youth and their imitators worship at the alter of the "complete tan" as increased pigmentation has become synonomous with youth and beauty.

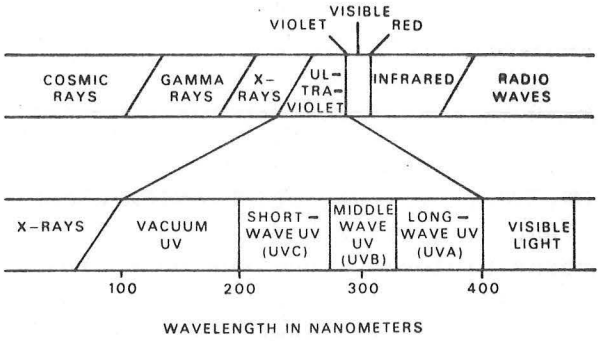
All substances which possess temperature above absolute zero emit electromagnetic energy. If such temperatures are high, a portion of this radiation will be energetic enough to interact in significant ways with many biological systems. Our own sun, which emits electromagnetic energy with a spectrum similar to that of a black body at 5600°K, is consequently able to initiate many important biologic processes on earth, processes which are as diverse as photosynthesis, vitamin D production, and carcinogenesis. Energy of this sort, which is emitted from the sun, or for that matter, from any light source, may be characterized in each of two contradictory ways. This paradox dates back to the time of Sir Isaac Newton.

Light as a Wave: In certain physical circumstances light energy acts as if it were transmitted in waves of energy, much as sound energy passes through air. In sound wave transmission, there is no net movement of air toward the ear, merely the vibration of molecules in between. For light, then, it is possible to characterize the waves either by their frequency of vibration or by their wave length. You will remember from elementary physics that the speed of light is constant at 186,000 miles per second (3×10^8 meters/sec.) and that assuming speed to be constant, a reciprocal relationship exists between frequency and wave length: Speed (rate) = Wave Length x Frequency ($c = \lambda f$).

With this in mind it is now possible to review the electromagnetic spectrum. Since the speed of light within a single material is, in fact, constant, then one can fully characterize a specific wave of light by stating its wave length. In this way, the determination of wave length is a useful way to characterize light energy. This is true even though no material (or ether) to propagate electromagnetic energy has ever been identified. Wave length descriptions are most useful in describing light and the concept makes intuitive sense to all amateur scientists who have employed a prism to view the visible light spectrum.

Light as Quanta of Energy: It is also possible to describe light as energy which travels in single packets or quantum units. Note that when light is described as a wave or net movement of a substance toward the light sensor is required; the transmission of energy occurs by wave vibration alone. In contrast, quantum theory models light energy as occurring in packets which move toward the observer (sensor). This second model is most useful to photobiologists who must describe biological systems in which light energy is seemingly absorbed in quanta by specific molecules within that system. For our purposes today we will rely on both notions. Fortunately, wave length and energy state of light quanta are related since they are inversely proportioned to each: Energy/Frequency = Constant (6.625×10^{-34} Joule/second).

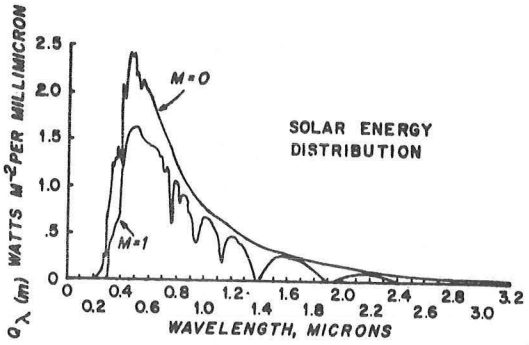
In descriptive terms, the electromagnetic spectrum extends from high energy cosmic rays down through X-rays to ultraviolet energy. Below that, beginning at a wave length of about 200 nm (.2 microns), are ultraviolet light, visible light with a complete spectrum from violet to red, followed by infrared energy, which is perceived as heat.



(Parrish, J.A. et al, 1979)

Longer still in wave length are radar and radio waves which are used for telecommunication and heating "leftovers" for lunch. At the center of this spectrum is our subject, visible and ultraviolet light. This ultraviolet (UVL) spectrum has been subdivided into three sub-regions UVA, UVB, and UVC.

As is seen in the figure from Koller (1969), the surface of the sun, acting as an emission source with a surface temperature of 5600°K, emits a continuous asymmetrical spectrum of electromagnetic energy from about 200 nm to more than 3000 nm in wave length.

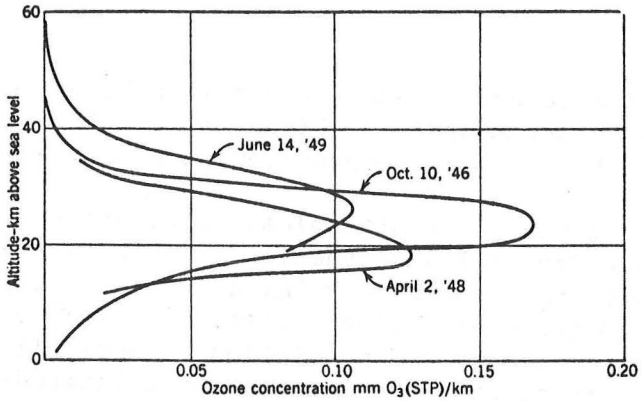


(Koller, 1969)

During solar flares, however, there are short bursts of radiation with both higher and lower energies emitted. These are thought to alter in significant ways both radio wave transmission and weather here on earth, but they play no known biological role.

The first and higher curve (M = 0) in Koller's work represents the spectrum of light which arrives from the sun at the earth's atmosphere. The sum of this energy represents the solar constant, that is, the sum of solar energy; its units are energy/surface area/second. The lower curve (M = 1) represents the energy which reaches the earth's surface on a clear day. Approximately 1/3 of the energy is lost by absorption in the

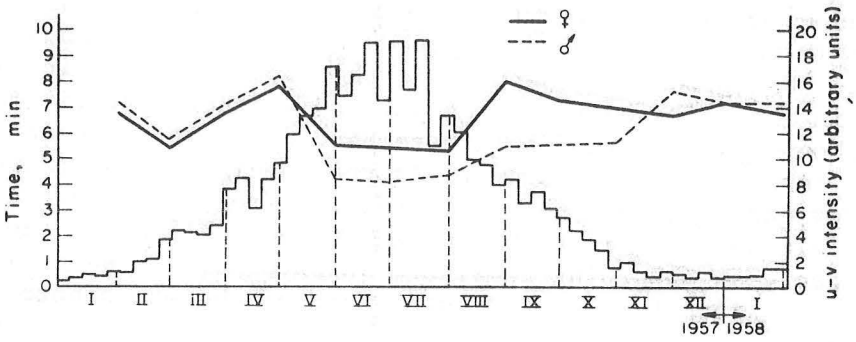
atmosphere, providing the surface of the earth with approximately 2 cal/cm^2/minute (Giese, 1976). If it were possible to harness even a fraction of this energy, all of man's needs would be fueled many times over. Obvious absorption bands appear in this spectrum, particularly above 800 nm in the infrared region as well as a general attrition of energy throughout the spectrum, but these bands are not biologically significant. More important, however, is the specific loss of energy at the high-energy end, near 200 nm. This results from the specific absorption of ultraviolet light, beginning at about 315 nm by ozone. Ozone is, in fact, an absorbing substance which occurs in a fragile band between 15 and 40 kilometers at the outer part of the atmosphere (Koller, 1969).



(Koller, 1969)

The presence of ozone in this region is interesting in that ozone is an absorber of UVL and it is also a product of even higher energy UVL interaction with atmospheric oxygen. This band is largely responsible for the absorption of radiation below 300 nm. You will also note the significant alterations in ozone density by season of the year.

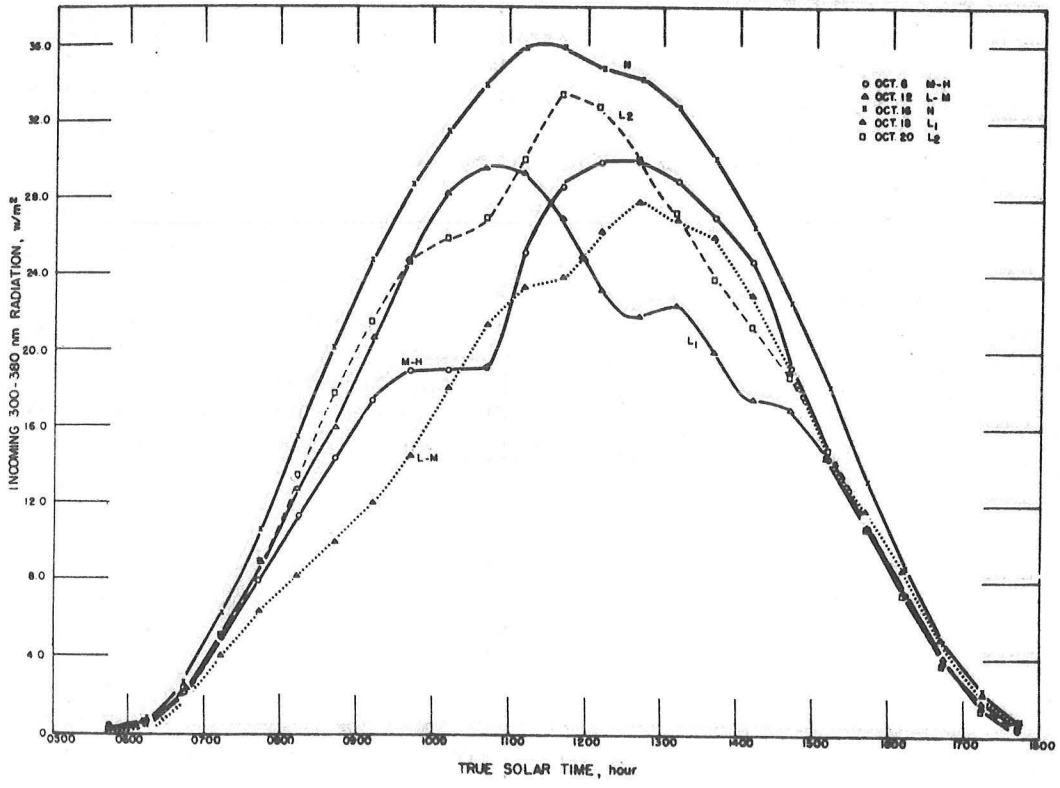
As surely as night and day, light penetration to the earth's surface varies by hour, season, and latitude. Because of the inability of high energy light to bend through the atmosphere and the greater attrition of UVL caused by the angle of the sun, there is an even greater effect of hour and season on UVL than on visible light. In view of the importance of sunburn and other biological events to man, these measurements of ultraviolet light at the earth's surface have been made repeatedly and with great care. Brodthagen (1969) integrated UVL intensity for Copenhagen during the year 1957.



(Brodthagen, 1969)

As clearly demonstrated by his data, there is profound seasonal variation. He has also superimposed on this data the slight reciprocal seasonal variation for the biologic responsiveness of skin.

Sunlight provides to man and to the elements of his environment components of a rhythmic (cyclic) and function. If it were not for a 5° tilt in the moon's orbit there would be solar and lumar eclipses every month (Giese, 1976). In terms of biologic effects of sunlight one must consider the spectrum, irradiance and modulation. These all vary with the earth's rotation, season, atmosphere, geographic latitude, and local topography. The UV portion of the spectrum, particularly UVB is selectively sensitive to angle of incidence, primarily due to the ozone layer (Giese, 1976). Nader (1969) has assessed the impact of time of day on UVL radiation in downtown Los Angeles in October.



(Nader, 1969)

The general curve is related to the time of day. Specific fluctuations are the result of local polution problems which have been common in Los Angeles in the last half century.

Other issues relating to the transmission and reflection of ultraviolet light are of importance to those who will advise patients about outdoor exposure. They relate to the capacity of water largely to transmit light and its capacity to bend and retransmit light when the water is present in spherical drops.

Data taken from Buettner, 1969 illustrates that fresh snow will reflect almost all visible light and almost all light of the UVB spectrum. In contrast, water reflects virtually no sunlight, including light of the UVB spectrum.

(Buettner, 1969)

	Total sun	UVB
Fresh snow	89%	85%
Old snow	50	(50)
Bright dry dune sand	37	17
Bright wet sand	24	9
Sandy grass area	17	2.5
Heather, berries	9	2
Water	9	(5)
Water above sand	12	10
White skin	35	1

Data taken from the review of Smith and Tyler (1976) corroborates these observations. The percent transmission of water to a one meter depth in seawater is approximately 37% at 280 nm, 61% at 310 nm, and 82% at 360 nm. In terms of photosynthetic or biochemical events at great depths in lakes or oceans this attenuation is significant limiting photosynthesis to near the surface, but in terms of sun worshipers in a swimming pool, water offers relatively little protection. These observations also mean, however, that virtually no UVL is reflected back from a water surface. One does not become burned more severely over water; not the same story as with sand or snow.

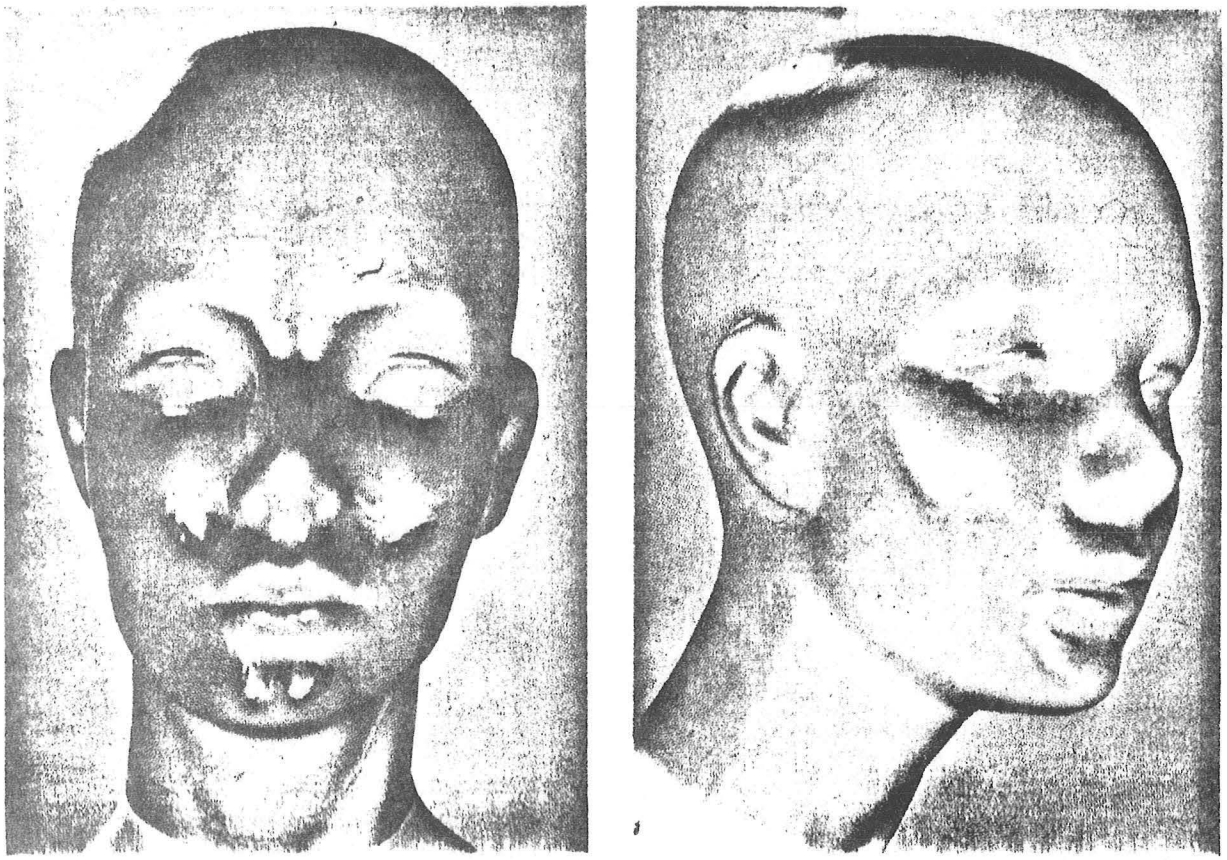
Perhaps of greater importance is the capacity of the sky, largely because of water, to bend light. This occurs because of the optical property of spherical water droplets to transmit light in a new direction, resulting in a "light" atmosphere. Consequently, light exposure occurs indirectly from the sky itself. Data taken from Buettner (1969) demonstrate that at sea level with the sun at a 60° angle, UVB exposure from the direct sun (7 units) equals the exposure from the skin (7 units). At high elevation, the sky contribution is unchanged while the direct sun exposure doubles. Consequently, one is able to experience significant ultraviolet light exposure even while in the shade.

UVB from sun and sky, reduced to scale of IG Farben-Dosimeter. Clear sky, summer

Solar altitude	20°	30°	40°	50°	60°
Sky alone (sea level)	1.4	3.0	4.8	6.0	7.0
Sky alone (Alps 3300 m)	1.4	3.1	4.8	6.2	8.0
Sun direct (sea level)	0.5	1.7	3.5	5.3	7.0
Sun direct (Alps 3300 m)	1.6	4.1	7.0	10.0	13.0
Sun × sin h + sky (sea level)	1.6	3.7	7.0	10.0	13.0
Sun × sin h + sky (Alps 3300 m)	1.8	5.0	9.3	14.0	18.0

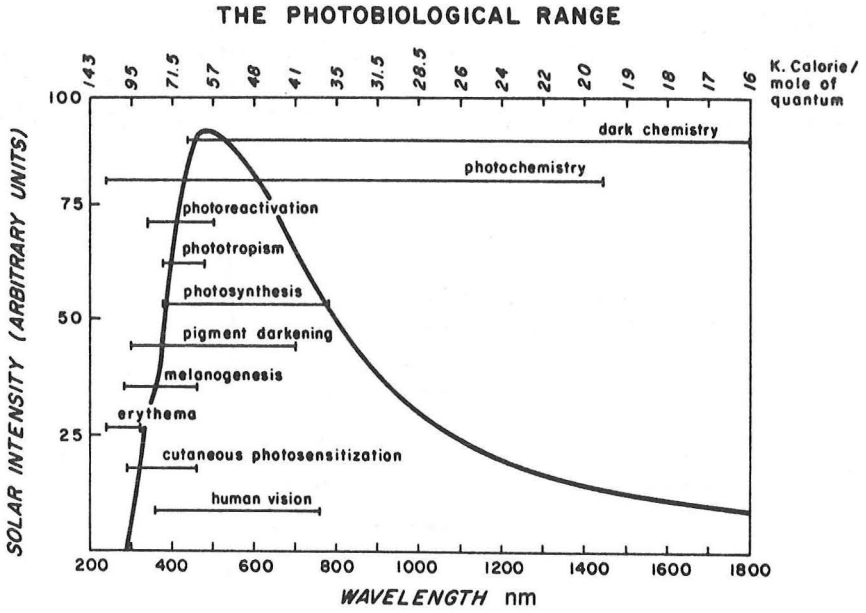
(Buettner, 1969)

These ideas were formalized into a rather humorour but instructive study in which manikins possessing a surface ultraviolet light-sensitive substance were fabricated (Brodkin, et al., 1969). With increasing light exposure the yellow surface turned brown. These manikins were used to judge how much light certain human skin surfaces might intercept. With direct light they demonstrated relative sun protection in areas beneath eyebrows and under the chin. They also demonstrated a significant and rather uniform light exposure by indirect skin light. Finally, as our earlier experimental data indicates water neither reflects nor absorbs significant amounts of light.



(Brodkin et al, 1969)

In his review of the interaction of sun-produced electromagnetic energy with our environment Pathak (1969) has superimposed on an idealized solar spectrum the wave lengths responsible for important interactions.



(Pathak, 1969)

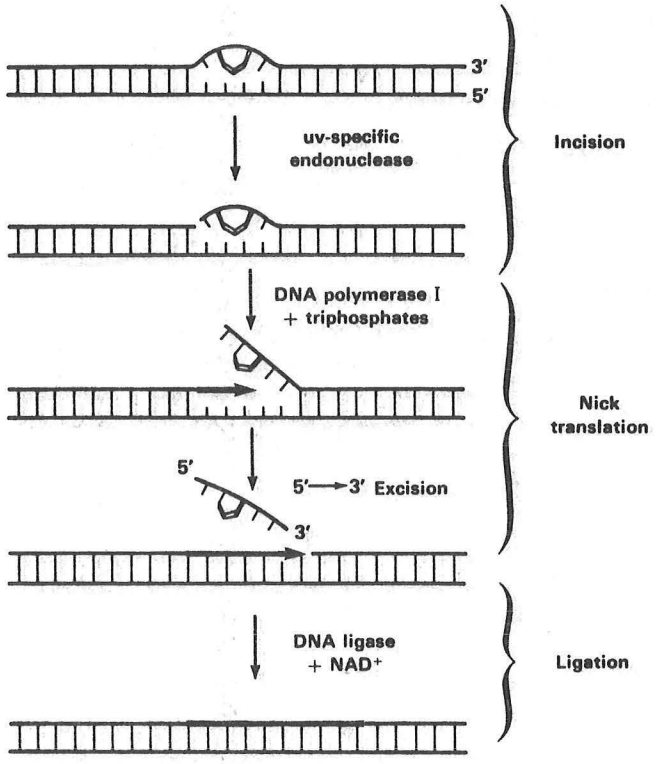
Note that both photosynthesis and human vision are adapted to the highest intensity portions of the spectrum while that portion responsible for erythema and damage in human skin accounts for a very small portion of the spectrum.

XERODERMA PIGMENTOSUM

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease of environmental-genetic interaction in which those individuals who are homozygous for the defect will develop malignant skin tumors at a very early age, most frequently basal and squamous cell carcinomas before the age of 20. In 1968, James Cleaver published an extraordinary paper in which he demonstrated defective biochemical repair of ultraviolet light-induced DNA damage in fibroblasts which were taken from patients with XP (Cleaver, 1968). Over the next decade this observation was pursued and a rather complete story fell into focus (Kraemer, 1980; Kraemer, 1977; Robbins, et al., 1974). This series of observations has given us enormous insight into one possible mechanism for the induction of skin cancer by ultraviolet light.

A major effect of ultraviolet light exposure to cells grown in culture is the production of inappropriate covalent bonds between adjacent thymine bases along single strands of DNA. Binding of thymine bases, in this way

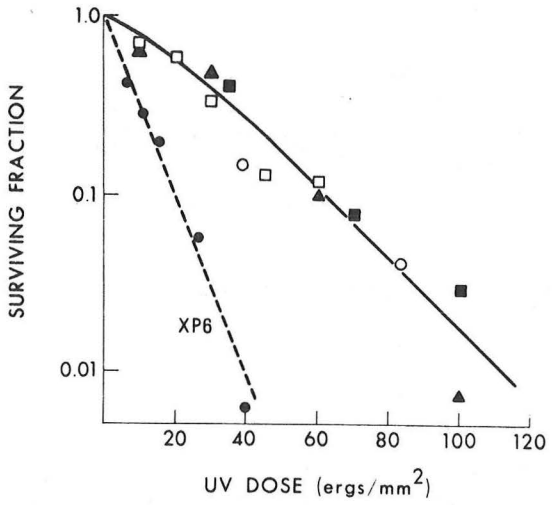
will interrupt the faithful replication of DNA which must occur prior to cell division, and presumably this prevents the faithful generation of new DNA and perhaps blocks the appropriate manufacturing of proteins or initiation of genetic signals from the information coded in DNA. It is easy to imagine that a defect which is permanently incorporated into DNA might eventually result in the failure of a clone of cells to respect normal biological controls of proliferation or to remain within the confines of the original tissue. Fortunately, most individuals possess enzyme systems which replace the regions of DNA which are damaged in this way. This process is outlined in the figure from Kelley, et al. (1969).



(Kelly et al, 1969)

Repair includes the identification of the defective region, incision of the DNA ahead of the defect by a specific endonuclease, removal of a portion of DNA, ahead of and behind the defect, replacement of the appropriate base pairs as dictated by the complementary bases on the adjacent DNA strand and finally refusing or ligation of the repaired strand with the original strand.

It appears that the specific aberration in xeroderma pigmentosum is an inability to make the initial incision; that is, there is defective UV endonuclease activity in the excision repair pathway. Data taken from one of Cleaver's original papers demonstrates secreased survival of fibroblasts from patients with XP when the fibroblasts are exposed to ultraviolet light.



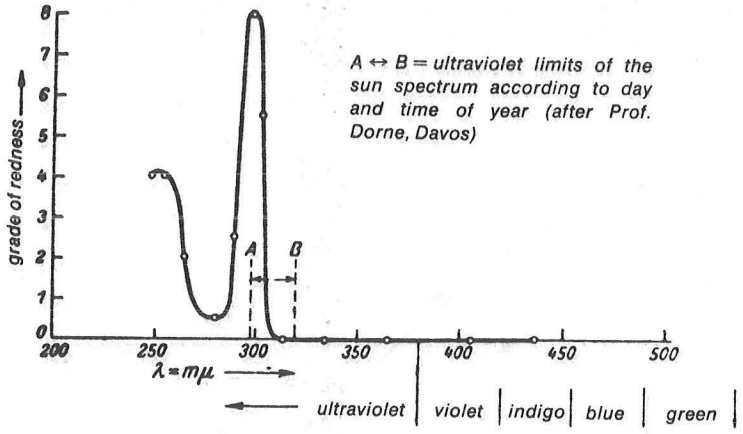
(Cleaver, 1973)

Investigators now feel that this defect results directly in the extreme burden of UVL-induced skin cancer which occurs in affected individuals. These notions are supported in part by the observation that some individuals who have been protected since early age from this defect fail to develop skin cancers (Lynch, et al., 1977).

II. ULTRAVIOLET LIGHT AND SKIN

ACUTE ULTRAVIOLET LIGHT EFFECTS ON SKIN

When human skin is exposed to natural sunlight in sufficient amounts, redness (erythema) followed by blistering will occur within 24 hours. This acute phototoxic reaction is a direct result of light interaction with components of the skin. Early investigators were concerned with the identity of wave lengths responsible for such effects and data from a classical study is illustrated in the figure from Hausser and Vahle (1969). This data is typical of many more recent studies. There exists no significant biologic effect of wave lengths in the visible or near ultraviolet >UVA) regions. Beginning at about 320 nm, which is also the approximately beginning of the UVB region, there is a peak response near 305 nm, followed by a trough near 280 nm and then a second peak. Since natural sunlight does not contain energies below about 290 nm, only the first peak is relevant to this discussion. This capacity of natural



(Hausser & Vahle, 1969)

ultraviolet, between the wave lengths of 290 and 320 nm and residing completely within the ultraviolet B (UVB) region, to produce erythema has led investigators to call UVB the erythema spectrum.

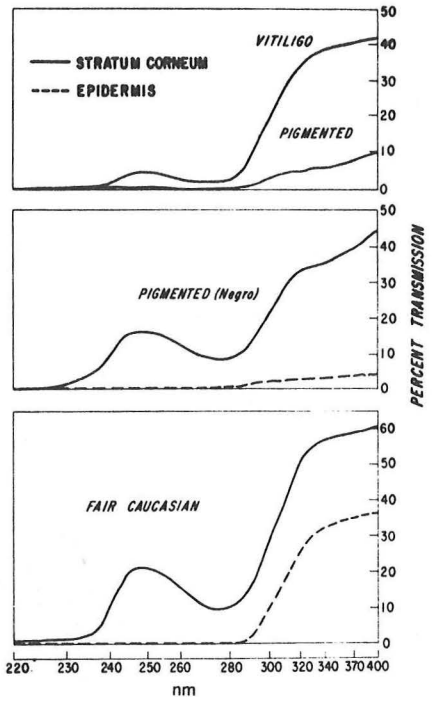
Numerous biochemical events occur in skin in response to this UVB exposure. At a histologic level, reasonably large doses of light will produce individual cell necrosis of scattered keratinocytes (Woodcock and Magnus, 1976; Daniels, et al., 1961). This is followed by intercellular edema and a subsequent failure of keratinocytes to mature into granular cells by 48 hours (Daniels, et al., 1961). Ultraviolet light exposure also produces biochemical changes involving altered levels of skin prostaglandins, released lysosomal enzymes (Johnson and Daniels, 1969; Ogura and Knox, 1974), and glycogen accumulation (Halprin, 1976). Functionally there is first a suppression of keratinocyte proliferation followed by a mitotic burst. During this time both melanocyte division and melanogenesis lead to increased skin pigmentation (Quevedo, et al., 1974).

MED

An important in vivo biologic unit for ultraviolet light which is absorbed by skin is the least amount of light capable of producing redness (erythema) in exposed sites. That amount of light is termed the minimal erythemal dose (MED). Obviously, the MED will vary from person to person, from site to site on one individual and from time to time at a single site, depending on the amount of tanning which has been induced previously. Although there is acknowledged variability in this assay, the utility of the MED as a biologic assay lies in the fact that it represents a standard phototoxic dose of ultraviolet light in that patient. It may also be used to quantitate the protective capacity of various chemicals which may be placed adjacent to each other in exposed skin sites.

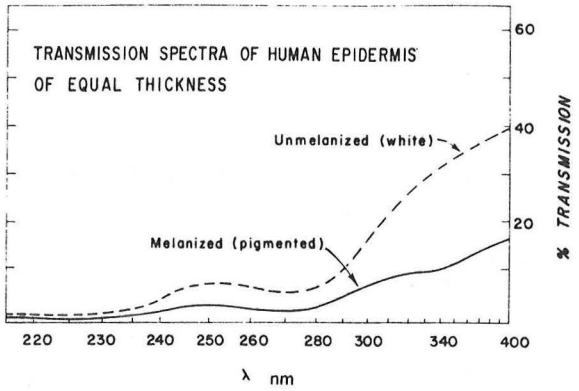
Before light can have a biologic effect in skin, however, it must penetrate the skin. As one might expect, the capacity of light to penetrate

is dependent on a variety of factors, the first being wave length. Pathak and Stratton (1969) investigated the capacities of various skin surface structures to transmit light over the entire ultraviolet spectrum. Their work is summarized in the figure.



(Pathak & Stratton, 1969)

In the middle graph it is observed that whole skin from heavily pigmented indivisuals transmits little light throughout the entire spectrum, but that it is the entire epidermis and not the stratum corneum alone which is responsible for these effects. Compare that absorption curve with the one below, taken through skin with little pigment; it demonstrates a significant transmission of light throughout the spectrum above 290 nm.



(Pathak & Stratton, 1969)

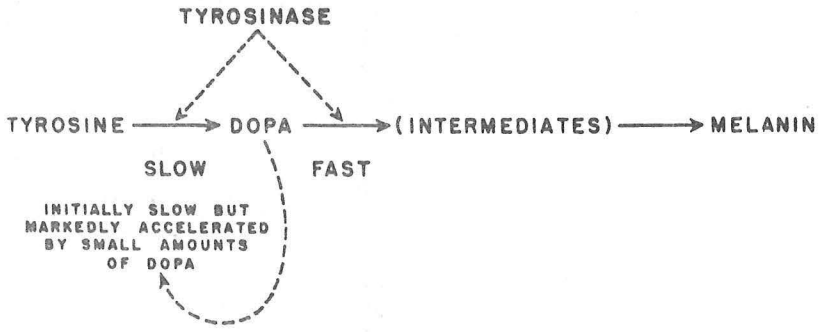
MELANIN

Data contained in these figures demonstrate convincingly that melanin is a significant absorber of ultraviolet light. Melanocytes are ectodermally derived cells which emigrate during fetal life from the neural crest into skin. They occur primarily in the epidermis of human skin, at the bottom of epidermis, distributed in a regular pattern. Numerically they represent approximately 1-2% of epidermal cells and each melanocyte has numerous

(Fitzpatrick et al, 1967)

long dendritic processes which course an epidermal region occupied by about 50 keratinocytes. This group has been termed the epidermal melanin unit.

Melanocytes produce malanin, which is a complex polymer derived in a series of biochemical reactions from the amino acid tyrosine. Melanin

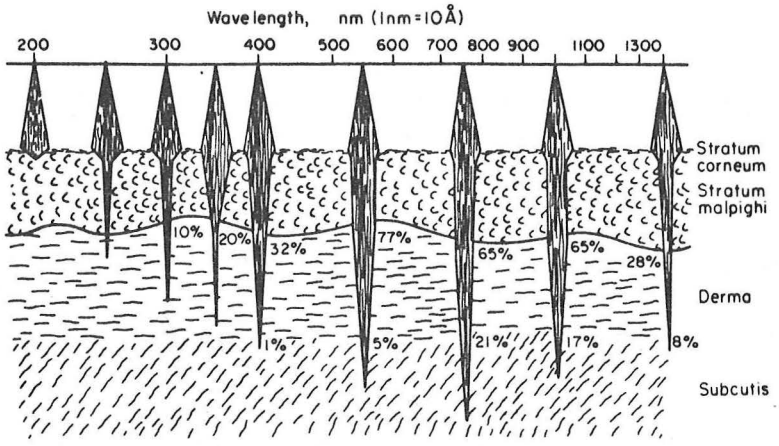


(Fitzpatrick et al, 1967)

itself is fabricated on a submicroscopic structure called the melanosome, and then melanosomes pass out through the dendritic processes where they are released to the extracellular space and then engulfed by keratinocytes. Thus, the major share of light absorption in skin occurs in melanosomes contained within keratinocytes. Two important defects of melanocyte function exist: a) vitiligo, an acquired condition in which the normal complement of melanocytes leave the skin, and b) autosomal, recessive albinism in which the melanin biosynthetic pathway is faulty. Such patients have melanocytes and melanosomes, but no melanin.

As mentioned previously, melanocytes respond physiologically to ultraviolet light with proliferation and the increased production of melanin. This negative feedback system is then responsible for the attenuation of light during subsequent exposure. This is the "protection" of "tanned" skin. Those wave lengths responsible for the tan are identical to those responsible for erythema.

Data of this sort has been idealized into an instructive figure by Ippen (1969). It demonstrates the capacities of electromagnetic radiation across the entire solar spectrum to penetrate skin.



(Ippen, 1969)

It has become clear that different wave lengths of light do not have equal capacities to produce phototoxicity in skin. Unfortunately, much of the enormous literature concerning UVL effects in skin was developed with the aid of low pressure mercury light sources which emit several sharp bands with the greatest intensity at 254 nm (UVC). Since this wave length is not available in natural sunlight, results from such studies are not applicable to the human-sunlight problem. In one of the few attempts to rectify this discontinuity Parsons and Goss (1980) made direct comparisons between artificial ultraviolet light effects on cultured fibroblasts and effects of natural sunlight in similar circumstances

of cell culture. Their results confirm the problem of different photobiologic effects. Sunlight produced similar levels of DNA strand breaks as equitoxic 254 nm UVL, whereas DNA breaks produced by sunlight were removed more rapidly. Thus, the repair of solar damage different significantly from 254 nm UVL repair. Significantly, they also observed that filtered sunlight enhances slightly both UVL-induced repair synthesis and UVL toxicity. Consequently, it is important to know characteristics of light sources used in all studies (National Program, 1974).

ALBINOS AND BLACKS

Perhaps the most striking demonstration of the importance of melanin in protecting the skin from ultraviolet irradiation is the fate of albino natives who live in tropical environments. For the Cuna Indians of San Blas, Panama, the incidence of occulocutaneous albanism is the highest in the world, estimated to be as high as 1% of the total population (Keeler, 1970). Although there are several independent enzymatic defects which lead to albinism the ultimate result in each individual who is homozygons for the defect is the complete inability of their melanocytes to manufacture melanin. In such individuals their hair is yellow to white, their skin faint pink and even their eyes may be pink. Albinos among adult Cuna Indians who live in the hostile, sundrenched, Tropical Panamanian environment, the chief cause of death is metastatic skin cancer (Keeler, 1970).

On the other hand skin cancer is rare in black patients (White, et al., 1961). Fleming and his associates (1975) examined the clinical course and pathology of 58 black patients with skin cancer. The majority of squamous cell carcinomas developed in skin sites not ordinarily exposed to sunlight and many originated in sites of chronic infection or scar. Malignant melanomas were frequently acral. These two contrasting observations highlight the impact of melanin on the induction of cutaneous cancers.

CHRONIC ULTRAVIOLET LIGHT EFFECTS

ELASTOSIS

The observation that individuals who have suffered chronic ultraviolet light exposure usually have protected areas of skin allows one to emphasize rather dramatically the most obvious clinical effects of chronic sun exposure on human skin. Examine the nape of the neck of your next male patient who engages in outdoor employment, and if he works fully clothed, compare the quality of his neck skin with that of the adjacent protected skin. The effects of chronic sun exposure on human skin include wrinkling, telangiectasia, yellowish appearance, and a pebbly surface. These changes are reflected histopathologically by dense dermal deposits of connective tissue which resembles elastic tissue in some ways. These clinical changes have consequently been termed elastosis. Gilchrest has shown that fibroblasts taken from sites of elastosis have fewer cummulative population doublings than do those from unexposed sites (Gilchrest, 1980). Since fewer population doublings are one measure of age and perhaps of sinescence (Hayflick, 1965) then such skin has perhaps aged prematurely.

ACTINIC KERATOSES

When examining sun damaged skin the most obvious change, aside from simple aging, is the development of scaling, red, and occasionally tender papules which are called actinic keratoses (Pinkus, 1979)(Graham and Helwig, 1972). These sun-induced lesions occur quite frequently, and they may be found on virtually all individuals with sun damage; exposed sites of some patients may be completely covered. Usually multiple, actinic keratoses vary in color from pink to yellow, brown, or black. An individual lesion may be felt by palpation more easily than seen, and its surface texture is often rough and horny. Common complaints include enlargement, bleeding, especially after trauma, tenderness, and not infrequently, pain. In the differential diagnosis one must exclude other common skin tumors such as seborrheic keratoses, flat warts, and melanocytic nevi, and one must exclude true squamous cell carcinomas as well. Patients with seborrheic keratoses usually have similar lesions in sun protected sites.

DIFFERENTIAL DIAGNOSIS OF ACTINIC KERATOSES

1. Seborrheic keratosis
2. Wart
3. Melanocytic nevus
4. Squamous cell carcinoma

These benign but bothersome keratoses are rarely tender and they do not adhere tightly to the skin surface. Warts, on the other hand, have a pebbly surface, and they will frequently appear or involute with great rapidity. Finally, melanocytic nevi rarely change in appearance during adulthood, they are never tender, and they do not bleed without significant trauma. Before one becomes cavaleer, however, about the ease with which this differential may be made, it should be remembered that all of these lesions, including actinic keratoses, may coexist. The definitive answer lies frequently in the skin biopsy.

Histopathologically one observes in actinic keratoses disordered epidermal maturation and proliferation. Epidermal cells do not mature vertically and there is erratic variation in size, shape, and staining characteristics of cells. There exist a wide spectrum of changes, from nearly normal appearance to what is clearly an <u>in situ</u> squamous cell carcinoma. It is characteristic to observe focal, vertical regions of normal epidermal maturation which are associated with adnexal structures, most often hair follicles. Presumably this occurs because the proliferative pool of keratinocytes which give rise to that portion of the skin lie deep in the dermis out of harms way. Also characteristic of actinic keratoses is the deposition of elastotic debris beneath the epidermis. In fact, the absence of such material alerts the dermatopathologist to the likelihood that the dyskeratotic lesion results from a cause other than ultraviolet light. Because of the close resemblance of actinic keratoses to squamous cell carcinomas and because of overwhelming epidemiologic association between the two, it is felt that the actinic keratosis itself is premalignant.

SKIN CANCER EPIDEMIOLOGY

The experience in Australia for the incidence of malignant melanoma illustrates several important epidemiological features. The incidence of melanomas in Australia is felt to be the highest in the world, estimated at 32.7/100,000 in 1977 (little, et al., 1980). A most useful analysis of the Australian experience was written this last year by Holman and his associates (1980). This paper assessed mortality rates for a melanoma in Australia as provided by the Australian Bureau of Statistics. From an age-standardized rate of 0.8/100,000 (men) and 0.6/100,000 (women) in 1931-34 the incidence of mortality from melanomas in Australia increased to 4.2/100,000 (men) and 2.5/100,000 (women) in 1975-77. This increase implies that the increasing mortality rate may be attributed to recent changes in sun exposure. However, the analysis of data from all patients who died between 1931 and 1975, with groups corrected for the effects of age, showed that virtually all the secular trend in rates could be explained by increase in sequential birth cohorts. This change began in cohorts born in 1865 and stabilized for cohorts born about 1925 in women and 1935 in men. This means that the increased rates attributed to increased light at an early life ceased between 1925 and 1935. Because of this (or despite this) the gross incidence has continued to rise up until the present. With life expectancies of more than 70 years, it is expected that these increase in mortality rates will continue for the next 30-40 years. These data imply that the changes in UVL exposure which leads to this stabilized among cohorts had no more effect after 1935. The implication of this is that the life styles which gave rise to the problem are now stable.

An extensive literature now documents the utility of ultraviolet light in producing cutaneous malignancies in laboratory animals. This literature began with the pioneering work of Blum (1948) and now ultraviolet light carcinogenesis is an investigative area of great importance. There can be no doubt that ultraviolet light (UVB) is able to induce cutaneous malignancies. Likewise, UVA is also carcinogenic in laboratory animals when combined with "psoralens" (Urbach, 1959; Griffin, et al., 1958).

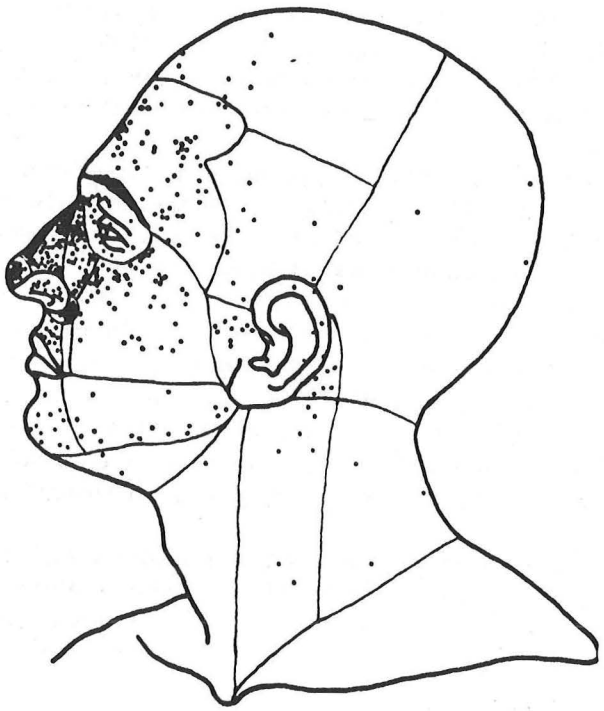
CLINICAL PRESENTATION OF SKIN CANCER

Epidermal cancers, like all other neoplastic growths, will occupy space, and in so doing they distort the normal or at least the expected anatomical features of the skin surface. This is, in fact, one reason why mortality and morbidity rates are so low for most cutaneous cancers. A second reason relates to visibility. It is impossible to recognize clinically a carcinoma of the lung or bowel, but to fail to recognize a tumor of that size on the skin would be impossible. In addition, the examination of patients with cutaneous malignancies quickly demonstrates the utility of regional distribution. Perhaps for no other skin disorder is this so apparent, and it reflects the direct (but not invarient) pathological relationship between sunlight and skin cancer. Human skin cancers occur most often on the head, neck, arms, and hands, areas of maximal sun exposure.

BASAL CELL CARCINOMA

The identifying terms "basal cell carcinoma" and "squamous cell carcinoma" were originally based on histopathological appearances of the predominant cell types within each tumor. As might be expected, since the cell of origin is the keratinocyte for both, intermediate forms and tumors with cells of both types may be found. Despite these occasional overlapping features, it has been most useful for dermatopathologists to continue this distinction since such histopathologic differences are reflected clinically.

Basal cell carcinomas may exhibit a variety of clinical features. They may occur as cystic tumors, slowly enlarging superficial ulcers, scars, scaling plaques, or even pigmented nodules resembling a malignant melanoma. A single tumor may even exhibit several different features simultaneously. The most common presentation is as a translucent waxy nodule, often with small superficial telangiectatic vessels on its surface and rolled, pearly borders. Frequently one observes a sharp transition to normal skin, and the surface morphology indicates the tumor to be part of the epidermis. Less commonly they may be pigmented or appear as yellowish indurated plaques, scaly plaques or pedunculated nodules. Tumors increase slowly in size and often undergo central ulceration. It is not uncommon to see several basal cell carcinomas in the same patient, and occasional tumors appear to heal spontaneously leaving depressed scar behind. As with actinic keratosis, there is an overwhelming predilection for sun damaged skin. But the distribution is not correlated with total light exposure precisely, as one would expect. The figure represents data from Brodkin, et al. (1969) and illustrates the anatomic location of basal cell carcinomas treated in their series. They occurred more frequently than one would expect in posterior auricular areas, the naso-libial fold and at the inner canthus



(Brodkin et al, 1969)

of the eye. Contrast this with the earlier figure from Brodkin, et al. (1969), demonstrating the amount of light falling on regions of the face. Several factors have been suggested as being partially responsible for this dyscordance but none are convincing.

Histopathologically the primary cell type in basal cell carcinomas is a cell which resembles epidermal basal cells, with little evidence of maturational progrssion toward keratinized squamous cells. One observes sheets, cords, and strands of regular-appearing basaloid cells. Histopathologic changes resemble the clinical appearance. In the projected, photomicrographs one observes the sharp transition to normal skin, severe dermal elastosis, and dilated dermal vessels which are features recognized clinically.

Gellin, et al. (1965) summarized in 1965 a four year experience at the Skin and Cancer Unit at the New York University School of Medicine concerning 861 consecutive patients with biopsy proven basal cell carcinomas. They documented for the first time many commonly held assertions concerning patients who develop basal cell carcinomas: a) Such tumors occur somewhat more commonly in men; b) Non-Caucasians rarely develop them; and c) The rate of basal cell carcinoma development increases progressively with age, with no leveling off even in the ninth decade when it represented the chief complaint in more than 10% of their patients. They also observed an overwhelming significant association with blue eyes and a fair complexion.

SQUAMOUS CELL CARCINOMA

Squamous cell carcinomas usually appear as keratotic nodules or as ulcers with wide indicated borders. Although these tumors are less common than BCCs, those which are light induced have a similarly low metastatic potential. Most squamous cell carcinomas occur in regions of the body which have received excessive amounts of ultraviolet light. Clinically, the most distinctive feature is keratinaceous debris on the tumor surface. The differential diagnosis is similar to that for basal cell carcinomas.

An important variant of the squamous cell carcinoma is the keratoacanthoma, which is a rapidly growing epidermal neoplastic growth with a large, central, keratin-containing cup. Keratoacanthomas occur in the same epidemiologic circumstances as dosquamous cell carcinomas, but their rapid growth and frequent spontaneous resolution suggest they they are virally induced, much as viral warts are. Squamous cell carcinomas which arise in special circumstances frequently exhibit much more agressive biologic behavior. These circumstances include: 1) chronic arsenic ingestion, 2) chronic infection or unhealing ulcers, 3) development in light protected areas, and 4) development near the junction with mucous membranes. Such tumors should be treated with great respect.

The histopathologic examination of squamous cell carcinomas reveals irregular masses of epidermal cells which proliferate downward to invade the dermis. These invading cells exhibit varying proportions of differentiated

basaloid cells. One observes frequent atypia of cell size and morphology. The keratoacanthoma exhibits similar histologic features but the overall pattern is that of a tumor perched on the skin surface.

MELANOMA

Malignant melanomas, which are the least frequent of the three UVL induced skin cancers, are by far the most agressive. Although melanomas do not show as striking a predilection for light-exposed skin, there exists excellent epidemiologic evidence to support an important role for sunlight in the development of this malignancy of pigment-forming melanocytes. World-wide, the highest incidence of melanomas occurs in Australia and highest rates within that continent occur in regions with the greatest amount of light availability. It is believed that much of this problem arises from the Northern European genetic origin of the citizenry and from the national fad of sun worship.

Melanomas occur in three distinct clinicopathologic forms: lentigo maligna melanoma, superficial spreading melanoma, and nodular melanoma (Mihm, et al., 1971). Each of these has a characteristic clinical evolution and distinctive microscopic feature. The lentigo-maligna melanoma arises slowly in characteristic hyperpigmented lesions of sun exposed sites in elderly persons (median age about 70 years). The initial lesion, termed a lentigo maligna (or Hutchinson's freckle) arises as a tan to black, and irregularly pigmented lesion which slowly enlarges by irregular centrifugal spread. It is premalignant. Although the incidence of melanomas in such lesions is high, melanomas which arise in them tend to be slow growing with less malignant potential than found with the other two types of melanomas. The superficial spreading melanoma occurs on any body surface, most commonly on persons of middle age. Such lesions are oval to circular in shape and the margins tend to be elevated. The most distinctive feature of these lesions in the unusual combinations of color including black, brown, tan, and even white or gray. The nodular melanoma appears as obviously as a circumscribed nodule and is a more uniform black or brown color.

In 1979 there were estimated to be 13,600 new cases of malignant melanoma in the United States and an estimated 4,300 deaths (Silverberg, 1979). Levin and Bardnovsky recently published survey incidence data for melanoma skin cancer in four geographic regions in the United States for the years 1950 to 1973: Connecticut, a portion of California, Charity Hospital in New Orleans, and the University of Iowa Hospital (Levin and Baranovsky, 1978). It was hoped that these four pools of patients might accurately reflect the experience of the entire United States. During that 24 year period, 5,840 patients were treated for new melanomas in the four regions. The sex ratio was 1.0 (2,891/2,949), although it was observed that anatomical distributions were not identical for men and women; women had a greater proportion of melanomas on their legs; men had them more commonly on the head and neck. Most striking was the relative broad age range for development with a significant percentage between 25 and 44, while more than half occurred before the age of 54.

YEARS		CASES	RELATIVE PERCENT SURVIVAL				
			under 25	25-44	45-54	55-64	over 64
1950-59	(10)	1,543	67%	62%	52%	43%	44%
1960-66	(7)	2,026	78%	73%	61%	58%	51%
1967-73	(7)	2,271	74%	71%	69%	63%	61%

Relative five-year survival rates (percent) for 5,840 melanoma patients. (Levin and Baranovsky, 1978)

Note also that there have been no changes in age distributions over the 24 year period although the incidence of melanomas has shown a steady rise.

Relative survival rates for all patients are recorded in the next table, illustrating a less favorable prognosis for melanomas which arise on the elderly.

YEARS		RELATIVE PERCENT SURVIVAL				
		under 25	25-44	45-54	55-64	over 64
1950-59	(10)	86%	80%	73%	61%	62%
1960-66	(7)	94%	85%	79%	75%	65%
1967-73	(7)	82%	84%	82%	76%	73%

Relative five-year survival rates (percent) for melanoma patients with localized disease. (Levin and Baranovsky, 1978)

These data are already corrected for expected mortality, indicating that the decreased survival is independent of the decreased life expectancy associated with advancing age. This observation of increased mortality associated with advancing age may even be seen in patients who have localized disease at the time of first operation.

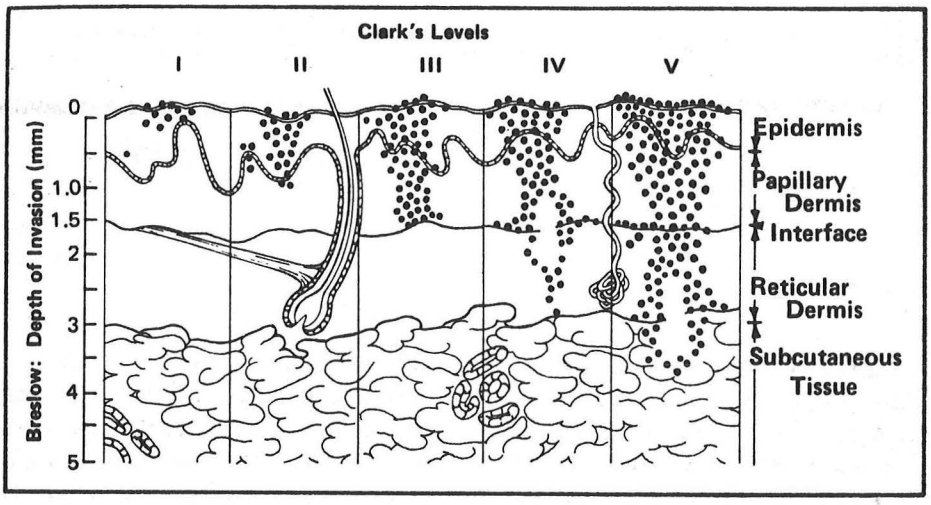
YEARS		CASES	PERCENT				
			under 25	25-44	45-54	55-64	over 64
1950-59	(10)	1,543	6%	32%	18%	17%	27%
1960-66	(7)	2,026	6%	6%	20%	16%	23%
1967-73	(7)	2,271	7%	30%	24%	18%	22%

Age distribution of 5,840 patients diagnosed with melanoma skin cancer: four geographic regions, 1950-1973.
(Levin and Baranovsky, 1978)

Prognosis for malignant melanomas is largely related to the depth of invasion of the primary tumor at the time of first operation. Clark and his associated have provided a depth staging system which has been most useful in giving a prognosis (1969). It is based on the relative depth of penetration of deepest most portions of the tumor mass:

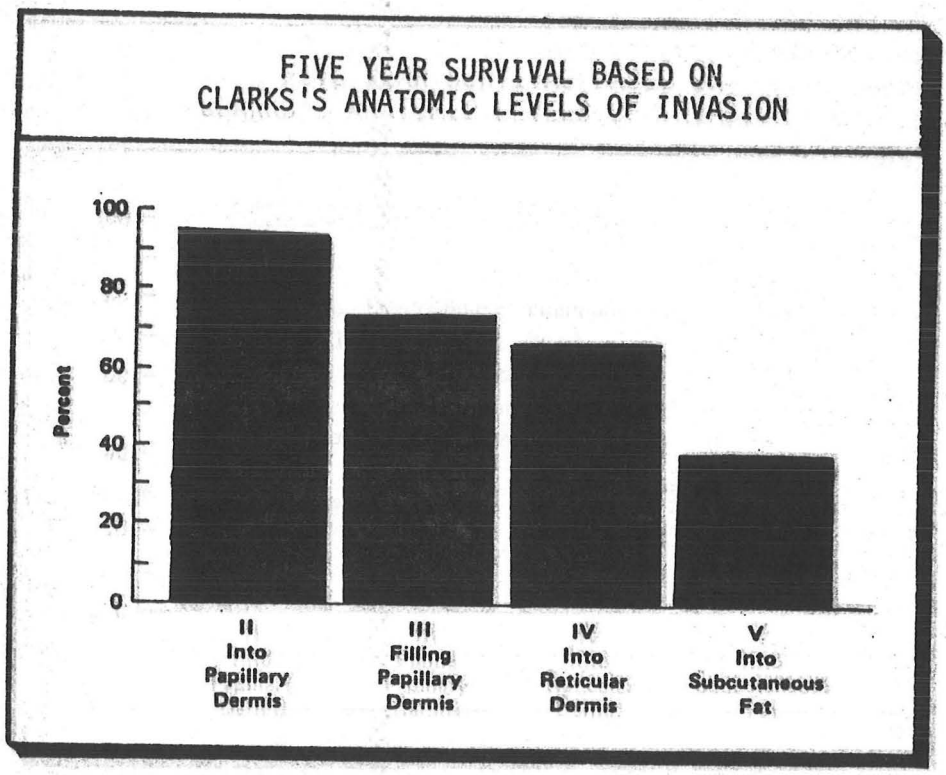
LEVEL	DEEPEST PORTION OF TUMOR
I	Epidermis
II	Dermal-Epidermal Junction into Papillary Dermis
III	Papillary Dermis
IV	Reticular Dermis
V	Subcutaneous Tissue

The utility of this system arises from the correlation these parameters have with prognosis.



(Goldsmith, 1978)

This is demonstrated by the data reviewed from Sober and Fitzpatrick (1979).



(Sober, A.J. & Fitzpatrick, T.B., 1979)

Five year survival decreased from greater than 90% for Level II to less than 40% for Level V, which includes tumors extending into the subcutaneous tissue and farther. Since Clark's original work, refinements in this staging system have been developed. Breslow has devised an absolute depth system (1970) and Schmoeckel and Braun-Falco have created a multiparameter index which is even more reliable (1978). It is now consequently possible to offer a relatively accurate prognosis to patients with melanomas.

Treatment of malignant melanomas will not be dealth with in this review. Suffice it to say, that treatment is an extraordinarily complex issue, to the extent that there is even now considerable debate as to the type of initial procedure which is most appropriate (Verones, et al., 1977). It should be noted, however, that diagnostic skin biopsies do not enhance the metastatic potential of melanomas, so that it is not detrimental to misjudge a minimally suspicious lesions by biopsying only a portion of it (Paslin, 1973). Treatment of choice for suspicious lesions is obviously complete excision.

III. THERAPY OF SKIN CANCER

It is not the intent of this review to train a group of internists in the fundamentals of skin cancer therapy. That arena constitutes an entire

field of inquiry, in and of itself, a field for which there are complete training programs and a large literature. But it is important for you as primary care physicians to know the options which are available so that your patients might be better informed.

Actinic keratoses are usually treated by one of three techniques: electrodesiccation and curettage, cryotherapy with liquid nitrogen, or with topically applied 5-fluorouracil (5-FU). The use of 5-FU is rather remarkable development, stemming from the pioneering work of Dillaha and his associates (1963) at the University of Arkansas in the 1950's. To use 5-FU, at any one of several concentrations, in any of several bases, the material is placed daily on the appropriate skin surface. Within several days to one week, a moderately severe dermatitis results in the treatment area, but primarily in the areas which contain actinic keratoses. This specificity for areas of actinic damage is rather remarkable in that the medication even has the capacity to "reveal" inapparent actinic keratoses to the patient and his physician. It is still debated whether actinic keratoses are usually susceptible to 5-FU or whether precutaneous of the medication is greater in such areas, permitting a greater effective dose (Eaglstein, et al., 1970). In any event, treatment is to be discontinued once a moderately severe inflammation has developed. After resolution of this inflammation, most keratoses are gone. Residual lesions are effectively treated with more aggressive methods or by repeating the 5-FU. A remarkable paper by Breza, et al. (1976) would indicate that inflammation *per se* is not necessary. The upshot of this discourse is that your patients or you may one day show up with iatrogenic dermatitis. It is also interesting that there exists no data to support the notion that treating actinic keratoses with 5-FU or for that matter with destructive therapy actually decrease the likelihood of squamous cell carcinomas, but it clearly is able to destroy the bothersome actinic keratoses.

Treatment of skin cancer *per se* cannot be approached in a review of this nature. To treat such lesions requires a comprehensive knowledge of skin biology and pathology and knowledge of treatment techniques which have been learned under supervision. It is, however, important for all physicians to become conversant with the possibilities. Squamous cell carcinomas and basal cell carcinomas may be treated successfully by one of three destructive techniques: X-ray irradiation, electrodesiccation and curettage, or by simple excision. Each of the techniques has certain limitations and each has certain attributes which make it useful. A description of these limitations and benefits would be a complete treatice in itself, but for the internist there are certain guidelines or rules to remember.

A. Squamous cell carcinomas which arise on non-sunexposed areas or on lips may be highly malignant.

B. Squamous cell carcinomas which arise in the context of chronic arsenic ingestion, X-ray irradiation are more likely to be aggressive.

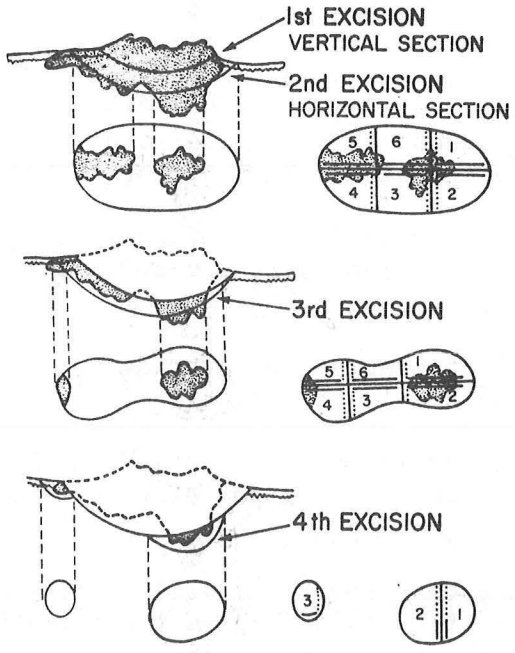
C. The recurrence rate for basal cell carcinomas is approximately 5%, no matter which of the three treatment modalities is chosen and the rate for recurrence after the second procedure is

approximately 50% (Menn, et al., 1971). This important problem has been solved only with the general availability of microscopically controlled surgery (Mohs chemosurgery) which is to be discussed below.

D. Patients with one skin cancer develop second cancer with high frequency. In fact, the vast majority of new tumors in patients with previous cancer develop in a second site (Bergstresser and Halprin, 1975). Therefore, the major function of follow-up examinations in patients with treated cancer is to find new ones which are developing at remote sites and not only to examine the previously operated site.

CHEMOSURGERY

A very special case may be made for chemosurgery, a term which is a misnomer, although it makes sense when viewed from historical perspective (Mohs and Guyer, 1941; Mohs, 1941). Frederick Mohs initiated in 1941 a technique of skin cancer removal which included tissue fixation with topically applied agents, usually $ZnCl_2$ followed by excision of the treated site, and then microscopic examination of the removed tissue. With a map based on a grid-like network, microscopic extensions of tumor could be followed by repeated applications and excision until the tumor had been removed completely. This technique is conceptually satisfying and it is extraordinary that it did not gain wide acceptance until the 1960's. Since then, however, the treatment of large skin cancers, recurrent cancers, and those in locations which are difficult to reach has been revolutionized. In the figure which is taken from Moh's review monograph the six section grid is outlined for the original tumor. With each excision a new grid is made, orientations are maintained and the tumor removal accomplished in four sittings.



(Mohs, F.E., 1978)

Dr. Mohs, whose practice was largely limited to patients with recurrent or large tumors reported in 1976 a five-year cure rate of 99.3% for more than 9,000 treated cancers (Mohs, 1976). Today the chemical portion of the treatment procedure has been eliminated and under local anesthesia appropriate excisions are made with the tumor being traced out in one sitting. Despite this adaptation which now excludes the chemocautery, the name chemosurgery persists (Mohs, 1978). Chemosurgery is now a specialized technique requiring an additional year of training, and those who are able to perform this technique are now in practice in most metropolitan areas.

IV. PHOTOPROTECTION

It is easy to imagine methods by which the destructive effects of natural ultraviolet light on human skin may be prevented. For those with severe photosensitivity or sensitivity which includes rapid development of cancer, total withdrawal from natural sunlight exposure is the only practical solution. Lynch, et al. (1977, 1967) describe identical twin boys from a family of seven siblings, the youngest two received maximal photoprotection including;

1. Topical sunscreens daily.

2. UVL-absorbing plastic covers over fluorescent lights at school.

3. Incandescent lighting at home.

4. Clothing: long trousers, long-sleeved shirts, wide-brimmed hats, and dark glasses.

5. Outdoor activities such as swimming and tennis were accomplished at night.

Under this regimen, the boys continued to be popular, and they became well adjusted honor roll students. By age 16 both had no clinical evidence of actinic damage; they had neither actinic keratoses nor cutaneous malignancies, including melanomas.

For the more usual sorts of patients, those who have no genetic predisposition of ultraviolet light damage, but who would like to spend time in the sun there are relatively easy ways of obtaining photoprotection. In fact, primary care physicians have an excellent opportunity to teach their patients methods by which they might protect against the ravanges of excessive sun exposure. If your patients are convinced, as I hope you now are, the sun does produce premature aging and that it does produce most skin cancers, then the major step has been taken. They must be convinced that:

1. Sun exposure causes premature skin aging and most skin cancer.

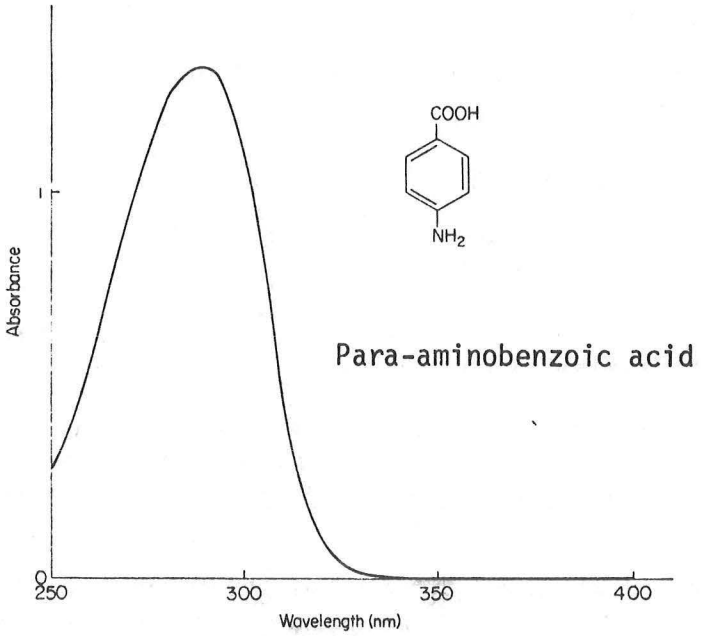
2. Those wave lengths of light (UVB) which produce both sunburn and tanning also produce aging and cancer. Both processes occur simultaneously.

3. The maintaining of a "healthy" tan although offering some photoprotection includes continuous damage. Maintaining a tan offers photoprotection (acute) and causes premature aging and cancer.

4. Those individuals with the least amount of natural pigmentation are at greatest risk.

SUNSCREENS

Ultraviolet wave-lengths within the B spectrum and for that matter within the A spectrum may be absorbed by certain small cyclic organic compounds. The prototype is para-amino benzoic acid. It was first compounded into Ruggles cream which was then applied topically in the 1950's (Rothman and Hanningsen, 1947). You will note in the absorbance spectrum a high absorption peak in the UVB region.

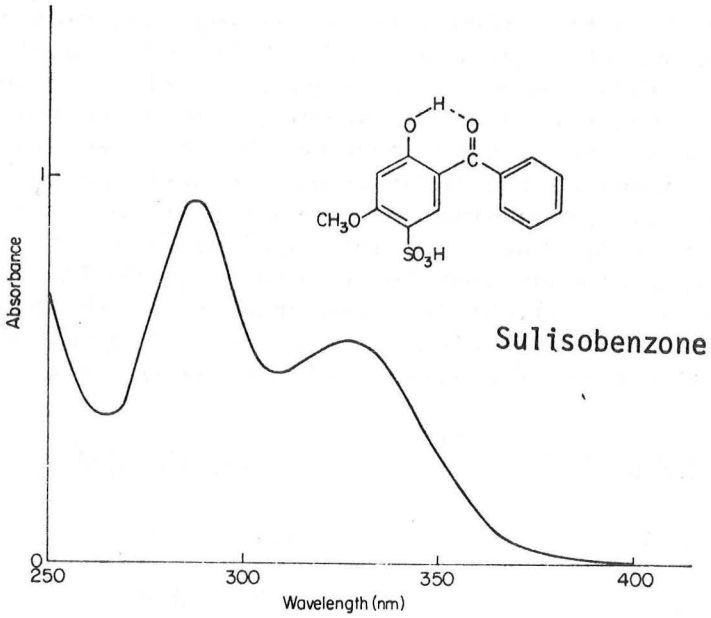


Para-aminobenzoic acid

(Magnus, 1976)

Early observations indicated that patients on whom such materials were placed, were less easily burned. Work on this compound was then followed over the next several years by variety of ultraviolet light absorbing compounds, which were placed in an even greater variety of bases. Later, compounds such as sulisobenzone, having a wider spectrum of absorption were developed.

One reads in 1979, papers similar to the one by Sayer, et al. in which formulation prepared by several manufacturers are compared (1979).



(Magnus, 1976)

In this report the following compounds were compared:

PRODUCT	COMMERCIAL NAME	SUNSCREEN
A	Block-out Cream Lotion	4% isoamyl-dimethyl p-aminobenzoic acid ester
B	Eclipse Lotion	3% glycerol p-aminobenzoic acid ester
C	Improved Super Shade Lotion	7% octyl-dimethyl p-aminobenzoic acid ester 3% oxybenzone
D	Presum	5% p-aminobenzoic acid
E	Sundown Sunscreens	3.3% octyl-dimethyl p-aminobenzoic acid ester
F	Uval Sunscreen Lotion	10% 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid

Six Commercial Sun Screens
(Sayre, et al., 1979)

These compounds are deposited either in solution or as a precipitate in the stratum corneum where they will absorb a portion of the incident the radiation. The amount absorbed depends on the uniformity of distribution, the amount deposited and the absorption characteristics of the compounds. Since they do not absorb visible light to any degree, they are not visible to the eye. Two important issues in evaluating sunscreens for patient use are: a) the amount of photoprotection offered, and b) how lasting the material is. This second issue is particularly relevant to those who want to swim and then return to sun worship without reapplying their medication. Of great benefit to consumers has been the recent federal regulation which requires the manufacturer to state on the bottle the extent to which their preparation is photoprotective. The SPF (skin protective factor) represents that information; it is the multiple by which time of light exposure may be increased, producing the same biologic response. Therefore in algebraic terms, the SPF is the MED with the sunscreen divided by the MED without th screen. You may now use the listed SPF to judge the effectiveness of the preparation. Higher is better.

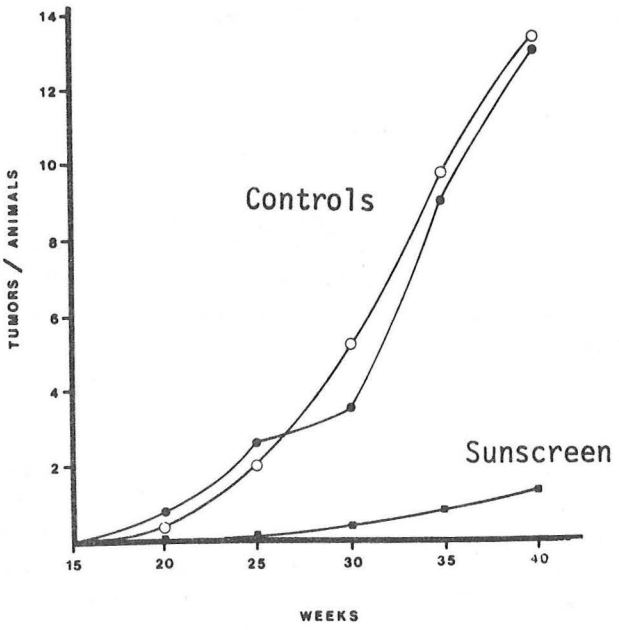
	SPF				USE TEST
PRODUCT	IMMEDIATE		AFTER WATER EXPOSURE		(RANK ORDER)
A	8.1	2.5	4.5	0.8	3
B	13.0	4.1	2.8	0.8	4
C	17.4	3.2	8.0	0.6	1
D	12.0	3.1	1.0	0.2	5
E	6.7	1.7	4.7	1.9	2
F	8.2	2.7	1.2	0.3	6

Sun Protective Factor and Use Test Results
for Six Commercial Sun Screens
(Sayre, et al., 1979)

The second column in the data from Sayre (1979) introduces a new problem, that of retention after water exposure. From it you can see that some preparations resist removal by swimming while others do not. Sunscreens were reviewed two years ago in The Medical Letter (1979).

A complaint may be made that there is no experimental data which indicates protection against sun damage with sunscreens actually decreases the incidence of skin cancer in humans. Indeed, a clinical study similar to the series of studies published by Doll and his associates on the decreased incidence of lung cancer among British physicians after discontinuing cigarette smoking has not been attempted. A study of this sort is, in fact, more difficult to do since discontinuing smoking is a more dramatic event and one for which noncompliance is easier to recognize or identify than is the failure to use sunscreens properly or reliably. However, laboratory animals studies are more easy to perform since it is easier to turn on UVL

lamps than to teach a mouse to smoke. Data from the recent study by Kligman, et al..is typical (1980). Hairless mice (Strains Skh-1 and Skh-2) were irradiated three times weekly with FS-20 fluorescent sun lamps. Experimental animals received a topical sunscreen prior to light exposure.



UVL-Induced Skin Tumors in Albino Mice

(Kligman et al, 1980)

By 25 weeks all surviving unprotected animals had developed cutaneous tumors and by 40 weeks the average tumor load per surviving animal was greater than twelve. In contrast, 22% of protected animals of the Skh-1 strain developed tumors in exposed sites and average tumor load were approximately 1 by 40 weeks. The only conclusion is that sunscreens do prevent skin cancer.

Photoprotection with oral agents would be much simpler. De Rios, et al. demonstrated that the antioxidant butylated hydroxytolnene (BHT) increased the MED approximately two-fold in albine mice (1978). Although erythema is difficult to measure in mice, their report is convincing, particularly in light to previous work by Black and his associates demonstrating that a diet supplemented with several antioxidants (ascorbic acid, BHT, Dl-anti-tocopheraol and reduced glutathione) protected against the development of epidermal cncers in light exposed animals (1975). Photoprotection for sunlight-induced tumors in humans was attempted earlier with psoralens. In two parallel clinical trials no short-term effect on the development of new human skin cancers by oral psoralens was observed (MacDonald, et al., 1963; Hopkins, et al., 1963). Psoralens

had been used for many years in treating vitiligo (Lerner, et al., 1953; El Mofty, 1948). In fact, psoralens had been used empirically to protect against skin cancer in humans (Hoekenga, 1959). It has been used because of the notion that the tanned skin would protect against the sun. The flaw in this concept is that the maintenance of a tan requires continuous damage. In view of what we now know, the clinical trial was too short, but in terms of carcinogenic potential of psoralens in laboratory animals it is not likely that the study will be repeated.

V. SPECIAL PROBLEMS

PSORIASIS

Psoriasis is an idiopathic hyperproliferative disorder of the epidermis which is characterized by the excessive release of corneocytes to the stratum corneum. Both the proliferative and maturation compartments of the epidermis in psoriasis are greatly enlarged, increasing many times in size. Psoriasis treatment consists of the removal of excess corneocytes with keratolytic agents and the inhibition of cell division with drugs and ultraviolet light.

Goeckerman (1931) was the first to publish an extensive experience using topically applied crude coal tar followed by ultraviolet light in the treatment of psoriasis. This technique quickly became the standard against which all other treatments were subsequently measured. In hospital therapy with ultraviolet light and crude tar is thought to be the safest most active treatment of psoriasis (Marsico, et al., 1976). It would be extraordinary if ultraviolet light (UVB) as used in psoriasis did not have detrimental effects similar to those seen in patients without psoriasis. There has been, however, no systematic investigation of this possibility. Since for many patients this is one of the few effective treatments its use requires wisdom in the application of scales which balance benefit with cost (Halprin, 1980; Stern, et al., 1980; Epstein, 1980).

An identical problem occurs with a more recently developed therapy, the combined use of ultraviolet light in spectrum A (UVA) and one of the photosensitizing drugs (psoralen).

PUVA

Psoralen belongs to a group of heterocyclic organic compounds called furocoumarius which in turn are considered to be a derivative of coumarin (1,2-benzopyrene) (Pathak, et al., 1974). Three derivatives, psoralen, 8-methoxypsoralen and 4,5',8-trimethylpsoralen have been studied most extensively. The ability to sensitize skin to ultraviolet light appears to be a unique capacity of these compounds, and in this regard an extensive literature documents a phototoxicity which results in increased melanogenesis and melanocyte proliferation (Fitzpatrick and Pathak, 1959; Fitzpatrick, et al., 1959).

In 1973 Walter, et al. observed that 4,5',8-trimethylpsoralen in association with "black" ultraviolet light (UVA) inhibited the incorporation of tritiated thymidine into mouse epidermis in vitro (Walter, et al., 1973). They observed a three-fold reduction in thymidine incorporation

of tritiated thymidine into DNA while neither the drug alone nor the light alone had any appreciable effect. The currently accepted mechanism by which psoralen and UVA interrupts the accelerated cellular proliferation of psoriasis is that the absorption of UVA light raises the energy of the psoralen molecule to the triplet state from which it reacts to form a covalent bond with pyrimidine bases in DNA (Musajo, et al., 1974).

Psoralen is highly reactive at several sites so that a variety of combinations occur with pyrimidine bases in DNA, primarily with thymidine. Pathak, et al. have demonstrated with several techniques that the bond between psoralen and DNA is permanent.

On the basis of inhibition of thymidine incorporation, Walter, et al. predicted that psoralen and UVL might be useful in hyperproliferative disorders such as psoriasis. One year later the successful use of psoralens and UVA in the treatment of psoriasis was announced at a press conference by investigators from Boston and Vienna (Parrish, et al., 1974). This was followed by additional reports (Wolff, et al., 1976; Swanbeck, et al., 1975).

The next year a randomized cooperative clinical trial was initiated among 16 centers to investigate in a systemic way the efficacy and short-term safety of PUVA therapy (Melski, et al., 1977). 8-Methoxypsoralen dosage was weight dependent but was about 40 mg/treatment for a 70 kg adult. Two hours after drug ingestion, patients were exposed for increasing amounts of time to high-intensity fluorescent lights with the predominant output in the UVA spectrum (320-400 nm). The results of this study clearly document the effectiveness of this treatment modality.

The induction of cutaneous malignancies in patients receiving PUVA treatment was predicted by earlier animal studies. Griffin and his associated documented in a series of papers the unequivocal propensity of psoralen and UVA to induce cutaneous malignancies in albino mice (Griffin, et al., 1958; Griffing, 1959).

The carcinogenic prophecy was demonstrated by 1979 (Stern, et al., 1979). In a prospective study of 1373 patients who received 8-methoxypsoralen photochemotherapy for psoriasis, 30 patients developed a total of 48 basal cell carcinomas and squamous cell carcinomas. This observed incidence of cutaneous carcinomas was 2.63 times that expected for a matched control population. Significantly, the increased relative risk was highest for patients with a previous cutaneous carcinoma (relative risk = 10.22). Two other observations were made which strengthen the thesis that PUVA itself does induce skin cancer. First, there was an increased frequency of cancers on the trunk and lower legs, body areas not normally exposed to sunlight, but areas exposed during PUVA treatment. Secondly, there was a reversal of the normal predominance of basal cell carcinomas over squamous cell carcinomas in these patients. The majority of tumors were squamous cell carcinomas. In view of this it was stated that cutaneous carcinoma function was a definite result of PUVA therapy and that patients with fair skin and with prior histories of cancer were at greatest risk.

PERCENTAGE DISTRIBUTION OF CARCINOMAS BY ANATOMIC REGION

Region	Tumor Type (percent)		
	Basal Cell (19)	Squamous Cell (29)	Total (48)
Head and Neck	63	3	27
Upper extremities	5	11	8
Trunk	21	31	27
Lower extremities	11	55	38
Totals	100	100	100

The major problem with a study of this sort is that there exists no control group to control for previous UVB exposure or for less common but clearly more important factors such as arsenic ingestion or X-ray irradiation. Perhaps the most difficult problem is that no funds have been generated to study the issue. At least now there is sufficient attention in Europe to this problem for the inclusion of psoralens in suntan lotions to be comdemned (Ashwood-Smith, et al., 1980).

ARSENIC

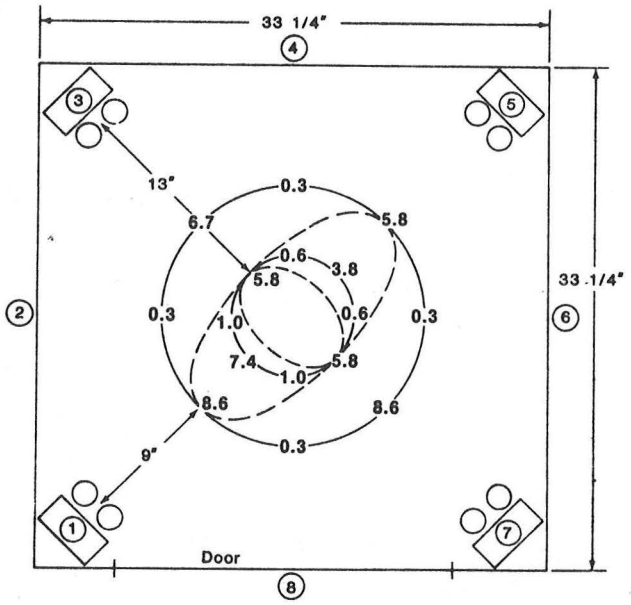
Inorganic arsenic in the form of Fowler's solution has been used to treat a variety of skin disorders including psoriasis. In addition arsenic has been used up until the 1950's as an insecticide and there are some natural waters in which the content of arsenic is sufficiently high to have some risk. Some individuals who have been exposed to such forms of arsenic have a propensity to develop malignancies (Bettley and O'Shea, 1968). With respect to the skin the effect is only partially co-carcinogenic in that the malignancies usually but not always occur in sites of ultraviolet light exposure. A useful marker of an individual who has received arsenic is the development of small scaling on hand or keratinaceous papules on hands and feet.

TANNING SALONS

With this information in mind, it should be possible at this point to take on the tanning salon. This section begins with the statement that no clinical investigator or basic scientist has ever been able to separate those wave lengths of light which produce tanning and erythema from those which produce detrimental effects: premature aging and skin cancer. If this were ever done, then it will be appropriate to invest the family resources and make a fortune in the "salon" industry, but there is at present, no prospect that it will ever happen. Knowing that the goal of tanning salons is to produce a luxurious tan, my goal is to convince you that such facilities will hasten the development of premature aging and will increase the incidence of skin cancer (Epstein, 1980).

This is not a trivial problem, as suntan centers have been started throughout the country. In 1980, the fee for a 20-visit membership varies from $35 to $55, that is $1.75 to $2.75 per visit. Incidentally, maximum gross revenue from a fully utilized booth has been estimated to be more than $5,000.00 per week and more than one-quarter dollars per year (Kaminester, 1980). The editorial in this reference concludes with the request that physicians warn their patients of the risks of exposure. In this way, patients will knowledgeably engage in their high-risk life style.

Nachtwey and Rundel have taken an even closer look at the biological effects of sun lamps which are used in tanning booths. One example of a booth with its complement of lamps is diagrammed in the figure (1981).

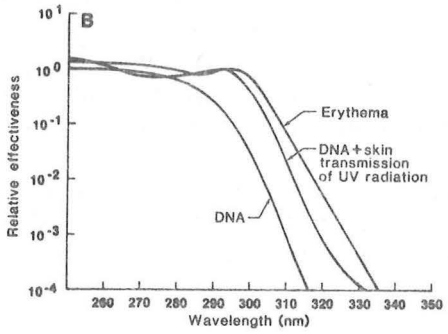


(Nachtwey & Rundel, 1981)

Several 72-inch fluorescent sunlamps in standard fixtures are mounted vertically in each corner; both surfaces are covered with a reflective metallized wall paper or with sheet metal. This material will reflect stray light back to the subject, increasing the rate of UVL delivery. The investigators first evaluated the radiation field produced by the lamps. Surprisingly, they found extreme anistropy of the radiation field with both hot and cold spots, as indicated in the figure. Consequently, only a regular rotary movement of the subject will prevent burning of some regions with minimal effect in others.

Nachtwey and Rundel also compared the spectral output of the fluorescent lamps with that of natural sunlight. One may look at this data in two ways.

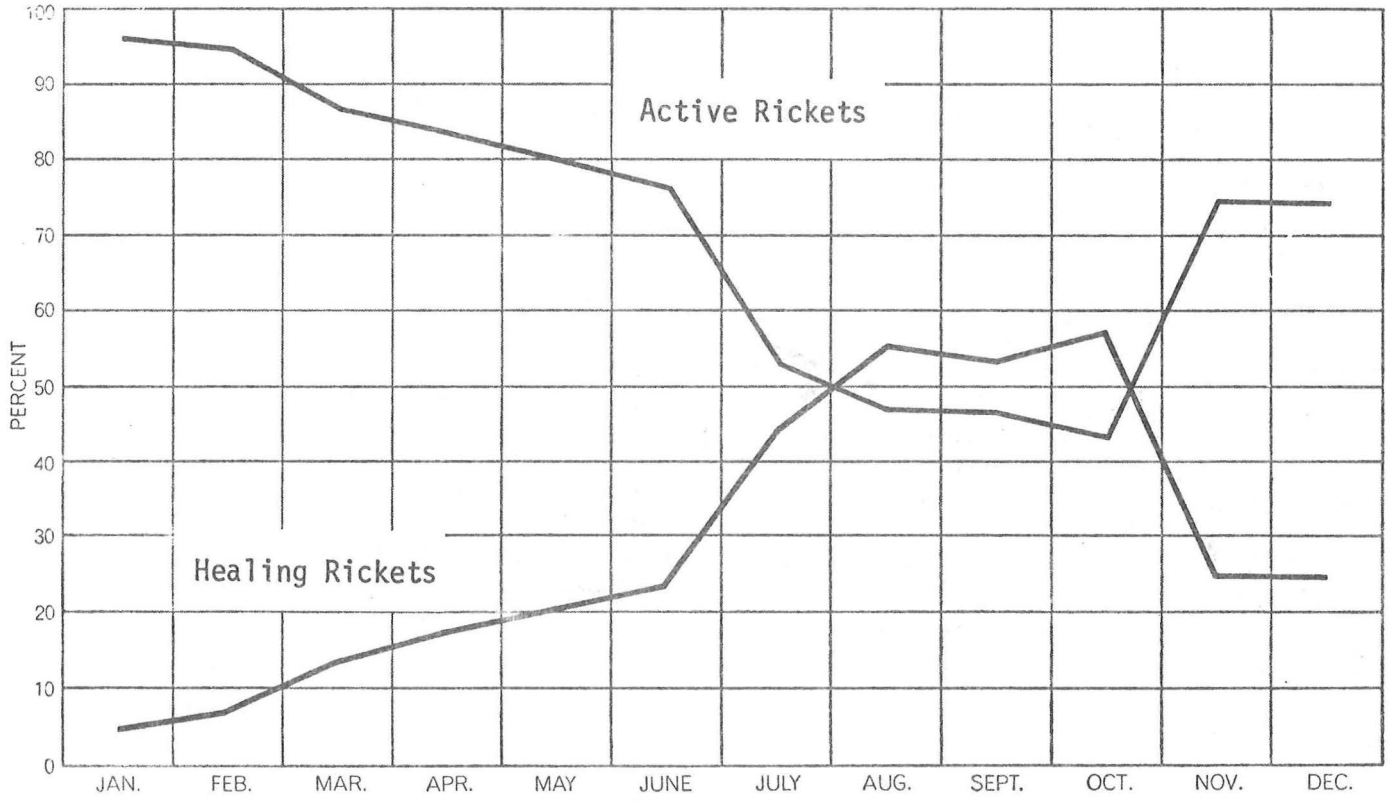
The first is to say that the spectral output of the lamps approaches that of the sun. But the truth of the matter is that they are if one examines the output carefully he will see crucial differences in the ultraviolet region. The shoulder of the two curves fall away in the different directions



so that the contribution of DNA damage is far greater with the lamps than with natural sunlight. Surprisingly, however, we do not know that it is the DNA damage spectrum which is responsible for carcinogenesis.

VITAMIN D

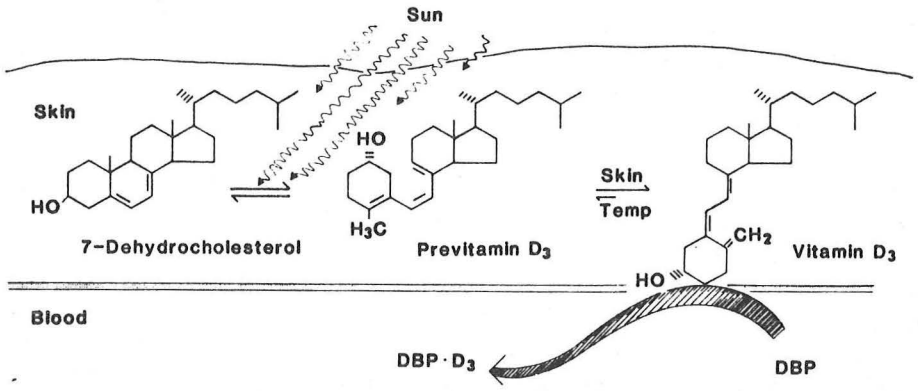
An important issue which has not yet been presented concerns the possible benefits of ultraviolet light. It arises from the complaint that if ultraviolet light is so detrimental, then why has natural selection not lead to adequate pigmentary protection for all populations. The postulated one answer may lie in the next figure. This epidemiologic evidence, taken from the review by Loomis (1970) indicates the incidence of rickets to be profoundly dependent on season.



Seasonal Variation in Rickets
(Loomis, 1970)

In fact, the production in vivo of biologically active vitamin D, that is vitamin D_3 requires a light-induced biochemical conversion. In humans this conversion occurs in the skin.

The location and mechanism of light-dependent synthesis of vitamin D in human skin was recently elucidated by Holick and his associates (1980). The production of biologically active Vitamin D_3 occurs by the outlined step. 7-Dehydrocholesterol (7-DHC) is converted in a photo-dependent step by breaking the bond between carbons 9 and 10. This occurs in two steps, the first one requiring UVL to go to Previtamin D_3 ($PreD_3$). The second step



(Holick et al, 1980)

is a temperature dependent but spontaneous one to Vitamin D_3. Removal from the skin of this lipid soluble compound is then dependent upon the vitamin D-binding protein for transport in the plasma.

The investigators measured 7DHC and $PreD_3$ levels in the respective levels of the skin.

SKIN STRATA	7-DHC	Pre D_3
S. corneum and granulosum	360	20
S. spinosum	2460	115
S. Basale	1890	115
Dermis	1670	3

ng/6.25 cm^2

7-DHC and Pre D_3 in human skin after UVL.
(From Holick, et al., 1980)

It is apparent that conversion occurs in the epidermis, where UVL is more available and that the short term rate limiting step is the removal rate of

the binding protein since the removal of D_3 drives the reaction to the right. Photoconversion of D analogs may also be of advantage to patients with Vitamin D resistant syndromes (MacDonald, et al., 1963).

IMMUNE SYSTEM INTERACTIONS

Within the last decade it has come to attention that ultraviolet light (UVB) may interact in a significant way with cells of the immune system. Kripke (1980) and then Daynes (1978) have each published a series of studies which demonstrate the ultraviolet light pretreatment of mice renders them less able to reject ultraviolet light-induced skin cancers. This phenomenon is probably due to the generation of suppressor cells which "suppress" the normal immune rejection response (Fisher and Kripke, 1978). This is an extraordinary set of observations and it implies that individuals who receive excessive amounts of ultraviolet light are altered in a systemic sense and can no longer recognize certain types of malignant cells.

In our own laboratories we have observed that modest doses of UVB will interrupt the function of epidermal Langerhans cells (Toews, et al., 1980). After UVB irradiation, exposure to a contact sensitizer which normally leads to allergic dermatitis renders recipient animals incapable of reacting to that sensitizer either then or at a future date. This phenomenon may result from the capacity of ultraviolet light to interrupt the function of epidermal Langerhans cells (Toews, et al., 1980; Aberer, et al., 1981). In both of these areas there seems to be a significant interaction between ultraviolet light and cells of the immune system, all of which illustrates the need to continue to investigate interractions which occur between man and his environment.

REFERENCES

Aberer W, Schuler G, Stingl G, Honigsmann H, Wolff K: Ultraviolet light depletes surface markers of Langerhans cells. J Invest Dermatol 76: 202-210, 1981

Ashwood-Smith MJ: Brit Med J 2:1144, 1979

Ashwood-Smith MJ, Poulton GA, Barker M, Mildenberger M: 5-Methoxypsoralen, an ingredient in several suntan preparations, has lethal, mutagenic and clastogenic properties. Nature 285:407-409, 1980

Bergstresser PR, Halprin KM: Multiple sequential skin cancers. Arch Dermatol 111:995-996, 1975

Bergstresser PR, Taylor JR: Epidermal "turnover time" - a new examination. Brit J Dermatol 96:503-506, 1977

Bettley FR, O'Shea JA: The absorption of arsenic and its relation to carcinoma. Brit J Dermatol 92:563-568, 1968

Black HS, Chan JT: Suppression of ultraviolet light-induced tumor formation by dietary antioxidants. J Invest Dermatol 65:412-414, 1975

Blum HF: Sunlight as a causal factor in cancer of the skin of man. J Natl Cancer Inst 9:247-258, 1948

Breslow A: Thickness, cross-sectioned areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 172:902-908, 1970

Breza T, Taylor JR, Eaglstein WH: Noninflammatory destruction of actinic keratoses by fluorouracil. Arch Dermatol 112:1256-1258, 1976

Brodthagen H: Seasonal variations in ultraviolet sensitivity of normal skin. In Urbach F, ed. The Biological Effects of Ultraviolet Radiation. Pergamon Press, Oxford, 1969, pp 459-467

Buettner KJK: The effects of natural sunlight on human skin. In Urbach F, ed. The Biological Effects of Ultraviolet Radiation. Pergamon Press, Oxford, 1969, pp 237-249

Clark WH Jr., et al.: The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res 29:705-726, 1969

Cleaver JE: Defective repair replication of DNA in xeroderma pigmentosum. Nature 218:652-656, 1968

Daniels F, Brophy D, Lobitz WC: Histochemical responses of human skin following ultraviolet irradiation. J Invest Dermatol 37:351-357, 1961

DeRios G, Chan JT, Black HS, et al.: Systemic protection by antioxidants against UVL-induced erythema. J Invest Dermatol 70:123-125, 1978

Dillaha CJ, et al.: Selective cytotoxic effect of topical 5-fluorouracil. Arch Dermatol 88:247-256, 1963

Eaglstein WH, Weinstein GD, Frost P: Fluorouracil: mechanism of action in human skin and actinic keratoses. Arch Dermatol 101:132-139, 1970

El Mofty AM: A preliminary cinical report on the treatment of leukoderma with Ammi majus Linn. J Roy Egyptian M A 31:651, 1948

Epstein JH: "Suntan salons", letter. J Am Acad Dermatol 1:564, 1979

Epstein JH: Psoralen photochemotherapy, editorial. J Am Acad Dermatol 2:239, 1980

Fisher MS, Kripke ML: Further studies on the tumor-specific suppressor cells induced by ultraviolet radiation. J Immunol 121:1139-1144, 1978

Fitzpatrick TB, Arndt KA, El Mofty AM, Pathak AM: Hydroquinone and psoralens in the therapy of hypermelanosis and vitiligo. Arch Dermatol 93:589-600, 1959

Fitzpatrick TB, Pathak MA: Historical aspects of methoxsalen and other furocoumarins. J Invest Dermatol 32:229-231, 1959

Fitzpatrick TB, Miyamoto M, Ishikawa K: The evoluation of concepts of melanin biology. In Montagna W, Hu F, eds. Advances in Biology of Skin. Oxford, Pergamon Press, 1967, pp 1-28

Fleming ID, Barnawell JR, Burlison PE, Rankin JS: Skin cancer in black patients. Cancer 35:600-605, 1975

Gellin GA, Kopf AW, Garfinkel L: Basal cell epithelioma: A controlled study of associated factors. Arch Dermatol 91:38-45, 1965

Giese AC: Living With Our Sun's Ultraviolet Rays. Plenum Press, New York, 1976, p 4

Gilchrest BA: Prior chronic sun exposure decreases the lifespan of human skin fibroblasts in vitro. J Gerentol 35:537-541, 1980

Goeckerman WH: Treatment of psoriasis: Continued observations on the use of crude coal tar and ultraviolet light. Arch Dermatol 24:446-450, 1931

Goldsmith HS: Melanoma: An overview. Ca 29:194-215, 1979

Graham JH, Helwig EB: Premalignant cutaneous and mucocutaneous diseases. In Graham JH, Johnson WC, Helwig EB, eds. Dermal Pathology. Hagerstown, Mo., Harper and Row, 1972, pp 561-624

Griffin AC, Hakim RE, Knox J: The wave length effect upon erythemal and carcinogenic response in psoralen treated mice. J Invest Dermatol 31:289-295, 1958

Griffin AC: Methoxsalen in ultraviolet carcinogenesis in the mouse. J Invest Dermatol 32:367-372, 1959

Halprin KM: Cyclic nucleotides and epidermal cell proliferation. J Invest Dermatol 66:339-343, 1976

Halprin KM: Psoriasis, skin cancer and PUVA. J Am Acad Dermatol 2:334-337, 1980

Hayflick L: The limited in vitro lifetime of human diploid cell strains. Exp Cell Res 37:614-636, 1965

Hoekenga MT: Experiences with methoxsalen in the American tropics. J Invest Dermatol 32:351-353, 1959

Holick MF, Uskokovic M, Henley JW, et al.: The photoproduction of 1γ, 25-dihydroxy vitamin D_3 in skin. An approach to the therapy of vitamin-D-resistant syndromes. NEJM 303:349-354, 1980

Holick MF, MacLaughlin JA, Clark MB, et al.: Photosynthesis of previtamin D_3 in human skin and the physiologic consequences. Science 210:203-205, 1980

Holman CDJ, James IR, Gattey PH, Armstrong BK: An analysis of trends in mortality from malignant melanoma of the skin in Australia. Int J Cancer 26:703-709, 1980

Hopkins CE, Belisario JC, MacDonald EJ, et al.: Psoralen prophylaxis against skin cancer: report of clinical trial II. J Invest Dermatol 41:219-223, 1963

Johnson BE, Daniels F: Lysosomes and the reactions of skin to ultraviolet radiation. J Invest Dermatol 53:85-94, 1969

Kaminester LH: Suntanning centers. JAMA 244:1258-1259, 1980

Keeler C: Cuna Moon-child albinism, 1950-1970. J Hereditary 61:273-278, 1970

Kligman LH, Akin FJ, Kligman AM: Sunscreens prevent ultraviolet photocarcinogenesis. J Am Acad Dermatol 3:30-35, 1980

Knox JM, Guin J, Cockerell EG: Benzophenones. Ultraviolet light absorbing agents. J Invest Dermatol 29:435-444, 1957

Koller L: The physics of the atmosphere. In Urbach F, ed. The Biological Effects of Ultraviolet Radiation. Pergamon Press, Oxford, 1969, pp 329-333

Kondratyev KA: Radiation in the Atmosphere, Academic Press, 1969, p 912

Kraemer KH: Progressive degenerative diseases associated with defective DNA repair: xeroderma pigmentosum and ataxia telangiectasia, in Nichols WW and Murphy DG, eds. DNA Repair Processes. Miami Symposium Specialists, 1977, pp 37-71

Kraemer KH: Xeroderma pigmentosum. A prototype disease of environmental genetic interaction. Arch Dermatol 116:541-542, 1980

Kripke ML: Immunology of UV-induced skin cancer. Photochem Photobiol 32: 837-839, 1980

Lerner AB, Denton CR, Fitzpatrick TB: Clinical and experimental studies with 8-methoxypsoralen in vitiligo. J Invest Dermatol 20:299-314, 1953

Levin DL, Baranovsky A: Survival for melanoma of the skin. DHEW Pub. No. (NIH) 78-1545, 1978

Little JH, Hold, Davis N: Changing epidemiology of malignant melanoma in Queensland. Med J Austr 1:66-69, 1980

Lynch HT, Anderson DE, Smith JL, Jr., et al.: Xeroderma pigmentosum, malignant melanoma, and congenital ichthyosis. A family study. Arch Dermatol 96:625-635, 1967

Lynch HT, Frichot BC III, Lynch JF: Cancer control in xeroderma pigmentosum. Arch Dermatol 113:193-195, 1977

MacDonald EJ, Griffin AC, Hopkins CE, et al.: Psoralen prophylaxis against skin cancer: Report of clinical trial I. J Invest Dermatol 41:213-217, 1963

Marsico AR, Eaglstein WH, Weinstein GD: Ultraviolet light and tar in the Goeckerman treatment of psoriasis. Arch Dermatol 112:1249-1250, 1976

Melski JW, Tanenbaum L, Parrish JA, Fitzpatrick TB, Bleich HL: Oral methoxsalen photochemotherapy for the treatment of psoriasis: A cooperative clinical trial. J Invest Dermatol 68:328-335, 1977

Menn H, Robins P, Kopf AW, Bart RS: The recurrent basal cell epithelioma. Arch Dermatol 103:628-631, 1971

Mihm MC, Clark WH Jr., From L: The clinical diagnosis, classification and histogenic concepts of the early stages of cutaneous malignant melanomas. New Engl J Med 284:1078-1082, 1971

Mohs FE, Guyer MF: Pre-excisional fixation of tissues in the treatment of cancer in rats. Cancer Res 1:49-51, 1941

Mohs FE: Chemosurgery, a microscopically controlled method of cancer excision. Arch Surg 42:279-295, 1941

Mohs FE: Chemosurgery for skin cancer. Fixed tissue and fresh tissue techniques. Arch Dermatol 112:211-215, 1976

Mohs FE: Chemosurgery. Microscopically controlled surgery for skin cancer. Charles C. Thomas, Springfield, Il., 1978

Musajo L, Rodighiero G, Caporale G, et al.: Photoreactions between skin-photosensitizing furocoumarins and nucleic acids. Sunlight and Man. Edited by T. B. Fitzpatrick, et al., University of Tokyo Press, Tokyo, 1974, pp 369-387

Nachtwey DS, Rundel RD: A photobiological evaluation of tanning booths. Science 211:405-407, 1981

Nander JS: Pilot study of ultraviolet radiation in Los Angeles. In Urbach F, ed. The Biological Effects of Ultraviolet Radiation. Pergamon Press, Oxford, 1969, pp 417-431

Neer RM, Davis TRA, Walcott A: Stimulation by artificial lighting of calcium absorption in elderly human subjects. Nature 229:255-257, 1971

Ogura RM and Knox JM: Biochemical changes in ultraviolet light-irradiated epidermis. In Sunlight and Man. Edited by T. B. Fitzpatrick, M. A. Pathak, L. C. Harber, M. Seiji and A. Kukita. University of Tokyo Press, Tokyo, 1974, pp 147-156

Parrish JA, White MB, Pathak MA: Photomedicine. In Fitzpatrick TB, et al., eds. Dermatology in General Medicine, McGraw-Hill, New York, 1979, pp 942-994

Parrish JA, Fitzpatrick TB, Tanenbaum L, et al.: Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. N Engl J Med 291:1207-1211, 1974

Parsons PG, Goss P: DNA damage and repair in human cells exposed to sun light. Photochem Photobiol 32:635-641, 1980

Paslin DA: The effects of biopsy on the incidence of metastases in hamsters bearing malignant melanoma. J Invest Dermatol 61:33-38, 1973

Pathak MA: Basic aspects of cutaneous photosensitization. In Urbach F, ed. The Biological Effects of Ultraviolet Radiation. Pergamon Press, Oxford, 1969, pp 489-511

Pathak MA, Kramer DM, Fitzpatrick TB: Photobiology and photochemistry of furocoumarins (psoralens). Sunlight and Man. Edited by T. B. Fitzpatrick, et al. University of Tokyo Press, Tokyo, 1974, pp 335-368

Pinkus H: Epithelial neoplasms and precancerous lesions. In Fitzpatrick T.B., et al., eds. Dermatology in General Medicine, McGraw-Hill, New York, 1979, pp 354-361

Quevedo WC, Jr., Fitzpatrick TB, Pathak MA, Jimbow K: Light and skin color. In Sunlight and Man. Edited by T. B. Fitzpatrick, M. A. Pathak, L. E. Harber, M. Seiji and A. Kukita. University of Tokyo Press, Tokyo, 1974, pp 165-194

Robbins JH, Kraemer KH, Lutzner MA, et al.: Xeroderma pigmentosum: An inherited disease with sun sensitivity, multiple cutaneous neoplasms, and abnormal DNA repair. Ann Int Med 80:221-248, 1974

Rothman S, Henningsen AB: The sunburn protecting effect of para-aminobenzoic acid. J Invest Dermatol 9:307-313, 1947

Sayre RM, Marlowe E, Agin PP, et al.: Performance of six sunscreen formulations on human skin. Arch Dermatol 115:46-49, 1979

Schmoeckel C, Braun-Falco O: Prognostic index in malignant melanoma. Arch Dermatol 114:871-873, 1978

Scotto J, Kopf AW, Urbach F: Non-melanoma skin cancer among Caucasians in four areas of the United States. Cancer 34:1333-1338, 1974

Silverberg E: Cancer statistics, 1979. Cancer 39:15, 1979

Smith RC, Tyler JE: "Transmission of solar radiation into natural waters" in K. C. Smith, ed. Photochemical and Photobiological Reviews, Vol. 1, Plenum Press, New York, 1976, pp 117-155

Spellman CW, Daynes RA: Ultraviolet light induced murine suppressor lymphocytes dictate specificity of anti-ultraviolet tumor immune responses. Cell Immunol 38:25-34, 1978

Stern RS, Parrish JA, Fitzpatrick TB: Letter. J Am Acad Dermatol 2: 337-339, 1980

Swanbeck G, Thyresson-hok M, Bredberg A, et al.: Treatment of psoriasis with oral psoralens and longwave ultraviolet light: Therapeutic results and cytogenic hazards. Acta Dermatol Venereol (Stockh) 55:367-376, 1975

Task force on photobiology: report on ultraviolet light sources. Arch Dermatol 109:833, 1974

The Medical Letter: Sunscreens 24:46-48, 1979

Thorington L: Actinic effects of light and biological implications. Photochem Photobiol 32:117-129, 1980

Toews GB, Bergstresser PR, Streilein JW: Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. J Immunol 124:445-453, 1980

Urbach F: Modification of ultraviolet carcinogenesis by photoactive agents. J Invest Dermatol 32:373-378, 1959

Veronesi U, et al.: Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. New Engl J Med 297:627-630, 1977

Walter JF, Voorhees JJ, Kelsey WH, Duell EA: Psoralen plus black light inhibits epidermal DNA synthesis. Arch Dermatol 107:861-865, 1973

White JE, et al.: Cancer of the skin in Negroes. JAMA 178;149-151, 1961

Wolff K, Fitzpatrick TB, Parrish JA, et al.: Photochemotherapy for psoriasis with orally administered methoxsalen. Arch Dermatol 112:943-950, 1976

Woodcock A, Magnus IA: The sunburn cell in mouse skin: preliminary quantitative studies on its production. Brit J Dermatol 95:459-468, 1976