MALIGNANT MELANOMA AND THE DYSPLASTIC NEVUS SYNDROME

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July 31, 1986

A. ABSTRACT

Although skin accounts for a relatively large percentage of human malignancies, the ease with which skin cancer is identified as well as the availability of effective treatment has given such malignancies a "benign" reputation. Two observations contradict that reputation. Malignant melanoma accounts for as few as 5% of skin cancers, but it is responsible for virtually all deaths, approximately 5,000 each year in the United States. Moreover, there has been a significant and substantial increase in the incidence of melanoma skin cancer over the last three decades in all of the Western World. Two factors are available to counterbalance these pessimistic observations. First, the early identification of malignant melanoma is relatively easy, and when effective treatment is not delayed, the prognosis for most patients becomes relatively optimistic. Secondly, the evidence that ultraviolet radiation is ultimately responsible for most skin cancer, including malignant melanoma, remains substantial, giving credibility to the recommendation that protection from outdoor light exposure is of benefit. The important role of primary care physicians is to examine the skin of their patients and to identify correctly those pigmented skin lesions which require additional study.

B. INTRODUCTION

Skin cancer accounts for a disproportionate number of human malignancies in Western Societies. By contrast, people who possess, on a genetic basis, greater amounts of epidermal melanin are relatively protected. Although most patients' skin cancers are treated effectively, those with melanoma have a substantial risk of metastatic spread and eventual death. This review focuses on cutaneous structure and function, the role of melanocytes and melanin in photoprotection, and recent developments in the epidemiology, treatment, and ultimate prognosis of skin cancer. It is based on the following outlines:

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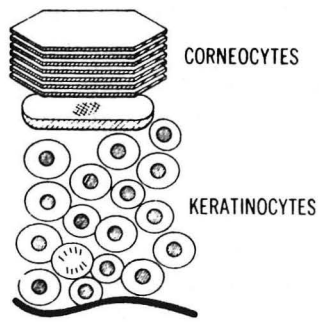
C. CUTANEOUS STRUCTURE AND FUNCTION

A major function of skin is to elaborate the structure which serves as a diffusion barrier between man and his environment. This barrier consists of the outermost portion of skin, stratum corneum, which in turn is a laminated aggregate of terminally differentiated keratinocytes. Stratum corneum, a composite of lipid-rich cell walls, intercellular glycoproteins and a keratin-rich cytoplasmic remnant, is relatively impervious to chemicals, solvents, and microbiologic organisms. Moreover, it is both resilient and elastic, giving skin its structural integrity as well as elasticity. A different barrier property of skin is found in its capacity to restrict the penetration of electromagnetic radiation, particularly those wave lengths which are found within the ultraviolet spectrum. In a provocative discussion Arndt et al (1969) summarizes these capacities of skin to serve as a self-renewing interface, one which effectively withstands mechanical, chemical, electromagnetic and biologic insults.

The cutaneous diffusion barrier, stratum corneum, measures 10 microns in thickness, and is made up of flattened, dead epidermal cells (corneocytes) which are locked together, laterally and vertically, into a laminated membrane. Barrier properties of stratum corneum are similar to that of polyethylene film, which also is 10 microns thick. An important aspect of stratum corneum homeostasis is that the individual cells from which it is constructed are lost continuously from the skin surface. In turn, cellular proliferation by underlying germanitive keratinocytes replaces, in a steady state fashion, the single cells which exfoliate from the outer surface. Investigators have made use of the concept of an "epidermal proliferative unit", that volume of epidermis which underlies the surface area of corneocyte (Bergstresser and Taylor, 1977).



Epidermis, the outermost compartment of skin, consists of the aggregate of cells found above a well-defined histologic boundary which is identified as a basement membrane. It consists primarily of a cellular matrix, with more than 90% of the cellular volume within epidermis consisting of proliferating and maturing keratinocytes. As described, these cells arise from a germinative pool and subsequently undergo a series of maturational steps from which they emerge to become the flat, dead, laminated cells of stratum corneum. For the purposes of this review, attention will be paid to these cells only in their capacity to serve as the cellular origin of two important skin cancers: basal cell carcinoma and the squamous cell carcinomas. In recent years the model of epidermis as a singularly dynamic and proliferating structure has been expanded to recognize its dynamic nature in terms of cellular composition. Langerhans cells constitute approximately 2% of epidermal cells, and they reside as a distributed network which covers the entire skin surface. Their importance to this review lies in their capacity to serve as antigen presenting cells for certain immunologic processes in skin. Moreover, the capacity of ultraviolet radiation selectively to alter their function suggests an important mechanism by which such radiation might prevent the immunologic recognition and destruction of malignant clones of cells. (Toews, Bergstresser and Streilein, 1980; Bergstresser and Streilein, 1985).

Melanocytes also constitute approximately 2% of epidermal cells, residing lower in the epidermis, adjacent to the basement membrane. An important lesson may be found in the dynamic nature of these cells. Both are derived from other tissues, Langerhans cells from bone marrow and melanocytes from neural crest. If damaged or destroyed, both may be replaced by mechanisms which are not fully understood, but in the interval between damage and replacement, their functional attributes may be missed. This may lead to at least two disease states, specific immunologic incompetence and vitiligo.

As alluded to above, epidermis forms an incomplete barrier for ultraviolet radiation. The biologic effects of the penetrating portion of environmental radiation constitutes the major portion of this review.

D. ELECTROMAGNETIC RADIATION: PHYSICS AND PHOTOABSORPTION

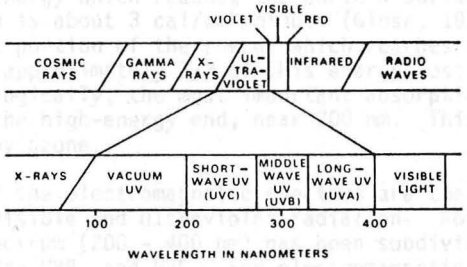
Electromagnetic radiation travels in single packets or quantum units which may be characterized by wave length or by their obligate energy state, with the relationship between wave length and energy state remaining constant and related to Planck's constant ($h = 6.63 \times 10^{-34}$ Joule/sec).

Energy (E) of photon = h/wave length (λ) single line

or

$$(E)(\lambda) = h$$

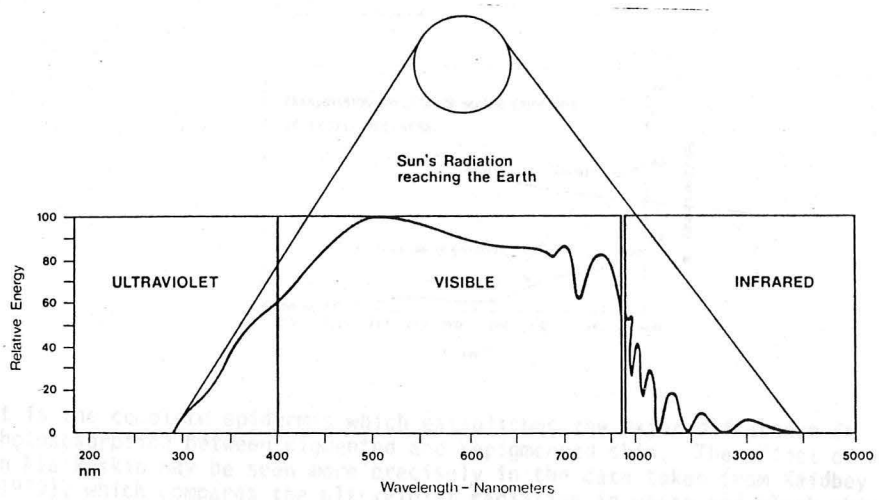
Thus, the energy states of photons increase as wave length decreases. In descriptive terms, the electromagnetic spectrum when stratified according to wave length, extends from high energy cosmic rays down through X-rays to ultraviolet radiation. Below that, beginning at a wavelength of about 200 nm (0.2 microns), one finds ultraviolet light visible light, with a complete spectrum from violet to red, followed by infrared energy, which is perceived as heat.



Parrish JA, et al., 1979

Longer still in wave length are radar and radio waves which are used for telecommunication.

As can be seen in the figure from Harber and Bickers (1981), 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.



Electromagnetic radiation reaching the earth from the sun contains wavelengths from 290 nm to 4000 nm (long-wave infrared).

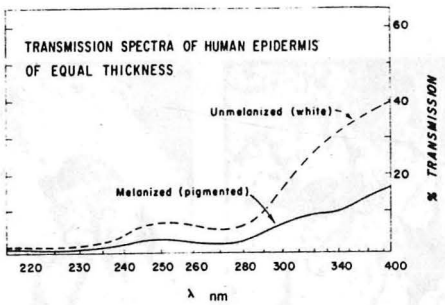
(Harber and Bickers, 1981)

The sum of the energy which reaches the earth's surface is known as the solar constant, which is about 3 cal/cm^2/minute (Giese, 1976). The lower curve represents that portion of the energy which reaches the earth's surface on a clear day, with approximately 1/3 of this energy lost by absorption in the atmosphere. Biologically, the most important absorption of ultraviolet radiation occurs in the high-energy end, near 200 nm. This results from the specific absorption by ozone.

At the center of the electromagnetic spectrum are the biologically important portions, visible and ultraviolet radiation. For convenience, the ultraviolet (UVL) spectrum (200 - 400 nm) has been subdivided arbitrarily into three sub-regions, UVA, UVB, and UVC. For electromagnetic radiation to have a biologic effect, it must first penetrate to the relevant chromatophore(s) with the capacity to penetrate being a function of several factors, most importantly wave length. The conversion of electromagnetic energy into a biologic response occurs at the level of individual photons, with each event

requiring an intermediate photochemical event which then results in an altered or "toxic" molecule. Thus, photocarcinogenesis resembles chemical carcinogenesis in that both result ultimately from chemical reactions. They differ in that environmental chemical carcinogens and photons have different capacities to reach various targets.

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 accompanying figure.



It is the complete epidermis which establishes the major difference in photoabsorption between pigmented and repigmented skin. The effect of melanin in black skin may be seen more precisely in the data taken from Kaidbey et al (1979), which compares the ultraviolet radiation in white and black skin.

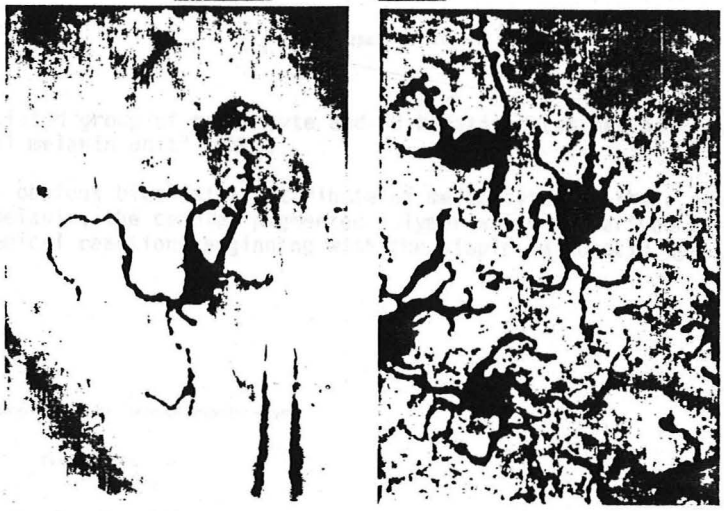
RELATIVE PERCENT ULTRAVIOLET LIGHT TRANSMISSION BY BLACK AND WHITE EPIDERMIS

Wave Length (nm)	White	Black	Black/White
290	0.083	0.011	0.13
295	0.171	0.025	0.15
300	0.270	0.041	0.15
305	0.348	0.056	0.16
310	0.407	0.068	0.17
315	0.453	0.078	0.17
320	0.488	0.086	0.18
325	0.515	0.092	0.18
330	0.537	0.097	0.18
335	0.550	0.100	0.18
340	0.562	0.103	0.18

(From Kaidbey et al., 1979)

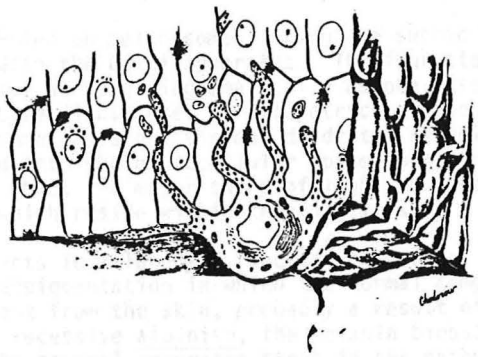
E. MELANOCYTES AND MELANIN BIOLOGY

During the first three months of development the epidermis is invaded by cells of neural crest origin. These dendritic cells gradually acquire the capacity to produce melanin, and by the time of birth they are found primarily in lower portions of the epidermis, distributed in a regular pattern.



Dendritic Epidermal Melanocytes

Both the dendritic configuration and the spatial relationship between adjacent melanocytes may be seen in the illustration. Numerically melanocytes represent approximately 1-2% of epidermal cells, with the long dendritic processes of each melanocyte coursing out into the vicinity of approximately 50 keratinocytes.

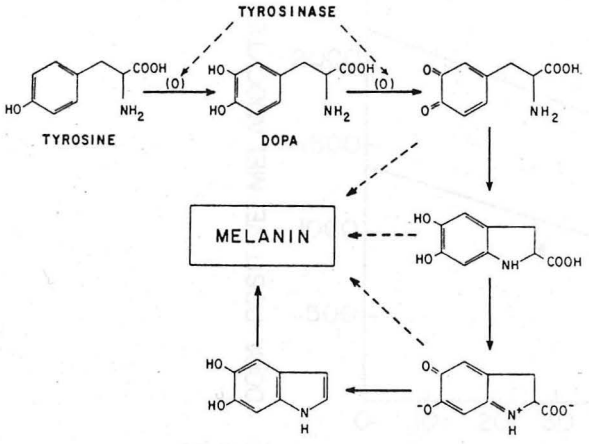


(Fitzpatrick et al, 1967)

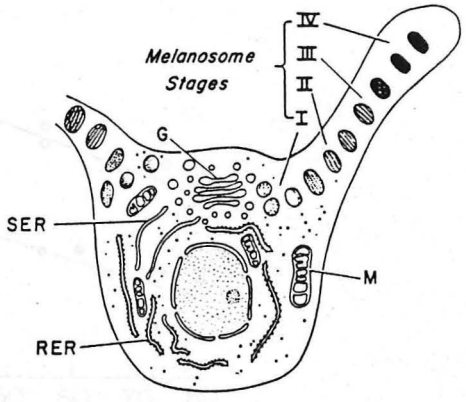
The associated group of melanocyte and 50 keratinocytes has been called the "epidermal melanin unit" (EMU).

Most obvious biochemical attribute of melanocytes is their capacity to produce melanin, the complex pigmented polymer which is derived from a series of biochemical reactions beginning with the simple amino acid tyrosine.

Biology of the melanin pigmentary system



(Fitzpatrick, 1979)



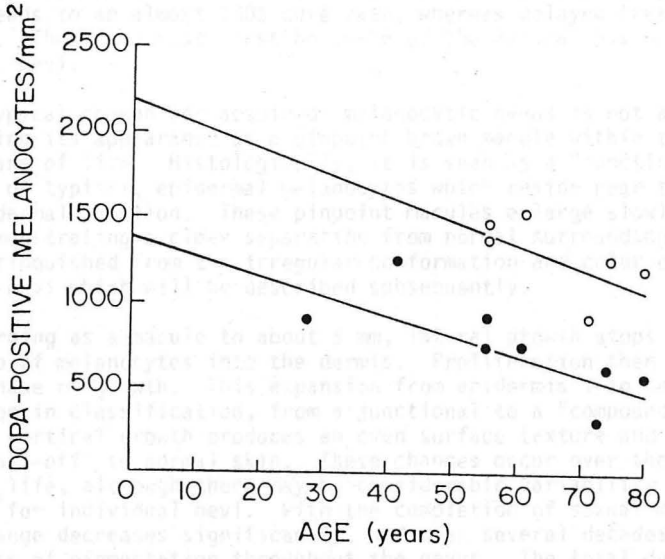
MELANOCYTE

(Fitzpatrick, Szabo and Wick, 1983)

Melanin itself is assembled on melanosomes, which are submicroscopic structures associated with the Golgi apparatus. The four stages (I-IV) of melanosome maturation may be seen diagramatically as one passes out along the dendrite of the melanocyte illustrated by Fitzpatrick, Szabo, and Wick (1983). After assembly, melanosomes pass out through dendritic cellular processes from which they are released into the extracellular space to be phagocytosed by nearby keratinocytes. Thus, the major share of light absorption in skin occurs in melanosomes which reside within keratinocytes.

Two important defects in melanocyte function exist: a. Vitiligo is an acquired condition of depigmentation in which the normal complement of melanocytes become absent from the skin, probably a result of immunological injury. In autosomal, recessive albinism, the melanin biosynthetic pathway is faulty at any one of the several enzymatic steps in the pathway from tyrosine to melanin. A striking demonstration of the importance of melanin in protecting the skin from ultraviolet radiation may be found in the fate of albino natives living in tropical environments. The Cuna Indians of San Blas, Panama, have an inordinately high incidence of occulocutaneous albinism, estimated to be 1% of the total population (Keeler, 1970). Members of this tribe resemble most individuals with albinism, having yellow to white hair and a faint pink skin color. Albinos among adult Cuna Indians, who happen to live in a sundrenched tropical environment, die most often of metastatic skin cancer.

Melanocytes respond physiologically to ultraviolet radiation with proliferation and an increased production of melanin.



AGE, SUN EXPOSURE AND MELANOCYTES (Gilchrest, 1979)

This figure, taken from the work of Gilchrest, Blog, and Szabo (1979), is a graphic representation of surface densities of DOPA-positive dendritic melanocytes in whole mounts of human epidermis, from sun-protected and sun-exposed regions. It demonstrates a gradual decline in the number of melanocytes with age as well as the significant effect of environmental ultraviolet exposure on the surface density of DOPA-positive melanocytes. Thus, ultraviolet radiation has the capacity to increase the production of melanin by melanocytes as well as to increase the absolute number of melanocytes. This "negative feedback" system is in turn responsible for the absorption of ultraviolet light during subsequent exposure. This is the "protection" of "tanned" skin. To this date investigators have been unable to separate those wave lengths responsible for increasing skin melanin content from that which is responsible for the chronic damaging effects of skin. For some time it has been known that the most efficient wave lengths for both effects are contained within the ultraviolet B spectrum. In recent years, it has been recognized that enormous amounts of irradiation from the ultraviolet A spectrum also have the capacity to induce tanning. These are amounts of UVA which are not available by natural exposure and amounts which have never been tested for their carcinogenic effect. Despite this severe limitation, UVA is the spectrum now used by the "tanning salons" which now claim safety.

F. MOLES AND NEVI

NATURAL HISTORY OF NEVI (Stegmaier et al., 1959; Lund HZ et al., 1949; Maize & Foster, 1979). Physicians who examine relatively large numbers of patients and who have only intermittent experience with the issues of skin cancer must first be able to differentiate normal or "typical" melanocytic nevi from both dysplastic nevi and from an early melanoma. This is particularly important in view of the observation that the early treatment of melanoma leads to an almost 100% cure rate, whereas delayed treatment may be disastrous. Thus, one must first be aware of the natural history of melanocytic nevi.

The typical common (or acquired) melanocytic nevus is not apparent at birth, making its appearance as a pinpoint brown macule within the first several years of life. Histologically, it is seen as a "junctional" collection of typical, epidermal melanocytes which reside near to the dermal-epidermal junction. These pinpoint macules enlarge slowly over time, usually demonstrating a clear separation from normal surrounding skin. This may be distinguished from the irregular conformation and color of the dysplastic nevi which will be described subsequently.

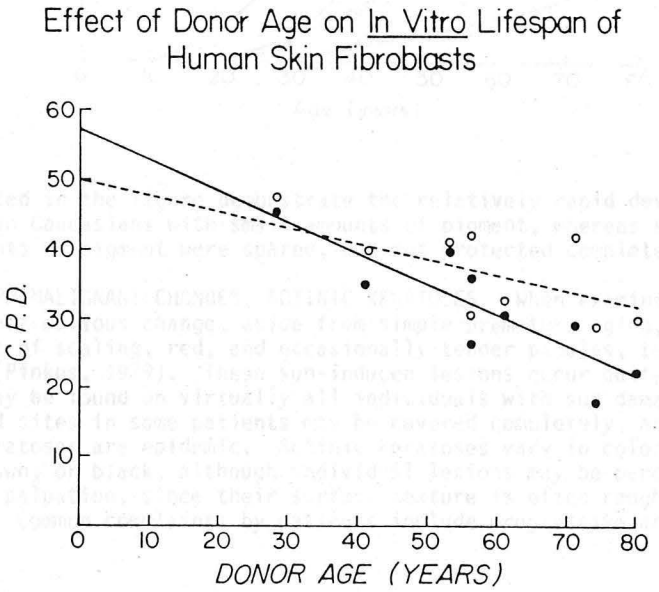
After enlarging as a macule to about 5 mm, lateral growth stops and there is penetration of melanocytes into the dermis. Proliferation then leads to a vertical phase of growth. This expansion from epidermis into dermis leads to a transition in classification, from a junctional to a "compound" nevus. The pattern of vertical growth produces an even surface texture and a sharp, regular "fall-off" to normal skin. These changes occur over the first two decades of life, although there may be considerable variability in the rate of maturation for individual nevi. With the completion of sexual maturity, the rate of change decreases significantly, and over several decades there is a gradual loss of pigmentation throughout the nevus. The total duration of this

"natural" process is from 4 to 5 decades. Importantly, one may observe a permanent arrest of this process at any point along its course, so that elderly and middle-aged patients may exhibit all of the above-mentioned forms.

With respect to numbers, Nichols has reported that nevi increase in number until a peak is reached at the age of 15 in men and about 25 in women. At that point the number of nevi then decreases with increasing age (Nichols, 1973). This should be contrasted with dysplastic nevi, which continue to appear throughout life. As will be discussed, people with dysplastic nevus syndrome also have far more nevi than do most individuals in the general population. (Greene, 1984).

G. CHRONIC ULTRAVIOLET RADIATION EFFECTS ON SKIN

1. NON-CANCER EFFECTS. To judge the effect of chronic ultraviolet radiation exposure on skin, examine the neck of male patients who engage in outdoor employment, and if they work fully clothed, compare the quality of skin on the neck with that of adjacent, more protected skin. Chronic sun exposure of human skin leads to the development of wrinkling, telangiectasia, a yellowish color, and a rough surface. These changes are reflected histopathologically by dense dermal deposits of a disorganized connective tissue which resembles elastic tissue, and these clinical and histopathological changes have been termed "elastosis". In association with the histopathologic changes produced by chronic ultraviolet light exposure, investigators have observed cellular alterations as well. Gilchrest has shown that fibroblasts taken from sites of elastosis have fewer cumulative population doublings than do those from unexposed sites (Gilchrest, 1980).

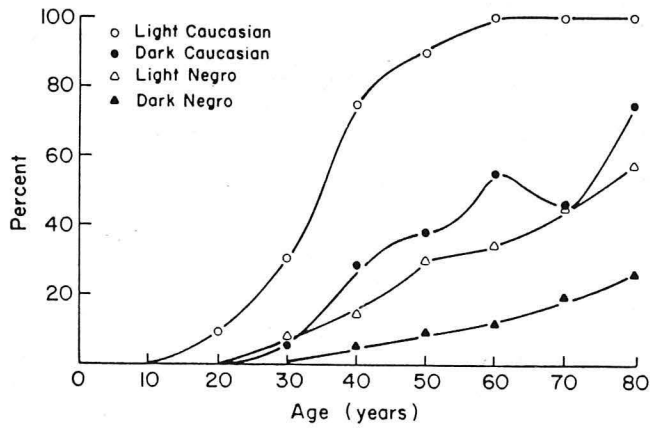


(Gilchrest, 1984)

In the experiments illustrated in the figure, Gilchrest determined the number of cumulative population doublings (C.P.D.) for fibroblast cultures established from sun-exposed (closed circles) compared with sun-protected (open circles) skin sites. In this matched pairs experiment, sun-protected sites exhibited invariably a larger number of skin fibroblast doublings, with intersecting regression lines at about 35 years of age.

The relationship among pigmentation, photoprotection and elastosis may be found in a study conducted by Kligman (1974) and summarized by Gilchrest (1984). In this study, skin specimens were taken from the unexposed (buttocks), partially exposed (legs), and fully exposed (forearm and cheeks) skin of Caucasian and Black subjects ranging in age from 17 to 91.

PREVALENCE OF ELASTOSIS (Gilchrest, 1984)



Data reported in the figure demonstrate the relatively rapid development of elastosis in Caucasians with small amounts of pigment, whereas Blacks with large amounts of pigment were spared, but not protected completely.

2. PREMALIGNANT CHANGES: ACTINIC KERATOSES. When examining sun damaged skin the most obvious change, aside from simple premature aging, is the development of scaling, red, and occasionally tender papules, termed actinic keratoses (Pinkus, 1979). These sun-induced lesions occur quite frequently, and they may be found on virtually all individuals with sun damage. Sun-exposed sites in some patients may be covered completely, and in Texas, actinic keratoses are epidemic. Actinic keratoses vary in color from pink to yellow, brown, or black, although individual lesions may be perceived more rapidly by palpation, since their surface texture is often rough and irregular. Common complaints by patients include progressive enlargement, bleeding,

especially after trauma, tenderness, and pain. Most important in the differential diagnosis are benign skin tumors such as seborrheic keratoses, flat warts, and melanocytic nevi. On the other hand, one must also exclude true squamous cell carcinomas as well. Seborrheic 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 speeds. Finally, melanocytic nevi rarely change in appearance during adulthood, they are never tender, and they do not bleed without significant trauma. Before one becomes cavalier, 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.

3. CLINICAL PRESENTATION OF NON-MELANOMA 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. 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 nearly 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 invariant) 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.

4. BASAL CELL CARCINOMA. The identifying terms basal cell carcinoma and squamous cell carcinoma were originally based on histopathological appearance of the predominant cell type within each tumor. As might be expected, since the cell of origin is the keratinocyte for both, intermediate forms and overlapping features may be found. Despite this, it has been most useful for dermatopathologists to continue this distinction since such histopathologic differences are reflected clinically.

Basal cell carcinomas 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 keratoses, there is an overwhelming predilection for sun damaged skin.

Histopathologically the primary cell type in basal cell carcinomas is a cell which resembles epidermal basal cells, with little evidence of maturational progression 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 dilate dermal vessels which are features recognized clinically.

5. SQUAMOUS CELL CARCINOMA. Squamous cell carcinomas are usually keratotic nodules or ulcers with wide indurated borders. Although these tumors are less common that basal cell carcinomas, 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 sun exposure. The differential diagnosis is similar to that of basal cell carcinomas.

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 cells. One observes frequently atypical cell size and morphology.

H. FAMILIAL DYSPLASTIC NEVUS SYNDROME

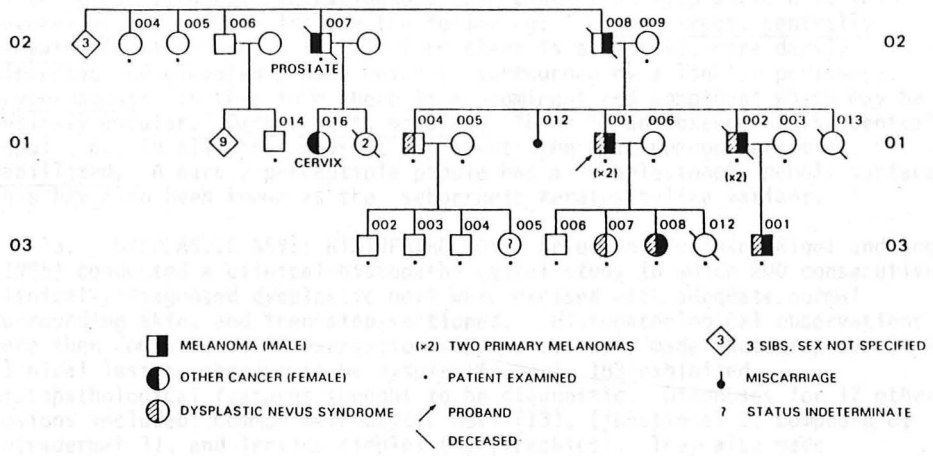
1. INTRODUCTION

The familial dysplastic nevus syndrome is an autosomal dominant disorder which is characterized by a high frequency of melanomas arising in pre-existing, atypical nevi. Affected patients have large numbers of nevi which are have an atypical clinical appearance (largely that of lack of uniformity), atypical clinical course (continuing evolution well past puberty, and atypical histologic features (melanocyte cellular dysplasia).

Within the last decade several groups of investigators became aware of a surprising number of kindreds which had a high frequency of malignant melanoma (Greene and Fraumeni, 1979). Two important observations were made by these investigators and by others: first, up to 6% of patients with malignant melanoma come from families with melanoma. Secondly, they observed that many of these patients displayed large numbers of distinctive, abnormal moles, as did other family members, even those without melanomas. Originally, this constellation of findings was identified by the term "B-K mole syndrome" (Clark, et al, 1978), and subsequently by a variety of terms, including: a. familial atypical multiple mole-melanoma syndrome, b. large atypical mole syndrome, c. activated melanocyte syndrome. Eventually, agreement was reached on the "dysplastic nevus syndrome" (Greene, et al, 1980).

Estimates for the number of patients with the familial dysplastic nevus syndrome within the United States range up to 30,000. Greene, et al (1983) examined 14 kindreds with the syndrome, demonstrating an autosomal dominant inheritance, with reduced penetrance. Linkage studies have suggested that the syndrome gene may be located on the short arm of chromosome 1, near the gene for Rh blood type (Greene et al., 1983). The typical pedigree of Family #1016 is listed in the figure taken from Kraemer and Greene (1985).

FAMILY #1016



DYSPLASTIC NEVUS SYNDROME (Kraemer & Greene, 1985)

2. DYSPLASTIC NEVI: CLINICAL FEATURES

Clinical features of dysplastic nevi differ considerably from those of melanocytic nevi, although even practiced dermatologists may have difficulty with certain lesions. As demonstrated in the table the majority of important features concern color, shape, size, and number.

CLINICAL FEATURES OF DYSPLASTIC NEVI

Color:	variegated tan, brown, pink, and black (focal) areas of depigmentation lesion-to-lesion variability
Shape:	irregular, with indistinct borders macular with central papule
Size:	greater than 6 mm
Number:	few to hundreds

Most important is the great irregularity in shape, size and color. There is also great irregularity in the appearance of nevi across the surface of the skin. With respect to surface distribution, virtually all surfaces may be involved, although the trunk is by far the most frequently affected site.

After considerable study and correlations between clinical and histological findings, investigators have classified dysplastic nevi into several groups. These include the following: Dark target, centrally elevated (most common): In this form there is a central, more darkly pigmented and elevated papule which is surrounded by a lighter periphery. Erythematous: In this form there is a prominent red component which may be entirely macular. Dark target, macular: There is an absence of the central papule, but in all other ways it represents the most common varieties. Papillated: A barely perceptible papule has a "cobblestone", pebbly surface. This has also been known as the seborrheic keratosis-like variant.

3. DYSPLASTIC NEVI: HISTOPATHOLOGY. Friedman, Heilman, Rigel and Kopf (1985) conducted a clinical-histopathological study in which 200 consecutive clinically diagnosed dysplastic nevi were excised with adequate normal surrounding skin, and then step-sectioned. Histopathological observations were then compared with observations from previously made photographs. Of 200 clinical lesions thought to be dysplastic nevi, 183 exhibited histopathological features thought to be diagnostic. Diagnoses for 17 other lesions included: common melanocytic nevi (13), (junctional 2; compound 8; intradermal 3), and lentigo simplex (4) (freckles). They also made observations concerning the histological appearance of these lesions. There was poor circumscription. Melanocytes within the epidermis were observed to extend both as single cells and as nests of cells beyond the major part of the nevus. They observed both lentiginous melanocytic dysplasia and epitheloid-cell melanocytic dysplasia. In the former the rete ridges were elongate and the melanocytes were seen replacing nearly all of the basilar keratinocytes. In the latter there are increased numbers of melanocytes, singly and in nests along the basal layer. With respect to the dermis, most dysplastic nevi had dermal elements which included nests, cords and strands of cells confined largely to the papillary dermis.

4. DYSPLASTIC NEVI: PATHOGENESIS. Kopf and his associates (1985) have attempted to establish a relationship between sun exposure and the development of nevocytic nevi in patients with the dysplastic nevus syndrome. They document rather conclusively in eighty patients with the dysplastic nevus syndrome that there are substantially more nevi in areas of higher sun exposure: back greater than anterior chest greater than lateral chest. Since they have no control population which did not receive sun exposure in any of the three areas, their conclusion cannot be assured.

5. DYSPLASTIC NEVI: MANAGEMENT. Management of melanoma-prone families and of patients with the dysplastic nevus syndrome includes the following recommendations (Kramen and Green, 1985).

a. Monthly self-examination of skin lesions (indefinitely)

b. Biannual examination by a dermatologist or other knowledgeable physician

c. Minimal sun exposure

d. Increased vigilance during times of hormone change: adolescence, pregnancy

e. Examination of all first degree relatives of patients with melanomas for the presence of the dysplastic nevus syndrome.

Prophylactic excision is not recommended except on the scalp where changes may be difficult to see. Otherwise, surgical, excisional biopsies are reserved for lesions which exhibit change.

An important additional precursor lesion which appears to be associated with the development of malignant melanoma is the congenital nevocytic nevus. The typical congenital nevus is a lesion present at birth, appearing as a mottled tan-brown macule, patch or plaque, with accentuated skin markings. Over time it becomes more hyperpigmented, its surface more irregular, and frequently hypertrichotic. Congenital nevocytic nevi exhibit great variation in size and shape, and may involve large areas of skin surface. Unfortunately, there is no unanimity in the literature concerning the frequency with which malignant melanomas arise from within such nevi. Reported incidences for malignant melanomas developing within giant congenital nevocytic nevi range from 2% to as high as 30% (Kopf, Bart, and Hennessey, 1979). The issue of whether to excise such lesions or even to excise small congenital nevi has not been resolved, although careful, periodic examination of the skin is clearly warranted.

I. MALIGNANT MELANOMA

1. INTRODUCTION

Malignant melanoma, which is the least frequent of the three ultraviolet radiation induced skin cancers, is by far the most aggressive. Although melanomas do not show a striking predilection for sun-exposed skin, there exists good epidemiologic evidence to support an important role for sunlight in the development of this malignancy of pigment-forming melanocytes.

It has been predicted that 500,000 new skin cancers would be diagnosed in 1985, with 22,000 (4%) of them being melanoma (Silverberg, 1984). The incidence of melanoma has increased over 1700 per cent in the last half century, with approximately one American in 185 developing malignant melanoma in their life (Kopf, Bart, and Rodriguez-Sains, 1979).

2. CLINICAL PRESENTATION

Melanomas occur in four distinct forms: lentigo maligna melanoma, superficial spreading melanoma, nodular melanoma and acral-lentiginous melanoma (Kopf et al, 1982). Ackerman (1979) contends that all four of these varieties may be unified under a single concept of cutaneous malignant melanoma although they provide a useful framework from which to describe clinical presentation and histogenesis.

Lentigo maligna melanoma occurs most often on sun-exposed skin of elderly individuals, most commonly on the face. It arises from an unusual precursor, the "lentigo maligna", which has been known as the Hutchinson's melanotic freckle. This precursor has the capacity to enlarge progressively for many years, reaching a diameter of up to 20 cm. Histologically one observes in the lentigo maligna a relatively large number of atypical melanocytes predominantly in the lower portions of the epidermis and often extending into follicular epithelium.

Superficial spreading melanoma, the most common melanoma, may occur almost anywhere on the body, but most commonly on the backs of men and on the legs of women.

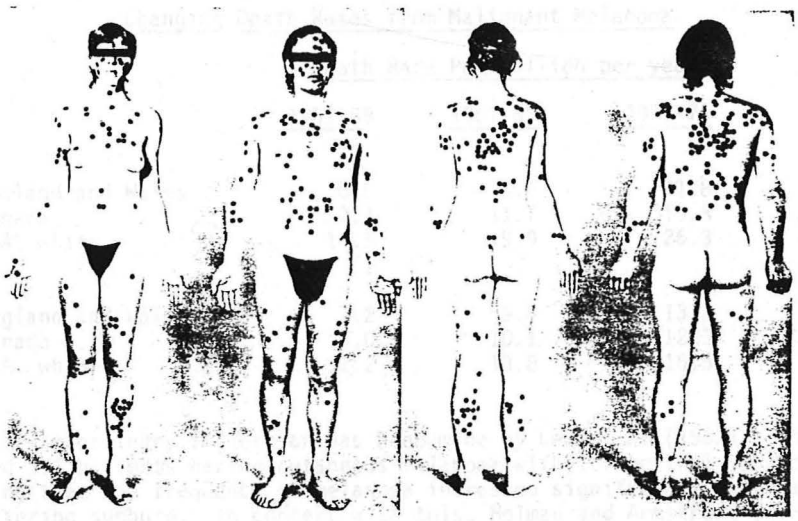


Fig. 1. Exhibition of localization of malignant melanoma in 534 males and females. From *Halocarbons*: Environmental Effects of Chlorofluoromethane Release (National Academy of Science. Washington 1976).

As with lentigo maligna melanoma, there is an invasive dermal component within a preexisting area of atypia. Histologically the superficial spreading melanoma shows proliferation of atypical melanocytes singly and in nests at all levels of the epidermis.

Nodular melanoma develops rapidly a vertical component. Histologically one observes penetration of melanoma into the dermis with minimal epidermal component.

Acral lentiginous melanoma. This form occurs on non-hair-bearing portions, primarily the soles, and palms, and is the most common type of melanoma in heavily pigmented individuals.

3. PATHOGENESIS

Lew, Koh and Sober (1985) have reviewed the epidemiology of melanoma. Between 1985 and 1970 the death rate from melanoma doubled and the incidence tripled (Lee, 1982). Although a variety of features have been proposed to be related, including oral contraceptive, estrogens, fluorescent lights, radiation, diets, and sun exposure. From among these, only ultraviolet radiation holds up consistently. Changes over the last 30 years may be seen in the data taken from their review (Lew, Koh and Sober, 1985).

Changing Death Rates from Malignant Melanoma

	Death Rate Per million per year		
	1951-55	1961-65	1971-75
Male:			
England and Wales	6.8	8.6	11.8
Canada	7.1	11.7	15.8
USA, white	14.5	19.9	26.3
Female:			
England and Wales	7.2	9.8	13.3
Canada	6.0	10.1	12.3
USA, white	11.2	13.8	16.5

An extraordinary suggestion has been made by Lew et al (1983). They compared 111 patients having cutaneous melanoma with 107 control subjects, observing that the frequency of melanoma increased significantly with a history of blistering sunburn. In concert with this, Holman and Armstrong (1983) compared 511 patients with 511 control subjects. From this they developed an odds ratio table for the development of melanoma according to the decade of excessive sun exposure. Note that the years 10 to 24 seem to be the most important.

Relationship of Malignant Melanoma to Natural Sunlight Exposure.

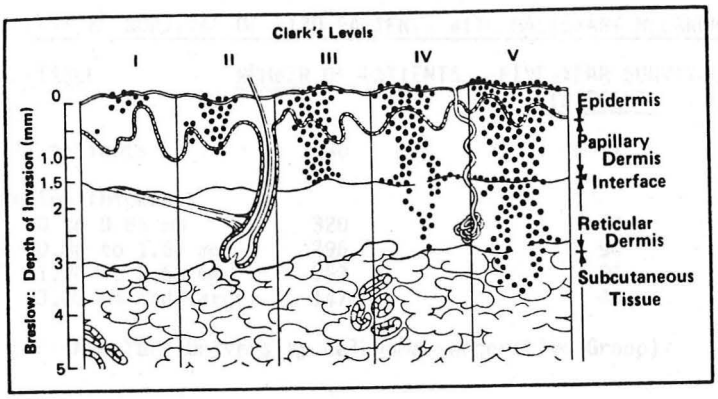
Parameter	Never Exposed to over 2800 hrs	Ages exposed to 2800 mean annual hours of bright sunlight				
No. Subjects		0-9	10-24	25-39	Above 40	Other
All Melanomas	(622)	(85)	(25)	(50)	(15)	(191)
odds ratio	1.00	1.42	2.47	2.16	0.99	1.68
Superficial Spreading M.						
odds ratio	1.00	1.06	11.31	3.40	0.99	1.42

(Holman and Armstrong, 1984)

4. INDICATORS OF PROGNOSIS

HISTOGENESIS. Current models hold that primary melanomas begin by a proliferation of melanocytes, presumably from a single clone of cells, within the lower portion of the epidermis. As each tumor progresses there is movement of malignant cells to higher levels of the epidermis, followed by the formation of nests of cells within the epidermis. At the same time additional malignant cells may be found in epidermal appendages such as hair follicles. Since these appendages are derived from epidermis, the tumor may still be defined as being limited to that structure. Clinically, such early lesions are seen as a pigmented macule. Each has a diameter of at least 6 mm; there is asymmetry with poor circumscription. As mentioned, the histological picture is that of atypical melanocytic hyperplasia with variation in the size and shape of nests of atypical melanocytes. This corresponds to the controversial Level I, in situ, melanoma.

HISTOPATHOLOGY. The first major advance in using histopathological observations to predict prognosis was developed by Clark and his associates. He observed that prognosis for malignant melanoma was largely related to the depth of invasion of the primary tumor at the time of first operation. The anatomical locations of the levels of skin are illustrated in the figure from Goldsmith (1978).



(Goldsmith, 1978)

MALIGNANT MELANOMA: Clark's Level of Penetration

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

Note as well from the figure that penetration into various parts of the dermis correspond to depths of penetration according to the system developed by Breslow.

Estimates of survival have been correlated with various clinical and histological factors as reported by the New York University Melanoma Cooperative Group (Rigel, Rogers and Friedman, 1985). These tables are useful in describing prognosis to either patients or physicians, and they are included without additional comment.

FIVE-YEAR SURVIVAL OF 1130 PATIENTS WITH MALIGNANT MELANOMA

VARIABLE	NUMBER OF PATIENTS	FIVE-YEAR SURVIVAL (PERCENT)
All patients	1130	87
Lesion thickness		
0 to 0.85 mm	320	99
0.86 to 1.69 mm	296	94
1.70 to 3.59 mm	253	81
3.60 mm and larger	147	49

(New York University Melanoma Cooperative Group)

FIVE-YEAR SURVIVAL OF 1130 PATIENTS WITH MALIGNANT MELANOMA

VARIABLE	NUMBER OF PATIENTS	FIVE-YEAR SURVIVAL (PERCENT)
All patients	1130	87
Level		
I	43	98
II	259	96
III	257	94
IV	457	78
V	51	44

(New York University Melanoma Cooperative Group)

FIVE-YEAR SURVIVAL OF 1130 PATIENTS WITH MALIGNANT MELANOMA

VARIABLE	NUMBER OF PATIENTS	FIVE-YEAR SURVIVAL (PERCENT)
All patients	1130	87
Stage		
I	1028	89
II	86	61
III	5	0

(New York University Melanoma Cooperative Group)

FIVE-YEAR SURVIVAL OF 1130 PATIENTS WITH MALIGNANT MELANOMA

VARIABLE	NUMBER OF PATIENTS	FIVE-YEAR SURVIVAL (PERCENT)
All patients	1130	87
Anatomic site		
Head and neck	168	82
Trunk	411	84
Upper extremity	195	94
Lower extremity	245	93
Acral	88	83

(New York University Melanoma Cooperative Group)

FIVE-YEAR SURVIVAL OF 1130 PATIENTS WITH MALIGNANT MELANOMA

VARIABLE	NUMBER OF PATIENTS	FIVE-YEAR SURVIVAL (PERCENT)
All patients	1130	87
Histologic type		
Lentigo maligna m.	43	92
Superficial spr. m.	802	91
Nodular m.	101	62
Acral lentiginous m.	35	79

(New York University Melanoma Cooperative Group)

FIVE-YEAR SURVIVAL OF 1130 PATIENTS WITH MALIGNANT MELANOMA

VARIABLE	NUMBER OF PATIENTS	FIVE-YEAR SURVIVAL (PERCENT)
All patients	1130	87
Sex		
Female	578	90
Male	550	84

(New York University Melanoma Cooperative Group)

FIVE-YEAR SURVIVAL OF 1130 PATIENTS WITH MALIGNANT MELANOMA

VARIABLE	NUMBER OF PATIENTS	FIVE-YEAR SURVIVAL (PERCENT)
All patients	1130	87
Associated nevus		
Present	188	95
Absent	638	85
Ulceration		
Present	188	71
Absent	792	91

(New York University Melanoma Cooperative Group)

5. THERAPY AND PHOTOPROTECTION

NON-MELANOMA. 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 treatise 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 or 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 (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 is the treatment of choice for large skin cancers, recurrent cancers, and those in locations which are difficult to reach. With this technique, serial excisions are examined microscopically for the adequacy of that excision. Under local anesthesia appropriate excisions are made with the tumor being traced out in one sitting. 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.

MALIGNANT MELANOMA: There is general agreement that surgical excision is the treatment of choice for malignant melanoma. Still under debate, however, are: 1) surgical margins for the primary tumor, and 2) excision of draining lymph nodes. Current experience suggests that for "thin" melanomas, generally less than 0.5 - 0.75 mm, conservative excisions with primary closures are appropriate. By contrast, metastatic spread is almost assured for lesions which measure more than 4.0 mm in thickness. Thus, the major debate usually concerns lesions of intermediate size. It is not within the scope of this review to address such issues, as they can only be approached by those who have invested considerable study and experience (Balch et al., 1979; Krementz et al., 1979).

PHOTOPROTECTION: For patients 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 ravages of excessive sun exposure. If your patients are convinced, as I hope you now are, that 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:

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

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

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

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

Photoprotection may be obtained by avoiding sun exposure during the middle of the day, wearing protective clothing, or by using one of the commercially available sun screens (SPF 15).

6. CONCLUSION

Ackerman has concluded that with appropriate inspection by well-informed physicians, no patients should die of malignant melanomas (Ackerman, 1985). He concludes that since only thick melanomas have an ominous prognosis, and since the color and morphologic changes are so typical, most physicians can be instructed in the evaluation of pigmented lesions.

J. GLOSSARY

MELANOCYTE: A cell of neuroectodermal origin which synthesizes the melanosome, a melanin-containing organelle.

MELANOSOME: A discrete, melanin-containing organelle in which melanization is complete.

MELANOPHORE: A type of melanocyte which has the capacity to displace its melanosomes rapidly, through aggregation and dispersion. These changes in melanosome dispersion produce equally rapid changes in skin color.

NEVUS: A malformation. The term nevus is frequently used to identify the most prominent skin malformation, the melanocytic nevus.

MELANOPHAGE: A tissue histiocyte which has phagocytized melanin. It may be confused with a melanin-containing melanocyte.

MELANOCYTIC NEVUS: A skin malformation in which the primary alteration is an accumulation of melanocytes.

FRECKLE: (ephelis) A hyperpigmented macule, ranging in size from pinpoint to 0.5 mm in diameter; they are acquired early in life. Histologically one observes increased amounts of epidermal melanin without increased numbers of melanocytes.

LENTIGO: A hyperpigmented macule, ranging in size from pinpoint to 0.5 mm in diameter; they are acquired by persons of middle and elderly age. Histologically one observes elongation of the of the epidermal rete ridges and a substantial increase in the number of epidermal melanocytes. Clinically a lentigo may be difficult to differentiate from freckles, junctional nevi, and seborrheic keratoses.

LENTIGO MALIGNA: (Melanosis circumscripta preblastoma of Dubreuilh) An irregularly pigmented macule that gradually extends peripherally. While progressing in some areas, it may show signs of regression in others. Arising usually in the elderly, it is seen commonly on sun-exposed areas, most often the face. It possesses increased numbers of atypical melanocytes in the basal layer. There is no tendency to form nests or to migrate into higher layers.

JUNCTIONAL NEVUS (MELANOCYTIC): Proliferative aggregate of apparently normal melanocytes which is confined to the epidermis.

DERMAL NEVUS (MELANOCYTIC): Proliferative aggregate of apparently normal melanocytes which is confined to the dermis.

COMPOUND NEVUS (MELANOCYTIC): Proliferative aggregate of apparently normal melanocytes which includes both epidermis and dermis.

MACULE: A circumscribed area of change in normal skin color without elevation of depression of the skin surface.

PAPULE: A solid, elevated skin lesion which is less than about 1 cm in diameter. Many papular eruptions tend to evolve into aggregates, creating confluent plaques.

NODULE: A single, solid, elevated deformation of the skin, most commonly involving a space-occupying deposition of cells within the dermis.

TUMOR: A large nodule.

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