On the Causes of Melanomas

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A large number of factors have been identified which seem to predispose an individual to develop melanoma. Black-skinned individuals rarely have melanomas, but this variety of tumors is common in red-haired or blond subjects. The incidence of melanoma is particularly high if such fair-skinned subjects are exposed for long periods of time to intense sunlight. Nevi, congenital or acquired, can degenerate into melanomas. In some families, many of the family members develop multiple nevi that are unusually large and red in color. All of these appear to degenerate into melanomas with time. Nature has provided other examples of genetic factors which induce melanomas, i.e., the melanomas which form in the platyfish and Sinclair miniature swine. (Am J Pathol 89:443–448, 1977)

THOSE SPECIAL CHARACTERISTICS of a tissue or organ which presage the development of a malignancy are important clues for the biologist investigating the cancer process. Practically, such signs can alert physicians and patients about potentially dangerous conditions for which prompt and appropriate therapy may prolong the patient's life. For many forms of cancer, specific biochemical, cytologic, or chromosomal aberrations have been identified which foretell the beginning of a cancer. A few specific markers are known to herald the formation of a melanoma in an individual. Other less specific factors such as skin color, pigmented skin lesions, and some inherited traits identify large sections of the human population as more liable to develop melanomas than others. Each of these factors, e.g., skin color, nevi, etc., may be considered a preneoplastic condition.[1]

Skin Color, Synthesis of Melanin, and Sunlight

Black and white individuals have equal number of pigment cells within their skin. The color of a person's skin depends upon the capacity of his pigment cells, i.e., melanocytes, to synthesize and transfer melanin into keratinocytes. Anyone can develop a melanoma. In general those patients with fair complexions, blue eyes, red or blond hair, and freckles, i.e., those persons whose cells synthesize melanin most slowly, such as Celts and

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Scandinavians, are most liable to have a melanoma.[2,3] Blacks rarely have melanomas. The low capacity of patients with melanomas to produce melanin was dramatically documented in one clinical experiment. Four patients with metastatic melanomas were given melanocyte-stimulating hormone intramuscularly, 10 mg twice daily, for 2 months, and large doses of tyrosine, the substrate for melanin.

Dark-skinned individuals in a few days turn black with this treatment. After 2 months, the 4 patients with melanomas showed a barely detectable darkening of their skin color.[4] Celtic and Scandinavian patients have the highest incidence of melanomas, but blacks do develop them on the mucous membranes or on the sides of the palms and soles.[5] These latter tumors arise from preexisting pigmented spots which probably are junctional nevi. Even in the blackest individual the mucous membranes, the palms, soles, and the nevi in these areas are lightly pigmented. All of these observations link the cell's ability to synthesize melanin in some fashion to susceptibility to malignant degeneration.

Sunlight may be one of the missing links between skin color and melanomas. The ultraviolet spectrum of sunlight, 290 to 320 nm, causes sunburn. This spectrum is most effective in inducing melanin production i.e., tanning, but also in producing skin cancers. Patients who produce melanin poorly (tan poorly) sunburn easily and develop frequently basal and squamous cell carcinomas [6] or occasionally a melanoma.[7] Most skin cancers (including melanomas), because they are induced by sunlight, are found on sun-exposed skin: the face, the backs of men, and the calves of women. The incidence of melanoma in the United States has doubled during the last 10 years, from one to two melanomas per 100,000 subjects, a trend which is consistent with the increased exposure of citizens during recreation—on boats, at the beach, on Caribbean vacations—to intense sunlight. Patients with xeroderma pigmentosum suffer the ravages of sunlight because their cells are unable to repair the alterations in their chromosomes caused by ultraviolet light. Although squamous and basal cell cancers are the most common tumor found on these patients, the subjects most frequently die from metastatic melanomas.[9] In Australia, melanomas are endemic among the immigrant red-haired Celtic population but are rare among the very black aborigines. The incidence near the Australian equator, where the sunlight is intense, is four to five times higher than at the distant latitudes near the Antarctic.[10,11] In the United States, the southern-most states near to or bordering the Gulf of Mexico have a disproportionately high incidence of melanomas.[11] But the correlation of melanomas with latitude and sunlight is found only among Caucasians. Melanomas in blacks tend to be randomly distributed throughout the United States.[8,12,13] Experimentally, melanomas can be induced in

mice with ultraviolet light and a chemical carcinogen, 7,12-dimethylbenz[α]anthracene (DMBA).[14]

The precise role that ultraviolet light plays in causing melanomas is not known, but the relationship is hard to ignore. The most obvious explanation for the association suggests that the melanin of dark-skinned patients acts as a sunscreen to protect the cells from the carcinogenic affects of ultraviolet light. On the other hand, the low ability of some pigment cells to synthesize melanin in some fashion may cause these cells to be biologically more susceptible to the effects of carcinogenic agents. A third hypothesis which we believe is the most attractive suggests that the inflammatory events in the skin which are induced by sunburn and which tend to be more severe in fair-skinned subjects in some way act as promoters for some other viral or chemical carcinogens.[15]

Pigmented Lesions on the Skin

Pigmented spots found on the skin have a varied histologic appearance, e.g., freckles, lentigines, blue nevi, or pigment cell nevi. A nevus is a benign neoplastic growth of any tissue within the skin. Pigment cell nevi can be *congenital*, present at birth; others are *acquired*, appearing a few months postpartum. Only 3% of the population is actually born with a pigmented lesion. Many of these begin as lentigenes but later acquire a histologic appearance which is distinct from that of acquired nevi.[16] Most pigment cell nevi arise after birth, i.e., are acquired.

Acquired nevi begin as theques or nests of pigmented cells confined to the epidermis. Gradually the cells move to or are replaced by other nevus cells in dermis. Only those nevi with melanocytes in the epidermis, i.e., junctional or compound nevi, are capable of malignant degeneration. It has been said that 50% of the melanomas arise out of a preexisting nevus and that each person has twenty to thirty such nevi. If the incidence of melanomas is 1 to 2 per 100,000 persons, then one can calculate that one of 5 to 10 million moles becomes a melanoma. But the significance of this data is questionable. The most easily observed pigment cell nevi are dermal nevi which are large and pedunculated but which are not precancerous. The junctional nevi which occasionally form a melanoma are flat and often less than 1 mm in diameter. The number of junctional nevi per person is the critical factor but is almost impossible to ascertain with accuracy. Moreover, this type of calculation presumes that a benign mole undergoes a carcinogenic transformation after it is clinically visible. However, some cells within these nevi could be cancerous prior to the clinical appearance of the mole on the skin. The malignant cells could lie dormant until activated by some environmental stimulus such as sunlight or sunburn.

Congenital pigment cell nevi can be very large, covering much of the integument, i.e., bathing trunk nevus. Most physicians agree that the probability of the melanoma arising from this type of nevus is very high, somewhere between 4 and 30%. When feasible, such nevi should be excised *in toto* prophylactically.[17] Fortunately, most congenital nevi are only a few centimeters in diameter. What is their potential for malignant transformation? The answer is unknown, although we have observed melanomas arising in several such smaller lesions.[4,18] One may hypothesize that the incidence of melanomas in very large congenital nevi is high only because the number of pigment cells which are available as targets for a carcinogen is so great. If this is true, then small congenital nevi have a less urgent need for prophylactic removal. On the other hand, the cells of all congenital nevi may have an inherent propensity for malignant degeneration. It is known that mitosis makes cells more susceptible to the effects of carcinogens but also is needed for expression of malignant transformation. To produce the number of pigment cells in a congenital nevus, large or small, a clone of cells must undergo repeated cell division during which malignant transformation may take place.

A lentigo maligna is a classic preneoplastic lesion which occurs in elderly patients in the eighth or ninth decade of life. Typically, the lesions are absolutely flat and have black advancing borders and gray or white regressing edges. On microscopic examination of biopsy sections, malignant melanocytes are visible invading the epidermis, e.g., a melanoma *in situ*. The cells usually remain confined to the epidermis for years. Eventually they will break through the epidermal basement membrane, forming a nodular lesion, clinically termed a *lentigo maligna melanoma*. If not treated, ultimately the cells metastasize to local and distal lymph nodes. Lentigo maligna occurs exclusively in sun-exposed areas of skin in patients with white complexions. These lesions have biologic similarity to another sun-induced cancer, i.e., squamous cell carcinoma arising in an actinic keratosis. Sun-induced malignancies are biologically rather nonaggressive and carry an excellent prognosis for longevity, in contrast to the nodular melanoma or squamous carcinoma arising on the genitalia, both very malignant tumors with high mortality rates.

Inherited Traits

Finally, the genetic constitution of an individual can be an important factor in causation of melanomas. Two animal models illustrate very well the effect of gene interaction on induction of melanomas. Two varieties of fish, the platyfish and the swordtail, make their habitats side by side in the

rivers of Central and South America.[19] In nature they apparently never interbreed. In the laboratory interbreeding can be forced. Platyfish have a pigment cell, the macromelanophore, which exhibits many different patterns of distribution and function. In their natural habitat, platyfish display a wide variety of normal color patterns. Several genes control the anatomic distribution of macromelanophores. One gene is a tumor gene. The platyfish possesses other regulatory genes which are responsible for control of this tumor gene. In contrast, swordtails have no macromelanophores and no regulatory genes. By cross-breeding the two species, the tumor gene can be separated from some of the regulatory genes, causing an imbalance among the genetic controls. The imbalance of genes produces malignant melanomas which destroy their host.[19]

The Sinclair mini-swine exhibit a variety of flat pigmented spots and black tumors on the skin. Some of these are present at birth.[20] Some melanomas arise after birth from normal skin, others from the pigmented spots. Not all pigmented spots turn into cancers. But the black tumors are malignant melanomas which are capable of metastasizing and killing the host. At least one dominant gene determines whether an animal will have a melanoma. Undoubtedly several other genes must interact with it to produce the combination of tumors and pigmented spots observed in the animals.

Many members of a few human lineages develop melanomas.[21,22] On occasion two siblings develop melanomas on identical areas of skin.[23] Dr. Wallace Clark and Dr. M. Green of Temple University, in cooperation with Dr. Reimer and Dr. Ainsworth of the Epidemiology Branch of the National Cancer Institute and others, have described a most interesting syndrome, the B-K nevus syndrome.[24] The descendants of two families, which have an ancestor in common, have peculiar nevi. The nevi are exceptionally large, greater than 1.5 cm, and have irregular coloring, irregular borders, and a reddish hue. The reddish hue is from neoproliferation of capillaries within the lesion and increased blood flow. Many areas of the lesions on examination of biopsies are similar to compound nevi. In other areas, one finds a proliferation of capillaries, a dense lymphocytic infiltrate, and a nest of very atypical pigment cells. The lesions evolve with time into invasive melanomas. Inheritance pattern for these nevi-melanomas is thought to be autosomal dominant.

In summary: Many factors are known which predispose a patient to develop a melanoma. At least the knowledge of these factors can aid the physician in counseling his patients about exposure to sunlight and the care of pigmented lesions. In our laboratories, we are using some of the facts as a basis for our research.

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