

REVIEW ARTICLES

Two Rare Manifestations of Melanomas: Generalized Cutaneous Melanosis and Rapid Solar Induction of Showers of Small Pigmented Lesions

A Critical Review of the Literature and Presentation of Two Additional Cases

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Two unusual patients with metastatic melanoma are presented. One had generalized melanosis, and the other a rapid induction of multiple small pigmented lesions within a day of exposure to the sun. From a variety of clinical observations on these 2 patients and ones reported in the literature, and from recent advances in basic biomedical knowledge, we conclude that in both conditions the anomalous presence of growth factors that stimulate the proliferation and melanogenic differentiation of normal and malignant melanocytes played a major role in producing the clinical events. Key word: Epidermal melanocytic hyperplasia.

(Accepted January 4, 1993.)

Acta Derm Venereol (Stockh) 1993; 73: 241–250.

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Even though only 1.3% of deaths from cancer come from melanomas (1), there is special interest in this malignancy: the incidence of melanomas keeps rising, so that by the year 2000 the life-time risk is estimated at 1:75 (2); because melanoma cells readily evoke an immune response, they are used in studies of tumor immunology (3); metastatic lesions may regress after immune-enhancing therapy (4); spontaneous cures of patients with advanced disease have been reported (5); the relationship of vitiligo to melanomas is of prognostic significance (6); melanocytes in certain types of nevi are pre-disposed to transformation (7, 8).

We here discuss two rare conditions that occur in patients with melanomas: generalized melanosis, and the sudden appearance of multiple pigmented lesions. The two conditions may seem far apart, similar only because they are so striking, but the discussion of one leads to the other. They may share important basic features.

MELANOSIS

At least 41 cases of melanosis secondary to melanoma have been reported (9–42). Because the condition is so rare, most publications are on one patient only. In 1864 a German pathologist, Ernst Wagner, described a man in his thirties who had developed a melanoma in a congenital nevus and subsequently acquired a generalized uniformly bluish-gray discoloration (9). Wagner's paper may be the first on this subject. A second report appeared in *The Philadelphia Medical Times* of October 6, 1883, concerning notes by a correspondent from Cincinnati with the initials A.B.T. (10). The correspondent mentioned that a

Dr. W. H. Falls had seen a patient who "turned absolutely black before dying" from a melanoma. An elegant clinical case report by J. Wickham Legg, M.D., entitled "Multiple Melanotic Sarcomata Beginning in the Choroid Followed by Pigmentation of the Skin of the Face and Hands" appeared in the *Transactions of the Pathological Society of London* in 1884 (11). Legg described a 59-year-old shoemaker who had a primary ocular melanoma that was followed by numerous metastases. The patient developed uniformly intense darkening of the face, neck, and hands and less intense hyperpigmentation over the rest of his body. The darkening was noted to be similar to that seen in people who had ingested silver nitrate. A drawing of the patient was included in the paper and is reproduced in Fig. 1. Our patient and his healthy daughter are shown in Fig. 2, and a scheme illustrating the physical basis for the altered skin color in melanosis is given in Fig. 3.

Our Case 1

In 1977 a 57-year-old salesman for a chemical company became aware of a 1-cm² ovoid brown nevus beneath his right nipple. Two years later he noticed a pinkish discoloration of the lesion, an enlargement by several millimeters, and also an increase in height but no ulceration, bleeding, or itching.

Histological examination showed a Clark level IV superficial spreading melanoma, 3.5 mm thick. Extensive surgery followed and included a right axillary resection. One of the 22 lymph nodes examined was positive. For 18 months, beginning in 1982, he received dacarbazine (DTIC) and BCG, and later interferon α -2.

This man had a variety of medical problems, among them hepatitis in 1944, diabetes from 1976, a meningioma, removed in 1979, and several squamous-cell carcinomas, excised from his chest and forehead in 1981.

There was no family history of melanomas. The patient was by nature fair-complexioned, with dark-blond hair that had turned gray, and pale blue eyes. As a boating enthusiast he had significant exposure to the sun and had suffered several severe sun burns. Early in 1983 he developed diffuse hyperpigmentation of the skin (Fig. 2) and darkening of the urine. His hair assumed its original color. The cutaneous hyperpigmentation was particularly startling in the sunexposed areas, where it resembled a deep natural tan, setting off his light blue eyes. On his return from a brief, sunfilled vacation in Mexico, he had become almost black. He died 2 weeks later on May 31, 1983. An autopsy was not obtained.

Electron microscopy: The number, size and distribution of melanosomes in the epidermis resembled those of a naturally brunette and sun-tanned person (Fig. 4). The basal keratinocytes contained mostly singly dispersed, large, morphologically normal and fully melanized eumelanosomes, many of which survived into the spinous layer and stratum corneum. In some places, intercellular spaces in the stratum basale were packed with extracellular granular material (EGM) of the kind seen in the normally pigmented epidermis of patients with vitiligo (Fig. 4, inset) (43).

The ratio of melanocytes to basal keratinocytes was equal to or greater than 1:4 (normal ratio 1:10 to 1:30). Many pigment cells had double nuclear profiles that denote the presence of multiple or seg-

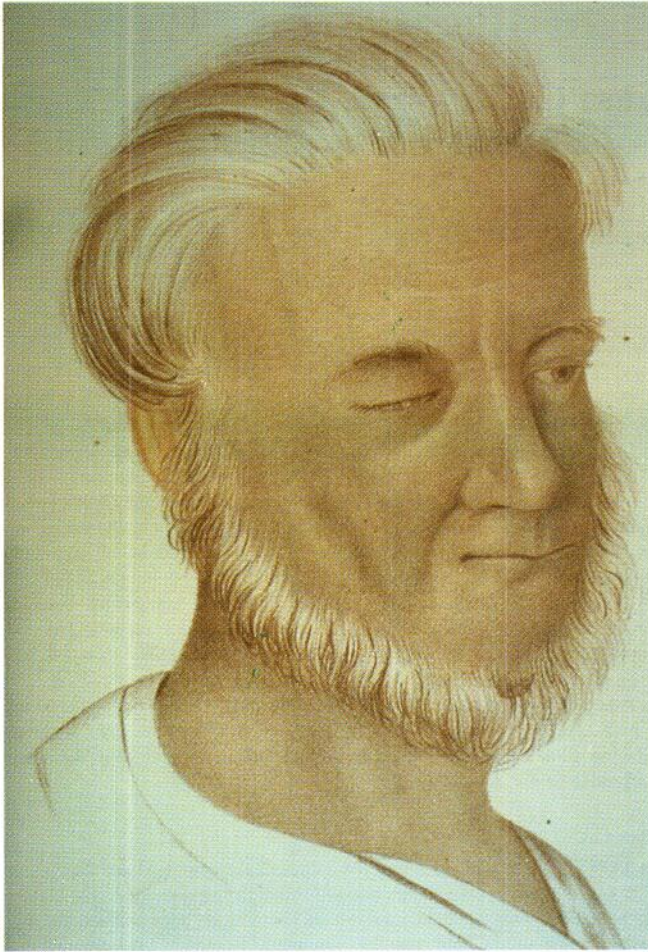


Fig. 1. Historical case of melanosis. This drawing by T. Godart in 1884 is of a patient who developed generalized melanosis following metastasis from an ocular melanoma.

Fig. 2. Our case 1. The patient is shown with his daughter. Before he developed the melanosis, his skin coloring was similar to hers and his hair gray. Note the contrast between his pale blue eyes and darkened skin; he previously did not tan.

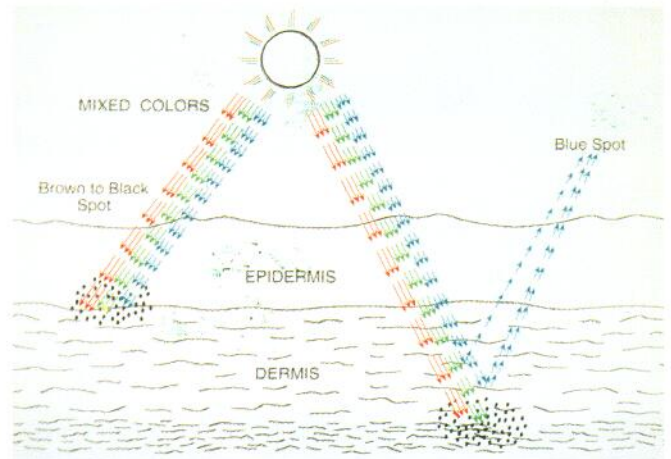


Fig. 3. The physical basis for the altered skin color in melanosis. Brown color (left): When melanin is located within the epidermis or immediately beneath the basement membrane, the skin appears brown to black depending on the amount of eumelanin present and therefore the amount of light absorbed. Eumelanin absorbs light of all wavelengths. Blue color (right): When the bulk of the melanin is located more deeply, e.g. in the reticular layer of the dermis as in a deep congenital nevus, much of the higher-energy, shorter-wavelength (blue) light is scattered by colloidal components of the papillary dermis before having a chance to be absorbed by the melanin, and some is reflected back to the surface. Hence, melanin deep in the dermis causes the skin to look blue.

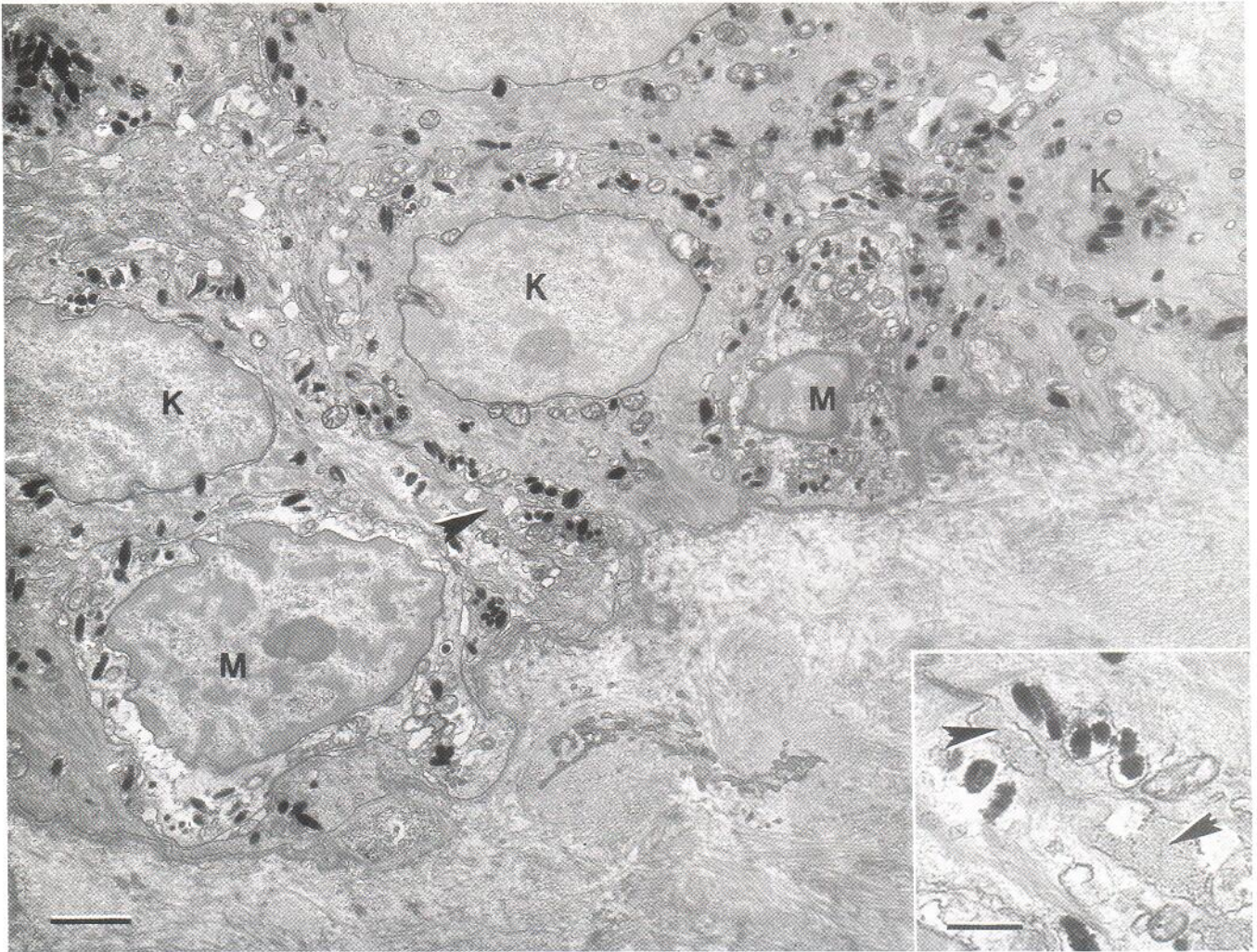


Fig. 4. Electron micrograph, basal epidermis case 1. Shown is a sample from an abdominal skin biopsy specimen taken 10 days before the patient expired. Letters indicate nuclei of melanocytes (M) and keratinocytes (K). Arrowheads = extracellular granular material (EGM) (scale bar = 0.5 μ m). Inset: Higher magnification of EGM (scale bar = 1 μ m).

mented nuclei. All melanocytes were "turned on" to produce melanin. Not a single "pale" melanocyte, characteristic of this patient's original complexion, was found. There were no intermediate- or high-level pigment cells or nests of melanocytes that suggested metastasis to the epidermis.

Melanophages were abundant in the papillary dermis and more deeply along microvascular channels. They contained melanosomes in addition to structureless electron-dense debris. Despite an extensive search, no pigment-producing cells or suspiciously malignant-looking amelanotic ones were identified in the dermis.

MULTIPLE SMALL CUTANEOUS MELANOMAS

In the one remarkable paragraph of the report from Cincinnati in 1883 by the correspondent "A.B.T." (10), mentioning Dr. Falls' patient with melanosis, a second "similar case" of a Dr. Thomson is described, in regard to which, however, no direct comment is made about a generalized melanosis. Instead, this patient, a 57-year old male, had developed "small diffuse tumors from the size of a pea to that of an almond - they are dark in color and pretty well distributed over the whole of the surface of the body, numbering 561 in all, 232 being attached to the skin". In 1930, Way & Light published a case report entitled "Generalized Melanosis" (44). Here too, no comment was made of a uniform background darkening of the skin. Instead, the patient, a 66-year-old woman with melanoma and melanuria, was "deeply pigmented with various sized macules, papules and nodules

which covered the entire body". These discrete lesions "were present by the hundreds on the face, arms, legs, chest, back, buttocks, palms, soles, nail beds, ears, conjunctiva, eyelids, cheek, palate, tongue and mucous membranes".

Our Case 2

Within 24 h after a hefty exposure to the sun during a boating excursion, a healthy 55-year-old male of very light complexion and blue eyes developed numerous small pigmented spots on the upper part of his trunk and on the scalp. When seen 3 weeks later in June of 1988, he had more than 200 minute black spots, 2 mm or less in diameter (Fig. 5). Some of the lesions showed central crusting, others an erythematous rim. The lesions appeared to be angiokeratomas or lentiginosities but were, on histopathological examination of two samples, diagnosed as metastatic melanomas extending from the papillary into the reticular dermis and focally infiltrating the epidermis without pagetoid spread. A primary lesion was never found. A dysplastic nevus, excised in 1986, had turned out to be just that.

Over the next few months of immuno- and chemotherapy, including cis-platinum and DTIC, the smallest pigmented spots disappeared, and others were reduced to dermal melanosis in macrophages without evidence of tumor cells. In December 1988, two additional lesions were removed and found to be metastatic melanomas. During early 1989, the patient participated in a vaccination program with BCG while remaining in good general health. He continued to harbor numerous pigmented nevi over his body surface as well as a few mildly



Fig. 5. Our case 2. Frontal photograph of chest showing miliary distribution of small skin tumors elicited by direct exposure of the skin to the sun. Inset: Enlarged area from left midsternal margin. Note that some tumors look like petechiae; others resemble melanocytic nevi.

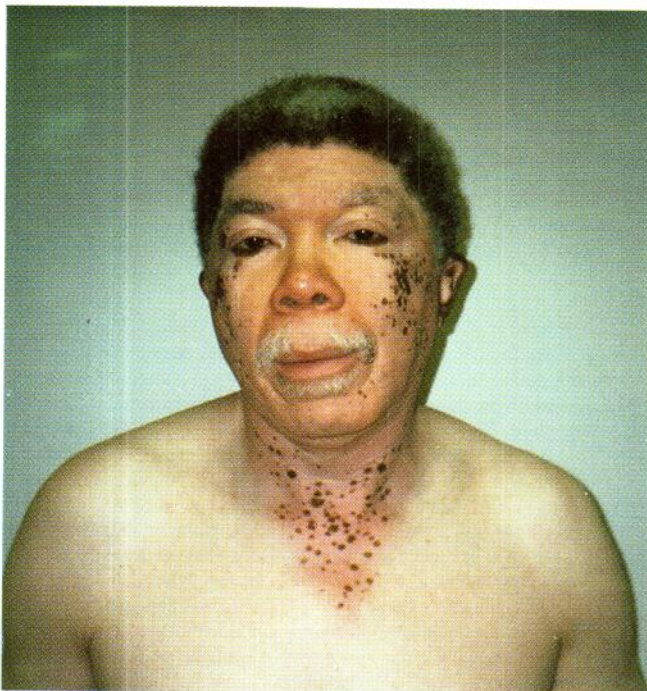


Fig. 6. The effect of light on the proliferative and melanogenic behavior of pigment cells. (A) This man with vitiligo was totally depigmented by topical applications of monobenzylether of hydroquinone (Benzoquin) but developed spots of repigmentation following exposure to sunlight. (B) A young African tyrosinase-positive albino shows focal activity of melanocytes in light-exposed areas. (Photograph courtesy of Dr. Richard King, the University of Minnesota.)

Table I. Frequency of reported metastatic organ involvement in 30 patients with cutaneous melanosis

(9, 11, 12, 15-25, 27-33, 36-42)^a

Liver		xxxxxxxxxxxxxxxxxxxxxxxxxxxx
Skin	o ^b	xxxxxxxxxxxxxxxxxxxxxxxxxxxx
Lymph nodes		xxxxxxxxxxxxxxxxxxxxxxxxxxxx
Spleen		xxxxxxxxxxxxxxxxxxxxxxxxxxxx
Heart	o	xxxxxxxxxxxxxxxx
Kidney	o	xxxxxxxxxxxxxxxx
Bone marrow		xxxxxxxxxxxxxxxx
GI tract		xxxxxxxxxxxxxxxx
Adrenal	o	xxxxxxxxxxxx
Skeletal muscle	o	xxxxxxxxxxxx
Lung	o	xxxxxxxxxx
Brain	o	xxxxxxxxxx
Ovary		xxxxxx
Pancreas		xxxxxx
Meninges		xxxxx
Pleura		xxxxx
Thyroid		xxxxx
Peritoneum		xxx
Breast		xx
Hypopharynx		xx
Testis		xx
Urinary bladder	o	xx
Uterus	o	xx
Miscellaneous ^c		x

^a Data slightly underrepresentative because five of the authors failed to break down the "widespread internal metastases" by organ site.^b Cases of widespread metastasis despite absence at indicated site.^c Single incidences of metastasis to adenohypophysis, bronchus, conjunctiva, epididymis, eyeball, larynx, mediastinum, placental villi, spinal cord, trachea, ureter, vagina, viscera.

suspicious new lesions, two of which were excised on June 1, 1989, and found to be metastatic melanomas. On June 12, 1989, the patient was hospitalized because of sudden-onset subacute dementia, ataxia, and headache. The spinal fluid contained melanoma cells. Diagnosis was

Table II. Patients with showers of metastatic spots

Reference	Number of cutaneous metastases	Generalized melanosis
Dixon (18)	>50 from photo	+
Pack (23)	Innumerable	+
Fitzpatrick (24)	Numerous	+
Goodall (27)	Numerous	+
Steiner (42)	Multiple (photo: >100)	+
Thomson (A.B.T.) (10)	>500	? ^a
Way (44)	Hundreds	?
Warner (49) ^b	Myriad	?
Kahn (50) ^c	>100	?
Marschall (47)	>50	o ^d
Bergfeld (48) ^b	>100	o
Our case 2	>200	o

^a No mention of an underlying melanosis.^b The authors initially considered their patients to have multiple primary melanomas but later changed their views and suggested that the patients had multiple metastases.^c The authors considered the patient to have over 100 primary melanomas, not metastatic lesions.^d Absent.

melanoma carcinomatosis of the meninges. He died on August 2, 1989, without having developed an interlesional generalized cutaneous melanosis. An autopsy was not obtained.

DISCUSSION

Generalized cutaneous melanosis

Including our case 1, the 42 reported patients comprise 20 males, 14 females, and 8 whose sex was not recorded. The range in age of the women was 20-67 years (mean 40, median 41) and for the men 31-70 (mean 50, median 49). Three women were pregnant (23, 32, 39). All patients had widespread metastatic disease (Table I). Some had spectacular showers of hundreds of cutaneous metastases that ranged in size from less than 1 mm² to larger than 1 cm² (Table II). In nearly all patients, light-exposed areas were considerably darker than the covered parts, and a diminishing cephalo-caudal gradient of the melanosis has been noted that may be independent of sun exposure. The conjunctiva and oral mucosa may be involved, and even the hair may darken, as in our case 1. The melanosis also affects internal epithelia and connective tissues. The urine is usually black or turns black on exposure to air and light. Not one patient was reported to have vitiligo.

The location of the primary lesions varied. In at least 7, perhaps 10, of the 35 patients for whom attempts of identifying the site of origin of the melanoma were reported (including our case 1), the malignant transformation had occurred in congenital nevi (9, 15/16, 20, 21, 27, 28/29, 38; 17, 22, 24), none larger than 5-7 cm in its broadest dimension. Two, perhaps 4, patients had unknown primaries (36, 41; 34). In the 2 questionable ones, the disease was said to have arisen in one or both adrenal glands (34). Only one patient had a primary melanoma of the eye (11). In the remaining cases, the melanoma had developed in an acquired nevus or independently of an existing melanocytic lesion.

At least half of the authors reported histological observations in the skin, including ultrastructure (28, 30, 31, 36-40, 42). The findings, summarized in Table III, can be divided into two groups according to the location of the excess pigment: dermal alone and dermal plus epidermal. Dermal pigment is the hallmark of all melanoma-associated cases of cutaneous melanosis and the cause of the blue hue (Fig. 3) (45). The pigment is primarily in macrophages, especially those located in the vicinity of microvessels. In addition, melanin may be found free among the connective tissue fibers, as part of cellular debris, or in dermal fibroblasts, endothelial cells, and disseminated melanoma cells when such are present. Melanoma cells have been noted singly or in microscopic tumors in the dermis and in the lumina of dermal blood and lymphatic capillaries.

Increases in epidermal pigment are not as universal. When present, they are seen predominantly in the keratinocytes of the stratum basale, and the skin color tends toward brown or black (Table III, Fig. 3). The appearance is that of a normal epidermis, albeit one more darkly pigmented than would be expected on the basis of genetic skin type. Melanocytes may or may not appear to be "turned on" to produce more melanin. Even where turned on, they have been reported as normal in

Table III. Localization of pigment in cutaneous melanosis

Reference	Dermis				Epidermis					Color of skin	
	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>e</i>	<i>f</i>	<i>g</i>	<i>h</i>	<i>i</i>		
Schuler (37)	+	+	+	+	○						Slate-blue
Eldar (36)	+	+	+	○	○					○	Slate-blue
Wagner (9)	+	+			○						Bluish-gray
Albertini (15)	+		+		○						Grayish-bronzed
Fitzpatrick (24)	+	+			○	○					Slate-gray
Geerts (30)	+	+	+	○	○	○		○			Slate-gray
Sexton (41)	+	+		○	○						Slate-gray
Steiner (42)	+		+	○	○						Slate-blue
Holcomb (32)	+										Grayish-blue
Rorsman (40)	+										Blue-gray
Goodall (27)	+	+									Dusky-gray
Adrian (38)	+	○	+	○	+	+	+	○			Blue-gray
Legg (11)							+				As in argyria
Gebhart (39)	+	○	+	○	+	○		○		○	Metallic bluish-black
Matsunaga (12)	+	○		○	+					○	Grayish-brown
Møller (25)	+				+						As in hemochromatosis
Konrad (31)	+	+	+	+	++	+		○		+	Gun-metal black
Silberberg (28)	++	++	+	○	++	+		○		○	Gray-black
Bork (33)	+	+	+	○	+	+		○		○	Black-brown
Odel (17)	++	+			+	+					Blue-black
Albeaux-F. (21)	++	+			++	○					Brown-black
Our case 1	+	+	○	○	++	++		++	○		Brown-black

a macrophages and fibroblasts

b interstitium

c microvasculature

d micrometastases

e basal keratinocytes

f generalized melanocytic hyperactivity

g patchy melanocytic hyperactivity near dermal metastases

h increased number of basal melanocytes

i micrometastases

+ = present; ++ = copious; ○ = absent

blank = no information/not applicable

number. Our patient, case 1, stands out among all others by having epidermal melanocytic hyperplasia. Only in one patient have epidermal melanoma cells been noted. These considerations, plus the fact that no pigment cell nests were found in the epidermis or dermis, have led us to conclude that in our patient the cutaneous melanosis was accentuated by a systemic activation of the epidermal melanocyte system, potentiated by sun exposure, and was not due to epidermotropic melanoma metastases.

Views on source and mechanism of deposition of pigment

In a hypothesis published in 1954, Fitzpatrick et al. suggested that the darkening in generalized melanosis in patients with melanomas was due to an increase of soluble precursors of melanin produced by the transformed, metastatic melanocytes (24). These intermediates would reach the circulation, be deposited in the skin and other tissues to produce the melanosis, or be excreted by the kidneys, darkening the urine. The Swedish group of Rorsman et al. made the more specific suggestion that trichochromes, and possibly also polymers containing 6-hydroxy-5-methoxyindole-2-carboxylic acid (40), are deposited in tissues and cause the melanosis (35, 46). Trichochromes are pheomelanin pigments formed from 5-S- and 2-S-cysteinyl-dopa and are markedly elevated in the sera of patients with generalized melanosis due to melanoma.

Silberberg et al. were the first to examine melanotic skin with an electron microscope (28). They determined that co-

pious amounts of pigment were present in particulate form and that the epidermal component of the melanosis in their patient was due to increased melanogenic activity in melanocytes, possibly assisted by epidermal cytostasis secondary to chemotherapy.

A hypothesis proposed in 1974/1980 by the Viennese group of Klaus Wolff suggested that the melanosis may be due in part to pigmented single-cell metastases in the dermis and/or epidermis (31, 37). Observations reported by others in subsequent cases carefully examined on this point are not consistent with this view (38-40, 42). However, without immunocytochemical studies of larger areas by light microscopy with melanoma-specific antibodies, microscopically intermittent wide-spread single-cell metastases cannot be ruled out.

To this day a satisfactory general explanation for the melanosis has not been found.

Development and incidence of the melanosis

The initially insidious discoloration is usually noted as slate blue, even cerulean blue (23), and is probably missed in many cases of widely disseminated metastatic melanoma. This early, bluish coloration is an indication that the melanosis begins in the deeper layers of the skin. Later, in those few patients who live to develop a full-blown melanosis, pigment deposition progresses rapidly until the patient is very dark at the time of death. Legg, more than a century ago (11), asked repeatedly whether or not his patient had ingested silver nitrate, because

this man looked as if he were afflicted with argyria. Nevertheless, some patients turn brown to black and do not have the bluish cast.

The incidence of noticeable melanosis in patients with metastatic melanoma is probably around 1–2%, a figure confirmed by Rorsman et al., who observed 3 cases in a group of 161 patients in Sweden (35). A truly striking melanosis would occur at a lower frequency. If one were to scrutinize any group of patients with extensive metastatic melanoma, one would find many who have a mild melanosis that is clearly distinguishable from jaundice. The almost universal metastasis to the liver can, however, produce a superimposed jaundice. Added to the melanosis from melanoma may be darkening secondary to adrenal insufficiency, as in Addison's disease, if the adrenal glands have been destroyed by metastases. Patients with adrenal insufficiency without melanoma do not have melanuria and their skin darkens to brown without developing a bluish hue.

In a few patients with melanosis there are, in addition, pigmented spots that resemble lentiginos, or small vascular lesions with the appearance of petechiae or purpura hemorrhagica. Such spots contain accumulations of pigment cells, perhaps primarily of metastatic origin but including non-malignant melanocytes as well (see further discussion below).

The nature of multiple pigmented lesions

Our second patient, case 2, developed a shower of small metastatic spots following exposure to the sun. He did not have a generalized melanosis, but the two conditions can occur together (Table II). For example, the melanosis patient of Steiner et al. developed multiple spots after extensive sun exposure (42). Marschall et al. presented their patient, who did not have melanosis and no stated history of sun exposure, in terms of cutaneous, in-transit metastases (47). Bergfeld et al. (48), Warner et al. (49), and Kahn & Donaldson (50) discussed their respective patients as having more than 100 primary melanomas. Two of the latter groups concluded that the lesions were, after all, metastatic (48, 49), but Kahn & Donaldson (50) suggested that an activating factor was involved in the appearance of what they perceived to be multiple primaries.

The role of growth factors and light

What turns on pigment cells so that the entire body becomes dark or hundreds of metastatic spots appear in the skin? How does sunlight play a role? Answers to these questions will come from the convergence of two distinct paths: one clinical, the other basic.

Clinical observations: For many years it has been known that some patients with melanomas have more than one primary (51). In addition, it has been shown that clinically normal nevi in some of the patients contain cells that are unusual and appear to be activated or possibly in an early stage of transformation.

In 1953 the pathologists Arthur Allen and Sophie Spitz made the point that:

"In view of the [...] tendency for melanomas to be associated with activation of junctional nevi in the skin of other parts of the body, it is no surprise to find some of these [patients] producing multiple tumors" (52). They continued: "A patient with a melanoma exhibits a diathesis for the activation of junctional nevi in various parts of the body, particularly in the vicinity of the primary tumor. This latter phenomenon is a contributory factor in local recurrences."

In 1966, the Danish plastic surgeon Grete Olsen stated that:

"The theory is then that the melanoma, which is known to be able to activate neighboring melanocytes, presumably by a chemical action, may give off such a noxa, which in certain cases may activate retarded melanocytes" (53). She went on to say: "If the theory that metastases do not contain junctional activity is to be maintained, it must mean that in these very metastasis-like cases there must have been an activation of melanocytes due to some chemical action. If this should prove correct, it would not be so surprising that normally situated melanocytes could also be activated."

A clinical study on activation of normal melanocytes in the presence of widespread melanomas was made by Rosai et al. and published in 1980 (54). The study showed that nevi in patients with melanoma may appear activated, and that these changes are most pronounced in the same lymph drainage region as the melanoma, suggesting a local activating factor. These nevi clearly were not metastases. Using the histocytologic criteria of activation set by Allen, Spitz, Ackerman and colleagues (52, 55), the authors listed marked junctional activity, lack of lateral margination of junctional melanocytic activity, and, to a lesser degree, increased pigment production, inflammation, mitotic activity, and cytoplasmic atypia.

Exposure to sunlight brought out or intensified the darkening of our patient, case 1, and many others with generalized melanosis. In our case 2 and the melanosis patient of Steiner et al. (42), both of whom developed multiple pigmented lesions in response to the sun, an obvious explanation would be that the spots represented pre-existing foci of hypomelanotic metastatic melanoma cells that were stimulated by sunlight to produce melanin, so that suddenly they became visible as discrete clinical lentiginos.

A more daring hypothesis would be that only partially transformed cells were present and that sunlight in these cases acted as promoter rather than carcinogen, completing the transformation so that the rapid proliferation of the cells into small clusters made them appear as metastatic dots. One wonders whether the two melanosis patients of Wolff et al. (31, 37), with wide-spread cutaneous single-cell "metastases", would fit into such a category.

This hypothesis is not as far-fetched or original as it may seem. Holman et al., in Australia, found that nevi excised in summer looked different from those excised in winter (56), having more junctional activity and eliciting a greater inflammatory response. The authors suggested that sunlight had a short-term promotional effect in the junctional zone and was responsible also for the greater incidence of melanomas in the summer. The proliferative fraction among nevus cells in sun-exposed versus non-exposed nevi, even in the dermal portions,

was significantly higher in summer than in winter (57). In addition, over the years in a person's life, melanocytes in the exposed parts of the body become modified so that they are more easily stimulated than those in the covered parts. Two drastic examples are shown in Fig. 6.

Basic studies: During the past few years, a vast literature has evolved on growth factors and signal transduction pathways, including those regulating the mitogenic activity in melanocytes. Basic fibroblast growth factor (bFGF) and certain other members of the FGF family of peptides are mitogens for pigment cells. Basic FGF in particular plays a major role in the activity of normal and malignant human melanocytes (58), and so may the endothelins (ET) (59, 60), especially ET-1 and ET-2. In addition, mast-cell growth factor (MGF), the ligand of c-Kit receptor tyrosine kinase, and hepatocyte growth factor (HGF), the ligand of Met tyrosine kinase, are peptides that stimulate melanocyte proliferation and differentiation (61).

There already exists an impressive list of actions of light on pigment cells from various sources. Ultraviolet B (UVB) radiation, a substantial short-wave length component of sunlight, is an important cutaneous pigmentation agent, acting on melanocytes directly (62), as well as indirectly via irradiated keratinocytes (63). Proliferation of human melanocytes *in vitro* depends on the synergistic action of at least two agents, e.g. bFGF plus cyclic AMP (58). UV light causes increases of bFGF and ET-1 in human keratinocytes (60, 63), and the light-induced dispersion of melanosomes in isolated frog melanophores is associated with an increase in cAMP (64). The stimulatory effect of UVB on the number of melanocytes in irradiated human skin is not only local but carries over to protected parts, the relative increase being greatest in individuals with low initial melanocyte density (65). These observations suggest that, on UVB irradiation, melanocyte growth factors are released locally and into the circulation, to act in a paracrine as well as endocrine mode.

Human melanocytes also release an array of cytokines, up-regulated significantly by UVB and by some neuropeptides including α -MSH (melanocyte stimulating hormone) (66). In the skin of hairless mice and guinea pigs, the combination of topical application of MSH and irradiation with UVB produces an increase in the number of melanogenically active melanocytes that is four times greater than the increase with UVB irradiation alone and forty times greater than with MSH alone (67). UVB also causes a two- to tenfold increase in the MSH-binding capacity of MSH-responsive murine melanoma cells (67).

The absence of vitiligo

The lack of vitiligo in patients with cutaneous melanosis is perplexing because it is not unusual to see patients with metastatic melanomas who have vitiligo or halo metastases, regardless of whether the primary lesion occurred in the skin or the eye (6, 68). The appearance of vitiligo before the detection of a melanoma, or immediately after a melanoma has been identified, tends to predict a long period of remission (6). However, when vitiligo develops years after the diagnosis of a melanoma has been made, the further course of the illness is usually rapidly downhill. One would expect patients with a

generalized melanosis especially ones with epidermal melanocytic hyperactivity, to develop vitiligo, because the intermediates of melanin synthesis are cytotoxic (69, 70). Some patients with hypermelanosis secondary to adrenal insufficiency, because of idiopathic atrophy or destruction by tuberculosis, do develop vitiligo (71). Also, vitiligo often occurs for the first time after a sunburn or at the end of a summer subsequent to an intense tan, i.e. following intense melanogenic activity.

One possible explanation for the absence of vitiligo in patients with melanosis due to melanomas is the rapid deterioration in general health. Invariably these patients die within a few months of the onset of the melanosis. Also, the putative mitogens or melanotropins that stimulate the proliferative and melanogenic functions of melanocytes may be able to counterbalance a vitiligo-like destruction of epidermal pigment cells. With respect to our case 1, this view is borne out by a combination of ultrastructural features that occur in vitiligo (43) and in chronically tanned, aged skin (72). The latter contains epidermal melanocytes with features quite similar to the ones described by Konrad & Wolff in melanoma-associated melanosis (31), and interpreted by these authors as evidence of epidermal micrometastases.

CONCLUSION

These clinical accounts from our own experience and that of others, viewed in the knowledge of recent advances made in the understanding of pigment cell growth factors, suggest that in some melanoma patients mitogens are released systemically to stimulate proliferation and melanogenesis in normal and transformed melanocytes alike and that the combined processes are potentiated by sunlight. Such mitogens (growth factors) should be identifiable in the sera of these patients.

ACKNOWLEDGMENTS

We thank Dr. Peter Heald for sharing his patient (case 2), and Elizabeth Kuklinska for help at the electron microscope. This work was supported by Public Health Service grant AR39869 and the Eleanor Naylor Dana Charitable Trust.

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