EVOLUTION IN THINKING

Criteria for Histopathologic Diagnosis of Melanoma, 1947–2000: A Critique in Historical Perspective

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Introduction

"... no significant changes in histologic criteria had occurred over time that would explain the rise in melanoma incidence." Rigel DS, Friedman RJ, Kopf AW et al. The incidence of malignant melanoma in the United States: Issues as we approach the 21st century. J A M A 1996;34:839–47.

Is the statement of Rigel, Friedman, and Kopf true? A reader should be able to decide on the basis of the evidence that follows.

Becker and Obermayer

"A primary cutaneous nodule of melanoma is composed of melanoblastic cells which are of two types: the spindle-celled variety (sarcoma-type) as described for lentigo maligna and the round or oval variety (carcinoma-type). Section from an early lesion shows disruption of the epidermodermal junction with increase in number of melanoblastic cells in this region. During the early stage of the process the melanoblastic cells are confined to the superficial portion of the dermis and are limited internally by a moderate to extensive cellular infiltrate composed of lymphocytes and plasma cells. As the tumor enlarges, invasion of the deeper layers of the dermis takes place and the infiltrate decreases in amount. Of the two types of cells, the sarcoma type predominates in early lesions. The carcinoma type is usually seen later though occasionally early tumors may be composed of this type of cell from the beginning." (Fig. 1) Becker SW, Obermayer ME. Modern dermatology and syphilology. 2nd Edition. Philadelphia: JB Lippincott, 1947:709.
Fig. 1: Our diagnosis and comment: Melanoma. The "epithelial disintegration" is a consequence of poor laboratory technique, the "melanoblastic cells" are abnormal melanocytes, and the "round cell infiltration" is of lymphocytes.

**Brief Critique**

Nothing in these sentences enables a histopathologist to come to a specific diagnosis of melanoma. In fact, the authors do not set forth a single useful criterion for that diagnosis. Moreover, much of what is written is wrong, for example, notions of melanoblasts and melanocarcinoma, the former being a fiction and the latter a misconception; melanoma is a sarcoma, made up as it is of non-epithelial cells (melanocytes).

**Ormsby and Montgomery**

"The histopathologic changes [in melanoma] are concerned with malignant metaplasia of the ordinary nevus cell . . . Most investigators are agreed that when a nevus undergoes malignant change the earliest changes, in the majority of the cases, are seen in nevus cells at the epidermal cutis junction. Exceptionally, the first malignant changes are seen in nevus cells deep in the cutis, in the so-called subdermal type of nevus. The nevus cells increase in size, and usually there is an increase in melanin pigment and the dopa reaction is definite and positive. The proportion of the nucleus to the cytoplasm is increased. A varying number of mitotic figures are seen, the cells usually proliferate into the cutis in an alveolar-like arrangement. Early invasion of the lymph and blood vessels occurs, so that metastasis may result through either system. Destruction of elastic tissue and dermal appendages in the path of the growth of the tumor occurs. As the cells invade the cutis, they seem to lose their ability to form pigment." (Fig. 2) Ormsby OS, Montgomery H. Diseases of the skin. 7th edition. Philadelphia: Lea and Febiger, 1948:844.
Fig. 2: Our diagnosis and comment: Melanoma. This so-called early melanoma is at least several years old, there is no evidence of a mole (melanocytic nevus) in this photomicrograph, and the "malignant nevus cells" are actually neoplastic melanocytes of melanoma. Parenthetically, what conventionally are called "nevus cells" are really abnormal melanocytes of a nevus.

Brief Critique

There is nothing in these lines that permits a histopathologist to arrive at a diagnosis of melanoma. Nary a single criterion requisite for that diagnosis is proposed. Furthermore, much that is written is wrong, such as the concepts of nevus cell, nevus undergoing malignant change, and cells of melanoma losing capability for producing melanin as they ascend progressively into the dermis. A so-called nevus cell, nevocyte, or nevomelanocyte is an abnormal melanocyte. It qualifies as a melanocyte because it has capability for manufacturing melanin. As a rule, melanocytes of a melanocytic nevus do not transform into melanocytes of melanoma. Even when a melanoma develops in continuity with a nevus, such as Clark's nevus, it seems to originate from melanocytes other than those of the nevus itself. Last, melanocytes at the base of a melanoma sometimes produce much more melanin than those at the surface of it.

Lever

"In early malignant melanoma and at the advancing border of older lesions one may find pathologic changes within the epidermis but little or no invasion of the corium by tumor cells. This stage may be referred to as malignant melanoma in situ. In some areas the epidermis, because of the presence of numerous atypical clear cells, appears vacuolated, torn apart and even disintegrated. In other areas the epidermis contains large, irregularly shaped, often deeply pigmented nests composed of nevus cells which appear atypical and may show mitotic figures. In the upper corium, close to the epidermis, one finds a dense, bandlike inflammatory infiltrate intermingled with numerous chromatophores." . . .

"In invasive malignant melanoma one finds considerable junction activity. The junction activity is more pronounced and more irregular than that seen in junction nevi. The nevus cells are large, atypical and show occasional mitotic figures in contrast to junction nevi which do not show them. One finds not only dropping off of nevus cells and cell nests downward into the corium, but also migration upward into the rete malpighii. The epidermis may become so fully permeated with tumor cells that it disintegrates and ulceration results . . . "

"The size and shape of the tumor cells in the corium show great variation. Nevertheless, two types of cells can be clearly recognized, a cuboidal and a fusiform type . . . Mitotic figures are usually present in malignant melanoma, but often only in small numbers. They should be searched for, because their presence is of great value as evidence that the tumor is malignant, inasmuch as in pigmented nevi mitotic figures are never found." (Fig. 3) Lever WF. Histopathology of the skin. Philadelphia: JB Lippincott, 1949:400–3.
Fig. 3: Our diagnosis and comment: Melanoma. The designations "early" and "late" for melanoma are not accurate. Abnormal melanocytes in a patch of melanoma may remain in situ, that is, confined to the epidermis and adnexal epithelium, for decades, whereas abnormal melanocytes in a papule of melanoma may have come to involve the dermis in a matter of but a few years. The melanoma pictured here cannot be deemed "early;" it measures about 1.0 mm in thickness to the base of the photomicrograph.

Brief Critique

The criteria utilized by Lever are as follows: (1) atypical clear cells, (2) mitotic figures, (3) pleomorphic nuclei of neoplastic cells, (4) dense, bandlike infiltrate of inflammatory cells, (5) chromatophores, (6) junctional activity, (7) dropping off of individual nevus cells and nests of nevus cells, (8) upward migration of nevus cells in the epidermis, (9) disintegration of the epidermis, and (10) ulceration. Apart from atypical melanocytes, mitotic figures in melanocytes, and melanocytes positioned above the dermo-epidermal junction, none of the criteria advanced by Lever benefits a histopathologist in coming to a specific diagnosis of melanoma. And each of those three findings that have validity are encountered also in Spitz's nevi. In addition, several ideas advocated by Lever are incorrect, among them disintegration of the epidermis, nevus cells, junctional activity, and mitotic figures never being encountered in nevi.

Some sense for how different was the use of the term melanoma in 1949 can be learned by glancing at the conditions said to be "Melanomas" in Chapter 19 of Walter Lever's first edition of the textbook. In brief, "pigmented nevus," "lentigo," and "blue nevus" were all considered by him to be melanomas, which in those days meant any melanocytic neoplasm.

Allen

"The decision as to whether or not a given lesion is to be diagnosed an active junctional nevus or a melanocarcinoma must, when juvenile melanomas are excluded, depend on this single fact: the presence or absence of dermal invasion. It is to be stressed, however, that awesomely little evidence of dermal downgrowth of malignant cells is required for the diagnosis of melanocarcinoma, as opposed to junctional nevus. Often, isolated or clusters of invading cells are recognized among the subepidermal lymphocytes by their circular shape and abundant spongy cytoplasm, finely sprinkled with granules of melanin. They are to be distinguished particularly from histiocytes or reticulum cells. The subepidermal zone of lymphocytes is usually present in both the activated junctional nevus and the superficial melanocarcinoma." (Fig. 4) Allen AC. The Skin. A
Fig. 4: Our diagnosis and comment: Melanoma in situ. The term "active junctional nevus" is wrong in all respects; activity cannot be observed through a microscope, the abnormal melanocytes are not situated only at the dermo-epidermal junction, and the lesion is not a nevus. Allen acknowledged that the neoplasm is a melanoma by stating, " . . . this lesion is equivalent to a melanocarcinoma in situ." In actuality, however, melanoma is a sarcoma, not a carcinoma.

Brief Critique

The idea of identifying "invasion" on morphologic grounds is wholly without justification; a compound nevus, such as Spitz's, is no less invasive, as judged morphologically than a melanoma of equal thickness. In fact, a Spitz's nevus often is more invasive biologically because of its capability for more rapid growth than melanoma, evidenced by readily discernible mitotic figures in many Spitz's nevi. In actuality, histopathologists make a determination of invasion based on reasoning in post hoc ergo propter hoc fashion: if a neoplasm is deemed to be benign, for example, a Spitz's nevus, it is said not to be invasive, but if a neoplasm of the same thickness is thought to be malignant, for example, melanoma, it is then claimed to be invasive.

In short, Allen provided no criteria for distinguishing melanoma from Spitz's nevus.

Percival, Montgomery, and Dodds

"The following criteria indicate malignant nature of the tumour [melanoma]: frequent and atypical mitoses, the overall large size of the cells and their lack of uniformity, large hyperchromatic nuclei, fusion of cells. Large amounts of pigment in the lesion, invasion of the epidermis by tumour cells, marked junctional activity at the periphery of the lesion, and a marked lymphocytic reaction in the surrounding dermis." Percival GH, Montgomery GL, Dodds TC. Atlas of histopathology of the skin. 2nd Edition. Maryland: The Williams and Wilkins Co., 1962:406.

Brief Critique

Of the criteria enumerated, only mitotic figures (some of them abnormal), nuclear atypia, and presence of melanocytes above the dermo-epidermal junction have merit in regard to specific diagnosis of melanoma. But none of them and all of them do not facilitate differentiation of melanoma from some examples of Spitz's nevus. Some precepts of the authors are without merit for specific diagnosis of melanoma, among them fusion of cells, abundant pigment, and junctional activity.

Montgomery

"One sees [in early melanoma] large atypical cells with relatively little pigment or even with mitotic figures, but apparently they still are confined within the epidermis." Montgomery H. Dermatopathology. New York: Harper and Row Publishers, 1967:1175.

Brief Critique

The three findings do not permit a melanoma in situ to be distinguished from some examples of Spitz's nevus confined to epidermal and adnexal epithelium.

Pinkus and Mehregan
“Criteria for malignancy of a melanotic tumor are several, and some are more significant than others. Presence of mitoses is of primary importance, although some mitotic figures may be found in benign juvenile melanomas and an occasional one even in benign nevi. Absence of mitoses does not rule out malignancy. The next important feature is inflammatory reaction composed of lymphocytes and possibly plasma cells. It is practically always present, but may also be found in benign juvenile melanoma, nevus incipiens, and Sutton's halo nevus. It must not be confused with the acute or granulomatous infiltrate that may be caused in a benign intradermal nevus by infection of a hair root or breakdown of a follicular cyst. Cells of malignant melanoma usually are much larger than even the large A type cells of benign nevi, a feature also true for benign juvenile melanoma. One should not be confused by large multinucleated nevus giant cells occurring in benign lesions. Distribution and amount of pigment usually is more variable in malignant melanoma, some nests containing much, others little or none. Particularly characteristic is dustlike pigmentation of large celled junctional nests. One should of course not be deceived by the presence of pigmented macrophages which occur in benign as well as in malignant lesions. Another factor helpful in some cases is the constitution of the dermal stroma. It was mentioned earlier that nests of benign nevus cells are often surrounded by collagen bundles, and even in their absence by fine elastic fibers and reticulum fibers making an orderly and distinct pattern. This is not so in malignant melanoma which outgrows and destroys stroma. Elastic fiber and reticulum stains assist in differential diagnosis between benign and malignant intradermal tumors.”


**Brief Critique**

As Pinkus and Mehregan acknowledge, the presence or absence of mitotic figures in abnormal melanocytes, atypical nuclei of melanocytes, and infiltrates of inflammatory cells are not helpful in differentiating a melanoma from a Spitz's nevus. The same is true, equally, for multinucleate melanocytes, amount of melanin, dustlike melanin in abnormal melanocytes, and stromal changes. For example, melanin may be distributed in asymmetrical or uneven fashion in certain combined congenital melanocytic nevi, dustlike melanin may be seen in some congenital nevi biopsied shortly after birth, and stromal changes, such as desmoplasia that destroys elastic fibers, may be observed in some Spitz's nevi, as well as in some melanomas.

**Wayte**

"... the microscopic diagnosis [of melanoma] is based on the following features. A. Junctional changes ... B. Intradermal invasion ... C. Loss of stromal relationship ... D. Lack of maturation ... E. Mitotic activity ... F. Melanogenesis ... G. Surface ulceration ... The following features seen on microscopic examination are of very little value. A. Epidermal invasion ... B. Dermal inflammatory reaction ... C. Epithelial hyperplasia ... D. Junctional ‘activity.’" (Fig. 6) Wayte DM. Pathology of nevi and melanomas. In: Helwig EB, Mostofi FK. The skin by 30 authors. Maryland: Williams and Wilkins, 1971:522–24.

![Fig. 6: Our diagnosis and comment: Melanoma in situ. The findings pictured are neither those of a "freckle" of any kind nor of "precancerous melanosis." The changes fulfill criteria for melanoma within the epidermis (melanoma in situ).](http://www.derm101.com/dynaweb/resources/milestones/4842/Generi...)

**Brief Critique**

Only lack of maturation of abnormal melanocytes with progressive descent into the dermis is a solid criterion for distinguishing melanomas from melanocytic nevi of various kinds, but that finding is not met with consistently in melanomas. All of the other criteria stated by Wayte to be characteristic of melanoma may be seen in Spitz's nevi.
Clark and Mihm

"Superficial spreading melanoma is characterized by a population of melanocytes appearing uniformly malignant; the striking melanocytic pleomorphism so characteristic of lentigo-maligna melanoma is not usually seen. Biopsy of the slightly raised hyperpigmented portion of superficial spreading melanoma reveals a 'pagetoid' distribution of large melanocytes throughout the epidermis. The large cells may occur singly or in nests and are uniformly atypical. Biopsy of markedly nodular areas of superficial spreading melanoma reveals, upon microscopic examination, dense accumulations of malignant cells in the dermis. In areas of invasion, large melanocytes are also observed. These large cells have an abundance of cytoplasm containing regularly dispersed fine particles of melanin; the 'dusty' appearance of the cells, when viewed with the microscope, is the result of these numerous granules. Occasionally, superficial spreading melanoma may show spindle cells and, rarely, a small cell that looks not unlike the cell of a mole. We, however, agree with McGovern (1968) that these cells are not nevus cells or cells of moles, but are small malignant melanocytes." (Fig. 5) Clark WH, Mihm MC. Moles and malignant melanoma. In: Dermatology in general medicine. New York: McGraw-Hill, Inc., 1971:506.

Fig. 11-16 Lentigo maligna. In this photomicrograph, there are a number of quite bizarre melanocytes. In the left portion of the field, there is a multinucleated melanocyte. Intraepidermal multinucleated melanocytes are seen more commonly in lentigo maligna and lentigo-maligna melanoma than in other forms of atypical growth affecting the intraepidermal melanocytic system.  300. Clark WH, Mihm MC. 1971.

Fig. 5: Our diagnosis and comment: Melanoma in situ. The term "lentigo maligna" is an evasion from a diagnosis of melanoma in situ on skin damaged badly by sunlight, usually of a face. The histopathologic findings of melanoma in situ are the same on all anatomic sites. It is curious that although this legend was written by proponents of Clark's "histogenetic" classification of melanoma, those advocates failed to conclude that the pagetoid melanocytes in pagetoid pattern, shown here, were stereotypical for what they, themselves, call superficial spreading melanoma.

Brief Critique

The combination of atypical pagetoid cells in pagetoid pattern is highly suggestive of melanoma, but pagetoid cells, themselves, are not present with repeatability in melanomas on any anatomic site, including the trunk and proximal extremities (so-called superficial spreading type of melanoma). Moreover, pagetoid melanocytes with small monomorphous nuclei may be observed in certain congenital melanocytic nevi, especially ones biopsied early in life. In short, on the basis of the criteria offered in these lines of Clark and Mihm, a histopathologist would not be able to diagnose melanoma with specificity most of the time.
Milne

"The term melanocarcinoma is preferred to the more common term malignant melanoma so that there cannot be any possible confusion with benign lesions such as the juvenile melanoma.

There are a number of histologic criteria which offer considerable help. These are:

1. The upward infiltration of the epidermis by abnormal melanocytes.
2. The size of the melanocytic nuclei.
3. The presence of an inflammatory process in the papillary dermis . . . "


Brief Critique

The three findings said by Milne to be of considerable help in diagnosis of melanoma are expected findings in many examples of Spitz’s nevus. As has been stated already, melanocytes are non-epithelial and, therefore, melanoma is a sarcoma, not a carcinoma.

Smith

"The principal histologic criterion for the diagnosis [of melanoma] is the presence of dermal invasion by atypical melanocytic cells (melanoma cells) from the overlying epidermis. In most tumors, the atypical cells within the epidermis are arranged in nests or clusters at the epidermal-dermal junction; however, individual cells or a row of cells may be present. If the cells are confined to the epidermis, but show definite atypical cytologic features, the designations atypical junctional nevus and melanoma in situ are used. Not until the atypical cells have actually invaded the dermis is the lesion diagnosed as a malignant melanoma."


Brief Critique

As mentioned already, the notion of invasion being recognizable morphologically is fallacious. The phrase "atypical junctional nevus" does not convey anything meaningful, especially in the context of that nevus being employed as a synonym for melanoma in situ. The other findings mentioned by Smith are of no assistance in coming to a specific diagnosis of melanoma, all of them being noted not uncommonly in Spitz’s nevi.

Sanderson

"Most tumours [of melanoma] show proliferating atypical melanocytes at the dermal-epidermal junction. In superficial and early lesions this is the main change [sic], in large ulcerating tumours it may be seen only in small areas around the ulcer. Malignant cells may invade the epidermis and be shed in the stratum corneum, extend laterally along the junction to produce a melanotic halo, or downwards as an invasive tumour."

"Early and superficial malignant melanoma may closely resemble an active junctional or compound naevus. The cells are usually larger, with more darkly stained nuclei, increased mitoses and, most characteristically, particles of melanin dispersed through the cytoplasm to give a ground-glass appearance." (Fig. 7) Sanderson KV. Tumours of the skin. In: Rook A, Wilkinson DS, Ebling FJG. Textbook of dermatology. 2nd Edition. Great Britain: Blackwell Scientific Publications, 1972:1981–2.
Fig. 7: Melanotic freckle. Atypical melanocytes are proliferating at the junction and there is a lymphocytic reaction beneath. H. & E. × 160 (St. George’s Hospital). Sanderson KV. 1972.

Fig. 7: Our diagnosis and comment: Melanoma. The photomicrograph, which is out of focus, shows a melanoma that at least is in situ. Some neoplastic melanocytes may be present amidst the infiltrate of lymphocytes in the upper part of the dermis. The term "melanotic freckle" fails to communicate that the neoplasm truly is a melanoma. Moreover, the atypical melanocytes within the epidermis cannot be seen "proliferating at the junction;" no movement of cells can be detected through a microscope!

Brief Critique

All of the changes alleged by Sanderson to be relevant to diagnosis of melanoma are seen in some lesions of Spitz’s nevus. His ideas of "active" nevi, invasive tumour, and malignant cells, as judged morphologically, are flawed.

Smith

"The histologic criterion generally used for the diagnosis of a primary malignant melanoma is invasion of the dermis, from the epidermis, by cytologically malignant melanocytic cells."

"Other histologic variables which have been documented in this study include the degree of inflammatory response, over-all surface dimensions of the tumor, cell type and degree of pleomorphism, nuclear and nucleolar characteristics, degree of mitotic activity, degree of pigmentation, degree of epidermal invasion, presence of ulceration, presence of vascular invasion, and evidence of spontaneous regression."


Brief Critique

The only findings mentioned by Smith as criteria for diagnosis of melanoma and that allow differentiation from some examples of Spitz’s nevus are "vascular invasion" and "spontaneous regression." Neither of them, however, is of worth to a histopathologist in the vast majority of instances in which melanoma must be differentiated from Spitz’s nevus; "vascular invasion" is seen rarely in sections of tissue that house a primary melanoma and regression of primary melanoma (in the form of fibrosis or melanosis or both together) is notable in only about one tenth of specimens. Ulceration may be a consequence of trauma, and that is the case in some Spitz’s nevi, especially those in young children.
Price, Rywlin, and Ackerman

"Summary of Morphological Characteristics of Superficial Spreading Malignant Melanoma Capable of Metastasis

I. Poor circumscription of the intraepidermal melanocytic component of the lesion with lateral extension of individual melanocytes.

II. Increased number of melanocytes, solitary and in nests, within and above the epidermal basal-cell layer and within adnexal epithelium (Pagetoid appearance).

III. Marked variation in size and shape of the melanocytic nests, and confluence of melanocytic nests rather than discrete nests.

IV. Absence of maturation of melanocytes with descent into the dermis.

V. Melanocytes with nuclear atypia

VI. Melanocytes in mitosis

VII. Necrosis or degeneration of melanocytes"


Brief Critique

Although this constellation of criteria for diagnosis of melanoma by conventional microscopy was an improvement over what had been advanced by authors previously, some important criteria were not included, chief among them asymmetry. Between 1976 and 1999, the criteria forged by Ackerman were honed considerably (see pages 14–15).

Pinkus and Mehregan

"Criteria for malignancy of a melanotic tumor are several, and some are more significant than others. Presence of mitoses is of primary importance, although some mitotic figures may be found in benign juvenile melanomas and an occasional one even in benign nevi. Absence of mitosis does not rule out malignancy. The next important feature is inflammatory reaction composed of lymphocytes and possibly plasma cells. It is practically always present, but may be absent in rapidly growing tumors and, on the other hand, may also be found in benign juvenile melanoma, nevus incipiens, and Sutton's halo nevus. This reactive infiltrate must not be confused with the acute or granulomatous infiltrate that may be caused in a benign intradermal nevus by infection of a hair root or breakdown of a follicular cyst. Cell size has considerable significance. Cells of malignant melanoma usually are much larger than even the large type A cells of benign nevi, a feature also true for benign juvenile melanoma. One should not be confused by large multinucleated nevus giant cells occurring in benign lesions. Distribution and amount of pigment usually is more variable in malignant melanoma, some nests containing much, others little or none. Particularly characteristic is dustlike pigmentation of large junctional nests. One should not be deceived by the presence of pigmented macrophages, which occur in benign as well as malignant lesions." Pinkus H, Mehregan A. A guide to dermatohistopathology. 2nd Edition. New York: Appleton-Century-Crofts, 1976:471.

Brief Critique

Pinkus and Mehregan did not add anything to what they wrote about criteria that enable differentiation histopathologically of nevi from melanoma in the first edition of their book. As in the first edition, they admit rightly that none of their criteria, and all of them together, do not permit a distinction to be made between Spitz's nevus and melanoma.

Ackerman and Su

"Histologic Criteria for the Diagnosis of Malignant Melanoma

Architectural Pattern

Increased number of atypical melanocytes, singly and/or in nests within the epidermis.

Horizontal extension of atypical melanocytes, singly and/or in nests, within the epidermis beyond the bulk of the intraepidermal and intradermal components of the neoplasm.

Failure of nuclei of the atypical melanocytes to become smaller with progressive descent into the dermis.
Atypical melanocytes present singly and/or in nests at all levels of the epidermis, even including the cornified layer.

Variation in size and shape of intraepidermal and intradermal nests of atypical melanocytes.

Confluence of the nests of atypical melanocytes within the epidermis and the dermis.

Extension of atypical melanocytes, singly and/or in nests, down epithelial structures of adnexa, namely, hair follicles and eccrine sweat ducts.

Cytologic Features

Atypical melanocytes with large, hyperchromatic, pleomorphic nuclei and prominent nucleoli.

Melanocytes in mitosis within the epidermis and the dermis.

Necrotic melanocytes." (Fig. 8)


Fig. 8: Our diagnosis and comment: Melanoma in situ. It is preferable to describe the presence of abnormal melanocytes at all levels of the epidermis as "pagetoid pattern," rather than as "'buckshot' scatter."

Brief Critique

Although these criteria probably were the most effective of those proposed until that time for specific diagnosis of melanoma, not included among them are important attributes of melanoma, such as asymmetry and predominance of melanocytes disposed as solitary units over nests of melanocytes in some high power fields within the epidermis and within epithelial structures of adnexa. Furthermore, some of the findings listed are seen also in some nevi, like involvement of the upper reaches of the epidermis and of epithelial structures of adnexa by atypical melanocytes in some examples of Spitz's nevus.

Kamino and Ackerman

"Criteria for the Histologic Diagnosis of Malignant Melanoma

Architectural Pattern:
Wide lateral extent of the lesion, i.e., greater than 6 mm

Asymmetry of the lesion

Horizontal extension of atypical melanocytes within the epidermis, beyond the bulk of the intraepidermal and intradermal components of the neoplasm

Increased number of atypical melanocytes, singly and/or in nests, within the epidermis

Atypical melanocytes at all levels of the epidermis, even the cornified layer

Variation in sizes and shapes of nests of atypical melanocytes within the epidermis; shapes irregular

Confluence of nests of melanocytes within the epidermis and the dermis

Presence of atypical melanocytes in epithelial structures of adnexa

Failure of maturation of atypical melanocytes with progressive descent into the dermis (i.e., the nuclei do not become smaller)

Cytologic Features:

Atypical melanocytes

Melanocytes in mitosis (some of them may be atypical)

Necrotic melanocytes


Brief Critique

Although the criteria for specific diagnosis of melanoma proposed by Ackerman in 1981 are an advance over those offered by him in 1976 and 1979, some of the criteria are flawed, such as diameter greater than 6 mm and shape of nests of melanocytes being described as irregular (no definition has been offered for "regular," let alone "irregular," in regard to outline of nests of melanocytes). Other modifications were to be added in the ensuing 20 years.

Domonkos, Arnold, and Odom

"At first atypical, but still dendritic, melanocytes are found at the dermoepidermal junction. These melanocytes are anaplastic or hyperplastic and contain vacuolated cytoplasm. Pinkus has emphasized the characteristic features of their nucleus: dark-staining and folded, not vesicular as in a junction nevus. As the melanocytes proliferate, the dermoepidermal border becomes irregular, while the melanocytic cells may form nests at the junction to give them a moth-eaten appearance. These atypical cells retain the cytologic features of melanocytes; they never become nevus cells. As the invasion extends into the dermis, an invasive melanocytic[sic] melanoma develops and metastasis is a possibility, though unlikely until a nodule is formed, as Hirsch and Helwig have long emphasized." Domonkos AN, Arnold Jr. HL, Odom RB. Andrews' diseases of the skin. 7th Edition. Philadelphia: WB Saunders Company, 1982:863.

Brief Critique

This description is replete with error, among them violations of fundamental precepts of pathology (e.g., hyperplasia rather than neoplasia), abstruse imagery (e.g., moth-eaten appearance), animistic interpretation (e.g., invasion), and misconception (e.g., nevus cells). Nothing stated by these authors permits a histopathologist to make a specific diagnosis of melanoma with surety.

Roses, Harris, and Ackerman

"The histological diagnosis of malignant melanoma is based upon both architectural pattern and cytological features, which may be summarized as follows:

Architectural Pattern:

1. Relatively large lesion (more than 6 mm. in greatest diameter)
2. Asymmetry
3. Poor circumscription
4. Failure of maturation of melanocytes with progressive descent into the dermis
5. Nests of melanocytes variable in sizes, irregular in shapes, and tending toward confluence
6. "Buckshot scatter" of melanocytes throughout the epidermis
7. Melanocytes within the epithelial structures of adnexa

Cytological Features:

1. Atypical melanocytes
2. Melanocytes in mitosis
3. Necrotic melanocytes

In addition to these criteria for the histologic diagnosis of malignant melanoma, there are also adjunctive clues for diagnosis, which are listed as follows:

Adjunctive Clues:

1. Signs of severe solar elastosis
2. Melanocytes in mitosis near the base of the neoplasm
3. Abundant melanin in melanocytes near the base of a neoplasm
4. Signs of regression of parts of the lesion, that is, fibrosis and/or marked melanosis in a thickened papillary dermis
5. Patchy, uneven distribution of melanin within the neoplasm
6. Satellite neoplastic melanocytes (a sign of local metastasis)
7. Melanocytes within vascular lumina
8. Presence of plasma cells
9. Single melanocytes predominate over nests of melanocytes in the epidermis
10. Presence of melanocytes with pagetoid morphology.


Brief Critique

Criteria that employ architectural pattern and cytologic features in conjunction with adjunctive clues enabled greater efficacy of the system being developed by Ackerman for specific diagnosis of melanoma. Also added to the criteria are asymmetry and predominance of single melanocytes over nests of melanocytes in some high power fields within the epidermis. The number 6.0 mm for diameter has no merit; all melanomas were once smaller than that. The word "irregular" is unhelpful and melanocytes as solitary units and in nests are expected findings in various kinds of nevi, as well as in melanomas. The distribution of those melanocytes is very different in nevi and melanomas.

MacKie

"The preinvasive or in situ phase of growth of these lesions [melanoma] is identified as an area of epidermis in which large numbers of atypical melanocytes are seen clustered together at the dermo-epidermal junction. Overlying these areas individual atypical melanocytes are seen in the upper layers of the epidermis. A scanty lymphoid infiltrate may be seen in the papillary dermis, but no invasive melanocytic cells. Such lesions are sometimes termed 'atypical melanocytic hyperplasia' or 'Clark level I malignant melanoma'." MacKie RM. *Milne's dermatopathology*. 2nd Edition. Great Britain: Butler and Tanner Ltd., 1984:303–4.

Brief Critique

All of changes recorded may be seen also in some examples of Spitz's nevus and, therefore, are not dependable criteria for diagnosis with specificity of melanoma.

Okun, Edelstein, and Fisher

"Microscopic features (superficial spreading melanoma in situ)

1. The epidermis is generally normal in thickness or acanthotic.
2. Tumor cells tend to be cuboidal or pagetoid and tend to show significant upward invasion of the epidermis. Nuclear pleomorphism may be pronounced. Cytoplasm may be very abundant, and "dust-like" melanin is often seen.
3. A lymphoid cell infiltrate intermingled with melanophages is often present in the upper dermis, but solar damage is usually not prominent, since lesions are not dependent on solar damage."


Brief Critique

Apart from reference to "dust-like" melanin in neoplastic pagetoid cells, nothing alluded to enables differentiation of melanoma from some examples of Spitz's nevus.

**McCarthy et al.**

"In particular, the irregular arrangement of variably sized nests of melanocytes in association with solitary atypical melanocytes well above the dermo-epidermal junction distinguishes in situ melanoma from acquired banal junctional naevi, and junctional types of dysplastic and Spitz naevi. Thus early melanoma can be diagnosed histologically when it is small, flat, and curable." McCarthy WH et al. Can early melanoma be diagnosed? In: Cascinelli N, Santinami M, Veronesi U. *Cutaneous melanoma biology and management.* Italy: Masson, 1990:120–1.

Brief Critique

The findings cited do not distinguish melanoma *in situ* from many examples of Spitz's nevus confined to epidermal and adnexal epithelium.

**Clark**

"The individual cells [of melanoma in situ] are large and epithelioid, and have an abundance of finely divided pigments [sic], giving the cytoplasm a tan, dusty appearance. The nuclei are large and hyperchromatic, and usually about 1.5 to 2 times the diameter of the surrounding keratinocytes. The cells are relatively uniform in relationship to each other; consequently, they are not strikingly pleomorphic. The cells are disposed individually and in nests." Clark Jr WH. Malignant melanoma in situ. *Hum Pathol* 1990; 21:1197.

Brief Critique

Except for reference to "finely divided pigments [sic] giving the cytoplasm [of melanocytes] a tan, dusty appearance," the changes cited do not permit a melanoma *in situ* to be distinguished from some lesions of Spitz's nevus in which abnormal melanocytes are housed entirely within epidermal and adnexal epithelium. The assertion that the melanocytes of melanoma are marked by uniformity and lack of striking pleomorphism, although patently incorrect, will be invoked subsequently, in parrot fashion, by several other authors who wrote about the subject.

**Kirkham**

"Most melanomas start as proliferations of atypical melanocytes at the base of the epidermis . . . As the tumour develops, the cells move in all directions. One of the most helpful features is the presence of individual melanocytes in the upper layers of the epidermis." (Fig. 9) Kirkham N. *Biopsy pathology of the skin.* London: Chapman and Hall Medical, 1991:112–3.
Fig. 9: Our diagnosis and comment: Melanoma in situ. This is not a "dysplastic naevus" because abnormal melanocytes disposed as solitary units and in tiny nests are present at all levels of the epidermis, including the spinous, granular, and cornified layers, a constellation of findings in this section that is diagnostic of melanoma.

Brief Critique

The findings said to be characteristic of melanomas are seen often in Spitz's nevi and, therefore, do not allow distinction between them.

Weedon and Strutton

"In this type (superficial spreading melanoma), there is proliferation of melanocytes singly and in nests at all levels within the epidermis and often the adnexal epithelium. This pagetoid growth pattern is sometimes referred to as "buckshot scatter" of melanocytes." Weedon D, Strutton G. In: Emmett AJJ, O'Rourke MGE. Malignant skin tumours. 2nd Edition. Edinburgh: Churchill Livingstone, 1991:72.

Brief Critique

The same changes are found in some Spitz's nevi and are not distinguishing of those nevi from melanoma.

Fitzpatrick et al.

"Superficial spreading melanoma, the most common subtype of malignant melanomas, histologically presents as a prominent intraepidermal proliferation of malignant melanocytes in a single-cell array throughout the epidermis. These cells resemble the cells of Paget's disease; hence the pattern is called pagetoid and the tumor is sometimes termed pagetoid melanoma. The pagetoid cells may spread up to and include the granular cell layer or may be confined to the lower portions of the epidermis. At times, two or more layers of the epidermis, including the basilar region, are replaced by these malignant cells."

"The cells have large cytoplasms [sic] that are round or ovoid (also called epithelioid) and that have round nuclei. The nuclei are large, have strikingly irregularly dispersed heterochromatin, especially around their margins, and possess nucleoli that usually stain pink. The nuclei vary in size, and multinucleate forms may be present. The cytoplasm has a finely granular texture and usually stains pink-tan. Mitotic figures occur among these intraepidermal cells. The epidermis itself is frequently hyperplastic but may be of normal thickness or atrophic."

"The radial growth phase of superficial spreading melanoma may be entirely intraepidermal (melanoma in situ or level I). More often, however, single cells or small clusters of cells similar in character to those in the intraepidermal component invade the dermis (level II). The papillary dermis may contain fibroplasia, a patchy or band-like lymphocytic infiltrate, occasional melanophages, and increased vascularity, especially in inflamed lesions. Mitoses may be noted among invasive
**Brief Critique**

The conjunctive of pagetoid melanocytes and pagetoid pattern in the epidermis usually is indicative of melanoma, but, as stated in a previous "brief critique," most melanomas are devoid of pagetoid melanocytes. All of the other findings said to be characteristic of melanoma are seen commonly in Spitz's nevi.

**Murphy**

"At scanning magnification, radial growth phase melanoma of the superficial spreading type is characterized by nested and single-cell spread of epithelioid malignant melanocytes within a normal or slightly hyperplastic epidermal layer. Pagetoid cells resemble those of mammary and extramammary Paget disease and are present in all layers of the epidermis, including the stratum granulosum."

"At slightly higher magnification, irregularities in the size and shape of nested malignant melanocytes are encountered . . . "

". . . Superficial spreading melanoma is typified by non-uniform, irregular, enlarged nests of atypical cells. Nests in superficial spreading melanoma may be observed in all layers of the epidermis in a manner similar to the pagetoid spread of individually malignant melanocytes."

"At high-power magnification, superficial spreading melanoma cells are characteristically epithelioid in shape, with visible, variably pigmented, granular cytoplasm. Nuclei are large, irregular in size and shape, and contain prominent, often eosinophilic nucleoli. An important feature of melanoma nuclei, with respect to differentiating them from Spitz nevus cells, which also may have prominent nucleoli, is the presence of coarsely clumped background heterochromatin and irregularly thickened nuclear membranes. The cytoplasm of melanoma nuclei is coarsely granulated, as opposed to the finely vacuolated cytoplasm in Spitz nevi. Moreover, dusty or muddy melanization may be observed in superficial spreading melanoma . . . " Murphy GF. *Dermatopathology*. Philadelphia: WB Saunders Company, 1995:246–7.

**Brief Critique**

Apart from the presence of pagetoid melanocytes in pagetoid pattern within the epidermis, none of the findings mentioned by Murphy enable melanoma to be distinguished from some examples of Spitz's nevus. The claim that the "cytoplasm of melanoma is coarsely granulated, as opposed to the finely vacuolated cytoplasm in Spitz nevi" is without foundation.

**Mehregan et al.**

"Histological features in the early, or radial, phase [of melanoma] consist of extensive proliferation of large melanocytic cells with abundant and dusty cytoplasms [sic] at the dermoepidermal junction. There is a great tendency for junctional nest formation. Mitotic figures are present, and upward transmigration of small nests or individual atypical melanocytes within the epidermis is common. Extensive transepidermal elimination of large melanocytic cells is characteristic of the pagetoid variety. A lichenoid tissue reaction with basal cell damage associated with a lymphohistiocytic infiltrate is observed in the clinically white, regressive areas. The upper dermis shows fibroplasia, macrophages containing melanin, and patchy lymphocytic and plasma cell infiltrate . . . " Mehregan A, Hashimoto K, Mehregan D, Mehregan D. *Pinkus' guide to dermatohistopathology*. 6th Edition. Connecticut: Appleton and Lange, 1995:502–3.

**Brief Critique**

Pagetoid melanocytes in pagetoid pattern within the epidermis is a sign of melanoma, but that finding is not come upon in most specimens of it. All of the other changes detailed are found in some Spitz's nevi.

**Weedon**

"Superficial spreading melanoma is characterized by a proliferation of atypical melanocytes, singly and in nests, at all levels within the epidermis. This pagetoid spread within the epidermis is sometimes known as 'buckshot scatter'. Superficial adnexal epithelium may also be involved." Weedon D. *Skin pathology*. London: Churchill Livingstone Inc., 1997:693.

**Brief Critique**

Pagetoid melanocytes in pagetoid pattern usually signify melanoma, but that finding is not invariable. Despite that reality, it is the lynchpin of the criteria advocated by Weedon.

**Elder and Elenitsas**
"Architectural pattern features of importance in the diagnosis (of superficial spreading melanoma) include the large diameter of the lesions, poor circumscription (the last cells at the edge of the lesion tend to be small, single, and scattered), and asymmetry (one half of the lesion does not mirror the other half). The epidermis is irregularly thickened and thinned. Rather uniformly rounded, large melanocytes are scattered in a pagetoid pattern throughout the epidermis. The large cells lie predominantly in nests in the lower epidermis and singly in the upper epidermis. The nests tend to vary a good deal in size and shape, and to become confluent. Dermal melanophages and a dermal infiltrate are regularly present. The lymphocytic infiltrate is typically dense and bandlike, especially in invasive lesions. This contrasts with the patchy perivascular infiltrate of dysplastic nevi.

Cytologically, the lesional cells are rather uniform and have atypical, hyperchromatic nuclei and abundant cytoplasm containing varying amounts of melanin that often consists of small, "dusty" particles. The tumor cells are almost entirely devoid of dendrites. This uniform cytological atypia is of considerable diagnostic importance and contrasts with the random atypia of dysplastic nevi." Elder D, Elenitsas R. Benign pigmented lesions and malignant melanoma. In: Elder D. Lever's histopathology of the skin. 8th Edition. Philadelphia: Lippincott-Raven Publishers, 1997:657.

Brief Critique

Most of the criteria included here are like those advocated by Ackerman and, in general, are helpful in guiding a histopathologist to a specific diagnosis of melanoma. Unhelpful, however, is the notion adapted from Clark of "uniform cytologic atypia," which is a contradiction in terms (pleomorphism is the most important attribute of cytologic atypia and pleomorphism, by definition, cannot be uniform).

Barnhill

"Almost all melanomas begin as proliferation of melanocytes initially confined to the epidermis."


Brief Critique

The findings presented are not distinguishing from those of Spitz's nevus.

Langley, Fitzpatrick, and Sober

"Histopathologic Criteria for the Diagnosis of Melanoma

Intraepidermal or microinvasive melanoma

Architecture

Size (usually >4 to 5 mm)

Asymmetry of general architecture

Poorly defined margins

Loss of nevus architecture

Variation in size, shape, placement of nests

Confluence and fusion of nests

Dyshesion (dyscohesion) of cells in nests

Upward migration of cells (pagetoid spread)

Lack of maturation

Cytology

Uniformly atypical (continuous as opposed to variable) population of cells exhibiting cellular enlargement, nuclear enlargement, nuclear pleomorphism, nuclear hyperchromatism, prominent nucleoli"

Brief Critique

Many of the criteria seem to have been adapted from Ackerman, and those criteria enable differentiation, in most instances, of melanoma from melanocytic nevi of various kinds. Some criteria used by Ackerman are not included here and in their stead are baffling notions, such as "uniformly atypical" cells.

Langley et al.

"SSM is characterized by a population of melanocytes appearing uniformly atypical; the striking melanocytic pleomorphism so characteristic of LMM is not usually seen. Biopsy of a slightly raised, hyperpigmented portion of SSM reveals a 'pagetoid' distribution of large melanocytes throughout the epidermis. The large cells may occur singly or in nests and have a monomorphous appearance. On microscopic examination, biopsies of markedly nodular areas of SSM reveal dense accumulations of malignant cells in the dermis. In areas of invasion, large melanocytes are observed. These large cells have an abundance of cytoplasm containing regularly dispersed, fine particles of melanin: the dusty appearance of the cells, when viewed with the microscope, is the result of these numerous granules. Langley RGB, Barnhill RL, Mihm Jr MC, Fitzpatrick TB, Sober AJ. Neoplasms: Cutaneous melanoma. In: Freedberg IM, Eisen AZ, Wolfe K, Austen FK, Goldsmith LA, Katz SI, Fitzpatrick TB. Fitzpatrick's dermatology in general medicine. 5th Edition. New York: McGraw-Hill, 1999:1087.

Brief Critique

The finding of pagetoid melanocytes in pagetoid pattern is helpful for coming to a specific diagnosis of melanoma, but that change is present in a minority of melanomas. The rest of the criteria are paltry and unhelpful because they are confusing, for example, melanocytes of melanoma "appearing uniformly atypical," "striking melanocytic pleomorphism" of LMM in contrast to SSM, and large melanocytes of SSM being "monomorphous."

Maize et al.

"The earliest lesions of most melanomas in situ, small macules clinically, appear microscopically as proliferations of solitary melanocytes at or slightly above the dermoepidermal junction, spaced at irregular intervals. The nuclei of melanocytes in these early neoplasms may or may not be cytologically atypical, but are almost always larger than those of the non-neoplastic basilar melanocytes. As lesions of melanoma in situ evolve, melanocytes can aggregate to form nests and spread to the upper spinous, granular, and cornified layers. Often, single neoplastic melanocytes will be visible beyond the last nest on either side of the lesion, and some of these cells may be situated above the basal layer. Melanoma in situ typically involves follicular infundibula and acrotrichia [sic] in a given lesion with melanocytes distributed in the same pattern as they are within the interadnexal epidermis." Maize JC et al. Cutaneous pathology. Philadelphia: Churchill Livingstone, 1998:689.

Brief Critique

Most of the criteria presented here were forged in conjunction with Ackerman, who, in 1987, together with Maize, did a book titled "Pigmented Lesions of the Skin."

Dewan and Ackerman

"Our criteria for histopathologic diagnosis of melanoma are as follows:

Architectural Pattern

1. Asymmetry
2. Poor circumscription
3. Nests of melanocytes within the epidermis not equidistant from one another
4. Nests of melanocytes within the epidermis vary in size and shape
5. Nests of melanocytes within the epidermis confluent in foci, the resultant aggregations thereby assuming peculiar geometric shapes sometimes
6. Melanocytes within the epidermis disposed as solitary units predominate over nests of melanocytes in some high power fields
7. Solitary melanocytes within the epidermis not equidistant from one another
8. Scatter of melanocytes, both those disposed as solitary units and those in nests, above the dermoepidermal junction
9. Uneven distribution of melanin within the epidermis
10. Involvement of epithelial structures of adnexa by melanocytes in the same manner as within the epidermis
11. Nests of melanocytes within the dermis vary in size and shape
12. Nests of melanocytes within the dermis confluent in foci; formation sometimes of aggregations with peculiar geometric shapes and/or sheets of neoplastic cells
13. Failure of maturation of melanocytes with progressive descent into the dermis
14. Base of neoplasm uneven
15. Uneven distribution of melanin within the dermis

Cytopathologic Features

1. Pleomorphism of nuclei of melanocytes
2. Mitosis, some of them sometimes abnormal, of melanocytes
3. Necrosis of melanocyte sometimes

Of the 15 criteria for histopathologic diagnosis of melanoma that pertain to architectural pattern, the first 10 apply only to epidermal and adnexal epithelium, whereas the last five pertain only to the dermis. In short, the first 10 criteria define melanoma in situ, i.e., melanoma confined to epidermal and adnexal epithelium." Dewan M, Ackerman AB. What is your diagnosis of these melanocytic neoplasms? Dermatopathol: Pract and Conc 1999; 5(4):334.

Brief Critique

A reader is encouraged to compare and contrast these criteria (1999) with those of Becker and Obermayer (1947), Ormsby and Montgomery (1948), and Lever (1949).

Farmer and Hood

"Melanoma in situ is defined by asymmetric, irregular growth of atypical melanocytes that are confined to the epidermis. This proliferation begins at the dermoepidermal junction, resulting in contiguous atypical melanocytes that may remain confined to the dermoepidermal junction or may involve the hair follicle epithelium or sweat duct epithelium. Atypical melanocytes then migrate above the basal cell layer either singly or in small nests and are present at all layers of the epidermis including the granular cell layer. The epidermis may be hyperplastic or retain its normal configuration, or, at times, the rete pegs may be flattened. The melanocytes themselves may have a variety of shapes that include small and cuboidal, epithelioid or spindled, or varying combinations of these. There is usually a brisk inflammatory cell response consisting of patchy aggregates of lymphocytes and melanophages in the papillary dermis and scant fibroplasia." (Fig. 10) Farmer ER, Hood AF. Pathology of the skin. 2nd Edition. New York: McGraw-Hill Companies, Inc., 2000:1137.
Fig. 10: Our diagnosis and comment: Melanoma in situ. The statement that "the cells are more numerous than the variably atypical melanocytes characteristic of melanocytic dysplasia" is dizzying because melanocytes in so-called dysplastic nevus are not atypical (nuclei of melanocytes in that kind of nevus are small, oval, and monomorphous), and melanocytic dysplasia has yet to be defined in a comprehensible, repeatable fashion. In short, melanocytic dysplasia is irrelevant to the melanoma in situ pictured here. "Melanocytic dysplasia" is for 2001 what "junctional activity" was for 1953.

Brief Critique

Although the authors utilize silhouette as a route to specific diagnosis of melanoma and differentiation of it from nevi of various kinds that simulate melanoma histopathologically, chief among them Spitz's nevus, they do not mention a variety of important findings that pertain to architectural pattern, such as poor circumscription, uneven base, uneven distribution of melanin, and predominance of solitary melanocytes over nests of melanocytes in some high power fields within the epidermis and within epithelial structures of adnexa. They do, however, include attributes of melanoma like asymmetry and pagetoid pattern. Most of the attributes referred to, however, are not differentiating from those met in many examples of Spitz's nevus.

Conclusion

A reader who returns to the statement quoted at the beginning of this essay should now be able to assess better the legitimacy of it:

"... no significant changes in histologic criteria had occurred over time that would explain the rise in melanoma incidence."


We are compelled to conclude that that statement is plainly untrue.