Pathologists have become increasingly aware of the many and sometimes subtle histopathologic guises of melanoma. No one who has a chance to identify a melanoma takes lightly the chance of missing that diagnosis. Aside from humanitarian concerns, the medicolegal ramifications of failure to diagnose malignant melanoma should concentrate the mind wonderfully.

Many pathologists do not regard 'over-diagnosis' of melanoma as an error of the same magnitude. In many respects it is not, as there usually is no potential loss of life. Yet, misdiagnosis of a benign neoplasm as melanoma can affect a patient profoundly. A patient who has been told that he or she has a malignant melanoma, when in fact they do not may make important decisions based on erroneous premises. Their health insurance may be cancelled (at least at present), or they may not be able to change jobs for fear of losing their insurance. They may elect not to have children, and some patients diagnosed as having melanoma have opted for sterilization even though there was no evidence of systemic spread. While complete excision with a margin of 1 cm. or less of uninvolved skin is becoming standard therapy for most melanomas, wider excisions of up to 5 cm. in radius, sometimes accompanied by removal of local lymph nodes are still performed in some centers, even without evidence of nodal involvement. Sentinel node biopsy is often employed for melanomas over 1 mm. in thickness. While the morbidity of this procedure is relatively little compared with other surgeries, there are cases of lymphedema following removal of a single node, and the subsequent misidentification of nodal nevus can lead to completion lymphadenectomy. Pathologists should certainly give careful thought to these ramifications before making a diagnosis of malignant melanoma 'just to be safe'.

We will review both benign and malignant, melanocytic and non-melanocytic simulants of malignant melanoma, with an emphasis on the pitfalls and repercussions of misdiagnosis. Following the suggestion of a former colleague, Dr. Richard Sagebiel, I have categorized simulants of melanoma into superficial (essentially intraepidermal or intraepidermal and papillary dermal) and deep (reticular dermal) groups.

I. Melanocytic proliferations whose intraepidermal features simulate melanoma in situ

A. Simple lentigo with suprabasilar scatter of melanocytes

Simple lentigines are small, darkly pigmented macules that often have a reticulated periphery. On close inspection, especially if the skin is spread or the lesion is examined under a dermatoscope, simple lentigines are almost always slightly asymmetrical and can have jagged contours. Because of the increasing attention that
Clinicians pay to pigmented lesions, simple lentigines are often biopsied to rule out melanoma in situ. In most cases, this differential diagnosis is straightforward. Simple lentigines are small, and sharply circumscribed proliferations in which single melanocytes are increased in number, but are confined to the sides and bases of club-shaped, hyperpigmented rete ridges. Sometimes giant melanosomes (visible by conventional microscopy as small round dark brown intracytoplasmic granules) are present. The papillary dermis beneath a simple lentigo is often fibrotic, although the well developed concentric and lamellar fibroplasia that accompanies some 'dysplastic' or Clark's nevi is seldom present. Sometimes a few clusters of small round melanocytes are evident in the papillary dermis. While their presence is not evident clinically (the neoplasm is still flat and the dermal nests do not affect its pigmentation in a discernable fashion), such a lesion is properly termed a lentiginous compound nevus. Even though most simple lentigines are stable, some develop many junctional nests and melanocytes may descend into the papillary dermis. Because of their capacity to progress, simple lentigines can be conceived of as embryonic junctional or compound melanocytic nevi. In fact, because serial sections of simple lentigines almost always show a few junctional nests, the distinction between a simple lentigo and a lentiginous junctional nevus is an arbitrary one.

Simple lentigines can be mistaken for melanoma in situ when melanocytes are present above the basal layer. This is fortunately a rare happenstance. In such lesions, most of the melanocytes are situated at the bases of rete ridges. The cytology of the upwardly migrating cells do not differ substantially from that of those in the basal layer. The melanocytes of simple lentigines have small nuclei with compact chromatin and scant cytoplasm; finding vesicular nuclei or abundant cytoplasm raises the possibility of malignant melanoma. Simple lentigines commonly have sparse perivascular infiltrates of lymphocytes and melanophages. In simple lentigines that simulate melanoma in situ there is no increase in the density of the lymphocytic infiltrate in association with the upwardly migrating cells compared with its density in parts of the lesion in which upward migration is absent. Dense band-like lymphocytic infiltrates, or infiltrates beneath only one portion of the lesion should raise the possibility of evolving melanoma in situ.

Upward scatter of single melanocytes is also seen in simple lentigines that have been traumatized. Parakeratosis, especially containing serum, spongiosis, extravasated erythrocytes, abundant melanin within suprabasilar keratinocytes which can be acantholytic and dyskeratotic, and subepidermal deposition of fibrin are all hints that a simple lentigo has been scratched or irritated.

Particularly florid upward migration of melanocytes is sometimes seen in simple lentigines in teenagers. Often these lesions have many vertically oriented, spindled or dendritic melanocytes. While these features suggest that the lesions are actually junctional pigmented spindle cell nevi, their nuclei are smaller than those of most such lesions and the epidermal changes (irregular hyperplasia of the spinous and granular layers of the epidermis, hyperkeratosis) seen even in early junctional Spitz's nevi are not evident.
Simple lentigines are sometimes misdiagnosed as malignant melanoma in situ because of prominent perinuclear halos around keratinocytes, and abundant melanin in dyskeratotic cells. The vacuoles surrounding melanocytes contain the entire cell, whereas those associated with keratinocytes encompass only the nucleus. Both malignant melanoma in situ and simple lentigines can have abundant melanin in the cornified layer. When pigmented keratinocytes cornify, they remain attached to their neighbors, and their flattened remnants can simulate parakeratosis (so-called pigmented pseudo-parakeratosis). When pigmented melanocytes ascend into the cornified layer, there are often clefts that separate them from adjacent keratin. However, similar clefts also surround acantholytic, dyskeratotic corneocytes in some simple lentigines and pigmented cells in the cornified layer with halos around them should not reflexively be interpreted as melanocytes.

One hallmark of the form of melanoma in situ known as lentigo maligna (melanoma in situ on the sun damaged skin of the head and neck of elderly patients) is extension of neoplastic melanocytes down adnexal epithelial structures. Some simple lentigines simulate this tropism by having more pigment in sebaceous glands and follicular mantles (rudimentary skirts of basaloid cells and sebocytes found especially in the vellus follicles of the skin around the eyes). In such cases, the increase in number of melanocytes is often minimal.

Lastly, and fortunately rarely, simple lentigines in patients who suffer from xeroderma pigmentosum can have simple lentigines whose melanocytes are markedly atypical. These may in fact be early lentiginous melanomas in situ.

B. Melanocytic nevi on acral skin

Junctional or compound melanocytic nevi on the skin of the palms, soles, nailbeds, knees and elbows feature upward scatter of melanocytes as often than not. Upward migration of melanocytes can be found even in relatively small, clinically banal nevi at these sites. In a study of over 90 such lesions, we found that melanocytic nevi with intraepidermal ascent of cells (MANIAC) occurred in younger patients than did malignant melanoma on acral skin. The lesions were smaller in diameter than acral melanomas (with the notable exception of a single broad congenital acral nevus), had only sparse lymphocytic infiltrates, and the nuclei of intraepidermal melanocytes were not markedly atypical. Although single melanocytes extended laterally beyond the last junctional nest in many cases, they were distributed homogeneously and stopped abruptly, a feature that we term lateral confinement. In contrast, acral melanomas are often very poorly circumscribed, with a periphery in which single cells are often widely scattered with irregular intervals between them. The dermal melanocytes of MANIACs are small, round cells that are often tightly clustered around the upper portions of eccrine ducts. A smooth transition occurs between the cytologic features of the intraepidermal component and the small round cells of the dermal portion of the lesion. The plane of section can influence the evaluation of these lesions, as a more orderly
pattern, with columns of pigmentation above sulci superficialis (the dells between fingerprint ridges) is evident if the specimen is sectioned perpendicular to these.

The reason that acral nevi so often have intraepidermal scatter of melanocytes is unknown. Increased epidermopoiesis can result in upward migration of melanocytes, and the skin of the palms and soles is certainly subject to repeated friction, pressure and minor trauma. Studies comparing the transit time that basilar keratinocytes take to become corneocytes show that the rate of epidermopoiesis of the skin of the hands and feet actually is slower than that of the keratinocytes on the face, although greater than that of the trunk. Thus, it is unlikely that upward migration of melanocytes on acral skin is merely a passive phenomenon due to their being swept up by keratinocytes.

When confronted with an inadequate biopsy specimen from an acral melanocytic neoplasm taken in such a way that size, circumscription, and symmetry cannot be judged, it is often wise to recommend complete excision of the lesion with conservative margins. Pathologists should be aware that this simple expedient can sometimes be problematic because of surgical considerations. If the pigmented lesion in question is situated on a weight bearing area of the foot, or if the patient suffers from venous stasis or is diabetic, complete excision can entail considerable morbidity. Discussion with the clinician, assessment of the reliability of the patient vis a vis follow up, and pathologic consultation may all prove necessary for optimal management. If a significant clinical residuum is present, dermatoscopic examination, looking for the “pigmented furrow pattern” typical of benign acral nevi can be helpful.

C. Inflamed melanocytic nevi

Melanocytic nevi become inflamed both exogenously and endogenously. Allergic contact dermatitis provoked by a substance applied to a nevus and excoriation are examples of exogenously generated inflammation.

Spongiotic dermatitis can occur in nevi due to endogenous causes. A small number of nevi, usually on the skin of the trunk, spontaneously become red and scaly, especially around their peripheries. This clinical change, referred to as 'halo eczema' can prompt a biopsy. On microscopic examination there are foci of spongiosis with lymphocytes, parakeratosis with serum, and perivascular infiltrates of mononuclear cells and eosinophils overlying the melanocytic nevus or extending slightly to either side beyond it. Single melanocytes can ascend into the mid-spinous zone of the epidermis or extending slightly beyond it. Single melanocytes can ascend into the mid-spinous zone of the epidermis, or sometimes higher, presumably due to more rapid epidermopoiesis. Further simulating melanoma in situ, the patchy distribution of the host response and thickening of the epidermis associated with the spongiotic dermatitis can result in a perception that the neoplasm is asymmetrical.

Nevi with spongiotic dermatitis were first described by Meyerson and have been named after him, expanding the series of eponymic nevi (Spitz's, Clark's, Miescher's, Sutton's, Tieche's etc.). While Meyerson's nevi are almost always solitary, some patients with pityriasis rosea can have the spongiotic dermatitis of that disease precisely superimposed on some of their melanocytic nevi. The inflammatory infiltrates in
Meyerson's nevi either subside spontaneously or respond to treatment with topical corticosteroids.

Pathologists unfamiliar with spongiotic dermatitis in nevi can become confused, especially if the initial section only includes the periphery of the lesion. In such cases, while the clinical history is often of a pigmented lesion, yet the slide appears to show an inflammatory one. One suggestion of the correct diagnosis is basilar hyperpigmentation, which is sometimes still present at the edges of spongiotic nevi. Level sections can reveal nests of melanocytes positioned more centrally in the dermal portion of the specimen.

Psoriasis can result in suprabasilar scatter of melanocytes when its changes are superimposed on those of a melanocytic nevus. Psoriasis drastically speeds epidermal transit time, and it seems likely that the upward migration of melanocytes in this setting is passive.

Melanocytic nevi on or near genital skin have unusual features that are specific to those sites (see below). On occasion, lichen sclerosus et atrophicus will occur on skin that bears such a nevus. Single melanocytes are often seen in columns immediately beneath junctional nests, and numerous melanophages can be present in the papillary dermis in such lesions. Key findings of lichen sclerosus include thickening, pallor and homogenization of the papillary dermis, often coupled with vacuolar change at the dermoepidermal junction, and compact hyperkeratosis. While vulvar melanoma occurs largely in older women, there has been one case of an authentic melanoma complicating lichen sclerosus in a 14 year old girl so that age should not be used as the sole criterion in this differential diagnosis.

Follicular cysts occur in melanocytic nevi due to constriction of follicular infundibula by the nevus, and cystic dilatation of the portion of the follicle inferior to the constriction. Rupture of the cyst results in a suppurative and granulomatous dermatitis. This process seldom simulates melanoma histologically, although the inflammatory process can do so clinically.

D. 'Dysplastic' (Clark's) nevi

Most acquired compound nevi on the trunk, and some on the extremities and scalp are proliferations of melanocytes restricted to the dermoepidermal junction and papillary dermis. Junctional nests extend laterally beyond the dermal component in the majority of such lesions and over time, may fuse to span adjacent rete ridges.

Junctional melanocytes express HLA-DR antigens and like cells of any organ expressing these antigens, can elicit lymphocytic infiltrates. The interplay between junctional melanocytes and lymphocytes, if prolonged, can lead to a distinctive form of fibrosis known as lamellar fibroplasia. In lamellar fibroplasia fibrocytes and collagen bundles are separated by clefts that lie parallel to the surface of the epidermis, beneath rete ridges bridged by horizontally oriented nests of melanocytes. The same lesions can show another pattern of fibrosis, termed concentric fibroplasia in which collagen bundles are arranged in parallel arcs around the bases of rete ridges. There are sparse
lymphocytic infiltrates and telangiectases at the peripheries of most such lesions, which have been termed dysplastic or Clark's nevi. Whether these nevi are common or rare depends in large part on the restrictiveness of the criteria used in their diagnosis.

'Dysplastic' nevi (the term dysplastic is used in quotation marks as the author is yet to be convinced that most of these nevi represent a step in neoplastic progression beyond other compound nevi) usually have only a few melanocytes with large or hyperchromatic nuclei. This feature was termed 'random cytologic atypia' by Clark and his colleagues who believe that its detection is an important diagnostic point, and was evidence that dysplastic nevi were proliferations of cells that occupied an intermediate biologic position between those of benign nevi and melanoma. They hold that dysplastic nevi are both precursors of melanoma in some cases, and markers for an increased risk of the disease.

Other authors, most notably Ackerman and various colleagues have held an opposite position, contending that the cytologic atypia in most 'dysplastic' nevi is so subtle that its detection is meaningless, and that the melanocytes in 'dysplastic' nevi are no more atypical than in other types of nevus. He and his co-workers termed nevi with a gently domed silhouette, slightly mamillated surface, and melanocytes arranged as nests at the dermoepidermal junction and within a thickened papillary dermis "Clark's nevi", to emphasize that these lesions are merely one form of melanocytic nevus rather than being exemplars of 'melanocytic dysplasia', an stage in neoplastic transformation.

Regardless of whether one accepts 'dysplastic' or 'Clark's' nevi as a way station between 'ordinary' nevi and melanoma, or as just another recognizable pattern of acquired benign melanocytic nevus there are several situations in which such lesions are repeatedly mistaken for malignant melanoma.

Suprabasilar scatter of individual melanocytes occurs in 'dysplastic' nevi when lesions are traumatized or when there is a superimposed inflammatory skin disease. Many Meyerson's nevi and halo nevi have the architectural features of 'dysplastic' nevi. One feature to look for in determining whether or not melanoma in situ is eventuating in a 'dysplastic' nevus is the consistency of the association between foci of inflammation and upward migration of melanocytes. If level sections show that suprabasilar melanocytes are confined to zones of spongiosis (sometimes resolving spongiosis leaves a cap of parakeratotic scale in its wake), the change is most likely innocent. If the areas in which melanocytes are situated in the spinous or granular layers are devoid of evidence of inflammation, that finding favors evolving melanoma in situ.

Some 'dysplastic' nevi can be poorly circumscribed in the sense that single melanocytes extend laterally beyond the lateral-most junctional nest. The distribution of single melanocytes differs from that seen in the intraepidermal portions of many melanomas in that they are evenly arrayed along the dermoepidermal junction throughout the neoplasm in 'dysplastic' nevi, and irregularly spaced along the junction or above it in malignant melanoma.

A small proportion of 'dysplastic' nevi have what has been termed "epithelioid melanocytic dysplasia". The junctional melanocytes in these nevi have abundant pale
cytoplasm with dusty pigment and centrally situated nuclei that have a dense chromatin pattern. These cells regularly elicit dense lymphocytic infiltrates. Because of these findings, a diagnosis of melanoma in situ or even superficially invasive melanoma is sometimes made or entertained. This error can be avoided by noting that the pattern of melanocytes is identical to that seen in more banal 'dysplastic' nevi. Upward migration is limited to one or two cells in a given section in the absence of irritation of the lesion. To date, there is no proof that a nevus with 'epithelioid melanocytic dysplasia' is more likely than any other type of Clark's or 'dysplastic' nevus to eventuate in melanoma or serve as a marker of an increased risk of a patient developing a melanoma elsewhere. Devotees of the eponymic school of describing nevi might term these lesions Clark's nevi with pagetoid melanocytes, but as the term pagetoid is usually used to describe upward migration of cells within an epithelium, a note explaining the diagnostic terminology is in order when using this construction in a pathology report.

Rare 'dysplastic' nevi have many melanocytes with obviously atypical nuclei. This is exceptional, and the uninterrupted behavior of such lesions has not been studied for understandable reasons. Some of these nevi may be combined nevi in which cells resembling those of Spitz's nevus are found in a background typical of a Clark's or 'dysplastic' nevus. Others are Spitz's nevi showing a pattern of growth more typical of Clark's or dysplastic nevi, with "shoulders" formed by lateral extension of junctional nests, bridging of rete ridges, lamellar fibroplasia, etc. The presence of large Spitzian cells in a central papule in this type of lesion can evoke a diagnosis of invasive, not merely in situ melanoma. Still more rare are 'dysplastic' nevi with large hyperchromatic cells that do not resemble those of a Spitz's nevus at all. It is reassuring that consultants do not routinely see cases in which melanoma evolved from incompletely excised lesions of this type. The junctional nests in these lesions bridge the bases of adjacent rete ridges. In many malignant melanomas, whether in situ or invasive, junctional nests are laterally confluent without any special relationship to rete ridges, and indeed are often attached to or embedded within the inter-retial epidermis.

Melanoma in situ does occasionally arise in 'dysplastic' nevi. Estimates of how many melanomas begin in nevi (as opposed to de novo, originating from single melanocytes at the dermoeidermal junction of clinically normal skin) have varied from under 10% to 80%. Even Ackerman and colleagues, who did not believe that 'dysplastic' nevi are of special significance still noted that of all of the forms of melanocytic nevus associated with malignant melanoma, 'Clark's nevus' is the most common. Signs that a melanoma in situ is evolving within a 'dysplastic' or 'Clark's' nevus include assymetrically distributed lymphocytic infiltrates, an area within the epidermis in which melanocytes have a different cytologic appearance from those in the remainder of the neoplasm, and upward migration many melanocytes into the upper spinous, granular and cornified layers. Tangential sectioning can result in a picture simulating upward migration of single melanocytes, as melanocytes situated in the basal layer of the epidermis overlying dermal papillae can appear to be one or two layers above the basal lamina. One should also discount some suprabasal scatter of melanocytes within
rete ridges themselves. Another hint that melanoma in situ is developing in a 'dysplastic' nevus can be gleaned by evaluating the profile of a lesion. As most 'dysplastic' nevi have evenly elongated rete ridges, extension of melanocytes within the epidermis lateral to the remainder of the lesion, distributed without regard to rete ridges can also be a sign of evolving melanoma in situ.

By far the most common situation in which we have seen lesions assessed as dysplastic nevi recur as melanoma in situ or invasive melanoma has been in the setting of broad lesions in sun-damaged skin, in which a predominance of single melanocytes is present. Some of these may represent lentiginous presentations of melanoma in situ. Others may be dysplastic nevi in which actinic mutations have accumulated, resulting in melanoma when the cells are prompted to proliferate by a partial biopsy.

E. Superficial Spitz's nevi

Spitz's nevi, even when unadorned by intraepidermal scatter of single melanocytes, can simulate malignant melanoma because they are proliferations of cells that have larger nuclei and more abundant cytoplasm than those of 'ordinary' nevi. The similarity to malignant melanoma is even more compelling when a Spitz's nevus is biopsied at an early stage at which there are many single cells, and especially when intraepidermal scatter of melanocytes is added to the picture. This can occur when a Spitz's nevus is situated on acral skin, and when one is traumatized, or inflamed.

The situation is even more difficult if one encounters a Spitz's nevus that is at an early stage of its intraepidermal development. Spitz's nevi begin as proliferations of single melanocytes within the epidermis, as do other acquired nevi and malignant melanoma. When the clinical lesions are less than 3 mm. in diameter, biopsy specimens of both Spitz's nevi and melanoma often show single melanocytes with few if any nests. Some of these melanocytes can be above the dermoepidermal junction, although the pattern is never as disorderly as it is in most examples of malignant melanoma in situ. Usually junctional Spitz's nevi elicit only sparse lymphocytic infiltrates. Other features that point to the diagnosis of an early junctional Spitz's nevus include monomorphous rather than pleomorphic nuclei, many cells with two or more nuclei, homogeneous rather than foamy appearing cytoplasm, clefts between melanocytes (when nests are present) and between melanocytes and keratinocytes even in the absence of nests, and vertical orientation of spindled melanocytes. If the epidermis demonstrates the repertoire of features common in compound Spitz's nevi, the diagnosis is assured.

Intraepidermal spread of melanocytes is common in Spitz's nevus in children and adolescents. It is generally limited to the epidermis overlying the center of the lesion. In compound Spitz's nevi, nests of melanocytes are more conspicuous than single cells, and the other well described features that enable a diagnosis of Spitz's nevus such as symmetry, sharp lateral circumscription, epidermal hyperplasia and hyperkeratosis, Kamino bodies, maturation of the dermal component, and paucity of mitotic figures can be used to distinguish the lesion from melanoma. Nonetheless, upward migration of melanocytes has been so enshrined as a feature of malignant
melanoma that some pathologists reflexively make the diagnosis of malignant melanoma on encountering a Spitz's nevus with suprabasilar scatter of melanocytes.

It should be kept in mind that Spitz's nevi have their peak incidence in children, adolescents, and young adults. They begin at the dermoepidermal junction, and evolve through compound and intradermal stages. While it is unusual (but not impossible) for a Spitz's nevus to occur in a patient over the age of 60, it is even more unusual (but again, not impossible) to correctly diagnose a Spitz's nevus at an intraepidermal stage in an older patient. The presence of abundant solar elastosis in the dermis underneath such a lesion (even in young adults) is grounds for exercising even greater caution.

The determination of whether an intraepidermal melanocytic neoplasm is an evolving Spitz's nevus or malignant melanoma in situ is one of the most difficult in dermatopathology even for consultants, and is often sabotaged by shave biopsies that preclude evaluation of circumscription and symmetry. Complete excision with a 5 mm radius of clinically normal skin to either side of the biopsy site will nearly always suffice to prevent regrowth, even if the correct diagnosis is malignant melanoma in situ.

F. Junctional and compound melanocytic nevi that recur at the site of biopsy

Melanocytic nevi are often only partially removed by shave biopsy. As early as six weeks following the attempt at eradication, a small pigmented macule may appear in the center of the scar. Because the term 'recurrent melanoma' has been used to refer to metastatic melanoma as well as melanoma that has reappeared at the sites of incomplete excision, some prefer the term 'persistent' to an unmodified use of the term 'recurrent' in reference to melanocytic neoplasms. However, to the clinician the lesion seems recurrent, and the term "recurrent at the site of biopsy" seems acceptable and lucid.

The histopathologic picture that results from regrowth of a persistent nevus is often alarming in its similarities to malignant melanoma in situ. Single melanocytes sometimes outnumber nested ones at the dermoepidermal junction, and sometimes melanocytes ascend into the mid - or upper spinous, granular, and cornified layers. There can even be small clusters of melanocytes with large nuclei in the scar just beneath the epidermis, and sometimes mitotic figures are evident in these cells.

The first step in evaluating a persistent melanocytic nevus is to obtain a slide showing the initial biopsy specimen. If the initial lesion was a banal nevus, and the interval between biopsies was short, there is no logical way that the recurrent neoplasm could be a melanoma, no matter how floridly atypical its histologic changes. If fulguration or caustic injury rather than biopsy was performed, evaluation of the pre-existent nevus becomes impossible and analysis of the histopathologic features of the persistent lesion becomes paramount.

Objective criteria can be used to distinguish recurrent nevi from melanoma in nearly all cases. In contrast to recurrent or persistent melanoma, the intraepidermal changes in recurrent nevi are confined to the area above the scar from the initial biopsy
and do not spread beyond it laterally. Instead, the intraepidermal proliferation is most cellular over the center of the scar, and diminishes laterally. In contrast, in recurrent melanomas the center of gravity of the lesion is often at the edge of a scar. The intraepidermal melanocytes of recurrent nevi are frequently hyperpigmented, due to inability of the keratinocytes that have recently covered the wound to take up melanin. Deep pigmentation of intraepidermal melanocytes in malignant melanoma is unusual. Dendritic melanocytes are frequent in recurrent nevi, but uncommon in melanomas outside of acral skin and mucosal surfaces. If the specimen is of sufficient depth, dermal cells of original nevus are often present beneath the scar. The histopathologic findings in recurrent Spitz's nevus are varied, and one pattern can simulate melanoma in situ with large solitary melanocytes situated over a dermal scar.

An immunohistochemical pitfall of recurrent nevus is related to its pathogenesis. Melanocytes in recurrent nevi ascend from epithelial adnexal structures at the base of the healing wound to repopulate the epidermis. They may also ascend through the developing scar itself, as an S100 immunoperoxidase stain demonstrates that some of the spindled cells, unlike those of a banal scar, are S100 positive. This finding should not be interpreted as indicating desmoplastic melanoma. The collagen pattern in desmoplastic melanoma random rather than horizontal and venules are not vertically oriented as they are in scars.

G. Melanocytic nevi on or near genital skin

Melanocytic nevi on or near genital skin have often been mistaken for melanoma because they demonstrate lateral confluence of junctional nests, and some of the cells that comprise those nests can ascend into the spinous and cornified layers. Additionally, some nevi on or near genital skin have dense lymphocytic infiltrates in the papillary dermis. Most of these unusual genital nevi have been noted in premenopausal women, but they occur in men as well. In contrast, vulvar melanomas have a peak incidence in older women.

Most of these nevi have the architectural features of so-called dysplastic or Clark's nevi- i.e. they only involve the epidermis and papillary dermis, and junctional nests extend laterally beyond the dermal component. Some so-called genital nevi are indistinguishable from Clark's or dysplastic nevi at other sites. The ones that pose diagnostic problems often have junctional nests composed of cells with abundant pale cytoplasm, and sometimes have dense lymphocytic infiltrates. Features that help to distinguish these lesions from melanoma involving genital skin include symmetry, lateral circumscription, and maturation of the dermal component in genital nevi. Some lesions with dense lymphocytic infiltrates can be especially challenging if there are melanocytes with large nuclei in the dermal component. Usually these larger cells are arranged singly or are in clusters along with smaller melanocytes.

H. Pagetoid intraepidermal proliferations of melanocytes in congenital nevi
Intraepidermal proliferations of melanocytes that simulate melanoma in situ can occur in the epidermis overlying congenital nevi. They were first discovered in lesions biopsied shortly after birth, but subsequently changes of this type have been noted in older infants and even in some young children. Pagetoid intraepidermal spread can be seen in either part of a congenital nevus, or in the case of small nevi, overlying most or all of its surface. The finding correlates with deeply pigmented macular areas clinically.

Pagetoid proliferations of melanocytes in the congenital nevi of newborns or infants can show upward migration of melanocytes within the epidermis, abundant cytoplasm with "dusty" melanin, and permeation of epithelial adnexal structures. Among the clues that pagetoid spread of melanocytes above a congenital nevus does not signify melanoma in situ are the uniform small round or ovoid nuclei, the presence of many nests and only a few single melanocytes above the basal layer, the absence of lymphocytic infiltrates, and a gradual transition from cells with abundant pale cytoplasm superficially to small round melanocytes with scant cytoplasm, as are otherwise characteristic of a congenital nevus deeper in the lesion. The dermal melanocytes in the congenital nevi in which this phenomenon occurs tend to be distributed around appendages, and to favor eccrine ducts over follicles, and to involve the superficial but not the deep reticular dermis. In many congenital nevi, both with and without pagetoid intraepidermal spread, a sparsely cellular zone of superficial dermis intervenes between the junctional melanocytes and a deeper component of small round melanocytes stranded between collagen bundles. This finding probably reflects differing times of migration of melanocytes from the neural crest, and the finding of a junctional component of larger cells separated from smaller ones by uninvolved dermis should not be interpreted as indicating melanoma arising in a congenital nevus.

I. Prominent single melanocytes overlying intradermal nevi

Many melanocytic nevi become largely intradermal as they age. In a minority of acquired nevi there is apparent re-activation of melanocytes at the dermoepidermal junction, evidenced by large single cells limited to the basal layer overlying the center of the nevus. This finding seems to occur most frequently overlying the wedge shaped nevi often found on facial skin, termed Miescher's nevi by Ackerman. In most cases it does not pose a diagnostic dilemma, but in specimens obtained by superficial shave biopsies large single melanocytes can be present above a zone of fibrosis that separates them from the subjacent cells of the nevus. In some specimens, only the fibrotic zone and not the underlying dermal portion of the nevus are present.

In such cases, level sections are sometimes useful in that they can show a broader portion of the lesion, that these single cells diminish in number laterally, and that they indeed overly a benign nevus.

J. Large single melanocytes in severely sun damaged skin
Among the histologic changes seen with severe solar damage are enlargement and cytologic atypicality of junctional melanocytes, which remain isolated as single cells in the basal layer. This phenomenon has been termed “actinic melanocytosis.” These aberrant melanocytes have large irregularly shaped vesicular nuclei and abundant cytoplasm. They tend to vary only slightly in size and shape, and occasional multinucleated forms occur. Often, patients with sun damage that is so severe as to derange melanocytes in a diffuse area of skin have superimposed solar lentigines whose borders are often poorly demarcated. Solar lentigines or "liver spots" are tan flat slightly keratotic areas of skin whose appearance is due to elongated, bulbous rete ridges and basilar hyperpigmentation. Often, areas of skin with this type of diffuse melanocytic damage have many small incipient solar lentigines in them that contain cytologically aberrant melanocytes which can even be present in between the lentigines.

It can therefore be difficult at times to distinguish between sun damaged melanocytes and early in situ melanoma of the lentigo maligna type. Both conditions have increased numbers of cytologically aberrant melanocytes situated as single cells at the dermoepidermal junction, above a dermis suffused with elastotic material. If the section of skin is being examined because a melanoma was nearby, it can be extremely difficult to determine where the borders of the melanoma are.

Useful in this distinction are an assessment of the numbers of melanocytes and whether nests of them are present. The skin of the face normally contains as many as one melanocyte for every four or five basal keratinocytes, and even a slightly irregular distribution can result in areas in which the ratio seems lower. Areas in which solitary melanocytes confluent replace the basal layer of the epidermis are indicative of melanoma in situ, as are the presence of nests of melanocytes, except on the skin of the eyelid. The eyelid has so many melanocytes normally that occasional nests of non-neoplastic melanocytes are found there, as evidenced by the examination of blepharoplasty specimens.

There are instances when it is impossible to determine by light microscopy whether the correct diagnosis is melanoma in situ or aberrant but non-neoplastic melanocytes on severely sun damaged skin, with or without a background of solar lentigo. In such instances a small (e.g. 2 mm.) punch biopsy of a contralateral site can indicate whether the enlargement of melanocytes is diffuse or focal. Immunoperoxidase staining is not useful at present in resolving this differential diagnosis. While the melanocytes of normal skin are HMB-45 negative, stimulated melanocytes and the cells of melanomas are often HMB-45 positive. Aberrant single melanocytes on severely sun damaged skin often express HMB-45.

K. Prominent single melanocytes adjacent to incision sites

Among the effects of wounding the skin is stimulation of melanocytes in the adjacent epidermis. Melanocytes adjacent to healing biopsy sites often are slightly enlarged and can be surrounded by retraction spaces, making them even more conspicuous. As mentioned above, normal melanocytes are HMB-45 negative.
Stimulated by the cytokines generated by wound healing, they express HMB-45 and thus can simulate melanoma both histologically and immunophenotypically.

An awareness that wound healing results in melanocytic activation that can simulate melanoma in situ can avert unnecessary surgery in many instances. The nature of the lesion that the original surgery was performed for has little bearing on this reaction to wounding- prominent melanocytes can occur next to biopsy sites of squamous and basal cell carcinoma. If the question is whether one is dealing with residual melanoma or wound-stimulated melanocytes, it is best to examine the cytologic features of the initial melanoma and contrast them with those of the melanocytes in the re-excision specimen.

L. Prominent melanocytes overlying angiofibroma

Angiofibromas are fibrous proliferations of the papillary dermis that include fibrous papule of the nose or face, pearly penile papules, hirsutoid papillomatosis of the vulva, and acral fibrokeratoma (a unifying term for the conditions reported as acquired digital fibrokeratoma, and periungual fibroma). Of these, fibrous papule of the nose or the identical lesions that occur elsewhere on the face can occasionally be difficult to distinguish from early melanoma in situ. This problem is exacerbated when the specimen in question is obtained by a superficial shave biopsy from severely sun damaged skin.

Fibrous papules are dome shaped lesions in which there are thickened collagen bundles arranged concentrically around blood vessels and hair follicles, and haphazardly in between them. Interspersed are stellate fibroblasts and multinucleated cells with dendritic processes. While at one time fibrous papules were thought to be senescent melanocytic nevi, immunohistochemical studies have indicated otherwise, as many of the stellate cells express factor XIIIa (as do dermal dendrocytes and many of the spindled cells of angiofibromas deeper cousin, dermatofibroma) but are S100 protein negative.

The melanocytes of the epidermis overlying many angiofibromas are more prominent than normal, with enlarged nuclei and retraction spaces separating them from neighboring keratinocytes. The epidermis overlying angiofibromas has a diminished rete ridge pattern, as do many melanomas on sun damaged skin. Vacuolar change at the dermoeipidermal junction and deposition of melanophages just beneath the junction also occur in many angiofibromas. When an angiofibroma is shaved off near its base, these findings do not loom large, but when shaved just beneath the epidermis, they can be striking. Often, level sections will reveal enough of the underlying fibrous proliferation and its domed contour to enable a specific diagnosis, and immunohistochemical studies can be performed to show that the dermal proliferation is non-melanocytic. Additionally, the large melanocytes in fibrous papules do not descend into adnexal epithelial structures, nor do they ascend into the upper spinous and granular layers. Upward migration may only be focally present in
melanoma in situ of the lentigo maligna type, but is sometimes evident on level sections.

II. Melanocytic neoplasms whose intradermal changes simulate malignant melanoma

A. Spitz's nevus

The determination of whether a compound proliferation of melanocytes that have large nuclei is a malignant melanoma or a Spitz's nevus has long been acknowledged as one of the most difficult and important determinations in dermatopathology. The hazards of failing to diagnose malignant melanoma are well known- an inadequate excision can lead to persistence of the neoplasm, and its subsequent metastasis. Even when excision is adequate, legal liability may result if a plaintiff's attorney can convincingly argue that the misdiagnosis was negligent and in some way contributory to a patient's demise (despite the likelihood that the melanoma had already metastasized prior to its excision). The hazard of mistaking a Spitz's nevus for malignant melanoma is that the patient may be subjected to needless surgery, be unable to plan for the future, and can be psychologically traumatized.

Spitz's nevi and malignant melanoma are often both neoplasms of melanocytes with abundant cytoplasm and large nuclei. Mitotic figures can be numerous in either condition. Some malignant melanomas are well circumscribed laterally, and appear symmetrical at scanning magnification. It is analysis of the arrangement of melanocytes and the distribution of mitoses that can best discriminate between these two neoplasms.

Stereotypic compound Spitz's nevi have a wedge shape, with an apex in the reticular dermis when viewed at low power, a silhouette that is uncommon in malignant melanoma. The epidermal changes above Spitz's nevi are distinctive - the epidermis is often irregularly hyperplastic, with hypergranulosis and compact hyperkeratosis that, except in early evolving lesions extends to cover the breadth of the entire neoplasm. Only rarely are comparable epidermal changes seen above malignant melanoma. Kamino bodies, dull pink in sections stained with hematoxylin and eosin, and globoid in shape, reside in the epidermis in many Spitz's nevi. Large Kamino bodies have scalloped borders and are surrounded by keratinocytes with compressed semilunar shapes. Well formed, large Kamino bodies are almost never numerous in melanoma. Many of the claims that Kamino bodies are a nonspecific finding derive from mistaking dyskeratotic cells for them. Single dyskeratotic cells or even small groups of them are a common finding that provides no useful clue as to the nature of a melanocytic neoplasm. Kamino bodies are more complex than mere dyskeratotic cells, consisting of not only the remnants of keratinocytes, but also of necrotic melanocytes, type IV and VII collagen (derived from basal lamina and anchoring fibrils respectively), and fibronectin.

It is exceedingly important to note symmetry, or the lack thereof, in making the differential diagnosis of Spitz's nevus vs. malignant melanoma. Symmetry can be
applied to many attributes of melanocytic neoplasms. It is usually only used to analyze the silhouette of a lesion, and if used simplistically it can fail as a criterion as many melanomas have symmetrical outlines. Other features whose symmetry should be evaluated by drawing an imaginary vertical line through the center of a lesion and comparing the right and left sides of the neoplasm are:

- The sizes of nests of melanocytes. At each level of the dermis, melanocytes on one side of the lesion should be organized into nests of approximately the same size as on the other side.

- Pigmentation. Melanin, either within melanocytes or melanophages should be relatively similar in amount on either side of the lesion at each level of the dermis.

- Lymphocytic infiltrates. In Spitz's nevus, lymphocytes are present in roughly equal numbers beneath both sides of a lesion. Usually, lymphocytic infiltrates in Spitz's nevi are perivascular and sparse. Even in the rare Spitz's nevi that have dense infiltrates, lymphocytes are evenly distributed beneath the lesion. In melanoma, some nests may elicit disproportionately intense reactions.

- Cytologic features. The nests of melanocytes on one side of a Spitz's nevus, at each level of the dermis, have essentially the same nuclear and cytoplasmic features as on the opposite side, while in melanoma there may be discrepant findings. For example, classic 'Spitzoid' cells with polygonal shapes, dense eosinophilic cytoplasm, and clefts separating melanocytes from one another can occur in melanoma, but are often not present on both sides of the neoplasm at the same stratum of the dermis.

After evaluating symmetry in all of its aspects, the pathologist should ascertain whether maturation of melanocytes is present. Maturation, like symmetry, is conventionally applied to only one feature when it should be applied to several. Most pathologists define maturation in melanocytic neoplasms as the tendency of melanocytic nuclei to diminish in size with descent into the dermis. While this is an important trait, it does not reflect the only way in which melanocytes mature. Other features to scrutinize in evaluating maturation include:

- Maturation of nucleoli. Do nucleoli diminish in size with descent into the dermis? Do they change in hue from reddish to blue? If large, eosinophilic nucleoli are present in the melanocytes at the base of a lesion, beware the diagnosis of Spitz's nevus unless all of the other features are classic.

- Diminution of cytoplasmic volume. Along with smaller nuclei, the cells of Spitz's (and other benign) nevi often have less cytoplasm in the deep portion of a lesion.

- Decrease in the sizes of nests. In Spitz's nevi, the largest nests are present at the dermoepidermal junction and in the papillary dermis. In malignant melanoma, the sizes of nests can be random, as dermal melanoma cells give rise to clones that have a higher proliferation rate than their neighbors. In Spitz's nevi that involve the reticular dermis, the deepest cells are generally scattered individually between reticular dermal collagen bundles. If a melanocytic neoplasm has large nests or fascicles as its deepest component, a diagnosis of Spitz's nevus should only be made with extreme caution. Many Spitz
nevus-like melanomas have large nests at their interface with the deep reticular dermis or subcutis, as do many of the cases reported as 'malignant Spitz nevus'.

-Diminution of pigmentation. In acquired nevi in general and in Spitz's nevus in particular, melanocytes respond to ultraviolet light in a physiologic way. Melanin is produced by cells in the superficial portion of the lesion that are more exposed to light, while melanocytes in the protected depths of the lesion remain nonpigmented. In many malignant melanomas, melanin in constitutively synthesized by neoplastic cells regardless of whether they are exposed to light or not. As blue nevi share this feature, constitutive pigmentation of deep melanocytes is not a feature of malignant melanoma per se, but is sufficiently rare in Spitz's nevi as to be a helpful discriminatory finding. There are two caveats that the surgical pathologist should bear in mind. One is that Spitz's nevi in people of Hispanic, Asian and African descent can have pigmented melanocytes throughout their thickness. Another is the so-called deep penetrating nevus (see below), a blue nevus variant that can be mistaken for Spitz's nevus because of its fascicular pattern and the large size of its ovoid cells.

A caveat about maturation is that it should be gradual. An abrupt change in the sizes or shapes of melanocytes or nests, or an abrupt change in the degree of pigmentation can indicate a transition from melanoma to an underlying nevus rather than maturation of melanocytes.

Cytologic features play a lesser role than pattern in the differential diagnosis of Spitz's nevus and malignant melanoma. Both can have large cells with abundant cytoplasm and large nuclei with prominent nucleoli, as outlined above. Several cytologic types of melanocytes are practically never found in Spitz's nevus, however. The most important of these is the 'pagetoid' melanocyte. The term pagetoid is an ambiguous one, as it is usually used to describe a pattern, namely buckshot scatter of neoplastic cells either individually or as small nests within an epithelium. However, it is the only current term for a melanocyte with abundant pale cytoplasm cytologically similar to that seen in mammary and extramammary Paget's disease. Pagetoid melanocytes often have finely vacuolated cytoplasm containing dusty or fine grained melanin. Pagetoid melanocytes can be seen in Spitz's nevi in children, but are almost never predominate in them in adults. It should be remembered that groups of pagetoid melanocytes are found in combined Spitz's nevi, and sometimes occur as the major cell type in a compound nevus. Because of these exceptions their presence in a melanocytic proliferation in an adult does not automatically signify melanoma, but should prompt careful evaluation of that possibility.

Several features that are commonly associated with malignancy in other settings, such as perineural and lymphatic invasion do no signify it in Spitz's nevus.

A form of Spitz's nevus that is particularly apt to be mistaken for melanoma is one in which a central papule or nodule is set in the middle of a patch or plaque. Clinicians often suspect that such lesions are dysplastic nevi, combined nevi or melanoma. Key features of this type of Spitz's nevus, which I have tentatively termed "superficial spreading Spitz's nevus" are sharp lateral circumscription, a peripheral component in which there are characteristic epidermal changes of Spitz's nevus,
discrete nests of spindled melanocytes at the junction separated from each other and from the epidermis by clefts, and papillary dermal fibrosis with small clusters of large melanocytes, and a central component in which there is a nodular proliferation of Spitzian cells, sometimes without overlying intraepidermal nests.

Small round melanocytes never comprise the majority of the cells within a Spitz's nevus. A few can be present at the base of a Spitz's nevus as the result of maturation, or they can be admixed with larger cells or seen to the side or even above them in a combined Spitz's nevus. If epidermal hyperplasia, hyperkeratosis, and subepidermal clefts are present above a neoplasm composed of melanocytes with small round nuclei and scant cytoplasm, the correct diagnosis may well be verrucous nevoid melanoma. While melanocytes with large vesicular nuclei and macronucleoli often occur in Spitz's nevus, cells with diffuse nuclear hyperchromasia are an uncommon finding. If present in abundance, the diagnosis is most likely 'ancient nevus' or malignant melanoma.

As Spitz's nevi mature, they become entirely intradermal. Intradermal Spitz's nevi can feature either polygonal or spindled cells, and either type can be associated with desmoplasia. Desmoplastic Spitz's nevi, sometimes simply termed desmoplastic nevi, maintain the inverted wedge shape characteristic of younger lesions. Their melanocytes are arranged largely as single cells or small nests, in contrast to those of desmoplastic melanoma in which melanocytes are arranged in long fascicles. Nodules of lymphocytes are often present in the subcutis just beneath a desmoplastic melanoma but are not characteristically present in desmoplastic Spitz's nevus. The differential diagnosis of desmoplastic Spitz's nevus and desmoplastic melanoma is discussed in more detail by Carlson and Egbert elsewhere in this monograph.

B. Cellular blue nevi

Blue nevi are dermal proliferations of dendritic or spindled melanocytes or both. Their color derives from the abundant melanin that their cells produce and transfer to melanophages. When the light that reaches them is refracted from deep in the dermis, the lesions appear blue-black or slate grey due to the Tyndall effect.

Blue nevi, unlike most acquired nevi, do not begin at the dermoepidermal junction but instead spare it. The periappendageal distribution of their melanocytes in blue nevi suggests that they may be congenital nevi 'tardive'; i.e. the melanocytes that comprise them arrived in the dermis prior to birth, but only proliferated and pigmented sufficiently to become noticeable later. Unlike acquired nevi, blue nevi show no gradation of features from top to bottom.

Cellular blue nevi have several different forms, each with a different proportion of spindled and ovoid melanocytes, sclerosis, and melanophages, sometimes with a component of bipolar dendritic melanocytes but occasionally without one. Repeatedly identified patterns of cellular blue nevi include spindle cells with sclerosis, spindle cells arranged in fascicles, ovoid cells arranged in nodules, and an unusual form in which spindled and ovoid melanocytes form elongated fascicles, adjacent to which there is
sclerosis with dendritic melanocytes and melanophages. This variant has been termed "Masson's blue neuronevus" and is exceedingly rare.

Cellular blue nevi can be mistaken for melanoma because they are often composed of large melanocytes with prominent vesicular nuclei, occasional mitotic figures, and absence of maturation. All of these features should in fact be expected in cellular blue nevi.

Deep penetrating nevus is a recently described neoplasm in which small fascicles of spindled and ovoid melanocytes form a wedge-shaped proliferation that extends into the deep reticular dermis or subcutis, hence its name. Melanophages are closely associated with both the superficial and deep nests of cells. Occasionally, a few junctional nests are present but these are usually small, giving the impression that the dermal cells do not derive from junctional nests, as they do in most acquired nevi (fig. 30). Because of the clinical appearance of these lesions, their diffuse admixture of melanophages, absence of maturation and rudimentary junctional component many consider deep penetrating nevi to be a form of blue nevus.

Because the lesions in question are usually large and deep, misdiagnosis of a melanoma as a cellular blue nevus can be disastrous as such lesions are at high risk of widespread metastasis with a high fatality rate. There are several features that should alert pathologists to the possibility of melanoma when examining a cellular blue nevus-like lesion. These include a proliferation of large ovoid or round melanocytes adjacent to a bland appearing dendritic-sclerotic or spindle cell-sclerotic blue nevus, a mitotic rate higher than 2 per 10 high power (400x) fields, atypical mitotic figures, necrosis of melanocytes, and lymphocytic infiltrates. In one series, the majority of neoplasms had mitotic rates below 2 per 10 high power fields so that a low rate does not rule out malignancy. Cytologic features are less specific. Most cellular blue nevi feature cells with small amphophilic nucleoli. Cells with large eosinophilic nucleoli can be a clue to the diagnosis of melanoma, but are occasionally seen in cellular blue nevi, and metastases have been seen in patients with cytologically unremarkable neoplasms. Comparative genomic hybridization has shown progressively more chromosomal gains and losses as ones proceeds from stereotypic blue nevi to ones with an atypical histopathologic appearance to blue nevus-like melanoma.

C. Combined nevi

Combined nevi are benign neoplasms composed of melanocytes of two or more types. The entire panoply of melanocytic cytology, including small round (ordinary), spindled, dendritic, pagetoid (in the cytologic sense, having abundant pale cytoplasm resembling the features of mammary and extramammary Paget's disease) and polygonal melanocytes can be found in discrete areas of combined nevi.

Combined nevi can simulate malignant melanoma because of their "biphasic" (or even triphasic) pattern. One clue to the diagnosis of melanoma is the finding of large melanocytes abutting smaller ones, signifying melanoma arising in a pre-existent...
benign nevus. It should be appreciated that this finding can be shared by combined nevi.

The most common combination is the finding of a small central zone of 'pagetoid' melanocytes in the center of a compound nevi composed of small round cells. The compound nevus in question is either a small, superficial one with features that suggest congenital origin (such as melanocytes arranged around appendages and in strands between reticular dermal collagen bundles at the base of the lesion) or a so-called dysplastic or Clark's nevus. The central zone of 'pagetoid' melanocytes is generally small, with only a scant junctional component. Most of the nests are situated in the papillary dermis, and are composed of cells with small monomorphous nuclei, and abundant pale cytoplasm that has minute vacuoles and dusty melanin. Nests of melanocytes are surrounded by melanophages. Mitotic figures are few, and lymphocytes are only rarely found in juxtaposition with these cells. Because the melanogenesis by the 'pagetoid' cells exceeds that of the surrounding population of ordinary melanocytes, a dark sport is usually evident clinically within the center of the lesion.

There are a variety of terms for this form of combined nevus. In addition to combined nevus with pagetoid cells, combined nevus, common type, nevus with focal clonal hyperplasia, and inverted type A nevus have all been used to describe these findings. The latter term refers to Miescher's classic description of the cells of melanocytic nevi, in which junctional cells capable of melanin synthesis were designated type A, small round melanocytes devoid of pigment type B, and spindled melanocytes resembling Schwann cells type C. Inverted type A nevus thus refers to the abnormally deep positioning of type A cells in the dermis beneath type B cells, instead of above them, in this type of combined nevus. Reed noted the similarity of the cells in this type of combined nevus to those of deep penetrating nevus (see above).

Occasional compound melanocytic nevi in children and adolescents are entirely or largely composed of 'pagetoid' cells and can thus simulate melanoma. Unless they are irritated, upward spread of melanocytes within the epidermis does not occur and junctional nests are uniformly distributed. Pure 'pagetoid' nevi are often intensely pigmented clinically. While HMB-45, which recognizes an antigen associated melanosomes labels few melanocytes in the mid- or deep dermis in most ordinary compound nevi, nevi in children who receive growth hormone therapy have intense labelling of deep dermal melanocytes with pagetoid cytology by HMB-45. Deep penetrating nevi (see above) are also similar to pagetoid nevi in their cellular composition, and perhaps pagetoid nevi, combined nevi with pagetoid cells and deep penetrating nevi comprise a spectrum of neoplasms of the same melanocytic subtype.

Another commonly encountered combination is the finding of pigmented dendritic melanocytes as would be found in a "common" blue nevus adjacent to the cells of an ordinary compound or intradermal nevus (the so-called "true and blue" type of combined nevus). Lesions of this type often appear atypical clinically because of its varied pigmentation, but seldom is problematic histologically.
The combined nevus that is commonly confused with malignant melanoma (and is the most difficult to distinguish from it) contains a population of melanocytes resembling those of Spitz's nevus. Some of the most distinctive findings of Spitz's nevi are to be found in the epidermis overlying them, namely irregular hyperplasia of the spinous layer, Kamino bodies, hypergranulosis, compact hyperkeratosis, and clefts between the epidermis and junctional nests. When a combined nevus has a spitzoid component that is superficially located, these findings can be present and may enable a facile diagnosis. When the spitzoid population is more deeply located, with only a tenuous connection with the epidermis or none at all, some or all of these epidermal signs can be absent.

In determining whether a biphasic melanocytic neoplasm is a malignant melanoma arising in a nevus, or a combined Spitz's nevus, the rules regarding pattern analysis of melanocytic neoplasms must be somewhat modified. Many combined nevi are asymmetrical, but each component taken in isolation is usually symmetrically arranged. Maturation of the nuclei of melanocytes with descent into the dermis is present in most Spitz's nevi, but is not always seen in the spitzoid portion of a combined nevus. Sometimes the only aspect of maturation is diminution in the size of aggregations of melanocytes. Cytologic features are sometimes useful in the differential diagnosis of combined Spitz's nevus. Only rarely are all of the cells of a melanoma spindled or polygonal, or do they uniformly have abundant amphophilic or eosinophilic cytoplasm separated by clefts.

Lymphocytic infiltrates can accompany the large cells of a combined Spitz's nevus, and if dense enough constitute a halo reaction. In distinguishing these changes from those of malignant melanoma arising in a nevus, one useful feature is that the halo reaction associated with spitzoid cells of a combined nevus is evenly distributed, and permeates the entire vertical domain of these cells up to the dermoeidermal junction.

D. 'Ancient' nevi

'Another' change in neurofibroma refers to the appearance within an otherwise conventional neurofibroma of cells with bizarre hyperchromatic nuclei. The atypia of these nuclei has been thought to be 'degenerative' in nature, perhaps due to anoxia as there is frequently abundant fibrin in the walls of nearby vessels and the nearby stroma is often edematous. Analogous 'degenerative' atypia occurs in so-called 'symplastic' or 'apolectic' leiomyomas.

Intradermal or largely intradermal melanocytic nevi of the type often found on the skin of the face (so-called Miescher's nevi) have a wedge-shaped configuration and have adnexocentrically distributed dermal melanocytes. Whether these nevi are acquired or are congenital nevi 'tardive' (in which melanocytes migrated to the dermis during embryonic life but the lesion became clinically evident only years later) is open to debate. Exceptionally, biopsy of such a lesion will demonstrate dermal melanocytes with large, irregularly shaped smudgily hyperchromatic nuclei similar to those seen in ancient neurofibromas. These large cells are usually arranged in clusters above or to the
side of the small round ones ordinarily seen in these nevi. Rarely, 'ancient' changes occur in Spitz's or blue nevi. Stromal changes similar to those seen in 'ancient' schwannoma, such as thrombosis, fibrin deposition and interstitial mucin are found in some 'ancient' melanocytic nevi. In some (perhaps later) 'ancient' nevi there is sclerosis between discrete clusters of melanocytes and lymphocytes can be present at the base of the process.

E. Halo reactions in nevi

A halo nevus is a melanocytic nevus that is surrounded by a ring of hypopigmented skin as a result of lymphocyte mediated pigment loss in the epidermis at the periphery of the lesion. Not all melanocytic nevi with the dense, permeative lymphocytic infiltrates that are found in halo nevi have a depigmented halo, and it is therefore safer for pathologists to render a diagnosis of a nevus with a halo reaction than a diagnosis of halo nevus, which may fly in the face of what a clinician's perceptions.

Halo reactions can occur in a single nevus, or in all of a patient's nevi simultaneously. They can also occur in melanomas, congenital nevi, blue nevi, dermatofibromas, and miscellaneous other non-melanocytic neoplasms. While most nevi in which halo reactions are present have depigmented halos clinically, some are erythematous and others unremarkable.

Histologically, halo reactions feature dense infiltrates of small lymphocytes that ascend to the dermoepidermal junction, infiltrating and disrupting junctional nests. At scanning magnification it can be difficult to discriminate between small round melanocytes and lymphocytes, and in some lesions even high magnification reveals a confusing melange of cells.

Most nevi that elicit halo reactions have the pattern of a dysplastic or Clark's nevus, i.e. are nested proliferations of melanocytes at the dermoepidermal junction and within the papillary dermis, and show some degree of bridging of adjacent rete, fibroplasia, and extension of junctional nests laterally beyond the dermal component. Features that sometimes result in confusion with malignant melanoma include the presence of large melanocytes in groups at the junction or within the papillary dermis, and misidentification of large immune cells (such as dermal Langerhans cells or immunoblasts) as melanocytes. Mitotic figures in lymphocytes are sometimes misinterpreted as occurring in melanocytes.

Melanocytes in nevi with halo reactions can have large nuclei, especially near the dermoepidermal junction. Sometimes the nests in such nevi are laterally confluent, furthering the similarity to some melanomas. Cytologic features are sometimes helpful in these cases. The large nuclei of melanocytes in halo nevi are often monomorphous, and hyperchromatic nuclei usually show some signs of pyknosis or karyorrhexis. Some of these dying cells also have brightly eosinophilic cytoplasm.

Halo reactions occur in Spitz's nevi, and especially in combined Spitz's nevi (see above). The lymphocytic infiltrates in halo reactions in Spitz's nevi are usually
uniformly distributed throughout the lesion, and permeate a proliferation in which large melanocytes are distributed individually. Large pyknotic or karyorrhectic nuclei are common in Spitz's nevi with halo reactions rather than extreme nuclear pleomorphism.

To complicate the situation, there are rare halo-nevus like melanomas. The lymphocytic infiltrates in these lesions may be an exaggeration of the more common host response of tumor infiltrating lymphocytes that is often seen in melanoma. Melanomas that resemble halo nevi are often multinodular lesions with moderate cytologic atypia in which part of the neoplasm is obscured by dense lymphocytic infiltrates. While individual fields can resemble those of a halo nevus, there are almost always some solid aggregations of melanocytes devoid of lymphocytes. In some lesions, halo reactions obscure the malignant portion, while a population of benign nevus cells at the base of the lesion is undisturbed. Care should be taken not to mistake a Spitz's nevus with a halo reaction for halo nevus-like melanoma. The same criteria that apply to the differential diagnosis between Spitz's nevus and melanoma can be used in this regard.

Some halo reactions result in the complete destruction of the nevus and a hypopigmented macule clinically. Biopsy of a halo reaction that has progressed to completion shows dense bandlike infiltrates of lymphocytes and sometimes melanophages within an edematous papillary dermis. The histologic differential diagnosis in such cases includes the late stage of a lichen planus-like keratosis and complete regression of malignant melanoma. Lichenoid keratoses are more apt to feature some remnant of their characteristic irregular epidermal hyperplasia and hyperkeratosis, and to have many clusters of colloid bodies (mummified necrotic keratinocytes) marking the sites of defunct rete ridges. Regression of melanoma usually affects broad lesions, and can result in a dense band of melanophages beneath an epidermis whose rete ridge pattern is entirely effaced. The pattern of ridges and papillae in halo nevi is at least partially preserve in most cases.

F. Intradermal nevi with mitotic figures

Some intradermal or predominately intradermal melanocytic nevi have one or a few mitotic figures. This finding, when present in isolation is innocuous. Certainly, mitotic figures in the dermal portion of a nevus are grounds for close scrutiny of the lesion for other changes of melanoma. There is one particular setting in which mitotic figures have been noted in the dermal portions of nevi- in polypoid intradermal nevi in pregnant women. "Polypoid nevus of pregnancy" is a term that has been coined to memorialize this finding, which usually includes ill-defined nests of melanocytes with pale cytoplasm and vesicular nuclei in the upper portion of the lesion. As melanocytes descend into the dermis, distinct nests appear and both nuclei and cytoplasm diminish in size. Care should be taken not to confuse such lesions with so-called verrucous nevoid melanomas, which can also have a polypoid contour and increased numbers of mitotic figures. In the latter condition, melanocytes have irregularly shaped dark nuclei,
discrete nests are not present in an orderly pattern as melanocytes mature, and lymphocytes are often present at the base of the lesion.

Pregnancy may have a number of other effects on melanocytic neoplasms. Indisputably, it intensifies pigmentation and flat melanocytic neoplasms may appear to enlarge because their amelanotic peripheries become pigmented. Aside from pigmentary changes, most of its other effects are anecdotal, and pregnancy should not be used to explain away pagetoid upward migration of melanocytes, deep mitotic figures in a lesion suspected of being a Spitz's nevus, or other suspicious findings. Indeed, some studies have found no differences in nevi removed from pregnant women and those taken from controls.

G. Dermal melanocytic proliferations arising in congenital nevi

Intraepidermal spread of melanocytes can occur above a congenital nevus in a neonate or infant and simulate melanoma in situ (see section I-H above). There are several simulants of melanoma that can occur in the dermal portion of a congenital nevus. These must be distinguished from melanoma arising in the dermal portion of a congenital nevus. Unlike the case in acquired nevi, in which melanomas almost always arise from intraepidermal melanocytes, melanoma in congenital nevi can arise from its intradermal portion.

Small papules or nodules sometimes occur within large congenital nevi, and can be darkly pigmented clinically. Histologically, these areas feature melanocytes with large vesicular nuclei that may have irregular nuclear membranes and a moderate (2-5 per 10 400x fields) mitotic rate. The large melanocytes can be arranged in sheets or in discrete nests. The nodules are internally symmetrical, mitotic figures are nearly always typical, and sometimes the larger cells blend with underlying small round melanocytes that constitute the remainder of the nevus, while in other examples there is a sharp demarcation between the two cellular populations. Lymphocytes do not demarcate the bases of these proliferations as they do in some melanomas arising in nevi. Comparative genomic hybridization shows gains or losses of whole chromosomes in some cases, while others are normal. The focused gains or losses (gains or losses of genetic material in only part of a chromosome) seen in melanoma is not present.

Proliferative neurocristic hamartoma is a designation given to rare large masses that can arise in congenital nevi. Usually the masses are deeply situated within the nevus but they can be pedunculated on occasion. Rapid growth in the first few weeks of life seems to be characteristic. Proliferative neurocristic hamartomas consist of a variety of mesenchymal tissues in addition to melanocytes. Some cases reported as malignant neoplasms arising in congenital nevi are probably also simulants of this type. Sometimes proliferative neurocristic hamartomas ulcerate and metastases that calcified and involuted following only a very short course of chemotherapy have been reported.

Microscopically, proliferative neurocristic hamartoma features large dermal or subcutaneous masses in which melanocytic differentiation may only be apparent.
focally. There are sometimes zones composed of spindled cells showing schwannian features, and simulants of Meissner's corpuscles or other neural end-organs can be present. The spindled areas can show crowding and cytologic atypia simulating neurofibrosarcoma or spindle cell melanoma, and can be associated with abundant stromal mucin. Cartilaginous foci, extramedullary hematopoiesis, and large melanocytes with vesicular nuclei similar to those described above as occurring in superficial nodular proliferations can also be present in proliferative neurocristic hamartoma 56.

Deep nodular proliferations of melanocytes with atypical vesicular nuclei and abundant rhabdoid cytoplasm can be present in large congenital nevi and as a component in smaller nevi in children. Until more is known about the biologic behavior of these lesions it seems prudent to conservatively re-excise such areas (or the entire lesion if it is small) and to report melanocytic neoplasms of this type as having unknown malignant potential.

The biologic attributes that account for these clinically and histologically alarming proliferations that seem to have little potential for metastasis are not fully known, but cultured cells from nodular melanocytic proliferations and proliferative neurocristic hamartoma show a number of attributes that differ from those of fully transformed cells of malignant melanoma. One case of each has been thoroughly studied, and the constituent cells apparently have a normal karyotype, and differ immunophenotypically and in their cell culture characteristics from the cells of fully transformed melanoma. Cultured cells from these simulants did not produce tumors when injected into nude mice but did persist at the injection sites 52.

Lethal malignant melanomas do in fact also occur in large congenital nevi during infancy. A population of melanocytes that have only scant cytoplasm and large hyperchromatic, round nuclei with a high mitotic rate seems to be characteristic of the fully malignant neoplasm 56.
References:


