THE BLUE NEVUS (JADASSOHN–TIECHE): ITS DISTINCTION FROM ORDINARY MOLES AND MALIGNANT MELANOMAS

HAMILTON MONTGOMERY, M.D.
Section on Dermatology and Syphilology, The Mayo Clinic

AND

JAMES E. KAHLER, M.D.
Fellow in Pathology, The Mayo Foundation, Rochester, Minnesota

The blue nevus was first recognized as such in 1906 by Tìeche (1), a pupil of Jadassohn, although similar lesions had been described previously by Riecke as chromatophoroma, in 1903, and by Kreibich (quoted by Miescher) as melanofibroma (2). From that time numerous reports of cases have been published in the European literature. Mention is made of blue nevus in articles on melanoma (3–8), and since 1930 cases have been briefly recorded in the English literature (9–16). Dermatopathologists (17–19) have recognized the blue nevus as an entity but the only clinical description in an American text-book on dermatology is that of Andrews (20), who fails to distinguish clearly between blue nevus and the Mongolian spot. The recorded cases number about 60. This paper is based on an analysis of 65 blue nevi in 62 patients seen at The Mayo Clinic in the past eleven years. Histopathologic studies were made in 38 of these.

CLINICAL FINDINGS

There are no statistics available to assist in approximating the incidence of blue nevus. Tièche collected the 17 cases forming the basis of his original description in eight months and one of the present writers (H. M.), looking for these tumors, collected half the cases in this series. This would indicate that the lesion is not as infrequently seen as is ordinarily supposed. A review of the clinical data for our 62 patients reveals a slight predominance in females, in the ratio of 3:2. Our youngest patient was sixteen years of age and the oldest sixty-six. With 4 exceptions the tumor had been present since birth or infancy. Two patients gave a history of ten years' duration, one of eight

1 Submitted for publication January 10, 1939.

527
FIG. 1. Typical Blue Nevus on the Foot

The photomicrograph shows irregular deposits of melanin pigment staining black in the basal cells of the epidermis and a mass of long spindle-shaped blue nevus cells laden with melanin lying deep in the cutis. Silver nitrate and hematoxylin stain. × 30.

years and one of one year. In only one case in the literature (21) was blue nevus first noted following trauma. No family history of the disease was elicited from any of the patients in our series, and there was no evidence of racial predilection. The association of blue nevi with independent pigmented nevi or lentigines in the same patient was not an infrequent occurrence. In none of our cases was there any history or evidence of a Mongolian spot.

In each of 3 cases two tumors occurred in the same patient. In one instance both tumors occurred on the forehead; in the second, a tumor was present on each forearm; in the third, one tumor was present on the left cheek and another on the left side of the forehead. The tumors tend to occur most frequently about the face and on the forearms and hands. The anatomic location of 64 of the tumors was as follows: head, 23, including 8 each on the forehead and cheek, 3 on the nose, and 1 each on the vertex, eyelid, lip and chin; trunk, 5, including 2 on the anterior chest, 2 over the sacrum, and 1 in the scapular region; upper extremity, 26, including 12 on the hand, 6 each on the wrist and forearm, and 2 on the upper arm; genitalia, 1 on the glans
The blue nevus (Fig. 1a) is a sharply circumscribed, round or oval, slightly elevated papule or nodule varying from 2 to 15 mm. in diameter, rarely exceeding the latter size. The majority of the lesions are rather firm to palpation and present a definite degree of induration. The characteristic feature is the color. In 52 per cent of the lesions in the present series the color was described as blue or mottled blue, in 32 per cent as blue-black, in 8 per cent as blue-gray, in 5 per cent as steel blue, and in 3 per cent as black. A tumor which is deep blue, blue-black, or even blue-gray in color, taken together with a history of onset shortly after birth without subsequent increase in size of the lesion, usually permits a definite clinical diagnosis of blue nevus. When, however, the lesion is steel blue or black, histopathologic studies may be necessary to differentiate it from a malignant melanoma.
Histopathology

Biopsy specimens were obtained from 38 of the 65 blue nevi of this series. Microscopic studies were done in all cases where malignancy was suspected or where the clinical diagnosis was in doubt. The tissue was fixed in formalin or alcohol or both, and multiple sections were made. Serial sections of the entire lesion were made in 8 cases.

The following stains were used: hematoxylin and eosin, van Gieson, elastin H, silver nitrate (22) and hematoxylin, Mallory's potassium ferrocyanide stain for iron, Maersch-Bielschowsky stain, and Masson's trichrome stain. In several cases frozen sections were stained with 3:4-dioxyphenylalamine (dopa) and Laidlaw's silver stain for neurites.

Histologically the typical blue nevus is composed of spindle-shaped melanoblasts grouped in irregular masses in the lower two-thirds of the cutis and separated from the overlying epidermis by normal cutis (Fig. 1b). The epidermis varies in the amount of pigment present but ordinarily does not reveal an increase in pigmentation. There may be a decrease in the pigment in the epidermis directly over the tumor.

The greatly elongated tumor cells are thickest at the center and gradually taper at each end to a fine point. They have very long wavy bipolar processes.

FIG. 3. SAME CASE AS FIG. 2

Note the vacuolated, pigmented cells in the basal layer of the epidermis characteristic of ordinary nevus and simulating cellules claires, a large pigmented cell at "x," and suggestive connection with elongated blue nevus cells in the cutis. Hematoxylin and eosin stain. X 180.
Some seem to have branching or dendritic processes. The cytoplasm is filled with a dark brown pigment occurring in fine granules distributed evenly throughout the cell. When the cells are seen in cross-section the nucleus may be surrounded by a clear halo, the pigment occupying a peripheral rim of the cytoplasm. The centrally located nucleus is oval, its chromatin equally distributed except for an eccentrically placed nucleolus. The tumor cells are irregularly grouped into bundles, which may be small and scattered throughout the lower cutis and even extend into the subcutis, or may be consolidated into one or more large masses. The cells tend to group themselves about sweat ducts, sweat glands, cutaneous nerves and blood vessels, and less frequently about hair follicles. Not all the cells of the individual tumor contain pigment; however, many apparently non-pigmented cells in a section stained with hematoxylin and eosin will show definite pigment granules on impregnation with silver nitrate. The pigment contained in these cells is melanin, as demonstrated by the fact that it darkens with silver, bleaches with hydrogen dioxide, and does not give a positive reaction for iron.

The typically elongated spindle-shaped cells of the blue nevus, with their long bipolar or dendritic processes (Fig. 4), are readily distinguished from the ordinary oval nevus cell. Even when seen in cross-section they may be differentiated from the nevus cell by their smaller size and absence of arrangement in columns, nests, or alveoli.
A more confusing picture is produced when the blue nevus cells are shorter, plump, and heavily laden with pigment, resembling chromatophores. However, the stellate or angulate phagocytic chromatophore containing large dark clumps or masses of pigment is usually in distinct contrast to the slender, fusiform blue nevus cell with its fine granules of pigment of light or darker brown. The final test for differentiation is the demonstration of a negative dopa reaction for the phagocytic chromatophore and a positive reaction for the blue nevus cells. Sato (23) was the first to prove that blue nevus cells are true melanoblasts by demonstrating a positive dopa reaction. These results have been repeatedly confirmed by other authors. The number of cells showing a positive dopa reaction in the blue nevus varies considerably in individual lesions.

Chromatophores not infrequently occur within and beside the masses of blue nevus cells. A reduction in the number of blue nevus cells and chromatophores is seen in tumors which have undergone fibrosis. Fibrotic changes in blue nevus have been reported by Tièche, Frei (24), and Alkieewicz (25). In our experience, fibrosis occurs most frequently in patients past fifty years of age and probably represents a regressive change. As in any tumor, the elastic and connective tissue in the area of the lesion is greatly disarranged, although there is no destruction of the elastic fibers.

In 14 of the 38 blue nevi on which histopathologic studies were made, tumor cells were found to occupy the upper cutis (Figs. 2 and 3) and in one case even to extend into the papillary layers (Fig. 5). A case of this type has also been reported by Marquardt (26). This change in the usual position of the tumor from deep in the cutis does not necessarily affect the color of the lesion, since 8 of these were blue in color, 3 steel blue, 2 blue-black, and 1 blue-gray. This might seem to refute Tièche’s conception that the color of the lesion results from viewing melanin pigment through a relatively wide zone of non-pigmented cutis covered by an unaltered epidermis containing either a normal or a subnormal amount of pigment. The clinical color of a cutaneous lesion, however, is affected not only by the pigment but especially by the thickness and vascularity of the skin and by its relative luminosity (brilliance), dominant wavelength (hue), and purity (saturation), as Brunsting and Sheard (27) have shown by spectrophotometric methods.

**Atypical Cases**

Cases in which blue nevus cells and ordinary pigmented nevus cells are intermingled in the same lesion have been described by many authors (28–35). Armuzzi (28) found 3 such tumors in a series of 6 blue nevi; and Stranz (36) saw 3 instances of this combination among 11 blue nevi. In the present series of 38 cases studied histologically, only 4 were found in which ordinary pigmented nevus cells lay directly beneath the epidermis and seemingly originated from it. Deeper in the cutis among the polygonal and oval nevus cells, long, fusiform, pigmented, dopa-positive cells occurred singly or in bundles. As the lower third of the cutis was reached, the fusiform blue nevus cell predominated; no definite transition from one type of cell to the other could be demonstrated. One of these cases was previously reported by Broders and Fletcher (30) as
FIG. 5. CLINICALLY BLUE-BLACK NEVUS ON DORSUM OF FOOT


b. Normal pigmented and non-pigmented basal cells apparently separated by a narrow border zone from chromatophores and blue nevus cells in the cutis. Silver nitrate and hematoxylin stain. × 160.

Also showing characteristics of a neuro-epithelial mole. Three of these 4 tumors were diagnosed clinically as pigmented nevi. A fourth was diagnosed as blue nevus. They represent a combination of two morphologically different types of nevus cell. This, however, is not surprising in view of the frequent occurrence of more than one type of nevoid disturbance in the same patient. In one of our cases, clinically and histologically a typical blue nevus, there
occurred in addition anomalous proliferation of sweat ducts and an increase in the number of sweat glands.

Cases have been described in the literature as blue nevi in which there were large flat plaques of pigmentation, in several instances located near the eye and extending to involve the sclera and eyeball (9, 10, 11, 37). In 3 of these cases the diagnosis was made on clinical grounds alone. In one case (10) the histopathologic picture was considered that of a blue nevus, although the question was raised whether the cells were true melanoblasts or simply represented chromatophores lying deep in the cutis. A similar case was seen by O'Leary (38) and by one of the present writers (H. M.), which we were inclined to regard at first as a blue nevus but which apparently was a benign melanosis, the result of some type of metallic deposit. These disseminated plaques certainly are not the usual picture of a blue nevus and are most likely the result of pigmentation from various other causes, possibly in some cases even representing aberrant and persistent Mongolian spots.

**Malignancy**

The blue nevus is fundamentally a benign lesion and like the ordinary pigmented mole (nevus) rarely undergoes malignant change except when subjected to prolonged and repeated trauma and irritation. In any pigmented nevus the history of an increase in size and in intensity of pigmentation raises the suspicion of a malignant alteration.

In all but three instances in the present series the lesions were entirely asymptomatic. In one case the lesion had appeared eight years previously and was associated with repeated formation of serosanguineous vesicles. Histologically it was a typical blue nevus, except that the papillary and subpapillary layers contained large numbers of chromatophores. Stains for iron were negative. In the second case the patient had noticed a light blue tumor one year previously. There was an occasional burning sensation and the tumor increased progressively in size. Microscopically the lesion was a typical blue nevus. The third patient had been cognizant as long as she could remember of a small "black mole" on the dorsum of the right foot. The lesion gradually increased in size to 4 mm. in diameter. Histologic examination revealed a tumor composed of blue nevus cells and chromatophores lying directly beneath the epidermis and in some places apparently arising directly therefrom (Fig. 5). Many blue nevus cells were scattered throughout the rather heavily fibrosed cutis. Stains for iron were negative.

In none of these three cases nor in any of the cases in our series of blue nevi was there any histologic evidence of malignancy. No attempt at follow-up was made because of the relatively short time which had elapsed since the majority of the patients were first seen.

Nine cases appear in the literature as blue nevi that have undergone malignant change. One of these is reported by title only (39). In Dörffel's case (40) a typical blue nevus had recently increased in size. There was no recurrence following wide excision and the histopathology remained that of a blue nevus. Bezecny (29) reported a case in which both ordinary nevus cells and blue nevus cells were present and in which malignant change ensued only after electrolysis had been used to remove a hair from the center of the lesion.
Reiss (41) described a small blue mole appearing on the chest, followed shortly by showers of similar lesions over the entire skin surface and conjunctiva. The cells in the metastatic lesions were described as being both fusiform and globular, which, together with the clinical picture, would suggest that the case was more likely one of metastatic melano-epithelioma than of melanosarcoma arising from a blue nevus. Rothfeld (42) reported a case in which there were a great many blue pigmented nodules and tumors on the forehead, which histologically were typical of a blue nevus. Metastasis occurred to the brain. There the histopathologic picture simulated that of an ordinary melano-epithelioma and Rothfeld did not describe typical blue nevus cells in the metastasis. The possibility remains, therefore, that there may have been two separate and independent tumors in this patient.

Darier (43) reported three examples of melanomas arising from blue nevi. In the first case there were innumerable bluish nodules involving the left shoulder and left side of the neck and face. The patient received intensive treatment of various types before generalized metastasis took place. It is not clear from the descriptions whether the histopathologic picture was that of blue nevus with malignant change. The second case was of an extensive pigmented plaque on the shoulder, 9 cm. in diameter, which had progressed in size and received intensive treatment with electrolysis. It was finally excised surgically and there was no immediate recurrence. Darier regarded the histopathologic picture as that of a melanoma arising from the blue nevus. His Figure 6, however, shows many polygonal and angular cells suggesting an epithelial origin and resembling a scirrhous type of melano-epithelioma. In a third case the lesions were associated with angiomata and the clinical photograph does not at all suggest a blue nevus. Darier in his discussion recognized the ability of some melano-epitheliomas to simulate a sarcoma; nevertheless he felt that all his three cases were melanomas and could be explained only on the basis that the original lesions were those of blue nevus, since melanomas could only arise from dermal melanoblasts.

Finally, Andrews (20) has clinical and microscopic pictures (Figs. 719 and 792) of a case of Stout's, of melanoma arising from a blue nevus on the dorsum of the foot. Stout (44) plans to report this case, which would seem to be a fairly clear-cut example of malignant change of a blue nevus in contrast to most of the other 8 cases just cited. We are in accord with the opinion of Miescher (2) and Jadassohn (45) that malignant change in a blue nevus is a rare occurrence.

**Etiology**

Space does not permit a discussion of Unna's concept of the origin of ordinary pigmented nevi from the epidermis (46), which was generally accepted in the past, nor the concept of the neuro-epithelial nature of moles as advocated by Soldan (47) and Masson (48) and recently supported by Foot (49), Laidlaw (50), Becker (3), and Ebert (51). In only one atypical case in our series, in which both ordinary nevus cells and blue nevus cells were present, was there apparent relationship of the latter to a myelinated nerve (see Figs. 5 and 6 of Broders and Fletcher's article, 30). Though Bouin's fixative was not used in any of the 38 cases studied histologically, no evidence
could be demonstrated of a neuro-epithelial origin or of the presence of lamées foliâcées or neuroglia-like tissue.

The origin of the blue nevus cell from ectodermal or mesodermal tissue again is dependent on whether melanoblasts (melanin-producing cells) are all of ectodermal origin—fundamentally basal and dendritic cells of the epidermis (52)—or whether there are true melanoblasts of mesodermal (53) origin.

Tièche drew an analogy between the cells of the blue nevus and those of the Mongolian spot and pointed out their similarity to those of the mesenchymal pigmentary apparatus of certain vertebrates. The majority of authors since then have concurred in this concept and have found the cells in both conditions to be dopa-positive. In support of a mesodermal origin for the blue nevus cell was our failure to demonstrate morphologically any connection between the blue nevus cells and the epidermis in 36 of the 38 cases studied histopathologically, including 7 of 8 cases in which serial sections were made. The morphologic appearance of the blue nevus cell is that of a connective-tissue cell and not that of an epidermal cell. It is true that in squamous-cell epithelioma of grade 3 and 4 malignancy, on a basis of 1 to 4, the histopathologic picture may simulate that of sarcoma, but even in these instances careful search will reveal some of the cells which have preserved their epithelial characteristics and usually in serial sections it is possible to demonstrate origin from the epidermis. The majority of dermatohistopathologists who have studied blue nevus concur in the belief that the cells are of mesodermal origin (Gans, McCarthy, Miescher, Becker, and Montgomery).

In support of an epidermal origin for blue nevus are two cases in the present series in which apparent connection of blue nevus cells to the epidermis was seen.

In the first case (Figs. 2 and 3) there was increased pigmentation of the basal-cell layer of the epidermis; the blue nevus seemed to lie separate in the cutis. In a few serial sections, however, from a small area, the tips of the rete pegs were occupied by large globoid cells differing in appearance from cellules claires only in that melanin-stained cell filaments of cytoplasm connected the nucleus with the cell membrane. Lying between and almost in contact with two adjacent rete pegs having this appearance were two melanin-containing cells which were short, plump, and without processes. By serial sections these could be traced to masses of typical blue nevus cells lying deeper in the cutis. In appearance these connecting cells suggested in some respects ordinary chromatophores rather than ordinary nevus or blue nevus cells.

In the second case there were active growth and increase in size of the lesion clinically. The histopathologic picture is shown in Fig. 5. There was marked increase in pigmentation in the epidermis, in chromatophores and in blue nevus cells in the cutis. The basal cells in some of the rete ridges seemed to merge imperceptibly into the tumor masses. There appeared to be morphologic transition between basal cells and typical blue nevus cells. In a major portion of the tumor, however, there was a definite border zone between the tumor cells and the chromatophores and normal appearing basal cells.

In both these cases there was active increase in pigment formation in the epidermis and in the cutis. The possibility exists, therefore, that there was
simultaneous stimulation of epidermal and mesodermal melanoblasts and that in the first case there was a beginning development of an ordinary pigmented nevus from the epidermis superimposed on the original blue nevus.

The four cases in which blue nevus was associated with ordinary pigmented nevi would tend to support an epidermal origin, although no transition between the two types of cells could be demonstrated. The cells still remained quite distinct from one another in their morphology. Broders would regard blue nevi as of ectodermal origin and believes that the blue nevus "differs from the usual pigmented nevus in that its cells show a marked tendency to assume a spindle form, thereby giving it a connective tissue effect." Various authors (29, 32, 34) have emphasized the presence of cholesterol and other lipoids in the cells of both blue nevi and ordinary pigmented nevi and hence believe the blue nevus cell to be of epidermal origin. Lipoids, however, are found most frequently in cells of mesodermal origin, as, for example, in xanthommas and dermatofibromas.

One of the present writers (J. E. K.) would suggest that, since increase in size of the tumor ceases early in life in the great majority of blue nevi, the tumor cells may therefore lose their connection with the epidermis, and that if blue nevi removed from infants and young children were studied there would be more cases revealing a direct connection between the tumor cells and the epidermis. Against this concept is the similarity of blue nevus cells and the cells in the Mongolian spot. El Bahrawy (54) in a study of a large series of specimens of the skin of fetuses and infants found no connection between the melanoblastic cells of the Mongolian spot and the epidermis. The Mongolian cells were laden with pigment early in fetal life before any deposition of pigment was to be seen in the epidermis. The evidence presented, therefore, would seem to favor a mesodermal origin for the blue nevus.

**Differential Diagnosis**

The blue nevus has been confused with the Mongolian spot. The latter is usually a solitary plaque 2 to 12 cm. in diameter occurring on the back, usually near the sacrum. It may be brown rather than blue. It is seen most frequently in the Mongolian race but occurs in the Caucasian, also. The pigmented area is poorly defined; it is not elevated or indurated. It is usually present at birth and, as a rule, disappears within the first few years. Occasionally multiple plaques are seen scattered over the body and solitary Mongolian spots have been described elsewhere than on the back (55). The cells in the Mongolian spot are histologically nearly identical in appearance with the blue nevus cells but are relatively few in number and occur singly rather than in clumps or in masses. There is no disturbance in the normal architecture of the connective tissue and elastic tissue fibers.

The blue nevus also must be differentiated from ordinary pigmented nevi, dermatofibroma with hemorrhage (histiocytoma), small deeply situated hemangioma, and finally from malignant melanoma. The blue to blue-gray color usually distinguishes the blue nevus, on clinical grounds alone, from the ordinary brown to brownish-black pigmented nevus. In typical cases the nevus cells in the two conditions present entirely different morphologic features.
Dermatofibroma occasionally presents a blue color, especially when deposits of hemosiderin are to be found histologically. A few chromatophores laden with pigment may be seen, but no elongated fusiform melanoblasts (blue nevus cells) are present. A small deep hemangioma may present a blue color but it is soft to palpation and blood is obtained on puncture of the lesion. The "tache bleu" of the morphine addict need only be mentioned.

In a few cases blue nevus may simulate the steel blue color of an early malignant melano-epithelioma in which radiating lines of pigment in the lymphatics have not yet developed. A wide surgical excision is indicated in these cases. The histologic picture is confusing only when the cells of melano-epithelioma elongate into spindle-shaped cells frequently containing much pigment. These cells, however, also have an increased amount of cytoplasm and their nuclei are hyperchromatic and frequently contain mitotic figures, three characters which are not seen in blue nevus cells.

SUMMARY AND CONCLUSIONS

Sixty-five cases of blue nevus occurring in 62 patients are recorded. Thirty-eight of the lesions were studied histopathologically. It is our belief that if blue nevi are looked for they will be found much more frequently than the literature would indicate and that they are of relatively common occurrence.

The onset in infancy or in early childhood of a firm, blue to blue-gray papule or nodule remaining as such, without increase in size, usually permits a clinical diagnosis of blue nevus.

The histopathologic picture is characteristic, although occasional cases are found in which ordinary pigmented nevus cells and blue nevus cells are found in the same lesion.

Blue nevus rarely shows malignant change. When this occurs it would seem to be that of a relatively slow-growing melanosarcoma. Like ordinary pigmented nevi, the blue nevus usually runs a benign course and there is no need for surgical excision unless for cosmetic purposes or where the lesion is situated in an area exposed to repeated trauma, friction, or irritation.

The problem of the mesodermal or epidermal origin of these tumors is discussed.

The blue nevus is differentiated from various conditions, especially from melano-epithelioma, with which it has been confused clinically and even pathologically. Occasionally a blue nevus may show increase in size or present a steel-blue color simulating that of a melano-epithelioma. In such instances wide and deep surgical excision is indicated.

REFERENCES

BLUE NEVUS (JADASSOHN-TIECHE) 539

33. Stout, A. P.: Personal communication to the authors.