MELANOBLASTOSIS AND MELANOBLASTOMA; PRIMARY AND SECONDARY INVOLVEMENT OF THE BRAIN

AN ANATOMIC STUDY

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INTRODUCTION

Difficulties have been experienced in classifying a large group of tumors, the common feature of which is the presence of melanin pigment (melanomas). These hardships in classification are attributable, in large measure, first to an attempt on the part of earlier observers to trace the origin of the tumor to one type of cell; second, to the existence of multiple and conflicting concepts throughout the literature on pigmented tissues; third, to the indiscriminate use of such terms as chromatophore, melanophore, melanoblast, mole, nevus, lentigo, café au lait spots, chromatophoroma, melanoma, etc.

According to the modern usage, there are recognized three types of melanoblasts, one derived from epithelium, one from connective tissue, and one whose origin cannot be definitely stated. The first is the commonly known basal cell of the epithelium and hair follicle. The second is illustrated well by the cells comprising the blue nevus of Jadassohn or the choroid of the eye. The third is that cell which is commonly found in clusters beneath the epithelium of the skin, surrounding the dendrites of peripheral nerves. In addition to these three types, there is a group of cells which has no melanoblastic function but contains pigment by virtue of its power to phagocytose melanin. These are called chromatophores and are usually connective-tissue cells, but may in certain instances be of epithelial origin.

There are several methods available for distinguishing the melanoblast from the chromatophore. One is a specific staining reaction; another, embryologic and comparative anatomic study; a third, the study of cellular morphology in conjunction with one of the first two modes of investigation.

Bloch (1, 2) and his associates worked out the "dopa" reaction, which they assert is positive in all melanoblasts at the time of pigment building, the intensity of the reaction being an indication of the amount of melanoblastic function. The specificity of the reaction has been questioned by Borst (3). One of the chief reasons for this doubt is the fact that leukocytes give intensely positive dopa reactions. Such a reaction is shown in Fig. 1. To meet this criticism, Bloch and Peck (4) have shown that by subjecting the tissues to a variety of stains the specificity of the dopa reaction may be maintained. Peck, Sobotka and Kahn (5) have shown that the levorotatory 3:4-dioxyphenylalanine alone gives the reaction with the melanin oxydase found in epidermal melanoblasts. Inasmuch as the dextrorotatory form fails to produce a positive reaction, there must be within the pigment cell an enzyme which is specific for levorotatory 3:4-dioxyphenylalanine. If "dopa" is the propig-
ment of melanin, the reaction becomes a specific indicator of melanoblastic function.

In the field of comparative anatomy, Laidlaw and Murray (6) have shown a relationship between the pigmented mole and the tactile spots of reptiles. Stockard (7), also working in the field of comparative anatomy and embryology, has shown that the chromatophore is a specialized cell derived from the mesoblast. Miescher (8) and Peck (9) have demonstrated that the melanoblastic function of the mesodermal cells of the choroid of the eye is present only during embryonic life.

On applying the above methods of investigation, certain conclusions have been reached with regard to the several forms of melanin-carrying cells. Concerning the nevus cell it is agreed that it has melanoblastic function and it is found within the true dermis in cell masses which surround the end arborization of peripheral nerves. But beyond this there is a disagreement. One group, consisting of Bloch, Fox (10), and others, considers it to be a cell which splits off from the ectoderm. In microscopic studies of the skin they report a down-growth of the epithelium into the dermis in the region of a tumorous nevus. Some pathologists, as Boyd (11) and Dawson (12), think that the transitions between the epithelium and the nevus rest can be definitely traced. The evidence presented by the other group, which includes Masson (13), Laidlaw and Murray, Foot and Zeek (14), and Snessarew (15), following the earlier work of Soldan (16), is supported by Ewing (17). These authorities have tried to prove that the nevus cell is derived directly from the nervous system. Their views are based chiefly on the observation that nerve fibers arborize about nevus cells. Certain chromatophore-like pigment cells, which lie at the periphery of the nevus clump in the dermis, are considered to be daughter cells of the nevus moiety, and to owe their anatomic position to the fact that growth is from within outward. Certain other cells lying within the epidermis, about which naked nerve fibers arborize, are also considered to be nevus cells. The remainder of the evidence presented by this group of investigators is concerned with the demonstration of morphologic differences between nevus cells on one hand and either epithelial or connective-tissue cells on the other. That the nevus cells constitute a special cell form is definitely shown, but what is not clearly demonstrated is that they are not epithelial in origin. Masson alone suggests that the nevus cell is a form of glia. The other adherents of the theory that the nevus cells are derived from neural structures are content merely with a vague reference to the "nervous" origin of the nevus.

There are certain objections to the work of this latter group. While subscribing to this theory, Ewing admits that no evidence has been offered that cells of the tactile corpuscle are other than ordinary epithelial cells, and acknowledges the fact that nerve fibers may end blindly within the epidermis. The tumor cells are not impregnated in silver and gold preparations as are cells arising in the central nervous system. If we are to accept Masson's view that the nerve end organ is glial in origin, then we must accept the concept that there are glial tumors which metastasize widely outside of the nervous system. Gliogenous tumors which act in this manner are relatively unknown. In their papers supporting the nervous origin of the nevus cell,
Foot and Zeek raise serious objections to their own impressions, chief of which is the observation that metastases of melanotic tumors show the same type of nerve fibers as the primary focus. In the light of all this controversial evidence, it seems best to consider the nevus cell to be a specialized epithelial cell with important relations to the nervous system.

For the purpose of this paper, which deals with primary melanotic conditions involving the cerebrospinal meninges, the above general concepts about pigmented cells and tumors need to be correlated with the findings in the meninges. The first question to be answered is then: are there epithelial and mesodermal melanoblasts as well as nevus clumps existing normally within the meninges?

The demonstration by Weed (18) that the meninges in which primary melanotic tumors arise are of mesoblastic origin serves to a degree as basis for the assumption that such tumors may also be mesodermal in origin.

Furthermore, the mesodermal melanoblasts constituting the choroid of the eye are in ontogenetic development not remote from the meninges of the brain. Inclusions of such melanoblasts may well occur during this phase of development. A fair number of our routine autopsies show on microscopic examination pigmented cells, which morphologically resemble connective-tissue cells, situated in the pia about the brain stem and cervical cord. In several instances the accumulation is so dense as to impart a brownish discoloration to the meninges. Additional evidence is given by Globus (19), who, in discussing meningeal tumors of several varieties, traces all of them on a phylogenetic basis to a mesodermal origin and includes among them the melanomatous pial meningioma.

Harvey and Burr (20) carried out the following experiments. Portions of the nervous system of *Amblyostoma* were autotransplanted into the mesenchyme of the trunk. In one group of operations the neural crest was included; in another group it was left out. Subsequent microscopic examination of the

![Image](image-url)
transplants showed that, where the neural crest had been included, a definite cellular layer was found to envelope the nervous system, while where the neural crest had not been left attached to the neural tube, no such layer could be found to surround the brain. It was thought, therefore, that these neuroepithelial elements of the neural crest were essential in the formation of the meninges. Many years before this work, Weidenreich (21) had suggested that the pigment cells in the leptomeninges took their origin in a detached portion of the neural tube. Thus a probable explanation is offered for the presence of pigmented epithelial tumors in the leptomeninges. However, repetition by Flexner (22) of the above experiments has failed to confirm the alleged results. Dieckmann (23) has described nevus-like patches in the leptomeninges. This observation has not been corroborated. Although epithelial melanoblasts have not been demonstrated as normal inclusions within the leptomeninges, their existence may be inferred from the presence of epithelial tumors found as primary meningeal growths.

A primary meningeal tumor which has the histologic appearance of a carcinoma is well exemplified by the case of Omodei-Zorini (24) among others. The cases of Lackerbauer (25) and Akelaitis (26) illustrate well the melanosarcoma type. The criteria for the diagnosis of carcinoma and sarcoma are satisfied in these cases. There are recorded in the literature the pathologic descriptions of 36 cases of melanotic tumors which arose as primary meningeal growths. Beginning with an observer quoted by Virchow (27), these cases number as follows: Valentin (28), Virchow (27), Sternberg (29), Rokitansky (30), Stoerk (31), Pick (32), Minelli (33), Boit (34), Thorel (35), Bosch (36), Lindbom (37), Lua (38), Hesse (39), Esser (40), Schopper (41), Koelichen (42), Kiel (43), Matzdorff (44), Neubürger (45), Omodei-Zorini

![Fig. 2. Case I: Base of the Brain, showing the Distribution of Pigment](image)
MELANOBLASTOSIS AND MELANOBLASTOMA

The material studied comprises a case of primary melanoblastosis of the pia mater, a primary melanosarcoma of the meninges, and four metastatic melanotic tumors of the brain.

CASE I: A five-year-old colored child died of a disease process unrelated to the condition to be described. The general autopsy revealed no evidence of a primary melanotic tumor nor were metastatic deposits anywhere demonstrable. The only finding in the brain, of significance, was a circumscribed melanoblastosis (Fig. 2). A grayish discoloration was observed over the orbital surface of the right frontal lobe. It extended from the frontal pole to the optic chiasm and from the ventral extension of the dorsal longitudinal fissure to the lateral margin of the frontal lobe, assuming a triangular outline with its apex at the frontal lobe and the base in the lateral fissure. A similar area of pigment was seen over the pons, particularly on the right side and over the right half of the upper portion of the medulla. A few small patches were seen over the left hemisphere. On cut section the subjacent cortex showed a grayish discoloration.
FIG. 4. CASE I: MELANOBLASTS IN THE PIA MATER

In A is shown the distribution of melanoblasts in relation to blood vessels. Note the many processed cells. B is a high-power study of two adjacent melanoblasts, showing the imminent separation of portions of their processes.

Histologic Observations: In studying the material, the following procedures were used. Portions of leptomeninges were stripped from the brain. The pia mater was carefully peeled from the arachnoid, as the former alone was seen to contain pigment. The strips were either mounted without further treatment or were subjected to various staining methods. These included hematoxylin-eosin stain, impregnation with silver after the Bielschowsky technic for demonstration of nerve fibers, and a procedure for decolorization of the melanin to show the character of the cytoplasm. Blocks of tissue from various portions of the cortex and brain stem were imbedded in paraffin and sections from these blocks were stained in hematoxylin and eosin. Nissl stains were performed upon celloidin sections, and routine silver stains (Bielschowsky and Cajal and Hortega after the Globus modification) were prepared from frozen sections. A special stain was used to rule out iron compounds as the source of the pigment. The van Gieson connective-tissue stain was employed to
demonstrate collagenous fibers. The dopa staining was performed following the technic outlined by Bloch (1). The buffering was scrupulously attended to, and the preparations were carefully watched during incubation.

Distributed throughout the affected pia mater were large, heavily pigmented, fusiform, stellate, and ovoid cells. Such cells were also found within the substance of the brain adjacent to the meninges and in the connective-tissue septa about blood vessels. Neither the subarachnoid space nor the arachnoid membrane contained pigmented cells. No nodules of pigmented cells were found within the brain except for the aforementioned collections about blood vessels. The cells for the most part lay individually in the connective tissue of the pia and were separated from one another by fibrous strands. The perivascular distribution of cells is well exhibited in Fig. 3.

The structure of the cells was best studied in the strips of pia mater. Here (Fig. 4a) the loose ameboid character of the cells was conspicuous. The cells were very large. Their processes, like pseudopodia, assumed a contour which conformed with the connective-tissue planes. Occasionally portions of these processes seemed so constricted that separation from the cell body appeared imminent (Fig. 4b). Small round pigmented bodies without nuclei were found free in the pial interstices, a finding which suggested that separation from the parent melanoblasts might actually have taken place. Coarse pigment granules were found free in the pial connective tissue or within swollen round cells with excentric nuclei.

In unstained preparations the nuclei showed up as pale, oval vacuoles usually occupying the central enlargement of the pigmented cell. Nuclear stains showed the chromatin material to be scanty in the few cells where the nucleus was visible. An occasional cell was seen containing two nuclei. The cytoplasm of the pigment cell viewed after decolorization of the melanin seemed filled with many large and small vacuoles. There was no evidence of reactive phenomena in the meninges or within the brain substance in response to the presence of the pigmented cells, as might be expected if the cells were invasive and neoplastic in nature. Certain minor changes in ganglion cells and a mild diffuse gliosis, which were present, could be attributed to the severe toxic infectious process which caused the patient's death. Pigment was not found within ganglion cells or glia cells. Small granules were occasionally seen within the endothelial cells lining blood vessels. Bielschowsky stains applied to fragments of pia mater showed an occasional fiber resembling an axis cylinder, but these seemed definitely to lie in a focal plane apart from the melanotic cells.

Case II: In this case, the general autopsy also failed to show primary or secondary melanotic tumors. The ante-mortem diagnosis had been posterior fossa tumor.

The leptomeninges over the base of the brain and brain stem were thickened and firm, and had a brownish-black coloration. The extent of this involvement was from the cervical cord to the optic chiasma and laterally into the fissures of Sylvius (Fig. 5).

Histologic Observations: In the region of the thickened portion of the meninges the subarachnoid space was filled with solid masses of tumor cells which had infiltrated both arachnoid and pial membranes. Solid columns of cells were seen in the pial septa deep within the substance of the brain. The cells frequently assumed what appeared to be an acinar arrangement (Fig. 6). This, on closer inspection, proved to be a false impression, as the arrangement was really perithelial. In the solid infiltrating masses, connective tissue could not be demonstrated between the individual tumor cells by ordinary staining methods.

Cuboidal and globoid cells with large vesicular ovoid and round nuclei were often seen in scattered groups or as isolated cells, but for the most part the plump fusiform and elongated narrow spindle cells were the most characteristic cell types. In none of the tumor cells were the nuclei totally obscured by pigment. The pigment existed as a fine brown and yellow dust within the cytoplasm, and there was no uniformity in the amount present within each cell. In the cell columns which infiltrated the brain, relatively fewer cells had processes, but within the meninges (Fig. 6) the cells were mainly fusiform and often assumed a palisade arrangement. The cytoplasm of all the neoplastic cells stained poorly, if at all, with routine silver and gold stains. Mitotic figures were not infrequently encountered.

On the other hand, the amount of pigment observed in the tissue surrounding these tumor rests was considerable. It was found either free in the tissue about the tumor or within the neighboring normal structures, i.e. in ganglion cells, astrocytes, microglia, and the endothelial cells lining vessels. The pigmented counterpart of the gitter cell was also fre-
Fig. 5. Case II: Drawing of the Base of the Brain

Fig. 6. Case II: Pseudo-acinar Arrangement of Melanosarcoma Cells, Shown Actually to Be Perithelial
quenty seen in the marginal tissues. The pigment within all of these cells appeared as coarse dark granules as contrasted with the pigment in the pale cell nests of the tumor. The tumor columns seemed actually surrounded by a halo of dark pigment-bearing cells.

The alterations in the brain tissue were dependent upon the disruptions produced in the fiber bundles and ganglion cell layers by the deeply infiltrating tumor. No nerve fibers were demonstrable within tumor nests.

Cases III–VI: These four cases are instances of metastatic melanotic tumors of the brain.

No single characteristic may be regarded as common to all these malignant neoplastic deposits. There were perithelial arrangements of cells; there were regions in which small clusters of tumor cells lay in isolation within surrounding brain tissue which was fairly normal; there were areas where mitotic figures appeared rampant, while other regions showed no evidence of cellular divisions. For the most part the tumor cells were polygonal with large highly chromatic nuclei, but occasionally bunches of spindle cells were seen interspersed between the tumor columns. Large areas of the new growth showed no pigment or it was seen on close inspection to be faintly and finely distributed within the cells. Small areas, usually consisting of isolated clusters of cells, however, showed a fairly uniform pigment content.

In addition to the distribution within tumor cells, dense accumulations of pigment were found in the marginal tissues or in gaps within the tumor proper (Fig. 7). These lakes of pigment were composed of coarse granules of melanin lying free in the tissue or within huge round cells which closely resembled glitter cells (Fig. 8). A slight similarity to a glandular structure in which there are colloid deposits was manifested in low-power study of the tissue. These areas, however, may well represent necrotic foci within the substance of the tumor whose only formed remnant is the agglutinated pigment.

Comment and Conclusions

In the first case of apparently congenital melanoblastosis of the meninges, the pigmented cells have the morphologic characteristics of ameboid connective-tissue cells. They are found only in the pia mater or pial septa which follow blood vessels within the brain. Pigment in this case is observed mainly within the melanoblastic cells. The ameboid cells often have portions of their cytoplasms pinched off and these appear as round bodies lying free within the connective tissue. Degeneration of these bodies leads to the deposition of coarse pigment granules in the pial stroma, where they are either phagocytosed by scavenger cells of the reticulo-endothelial series or mobilized directly into the cerebrospinal fluid. The case may be regarded, following Globus’ (19) classification, as an instance of mesoblastic (meningeal) melanoblastosis arising from some malformation originating during embryonal life.

As a result of malignant degeneration of such heterotopic deposits of melanoblasts, there arises a tumor which fulfills the criteria for melanosarcoma (Case II). The neoplastic cell resembles the ordinary benign quiescent melanoblast very little. In the former the cell outline is rounded and never attains the size of the resting pial melanoblast. The nucleus in the sarcoma cell is highly chromatic, whereas in the quiescent cell it is often difficult to outline the chromatin material even after decolorization and counterstaining. Finally, the mode of pigment handling seems clearly to differentiate the two cells. In the tumor, the pigment is handled somewhat as a product for excretion. Thus, the pigment does not tend to accumulate within the tumor proper but in the surrounding normal structures. In melanoblastosis, the pigment is found almost exclusively within the melanoblasts themselves.
This difference in pigment disposal is also seen in metastatic tumors. Here, however, the tumor nodules are of themselves so large that instead of deposition mainly within surrounding normal structures, the pigment is found concentrated in gaps within the tumor proper. Thus, it seems that malignancy alters the ability of the melanoblast to hold the pigment it creates within its cell boundaries. Peck, in a personal communication, suggests a possible explanation for the sparseness of the pigment in these malignant tumors by pointing out that during cell division the melanoblastic function is at its lowest ebb. This has been demonstrated by the "dopa" reaction.

To summarize the general concept at this point: (1) There are benign and malignant conditions involving melanoblastic cells. The benign conditions are congenital allotments of cells with melanoblastic functions to certain superficial tissues, the skin and its derivatives. This may be considered a normal distribution as in the skin of the negro, or heterotopic, as in the case of pigment cells found in the cerebrospinal meninges. The malignant conditions arise from sarcomatous or carcinomatous changes in these cells wherever they are situated. (2) The melanoblastic cells arise from both ectodermal and mesodermal tissues.

The following classification of melanotic conditions is suggested:

1. Non-neoplastic
   (A) Mesodermal melanoblastosis: A normal, though heterotopic, incidence of mesoblastic melanoblasts in sufficient numbers to produce noticeable discoloration of the structure involved. Example: Pigmented cells in the meninges, as in Case I of this presentation.
   (B) Epithelial melanoblastosis: A normal incidence of epithelial melanoblasts in sufficient numbers to be noticeable. Example: Skin of the negro; brain epithelial inclusions.

2. Neoplastic
   (A) Benign
      (1) Mesodermal melanoblastoma: A discrete, slowly proliferating (or quiescent) accumulation of mesodermal melanoblasts in any of the sites wherein such cells are normally found. Example: Blue nevus of Jadassohn. An accumulation of such cells within brain or meninges in circumscribed nodular collections would constitute a mesodermal melanoblastoma.
      (2) Epithelial melanoblastoma: A discrete, slowly growing or quiescent proliferation of epithelial melanoblasts occurring in any of the situations in which such melanoblasts are normally found. This group name may be modified by the term "nevoid" wherever the specialized nevus cell is met, or by "basal-cell" if the growth chiefly involves this cell. Example: The ordinary brown fleshy mole encountered on the face.
   (B) Malignant
      (1) Melanosarcoma: A rapidly proliferating, usually widely metastasizing melanin-forming tumor which answers the pathologic criteria of a malignant tumor arising in connective tissue. Example: Pigmented tumor arising in the choroid of the eye. Case II above is a probable illustration of this category of neoplasm arising primarily within the meninges.
      (2) Melanocarcinoma: A rapidly proliferating, usually widely metas-
FIG. 7. COLLECTION OF MELANIN-CONTAINING CELLS WITHIN A LARGE AREA OF NON-PIGMENT-BEARING TUMOR TISSUE

FIG. 8. LARGE CELLS CONTAINING COARSE GRANULES OF MELANIN PIGMENT FROM AN AREA WITHIN A METASTATIC NODULE
tasizing melanin-forming tumor which answer the pathologic criteria of a tumor arising in epithelial tissue. Example: Cases III–VI above.

Note: I wish to acknowledge a debt of gratitude to Dr. Joseph H. Globus and Dr. Samuel M. Peck for their invaluable assistance in the preparation of this paper.

References