There is considerable literature on the subject of new growths associated with hyperpigmentation. Most of this is concerned with certain benign lesions known as pigmented nevi, and malignant tumors known as melanocarcinoma or nevocarcinoma, melanosarcoma or nevosarcoma, malignant melanoma, melanocytoblastoma, melanoblastoma, or simply melanoma. Clinical considerations predominate, although some study of the pathological pigmentedary process has been made. This process

![Figs. 1 and 2. The Dopa Reaction](image)

has not been sufficiently appreciated, largely due to the methods of staining, employing hematoxylin and eosin or related stains, which tend to mask the yellowish brown melanin. The advent of new methods of study, the foremost of which are the silver method, which causes a darkening of pre-existing melanin, and the “dopa” reaction of Bloch (1), which demonstrates the pigment-forming cells, has revolutionized the study of normal pigmentation and made possible better evaluation of abnormal pigmentedary processes.

The normal pigmentedary process has been discussed recently by Bloch (1), Becker (2), Percival and Stewart (3), and others, and pigmented tumors have been considered by Dawson (4), Miescher (5), Becker (6), and Ewing (7). Albertini and Walthard (8) have dis-
cussed generalized melanomatosis with special reference to the "dopa" reaction. Hadwen (9) has recently discussed melanomas of gray and white horses. The normal cutaneous pigmen tary process may be briefly described as follows:

Embryonal pigmentation is first seen in branched cells in the hair matrix and later in branched cells in the epidermis. The first manifestation of pigment activity is a positive "dopa" reaction. This reaction is obtained by placing frozen sections in a 1:1000 solution of 3, 4-di-oxy-phenyl-alanine, called "dopa" for short. Peck (10) has recently shown that only the levo-rotary dopa gives the reaction. The pigment-forming cells show a darkening of their protoplasm (Figs. 1 and 2), which is believed to be due to the action of a ferment on the dopa, producing dopa melanin. The positive dopa reaction is followed in vivo by the appearance of melanin granules, first in branched cells and later in palisade basal cells. Pigment is found normally in the hair matrix, in the epidermis, in the epithelium of the oral mucosa, in the eye, and in the pia mater. Under pathological conditions, and perhaps normally, pigment occurs in the pharynx (Fig. 3). It is from these regions that pigmented neoplasms may arise. An overwhelming majority of them have their origin in the skin and eye.

**Epidermal Pigmentation**

If the pigmented epidermis or the oral mucosa is examined by suitable methods, two types of cells may be found. The usual text-book illustration of the basal layer shows it as consisting of palisade cells with finger-like processes interlocking with connective-tissue fibrils.
A second type of cell is also seen (Maximow, Bloom, 11), a fact not sufficiently appreciated in the past. It is more prominent in tissue undergoing pigment activity. It is a cell with its body at or near the epidermo-dermal junction, with long axis often parallel to the cutaneous surface, and, when active, exhibiting several processes extending along the basal layer and penetrating it for varying distances (Fig. 4). Pigment granules are of the same size and are uniformly distributed throughout the cell and its branches. This uniformity of size and shape of pigment granules seems to be of value in distinguishing non-

![Figure 5](image-url)

**Fig. 5. Section from Skin of Patient with Occupational Melanosisc**

The section is cut tangentially along a hair follicle. The branched dendritic cells are seen lying on the epithelium. Silver nitrate reaction, pyronin methyl-green counterstain. Oil immersion preparation. Courtesy of Dr. L. N. Wieder.

neoplastic from neoplastic melanoblasts, in which the size and arrangement of the granules vary considerably.

The author (6) has found the dendritic type of cell in all pigmented epithelium, especially in that of mucous membranes. The origin of this cell is not definitely known. Bloch, Kreibich and others believe that it is a modified basal cell, an idea supported by Peck’s work on pigment activity following irradiation with thorium-X (12). The other view is that of Soldan and Masson, who interpret these cells as having migrated to the epidermis from the dermis, and as being of nervous origin, possibly from the sheath of Schwann. This nervous origin is accepted by Ewing (7), Pautrier and others. Masson believes that these specialized cells are the only pigment-producing cells, and that
they transfer preformed pigment to the palisade basal cells. This is comparable to pigmentary processes in lower forms, as, for instance, birds. At any rate, the dendritic cells and their branches are always visible in greater numbers during pigment activity, showing that they are closely connected with the latter process.

**Hyperpigmentation**

The process of pigment increase is best studied when it is rapid, as following irradiation of the skin by ultraviolet rays from an arc lamp, or alpha rays from thorium-X (12). The first sign is an increased dopa reaction in branched cells. These cells then become hyperpigmented, with later hyperpigmentation of the ordinary palisade basal cells. As the process continues, the branched melanoblasts become less prominent, and a large part of the pigment is in the epidermal cells. As the epidermal pigment becomes more marked, it tends to mask the dendritic cells, so that their lack of prominence may not mean that they have become less extensive. Pigment in the palisade basal cells is located largely about the distal pole of the nucleus, and it persists in decreasing quantity as the cell works its way to the surface, some of it being found in the stratum corneum. After a time, considerable pigment is seen in the phagocytic cells of the papillae and
superficial dermis, which are called chromatophores, since they are merely pigment carriers, and do not themselves form melanin. The cells called chromatophores by many zoologists give a positive dopa reaction, are pigment-forming, and are preferably known as melanoblasts. In pigmentary processes which are slower in their evolution, as for example in Addison’s disease, the melanoblasts are not nearly as prominent as following ultraviolet irradiation. Pigmentary processes may be very marked following exposure to photosensitizing substances. A remarkable case was reported by Wieder (13) of a man who had been photosensitized by exposure to impure naphthalene and benzanthrone and in whom a marked pigmentary process had developed. Here the melanoblasts were especially prominent (Fig. 5).

**Neoplasms**

Melanotic neoplasms are of two types, those formed by melanoblasts or related cells, and those in which the melanoblasts are secondary factors. These may be classified as follows:

1. Neoplasms formed by melanoblasts or related cells
   - Benign
     - Nevus pigmentosus
       - Non-elevated (no nevus cells)
       - Elevated (with nevus cells)
   - Malignant
     - Malignant melanoma
     - Lentigo maligna
     - Melanocarcinoma or nevocarcinoma
     - Melanosarcoma or nevosarcoma
       - (a) pigmented
       - (b) non-pigmented

2. Neoplasms in which melanoblasts are secondary factors
   - Pigmented epithelioma
   - Pigmented epidermoid carcinoma
   - Carcinoma originating in deeper structures and invading the skin, becoming secondarily pigmented.

*Nevus Pigmentosus*

It may be argued with justification that pigmented nevi are not true neoplasms, but are rather the result of disturbances of development. Here, however, for purposes of classification they are considered as neoplasms. Their origin and nature are considered elsewhere (14).

Pigmented nevi vary from flat, non-elevated lesions to markedly elevated lesions, some of which are of considerable extent. They are sometimes hypertrichotic. When the simpler type, the non-elevated lesion, is examined microscopically, two things are found. At the epidermo-dermal junction is an increased number of dendritic melanoblasts, and the overlying epidermis is hyperpigmented (Fig. 6). No nevus cells occur in the dermis. In the slightly elevated lesions, however, a few, and in the markedly elevated lesions many so-called nevus cells are found in the superficial dermis (Fig. 7). These cells are...
round, oval, or polygonal, with pale-staining nuclei and pale-staining protoplasm. Their staining characteristics are especially pronounced with Masson’s trichrome stain (Fig. 8). They resemble the melanoblasts more than they do the palisade basal cells, and the superficial ones give a positive dopa reaction and contain pigment. Occasionally these cells are large and multinucleated. Nevus cells have so many similarities to melanoblasts that they are thought to have the same origin. In some quiescent nevi the epidermis is thinned, pigmented in varying degree, and only a few melanoblasts can be identified at the epidermo-dermal junction. At times these cells become more promi-
nent, branched and numerous (Fig. 9). The nevus is then said to be active, and it is activity at the epidermo-dermal junction which seems to presage development of malignant melanoma. The tumor probably never develops in benign nevus cells, though this opinion is not shared by Ewing (7). This point is discussed later. The statement has sometimes been made that late in the course of the process activity has been noted in nevus cells, but the picture of disorganization tends to make interpretation at this stage difficult and unreliable.

**Blue Nevi:** In some nevi, all pigment-containing cells are deep in the dermis. These cells give a positive dopa reaction and are therefore melanoblasts. Their arrangement depends on the connective-tissue pattern, and they are generally elongated, with processes at the cell ends (Fig. 10). The depth of the pigment-containing cells is such that the gross color of the lesion is blue, and the lesion is known as a blue nevus. Deeply lying melanoblasts are responsible for the blue color of the ape's skin and of Mongolian spots. In some nevi of this type, the pigment-containing cells extend to the surface, and in this case a mixture of brown is seen.

**Theories Relative to the Origin of Nevus Cells:** The older theories attributing the origin of nevus cells to endothelium or chromatophores (phagocytic cells) have been abandoned, and at present but two theories have sufficient support to warrant consideration. The older of these, and the one supported by a majority of dermatologists today (Bloch, Darier, et al.), assumes a double origin. In the usual type of nevus, in which nevus cells are found in close proximity to the epidermis, it is assumed that they are formed from epidermal cells. The basal cells are said to change their shape from palisade to oval or round, lose
their intercellular bridges, group together and descend into the dermis. The origin of cells found in the blue nevus is thought to be mesodermal.

The second theory is that of Soldan, recently revamped by Masson and others, and supported by Ewing, which assumes that nevus cells, regardless of the type of nevus, originate in the nervous system, possibly from the sheath of Schwann. This theory seems to be gaining ground, although the question cannot be regarded as settled. The association of pigmented plaques and nerve tumors in multiple neurofibromatosis of von Recklinghausen is advanced in its support.

The determination of the origin of pigment-producing cells is difficult, since the cells cannot be located prior to the appearance of the positive dopa reaction. At that time they occur in epithelial tissue

![Fig. 10. Section from Blue Nevus](image)

The mass of melanoblasts deep in the dermis produces a distinct bluish color in the clinical lesion.

(with the exception of the more deeply lying melanoblasts in the blue nevus or Mongolian spot). The origin and previous course of the cells have not yet been traced.

**Lentigo**

Lentigo is a brownish non-elevated lesion appearing in normal skin. It is usually dark brown, much darker than ephelids, which are more commonly known as freckles. It is more common in patients beyond middle life. It may be the precursor of malignant melanoma (75 per cent in Miescher's series), although malignant melanoma also arises in pigmented nevi (25 per cent of Miescher's series). Any new progressive melanotic lesion should be viewed with suspicion and should be removed. Reports follow of two cases of recently appearing melanotic
macules (lentigo), neither of which had as yet shown signs of malignancy.

Case 1: A woman, aged fifty-four, auburn-haired and very fair, presented a recently appearing lesion on the vermilion border of the lip. It was about 5 mm in diameter and slate gray in color. It was removed. Microscopic examination showed that the tissue had not undergone any gross change. Sections treated by the silver method showed marked hyperpigmentation at the center of the section, gradually fading out toward the borders. Pigment was present in largest amount along the tips and sides of the rete processes. In the center most of the pigment was present in non-dendritic cells, and extended to the surface. Toward the border more dendritic cells were seen, and the other epithelial cells were less pigmented. In sections stained with Masson's trichrome stain, dendritic cells were present in normal numbers, in contrast to non-elevated nevi, where they are markedly increased.

![Image of a lesion](image.jpg)

**FIG. 11. CASE 2: LENTIGO, A BROWN MACULAR LESION OF THE PALM PRESENT FOR EIGHT WEEKS AND INCREASING IN SIZE**

Case 2: A woman, aged fifty, had a dark brown lesion on the palm (Fig. 11), present for eight weeks and growing. It was removed, fixed in Bouin's picro-formol solution, stained with hemalum-erythrosine-saffron, Masson trichrome stain, and treated by the silver method. The stratum corneum, stratum granulosum, and stratum mucosum were of normal thickness. The stratum germinativum was somewhat disorganized in that the palisade cells were not uniformly arranged, but seemed to be encroached upon by large branched melanoblasts located between them. The nuclei of the melanoblasts were often parallel to the epidermal surface, and their branches extended in various directions. The melanoblasts differ from the palisade cells in that their nuclei are small or large, depending on the pigment activity of the cell, and their protoplasm is granular, more basophilic, and contains no fibrillae. Various degrees of activity were seen between the clear cells in the non-pigmented regions and the melanoblastic cells in the pigmented area. No actual increase in the number of cells could be determined in the pigmented region. In the non-pigmented region these cells are the "cellules claires" of Masson, which he thinks have a connection with the nervous system.

In sections treated with ammoniacal silver solution, pigment was seen in moderately increased amount, extending to the surface (Fig. 12). The basal portion of the epidermis contained a moderate number of dendritic cells, and the epidermal cells were moderately hyperpigmented. Very few chromatophores were seen, which is in accord with statements previously made that pigment is rarely seen in chromatophores in the
palms and soles. The pigment seems to be retained by the epidermal cells rather than being cast off into the dermis.

Lentigo may be interpreted as localized hyperpigmentation of unknown etiology in tissue containing a normal number of melano blasts, as contrasted with smooth nevi, where melanoblasts are found in excess. The reaction is identical with that of pigment activity following irradiation by ultraviolet or alpha rays.

![Fig. 12. Case 2: Section from Lentigo of Palm](image)

Dendritic melanoblasts at the epidermo-dermal junction denote pigment hyperactivity. This picture cannot be distinguished from pigment activity following irradiation by ultraviolet light. Here it is due evidently to some internal stimulus of unknown nature, and if this stimulus persists the lentigo may become malignant and melanoma may be formed.

**Growing Nevi**

Kreibich (15) stated that most nevi are elevated, a fortunate fact, since, as he says, it is the smooth brown nevus that is more apt to give rise to malignant melanoma. The familiar statement that the blue-black and black nevi are the dangerous ones probably originated in the fact that these lesions are already malignant. Any pre-existing melanotic lesion which shows peripheral extension should be considered with suspicion, and should be removed. The author has described elsewhere (6, Case 6) a small, slightly elevated nevus of the leg which was increasing in size, and which seemed on microscopic examination to be showing the various stages in malignant melanoma formation. In the periphery of the section, dendritic melanoblasts were prominent at the epidermo-dermal junction, but the palisade cells were only slightly pigmented. This was interpreted as hyperactivity. As the center was approached, melanoblasts were present in larger numbers and were somewhat irregular and contained in vacuole-like spaces. The palisade basal cells were markedly pigmented. At the center of the tumor, the epidermis itself was disintegrated and the melanoblasts had extended
more deeply. No nevus cells were found in the dermis. The following case is also illustrative of the growing nevus:

**Case 3:** A male, aged forty, had an elevated dark brown lesion over the left zygoma, which had been present all his life, but had recently increased in size. It was excised. Tissue was fixed in Bouin's picric-formol solution, stained with hemalum-erythrosine-saffron, Masson's trichrome stain, and treated with silver nitrate. The surface of the section was rounded, due to elevation of the lesion (Fig. 13). The epidermis was of

![Image of tissue sections](image)

**Fig. 13 and 14. Case 3: Elevated Nevus Containing Small Abscess**

Fig. 13 (above), hemalum erythrosin saffron stain. Nevus cells are seen throughout most of the superficial dermis.

Fig. 14 (below), ammoniacal silver nitrate, pyronin methyl-green counterstain. Pigment is seen in the superficial nevus cells and is found more deeply in the center of the lesion. The cells here are fusiform in shape and evidently constitute low-grade melanoma. The pigmentary process is seen to extend from the surface downward. Malignant change probably does not take place in pre-existing nevus cells.

approximately normal thickness or slightly thinned, with several surface indentations such as are often seen in elevated nevi; the inner surface was smooth, and normal papillae were rarely seen. The epidermis consisted of four to six layers of cells, with no marked abnormality except in the basal layer. This contained more than the normal number of melanoblasts arranged for the most part in a single layer between the innermost extremities of the palisade basal cells. They had the usual medium to large nuclei and
granular protoplasm, often branched, often in clear spaces surrounded by the fibrillar protoplasmic processes of the basal cells. In places the melanoblasts were grouped together and were only loosely attached to the epidermis, being separated from it by a large clear space.

Beneath the epidermis, at the border of the lesion, were islands of nevus cells of the usual type, not arranged in strands. The nuclei were moderately large and pale, and the protoplasm was pale and granular. A few of the more superficial cells contained pigment. In and near the center of the nevus the picture changed, in that the islands contained fusiform cells and much more pigment. Pigment also extended as deeply as did the islands of cells, a condition not found in a quiescent nevus.

In addition to the nevus features, the deeper portion of the lesion also contained a large area of inflammatory infiltrate, consisting mostly of lymphocytes and giant cells.

The silver reaction showed (Fig. 14) more than the usual number of melanoblasts at the epidermo-dermal junction. They contained uniform granules of normal size throughout. Where they were massed together, the melanin granules were more clumped,

FIG. 15. CASE 4: LENTIGO MALIGNA AND MALIGNANT MELANOMA: RECURRENT LESION FOLLOWING VARIOUS FORMS OF THERAPY

The original lesion appeared seven years previously. The lesion is dark brown, with the exception of the inferior-posterior portion, which is denuded of epidermis, erythematous, and elevated.

and probably of larger size. In the deeply lying fusiform cell nests the melanin varied from dust-fine particles to granules larger than normal, although they were uniform in a given cell. The large granules were often clumped together. Many chromatophores, at times crammed with melanin in large irregular lumps, were seen throughout the dermis.

Evaluation of the lesion from clinical and microscopic study is about as follows. Increase in size may be due, in part at least, to the local inflammatory change. The periphery of the lesion represents the picture of a quiescent nevus. The center, on the other hand, shows some activity, more epidermal pigment, more cell nests attached to the epidermis, cells fusiform in shape and irregular in size in the dermis, deep extension, and deep pigment formation. It would not be unjustifiable to class such a growth as a low-grade malignant melanoma. One could easily state that malignant changes had originated in pre-existing nevus cells, since deep-lying malignant appearing cells are present, but the silver method shows that the activity extends all the way from the epidermis downward, and I believe the original source of activity is always at the epidermo-dermal junction. It is true that the deeper cells may later take on a higher degree of malignancy, but they are probably already malignant.
Malignant Melanoblastic Tumors

In some cases, after a period of months or years, lentigo may develop into clinical malignant melanoma. The following case is illustrative:

CASE 4: A married woman, aged thirty, was first seen on April 2, 1930, with a lesion on the lateral aspect of the left foot, 3.5 by 7.0 cm. (Fig. 15). The anterior superior portion of the lesion was dark brown in color, and the posterior inferior portion was erythematous, vegetative, with serosanguineous discharge. The border was sharply demarcated, with no surrounding erythema. In the center was some scarring. The lesion had appeared in the normal skin seven years before admission. It had grown more rapidly in the past two years, and had been treated in various ways, including excision, electrolysis, and cautery. Clinical diagnosis was lentigo maligna with either infectious granuloma or non-pigmented melanoma. No enlarged nodes were found in the popli-

Figs. 16 and 17. Case 4: Lentigo Maligna

Fig. 16 (left), silver nitrate reaction, pyronin methyl-green counterstain. Melanoblasts are more prominent and increased in number at the epidermo-dermal junction. Groups of cells are being cast off in the epidermis. Round-cell reaction is marked.

Fig. 17 (right), oil immersion section, showing the increase in prominence and number of melanoblasts. This is the picture known as "melanosarcoma."

teal or inguinal regions. The lesion was excised and the patient returned home. She re-entered on Nov. 7, 1930, with enlarged nodes in the inguinal region, and they were removed. No local recurrence could be determined. The iron chloride test for pyrocatechin bodies was positive in the urine before the nodes were removed, but became negative after their removal.

Sections of the original lesion were fixed in formalin and alcohol, stained with hematoxylin-eosin, and treated with silver nitrate, with pyronin-methyl-green as a counter stain. In the peripheral portion of the lesion the brown color was seen to be due to epidermal hyperpigmentation, chiefly to a large number of melanoblasts at the epidermo-dermal junction (Fig. 16). Groups of pigment-containing cells were seen throughout the epidermis, including the thick stratum corneum. The author has shown previously that these cells give a positive dopa reaction all the way to the surface.

The stratum mucosum was thickened and the stratum germinativum was very much disarranged due to melanoblastic proliferation. The rete processes were elongated and frayed, so that they blended imperceptibly into the masses of melanoblasts and dermal tissue. The most marked change was in the melanoblastic cells themselves, which were markedly increased in number (Fig. 17). They were for the most part elongated and often massed together in large clear spaces. Some of these cells had become incorpor-
rated in the epidermis, and were being cast off at the surface. The dermis contained considerable round-cell infiltration.

Silvery preparations showed the epidermal cells to be almost non-pigmented. The melanoblastic cells were for the most part pigmented, although in certain regions they contained very little pigment. Melanin was present in fine granules, but most of the cells also contained large clumps of pigment. They differed from the histiocytic chromatophores of the dermis in that the latter rarely contain fine granules, but always large clumps of melanin. The disorganization of the epidermis and the large number of melanoblastic cells, along with the presence of cell groups extending toward the surface, make the diagnosis of malignant melanoma. The brown color of the lesion clinically makes the diagnosis of lentigo maligna.

The erythematous elevated portion of the lesion presented an entirely different picture. The epidermis was thinned and in places entirely absent. The tumor mass consisted of highly vascularized tissue composed almost entirely of round, oval, and polyhedral cells with an alveolar arrangement, and at times in strands (Fig. 18). The silver method showed no melanin whatever. The diagnosis was non-pigmented melanoma.

Two types of tissue were thus found in the same primary growth: pigmented spindle-shaped cells (melanosarcoma) and non-pigmented polyhedral cells (non-pigmented nevo- or melano-carcinoma). It is this association in a single primary tumor or in metastases that has led to the designation malignant melanoma.

The metastatic lesion in the inguinal nodes showed the entire node to be replaced by tumor cells of the same type as were seen in the non-pigmented portion of the primary tumor. No pigment was observed. There were a moderate number of mitotic figures and a few cells suggesting amitotic division.

The following case is also one of a fatal melanoma originating in a smooth brown nevus, according to the history.

CASE 5: A woman aged twenty-seven was first seen in the surgical clinic on Jan. 30, 1931. She had always had a smooth brown nevus on the left calf. Seven years before admission it had begun to enlarge. It was repeatedly traumatized, discharged serosanguineous material, crusted, and healed. Three years before admission a tumor mass had been observed on the right side above the iliac crest. Other tumors had appeared in the left axilla and below the left ear. Three months before admission a large,
slightly tender inguinal lymph node appeared on the left side. During the past year the primary and metastatic lesions had been treated by roentgen rays, with benefit. Four days before admission the mass in the left groin had enlarged and had become tender.

On admission, the temperature was 102° F. The mass was incised and drained of purulent material. The tumors in the right flank, in the axilla, and below the ear, were removed and proved to be neurofibromas. The lesion on the left leg was a large, moderately elevated, ulcerated, blackish tumor with a brownish portion about the border. It was removed, along with the mass from the left groin. Roentgenograms of the lungs and long bones showed no metastases. Local roentgen therapy was given. A retroorbital metastatic lesion developed, causing considerable discomfort. Multiple cutaneous metastatic lesions also appeared and the patient became progressively weaker and emaciated, and died Oct. 6, 1931.

Autopsy showed extensive disseminated metastatic malignant melanoma involving particularly the cutaneous tissues of the scalp, chest, and abdomen, secondary to a melanoma of the skin of the left leg. An ulcerating neoplasm was present on the inner aspect of the left upper thigh. Metastases were found in both ovaries, in the retroperitoneal lymph nodes, in the head of the pancreas, the spleen, the mesenteric lymph nodes, and the falciform ligament. The cystic duct was compressed by metastatic nodules surrounding it. There was marked left exophthalmos with retrobulbar metastases.

Histologic examination of the original tumor of the calf showed an ulcer with a granulating base. At the border of the ulcer the epidermis was thinned, and the superficial corium was filled with oval and polygonal cells, often multinucleated. Some of the more superficial ones were filled with brown pigment, but most of them were non-pigmented. In another portion of the ulcerated region, the base of the ulcer was composed of granulation tissue containing large quantities of tumor cells, many of which were of spindle shape. In this region the epidermis had proliferated and extended deeply, and in places had formed epithelial pearls. The epithelial pearl formation has been mentioned by Miescher (5). The author (6) has seen epithelial pearls more superficially which seemed to be merely invaginations of the surface epithelium, but in this particular tumor these structures were too deep to be considered as such. The epithelial tissue was very similar to that found in squamous-cell carcinoma and may possibly have been due to roentgen treatment. This portion of the tumor seemed to be the primary tumor, and consisted of spindle-shaped cells containing considerable pigment. That portion of the tumor containing cuboidal and oval cells appeared to be metastatic or infiltrated. This primary lesion again illustrates the presence of both sarcoma-like cells and carcinoma-like cells in the same tumor.

Microscopic examination of the metastatic nodule in the lymph node showed most of the tumor to be composed of oval or polygonal cells with large pale nuclei, often with two or more large nucleoli. This portion of the tumor contained little pigment. Other parts of the metastatic tumor showed a tendency toward the spindle-cell type, and here more pigment was found. A few mitotic figures were seen, and in some places there was a suggestion of amitotic division, resulting in cells with two nuclei.

In general, two types of cells are seen, the spindle-shaped or the so-called sarcoma cell and the polyhedral or so-called carcinoma cell. This has given rise to the two designations, "nevo-" or "melanosarcoma," and "nevo-" or "melanocarcinoma." The acceptance by most dermatologists of the epithelial origin of the nevus cell has led them to use the term "carcinoma," while pathologists have been accustomed to designate the tumors as "sarcoma." The most conservative term is "malignant melanoma," which may be modified later as more is learned about the nature of the cell. Karsner (16) used the terms "melanoma" and "melanotic sarcoma"; MacCallum (17) called the tumors "melanoma" or "melanosarcoma"; Delafield and Prudden (18) designate them "melanosarcoma" or "melano-epithelioma." Kaufmann (19) says: "It is probably better at present to retain the division
into epithelial (melanotic carcinoma) and connective-tissue (melanotic sarcoma) tumors. Both kinds can perhaps be grouped under the neutral designation of melanocytoblastomas (Lubarsch)." Ewing (20) uses the term "melanoma." Boyd (21) says: "A melanoma may simulate a carcinoma, a sarcoma, an endothelioma, a perithelioma and even a lymphosarcoma. In common practice it is common to refer to the innocent tumor as a nevus and to the malignant tumor as a melanoma." Most of the tumors show melanin, and this is especially true of the spindle-cell variety. The author has never seen a case where special pigment stains did not show melanin in at least some part of the original growth or in metastatic nodules. It sometimes cannot be seen, however, with hematoxylin and eosin stains.

![Figs. 19 and 20. Case 6: Non-pigmented (left) and pigmented (right) melanoma from the same liver.](image)

In the non-pigmented area many nuclei are constricted as though the cells were undergoing amitotic division. The cells in the pigmented area are fusiform and contain varying amounts of pigment. Those which appear stuffed with pigment are chromatophores.

The following case is representative of cutaneous and visceral metastases of malignant melanoma possibly originating in an eye, which had been removed (22).

**Case 6:** A woman aged forty-four was first seen in the Department of Surgery in December 1929, complaining of pain in the right upper quadrant. Her right eye had been removed four years previously for glaucoma. There had been no sign of melanoma at that time. The urine had been brown three months before admission, but was now normal in appearance. The liver was enlarged, and roentgen-ray studies revealed gallstones. Cholecystectomy was performed. At operation the liver was found to be large and black, and a diagnosis of malignant melanoma was made. One month later some small tumors of the scalp were removed, which proved to be sebaceous cysts. At the same time a small cutaneous tumor was removed from the chest wall; this proved to be malignant melanoma. There was infiltration of non-pigmented cells with medium-sized, mostly non-lobulated nuclei. Some cells were larger and contained more than one nucleolus. Both mitotic and amitotic divisions were apparent. In some places an acinar arrangement was seen.

The urine gradually became brown in color and turbid, and showed pyrocatechin bodies, which were probably the result of the breaking down of melanin, rather than constituting melanogen, as is sometimes stated.
The upper abdomen increased in size and was of board-like rigidity. The skin became darker and the hair developed the brownish hue which often accompanies generalized cutaneous melanosis, such as that in Addison's disease. The patient became weaker and died on March 20, 1930.

At autopsy the chief finding was an enormous liver, weighing 10.4 kg. Metastatic lesions were found in the skin of the abdomen and scalp, calvarium, peri-aortic and tracheobronchial lymph nodes, diaphragm, and lungs. The skin and hair were brown, and melanemia was apparent from the dark color of the kidneys, bone marrow, spleen, and suprarenal glands, all of which turned darker on exposure to air. Careful examination of both orbits showed no tumor. No possible primary focus was found in the skin or elsewhere.

The tumor foci in the liver were pigmented for the most part, being jet black, but on the dorsal surface was a plaque about 5.0 cm. in diameter, which appeared non-pigmented. In the center of the liver was a necrotic area, about 10 cm. in diameter, containing tarry material. Sections of the non-pigmented portion showed no pigment, except occasionally in macrophages. The cellular protoplasm was so vacuolated that it was impossible to determine cell morphology. Nuclei were pale, variously sized, tending to be large, and were vacuolated and lobulated, often with many lobules, large and small (Fig. 19). Each nucleus generally contained one nucleolus, one-third to one-fifth the diameter of the nucleus. Sometimes two nucleoli were present, especially in elongated nuclei, where they were situated at each end. At times, one lobule, with or without a nucleolus, was more or less incompletely pinched off. These were cells apparently undergoing amitotic division. No mitotic figures were seen.

The cells in the pigmented tumor foci were not all the same, but varied in different regions. Some small foci contained no pigment, and the cells were similar to those in the large non-pigmented focus, but with fewer cells undergoing amitotic division. Other portions contained ovoid cells, some pigmented. Most of the pigmented cells were fusiform (Fig. 20), with elongated non-lobulated nuclei, and a single long process at each

FIG. 21. CASE 7: MELANOTIC EPITHELIOMA

The growth is mainly epidermal and is, in all probability, neoplastic but benign.
end of the cell. The pigment granules were globular, of the same size in any one cell, but varying in size in the different cells. The only sign of cell division in this portion were occasional mitotic figures in large ovoid cells containing little pigment.

**Pigmented Epithelioma**

This designation was first used by Bloch (23) to designate benign epidermal neoplasms containing considerable pigment. The author (6) also reported a case, the essentials of which are as follows:

**Case 7**: A man aged fifty-nine had a small tumor, 1 by 2 cm., in the left groin. It was pedunculated, dark brown in color, with keratotic plugs. Histologic section showed the growth to be largely epithelial, with an insignificant connective-tissue pedicle (Fig.

![FIG. 22. CASE 7: MELANOTIC EPITHELIOMA](image)

Dendritic melanoblasts are seen at the epidermo-dermal junction. Silver nitrate reaction, pyronin methyl-green counterstain.

21). The epithelial surface was invaginated and contained masses of cornified epithelial cells. The stratum corneum was thickened in these places. The stratum granulosum was normal. The stratum mucosum was markedly thickened. The cells were smaller than in acanthotic processes, such as condyloma acuminatum, and the nuclei were hyperchromatic. Sections treated with silver nitrate showed marked pigmentation in the palisade basal cells, and also a moderate number of dendritic melanoblasts at the epidermo-dermal junction (Fig. 22). The papillae were narrow and long. No nevus cells could be found. Chromatophores were present in the papillae and pedicle. A diagnosis of pigmented epithelioma was made.

Ewing (7) mentioned a case of pigmented epithelial papilloma, with extensive black papillary tumors covering much of the trunk on one side of the body only, showing a characteristic segmental distribution on the trunk and a linear extension along the entire ulnar nerve. On section they showed simple, very cellular, benign epithelial papilloma without any features of melanoma except abundance of wandering chromatophores. This may well have been pigmented epithelioma.
The most remarkable case of this type of tumor was that reported by Pautrier and Hügel (24) and Pautrier and Lévy (25), in a man aged forty-nine, who had had tumors on the body since the age of five years. He had been presented by Wolff at the sixth Congress of the German Dermatological Society at Strasbourg in 1898, at the age of twenty-four, as a peculiar case of acanthosis nigricans. There had been no skin disease in his family. The lesions began about the neck, spread to the axillae, and progressed further. At the age of twenty-four they occupied the neck, axillae, chin, thorax, abdomen, back, and upper thigh. Since then they had extended to the wrists and the ankles, occupying the entire body except the hands and feet. They varied from slightly elevated brownish tumors to markedly elevated lesions.

In the left inguinal fold was an ulcerated area 6 × 8 cm., with a hard border and base, with sanguineous discharge, which had been present a year and a half. This lesion had been enlarging more rapidly recently. Inguinal nodes were enlarged on that side.

Six biopsies were performed; all sections showed a fundamental hyperplasia of the surface epithelium with abnormal evolution of a majority of the malpighian cells, which were hyperpigmented, often enormously. The cells were not normal malpighian cells, but differed by their individual character and by their relation to each other and their abnormal pigment content. They were more acidophilic than normal cells, were smaller, and the intercellular spaces tended to disappear. The nuclei were large for the size of the cell, vesicular, oval, and possessed hyperchromatic nucleoli. No nevus cells were found. The dopa reaction showed many dendritic melanoblasts.

The inguinal ulcer proved to be squamous-cell carcinoma, the origin of which could not be definitely determined. The author examined the sections from this case and concluded that the cancer had originated in one of the tumors. Very few bona fide cases of malignant degeneration of this type of tumor are on record. The picture of the tumors in this case is the same as in one of Bloch’s case of melanotic epithelioma and the author’s case of the same condition. These tumors are closely related to the benign epidermal neoplasms which have been called senile or seborrheic verrucae, but which are better termed “epithelioma,” meaning thereby benign neoplasms in contradistinction to the malignant epidermal tumors, such as basal-cell and squamous-cell carcinoma, and the intermediary and mixed types, which are often called “epithelioma” by English and French speaking dermatologists. This subject has been considered in greater detail elsewhere (26).

Pigmented Basal-Cell Carcinoma

Basal-cell carcinoma may at times contain considerable pigment, which, due to its depth, produces a slate gray or blackish hue. The author has examined, by the silver method, specimens of cutaneous carcinoma from the University of Chicago Clinics and the Strasbourg
Dermatological Clinic (through the courtesy of the director, Professor L. M. Pautrier) and has found pigment in the tumors as follows:

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Pigment found</th>
<th>Per cent of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-cell carcinoma</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>Intermediate type of carcinoma</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Mixed type of carcinoma</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>43</td>
<td>3</td>
</tr>
</tbody>
</table>

Five specimens were from lesions diagnosed clinically as pigmented basal-cell carcinoma.

Caudivre found pigment in a tumor of the mixed type. Kreibich stated that pigmented squamous-cell carcinoma is rare. Schröpl (27) reported two cases from Kreibich’s clinic of pigmented basal-cell car-

cinoma. Bloch found a positive dopa reaction in some basal-cell tumors. Eller and Anderson (28) reported two cases of pigmented basal-cell carcinoma, and gave an excellent discussion of the subject.

The origin of dendritic melanoblasts in these tumors is explained by the same theories as in the normal epidermis, being attributed by some to the tumor cells, and by others to the nervous system. Bloch believed that they arose from tumor cells, Bezeeney believed they had wandered down from the epidermis, while the proponents of the nervous theory hold that they are of the same origin here as in the epidermis. The regularity in size and arrangement of the granules strongly suggests that these cells are not themselves neoplastic, because even in benign melanoma (nevus pigmentosus) the granules tend to be of various sizes and clumped together.

Pautrier and Diss (29) reported a pigmented basal-cell carcinoma of the scalp of the pseudocystic type. The following is a typical case of the condition:

**Case 8:** A man, aged seventy-one, had two basal-cell carcinomas of the face, one on the right upper lip and one on the right side of the nose. The lesion on the nose was of fif-
teen years' duration and presented several slate gray nodules 2 to 3 mm. in diameter. The clinical appearance differed from that of non-pigmented basal-cell carcinoma only in the color. A nodule was removed for biopsy and showed basal-cell carcinoma in the form of small islands in the superficial dermis. The silver method showed pigment activity in the epidermis in the form of melanoblasts with many branches. In the islands of neoplastic tissue two types of cells were found: (1) the usual type found in basal-cell carcinoma and (2) branched melanoblasts. The dopa reaction was positive (Fig. 23) only in dendritic cells and not in the ordinary tumor cells. Melanoblasts were seen especially at the periphery, with branches extending into the cell masses. They showed the type and arrangement of melanin described above for normal melanoblasts. The cells of basal-cell type also contained melanin granules, often about the nucleus, in irregular masses and not in fine granules and regular arrangement as in the normal basal cell. The regular arrangement of pigment in the melanoblasts shows that they are not neoplastic cells, since even in benign melanoma there is a tendency toward clumping of pig-

![Fig. 24. Melanoblasts in the Periphery of Islands of Carcinoma Cells which Have Approached the Epidermis](image)

The cells containing the largest amount of pigment are phagocytic chromatophores.

Schröpl (27) also concluded that the presence of this type of melanoblasts did not signify a malignant tendency of these cells.

**Pigmented Carcinoma of Mammary Gland**

Through the kindness of Professor P. Masson, of the University of Montreal, the author has had the opportunity of studying two cases of carcinoma of the breast, one from a man and one from a woman. In both instances the tumor had invaded the skin and had become pigmented. Variously sized groups of cancer cells were seen adjacent to and actually within the epidermis, particularly the rete processes. In the superficial groups were many branched melanoblasts of the type found normally in the epidermis (Fig. 24). The cancer cells differed from those of the pigmented basal-cell carcinoma in that they did not themselves contain pigment granules. A few large pigment granule
groups were seen throughout the cancer tissue, but were apparently intercellular. The picture produced by the cells which had invaded the epidermis was not unlike that seen in Paget's disease, except that the epidermis was not so disrupted. This same picture has been reported by Caudière (30), Masson (31), and Bezecny (32).

It is not definitely known just why there should be an increased number of melanoblasts in certain mammary gland carcinomas approaching the epidermis or why basal-cell carcinomas should at times contain many melanoblasts. Bloch (33) believes that even in the case of mammary gland carcinoma the melanoblasts probably originate from the carcinoma cells. These cells are derived from glandular epithelium, the cells of which originate from epidermal inbuddings, and are therefore of epidermal origin. If we assume the extra-epidermal origin of these melanoblastic cells, then we may assume a benign hyperplasia of melanoblasts not unlike hyperplasia of other cutaneous cells. Along the borders of some leg ulcers, for instance, marked hyperplasia of epithelial cells may occur, often simulating carcinoma. This is only an occasional finding and may be due to some stimulus with which we are not familiar. There is no particular reason why melanoblasts cannot be stimulated to benign proliferation the same as other cells.

Summary

Modern pigment study, carried out mainly by means of the silver and "dopa" reactions, shows that there are specialized cells at the junction of the epidermis and dermis which are capable of forming pigment. The first sign of pigment activity in the embryo is the positive dopa reaction in a branched cell in this location. This is followed by the appearance of melanin granules in the branched cells and later in the palisade basal cells. These pigment-forming cells are called "melanoblasts," in contradistinction to phagocytic dermal cells which are called "chromatophores." An increase in the number of melanoblasts at the epidermo-dermal junction results in a smooth brown nevus. In elevated nevi masses of pale-staining cells are seen in the dermis which are similar in staining properties and pigment content to the epidermal melanoblasts and are thought to be derived from the same source. The source of melanoblasts is not definitely known, but more and more workers are accepting the nervous origin. If melanoblasts are located deeply in the dermis a blue nevus or Mongolian spot results. The distribution here is essentially the same as in the blue skin of the ape.

Pigment activity due to irradiation by ultraviolet or alpha rays consists first of prominence and branching of melanoblasts, followed by hyperpigmentation of palisade basal cells. Pigment activity occurring spontaneously with no demonstrable cause results in the same histologic picture and the lesion is known as "lentigo," which has nothing to do with the common freckle known as "ephelid." If this stimulation of pigment activity increases to a point where melanoblastic proliferation occurs, the lesion is known as "lentigo maligna" and is already malig-
nant melanoma. Further activity results in melanoma, either of the fusiform-cell type—the so-called melanosarcoma—or of the ovoid-cell type known as melanocarcinoma. The occurrence of both types of cell in the same primary or metastatic growth demonstrates the futility of trying to classify them as “sarcoma” or “carcinoma,” the best designation being “malignant melanoma.” Melanoma arising from pigmented nevus has its origin in the melanoblastic cells at the epidermo-dermal junction and not in deeply lying nevus cells as has been sometimes supposed.

Melanotic epithelioma or pigmented epithelioma is a term used to designate a benign epidermal neoplastic tumor containing considerable melanin. These lesions are closely related to the so-called senile or seborrheic verruca and almost never undergo malignant degeneration. Study of cutaneous carcinoma showed that 33 per cent of the basal-cell tumors, 14 per cent of the intermediate, 9 per cent of the mixed, and 7 per cent of the squamous-cell tumors contained melanin demonstrable by the silver technic. The pigment in these tumors is due to the presence of melanoblasts which cannot be distinguished from normal melanoblastic cells, as regards type and arrangement of melanin granules. In rather unusual cases carcinoma of the breast which has invaded the skin is intimately associated with melanoblastic cells which are also normal.

**Bibliography**

33. Personal communication.