

MELANOMA OF VATER'S DIVERTICULUM AND
LOWER PORTION OF COMMON BILE DUCT
CAUSING COMPLETE OBSTRUCTION.¹

By CHARLES W. DUVAL, M.D.

*Director of the Pathological Laboratory of the Montreal General Hospital.
(From the Pathological Laboratory of the Montreal General Hospital.)*

PLATE XXVIII.

According to our present conception of pigment-producing cells melanotic tumors do not occur outside the skin, eye and central nervous system, except as metastatic growths. Pigmented tumors that arise in the internal organs are traced in almost every case to a primary growth in a situation where pigment cells normally exist. Most commonly the black moles of the cutaneous surface and the pigment cells of the choroid are responsible for these metastases. Occasionally, however, one cannot find the slightest evidence of abnormal cell activity in the normally pigmented sites, though distant parts show well-advanced melanotic growth. Hence the possibility must be borne in mind that a dislodgment of one or more pigment cells may occur at some time from a normal situation and subsequently become arrested at a distant point. In this way we may account for the occurrence of a melanoma in an internal organ where no primary tumor actually exists.

The neoplasm which is the basis of this study is definitely a melanophoroma and has occurred in the common bile duct of man. The duct was completely obstructed throughout the full extent of the growth. An obstruction of this nature and in this location is, to say the least, unique and aside from its surgical importance affords a most interesting histological study.

A careful search failed to establish the metastatic nature of the obstructing growth. The close resemblance of the cells of this tumor to epithelium renders the microscopic findings of sufficient importance to warrant a detailed description.

¹Received for publication April 18, 1908.

The clinical history and autopsy protocol are as follows:

Patient, male, white, aged 44, was admitted to the Montreal General Hospital in the spring of 1907, suffering from acute biliary obstruction. The first symptom appeared two months prior to admission as a cutaneous irritation, especially of the skin of the feet; the patient later became jaundiced and jaundice gradually deepened and was associated with great weakness and loss of weight. There was no vomiting at any time.

Shortly after admission a biliary fistula was established and in addition to bile, small granular bodies were intermittently discharged but at no time were definite calculi noted. At the operation a slight cholecystitis but no evident cause for the biliary obstruction was found. Throughout the period of observation the stools were fatty. The patient died early in September, two months after the operation and four months after the first symptoms were noted.

Autopsy was performed fourteen hours post-mortem. The body is that of a white adult male, fairly well developed but emaciated, with marked icterus of the skin, conjunctivae and mucous membranes. Rigor mortis is present. There is slight lividity over the dependent parts. The pupils are unequal, the left being 4 mm. in diameter, the right 2 mm. There is no œdema. In the right hypochondrium is a linear scar 10 cm. in length which traverses the right rectus muscle parallel to the median line. In the line of the cicatrix is a fistulous opening communicating with the gall bladder and on pressure over the upper abdomen the fistula discharges bile. The left parotid gland is the seat of extensive suppuration. Thick purulent material is easily expressed through an existing fistula.

There are no pigmented moles on the surface of the body.

Peritoneal Cavity.—The parietal and visceral peritoneum is deeply stained with bile. The appendix is 12 cm. in length, retrocæcal and twisted upon itself in its outer third. There is no enlargement of the mesenteric or retroperitoneal lymph nodes. The height of the diaphragm is normal. In the region of the gall bladder are numerous old fibrous adhesions especially about the fundus, formed after its attachment to the abdominal wall.

Pleural Cavities.—The right pleural cavity shows a few old fibrous adhesions over the upper lobe.

Pericardial Cavity.—There is the normal amount of fluid deeply bile tinged.

Heart.—Wt. 215 grm. The subepicardial fat is slight in amount. Pulmonary artery opened *in situ* contains post-mortem clot and fluid blood. The myocardium is of good color and consistence. The endocardium and valves are normal. The aorta and coronaries show nothing remarkable.

Lungs.—In the right upper lobe there is a small calcareous nodule the size of a pea (healed tuberculosis).

Spleen.—Wt. 150 grm. Organ shows nothing abnormal. The gastrointestinal tract and pancreas are normal. There is a firm gland 1 cm. by 0.5 cm. in the region of the cœliac axis, which on section is deeply discolored with bile, but otherwise shows no abnormality.

Liver.—Wt. 1,580 grm. The lobules are accentuated in outline because deeply bile stained; aside from this discoloration there is nothing noticeable.

Gall Bladder and Ducts.—The inner surface of the gall bladder appears

normal. The fundus is found opened and sutured to the abdominal parietes and communicates through a fistulous opening with the exterior. The cystic duct opened *in situ* is seen to be S-shaped—apparently the result of old adhesions. The wall of the cystic duct is of normal thickness and its inner surface smooth throughout. On opening the common duct it is found to be uniformly dilated to about three times its normal caliber. Its wall is somewhat thinned and the rugæ of the tunica propria present marked fenestration—presumably the result of long-continued distension. *In the lower portion of the duct there is a soft brownish black mass, 2.5 cm. in length, which completely occludes the lumen.*

Kidneys.—Wt. 260 grm. Both organs on section show a dark greenish discoloration of the cortex and medulla. The lining of the pelvis is bile stained and presents numerous small superficial hemorrhages.

The urinary bladder and genital organs are normal.

Brain.—Wt. 1,280 grm. Surface presents nothing remarkable. The pia-arachnoid shows the general deep bile discoloration. Lateral ventricles, pons, medulla, mid-brain and basal ganglia are negative. There is no evidence of abnormal pigmentation. The hypophysis, spinal cord and membranes are apparently normal.

Description of the Tumor.—The growth consists of a soft fungoid brownish black mass 2.5 cm. in length which completely fills the lower portion of the common bile duct, including part of Vater's diverticulum but without encroachment upon the duodenal passageway.

A grooved director was first passed down the lumen of the common bile duct into the gut without meeting the least resistance. Only after the duct had been laid open was the obstruction discovered. The tumor now presented itself as a soft black cylindrical mass which bulged over the edges of the opened duct. It was only with great difficulty that the tumor could be returned to its original place and the severed edges of the duct brought again into apposition.

The tumor throughout its extent was intimately attached to the duct wall and appeared to have started in the tunica propria. There was no thickening of the wall, which seemed abnormally thin. The upper and lower margins of the growth were sharply defined. The base of the growth maintained an even line 2 mm. below the surface epithelium as indicated to the naked eye by the pigment limit. The tumor was confined entirely to the common duct and ampulla. The pancreas and the duct of Wirsung were in no way involved by the growth.

At first it was thought that the tumor consisted of altered blood or inspissated bile; its true nature, however, was discovered after a more careful examination. The melanoma on closer inspection showed innumerable densely arranged flattened finger-like projections which floated free at their distal extremities, but remained firmly attached at their bases as demonstrated by immersion in water.

The tumor with its curious villous structures resembles certain forms of vegetable algæ growing under water. It is noteworthy that no part of the mass could be washed away, nor was the water discolored by the coloring matter of the tumor. On removing the mass from the water the villi immediately collapsed allowing the tumor to again assume a smooth dull black surface.

Microscopic Examination.—Longitudinal strips of the tumor throughout its whole extent were incised for microscopical study. The sections not only included the duct wall, but a part of the pancreas and the surrounding tissues. A portion of the uninvolved duct was included in the sections from the upper and lower limits of the mass in order that the outer cells and their relationship to the normal tissues might be studied. The tissues were fixed in Zenker's fluid, alcohol and formalin, and embedded in paraffin. The material, hardened in Zenker's fluid, was subsequently stained with eosin-methylene-blue for the routine study. Mallory's connective tissue, phosphotungstic-acid-hæmatoxylin and fibroglia stains were employed for the differentiation of special tissues. The material preserved in alcohol was used for the determination of iron-containing pigment; the test, however, was negative.

The growth, in general, under low magnification presents an alveolar structure which is irregularly and loosely formed. In some parts the cells are densely packed, while in others they are loosely arranged without any intercellular supporting tissue.

Sections treated with Mallory's special stains for connective tissue and fibroglia fail to show either of them. As a whole the tumor is without intercellular supporting tissue; an exception to this statement are some alveoli in the periphery of which the lining cells rest upon a delicate basement membrane. This membrane where present consists of fibers which run lengthwise to the glands and contain widely separated flattened cells from which the fibers are apparently derived. In addition to the cell groups which possess these supporting fibrils, there are those which apparently are held together only through cellular cohesion.

I believe that these basement supporting fibers and their cells are the same as those described by Mallory (1) as forming the true basement membrane of adeno-fibromata of the breast. As he points out, these fibrils always accompany the epithelium of the newly formed glands (adenomata) and seem to form as much a part of the tumor as the epithelium.

It is of interest to note that the villous masses comprising the tumor are covered by a thin though well-defined connective tissue envelope, in whose fibrils are elongated cells arranged end-to-end

in an unbroken chain. There is no pigment either intra- or extra-cellular in this supporting tissue, and in no way does it resemble the melanoma.

The growth apparently started in the gland follicles of the tunica propria where the pigment cells are more numerous within and around the lining epithelium than in any other part of the involved duct wall. Microscopic examination shows that the pigment cells do not extend below the level of the gland follicles, and are so intimately associated with the epithelium of the follicles that it is impossible to distinguish them. This is so striking in some sections that one is inclined to regard the growth as epithelial in origin. Either the normal gland epithelium has become phagocytic to melanin granules of neighboring mesoblastic cells or the epithelium here represents a malignant metamorphosis. Certainly in no portion of the duct throughout the entire basal length of the tumor can one find pigment-producing cells that have involved the vessels beyond the tunica propria.

Many of the glands are composed of single layers of evenly arranged columnar cells that show all grades of pigmentation. Occasionally follicles are lined with two distinct types of cells; the one columnar, mononuclear and non-pigmented; the other bizarre in outline with two or more nuclei and protoplasm completely filled with pigment granules. These two types of cells alternate to form the basal layer of the mucous glands. Possibly these chromatophors should be regarded as foreign cells which have invaded the gland epithelium, since they differ in size, shape and position from the normal columnar cells of the follicles.

These pigmented cells with their long protoplasmic processes frequently alternate with the non-pigmented epithelium, and in places the cell body may be seen pushing its way through the basement membrane of the gland or projecting into the lumen. The processes filled with pigment stream out like tentacles between the normal columnar epithelium. Invariably the protoplasmic prolongations are directed toward the gland lumen; only rarely, indeed, do they point in the opposite direction, though the cell body proper is often beyond the basement membrane or even in the periglandular space.

As a rule the outline of each pigment cell is sharply defined by the brownish black granules, which completely fill every part. The whole is a striking picture of abnormal epithelial activity and suggests that the gland follicle is probably the true generic center of the melanophoroma.

The cells which are free in the lumen of the gland are decidedly angular in outline, especially where they are crowded together. This appearance is even more noticeable in the cells lying free in the alveoli of the melanoma (see Plate XXVIII, Fig. 3). Commonly they are hexagonal, though the chromatophors not associated with an alveolus are round or ovoid. In neither situation, however, are they provided with the protoplasmic extensions which are so characteristic of the pigment cells found in the normal gland follicles. In general the size of the ovoid and hexagonal cells varies greatly, the larger ones measuring 40 to 60 microns and the smaller 4 to 8 microns in diameter.

The new growth is almost entirely composed of pigmented cells; only occasionally are the cells non-pigmented and here apparently they do not belong to the normal tissues. The pigment is most marked in the outer extremities of the villi where the alveolar structure is most pronounced.

The cells have a large distinctly lobulated vesicular nucleus with one or more nucleoli. The nucleolus is always sharply defined and may be very large, sometimes the size of the nucleus of a small lymphocyte. There is often only a narrow rim of nuclear material surrounding an enormous nucleolus. The great variation in size and density of the nucleoli is another prominent feature of the tumor. It is not uncommon to find cells with two or more nuclei held together by narrow bands of basophilic material, each nucleus provided with its nucleolus and normal amount of chromatin.

Mytotic figures are only occasionally found and then in cells sparsely provided with pigment. In certain amœboid cells there may be seen a nucleus in the protoplasmic extension, while a second exists in the cell proper.

Pigment production is apparently in direct proportion to cell activity; the large active cells with deeply staining nuclei containing an abundance of pigment, the small cells with pale nuclei containing

but few granules. The pigment generally occurs in the form of globules arranged in the cell protoplasm equidistant from one another. These globules vary greatly in size, from mere points to that of the ordinary eosinophilic granule. Their color ranges in tint from a light mahogany to a dark blackish brown.

In many cells the pigment granules have coalesced to form one large globular mass which is either centrally or excentrically situated. About such a mass there are apparently as many pigment granules as in the cells of the same size which show no fusion of the pigment. Often the coalesced pigment forms a dense brownish black mass which occupies the inner two thirds of the cell, whilst the periphery is formed by a narrow band filled with light brown granules. Large vacuoles are seen in some cells and undoubtedly represent spaces where the coalesced pigment has dropped out. Many cells are so densely crowded with the granules that the nucleus is not discernible even on change of focus.

The nuclei often contain masses of chromatin-like material which strongly resembles melanin. Whether an excess of nuclear pigment is thrown out and constitutes subsequently the pigment of the protoplasm cannot with certainty be determined.

The pigment differs from that of the melano-sarcoma in that it occurs in the form of evenly arranged intracellular globules instead of irregular scattered masses. The distribution is so regular that it does not seem to be a by-product, but rather an integral part of the cell.

Some chromatophors are phagocytic to others and, in such instances, are easily distinguished from the common endothelial scavenger of blood pigment. The inclusion often fills the greater part of the phagocytizing cell, displacing its nucleus to the extreme periphery. Sometimes there is a broad clear zone about the engulfed cell, outside of which is the protoplasm of the phagocyte.

Occasionally a small vessel in the submucosa of the common bile duct and in close proximity to the tumor contains pigment cells. These cells have the same general morphology and are filled with dark brown granules similar to those of the cells above described. They are not free in the lumen, but appear from their close relation to the intima to be part of the lining endothelium, except that they

are deeply pigmented and bulge into the lumen far beyond the normal cell line. With the exception of these vessels near the tumor the melanotic cells are strictly confined to the main mass. Although some vessels contained chromatophors, contrary to what might be expected, no metastases were found.

A few eosinophile, lymphoid and plasma cells are scattered through the basal portion of the tumor. Below the region of the involved part of the duct there is a well-marked peri-glandular inflammation of lymphoid and plasma cells, but no pigmented cells of any description. Here the cylindrical epithelium of the glands is normal in appearance, though it is evident from the leucocytic infiltration that the follicles are the seat of a chronic inflammation. As far as can be determined all the gland follicles in the tunica propria above and below the growth show a low grade of chronic inflammation, though the other tissues are normal. This fact, in view of the inadequate explanation of the occurrence of this melanoma, strongly inclines one toward Ribbert's (2) theory that there may be some connection between the tumor and this inflammation.

On microscopic examination the pancreas, liver and other organs of the body show nothing remarkable.

Discussion.—The melanophoroma here described is of considerable histopathological as well as surgical interest. We not only have a pigmented tumor unique in its situation, and apparently primary in the common bile duct, but one whose cellular structure resembles epithelium in many ways.

Though secondary growths from melano-sarcoma are common in the liver there is, to my knowledge, no reported case of such a growth occurring in the common bile duct. Statistics show that the gall bladder and ducts are far more frequently the sites of primary non-pigmented sarcomata. In view of this fact the presence of melanin in the tissues where normally it does not exist, as in this case, might impose an insuperable objection to the belief that this is a primary growth. The tumor under consideration, it would seem, originated in the normal cells of the wall of the common bile duct, for the most careful search of the cutaneous surface and central nervous system failed to show anything that would

indicate its metastatic nature. It is to be borne in mind, however, that there is the possibility of a dislodgement at some time of one or more pigment-bearing cells which subsequently have been arrested at the site of growth. In support of this one can advance the recognized metastasis of thyroid cells in remote parts of the body in cases where there is no primary growth in the gland itself.

There are many features of the tumor which suggest an epithelial origin; on the other hand, there are points in favor of its being an alveolar melano-sarcoma. In considering an epithelial histogenesis one is struck with (1) the unusual situation of the growth in a tissue where melanoma have never before been noted, (2) the epithelioid character of the cells and their tendency to mimic in arrangement glandular structures, (3) the intimate association of the cells with those of the normal gland follicles, and (4) the unusual regularity in size, color and distribution of the pigment in each cell, compared with that of the ordinary melano-sarcoma. Of course it is difficult to conceive that a primary melanoma, no matter whether mesoblastic or epiblastic, could arise from cells in this location.

Undoubtedly the strongest point in favor of sarcoma is the presence of melanin, though even here the pigment is atypical in its arrangement and distribution. Ordinarily in melano-sarcoma there are areas that contain no pigment, while others are sparsely supplied and in still other areas pigment is in considerable amount.

If we disregard the pigment for the time, the nature of the growth is only to be determined by its structure and cell morphology. After all the morphological character of the cell is of little value as an aid toward classifying tumors, especially where there is no definite arrangement. The inter- and intracellular fibrils produced by cells certainly offer a more reliable means. In this melanoma of the common bile duct the cells in many parts are similar in morphology to glandular epithelium. They show, moreover, a decided tendency to form alveoli; this fact, considered with the epithelial character of the cells, would make it impossible to class the tumor among the sarcomata were it not for the presence of melanin.

The question naturally arises, can we have a melanophoroma

either meso- or epiblastic in nature which is primary in a situation where normally there are no pigment cells? It is conceivable that epithelial as well as mesothelial cells normally not pigmented may produce pigment under certain conditions.

Hertwig (3) suggests that the pigment of melano-sarcoma is formed from chromatin extruded from the nucleus in an effort of the cell to reduce its nuclear mass, and thus to reorganize itself. In a later paper (4) he describes the transformation of chromidia into pigment. Rössle (5) claims to have traced in the cells of melano-sarcoma the wandering of nuclear substance from nuclei over-rich in this material, and its transformation into pigment in the protoplasm. He suggests that the pigment formation of senile atrophy is produced in the same way as the pigment of actinosphærium and shows, as far as microchemical methods go, the pigments of actinosphærium, melano-sarcoma and brown atrophy to be apparently identical and iron free. Meirowitz-Grandenz (6) in their study of pigment formation in the skin after exposure to light were able to trace both in the nucleus and in the protoplasm pigment from nucleolar substance.

I have observed the formation of autochthonous pigment in corneal epithelium where the cells under toxic irritation become filled with pigment granules. Whether or not this pigment is altered and extruded nucleolar material I am not prepared to say. In consideration of the above facts, I am inclined to believe that the tumor here reported has its origin in cells of the common bile duct.

There is also much evidence in favor of an epithelial histogenesis, especially when we consider that the cells do not produce fibrils or intracellular fibers. Also the more recent work on melanin-producing cells tends to strengthen the conception of their epithelial origin. The pigment may be the result of some peculiar action of certain products of liver metabolism on the mucous gland cells in the common duct, and, as Hertwig suggests, represents the by-product of over-active cells in their attempt at reorganization.

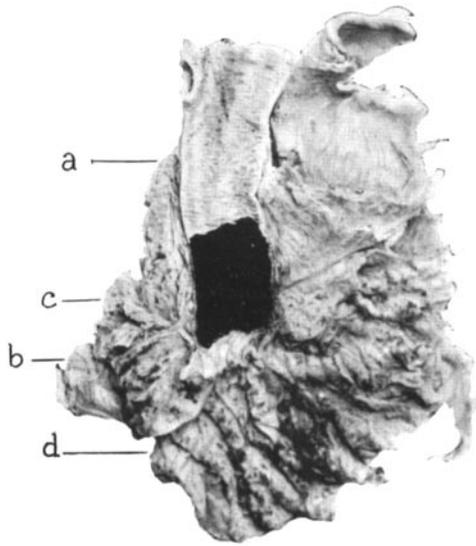


FIG. 1.

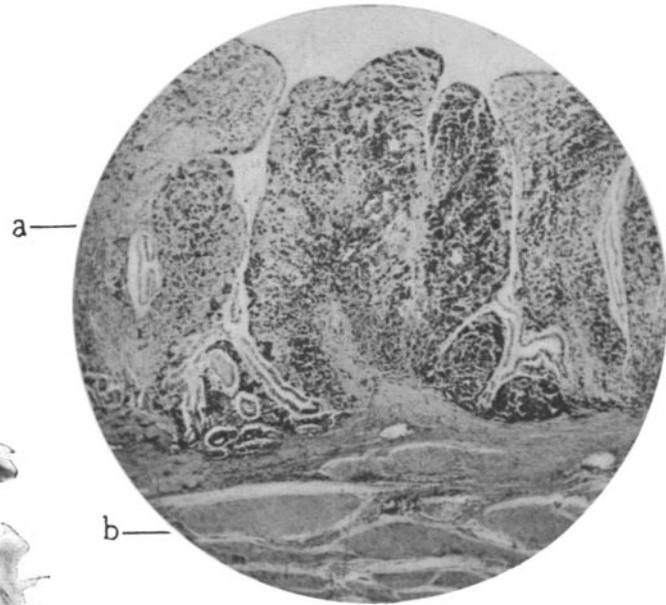


FIG. 2.



FIG. 3.

BIBLIOGRAPHY.

1. Mallory, F. B., *Jour. of Med. Research*, 1905, viii, 113.
2. Ribbert, H., Beiträge zur Entstehung der Geschwülste, 1906.
3. Hertwig, R., *Sitzungsber. Gesellsch. für Morph. u. Physiol.*, 1902, xviii, 77.
4. Hertwig, R., Festschr. für Ernst Haeckel, 1904, 301.
5. Rössle, *Zeit. für Krebsforschung*, 1904, ii, 291.
6. Meirowitz-Grandenz, E., *Monatshefte für praktische Dermatol.*, 1907, xlv, III, 166.

EXPLANATION OF PLATE XXVIII.

FIG. 1. Gross appearance of the tumor *in situ*. (a) Upper part of the common bile duct. (b) Ampulla of Vater. (c) Obstructing melanotic growth. (d) Duodenum.

FIG. 2. Section through the common bile duct including the melanoma under low magnification. (a) Pigmented villous projections which in parts show an alveolar construction. (b) Muscularis of the common duct.

FIG. 3. Represents a camera lucida drawing, Leitz, ocular 3, immersion lens 1/16. Note size, shape and arrangement of the pigmented cells.