THE ORIGIN OF THE MALIGNANT MELANOMATA*

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It is presumption on my part to cross the Border into the land of Dawson and his great work on the melanomata and read a paper on that very subject.

I would, however, like to say at the outset that I owe all my basic knowledge of our problem to him; and it must be remembered that Dawson himself hoped his work would be made the stepping stone for further investigation. It seemed to me also that it was perhaps opportune to try and sum up the valuable, and I would say indispensable, evidence which ophthalmic pathology furnishes.

Ribbert a long while ago showed that malignant melanomata could arise from branched chromatophores, and it has now been confirmed many times that a teased preparation of what on microscopic section appears to be a spindle-celled tumour of the choroid is in fact composed of chromatophores in all stages of development. The most important fact brought about by Ribbert's work was that in secondary nodules found in the brain and liver the cells were identical with choroidal chromatophores. Having proved this point the unfortunate thing is that he then attempted to show that all melanomata had this origin.

Similarly Unna and Dawson found that these tumours could arise from downgrowths of the surface epithelium. This, too, has been confirmed time and time again. But they then attempted to prove that all malignant melanomata arose in this way.

Lastly Masson has brought forward evidence to show that the much disputed naevus cells are really developed from the end apparatus of the sensory nerves. As a result of this it is now very widely held that all pigmented growths have a neurogenic origin. It is one of the main purposes of this paper to attempt to show, what indeed has been done before, that a unitary theory both of the origin of melanin and of malignant pigmented growths is not tenable.

It is essential for our purpose to decide on a proper definition of what is meant by a naevus cell; for some say they are large and others small; some describe them as clear, others dark. I agree with the following which is that of Dawson:—Naevus cells

* Being the William Mackenzie Memorial Lecture read at Glasgow on October 24, 1947. Received for publication, December 8, 1947.

(Figs. 1, 2, 3, 4, 5) are small, almost atrophic cells, polymorphic in outline with little cytoplasm. They are separated by a varying amount of connective tissue from each other and are usually arranged in what are termed cell columns or groups or nests which are separated from each other by fibrous tissue septa and the whole usually from the epidermis by a narrow zone of almost homogeneous connective tissue. It was the arrangement of the

FIG. 1.

Conjunctival naevus at limbus. Note dark staining nuclei of naevus cells and downgrowths of epithelium. An island of epithelial cells among naevus cells.

cells in columns and groups that first led von Recklinghausen to trace their origin to the lymph-channel endothelium. The naevus cells as they grow older tend to resemble lymphocytes and may become drawn out into filaments.

The main reason for deciding at the outset what we mean by a naevus cell is that we may distinguish them from epithelial cells derived from the downgrowths of surface epithelium. I believe this to be of vital importance and yet, very curiously, it is only very rarely discussed even in the most important works on the subject.

As a rule it is quite easy to distinguish naevus from epithelial

cells. So long as the epithelial cells are part of the club-shaped downgrowths there is, of course, no difficulty in differentiating them from the naevus cells. This also applies to islands of epithelial cells found as a result of the epithelial columns being cut across. Also the central portions of the epithelial downgrowths may degenerate and then a cystic condition is produced (naevus glandulosus cysticus). Although often described I have

FIG. 2.

FIG. 1 under higher power. Arrow points to process of a chromatophore.

never seen such a cystic tumour formed as a result of degeneration of the naevus cells. When the epithelial cells no longer form part of the downgrowths or of the islands they are differentiated by the characteristics of the cells themselves. The typical epithelial cell has a large vesicular nucleus staining much paler than that of the naevus cell. Also it has an abundant cytoplasm. In certain cases the proliferating epithelial cells are fairly closely packed and then one has to rely on the staining properties of the nucleus only to differentiate them. But where there are masses of the two types of cells next each other the difference between the paler epithelial nuclei and the darker nuclei of the naevus

cells is very striking (Fig. 4). It will be noted as in Fig. 4 that epithelial and naevus cells may proliferate side by side in the same tumour. This fact, provided one is not wedded to a unitary theory for the origin of these growths, is obviously of great importance. A very important point which applies only to conjunctival naevi is that the downgrowths of epithelium may contain mucous cells (Fig. 7). Indeed, P. Veil in his thèse de

FIG. 3.

Conjunctival naevus. Note islands of epithelial cells and nests of naevus cells.

Paris goes so far as to say that because there are mucous cells among the naevus cells therefore these latter are epithelial in origin! But at any rate the mucus stamps the cells as epithelial.

As stated above, it is usually easy to distinguish naevus from epithelial cells; but at times, owing possibly to the method of fixation and staining, it may be very difficult or impossible.

The epithelial theory of origin of the naevus cells is usually said to have received important support from the work of Bruno Bloch, who treated sections of normal skin with dopa and found that the basal layers of the epithelium were coloured grey or

black; the branched intra-epidermal cells of Langerhans being particularly dark. Also in the masses of naevus cells the superficial ones gave the dopa reaction. This colouration was held by Bloch to be due to the formation of dopa-melanin resulting from the presence of dopa-oxydase in the cells. All cells giving this reaction were held to be capable of producing melanin and were therefore melanoblasts. But while in general Bloch finds

FIG. 4.

Deeper portion of same tumour as FIG. 3. *Note*: proliferation of naevus cells (dark nuclei) and epithelial cells (pale nuclei) side by side in same tumour.

no cells of the normal dermis to be dopa-positive the cells of the Mongol spot are. Now the Mongol spot in the sacral region consists of branched chromatophores like those of the choroid and generally recognised as mesodermal in origin. In making this exception, therefore, Bloch in fact helps to prove the dual origin of the pigment.

It is often stated that the problem of the origin of the malignant melanomata is synonymous with the problem of the origin of the naevus cell. This I believe is a fundamental error and has led to a great many unjustified conclusions. In the first place it

cannot be too strongly emphasised—a point that is often forgotten—that although there are naevi in the uveal tract there are no naevus cells. In fact, Morax would regard the naevi of the skin and conjunctiva as quite different tumours from those of the uvea. Also we find that Bloch, like so many others, having decided that the naevus cells are epithelial in origin makes no distinction between them and the epithelial downgrowths. You

FIG. 5.

Melano-carcinoma of limbus. Note growth adherent to anterior surface of cornea. $\times 25$.

will see by the figure taken from Bloch's article in the Jodassohn Handbuch that he describes an obvious downgrowth of epithelium as consisting of naevus cells.

Further, Dawson's well-known figure of the formation of a malignant epithelial pigmented growth shows this arising from downgrowths of epithelium and not from naevus cells.

I would next like to draw attention to a paper by D. T. Smith in the Bulletin of the Johns Hopkins Hospital for 1925, which I think has received nothing like the attention it deserves. After pointing out that if pigment is formed in a cell the granules are the same size, he says: "When granules of pigment were taken in by cells not normally pigmented, the picture was distinctly

different from that described above. In this case the pigment was a foreign body in the cytoplasm, and the cell reacted in such a manner as to clump it into masses of irregular size and shape. Cultures of various types of embryonic chick cells were grown and pigment granules then added to the culture fluid. The whole process of ingestion and clumping of the granules into masses in the cytoplasm, with the formation of a vacuole about each

FIG. 6.

Detail of Fig. 5 under higher power. Note formation of theca containing *epithelial* cells and the place where the epithelial cells have grown down through basement membrane (Zenker Mallory's triple stain).

mass, could be followed with the microscope (Smith, 1921). The reaction was always the same, regardless of the source of the pigment. Melanin granules from the eye (chick, pig, dog or human), carbon particles, carmine granules, indian ink and blood pigment, all became clumped in the cytoplasm into masses of irregular size and shape. When once the pigment had been taken into the cytoplasm it was not given up until death of the cell.

"It is evident from these observations that here is a practical method of determining from the appearance of the granules, when examined with the oil immersion lens, whether they have been produced by the cell or have been taken in as foreign bodies. In studying the pigment cells we need no longer be confused by the question whether a particular cell under observation is a pigment producing or a pigment carrying cell."

Dawson and others, in order to bring the origin of the choroidal melanomata into line with the epithelial theory, have suggested

FIG. 7.*

Section of naevus of conjunctiva to show mucous cells (stained green), both in surface epithelium and in epithelial downgrowth (Masson's stain).

that the choroidal pigment was derived from the retinal pigment epithelium. As has now often been pointed out there is a great deal of evidence which makes this impossible, or at any rate extremely unlikely.

In the first place the retinal pigment is morphologically different from the choroidal. The retinal pigment most characteristically occurs as spindles or rods; it is true that in the bases of the cells rounded forms are found, but these are much larger than the fine particles in the choroidal chromatophores. Also the retina is fully pigmented by the fifth month of intra-uterine life, whereas no pigment occurs in the choroid till a few months before birth, and then first in the outer layers. Treacher Collins showed, too, that the pigment epithelium of the retina though amoeboid

* Unfortunately reproduction in monochrome does not show the difference.

throughout life does not pass through the membrane of Bruch. He also brought forward evidence to show that the uvea produces its own pigment: tags of pupillary membrane which have been completely isolated before the ingrowth of the secondary optic vesicle may become normally pigmented; and in rudimentary eyes in which no epiblastic tissue was present the uvea was found normally pigmented. Then, too, it has been repeatedly shown that in tissue culture the retinal pigment cells grow out in sheets like epithelium while the choroidal chromatophores grow like fibroblasts, *i.e.*, as isolated cells. Lastly, the choroidal pigment particles are all the same size. According to Smith, therefore, the pigment has formed in these cells which are therefore melanoblasts.

As further evidence against a unitary theory of the origin of malignant melanomata I would remind you of the well-known difference in the method of growth between the sarcoma and carcinoma or epithelioma of the limbus. The epithelial tumours tend to grow over the cornea like a pannus being closely adherent to it; while the sarcoma usually forms a mushroom-shaped pedunculated growth which tends to cover but not to get adherent to the surface of the cornea.

We now come to a consideration of Masson's neurogenic theory. This is a beautiful, detailed and suggestive work which has received almost universal acceptance. The following points also seem to favour it: The association of neurofibromatosis with café-au-lait spots and pigmented growths; the interesting demonstration by Laidlaw and Murray that naevi probably represent the touch corpuscles of reptiles and amphibia; the suggestion latterly put forward that the pigment cells are derived from the neural crest and grow down with the nerves to the skin, etc., and finally, possibly the curious insensitivity of pigmented growths to X-rays. But there are a number of important facts which call for criticism. In the first place, and this is a fundamental point, the theory has no room or explanation for the downgrowths of epithelial cells, both in the naevus and in the malignant melanoma. Thus in agreeing with Masson's theory Boyd in his excellent Pathology says: "In many cases there is an apparent proliferation of the basal layer of epidermal cells with the formation of downgrowths of cells which penetrate into the dermal portion of the naevus and thus gives the impression that the tumour has arisen from the epidermis. It seems more probable that these basal epithelial cells are merely pushed aside and displaced downwards by the proliferating naevus cells and melanoblasts originating in the epidermal portion of the sensory organs."

Now there is in my preparations no evidence that the epithelial cells are pushed down. They grow and proliferate as typical epithelial cells.

In the second place Masson says that the cells of the Merkel-Ranvier corpuscles are represented in the human by the clear cells (*cellules claires*) and what he calls the branched pigmented Langerhans cells and that these are therefore really modified cells of Schwann. Now the clear cells occur at regular intervals at the junction of the dermis and epidermis. They have a rounded or kidney-shaped nucleus which stains denser and is larger than that of the neighbouring epithelial cells. Around this is a well-defined clear space. From the base of the cell Masson describes a process which, continuous with a nerve fibre, runs down into the dermis. Masson holds that the clear cells are derived from Schwann cells, which migrate and insinuate themselves between the epithelial cells of the basal layer during foetal life.

Now up to the present there has been no embryological proof of this. Also it has been shown that after the destruction of certain sense organs, for instance the Gandry corpuscles of the duck, the cells of these are regenerated locally and not from the nerve fibres; and further the cells of the Merkel-Ranvier bodies appear to be developed from the surface epithelium and not from the cells of Schwann. (Szymonowicz).

Also Masson describes the Langerhans cell as a branched pigmented cell lying in the basal layers of the epidermis and sending processes into the dermis. It must be clearly understood, however, that the cell Langerhans described has only been demonstrated with gold chloride and lies 3-5 cells up from the basement membrane. It has never been shown to have a nucleus and Langerhans insisted that it had nothing to do with pigment function.

Masson believes that what he calls the Langerhans cell* is the sole producer of pigment and that it acts like a gland pouring its pigment into the neighbouring cells. But Smith has shown that the pigment granules in the basal cells are small and rod-shaped, while in the Langerhans cells the pigment is rounded; moreover they are all of the same size and therefore formed primarily in the epithelial cell.

A great difficulty also arises from the fact that Masson does not say whether these tumours are mesodermal or ectodermal. This naturally follows from the fact that there is still dispute as to the origin of the cells of Schwann. Many of those who uphold the neurogenic theory, however, use such terms as neuro-epithelial and neuro-sarcoma.

* I find however, that this is now the accepted meaning of the Langerhans cell and must presumably remain so.

Further, the neurogenic theory is another attempt at bringing all pigmented tumours under one roof, and as such it cannot be accepted.

Next I would refer to those rare but definitely established growths which arise from the pigment epithelium of the retina, ciliary body and iris.

Only one, that of Griffith, has been described as arising from the pigment epithelium of the retina; a fair number have been found coming from ciliary epithelium, the best known being that of Treacher Collins, which was later included in the work of Fuchs.

A number of growths also have been described arising from pigmented epithelium of the iris. I show you the picture of Morax's case. The actual growth is dense black; a bleached section shows that the growth is composed of cells exactly like those of the pigment epithelium of the iris. Here then we have pigmented growths arising from epithelium. There can be no question of their coming from sensory nerve endings.

We see then that melanomata may arise from naevus cells, epithelial cells and from branched chromatophores and, as in Fig. 4, naevus and epithelial cells may proliferate side by side in the same tumour.

I would suggest, therefore, that the naevus should be regarded as a composite or mixed tumour consisting, for our purpose, of naevus cells, epithelial cells, and branched chromatophores. Each of these may proliferate alone or with the others and produce a malignant pigmented tumour. The final structure will depend on the relative proportions of the three types of cell.

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