

On the origin of the so-called naevus cells of soft moles and the formation of the malignant growths derived from them / by Arthur Whitfield.

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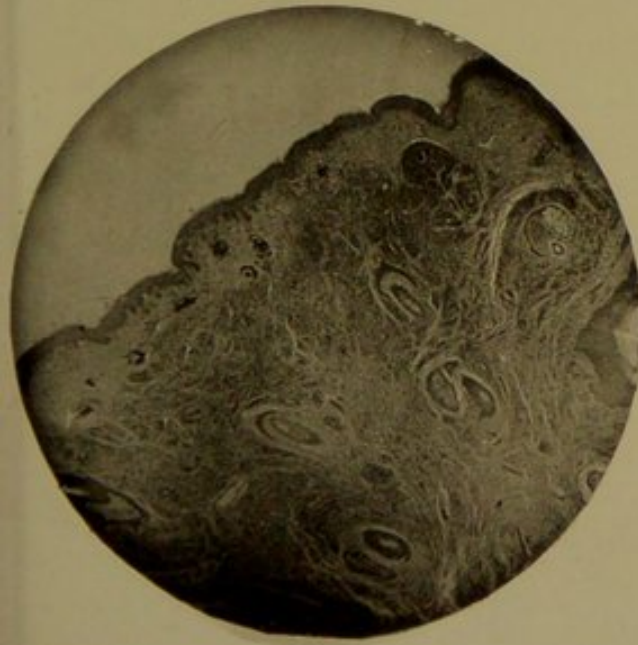


Fig. 1.

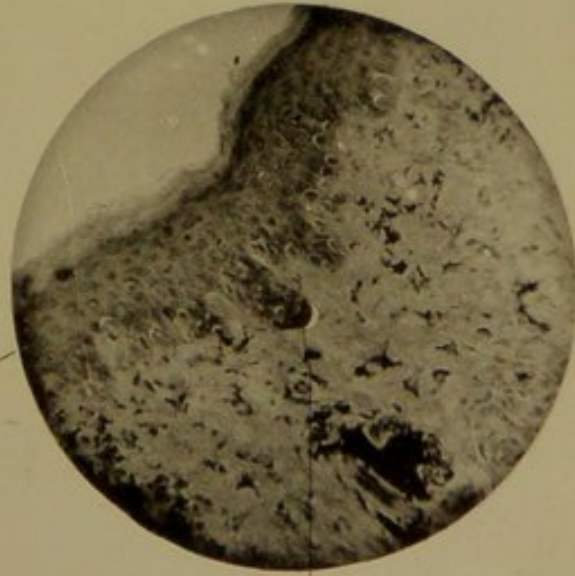


Fig. 2.

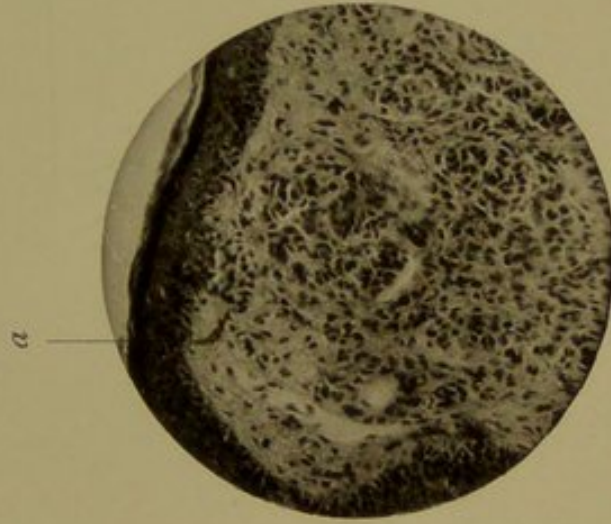


Fig. 3.



Fig. 4.



Fig. 5.

Plate I.

WHITFIELD "NÆVUS CELLS AND MALIGNANT GROWTHS."



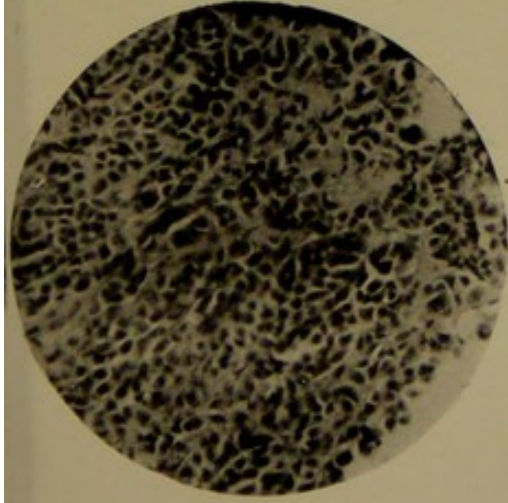


Fig. 6.



Fig. 8.

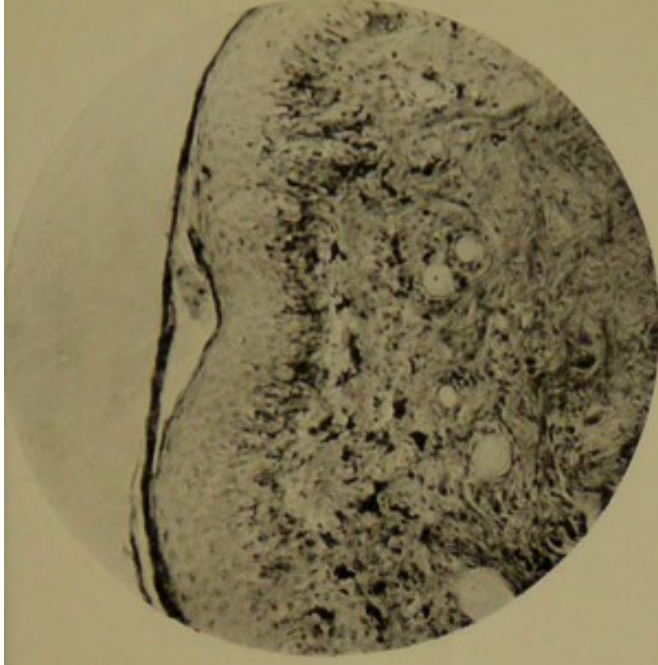


Fig. 9.

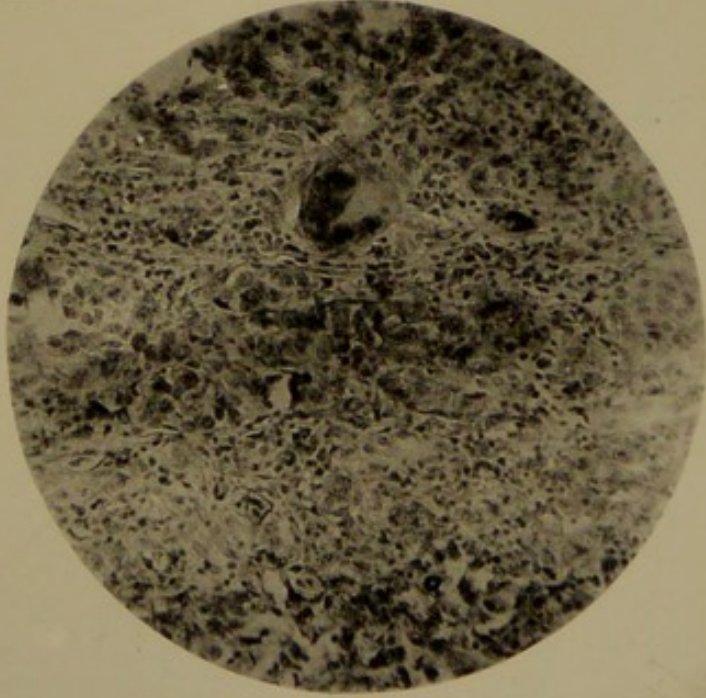


Fig. 7.



Fig. 10.

Plate II.
WHITFIELD "NÆVUS CELLS AND MALIGNANT GROWTHS."



ON THE ORIGIN
OF THE
SO-CALLED NÆVUS CELLS OF SOFT MOLES
AND THE FORMATION OF THE
MALIGNANT GROWTHS DERIVED FROM THEM.

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AFTER the description of the fleshy mole by von Recklinghausen as a lymphangio-fibroma, the question of its origin seems to have been regarded as settled, until Unna, in his paper "On Nævi and Nævocarcinoma," brought forward the view that these growths were not due to proliferation of lymphatic endothelium, but were the result of snaring off of parts of the deep epidermis so as to form masses of epithelial cells embedded in the corium.

The appearance of Unna's paper has been the signal for a somewhat hotly-contested argument, in which many eminent pathologists have taken part, the chief opponents being Leedham Green, Bauer, Ribbert and Lubarsch, with Hanseemann, as regards the malignant growths only, while Menahem Hodara, Delbanco, Gilchrist, and Kromayer have written in support of the epidermic theory. Recently I observe also in the new dermatological work of the French School that Darier regards Unna's contention as justified.

Although it is not my intention to give an exhaustive survey of the somewhat voluminous literature on the subject, it may be of interest to recapitulate some of the main arguments used on both sides.

von Recklinghausen wrote before the time of the controversy, and

described very accurately the appearances of these growths. His reasons for believing them to be lymphangio-fibromata were the forms of the cells, which certainly bear a strong resemblance to endothelium, and the columnar grouping, which suggests in its arrangement that of the normal lymphatics of the skin. He, however, in his book expressly stated that the spaces in which the cells lay were not lined with endothelium, that he had never seen an undoubted lumen in the columns of cells, and that the cells were not arranged upon the wall in regular layers as one would expect in typical, though perhaps thickened, endothelium. Unna's main argument for the epithelial origin of the cells is that if the nævi be examined in a young stage—*i.e.*, from children—the process of snaring off can actually be observed to be taking place. He further points out that, if this process has been once seen in young cases, where it is very obvious, it may be recognised as occurring, although to a much less marked extent, in the nævi of adults. According to him the process is one of downgrowth of the epidermic cells with snaring off of the downgrowth by the connective tissue of the corium and a metaplasia of the sequestered cells into a more plastic material with loss of prickles. Bauer brings forward the following points as arguments against Unna's theory:—

(1.) The groups of nævus cells are separated from the epidermis by a margin of cell-free corium.

(2.) The epidermis generally leaves off with a well-defined edge, this being true also in those cases where some prolongation of the normal epithelial folds has taken place.

(3.) The cells in the nævus groups differ from epidermic cells in the shape of their nuclei, these being round, oval, or polygonal, while the cell protoplasm is scanty and irregular. Some of the cells also show more than one nucleus.

(4.) In connective tissue one meets with two forms of nuclei:—(a) typical, small connective tissue nuclei; and (b) more rarely, vesicular nuclei whose cell-body is easily seen when lying in a connective tissue space. The latter variety is exactly similar to the cells forming the groups in nævi.

(5.) It is rare to meet with cells which are not individually separated by connective tissue, and in this he has the support of Ribbert, also, curiously enough, of Kromayer from the other side.

(6.) In some cases a lumen is present in the columns of cells. Delbanco agrees almost entirely with the description of von Recklinghausen, with the exception that he finds that the cells lie in spaces lined with endothelium, which he figures. He adopts, however, Unna's explanation of their origin, and regards them as having grown down into the superficial lymphatics.

Hodara bases most of his arguments in support of Unna on the apparent presence of prickles in the snared off cells.

Kromayer, whose views are particularly interesting because, in addition to being an accomplished histologist, he is a convert to Unna's side, having at one time held the opposite opinion, calls attention to the peculiar degeneration of the cells in the epidermis and their loss of prickles, leading to the formation of encysted masses which later on pass downwards into the corium. He also admits the presence of collagenous and elastic tissue between the deeper cells, but puts forward the heretical, but not necessarily erroneous, view that this tissue is of new formation and produced by the nævus cells themselves. He therefore assumes a metaplasia of epithelial into connective tissue-cells, and remarks that one may classify these cells as epithelial from their parentage or connective tissue from their later behaviour. Lubarsch throws doubt upon the genuineness of the encysted epidermic masses, and points out that such appearances may be often obtained in oblique sections; at the same time he thinks that the metaplasia of epithelial into connective tissue-cells in post-embryonic life has not been proved to occur.

From the foregoing sketch of the discussion it will be seen that many of the investigators have attached great importance to minute differences or similarities in the structure of the cells, and some have tried to prove their epithelial or connective tissue character from these structural peculiarities. In this connection, the remarks of Hansemann, in his admirable brochure on the microscopic diagnosis of malignant tumours, are both interesting and important. He points out that no reliance should be placed upon the characters of a cell for the purpose of discovering its origin, and in support of this statement quotes Kölliker and His, finally expressing his opinion that "epithelial character can only mean the juxtaposition of many cells and the covering of a surface, never a morphological peculiarity of any individual cell."

Feeling myself in entire agreement with this view, I determined to investigate the matter purely from the standpoint of trying to demonstrate the actual connection of the cells with either the lymphatic vessels or the surface epithelium. Unna has, of course, claimed to have demonstrated the latter, but he has not figured it clearly, and his specimens have failed to convince his opponents. Several investigators have figured these appearances very beautifully, but their figures have been open to the objection that cells may have been figured from two planes of the section, so that what looks like a definite connection may be an optical illusion. I have already mentioned that Lubarsch has criticised Kromayer's figures of the encysted epithelial cells in the epidermis by pointing out that in oblique sections the same appearances might be produced, though the so-called epithelial cells were in reality situated in the tops of the papillæ. In order to avoid these two fallacies I therefore set myself the task of, first, reproducing the appearances by photomicrography, since with even moderately high powers it is impossible to obtain two planes in focus at once, and, secondly, to demonstrate a stage previous to that described by Kromayer, so as to show the connection of the cells with either the epidermis or the lymphatic endothelium. This has, of course, necessitated a large number of sections, but I have only reproduced those that appear to me to be convincing. I obtained the earliest stage from a tumour the size of a dried pea (a general view of which is shown in Fig. 1), situated at the junction of the left ala nasi with the upper lip in a girl of 20. Owing to the age of the patient the process of mole formation is almost at a standstill, and, therefore, where it is still taking place, does not give such complicated appearances as in the younger growths. It is perhaps worthy of note that the position of this mole is that described by Bland Sutton as "sequestration dermoid" of the naso-facial sulcus, and the growth would *a priori* be expected to be of epidermic origin.

The low power appearances as seen in Fig. 1 are those described by Bauer, and especially is this the case with regard to the cell-free margin of corium separating the groups and columns of nævus cells from the epidermis. On examining the lower margin of the epidermis, however, with a high power, one notices here and there the appearances which are photographed in Fig. 2 (a). In this figure one

notices at once that one of the epithelial folds is undergoing an alteration. The cells have lost their prickles, the cell bodies have become smaller and less definite, some pigmentation is occurring, and splitting off of the epidermis from the corium has taken place at the lowest point of the fold. This last may very well be artificially produced by the hardening, though this was done by means of the formaline-Müller mixture which usually preserves tissues with a minimal amount of shrinking. Be this as it may, it is not very important from the point of view of its significance, since it has only taken place where this pigmentary and plastic change in the deeper layers of the epidermis is occurring, so that, if it be artificial, it must nevertheless indicate a greater delicacy than normal of the connection between the epidermis and the papillæ, a fact which would be accounted for by the loss of the supporting epithelial threads and prickles. This photograph seems to me, therefore, to be very important, as it is certain that the change is in the epidermis and in no other structure, and it shows that that loss of cohesive power is taking place which renders the later occurrences so difficult to follow.

Fig. 3 is a photograph of a rather more advanced stage of the process. It was taken from the surface of a large hairy mole on the face of a young child, and I am indebted to my colleague, Mr. Watson Cheyne, for the tissue. Here one can distinctly see at (*a*) the alteration in the character of the cells in the epidermic down-growth, and a fissuring, also possibly due to the hardening reagent, has occurred so as to slightly separate the mass of the cells from the main epidermis. The character of these cells is now that of the nævus cells beneath, and I do not think that, without the evidence of the preceding photograph, it could be said whether these cells were growing up from the tissue below or down from the epidermis above. Fig. 4 simply shows the deep structure of the mole from which Fig. 1 was taken, and is given to show, first, that it is quite a typical soft mole as regards its deep alveolar structure; secondly, because of the very well-marked giant cells that are present, structures that are frequent in the malignant growths but not in the simple moles.

From the simple moles I then turned my attention to the melanotic malignant tumours in order, if possible, to demonstrate the same progress of events. To my surprise I found that this was much

more easily done than in the case of the moles. The only difficulty has been to obtain material for the purpose, and consequently I have had at present to draw my conclusions from four cases only, and in one of these from a very small amount of tissue.

In all these cases the malignant tumour may be said to have developed from a mole, because in the first two there is still present what is practically unaltered mole tissue, and in the second two the history is definite. This is fortunate, since in the latter two cases it would not have been possible to state from the microscopical appearances that the growths were secondary to moles.

The tumour from which Figs. 5 and 6 are taken was a rapidly growing melanoma of the skin which had already affected glands, and therefore may be reckoned as highly malignant. Fig. 5 is taken from the surface at the edge of the growth and shows in a very distinct way, entirely precluding the possibility of an appearance due to oblique sections, the metaplasia of the epidermic cells with down-growth, proliferation, and loosening of the normally close connection. In the main mass of the superficial part of the tumour the character of the cells is very different from what it is in the deeper part. In the superficial part the cells, although here and there laterally compressed and drawn out in length from pressure and tension, still resemble to a noticeable degree the epidermic cells from which they are derived, though there is a good deal of pigmentation in most of them. In the deeper part of the growth, however, the cells have almost entirely lost their resemblance to the cells of the epidermis, and resemble exactly those found in the deep parts of the ordinary mole (compare Fig. 6 with Fig. 4), the only obvious difference being that in the malignant growth the fibrous tissue has largely disappeared owing to the proliferation of the cells, and the alveolar arrangement is consequently less distinct. There thus appear to be two varieties of cell in the growth—namely, those freshly snared off from the epidermis as a consequence of malignant proliferation, and those which formed part of the original mole before the malignant change developed, but which have since also been affected by the malignant change with the result of rapid proliferation. The importance of this distinction will be alluded to again in discussing the third and fourth tumours.

The second malignant growth was exactly similar to the first, and

I need not therefore describe it, as to do so would be merely a useless repetition, but it is worthy of remark that it was also of highly malignant character.

The third and fourth tumours which I owe to the kindness of Mr. Malcolm Morris and Mr. Carless, respectively, were extremely similar to one another in mode of growth, clinical history, and morbid appearances. Both cases were shown at the Dermatological Society of London,* and both were excised on two occasions at intervals of two or three years, and in neither was there any secondary deposit in glands. These tumours must therefore be viewed as locally malignant with very little tendency to metastasis. In each case also the tumour itself was not very markedly pigmented, but was surrounded with a large area of dark pigmentation an inch or more in width.

The description is taken from the material which I obtained from Mr. Morris's case as I had not sufficient from the other to make as complete an investigation as I could wish.

Figs. 7-10 inclusive therefore refer to the case under the care of Mr. Morris.

Fig. 7 represents part of the main mass of the tumour, and bears some resemblance to the superficial part of the first malignant tumour, with the exception that there are large oval and spindle cells, small round cells, and a few giant cells mixed up with the utmost irregularity. The large cells are such as are shown in Fig. 8, and must be considered as derived from the epidermis, the small round cells seem to be part of the lymphocytic wall of reaction, while the giant cells are found at the edge of the tumour also present, and forming part of the basal layer of the epidermis.

Fig. 8 represents part of the edge of the growth at the level of the epidermis, and shows distinctly the same appearances as are seen in Fig. 5, but as the part affected is a little smaller I have been able to get it on to the plate under a higher power.

No deep alveolar arrangement was to be observed either in this or in Mr. Carless's tumour. The next point was to examine the skin from the pigmented area around, which was in all probability potentially malignant. On examining sections of this skin in the unbleached condition (Fig. 9) one sees that there is a large amount of black pigment in the upper part of the corium and in the basal layers

* Morris, *Brit. Journ. of Derm.*, Vol. XII., p. 19; Carless, *Ibid.*, Vol. X., p. 7.

of the epidermis, and the epidermis looks a little irregular, but owing to its intense pigmentation it is impossible to make out any of the finer details. I therefore bleached out the pigment from some sections taken from the same part, and was rewarded by the truly striking appearances shown in Fig. 10.

On examining this figure it will be at once observed that the basal layers of the epidermis are undergoing a peculiar change which is exactly similar, though slighter in degree, to that shown in Fig. 8. That is a change in shape, loss of the typical epithelial connection, and a tendency to grow downwards. This change I take to be also similar to that which is depicted in Fig. 2, and shows that the pigmented skin is not only potentially malignant but actually so.

In the above descriptions I have endeavoured to limit myself as far as possible to actual facts, such as are easily demonstrated from the accompanying photographs, but I should now like to throw out a few suggestions of a more speculative nature. Before doing so, however, I may point out that, although I consider that my specimens and photographs prove the derivation of some at least of the nævus cells from the epidermis, the actual proof that all are of similar descent is apparently not possible. One can only reason from the similarity of the deeper cells to those in the process of snaring off, and, as I have already pointed out, it is not justifiable to lay too much stress on the character of a cell. Nevertheless it seems to me to be simpler to regard all the groups of cells as the result of the same process than to invoke another agency to produce exactly the same appearances.

It will be noticed in the discussion of the malignant tumours that of my four of which I have some clinical details, two belonged to a highly malignant type, in fact, the type which is usually suggested by the term melanotic sarcoma, while two were slowly growing tumours with little tendency to metastasis and of very low degree of malignancy. I therefore examined all these tumours minutely in the endeavour to find some criterion which would enable one to judge in a given case to which class a tumour probably belonged. This seemed to me to be a very important point, since in the case of the tumour's belonging to the former class many authorities would recommend the removal possibly of a whole limb, while in the second latter class it would be sufficient to cut wide of the pigment and simply remove the local manifestations, as one does for rodent ulcer.

In examining and comparing the two classes I was struck by the fact that in the highly malignant variety two classes of cell could be seen. One, as already mentioned, was found either in the process of snaring off from the epidermis, or had evidently just been snared off, thus retaining much of its resemblance to its parents, the other was deeply situated in the corium and arranged in good alveoli, having lost nearly all its protoplasm, and corresponding to the typical cell in *nævus cords*. The inference may, perhaps, be made that the former cells become actively separated from the epidermis as the result of the malignant process, while the latter had lived for years in the corium constituting part of the original innocent mole. In the case of the less malignant type only the growth of the first class was found, and none of the deep groups and cords of *nævus cells*; in fact, as I mentioned above, but for the history I think it would have been impossible to state that the growth was secondary to a mole at all. I am very conscious that four cases is by no means a safe number to argue from, but I would point out a line for future examination, suggesting that this point of the deep structure be especially investigated with a view to ascertaining whether one is justified in separating the highly from the slightly malignant in this way. A further point that is desirable is to discover the kind of mole from which the second type grows. This I have not yet been able to do, for although moles are common these cases are rare, and it will probably mean a long search before this very superficial type is discovered.

In conclusion, for the use of others working with pigmented growths, I should like to mention a method of bleaching which I have found rapid, certain, and not liable to injure the section or to render after-staining difficult. The sections are first soaked for from five to ten minutes in a strong solution of potassium permanganate of potash (exact strength not important), washed in water, and then decolourised in sulphurous acid solution (B.P.). After a very few minutes' washing in water the sections may be stained in almost any of the ordinary ways with great ease.

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(NOTE.—This last reference appeared, and the photographs which followed it were published, while this paper was in the process of writing.)





