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SOME ASPECTS OF OCULAR MELANOTIC GROWTH*

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IDA MANN (1926) stressed some years ago her conviction that the question of pigment origin must not be looked upon from the narrow sphere of ophthalmological pathology. Jean Nordmann (1947), indeed, has subscribed to this demand in an admirable way, so far as could be achieved in a short survey attempting to follow up the origin of the pigmented cells in the higher vertebrates. Relationship to light is one aspect, the influence of the hypothalamus another; such views are plentiful. Restriction to higher vertebrates appears to be dictated by sheer necessity.

Even the narrow ophthalmological outlook, however, offers a tremendous mass of unsolved puzzles involving embryology,

Dedicated to Professor J. Meller.

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anatomy, physiology and, especially, pathology. The ophthalmologist's interest is certainly not limited to theoretical considerations as the growth of pigmented tumours engages our clinical interest so frequently. Basic difference of opinion is rife in the assessment of many pigmented growths, not only with regard to origin, but also to clinical behaviour and, last but not least, to treatment. Investigation of new material, especially if examined with varying technique, appears indicated in spite of the presence of a considerable literature covering this subject.

It is pigment production, the deposition of melanin, or one of the melanin substances, in these blastomata which dominates our attitude towards them. A non-pigmented wart growing at the lid margin would hardly worry us, while a pigmented new growth is the object of our justified concern.

Ribbert's conception (1911) of the mesodermic origin of the pigmented uveal growth remained unchallenged for years, and the malignant choroidal melanoma, the chromatophoroma, was considered as a melanosa sarcoma. This was hardly changed when T. W. Dawson (1925) and his Edinburgh school (E. K. Dawson, Innes and Harvey, 1939) tried hard to prove that these melanotic blastomata are ectodermal, and derive from the retinal pigment epithelium. Single cases of bulbus-filling melanotic masses of epithelial character have been described by Schuster (1918) and Pascheff (1929). Both assume an origin of the growth in the hexagonal layer. In recent years the name melanosa sarcoma—although still used clinically—is more and more abandoned in favour of the less committal "malignant uveal melanoma" as the shape of the tumour cells does not correspond frequently to the sarcoma type. Levkojeva (1940) found out of 202 malignant uveal blastomata only a small group which she considered as sarcoma type. We stress, however, here the fallacy of a decision reached from examination of routine sections, unless supplemented by flat sections or bulk examination of the cleared specimen.

A great change in the conception of pigmented growths came with Masson's papers (1926) which went back to Verocay's publication (1910). Verocay had shown that the neuro-fibromatous tumours in von Recklinghausen's disease were outgrowths from Schwann's sheath. Masson's revolutionizing work was concerned with the cutaneous naevus which he assumed to be a neural tumour, a Schwannoma. Schwann's cells are the melanin producing units, the melanoblasts. G. Dvorak-Theobald (1937) took up Masson's new idea and showed, investigating 6 malignant choroidal melanomata, that in 5 of them a tumour growth might have started in the long posterior ciliary nerves. Her paper influenced the English-speaking ophthalmological world in favour of Masson's theory.

She quoted Berger and Vaillantcourt (1934), who had already assumed that ocular melanomata are derivatives from Schwann's cells. Nordmann (p. 116) is sure that uveal tissue generally is not simply mesodermal. Its mass of nerve fibres and nerve cells are closely interwoven with the pigment network. The malignant uveal blastoma is a special type of new growth in which choroidal melanophores and glial cells are a product of selective disintegration of Schwann's sheaths.

General pathologists and ophthalmologists were soon ready to accept the neuro-ectodermal theory of the origin of the naevus growth and consequently of the malignant uveal melanomata which were considered generally as neuro-ectodermal with no exception. Dawson's ectodermal theory was hardly mentioned in ophthalmological literature.

Eugene Wolff in his W. Mackenzie Memorial lecture (Glasgow, October 24, 1947) challenged the general validity of Masson's theory and added new material against it in a paper read at the meeting of the Ophthalmological Society, London, April 8, 1948. According to Wolff the naevus is regarded as a composite or mixed tumour consisting of naevus cells, epithelial cells and branched chromatophores. Each of these cell types may proliferate alone or with others and produce a malignant pigmented tumour. The final structure depends on the relative proportion of the three types of cells.

Wolff's lecture stimulated a revision of material which I had collected over some years, the pigmented benign naevi at the lid margin and limbus and the malignant pigmented types of these regions, the naevi from the iris and choroid and finally the frequent iridic and choroidal malignant melanomata. It will be understood that certain aspects only will be discussed, seen from the point of view of classification, pathogenesis, propagation, etc.

The first type of melanotic growth which deserves special attention is the so-called naevus cysticus. There was a dark patch on the left eye at the limbal conjunctiva of a 16-year-old boy which was observed growing during a few weeks. Prof. A. J. Ballantyne, to whom I am indebted for the specimen, excised the growth, which could be peeled off easily from the sclera. It started growing again after two years. The tumour consists of normal conjunctival tissue with many goblet cells. There are (Fig. 1, A and B) densely packed, mostly round, dark-stained naevus cells with hardly any plasm. There is no typical gland formation, but great numbers of cystic spaces, mostly empty, some containing a fibrinous substance. Mucicarmin staining shows many goblet cells filled with mucin, and mucin is proven to be within the cystic spaces. Epithelial bridges link the conjunctival epithelium with

FIG. 1.

Naevus cysticus (M), at limbus area. H.E. 150×
Naevus cells with many mucous patches (goblet cells).

↑ mucin stained ↑ "goblet cells"

FIG. 1A.

↓ cystic spaces

FIG. 1B.

Naevus pigmentosus cysticus. Mucicarmin staining. Note the (carmin red) swollen mucin containing naevus cells. 300×.

the naevus-cell tumour. There is a moderate pigmented content, best visible in unstained specimens. Cuenod and Nataf (1934) have shown several conjunctival cystic naevi in slit-lamp pictures.

The naevus nature of this growth is beyond doubt. So is the mucin production of its cells. The goblet cells within the tumour cannot be distinguished from those of the bulbar conjunctiva. The linkage between the conjunctival epithelium and the naevus growth is obvious. We do not doubt, therefore, that this type of cystic naevus appears to be derived from the epithelium as Unna (1893), Dawson (1925) and many others have assumed for the naevus generally.

There is another pigmented growth to be discussed which grew at the lid margin and appeared clinically as a pigmented rodent ulcer. It was excised in the whole thickness and the defect closed with a Buedinger-Mueller—whole thickness—auricle-flap (J. Foster). Histological investigation showed a naevus cell growth of unusual size which invaded (Fig. 2, A, B, C) the area of skin, Meibomian glands and palpebral conjunctiva. The epithelium of the skin as well as that of the conjunctiva has sent out down-growths of considerable depth of a controlled cell type. The majority of the naevus cells are typical, small, dark, without cytoplasm, and with a moderate pigment content. Some of the islets

FIG. 2A.

Naevus pigmentosus of lower lid margin. H.E. 150 $\times$. Note thinning of epithelial cover over naevus growth and down growth of the skin epithelium at both sides of the naevus.

consist of larger cells with a clear plasm (Fig. 2, B) which have real epithelial character. Mucin reaction was negative everywhere except in the epithelial downgrowths of the conjunctiva.

FIG. 2B.

Pigmented naevus at lower lid margin, H.E. 450 $\times$. Note the clear epithelial naevus islets to the left while the remaining naevus cells are dark with very little plasm.

FIG. 2c.

Naevus pigmentosus of lower lid margin. H.E. 60 $\times$. The benign-looking naevus cells infiltrate the sebaceous glands. Note the downgrowth of the conjunctival epithelium.

The presence of both naevus cell types, the small, dark one with no cellular plasm, and the epithelial type side by side, is one point of interest. The other is the new growth of skin and conjunctiva which had created clinically the impression of a pigmented rodent ulcer. Our conception of this case is a primary growth of the

naevus cell explantate resting at the lid margin, probably since birth or earlier. It started growing at a certain age. We feel that this naevus cell growth is the stimulus for both types of *epithelial* outgrowth in conjunctiva and skin. Products of the naevus cell metabolism might work as growth promoting factors, as do the large groups of carcinogenous compounds. The "Melanins" are different chemically from all so far known carcinogenous substances.

Wolff's conception of the naevus as a mixed group of cells, typical naevus and epithelial cells, here seems to receive confirmation. Even branched chromatophores were present in small

FIG. 3.

Choroidal naevus discovered by chance in flat choroid unstained seen from scleral side. 60× approx.

numbers, which might originate in the cells of Langerhans (Pascheff, 1946).

Choroidal naevi are certainly more frequent than we assume or than the scanty literature suggests. There is practically no possibility of a differential diagnosis between a beginning malignant melanoma and an innocent naevus, clinically. Such a diagnosis is frequently not even anatomically secured, as we shall show. Ophthalmoscopic control with repeated fundus photography seems to be the only way to discover the first sign of growth.

We were able to demonstrate two choroidal naevi anatomically, both found by chance in fixed, opened eyes, by routine slit-lamp examination. In neither case was a new growth, pigmented or unpigmented, present.

In the first case the dark choroidal patch was excised with a 4 mm. trephine, cleared in glycerine and photographed unstained (Fig. 3). Then the piece of choroid was embedded in paraffin,

cut and stained; depigmented slides showed the cell structure considerably better (Fig. 4).

The cell type is a spindle-cell form, denser in the outer choroidal layer, where pigmentation is heavier. The nuclei are of great inequality; although most of them are slim, they range from 2 to 15 μ in length, and from 2 to 5 μ in cross diameter. The pigment is in fine granules, round, resembling cocci of less than 1 μ diameter; where it is packed in branched melanophores it appears darker brown, but the size of the granules is still the same. The distinction from the rod-like retinal pigment in the same microscopic field is obvious. Some of the bigger "chromatophores" have no branches left. They are huge round cells packed with brown granules. Here we discover larger pigmented granules, which are caused, obviously, by fusion of the small equal granules. We have, therefore, to call the cells with the small

FIG. 4.

Choroidal naevus, depigmented. H.E. 300X.

brown granules of equal size melanoblasts, according to D. T. Smith (1925), while the bigger, heavier pigmented cells containing pigment granules of different size are chromatophores. The first produce the pigment granules, the latter store them.

The majority of these cells do not resemble a naevus-cell growth. They are mostly longer and spindle-shaped, that being the reason why older authors protested against the name choroidal naevus. Some cell groups of our two cases consist of small dark stained cells without cytoplasm, and are reminiscent of naevus cells of the skin. But we must not lay too much stress on the morphology of the cell type, generally. The great polymorphism of the melanoma cells is quite evident from the 14 different types of this blastoma distinguished in the classical work of Ernst Fuchs (1882). Even the retinoblastoma with its foetal, small, dark, round nuclei shows spindle-shaped cells in cases where the tumour has perforated the bulbar coats and grows in the soft orbital tissue.

This, indeed, was so striking that early authors spoke of a transformation of glioma to sarcoma. The tissue pressure undoubtedly exerts great influence upon the shape of the growing cells.

The choriocapillaris is nearly everywhere well preserved and Bruch's membrane intact. In our second case the structure of the growth is denser, the spindle cells are close together, the nuclei mostly dark stained, the pigment forms clumps, its granules are of different size, "melanoblasts" are absent. Branched chromatophores in the sclera are numerous, especially surrounding the pigmented ciliary nerve which joins the choroid in the naevus

FIG. 5.

Choroidal naevus 2. H.E. 300 $\times$. Note: subretinal exudate over naevus.

area. While the greater part of the naevus leaves the choriocapillaris intact, there is a region where the naevus growth reaches Bruch's membrane and interferes with the choriocapillaris. Here a granular substance with eosin red shadows and empty vacuoles lifts the hexagonal cells (Fig. 5). It looks like an exudate between the intact Bruch's membrane and pigment epithelium. There is little doubt that this exudate is caused by the choroidal change, which here reaches its greatest intensity.

We have observed retinal disintegration frequently over choroidal malignant melanomata, even over small tumours (Fig. 6). It is interesting to note that this regressive process is present directly over the new growth and not over subretinal fluid often found adjacent to the tumour. This cystic degeneration of retinal tissue situated over a choroidal melanoma might be used diagnostically for tumour identification, as we have seen lately. We conclude that retinal nutrition might suffer when the vascular tissue

FIG. 6.

Malignant choroidal melanoma. H.E. 60 $\times$ approx. Note cystic retinal degeneration over the tumour area exclusively. Not present over the serous detachment without tumour infiltration.

of the choroidal sponge is partly replaced by tumour growth. It seems interesting that a disturbance of such small size could be observed in a non-malignant growth of naevus character.

Anatomical investigation of these two choroidal naevi does not permit conclusive opinion as to the origin of these pigmented cells. At any rate, melanophores are present besides melanoblasts and the cells resemble a neurofibroma. We assume cell rests possibly of Schwannoma character, but we would not exclude displaced cells of the outer layer of the secondary eye vesicle.

We discuss a case of flat small malignant melanoma of mixed cell type with moderate histological malignancy and fatty necrosis. The small tumour was linked with the posterior ciliary nerve. The same cell type was present in the tumour tissue infiltrating the ciliary nerve. The branched chromatophores in the nerve tissue were especially well developed. Branched chromatophores were present in the sclera as well. Here we might assume the melanotic growth to have arisen from Schwann's sheath of the ciliary nerve. But it might be the other way; the malignant melanoma might have grown out from the choroidal tumour through the scleral emissarium following the line of least resistance. We are inclined to this conception, especially in a case of a more developed malignant melanoma in which huge contracted melanophores are amassed in the choroidal tumour and in the pigmented infiltrate of the ciliary nerve. The old conception of growth through the emissarium appeals especially in a case of big malignant melanoma which grew through the whole scleral thickness and ended in a black knob of about $\frac{3}{4}$ mm. diameter.

Loewenstein (1945) has described an interesting pigmented growth of the disc. This eye showed with other features a heavily

pigmented ciliary nerve entering the choroid where this tissue is thickened to twice its normal thickness. Nearly the whole choroidal tissue is formed by branched chromatophores. Between the dark pigmented chromatophores slim parallel arranged nuclei are visible of the same shape and size as the nuclei of Schwann's sheath in the adjacent posterior ciliary nerve. Loewenstein has explained the pigmented disc tumour as misplaced cells of the outer layer of the secondary eye vesicle, primitive cells, cell rests in the sense of Cohnheim, a phakoma with the inherent power of pigment production. Something similar might have happened in the same eye in the choroid where cell rests have produced a tissue belonging to the choroidal naevus group.

Summarizing our conception about choroidal naevi we assume the existence of cell rests possibly developmentally displaced. Schwann's cells might be the origin. The possibility that the outer layer of the secondary eye vesicle might be the source must be fully acknowledged. Both sources have the power of forming pigment. There is no reason to put the origin of malignant melanomata on another footing from the benign ones. Both types start in the outer layers of the choroid.

Wolff has found typical chromatophores in pigmented naevi of the conjunctiva. He identifies them with the mesodermal chromatophores (melanoblasts). We have seen similar structures in a malignant degenerated pigmented naevus at the limbus in flat sections and razor slides. We know fibroblasts of the conjunctiva have a great phagocytic power. The same is true of the cells of preretinal tissue. Seen in flat specimens these fibroblasts are branching and the tentacles are full of fat granules and pigmented corpuscles. They resemble, indeed, the choroidal chromatophores, especially those of the superficial layers. If we spread a choroid from a case of old chronic uveitis and stain it for fat with scarlet red the dendritic chromatophores are full of shining red fatty globules of different size and light brown pigment granules. We assume that these chromatophores have taken up pigment granules produced by the melanoblasts. The phagocytic power of these chromatophores is not exhausted by the absorption of pigment debris as they are able to absorb fatty droplets in addition. These cells belong, in our opinion, to the reticulo-endothelial system, which forms another group of melanotic growth.

Loewenstein (1930) has seen a man of 41 years of fair complexion with no other clinical signs of a melanotic tumour. Small blackish nodules were discovered in the conjunctiva of all four of his lids. These nodules varied in size from 0.2 to 2.0 mm., they were mostly round or nearly so, one had a morular form. The conjunctival vessels surrounding the nodule were definitely

dilated. The colour of the pigmented nodules was not homogeneous, some were dark coffee brown, others light brown and some had a slight greenish hue.

The patient had used a collyrium once or twice daily for about ten years. It contained, besides zinc sulphate, adrenalin. No biopsy was possible. Animal experiment (rabbits) were performed. A collyrium with adrenalin was applied twice daily for a year without result. Subconjunctival injection for 18 months twice weekly approx., however, produced besides an increase in physiological epithelial pigment at the limbus, a group of blackish

FIG. 7A.

FIG. 7B.

nodules, similar, indeed, to those seen in the patient. Histologically (Fig. 7, A and B), there were melanin granules within the conjunctival epithelium, especially within the basal cells. Besides this epithelial pigment, there were many huge round or polyhedric reticulum cells filled with melanin granules.

The relationship of adrenalin and melanin is well established (Neuberg 1908). We know that homogentisinic acid is a product similar to adrenalin, and is the basic substance in alkaptonuria and ochronosis (deposits of melanin in many tissues). Naevus-like conjunctival pigmentation was shown by Cuenod and Nataf (1934) in a case of alkaptonuric ochronosis.

Similar melanotic changes in the conjunctiva have been described by Velhagen (1931) among workers in hydroquinone, a

substance belonging to the adrenalin group as well. Banks Anderson (1947) has published kodachromes of these melanotic changes in the conjunctiva, cornea and sclera in this industrial disease. Anderson's histological findings in biopsies are very similar to our own in the rabbit. He did not succeed in producing the changes in the animal experiment (continuation of the experiment was not long enough). Some lesions in the workers investigated by Anderson resembled the precancerous Bowen's disease, an observation which deserves careful consideration.

Describing precancerous melanosis Reese (1943) mentions varying numbers of cells in the submucosa, containing phagocytosed pigment. This might, according to Reese, originate in the basal epithelial layers. The exact mode of malignant transformation is not known. It seems to be the activity of basal epithelial layers from where the malignant proliferation spreads.

Observation of the adrenalin melanomata of the patient and of the rabbit has proved that adrenalin and its pigmented derivatives are reabsorbed by the cells of the reticulo-endothelial system and stored. The same procedure seems to occur with hydroquinone workers. These little tumours are pigmented reticulo-endotheliomata. Future investigation may show whether they are the first stage of a malignant development or not.

The nature of the pigmented granules within the melanophores (or melanoblasts) is, unfortunately, completely obscure. Have they an independent life, reproducing by division, or are they a secreted end-product? It is of the same great interest whether, in the case of malignant melanoma, the pigment granules represent the tumour elements or only the innocent result of cellular disintegration. As far as is known this important problem is still unsolved. Pigment infiltration in the trabecular area and in the wall of the collector veins was demonstrated at Oxford in 1948.

We have investigated in a case of malignant melanoma of the iris and ciliary body the paths of elimination, from the anterior chamber. In one part of the specimen routine sections were performed. They showed (Fig. 8) the pigment growth in iris and ciliary body. The trabeculum is filled with a blackish mass. Schlemm's canal and collector veins are embedded in blackish granules. With oil immersion we can study the granules in the scleral part of a collector vessel. There are no cells visible, but granules of different size distributed in the wall of these "aqueous" veins (Ascher) in varying density. We get the impression that the pigmented detritus from the uveal melanoma suspended in the aqueous floated with the aqueous movement into the collector vessels. Many of these pigmented granules are taken up by reticulum cells.

FIG. 8.

W., female. Malignant melanoma of iris root and ciliary body. H.E. 60 $\times$. The dark infiltration of the circulus venosus is restricted to the area of the uveal melanoma.

Mayou (1930) has shown a similar appearance in his first case, in which the area of Schlemm's canal was infiltrated with pigment. He attributes importance to this involvement since in his opinion it might be the only means of distinguishing an innocent from a malignant growth. Gonioscopic investigation of these cases appears indicated.

This type of distribution of the melanoma debris was even more evident with another kind of preparation. In the remaining tissue of the excised eye the uvea was removed by a cyclodialysis from the sclera and the anterior part, cornea and sclera, was cleared with wintergreen oil and studied unstained. Here the blackish infiltration of the drainage area is evident (Fig. 9). With

FIG. 9.

W.f. malignant melanoma of iris root and ciliary body. Hem. Cleared sclera and cornea. 60 $\times$. Seen from ant. chamber. Tumour infiltrated areas of trabecular network restricted to uveal tumour area. Pigment.

high power we recognise that the pigmentary granules are present along the aqueous veins (Ascher), but no cellular structures are visible. Although no metastatic cells are found the impression of a propagation of the melanoma along the drainage system is strong. This kind of pigment infiltration is different from the common one we find in cases of iridocyclitis, glaucoma or even in healthy eyes of elderly people. Here, the specimen is prepared in a similar way, the pigment in the endothelial cells of the trabeculum fibres is dirty-brown, of irregular shape, the product of wear and tear of the uveal tissue. We think that the pigmentary elements found in the anterior drainage system of the case of malignant melanoma in the anterior uvea might contain the living tumour granules. No definite decision is possible if based on anatomical findings exclusively.

The propagation of a choroidal malignant melanoma is even more complicated if we consider the reaction of the hexagonal cells. The pigmented cells of the retinal layer start growing into retinal tissue under varied conditions, so that pigment cells found in the retina in cases of malignant choroidal melanoma cannot be reasonably regarded as tumour cells.

We peeled off parts of the retina from several malignant choroidal melanomata, stained the pieces in bulk, cleared the tissue and studied the situation in the flat specimen. Retina can be separated from the tumour with difficulty only, but we succeeded at some places. The retinal tissue is infiltrated with huge dark cells where the tumour has broken into it. There is an outstanding polymorphism of these black chromatophores. Some are like typical clump cells of the iris, roundish, like amoebae which have drawn in their pseudopodia, others show

FIG. 10.

Case of malign melanoma of ciliary body and choroid. Retina peeled off and cleared (Hem.—150 $\times$). The pigmented cells are spreading within the retina especially along the retinal vessels.

branching processes. The granules are brownish to deep black. The chromatophores look different from those seen in bulk specimens of retinitis pigmentosa or chorioretinitis syphilitica. The propagation occurs along retinal vessels predominantly although free "clump cells" are frequent. Even massive migration along vessels (Fig. 10) can be demonstrated. Treacher Collins (1926) mentions in his report on "Melanomata of the Eye" this Ginsberg type of clump cells which rise from chromatophores undergoing malignant degeneration. This change of large branching uveal chromatophores into spherical or polygonal deeply pigmented cells without processes occurs according to Treacher Collins during a phase of deranged metabolism.

Bulk specimens of choroid are possible only at the outskirts of the melanoma, as no view can be achieved over a certain thickness of the specimen, even after long protracted depigmentation. Although the spindle-cell type predominates there a considerable polymorphism is to be observed. It seems that the different stages of contraction of the branched chromatophores are responsible for this polymorphism, for the explanation of which Treacher Collins' theory appears adequate. The amoeboid character of the chromatophores seems to be the main cause of the varying shape of chromatophores found with the melanomata, even in different parts of the same growth. Another reason is the reaction of the phagocytic reticulum cells engulfing pigment and other débris. These cells are protean, varying in shape, size and pigment content.

Finally, reference must be made to the special position of the hexagonal cells detached from this single layer. Pigmented epithelial cells are produced in great masses in many disorders of the uvea. They do not remain, practically, in a cell unit, as to create a kind of tumour, but are freed, swell, undergo fatty degeneration frequently and may extrude their whole content. This kind of production occurs at high velocity, as we do not usually discover any defect in the hexagonal layer despite the massive loss. Retinitis exudativa externa (Coats) is a typical example of this kind of hyperproduction and fatty changes, in which the mass of "ghost" or "bladder" cells might be taken for a blastomatous growth of this primitive layer, a blastoma as, e.g., leukaemia is considered a tumour of the blood.

The true tumours of the hexagonal layers in the common sense might be expected in the shape of an epiblastic growth, a melanocarcinoma. We have seen, however, a growth of hexagonal cells in a case of dystrophia adiposa of the eyeball (Fig. 11), of undoubted fibromatous character. Here the fibroblasts grew out

from the hexagonal cells which produced therefore cells of mesodermal type. Here we want to stress the unique position of this primitive layer which remains, as far as can be observed microscopically, unchanged from early foetal life.

A similar behaviour of the epithelium of the lens capsule is recognized (Samuels, 1946 and otherwise) (Loewenstein, 1934), which produces under certain circumstances a fibroblastic tissue.

FIG. 11.

Dystrophia adiposa. H.E. 150 $\times$. The pigmented epithelium grows out into the fibroma-like tumour.

We conclude that hexagonal cells add a great variety of pigmented cells of very different shape to the pathological melanomatous growth in which even spindle-shaped units may be present. The presence of this type of cell, therefore, is no proof against the origin of a melanotic growth in the hexagonal layer.

SUMMARY AND CONCLUSIONS

(1) Naevi are generally inherited as are markings of domesticated animals (Meirowsky, 1942). They are developmentally arrested and often displaced tissues which might or might not, under unknown conditions, start multiplying from the point of development at which they have arrived. There is no basic difference between a naevus and a phakoma (Van der Hoeve).

(2) In tissues where these naevus cells produce pigment (melanoblasts), pigment granules are also stored in branched reticulum cells (melanophores).

(3) Pigmented naevi may be derived, as far as we know, from early stages of Schwann's sheath, from the primitive epithelium of the skin or from the outer layer of the secondary eye vesicle.

(4) No doubt exists about the epiblastic origin of the naevus mucosus cysticus of the conjunctiva.

(5) Pigmented naevus cell growth, at the margin of the lower lid, may contain, besides typical naevus cells, islets of epithelial structure and branched chromatophores.

(6) Naevus cell metabolism may set free growth-promoting factors responsible for controlled or uncontrolled new growth. These growth-promoting factors might be related to the melanins, being different from known carcinogenic substances.

(7) Distinction between innocent choroidal naevus and malignant choroidal melanoma is difficult ophthalmoscopically and histologically.

(8) The simultaneous presence of an identical pigmented melanoma in choroid and ciliary nerve is no proof of the origin of the blastoma from Schwann's sheath.

(9) There is a greater polymorphism of melanoma cells in flat sections and bulk specimens of melanoma invaded retina than in routine sections.

(10) Mesodermal structure of a pigmented malignant choroidal blastoma does not exclude origin in the hexagonal layers because out-growth from the pigmented epithelium may show typical mesodermal character. The unique developmental position of the pigmented epithelium, the outer layer of the secondary eye vesicle may account for this.

(11) The adrenalin melanoma is described clinically and histologically, and is explained, as is the conjunctival melanosis of the hydroquinon workers, by melanotic reticulosis. Although no malignant evolution is known, the corneal changes in hydroquinon damage are reminiscent of precancerous Bowen's disease. Adrenaline, hydroquinone and melanin are chemically related. Asthmatic persons receiving adrenaline for a long period ought to be observed carefully.

(12) Melanotic debris marked the path of elimination in cases of malignant melanoma of the iris. It is likely that the pigment granules in the trabeculum and vessels carry the tumour elements and show the course of the metastases. That might be a warning against "conservative" operation for localized malignant iris melanomata. Gonioscopic investigation of these cases before local excision of the melanoma is indicated.

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BLINDNESS ASSOCIATED WITH HAEMORRHAGE*

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DURING the syncopal phase which may accompany or immediately follow massive haemorrhage, it is not uncommon for the patient to complain of visual disturbances and even blindness. This condition is invariably brief and seldom exceeds one hour in duration. More often it only lasts a few minutes. Jones (1947) describes a typical case of this kind. (Also see Appendix.) Blindness of a longer duration and in most cases associated with permanent damage to the visual apparatus is a rare though well-recognised complication of massive and repeated haemorrhage.

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