PATHOLOGY

In many cases of choroidal sarcoma it is difficult or impossible to determine with certainty the point of origin of the tumour when it has spread over a considerable area of the uvea. This difficulty arises occasionally even when the whole eye is available for pathological examination, and it will be readily realised that the problem is intensified in those cases where one is left with only a section of the original specimen to study. In the following series (see Table A) I have included only those cases in which their origin is certain enough for classification purposes, and I have excluded those tumours which have spread over such a large portion of the choroid as to make them impossible for classification. Examples of these are those tumours that extend from the optic papilla posteriorly, to the ciliary body anteriorly, and those in which the neoplasm occupies the whole or the greater part of the vitreous chamber.

With regard to the remainder of the uveal tract, two zones are easily separated for classification purposes. These are the ciliary body and iris. The remaining divisions in Table A., i.e., the choroid and ciliary body, the ciliary body and iris, and the choroid and iris, are included because it was found that it was impossible to determine in which area the primary growth originated. The solitary case in the last division is interesting, as I have been unable to find any record in the literature of a choroidal sarcoma and a malignant melanoma of the iris occurring in the same eye. It is possible, of course, that the iris growth may be a local metastasis from the choroidal sarcoma, as neoplastic cells have been observed free in the anterior chamber in some cases of choroidal sarcoma.

For choroidal sarcomata three main divisional areas have been employed. Anterior, denoting that area of the uvea between the ciliary body and equator, equatorial, and posterior (see Table B). Circum-papillary tumours and tumours occurring in the macular region are included in the posterior group, those occurring in the latter region being of extreme interest when their previous clinical history is studied; and several of these cases are described in detail in the appendix.
TABLE A.—CLASSIFICATION OF THE UVEAL SARCOMATA.

<table>
<thead>
<tr>
<th></th>
<th>Present Series</th>
<th>Fuchs</th>
<th>Lawford and Collins</th>
<th>Kronenberg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Per cent.</td>
<td>No. of Cases</td>
<td>Per cent.</td>
</tr>
<tr>
<td>Choroid alone</td>
<td>196</td>
<td>84.49</td>
<td>221</td>
<td>85</td>
</tr>
<tr>
<td>Choroid and Ciliary Body</td>
<td>5</td>
<td>2.28</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ciliary Body</td>
<td>10</td>
<td>4.36</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Ciliary Body and Iris</td>
<td>3</td>
<td>1.36</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Iris</td>
<td>3</td>
<td>1.36</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Choroid and Iris</td>
<td>1</td>
<td>0.45</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ring Sarcoma of Iris</td>
<td>1</td>
<td>0.45</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Unknown location</td>
<td>44</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

TABLE B.—TOPOGRAPHY OF THE CHOROIDAL SARCOMATA.

<table>
<thead>
<tr>
<th>Zones</th>
<th>Present Series</th>
<th>Kronenberg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior</td>
<td>109</td>
<td>86</td>
</tr>
<tr>
<td>Equatorial</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Anterior</td>
<td>9</td>
<td>33</td>
</tr>
</tbody>
</table>

There were 29 choroidal growths which extended over such a considerable portion of the uvea as to render them uncertain as to their point of origin, and 18 growths which filled the vitreous chambers.
I have not been able to determine, in a sufficient number of cases to be of any value, the quadrants of the choroid in which these growths are found, as the clinical notes are more often than not silent on this point, but Kronenberg states "Most sarcomas of the choroid arise posteriorly and especially temporally, this is, of course, fortunate since central vision is affected early and attention drawn to the eye."

An intra-ocular sarcoma can arise from any part of the uveal tract, the commonest growth being the choroidal type, the next in frequency being the ciliary body neoplasm, and finally the rare iris sarcoma. In size, they may vary from an extremely small growth confined to the choroid itself to one that fills the vitreous chamber. Fuchs, in 1909, reported three extremely small sarcomata of the choroid, the smallest occurring in a man aged twenty-six. The site of the growth was to the temporal side of the disc, a little beyond the fovea and a trifle lower. It measured in the horizontal and vertical diameters 0·7 mm. and 0·15 mm. in thickness. It was composed of spindle cells.

Parsons in his book "Diseases of the Eye," states "It is always primary, single and unilateral." This statement is correct in the vast majority of the cases seen, but secondary sarcoma, multiple sarcomata in the same eye, and cases of sarcoma occurring in both eyes are recorded.

Weiner, in 1902, described a case of metastatic sarcoma of the choroid, the primary growth being in the mediastinum, and he states that authentic reports of the same occurrence are recorded by Shiess-Gemusens, Pflüger and De Schweinitz.

This must be a very rare happening indeed; Virchow stated "that in those organs which show a special disposition to nurture neoplasms, metastatic foci are seldom seen," and this statement is well illustrated in the case of the liver, in which metastases are commonly seen from many types of neoplasm. Primary growths of the organ are, however, of extreme rarity.

A case is reported of two separate sarcomata being present in the same eye by Treacher Collins in 1892. A woman aged sixty had her eye removed for growth, and on opening the eyeball by equatorial section, the anterior half showed two tumours in the ciliary region on opposite sides of the eye.

Each growth was about half the size of a cherry stone, white in colour, slightly mottled with grey, and on microscopic examination these growths proved to be small spindle-celled sarcomata.

A case is described, in the appendix, of a male whose eye contained a choroidal sarcoma, together with a growth on the iris of the same character.

Bilateral sarcoma of the uveal tract must be of extreme rarity. Shine reports the case of a male aged thirty-five, whose right eye
was enucleated for a large sarcoma of the iris. Three years later
the left eye was removed and was found to contain a sarcoma of
the choroid, the patient dying four years later with metastases in
the liver.

A case of bilateral sarcoma of the choroid occurring in a male is
reported in the appendix to this paper.

The growth commences in the stroma of the choroid, and is at
first lenticular in shape. It progresses along the lines of least
resistance, that is, in the plane of the choroid, the sclera offering
great resistance as does to a less extent, the membrane of Bruch,
supported by the vitreous.

As the tumour progresses in size, it eventually breaks through
Bruch's membrane, and once through this membrane, finding
the surrounding pressure equalised on all sides, the tumour rapidly
becomes globular in shape.

This sequence of events is the explanation for the "collar stud"
or "cottage loaf" appearance seen in the typical choroidal sarcoma,
the constriction or neck of the growth being situated at the
perforation in Bruch's membrane, which, according to Parsons
"results from an equable stretching, rather than from any
localised attack by the growth upon any spot on the membrane."

If the growth is situated in close proximity to a perforating
channel in the sclera, the typical form of the growth just described
may be much altered.

The growth may then spread between the scleral lamellae,
gaining entrance either by way of a vortex vein, ciliary vessel or
nerve.

Another variety in shape is seen in growths extending through-
out the uveal tract from the ciliary body to the optic disc, the
point of origin of the growth being uncertain.

The neoplasm may be pigmented or non-pigmented, the former
variety being the more usual; mottled growths are often seen
too, pigmented and non-pigmented areas alternating with one
another.

The cellular pathology of choroidal malignant melanomata is
very variable. The growth may be composed of one cell type or
another, or a mixture of cell types.

Recently Callender investigated a large series of cases and
described five specific types of cell into which all primary malignant
choroidal sarcomata can be classified. This work is discussed more
fully in the section devoted to prognosis.

The enormous amount of pathological investigation involved in
acquiring statistics similar to those in Callender's work is
obviously not within the scope of this paper, and the older and
perhaps more familiar classification by cell type is employed,
namely, the following groups:—
1. Spindle.
2. Round.
4. Epithelioid.
5. Mixed (varying proportions of 1, 2, 3 and 4).

It might be mentioned in passing that it is often difficult to diagnose with certainty the presence of round cells unless a very careful microscopic examination is carried out, bundles of spindle cells cut transversely resembling the round celled type of growth very closely, and although the practice of examining teased preparations has fallen from favour, there is much to be said for this method of examination, deductions from studying sections alone being liable to error.

The spindle celled growths are the most common; in the series of cases investigated in this paper one hundred and forty, out of two hundred and twenty-five, were composed of spindle cells.

The spindle cells vary in size and often resemble young connective tissue cells. They have a large well staining nucleus and the nucleolus is clearly seen. The cells are densely packed and run in various directions, interlacing with one another, and sometimes forming a well marked pseudo-alveolar arrangement.

The round celled type of growth is far less common than the spindle variety; in the present series thirty-five growths were composed of round cells, while spindle and round cells were seen in twenty-eight growths.

The round cell takes its name from the shape of its nucleus rather than from its protoplasmic shape. It may be large or small showing every gradation in size up to the so-called epithelioid cell, which in this series has been classified separately.

The cells are closely packed together and are often polygonal or square in shape, showing short cell processes. The nucleus does not stain deeply but a well marked nucleolus is evident.

The growth of these tumours is more rapid than that of the spindle type, and pigmentation is generally moderate in degree.

The mixed variety of spindle and round cells needs no further description.

Tumours composed of epithelioid cells alone are rare, six cases only being recorded in this series.

The cells are large in size, polygonal or square in shape, and contain a large poorly staining nucleus which is either round or oval, a well staining nucleolus being present.

The mixed cell tumours are composed of varying quantities of the spindle, round and epithelioid types and are the most fatal variety of choroidal sarcomata. Multi-nucleated cells are occasionally seen in these neoplasms. They are not true giant cells
as are common in tuberculosis, and are evidence of extremely rapid nuclear division.

Pigmentation in these tumours is variable and may be either intra- or extra-cellular, the intra-cellular pigment being carried either in the typical chromatophores, which are spindle or star shaped cells with long processes, or in the tumour cells themselves. The pigment may be of two kinds, a metabolic product of the cell, or haematogenous derived from haemoglobin. The latter is often seen in close proximity to the blood spaces or haemorrhages in the growth.

Degeneration and necrosis is often observed, Parsons stating "necrosis is the rule in ordinary sarcomata of the uveal tract after they have reached a certain size."

Necrosis is shown by areas in the growth in which the nuclei fail to stain normally, it is usually localised and patchy although the whole tumour is sometimes found to have become necrotic. This is often the case in phthisical globes containing a neoplasm of the choroid.

The mechanism of this necrosis is due to various causes; malnutrition of the growth by the rapid proliferation of the cells, haemorrhagic necrosis, due to pressure on the cells from haemorrhage, and necrosis following upon thrombosis of blood spaces within the growth.

That the necrosis is not due to the increased intra-ocular pressure is proven by the fact that globes are seen in the state of absolute glaucoma without any evidence of necrosis in the tumour. Samuels, when investigating the subject of necrosis, found that in one hundred and six sarcomatous eyes examined microscopically, thirty-one were highly necrotic.

He believes this degeneration of the cells to be due primarily to deficient nutrition of the growth and, secondarily, to cytotoxins from the necrotic cells which, in themselves, have a necrotizing effect on the remainder of the growth.

In this series of cases, eighteen out of two hundred and twenty-one growths examined microscopically showed evidence of well marked necrosis (this number does not include those cases in which small areas showed degenerative changes). This is not such a high incidence as is usually stated and may possibly be due to the fact that intra-ocular sarcoma are now perhaps diagnosed earlier in the disease than was formerly the case, the growth being relatively small in size and adequately nourished by its blood supply.

The choroidal sarcomata are usually extremely vascular. The vessels are of simple character composed of endothelial tubes with a large lumen. Large blood spaces are also seen with no lining of endothelial cells, the tumour cells being in direct contact with
the blood. Small haemorrhages are extremely common, and not infrequently massive haemorrhages occur, these cases being very difficult to distinguish from the so-called haemorrhagic glaucoma.

Eleven cases in this series showed that large haemorrhages had occurred, while the majority showed small haemorrhages present in the tumour.

Verhoeff reported fifty-five cases of sarcoma of the choroid, twenty-five of which showed comparatively large haemorrhages, and three cases of ruptured cornea associated with sarcoma of the choroid with destructive haemorrhages. He states that this is a rare occurrence and may be easily mistaken for haemorrhagic glaucoma, even after enucleation, the tumour being overlooked in the massive blood clot within the globe.

Ossification of the choroid is occasionally observed in eyes containing a choroidal sarcoma: Hulke, in 1857, being the first to show the occurrence of bone within the globe.

According to Parsons, the bone originates in fibrous tissue in the neighbourhood of the chorio-capillaris.

This fibrous tissue is the result of the chronic inflammatory processes occurring within the globe, bone formation being not uncommonly seen in shrunken globes due to inflammation.

In the present series under investigation ossification was observed in three cases, two of which gave a very definite history of previous trauma.

In all three cases the eyes had been blind for many years, one for six years, another for eight and another for twelve, and all showed evidence of previous inflammatory disease.

Sarcoma of the iris is rare; it arises from a proliferation of the stroma cells of the iris and is, in most cases, situated on the lower half of the iris.

Analysing seventy cases of sarcoma of the iris, Morax found that 63 per cent. occurred at the lower pole, 25 per cent. at the upper pole, 8 per cent. on the temporal side, and 4 per cent. on the nasal side, while Duke-Elder and Stallard found that in twenty-six cases of leucosarcoma of the iris reported in the literature, nineteen occurred on the lower half of the iris.

The growth is usually pigmented, but the unpigmented variety does occur, sometimes subsequently undergoing pigmentation.

The neoplasm is at first small and nodular in shape, and is generally very slow in growth; it may be present for years causing no symptoms. In the later stages, however, growth is more rapid and the tumour may fill the anterior chamber and perforate the globe.

Satellite tumours are occasionally seen, and are probably due to local dissemination of neoplastic cells by way of the aqueous.
Haemorrhages may occur from the growth, giving rise to recurrent hyphaemata—one such case is reported in the appendix. A rare type is the ring sarcoma of the uveal tract. This usually involves the ciliary body and iris throughout their circumference, and the glaucomatous stage is reached early in this particular type of neoplasm, the angle being invaded in all cases.

Microscopically an iris sarcoma is a diffuse growth throughout the stroma of the iris, the commonest cell type being the mixed spindle and round; pure spindle and round cells are less common. The round celled variety is sometimes extremely difficult to distinguish from localised inflammatory lesions in the iris.

The three primary sarcomata of the iris in the present series were pure spindle growths, the ring sarcoma reported also being composed of spindle cells.

The following tables of cellular content are shown for comparison of the present series with other observers.

<table>
<thead>
<tr>
<th>Present Series</th>
<th>Lawford &amp; Collins</th>
<th>Fuchs</th>
<th>Kronenberg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spindle</td>
<td>140</td>
<td>8</td>
<td>67</td>
</tr>
<tr>
<td>Round</td>
<td>35</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Spindle and Round</td>
<td>28</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Epithelioid</td>
<td>6</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Mixed</td>
<td>16</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Unrecorded</td>
<td>38</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>

From these figures it appears that the commonest type of cell found in intra-ocular sarcomata is the spindle, the next in frequency being the round. It will be noticed that apart from the present series, no mention is made of the epithelioid cell, nor of the mixed variety. The former may have been classified under the round type, and it is, of course, realised that comparing statistical tables of this kind is not strictly scientific; but it is, however, I think justified here as it clearly shows that the commonest type of cell in these growths is the spindle type.

BIBLIOGRAPHY


Although the pigmented malignant tumours of the choroid are commonly known as sarcomata, much doubt exists, especially among pathologists, as to the origin of these tumours. Are they derived from mesoblastic or epiblastic tissue?

Before commencing on a discussion of this kind, it is necessary to understand the origin of the pigment melanin, as far as is known.

Formerly it was thought that melanin was a derivative from the blood pigment haematin, but this has now been shown to be untrue, since melanin contains no iron. Moreover, the pigment is observed in frog embryos where blood is not present, and it is now generally accepted that it is a product of the metabolic activity of the cell protein.

It was suggested that melanin was an oxidation product from a colourless precursor and that the oxidation was activated by a ferment.

Bloch isolated from the embryo of the broad bean \( 3:4 \) dihydroxyphenylalanine, which, for the sake of brevity, he called "dopa." This "dopa" substance was seen to be readily changed to melanin by a ferment or oxidase present in the cells of pigmented tissues. When the "dopa" was added to epidermal cells of the skin in frozen formalin fixed sections, melanin granules appeared, and it was assumed that these cells of the epidermis, in which the pigment appeared, contained the ferment or dopa-oxidase which converted the "dopa" into melanin.

It was noticed also that this reaction was much stronger in tissues which had been irradiated by radium or X-rays, and that it was not present in scars and in albinos.

It will be readily realised how important this discovery was, for it made it possible, by staining sections from embryos, to foretell the exact cells of the germinal layer which later were to give rise to melanin.