AETIOLOGY

Intra-ocular sarcoma is a rare disease. Fuchs collected ninety-one cases in one hundred and thirty seven thousand five hundred and forty-five eye patients (0.07 per cent.), Pawel two hundred and forty-eight cases in three hundred and fifty-one thousand seven hundred and seventy nine (0.07 per cent.) and Stallard found, during 1925-1931 at Moorfields, one case in every four thousand patients attending the Out-Patient Department.

On investigation of the present series there was no evidence to show that the disease is hereditary, but in the literature on the subject certain cases are recorded which certainly warrant further description.

Two in the series described by Lawford and Collins in 1893 were mother and daughter. The mother, aged thirty-eight years, had been blind in the left eye for four years, and on removal of the eye, one year after the birth of her daughter, a large pigmented sarcoma of the choroid was discovered. Her father and her twin sister each had an eye removed for something other than injury, but there is no evidence to show why the eyes were removed.

Two daughters of the original case had their left eyes removed for sarcoma of the choroid, the growth being in each case very similar in size and position to that found in the parent’s eye. This particular family history has now become even more striking, for Davenport in 1927 reported further members of the family affected with sarcoma of the uveal tract. Two daughters of one of the previous cases had eyes removed for sarcoma of the choroid, and in each case it was the right eye.

The diagram taken from Davenport’s article shows the sequence of the growths through the generations.

I can find in the literature only one other reference to the possibility of hereditary transmission of the disease.

In 1921 Pfingst described melan-sarcoma of the choroid occurring in brothers, one aged forty-four years, the other forty-seven, the growth being in each case a deeply pigmented spindle cell sarcoma.
This author was obviously unacquainted with the cases described by Lawford and Collins in 1893, for he says "inasmuch as malignant growths of the eye, occurring in more than one member of the family have never been recorded in medical literature, I think these will be of interest."

Although contrary to the evidence submitted in these isolated cases, it is probably safe to presume that there is no hereditary factor in this particular type of neoplastic disease.

The subject of melanosis oculi, the first case of which was reported by Desmarres in 1847, has attracted great attention to the probability that individuals suffering from this abnormality have a tendency to develop pigmented intra-ocular neoplasms.

Hulke in 1860 recorded a pigmented sarcoma of the choroid associated with pigmented deposits elsewhere, his particular case being a female aged sixty-two who had a sarcoma of the choroid together with pigment spots on the lids and sclera.

Martin reported the case of a girl aged thirteen, who had naevi on the face, black spots on the sclera, a large mass of abnormal pigment on the lower part of the iris and a malignant pigmented tumour of the choroid.

Juler reports a case of unilateral melanosis oculi which developed a pigmented intra-ocular sarcoma, and states that there are seven cases recorded of this occurrence.
Doherty states that 29 per cent. of the cases of melanosis oculi develop melano-sarcoma, not necessarily intra-ocular.

Iris Melanomata.—That innocent pigmented naevi, or more properly melanomata of the iris, may undergo malignant changes is well known, and they are, rightly, always regarded with suspicion as there is abundant evidence in the cases reported, that eyes which exhibit these innocent growths are particularly liable later to develop a malignant melanotic sarcoma. Coats collected twenty-six cases of innocent naevi, seven of which became malignant whilst under his observation. Wood and Pusey reported eighty-six cases of iris naevi, ten of which became malignant. Hirschberg reported sixteen cases of sarcoma of the iris, three of which developed in positions which had previously been the seat of innocent melanomata, and Treacher Collins four cases, two of which he states were certainly preceded by an innocent melanoma, the remaining two probably so.

In the fundus oculi the possibility of distinguishing between an innocent melanoma of the choroid and the same condition commencing malignancy is obviously of the utmost clinical importance.

Foster Moore, who had the opportunity of examining microscopically two cases of melanoma of the choroid, and of observing others for periods up to five years, states "... They have a characteristic appearance and are entirely innocent in nature, and are very likely congenital in origin or developed early in life."

Scheerer stated that malignant degeneration of a melanoma of the choroid had never been observed.

Schappert-Kimmyser investigated histologically the occurrence of benign melanomata in the eye with, and without sarcoma, and found five separate melanomata in fifty sarcomatous eyes, and two in fifty non-sarcomatous eyes.

Wagener and Wellbrock report a case of an innocent choroidal melanoma which four years later had become a malignant melanotic sarcoma.

They state that it might be argued that the original patch was a slowly developing, or early melanotic sarcoma, but it did not look like one, having the characteristic appearance of a melanoma and they give microscopic evidence of a definite melanoma pre-existing the growth, the sarcoma being seen as a small group of cells lying within a large pigmented mole.

A case in the present series was diagnosed as possibly sarcoma, possibly innocent melanoma of the choroid, which ten years later, when the eye was removed for glaucoma, showed a heavily pigmented melanotic sarcoma originating in the pre-existent choroidal mole. This case is described fully in the appendix at the conclusion of this paper.
Taking into consideration the foregoing evidence, which is in my opinion sufficient, I think abnormal ocular pigmentation must be considered an aetiological factor in some cases of sarcoma of the uveal tract, and in my view an eye in which this pigmentation is observed must be regarded as a neighbourhood in which a malignant growth may later develop, the evidence, however, being more in favour of abnormal masses of pigmentation in the iris becoming malignant, than those of the choroid.

There always has been, and there still-is, great difference of opinion on the question of the possibility of previous trauma being an aetiological factor in neoplastic diseases.

Since the advent of the Workmen's Compensation Act, this subject has become more than one of academic interest, for it is an important problem for the courts to decide the much debated question of liability in cases of neoplasms with a previous history of injury.

It is well known that a patient can usually remember some trivial injury to the part under investigation if asked if such ever occurred, and therefore it is of the utmost importance, when interrogating patients, to avoid, if possible, leading questions bearing on injury, and to consider carefully the truth of the patient's statement, and the tendency of human beings on finding a defect to say: "Did I injure it?"

Ewing, in his text-book of neoplastic diseases, postulates six conditions, all of which must be present before one can suppose the injury to have been instrumental in causing the neoplasm. They are as follows:

1. Authenticity of the trauma.
2. Sufficient importance or severity of the trauma.
3. Reasonable evidence of integrity of the part just before the injury.
4. Correspondence of site of tumour to site of trauma.
5. The date of appearance of tumour not too remote from the time of the accident to be reasonably associated with it.
6. A diagnosis, established by clinical and radiological evidence, supported if possible by microscopical evidence.

The evidence in support of trauma being an important factor in the aetiology of uveal sarcomata consists for the most part in a series of isolated cases reported by various authors—there being in very few, if any, cases positive answers to the six postulates of Ewing as set forth above. That repeated irritation can cause cancer is admitted—but it is improbable that this state of affairs can occur within the globe and in this discussion trauma is intended to convey the impression of a single isolated injury.
The theory of Cohnheim states that trauma releases and sets growing slumbering misplaced embryonic elements, and that these grow into a tumour. There is no proof, laboratory or clinical, of this, nor is there proof, to my knowledge, that experimental trauma has ever caused cancer, but it is stated that severely traumatised tissues have been followed by new growths.

Growth are more frequent in those parts of the body exposed to trauma—for example carcinoma of the breast in women, and of the lips in men, more especially when clay pipe smoking was commoner than it is now. The infrequent occurrence, however, of growths developing, compared to the frequent injuries the body sustains tends to negative the view that trauma is an important aetiological factor.

Parsons states in his text-book on diseases of the eye:—"There was a history of injury in 29 of Fuchs' cases (11 per cent.), and in five of Lawford and Collins; there is no sufficient evidence that it is of aetiological moment."

Verhoeff, after examining pathologically over three hundred eyes removed for sarcoma, did not recall a single case that showed any definite evidence of trauma.

More recently Nitsch in 1925 made a study of one hundred and forty-one cases of sarcoma of the uveal tract associated with trauma, and came to the conclusion that in the scientific sense there was no connection whatever between the growth and the trauma.

The earliest case of trauma to the eye followed by sarcoma of the uveal tract was recorded by Coleman in 1901.

A man aged twenty-three years was struck in the eye by an exploding gun cap. Eight months later an elevation of the iris was excised and microscopic examination proved the tissue to be a melanotic sarcoma.

Kipp reported the case of a man aged forty, who had an eye removed for intra-ocular sarcoma, three months previously the eye having been injured by a piece of wood.

Chance records a case of a female, who three years prior to visiting him with a shrunken globe containing a sarcoma, received an injury to the eye.

Holloway reports the case of a man aged twenty-three years, whose eye was struck by a hammer three years previous to his having the eye enucleated for choroidal sarcoma.

Finally Stieren's patient was a man aged fifty-eight years, who, in 1923, was struck in the eye with the head of a flying nail. The patient was suffering from a subconjunctival haemorrhage and a laceration of the conjunctiva. Nine years later, after a history of failing vision in the eye for six months only, a choroidal sarcoma was diagnosed, and so it proved to be on enucleation of the eye.

Lane, on investigating five hundred and seven cases of sarcoma
of the uveal tract, found that trauma was mentioned in sixty-six,
the trauma in twenty-four cases varying from two weeks to one
year previous to the eye being removed, while in thirty-two, the
period of previous injury varied from one to thirty years.

At the Mayo Clinic the incidence of injury in one thousand four
hundred and thirty-nine cases of tumours of the eye and orbit
showed that one hundred and nineteen (or 82.6 per cent.) gave a
history of injury.

On analysing two hundred and sixty-three cases in the present
series, it is found that seventeen (or 64 per cent.) have a
definite history of previous trauma.

Below is a table showing the number of cases with the
approximate time interval between the alleged trauma and the
diagnosis of intra-ocular neoplasm.

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>One Day</td>
<td>... ... ... ... 1</td>
</tr>
<tr>
<td>Six months</td>
<td>... ... ... ... 3</td>
</tr>
<tr>
<td>One year</td>
<td>... ... ... ... 1</td>
</tr>
<tr>
<td>Two years</td>
<td>... ... ... ... 3</td>
</tr>
<tr>
<td>Three years</td>
<td>... ... ... ... 1</td>
</tr>
<tr>
<td>Four years</td>
<td>... ... ... ... 4</td>
</tr>
<tr>
<td>Six years</td>
<td>... ... ... ... 2</td>
</tr>
<tr>
<td>Twelve years</td>
<td>... ... ... ... 1</td>
</tr>
<tr>
<td>Fifteen years</td>
<td>... ... ... ... 1</td>
</tr>
</tbody>
</table>

I have an open mind on the statement that trauma is of no
moment in predisposing an eye to malignant changes, but from
the practical and scientific view-point I cannot subscribe to the
view that it is of any material aetiological importance.

Previous intra-ocular disease.—Eyes exhibiting chronic inflam-
matory changes with increased tension and secondary cataract are
surprisingly often found to contain a malignant uveal growth.

Neame and Wajid Ali Khan showed that in four hundred and
two blind painful eyes removed at Moorfields Eye Hospital in an
eleven year period, forty, or 10 per cent. of these globes contained
a sarcoma of the uveal tract; moreover no suspicion of a growth had
been entertained in at least sixteen of these cases.

In the present series under investigation, thirty-six or nearly
14 per cent. were blind painful eyes in which the presence of a
growth had been suspected in some, no definite diagnosis being
possible in the majority of the cases.

There were seventeen eyes, or 64 per cent. of the total, which
showed clinical evidence of inflammatory changes, old or recent,
but it is extremely difficult, and in many cases impossible, to
state with certainty whether the inflammatory changes are
secondary to the growth, or whether they had been present before
the commencement of the growth.
This statement, I think, applies equally well in the case of blind painful eyes.

Parsons states "There is a feeling current that sarcoma is more likely to grow in a shrunken eye than a normal one; it probably originated in the opinion expressed upon the subject to that effect by Virchow; it is not borne out by careful investigation into the statistics."

I think it is possible to imagine that an eye which has been subject to a severe and chronic inflammatory irritation, and has perhaps started to shrink, might quite likely be more prone to the development of a sarcoma than a normal one; on the other hand, it is equally possible to imagine that necrosis and degeneration in a pre-existing, although unsuspected, growth might be quite sufficient in themselves to cause the intra-ocular inflammation and disorganisation of the globe.

Ewetzky considered that the inflammation in phthisical eyes containing a sarcoma was due to the irritating effects of the products of degeneration within the growth.

Leber, on the other hand, was inclined to refer it to infection, the necrotic parts in the growth offering a suitable culture medium for the pathogenic organisms.

The question of choroiditis, pigmentary disturbances and haemorrhages at the macular region, with subsequent malignant growth formation in these areas is interesting, and I think, an important aetiological factor, several cases having been recorded. These taken together with those cases discovered in the present series make the possibility of coincidence somewhat remote.

Nettleship reported the case of a patient aged twenty-four years, whose right eye had been blind since the age of twelve who had suffered from a choroiditis of an earlier date.

On enucleation of the globe for pain, a sarcoma was discovered, originating from the choroid in the area which had previously been the seat of the choroiditis.

Glover reports a case of a melanotic sarcoma arising from an area of choroido-retinitis, this occurring within the relatively short period of nine months from the onset of the choroido-retinitis.

Several cases in the present series are of extreme interest from this point of view, the previous fundus changes having been observed by ophthalmologists of note, and clinical records made of them.

Later melanotic sarcoma of the choroid arose in close proximity to the previously noted pathological area.

These cases warrant further description and this has been done in the appendix to this paper.

Sex of patients.—The disease appears, from a large number of
cases, to be equally distributed between the two sexes. Of the total number, 263, there were 124 (or 47.1 per cent.) males and 139 (or 52.9 per cent.) females.

The slight preponderance of females in this paper does not correspond with the statistics published by Fuchs, who found that out of 259 cases, 137 or 52.65 per cent. were males and 116 or 45.84 per cent. females, nor does it agree with the series of cases published by Lawford and Collins who state that out of a total number of 108 cases, there were 59, or 57.28 per cent., males, and 44, or 42.71 per cent., females.

Davenport, however, found on investigating 345 cases occurring at Moorfields between the years 1871 to 1925, 175 females and 167 males, the sex of 3 cases being unrecorded. These statistics tend to agree with the present series recorded.

It would be true to state that the majority of papers published on the subject agree that sarcoma of the choroid tends to distribute itself more or less equally between the sexes, but Martin reporting 49 cases found 29 were females, while Frudenthal found the disease very unequally distributed, only 20 per cent. of his 24 patients being women; the discrepancies in these last two cases are doubtless accidental and due to the small number of patients observed.

Primary sarcoma of the iris appears however to be definitely more common in the female. Of the three cases recorded here, two were women, and this appears to be in agreement with other observers who record larger numbers: in Pflüger's 23 cases, 15 were females and 8 males, and in Treacher Collins' 18 cases, 10 were females and 7 males, the sex being unstated in one case.

In the 10 cases recorded here of primary sarcoma of the ciliary body, 6 are males and 4 females. Lawford and Collins found the proportion equal in the two sexes, while Mules, publishing 17 cases, found 14 females and 3 males.

**Age incidence.**—The average age of 238 cases in this series was 51.9 years, the ages of 25 cases being unrecorded.

The youngest male was 1½ years old and the youngest female was 26 years old, the oldest male was 87 years and the oldest female 79 years.

Lawford and Collins give the average age of their cases as 48.42 years, Fuchs as 44.2 years. Frudenthal as 49.2 years and Kronenberg as 52.6 years.

It will be noticed therefore that the average age in this series compares very closely with those of the other observers.

If the ages are arranged in decades it is seen that the sixth decade is the commonest, Lawford and Collins found that the fifth was the commonest, whilst Terry and Johns agree with the sixth as being the most frequent.

With regard to the type of growth and age incidence, it is
stated by some authorities that the so-called leucosarcomata are more commonly met with in somewhat younger patients than is the case with the pigmented variety.

In this series there were 14 leuco-sarcomata and the average age of this group was 49.1 years, the youngest being 28 years old and the oldest 62 years old, the age of one patient not being recorded. This is a lower average than that for the total number of cases, but this is probably accidental and due to the comparatively small number of cases. Of three cases of primary growth of the iris, the average age was 66.3 years, the oldest being 79 years, and the youngest fifty-one years.

**Age of Patients arranged in Decades**

<table>
<thead>
<tr>
<th>Between</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>1-10</td>
<td>1</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>11-20</td>
<td>2</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>21-30</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>31-40</td>
<td>14</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>41-50</td>
<td>21</td>
<td>26</td>
<td>47</td>
</tr>
<tr>
<td>51-60</td>
<td>29</td>
<td>40</td>
<td>69</td>
</tr>
<tr>
<td>61-70</td>
<td>22</td>
<td>35</td>
<td>57</td>
</tr>
<tr>
<td>71-80</td>
<td>11</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>81-90</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>108</strong></td>
<td><strong>129</strong></td>
<td><strong>238</strong></td>
</tr>
</tbody>
</table>

The ages of 25 patients are not recorded, and there is one case in the first decade, the sex of which is unknown, making a total of two in this decade.

With regard to the eye affected, the results in the present investigation and those of other observers are given in the following table.

It appears that the disease attacks the eyes in nearly equal proportions.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Right</td>
<td>126</td>
<td>41</td>
<td>108</td>
<td>15</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>Left</td>
<td>122</td>
<td>60</td>
<td>101</td>
<td>19</td>
<td>14</td>
<td>48</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1</td>
<td>—</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
<td>2</td>
<td>45</td>
<td>9</td>
<td>—</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>263</strong></td>
<td><strong>103</strong></td>
<td><strong>259</strong></td>
<td><strong>43</strong></td>
<td><strong>24</strong></td>
<td><strong>100</strong></td>
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</table>
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VISUAL ACUITY

This was noted in 192 of the total number of cases recorded, and in 71 cases I have been unable to ascertain the vision.

It will be seen from the table of visual acuity that the majority of patients (74, or 38.5 per cent.), present themselves for examination with sight reduced to no perception of light, while 24, or