RADIOACTIVE PHOSPHORUS AS AN AID TO THE DIAGNOSIS OF MALIGNANT MELANOMA OF THE EYE*

BY

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The object of this investigation was to study the usefulness of radioactive phosphorus, $^{32}$P, as an aid to the diagnosis of malignant ocular melanomata. These tumours, particularly when choroidal, may present diagnostic problems; details of the tumour may be obscured by detachment of the retina, and, less commonly, the tumour may be completely hidden by opacity of the ocular media. An example of its unsuspected presence is given by Neame and Khan (1925) in a report on the pathological examination of 402 enucleated eyes, which had been blind and painful. Forty of these globes contained a malignant melanoma and in at least sixteen of the forty, no suspicion of the growth had been entertained.

Previous Investigations

A radioactive material administered to a patient is distributed throughout the body in the same way as the stable element from which it has been derived, and may subsequently be detected by external observation with a Geiger counter.

Many attempts have been made to demonstrate a difference between the uptake of radioactive material by a tumour and by normal tissue adjacent to it. LowBeer (1946) showed that most superficial breast carcinomata have a detectable differential uptake of $^{32}$P. Since then, radioactive isotopes used by other workers include copper ($^{64}$Cu), gallium ($^{72}$Ga), and iodine ($^{131}$I), which is usually incorporated in diiodofluorescein. Tumours investigated include those of the stomach (Gray and others, 1949), testis (Roswit and others, 1950), central nervous system (Selverstone and others, 1949), and bone (Mulry and Dudley, 1951).

Skin melanomata have been studied by Marcus and Rotblat (1950) using $^{64}$Cu, $^{131}$I, and $^{32}$P. They found $^{32}$P to be the most satisfactory material for the test; a significantly higher uptake was found in the melanoma than in the immediately surrounding skin. The concentration of phosphorus in the tumour could be resolved into two parts, the first occurring a few minutes after the intravenous injection of $^{32}$P and being probably due to the increased vascularity of the tumour area. The second rise occurred after more than 3 weeks and represented a genuine uptake of $^{32}$P by the tumour cells.

Ocular tumours, usually malignant melanomata, have been investigated by Trevor-Roper and others (1952), Thomas and others (1952), and Town (1952). The first of these groups used diiodofluorescein labelled with $^{131}$I and found no

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significant increase of radioactivity over the tumour area as compared with a corresponding site in the other eye.

Thomas and others (1952) and Town (1952) have published preliminary reports on the use of $^{32}$P, which they have found to be a valuable aid to the diagnosis of ocular tumours. In both investigations a Geiger counter was applied to the eyes one hour after the intravenous administration of $^{32}$P. Thomas and others (1952) report the maximum reading, in counts per min. obtained from both eyes in each of seven patients. In one other case all the readings appear to have been taken from the affected eye. In these patients there were four cases of malignant melanoma, and one of suspected metastatic carcinoma; the remaining three had simple unilateral ocular lesions. The Geiger counter readings for the four cases of malignant melanoma were from 50 to 100 per cent. greater over the tumour than over the corresponding normal area. In the other four cases the readings over compared areas varied by up to 25 per cent.

Town (1952) gives readings taken from eight cases, of which four had malignant ocular tumours, while the other four had non-malignant unilateral ocular lesions. In the non-malignant cases the maximum difference in the readings between the two eyes was about 50 per cent., and in two of the malignant cases there was a similar variation. In the other two malignant cases the readings in the affected eye were generally 50–100 per cent. more than in the compared areas.

Material and Method

In the present investigation it was considered advisable to observe the ocular uptake of $^{32}$P in persons with healthy eyes, before studies were carried out on patients with suspected malignant melanoma. Tests were made with four patients in a surgical ward (Prof. C. F. W. Illingworth, Western Infirmary, Glasgow) who were receiving $^{32}$P for another investigation.

The method used was similar to that of Thomas and others (1952). A dose of 100 microcuries of $^{32}$P was injected into an arm vein and cocaine hydrochloride drops 2 per cent. was instilled into each conjunctival sac. Readings with the Geiger counter† were taken for periods of a minute from alternate eyes at anatomically similar positions and were repeated at frequent intervals during a period of 2 hours after the time of injection. Readings so obtained are shown in Table I. In each case the background counting rate was measured and found to be negligible.

The following observations are made in connection with Table I. The Geiger counter was applied directly over the eyeball and held there for as long as the observer desired, in the absence of epiphora or ocular movement of the patient. It is interesting to note that an appreciable reading was obtained over the eye within 15 seconds of the administration of $^{32}$P.

In Case 4 the left pupil was dilated with a mydriatic, with no apparent influence on the counter readings; the cases of suspected malignant melanomata later examined were all atropinized before the counting tests began.

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*A dose of 100 microcuries, or at the most 200 microcuries, is enough for an investigation of this kind. Both Thomas and others (1952) and Town (1952) report that they gave a dose of 500 millicuries; more probably they gave 500 microcuries.

†The Geiger counter tube was supplied by Twentieth Century Electronics, Ltd., New Addington, Surrey (type MB4H). The sensitive volume is a glass cylinder with, at one end, a very thin window having an effective diameter of about 6 mm. B-rays from $^{32}$P cannot penetrate the side wall of the counter and can enter it only through the end window. The average range in tissue of the $^{32}$P B-rays is about 2 mm.; the counter therefore records the amount of $^{32}$P in a region under the end window, with a diameter of about 6 mm. and a depth of about 2 mm.
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TABLE I
COUNTING RATES OBSERVED IN FOUR NORMAL PERSONS BY APPLICATION OF A GEIGER COUNTER TO COMPARABLE AREAS OF BOTH EYES, AFTER INTRAVENOUS INJECTION OF 100 MICROCURIES OF $^{32}$P.

Figures represent counts per minute. R=right eye, L=left eye.

<table>
<thead>
<tr>
<th>Time after Injection (min.)</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Central</td>
<td>Central</td>
<td>Nasal</td>
<td>Temporal</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>5</td>
<td>119</td>
<td>93</td>
<td>86</td>
<td>106</td>
</tr>
<tr>
<td>15</td>
<td>144</td>
<td>153</td>
<td>156</td>
<td>156</td>
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<tr>
<td>30</td>
<td>124</td>
<td>107</td>
<td>194</td>
<td>415</td>
</tr>
<tr>
<td>35</td>
<td></td>
<td>136</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>215(3)</td>
<td>88</td>
<td>174</td>
<td>155</td>
</tr>
<tr>
<td>120</td>
<td>92</td>
<td>91</td>
<td>137</td>
<td>134</td>
</tr>
</tbody>
</table>

(1) Left eye dilated with atropine sulphate drops, 1 per cent.
(2) Epiphora.
(3) Epiphora: blotting paper soaked in tear fluid at this time gave a counting rate of 60 per min.
(4) Immediately after injection of 2.5 mg. histamine acid phosphate (given for another investigation).

Epiphora causes a significant increase in the activity recorded by the counter, and the tear fluid itself, if collected on a piece of blotting paper and applied to the Geiger counter, gives an appreciable reading. It is, of course, to be expected that $^{32}$P will appear in all body fluids shortly after administration.

The fluctuations in counting rate shown in Table I are quite substantial, but are not significant. They are due partly to the random nature of the counting process and partly to small movements of the eye and local variations in the circulation.

Tests were then made with four consecutive cases of suspected malignant melanoma of the eye, in patients admitted in 1953 to the Glasgow Eye Infirmary. The clinical details are given in Table II.

TABLE II
COUNTING RATES OVER COMPARABLE SITES IN DISEASED AND HEALTHY EYES IN FOUR CASES OF OCULAR MALIGNANT MELANOMA

Figures represent counts per minute. R=right eye, L=left eye. Left eye dilated with atropine sulphate drops (1 per cent).

<table>
<thead>
<tr>
<th>Time after Injection (min.)</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nasal</td>
<td>Temporal</td>
<td>Nasal</td>
<td>Temporal</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td></td>
<td>(affected)</td>
<td>(affected)</td>
<td>(affected)</td>
<td>(affected)</td>
</tr>
<tr>
<td>From 60 to 120</td>
<td>148</td>
<td>204</td>
<td>252</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>169</td>
<td>271</td>
<td>151</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>152</td>
<td>267</td>
<td>111</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>260</td>
<td>109</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>98</td>
<td>230</td>
<td>122</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>151</td>
<td>160(1)</td>
<td>93(1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>164</td>
<td>113(1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) Directly over tumour.
Case Reports

Case 1, male, aged 54, complained of dimness of vision of the left eye and left-sided headache of 3 weeks' duration. On examination, the right eye was healthy in every respect. The patient could only perceive hand movements at half an inch with the left eye, and external examination of the left eye was normal, as was the ocular tension recorded on a Schiötz tonometer. Ophthalmoscopy revealed a solid-looking globular detachment of the retina in the lower nasal quadrant extending anteriorly as far as could be observed. On its surface were some dilated retinal blood vessels. There was old choroidal degenerative change in the upper nasal quadrant peripherally. No retinal tear was seen. Transillumination showed a shadow in the area of retinal detachment. General medical examination revealed the presence of a firm enlarged liver and of melanuria.

Enucleation of the left eye was performed.

Pathological Report (Dr. J. D. Fraser):

The globe was cut just above the horizontal meridian. There is a necrotic choroidal tumour extending from the optic nerve forward to the equator in the lower nasal quadrant. There is detachment of the retina.

Histological Report: The appearances are those of a choroidal sarcoma. The cells are of amixed type—some being small round ones and some larger. Necrosis in the tumour is a marked feature. Extra-ocular spread through the scleral lamellae is present.

Case 2, male, aged 55, complained of flashes of light in front of the left eye of about one year's duration, and dimness of vision of the left eye of several weeks' duration. The right eye was healthy. On examination, the visual acuity of the left eye was 4/60. External examination showed a few dilated conjunctival and episcleral vessels near the limbus at “3 o'clock”. Ocular tension (Schiötz) was normal. Ophthalmological examination showed large vitreous opacities and a fine vitreous haze—probably due to red blood cells. A globular retinal detachment was present on the temporal half of the retina, fringed by retinal haemorrhages below and peripherally. Transillumination showed a slight shadow below and no shadow temporally. Several days later a massive vitreous haemorrhage occurred obscuring all detail. Nothing abnormal was found on general medical examination.

Enucleation of the left eye was performed.

Pathological Report (Dr. J. D. Fraser):

The globe was cut in the oblique meridian. There is a mushroom-shaped tumour of the choroid in the region of the equator on the temporal side of the globe, causing a primary and secondary detachment of the retina. There is haemorrhage into the vitreous.

Histological Report: The histological appearances are those of a choroidal sarcoma in which a recent haemorrhage has occurred. In addition there is a recent sub-retinal exudate. The angle of the anterior chamber is narrowed as in glaucoma. There is no evidence of extra-ocular spread.

Case 3, male, aged 49, complained of dimness of vision of the left eye of 2 or 3 months' duration. The right eye was healthy. Vision in the left eye was reduced to hand movements in the temporal periphery. Ocular tension (Schiötz) was normal. External examination of the eye revealed no abnormality. Ophthalmoscopic examination showed a large globular retinal detachment in the upper nasal quadrant overhanging the disc and macular area, and a shallow retinal detachment nasally below. After rest in bed for 4 days the shallow retinal detachment disappeared and the large detachment above became considerably smaller, more grey, and solid looking. Transillumination showed an indefinite shadow in this area. General medical examination revealed no evidence of metastasis.

Enucleation of the left eye was carried out.

Pathological Report (Dr. J. D. Fraser): There is a mushroom-shaped growth extending from the equator to within 3 mm. of the nervehead on the upper nasal quadrant. The growth measures 12 mm. across and 13 mm. into the vitreous. The nervehead does not appear to be involved. The tumour is vascular, the detachment extends round the equator on the temporal side.
**Histological Report:** The appearances are those of a choroidal sarcoma which has ruptured Bruch's membrane. No extra-ocular spread is visible.

**Case 4, male, aged 34,** had always had a defective right eye. He complained of a blur in front of the left eye of 2-3 hours' duration. On examination, corrected visual acuity of the right eye was 6/18 and of the left eye 6/12. Ocular tension (Schiötz) was normal. Slit-lamp examination of the left eye showed a rounded, brown, pigmented mass in the substance of the iris from "9 to 12 o'clock", appearing to block the angle of the anterior chamber. On its surface were many dilated blood vessels and a small hyphaema was present below (Fig. 1). Apart from slight ectropion uveae, the rest of the iris was healthy. Transillumination of the mass showed no shadow. Ophthalmoscopy was negative. General medical examination showed no abnormal findings.

Enucleation of the left eye was carried out.

**Pathological Report (Dr. J. D. Fraser):**

There is a tumour of the iris—limited to the iris in the upper temporal quadrant and measuring 7 x 5 mm. across—which is occluding the angle of the anterior chamber (Fig. 2a and b). Apart from this the eye appears normal.
Histological Report: The appearances are those of a melanotic sarcoma of the iris infiltrating the ciliary body and surrounding the region of the arterial circle (Fig. 3). There is blockage of the drainage angle and infiltration of Schlemm’s canal.

In each of those four cases, the dose of $^{32}$P was between 180 and 220 microcuries. After cocainization of the eye, the window of the Geiger counter was applied to different parts of the affected eye and to corresponding points in the other eye. The counting rates measured in this way are shown in Table II.

Only in Case 1 were the readings appreciably greater over the diseased eye. (Variations in counting rate of as much as 15 per cent. are to be expected because of the random nature of the counting process and are not significant for our present purpose). It will be observed that no enhanced activity was detected directly over the tumour itself which, in this case, was necrotic.

In Cases 2, 3, and 4, no significant difference in the counting rates was obtained, yet, in Case 4, the Geiger counter was sometimes separated from the tumour by only the thickness of the cornea. For testing the value of this method of diagnosis, no more suitable case of uveal malignant melanoma is likely to be found.

Discussion

Ocular malignant melanomata usually grow rapidly and metastases are common. Enucleation is therefore performed as soon as the diagnosis is reasonably certain. It would not be justifiable, unless the diagnosis was much in doubt, to wait for a further 3 weeks to find whether the tumour cells could metabolize significant amounts of $^{32}$P, as in the skin melanomata studied by Marcus and Rotblat (1950). No such attempt has been made in the cases reported here.

Statistical analysis of the results is difficult in the presence of so many extraneous factors, including, for example, local fluctuations in the circulation, and accumulation of tear fluid on the counter window. For this reason, a very substantial difference in the counting rates over the two eyes would be necessary before a diagnosis could be made with confidence; such a difference
was not shown in the cases we have investigated—even in Case 4, where the
tumour was situated only a millimetre or so from the counter window. It
seems unlikely that the use of $^{32}$P in this way will give useful guidance in
the difficult diagnostic problems sometimes associated with choroidal
tumours which most often arise in the less accessible posterior half of the
globe. Nor is it known whether the use of $^{32}$P will enable a distinction to be
made between malignant melanomata and conditions such as acute choroid-
itis, where the circulation may be increased locally.

Thomas and others (1952) found the test to be useful, though some of the
variations in counting rate which they considered significant are no greater
than those occurring in our control series. Their use of cases of simple detach-
ment of the retina as controls is interesting, since this condition simulates
many of the effects of choroidal melanoma.

Town (1952) used a wider range of malignant tumours and as controls
employed a variety of non-malignant ocular conditions. Here, too, the vari-
ations in counting rate were often no greater than in our control patients.

The negative results of Trevor-Roper and others (1952) are to be expected
from consideration of the technique which they used. The Geiger counter
had an aperture of diameter 2.5 cm. and the material employed (radioactive
iodine, $^{131}$I) gives penetrating Y-rays with a range of several cm. in tissue.
The counter therefore recorded activity from a considerable mass of tissue
in and near the eye, rather than from the tumour itself.

Summary

The uptake of radioactive phosphorus by the eye has been investigated
in four normal patients and four consecutive cases of ocular malignant
melanoma, at various times during the first 2 hours after intravenous in-
jection. No significant difference in uptake was found between diseased
and healthy eyes.

We are grateful to Dr. J. D. Fraser, pathologist to the Glasgow Eye Infirmary, for the patho-
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Board, Glasgow.

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