Retinoblastoma

A study of 139 cases

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The successful treatment of retinoblastoma with *x*-rays was first reported by Hilgartner (1903). Subsequently Foster Moore (1929) in London and Martin and Reese (1936) in New York confirmed that ionizing radiation could destroy this type of tumour, but the very high doses of radiation used by these earlier workers frequently caused severe complications sometimes leading to the loss of the eye.

From a study of the histological sections of eyes treated with radon seeds by Moore, Stallard, and Milner (1931), Stallard (1936) determined that a dose of 3,500r was lethal to retinoblastoma cells. Subsequent collaboration with Innes (1964) led to the development of Cobalt-60 applicators of varying size which could deliver a dose of 4,000r to the summit of the tumour in 7 days.

Because of the serious ocular complications and the occasional case of radiation-induced malignant change in neighbouring structures, Reese, Merriam, and Martin, (1949) gradually reduced their dosage of conventional *x*-rays from the original level of around 10,000r; they also independently confirmed that a dose of 3,500r (combined with chemotherapy) was lethal to most retinoblastomas (Reese, Hyman, Tapley, and Forest, 1958). This reduced dosage of radiation has enabled many of these patients to survive with cure of the tumour and with good vision in the treated eye (Ellsworth, 1968; Stallard, 1962, 1968; Cassady, Sagerman, Tretter, and Ellsworth, 1969).

Methods for the delivery of radiation have been improved since the earliest radon seeds and low-voltage *x*-rays; the former have largely been replaced by Cobalt-60 applicators whilst high energy Cobalt beam units and linear accelerators permit irradiation of the eye with little involvement of adjacent structures (Skeggs and Williams, 1966). In addition, light coagulation (Höpping and Meyer-Schwickerath, 1964) has proved useful for the treatment of small tumours, and more recently cryotherapy (Lincoff, McLean, and Long, 1967; Rubin, 1968) has been used successfully in similar cases.

The work of Gillette and Bodenstein (1946) demonstrated that developing retinal cells were especially susceptible to derivatives of the nitrogen mustard group of chemotherapeutic agents, one of which, triethylenemelamine (TEM), has been used extensively, particularly in New York, in conjunction with radiation, for the treatment of cases of advanced retinoblastoma (Ellsworth, 1968; Hyman, Ellsworth, Feind, and Tretter, 1968).

In this paper we have reviewed all the patients with retinoblastoma seen at this Unit since 1960. A total of 169 cases was seen and treated, thirty of which were not subsequently followed by us; as most of the latter had been referred from foreign countries for treatment and had subsequently returned home, they have been excluded from the analysis of results.

The subject matter of this paper will be presented in three parts with a separate discussion for each.

I. PRELIMINARY ASSESSMENT

There were 73 males and 66 females, which confirms the observations of other workers that the sex incidence of retinoblastoma is essentially equal, as it should be if the disease is transmitted by an autosomal gene.

Almost 80 per cent. (111) of our patients had bilateral disease and 28 were unilateral, which would not be the case in a random sample. The high percentage of bilateral cases in this series reflects our interest in this disease and the frequent referral of patients to us after the second eye had become affected. The family history was positive in 38, negative in 76, and not recorded in 25 cases.

Table I is interesting because it shows that we see a considerable number of bilateral retinoblastomas in cases with no family history of the disease. Genetic studies (François and van Leuven, 1964) indicate that a sporadic case can arise as a result of:

- (1) A germinal mutation affecting every cell and which can be bilateral;
- (2) A somatic mutation occurring in the precursor retinal cells developing in one eye;
- (3) A phenocopy which results in the tumour cells developing in one retina.

Table I *Comparison of family history and bilaterality in 114 cases*

<i>Family history</i>	<i>Unilateral</i>	<i>Bilateral</i>
Positive	22	54
Negative	2	36

The last two processes are usually held responsible for most sporadic cases and are always unilateral. It is, therefore, necessary to account for the high incidence in this series of bilateral cases with no family history. We do not usually investigate the family history of every patient in detail as this would be impossible without the assistance of a genetic team: therefore some of our patients, whose parents are unaware of any other member of the family with this tumour, may actually have a positive family history in a distant relative. Secondly, in about 20 per cent. of cases the gene will not penetrate completely, so that the mutation, having occurred in the parents, may not become manifest in the offspring. Thirdly, the referral of many patients when the second eye has become affected or who have bilateral tumours when first seen naturally overloads our statistics in favour of bilateral cases. However, the possibility remains that, in sporadic cases, unilateral or bilateral, there may be a germinal mutation or a positive family history which is not immediately apparent. It is of interest that we have two patients with a positive family history and unilateral disease, one with 18 months' and the other 5 years' follow up, who must nevertheless have a retinoblastoma gene in every cell in both retinae. We also have two other patients with no previous family history and whose siblings have developed retinoblastoma. Thus it is clear that every unilateral case must be followed lest a tumour develop in the other eye, and that all siblings and offspring of retinoblastoma patients must be seen soon after birth and subsequently at regular intervals.

Table II shows that the most frequent presenting abnormality recorded is a white appearance of the pupil, the next most common sign being the development of a squint. Rarely these patients are first seen because of a painful red eye due to secondary glaucoma with a shallow anterior chamber, raised tension, and rubeosis iridis.

We agree with Reese (1963) that retinoblastoma does not develop in a congenitally microphthalmic eye, but it is important to recognize that a phthisical eye may contain an active retinoblastoma. Two patients were seen with a spontaneous hyphaema due to iris seeding not unlike that which occurs characteristically with juvenile xanthogranuloma, but at this stage a retinoblastoma almost fills the globe and the main bulk of it can be easily seen when the pupil is dilated. Most retinoblastomas have large feeder vessels which may, when associated with a solitary retinal tumour, lead to the erroneous diagnosis of a vascular tumour or malformation (Bedford and MacFaul, 1969); furthermore, the presence of exudates with such vascular changes does not exclude the diagnosis of retinoblastoma, especially in the younger age group.

Table II *Presenting symptoms*

<i>Presenting symptoms</i>	<i>No. of cases</i>
White pupil reflex	44
Squint	28
Painful red eye	6
Hyphaema	2
Several of the above	10
None (examined because of positive family history)	13
Not recorded	36
Total	139

Table III *Age at presentation*

<i>All cases</i>	<i>Average Range</i>	<i>1 yr 1 mth to 5 yrs</i>
<i>Family history</i>	<i>Negative Positive</i>	<i>1 yr 5 mths 8 mths</i>

The average age at first examination (Table III) is slightly younger than in the series reported by Howard and Ellsworth (1965), who emphasized that the majority are diagnosed in the first 2 to 3 years of life. In general, it is earlier when there is a positive family history and in our Unit these patients at risk are now examined before symptoms arise. In this way thirteen new asymptomatic cases have been found. Occasionally, however, these tumours arise in older children; thus, of 57 cases reported by Damaske and Jünemann (1969), five were over 4 years of age, and we have recently seen the first single primary tumour in a child aged 7 with a positive family history.

The most important factor, however, in the preliminary assessment is a comprehensive examination of the fundus. We follow the policy established by Reese and Ellsworth (1963). The children are examined under general anaesthesia with the pupils fully dilated. The fundi are examined to the ora serrata, using the binocular indirect ophthalmoscope with scleral depression, as many retinoblastomas arise anterior to the equator. A diagram is made showing the site and size of all tumours and any lesion that can be photographed is recorded in this way, as we have found photographs especially helpful in following suspicious areas after treatment. For follow-up purposes all cases are grouped according to the scheme proposed by Reese and Ellsworth (1963) (Table IV, overleaf), to which we have added Group 6 to include those cases with residual orbital disease after enucleation associated with optic nerve involvement or extrascleral extension.

Table IV *Prognosis of retinoblastoma*

<i>Group</i>	<i>Prognosis</i>	<i>Characteristics</i>
I	Very favourable	Solitary and multiple tumours less than 4 disc diameters at or behind equator
II	Favourable	Solitary and multiple tumours 4 to 10 disc diameters at or behind equator
III		Any lesion anterior to equator Solitary lesion greater than 10 disc diameters behind equator
IV	Unfavourable	Multiple tumours greater than 10 disc diameters Any lesion extending anteriorly beyond the limits of ophthalmoscopy
V	Very unfavourable	Massive tumour involving more than half the retina Vitreous seeding
VI		Residual orbital disease Optic nerve involvement and extrascleral extension

After treatment the patient is examined in a similar manner initially at 3 to 4 weeks and then at increasingly longer intervals depending on the response to treatment. At the age of about 6 or 7 years the patients are seen without anaesthesia as out-patients and if all is well they are seen thereafter every 9 to 12 months indefinitely.

We do not normally examine older siblings if they have no ocular symptoms unless this can easily be done as an out-patient procedure. We do, however, examine all newborn siblings and offspring of retinoblastoma patients not later than 4 weeks after birth and then periodically depending on the likelihood of a retinoblastoma arising based on our knowledge of the family history. In all cases, however, the patient is seen at least four times during the first year, three times in the second year, every 6 months until the age of 6, and thereafter at yearly intervals. We stop seeing non-affected patients after the age of 10 years, but, as has already been mentioned, we follow treated and cured patients indefinitely in order to maintain contact with them, especially so that if the question of marriage arises, we can remind them of the possible hereditary nature of this disease. In this way also we can ensure that the children are examined as soon as possible after birth. We like to see newborn children at about 4 weeks of age, by which time they can be safely anaesthetized, and also because we have seen one child at 6 weeks with such an extensive tumour that local treatment was impossible. A further advantage of early examination is that in these young children the tumours are usually small and easily treated, often without recourse to irradiation of the eye.

II. PRINCIPLES OF TREATMENT

In this section we outline the various modalities of treatment that are at present available and our reasons for using each type. The treatment of retinoblastoma in England was initially based on focal irradiation culminating in the development of the Cobalt plaque, but it has become apparent that this form of treatment has some limitations; consequently there are definite indications for irradiation of the whole retina. The cases reviewed in this report include some treated during the period when the indications for total retinal radiation were being established.

COBALT APPLICATORS

These have the advantage that a continuous dose of radiation can be delivered to the tumour with little spread to the surrounding ocular structures. A dose of 20,000r to the sclera and choroid and 4,000r to the summit of the tumour can be delivered in 7 days. A chorio-retinal scar with resulting nerve fibre damage develops at the site of treatment. Cobalt applicators, therefore, should not be placed under or adjacent to the macula. We have also found that this dose of radiation cannot be tolerated by the major retinal vessels in the vicinity of the optic disc as severe vitreous haemorrhages often result (MacFaul and Bedford, 1970). For this reason we no longer use the C-shaped plaque which was designed to embrace the optic nerve, and we rarely place a circular plaque closer than 5 mm. to the optic disc. In this series nine C-shaped plaques were used and six cases also had either another plaque or whole-eye irradiation; in eight of these severe vitreous haemorrhage resulted in the loss of the eye or blindness from haemorrhagic glaucoma; only one boy in this group has retained normal vision and attends a normal school. Some of these haemorrhages resulted from the ill-effects of combined radiotherapy, but we feel that the risk of haemorrhage is significantly increased by C-shaped plaques and that tumours near the disc and macula are therefore best treated by external radiation. At present the indications for the use of a Cobalt plaque include single tumours less than 13 mm. in diameter or two separate tumours or groups of tumours that need no more than one 10 mm. plaque each, provided that the lesions are away from the optic disc and macula.

EXTERNAL BEAM THERAPY

Our method of external radiation with the Cobalt beam using a direct anterior field, which was developed by Skeggs and Williams (1966), has the advantage of treating the whole retina and vitreous without involving the other eye in a significant dose of radiation; in this way each eye can be treated independently. This type of radiotherapy is indicated for large tumours (over 13 mm. in diameter), multiple tumours of any size scattered over the retina, tumours with vitreous seeding, and tumours of any size near the optic disc. A total dose of 4,000r will destroy most retinoblastoma cells with as yet little clinical evidence of damage to normal retina elsewhere. Frequently, tumours which initially covered the macula will regress, leaving a relatively normal fovea with a good visual acuity. As more of these children survive, it will be essential to carry out electrodiagnostic tests to determine whether there is any subclinical damage to retinal function. With this form of radiation, of course, the normal ocular structures and brain are irradiated and a cataract of varying density inevitably develops within about 18 months (MacFaul and Bedford, 1970). This complication is amenable to surgical treatment and its management will be discussed in a subsequent report. A temporal approach with the linear accelerator is useful if the other eye has already been removed; otherwise it also would receive a large dose of radiation. However, the use of this method in an attempt to spare the lens also spares the anterior retina and vitreous from the full therapeutic dose—a region where many tumours first appear. We do not recommend this technique except for localized tumours at the posterior pole in an only eye.

LIGHT COAGULATION

This can be used to treat tumours 1 to 4 mm. in diameter, provided that they are not close to the macula or temporal edge of the disc where the resulting damage to the nerve fibres

would produce a large scotoma. We have found this method particularly useful with small recurrences following Cobalt plaque or beam therapy, thereby avoiding further radiation and its associated complications.

CRYOTHERAPY

This, when performed through the conjunctiva, has also proved valuable for the destruction of small tumours and recurrences, particularly those in the peripheral retina which may be difficult to reach adequately with the light coagulator.

CHEMOTHERAPY

This has been used extensively in some centres (Hyman and others, 1968); oral cyclophosphamide was used here up till 1966, but was then discontinued with no apparent adverse influence on the subsequent results. There is some doubt whether a significant concentration of cytotoxic drugs in the eye is reached after oral administration and we await with interest the results of treatment with these substances by the arterial route.

ENUCLEATION

We consider each eye separately and try to save both if there is any chance of restoring or preserving useful vision. In bilateral cases we do not necessarily remove the most severely affected eye and, as with unilateral cases, the only indication for enucleation is involvement of the optic nerve which is either clinically obvious or must be inferred from the presence of opaque media, shrinkage, or enlargement of the globe. It should, however, be emphasized that the total retinal detachment often seen with anteriorly-placed tumours is amenable to whole-eye radiation with an anterior field and does not demand immediate enucleation. At a later stage, however, enucleation may be required if the tumour has failed to respond to treatment or if the eye has been damaged by intraocular haemorrhage, secondary glaucoma, or other complications of irradiation (Table V). We do not insert an implant into the socket after enucleation because this prevents adequate palpation of the orbit at follow-up examination.

Table V *Enucleation*

No. of cases seen	139
Primary enucleation	7
Enucleation after conservative treatment	
Active tumour	9
Radiation complication	13
Tumour active at death	2
	22
No. of cases in which eyes were saved	108

III. RESULTS

Before 1967 patients were not classified according to the scheme by Reese and Ellsworth (1963) (Table IV). Since then, however, all patients have been classified at the first examination, although we do not entirely agree with the prognostic significance hitherto attached to each of these classes. Tumours anterior to the equator, which may frequently be seen only by indirect ophthalmoscopy and scleral depression, do not invariably carry

a worse prognosis merely because of their peripheral position. Such small tumours (1–4 mm.) can easily be treated with cryotherapy, whilst moderately-sized tumours (4–8 mm.) can be dealt with by the application of a Cobalt plaque and even larger tumours anterior to the equator can ideally be treated with a Cobalt beam using the anterior field. With peripheral tumours, therefore, the prognosis depends more on the size of the lesion than on its exact site. It is probable that this difference of opinion stems from the different route of radiation used by the New York Group; we do not use a linear accelerator with a temporal field in an attempt to spare the lens because this approach must also spare the peripheral retina, where many tumours first arise, from the full therapeutic dose of radiation. Furthermore, we have found that the presence of vitreous seeding does not invariably carry a poor prognosis. In our view this situation also is unsuitable for the use of a temporal field for the reasons previously stated.

The success rate, using all forms of treatment in each class, is 100 per cent. in classes I and II, 86 per cent. in Class III, and 75 per cent. in Classes IV to VI. The follow-up in this series has been continued for 2 years or more in 66 per cent., and for over one year in 81 per cent. It is our impression that the majority of tumours which appear inert for 9 months or more are probably cured, but the exceptions emphasize the necessity for continuous supervision.

A total of 132 cases was treated; eleven of these were children who have subsequently died, leaving 121 patients who are at present alive and well (Table VI).

Table VI *Recurrence*

<i>Therapy</i>	<i>Cobalt beam</i>	<i>Focal</i>
No. of cases treated	58	63
No. of cases with recurrence	28 (46 per cent.)	27 (42·8 per cent.)
Time when recurrence treated (mths) Average Range	10 At once to 22	6 24–4
Treated by enucleation	9	5
Eyes saved	19	22
Recurrence after second treatment	6	4

RECURRENT TUMOUR

Recurrence continues to be a problem because a second dose of radiation may result in severe intraocular haemorrhage and glaucoma (Table VI). In this series we have a big recurrence rate after whole-eye radiation (46 per cent.), but this does not mean that the focal method of treatment is more effective as the whole-eye method is essential for the more advanced cases and larger tumours are inevitably more difficult to destroy. It is generally true that if treated tumour appears inert for 6 to 9 months it can be regarded as cured, but exceptions occur and a recurrence has been noted as long as 2 years after treatment; this again emphasizes the importance of maintaining close supervision of all patients even when they appear to be doing well.

Our policy for the treatment of recurrent tumour is to avoid further radiation if the lesion is small enough to be destroyed by light coagulation or cryotherapy. A Cobalt plaque can be applied to an eye which has already received Cobalt beam therapy, but two courses of whole-eye radiation are undesirable in view of the severe damage which follows

when a total dose of 6,000—7,000r is exceeded. Most of our children are too young at present to permit formal testing of the visual acuity, but in nineteen cases with treated and cured recurrent tumours followed for more than one year, ten have vision good enough to permit normal schooling, two have sufficient to get around and play, and the remaining seven have light perception only. It should be noted in the last group that poor vision has, in some cases, resulted from macular damage due to the disease. At present we can say that eyes receiving a second course of radiation will probably do worse visually than those in which a recurrence can be destroyed by light coagulation or cryotherapy; it will need a longer period of follow up and the evaluation of more cases before we are able to predict the chances of retaining good vision after repeated radiotherapy.

NEW PRIMARY TUMOURS

Retinoblastoma is a tumour of multi-focal origin in one or both eyes, and in view of this Reese (1963) advocated irradiation of the whole retina. Our series includes 63 cases treated initially by focal means—Cobalt plaque, light coagulation, or cryotherapy—in the area of the tumour alone. We have analysed these cases for the incidence of new primary tumours as opposed to recurrences at the site of the original lesion (Table VII).

Table VII *New primary tumours after treatment*

<i>Treatment</i>	<i>Focal</i>	<i>Whole-eye</i>
No. of cases treated	63	58
No. with new primary tumour	12 (20 per cent.)	5 (8 per cent.)
Average time of appearance (mths)	4	10

In fact, sixteen new primary tumours were found in the twelve cases of recurrence after focal treatment, and they were dealt with by light coagulation or cryotherapy (7), Cobalt plaque (8), and Cobalt beam (1).

Three of the new primary tumours appearing after whole-eye radiation responded to a small Cobalt plaque, but in the other two cases enucleation was felt to be the only safe course.

These figures confirm the multicentric origin of retinoblastoma in one or both eyes. It is our opinion, however, that the appearance of new tumours in only 20 per cent. of eyes treated originally by focal means is not high enough to justify irradiation of the entire retina with the object of destroying subclinical foci. In our experience many of these new primary tumours can be successfully destroyed by the application of a small (5 mm.) Cobalt plaque, by light coagulation, or by cryotherapy. With careful follow up these new tumours can usually be detected while they are still small and easily controlled by these focal methods.

Summary

- (1) The history of the various forms of treatment for retinoblastoma is briefly noted.
- (2) The presenting symptoms and signs in 139 cases of retinoblastoma are reviewed, together with the results of conservative treatment by radiotherapy, light coagulation, and cryotherapy. The indications for each method of treatment are discussed in the

light of these results and it would seem that these patients are best dealt with in centres where all these facilities are available.

(3) Although retinoblastoma is a malignant tumour, the prognosis for vision and for life with these methods of examination and treatment is more favourable than in former years.

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