RETICULO-ENDOTHELIAL TUMOURS OF THE ORBIT*†

BY

JOHN NOLAN

Edinburgh

RETICULO-ENDOTHELIAL tumours of the orbit have been regarded as uncommon (Duke-Elder, 1952) until recently, when a 10 to 20 per cent. incidence has been found in several series of orbital tumours (Reese, 1963; Mortada, 1964; Haye and Haut, 1966). Fifteen cases of histologically-proven reticulo-endothelial tumours of the orbit have been seen in Edinburgh in the last 13 years.

The terminology of the subject is an eponymous jungle and drastic pruning is necessary for its comprehension. Table I shows the basic family tree of the reticulo-endothelial system of cells. The lymph node is the family home, but the progeny are constantly leaving it to dwell in the bone-marrow, the blood, and as histiocytes in many tissues throughout the body. Uncontrolled multiplication of any of the cells shown in Table I constitutes a reticulo-endothelial tumour.

TABLE I
BASIC FAMILY TREE OF RETICULO-ENDOTHELIAL
CELL SERIES

Such tumours are named according to the apparent tissue of origin (Table II, opposite). Lymphosarcoma is a tumour of the lymphocytic line. If it involves the blood it is recognized as a lymphatic leukaemia. Reticulum cell sarcoma is a tumour of the reticular line. Hodgkin's disease involves both the lymphocytic and reticular lines. Macrolfollicular lymphoma is a lymphosarcoma in which the follicular architecture of the lymph node is preserved: it may be microscopically identical with the benign lymphoma which remains localized for years and does not show blood involvement. Ewing's tumour is thought to be a variant of the reticulum-cell sarcoma of bone marrow (Boyd, 1961). Multiple myeloma is a disseminated tumour of plasma cells. There is a localized form, the plasma cell myeloma, and also a benign form called a plasma cell granuloma. If the multiple myeloma spills over into the blood it is recognized as a plasma cell leukaemia. Neoplasms arising from the histiocytes are known as the non-lipid reticuloses to differentiate them from the lipid reticuloses, which are primary diseases of lipid metabolism. The non-lipid reticuloses ("histiocytosis X") fall into three main groups with indistinct boundaries:

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† Address for reprints: Department of Ophthalmology, Royal Infirmary, Edinburgh.

- (1) Eosinophilic granuloma, benign.
- (2) Hand-Schüller-Christian disease affects mainly pre-pubertal children and is eventually fatal.
- (3) Letterer-Siwe disease affects babies and is rapidly fatal.

TABLE II
BASIC CLASSIFICATION OF ORBITAL RETICULO-ENDOTHELIAL TUMOURS SEEN IN EDINBURGH

Lymphoid Tissue	→	{ Lymphosarcoma Reticulum-cell Sarcoma Hodgkin's Disease Macrofollicular Lymphoma
Blood	→	Lymphatic Leukaemia
Bone Marrow	→	Myelogenic Tumour { Ewing's Tumour Reticulum-cell Sarcoma Multiple Myeloma
Histiocytes	→	Non-Lipoid Reticuloses { Eosinophil Granuloma Schüller-Christian Disease Letterer-Siwe Disease

All these tumours can involve the orbit. They may appear to be localized or there may be systemic manifestations also. Because of their common origin, histological classification of a particular tumour may be extremely difficult.

Reticulo-endothelial tumours in the orbit are never encapsulated and are, therefore, virtually impossible to remove surgically without an exenteration. However, they are all highly radio-sensitive and radiotherapy is the treatment of choice. The dosage of radiation to be given in treating a particular case is calculated according to the maximum tolerable by the normal tissue and the presumed radio-sensitivity of the lesion as judged from the histological appearance. The germinal epithelium of the lens is the most radio-sensitive part of the eye and can be affected by as little as 600 r, but under proper precautions, an adult eye is reasonably safe with considerably higher dosages. In assessing the necessary dosage each case has to be judged on its merits, with reference to (a) the actual location of the tumour in the orbit, which in turn determines the protection it is possible to give to the eyeball, and (b) its histology.

Table III (overleaf) shows the diagnostic incidence in the fifteen cases studied.

Case Reports

Case 1, a 63-year-old man, presented with an entropion of the left lower lid due to a thickened tarsal plate. This was excised and histological examination showed it to be a lymphosarcoma. Almost immediately he developed a lymphosarcomatous swelling at the left inner canthus. Following radiotherapy the swelling at the inner canthus disappeared, but he subsequently developed submaxillary gland enlargement which proved resistant to treatment and he died 2 years later.

Case 2, a 75-year-old female, presented with a 12 months' history of steadily increasing left proptosis. She refused treatment for 6 months but her proptosis had then become so bad that she submitted to radiotherapy after a biopsy had shown the lesion to be lymphosarcoma. All other investigations were negative. She received a total surface dose of 2,000 roentgens of 250 kv. therapy in five applications, and the proptosis disappeared completely. 13 months later the patient died. There was no clinical evidence of a recurrence of tumour, but unfortunately no *post mortem* examination was carried out.

TABLE III
PARTICULARS OF FIFTEEN CASES SEEN IN EDINBURGH

Case No.	Age (yrs)	Sex	Diagnosis	Systemic Lesions	Died after	Still Alive after
1	63	M	Lymphosarcoma	Yes	2 yrs	—
2	75	F	Lymphosarcoma	No	13 mths	—
3	11	F	Reticulum Cell Sarcoma	Yes	—	11 yrs
4	58	M	Lymphosarcoma	Yes	7 yrs	—
5	57	F	Lymphosarcoma	Yes	—	5 yrs
6	1	F	Promyelocytic Leukaemia	Yes	3 mths	—
7	81	F	Reticulum Cell Sarcoma	Yes	5 mths	—
8	29	M	Lymphoma	No	—	4 yrs
9	68	F	? Lymphosarcoma/? Pseudotumour	No	—	4 yrs
10	61	F	Lymphosarcoma	Yes	17 mths	—
11	60	M	Lymphosarcoma	No	—	2.5 yrs
12	83	F	Plasma Cell Myeloma	No	—	2 yrs
13	61	M	Reticulum Cell Sarcoma	Yes	—	1.5 yrs
14	1.5	F	"Histiocytosis-X"	Yes	—	9 mths
15	1.5	M	"Histiocytosis-X"	No	—	6 mths

Case 3, an 11-year-old girl, presented with a blind left eye which was proptosed 6 mm. and showed optic atrophy. She had bilaterally enlarged cervical nodes. X ray showed an eroded lesser wing of the sphenoid and an enlarged optic foramen together with some reactive hyperplasia of bone. Craniotomy revealed a very large extra-dural tumour, spreading from the left temporal fossa to the orbit. It was partially removed and histological examination showed it to be a typical reticulum cell sarcoma. She was treated by 250 kv. radiation to the anterior half of the head and both sides of the neck, but with protection to the right eye. She received a total dosage of 2,500 roentgens over 4 weeks. The proptosis subsided completely during the first 3 weeks of treatment. Now, 11 years later, the patient is still alive and well with no evidence of recurrence. There was no recovery of sight in the left eye.

Case 4, a 58-year-old man, presented with a 2 months' history of an inflammatory swelling in the left upper lid. It failed to settle with antibiotic treatment and a biopsy showed a predominantly lymphoblastic lymphosarcoma. He was treated by Mv. irradiation, receiving 3,000 rads in 3 weeks, and the swelling gradually disappeared over the course of one month. He subsequently had conjunctivitis for 3 months but this then cleared up. 2 years later he developed cervical node enlargement and biopsy showed lymphosarcoma. After further radiotherapy he remained well for 4 years when he had a recurrence of the cervical swelling. This again cleared with radiation, but the following year he developed nodules in the axillae. These were resistant to radiation and he died 7 years after the initial presentation of the tumour in the orbit. Unfortunately no *post mortem* examination was carried out, as he died at home.

Case 5, a 57-year-old woman, noticed enlarged cervical nodes, which proved on biopsy to be lymphosarcomatous. The nodes disappeared after radiotherapy. 2 years later she developed a fleshy swelling of the right caruncle. This was excised and histological examination showed it to be a reticulum cell sarcoma. 2 years later, a palpable nodule 1 cm. across appeared at the superio-medial corner of the orbital rim. This was treated as a recurrence of reticulo-endothelial tumour and she was given 2,000 rads of 250 kv. irradiation over 5 days. The lesion disappeared before the completion of treatment and the patient is still alive and well with no evidence of recurrence.

Case 6, a 12-month-old baby girl, developed a right proptosis after a blow on the eye. This failed to regress and on examination under anaesthesia a hard mass was felt in the orbit. The eventual diagnosis, following bone-marrow examination, was promyelocytic leukaemia. The right orbit

was irradiated and systemic treatment started with 6-mercaptopurine. Within 4 days the proptosis had subsided and did not return. The baby died 3 months later from generalized leukaemia, but a *post mortem* examination showed "little evidence" of tumour in the right orbit (Crombie, 1967).

Case 7, an 81-year-old woman, presented with a 6 weeks' history of a swelling of the right upper lid. A firm swelling was palpable above the globe. All investigations gave normal results. Biopsy revealed a typical reticulum cell sarcoma. She was treated by Megavolt irradiation, a total dosage of 2,920 rads to the orbit. The proptosis rapidly disappeared and did not recur. There was slight residual restriction of depression of the eye and some conjunctival injection, but both eyes were otherwise normal. The patient died of pneumonia 5 months later and a *post mortem* examination showed generalized malignant deposits but unfortunately there was no report on the orbit.

Case 8, a 29-year-old man, presented with a 4 weeks' history of a congested, cystic swelling over the right medial rectus insertion. Biopsy showed this to be a lymphoma of doubtful malignancy. The lesion was treated by beta-radiation, 3,000 roentgens over 5 days. The swelling disappeared. All systemic investigations gave negative results and the patient has since had no further trouble.

Case 9, a 68-year-old woman, presented with a 6 months' history of a swelling of the nasal side of the left upper lid (Fig. 1). It was not attached to skin and appeared to extend forwards from deep in the orbit. The only suggestive results of systemic investigations were a relative lymphocytosis of 41 per cent. in a normal total white cell count, and an erythrocyte sedimentation rate of 43 mm./hr. It was impossible to decide on biopsy (Fig. 2) whether the lesion was a lymphosarcoma or a pseudotumour. It was decided to treat it as the former and the patient received 4,000 rads of 4 Megavolt radiation in a course of twenty treatments. The mass disappeared (Fig. 3).

FIG. 1.—Case 9, left eye before radiotherapy. Note biopsy scar on upper lid.

FIG. 2.—Case 9, biopsy specimen. $\times 280$

FIG. 3.—Case 9, 1 month after radiotherapy.

The pathologist's report reads: "This specimen of fibro-fatty tissue has been invaded by a highly cellular tumour. The cells grade from reticulo-endothelial to small, mature lymphoid in type, but are mostly of the latter species. Only rare mitotic figures are noted. The cells are supported by a reticular framework and supplied by numerous thin-walled vessels ranging to sinusoidal proportions.

Diagnosis—? lymphosarcoma, ? pseudotumour."

There was some post-radiation blepharitis but this gradually cleared up. The patient is still alive and well with no evidence of recurrence. The visual acuity in the irradiated eye is 6/6.

Case 10, a 61-year-old woman, presented with a right periorbital tumour of 3 months' duration. Biopsy showed an orbital granuloma (Fig. 4). No treatment was given but 7 months later she developed a swollen lower lid on the same side and also abdominal pain. Biopsy of the lower lid mass (Fig. 5) now showed a lipoid histiocytosis.

FIG. 4.—Case 10, biopsy of mass in right upper lid. $\times 66$.

The pathologist's report reads: "Section shows a fibrosing nodule with prominent vascularisation by capillaries. There is scattered perivascular lymphocytic infiltration and also chronic inflammatory infiltration between muscle fibres. There are also islands of fatty tissue.

Diagnosis—orbital granuloma."

FIG. 5.—Case 10, biopsy of mass in right lower lid. $\times 66$.

The pathologist's report reads: "The important feature is now the infiltration of the fibrous tissue and muscle fibres by cells with a densely staining nucleus and cytoplasm which is fairly granular. These cells appear to be histiocytes containing lipoid material. Their infiltration is fairly diffuse, although in some areas they are closely packed together. Mitotic activity is not seen. This section does not have the appearance of a lipoid granuloma, which is not uncommon in the orbit.

Diagnosis—lipoid histiocytosis."

This was treated by irradiation, 2,400 rads being given in a course of twelve treatments. The swelling gradually subsided and 3 months later there was no evidence of tumour present. 3 months later still, the patient had a laparotomy for abdominal pain, and a mass involving omentum, mesentery, stomach, and liver was found. Biopsy (Fig. 6, opposite) showed a probable reticulosis. She died shortly afterwards at home and no *post mortem* examination was carried out.

FIG. 6.—Case 10, biopsy of mass involving omentum, mesentery, stomach and liver. $\times 66$.

The pathologist's report reads: "... tissue which is focally but quite heavily infiltrated by groups of cells. Some of these are recognizable as lymphocytes, plasma cells, and probably reticulum cells, but there are also numbers of large, rather irregular cells, with pale, mainly spheroidal nuclei.

"... the haematoxylin and eosin sections would be quite compatible with a diagnosis of a reticulosis such as a reticulum cell sarcoma or lymphosarcoma, but it is not possible to come to an entirely conclusive diagnosis."

Case 11, a 60-year-old man, presented with a complaint of right epiphora and with an apparent mucocoele of the right lacrimal sac. At operation this was found to be a solid swelling extending into the orbit, and biopsy showed it to be a lymphosarcoma. This was treated by 3,160 rads of Megavolt radiation over 3 weeks. The swelling disappeared and 2½ years later the patient is still alive and well, even the epiphora having cleared up.

Case 12, an 83-year-old woman, presented with a 6 months' history of diplopia. She had a right proptosis, defective elevation of the right eye, ptosis, and a palpable soft mass below the superior orbital margin. X ray showed thickening of the supra-orbital margin and some erosion. The blood picture was normal. Biopsy revealed a plasma cell myeloma. 1,500 rads of Megavolt radiation were given over one week and the proptosis resolved completely. The visual acuity has remained unchanged at 6/18 and now, 2 years later, she is still alive and well with no evidence of recurrence.

Case 13, a 61-year-old man, presented with a similar history and findings to those in Case 12. Biopsy showed a reticulum cell sarcoma. Because of the histological appearance of the tumour and the amount by which it was extending forwards, the radiation involved deliberate risk to the eye. He was given 3,750 rads of Megavolt radiation over one month with the maximum dose at the surface, and the proptosis resolved completely. In addition to the ptosis the patient had corneal anaesthesia and he did not complain of any discomfort during his irradiation. It was only on a routine eye examination that a penetrating corneal ulcer was discovered and the vision in the eye is now perception of light only. He subsequently developed intestinal obstruction and a laparotomy revealed masses of lymphosarcoma in the abdominal cavity. Following abdominal irradiation, he regained 3 stones in weight and 1½ years later he is extremely fit with no further evidence of tumour.

Case 14, an 18-month-old baby girl, presented in November, 1966, with a right proptosis. X rays (Fig. 7, overleaf) showed a typical Hand-Schüller-Christian type of punched-out lesion in the upper and outer part of the right orbit. A lateral orbitotomy was done and the mass found and removed.

Biopsy (Fig. 8, overleaf) showed an histiocytosis-X picture which it was impossible to group accurately. The orbit was given 2,500 rads over 9 days with excellent results, the proptosis disappearing completely with no ocular sequelae. The family then emigrated. 5 months later the patient showed evidence of systemic lesions and deterioration in her general condition. She is now being treated with systemic radiotherapy and antibiotics.

FIG. 7.—Case 14, x ray shows a typical punched-out Hand-Schüller-Christian lesion in the right orbit.

FIG. 8.—Case 14, biopsy specimen from the right orbit. $\times 160$.

Diagnosis: Histiocytosis-X. The eosinophils show up on this photograph as lighter staining, more sharply demarcated cells. (Courtesy of Dr. A. F. J. Maloney).

Case 15, an 18-month-old boy, presented in February, 1967, with an apparent abscess of the left upper lid. The temperature and white cell count were normal, and the apparent abscess was not tender. Biopsy showed an eosinophil granuloma, although there were some doubtful features such as the presence of apparent reticulum cells, and it is just possible that this is a case of Letterer-Siwe disease. The lesion has ceased to progress since the biopsy and no further treatment has yet been given, but the patient is being kept under close observation.

Comment

The diagnosis of a reticulo-endothelial tumour is usually established by biopsy following the elimination of other possible causes of unilateral proptosis. The two other tests which are occasionally helpful are:

- (1) A blood examination, which may reveal the diagnosis as in Case 6, or point towards it as in Case 9;
- (2) An x-ray examination, which may be diagnostic as in Case 14, or reveal the site or extent of the lesion as in Cases 3 and 12.

However, negative results from these examinations do not rule out the diagnosis of reticulo-endothelial tumour. Thirteen of the cases in this series had completely normal blood pictures and twelve had normal x ray appearances. Histological classification of a reticulo-endothelial tumour is important prognostically but can be difficult, as in Cases 9, 14, and 15. Histological variation of a lesion from site to site is common, as in Cases 5, 10, and 13, in which the lesions were presumably of the same basic aetiology throughout the respective body. Case 10 also showed the progression from an apparently benign to a malignant appearance.

The results of irradiation in our cases have been most encouraging and have invariably resulted in complete and permanent recession of the proptosis. The prognosis appears to be very good in patients with lesions clinically confined to the orbit. Only one (Case 2) of the six deaths occurred in this type of patient and in this instance death may well have been due to some cause other than the tumour. These hopeful findings tend to confirm those of McGavie (1955), who found an average survival time for reticulum cell sarcoma treated by irradiation of 7 years, and for macrofollicular lymphoma of 13 years in twenty patients followed up for 16 years. He also noted the good prognosis in lesions confined to the orbit. The longest Edinburgh survivor to date is Case 3, who is of particular interest because some authorities believe that hormonal influences play a part in reticulo-endothelial disturbances. The onset of puberty shortly after she had completed her treatment may be responsible for her survival, since the prognosis appeared to be hopeless at the outset.

It is also agreeable to find that the excellent results of irradiation were accompanied by so little in the way of ocular radiation complications. With the exception of Case 13, the only complications were mild blepharitis and conjunctivitis which all cleared up within a few months. Cases 9 and 11 have some posterior subcapsular opacities in the lens, but it is impossible to say whether these are due to radiation. In Case 13 the combination of high surface dosage, corneal anaesthesia, and ptosis all contributed to the catastrophe which might have been averted by earlier recognition of the ulcer. It is recommended that a daily ophthalmological examination be carried out on such patients in the future.

Summary

Ten per cent. of primary orbital tumours are reticulo-endothelial in origin. Fifteen cases seen in Edinburgh in the last 13 years are described. The diagnosis may be indicated by blood and x ray examinations, but a biopsy is always a necessity. The classification of a reticulo-endothelial tumour is important from the prognostic viewpoint, but can be extremely difficult histologically: indeed, the microscopic appearance may differ from site to site throughout the body, or possibly in the same site from time to time through the increasing anaplasia in the tumour. All reticulo-endothelial tumours respond extremely well to radiation, and where the lesion is clinically confined to the orbit the prognosis appears to be very good. The side-effects with carefully controlled radiation are few and it is noteworthy that in every one of our cases the proptosis disappeared completely and permanently after radiation.

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