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INFLAMMATORY PSEUDOTUMOUR OF THE ORBIT*†

BY

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THE term "orbital pseudotumour" has been used to describe inflammatory lesions of the orbital tissues of unknown aetiology simulating a neoplasm of the orbit. The term is widely accepted by ophthalmologists, little known to neurosurgeons, and puzzling to pathologists. The term is inadequate and, to a certain extent, even misleading.

It is inadequate because it denotes a completely negative approach to this condition. These lesions present a definite clinical entity. The similarity to an orbital neoplasm is only superficial. The name is also misleading because the condition presents itself quite frequently as a true tumour, though this is an inflammatory tumefaction and not a neoplastic one.

An alternative name for this lesion is "nonspecific granuloma of the orbit". This term, which has found some favour among pathologists (Easton and Smith, 1961), is correct if the word granuloma is used in the ancient, macroscopic way, characterizing a tumefaction not caused by a neoplasm. However, the term granuloma is nowadays used in the microscopic sense to designate an inflammatory reaction characterized by the presence of epithelioid cells and giant cells, and such a histological picture, though occasionally present, is the exception, not the rule.

In the absence of any better name and because of the impossibility of using an aetiological designation, the widely-accepted term "inflammatory pseudotumour of the orbit" will probably remain in use.

Since the original description and classification of Birch-Hirschfeld (1905), the approach to this problem has been somewhat negative; he included cases of exophthalmos which disappeared spontaneously or on oral medical treatment, as well as cases in which at operation no tumour could be found at all. These latter cases could have been examples of endocrine exophthalmos, angiomatous malformations, or orbital cellulitis secondary to an inflammation of an adjacent structure. As we are evaluating only cases in which biopsy material is available, we are concerned only with the third group of the Birch-Hirschfeld classification which comprises patients with exophthalmos in whom a definite tumefaction can be found. These tumours are, however, inflammatory and not neoplastic.

Clinically, the condition is characterized by the sudden onset of exophthalmos, by the accompanying lid or conjunctival oedema, by decreased ocular motility, and occasionally by pain or other inflammatory signs. On palpation a hard mass is often found in the orbit.

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We have attempted to solve two problems connected with this orbital disease.

(1) We tried to establish the clinical course and prognosis of the condition. What are the chances of a recurrence or of an attack in the other eye? How many patients are completely cured and how many are left with residual symptoms?

(2) We classified our cases into histological types, trying to find a correlation between a specific histological type and a definite clinical course, symptomatology, or prognosis.

Material

We collected 140 biopsies from patients with orbital pseudotumour. No patient was included in whom a systemic disease (leukaemia, endocrine exophthalmos, etc.) present at the time of biopsy could account for the orbital lesion, but cases were included if systemic disease developed after the biopsy was taken and the original diagnosis was orbital pseudotumour.

The clinical history, if available, was reviewed and a follow-up evaluation was attempted. The biopsy specimen was examined and classified into nine types according to the histological appearance.

The results were then tabulated, put on punch cards, and computer-analysed. The programme was written in such a way that each of the nine histological groups was evaluated by clinical history, symptoms, signs, clinical course, and result.

The biopsies were obtained from the Armed Forces Institute of Pathology, the Department of Ophthalmology of the University of Iowa, the Wilmer Institute of the Johns Hopkins University, and the Bascom Palmer Eye Institute of the University of Miami.

Sex.—There were 69 males and 61 females. In ten cases the sex of the patient was not given.

Race.—The distribution approximately corresponds to that in the population of the United States (81 white, 20 Negro, and 1 oriental); in 38 cases the race of the patient was not known.

Age.—The condition occurs in every age group; it is perhaps more frequent in middle age, but the frequency is nearly as high in the seventh and eighth decades if the absolute figures are corrected for the age distribution of the general population.

It may occur in the first decade, but is comparatively rare in children.

Age Group	1–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80
No. of Cases	6	17	15	24	20	23	13	12

Findings

SIDE AFFECTED.—There seems to be a slight preponderance of the right orbit (63 cases) over the left (48 cases). Among the thirteen bilateral cases were five (which will be discussed later) in which the diagnosis had to be changed to "orbital involvement within a systemic disease". There thus remain eight patients in whom the diagnosis of "inflammatory orbital pseudotumour" was made in both orbits and who showed no subsequent systemic disease to account for the orbital inflammation. In three patients the lesion occurred simultaneously in both orbits, in three there was an interval of 1 to 3 years, and in two an interval of 4 to 6 years.

DURATION OF DISEASE.—Because it has usually been claimed that inflammatory pseudotumour of the orbit develops faster than most orbital neoplasms, the duration of disease

(the interval between the first definite symptom and the date of the biopsy) was recorded when known.

Duration of Disease	Under 1 mth	1–3 mths	4–6 mths	7–12 mths	1–5 yrs	More than 5 yrs
No. of Cases	15	31	22	16	17	3

SIGNS AND SYMPTOMS.—These are set out in Table I. The majority of our patients had proptosis, the second most frequent symptom being lid oedema. The most frequent objective sign was exophthalmos.

TABLE I
SIGNS AND SYMPTOMS

Observations		Present	Absent
Symptoms	Proptosis	65	49
	Swollen lids	48	65
	Pain	27	86
	Diplopia	21	29
	Loss of vision	19	94
Signs	Exophthalmos	85	25
	Ptosis	21	90
	Inflammation	50	60
Motility of Globe	Immobile	10	
	General Limitation	24	
	Horizontal Limitation	3	
	Vertical Limitation	13	

Loss of vision was due to a variety of factors; in some patients it was only temporary, being due to exposure keratitis, transient changes of refraction, papilloedema, etc., but in seven patients the loss of vision was permanent, being due to corneal ulcers, optic atrophy, or occlusion of one of the central retinal vessels. 21 eyes were lost because of enucleation or exenteration.

The motility of the globe was reduced in fifty cases.

HISTOLOGICAL CLASSIFICATION.—In Table II the cases are grouped into nine histological types modifying the classification of Forrest (1963).

TABLE II
CLASSIFICATION INTO NINE HISTOLOGICAL GROUPS

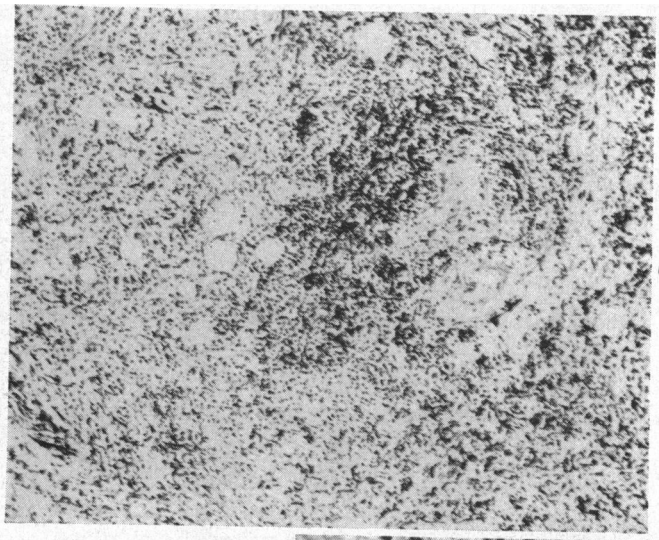
Group	Lymph Follicles	Diffuse Lymphocytic Filtration	Benign Lymphocytic Hyperplasia	Granuloma	Dense Collagen	Vasculitis	Myositis	Dacryo-adenitis	Miscel-laneous
No. of Cases	25 (1)*	46 (2)	18 (2)	11 (1)	13 (2)	2	6	9	9

* No. of bilateral cases in each group is added in parenthesis

Groups 1–3.—The first three groups (formation of lymph follicles, diffuse lymphocytic infiltration, and lymphoid hyperplasia) were the most common. These groups are closely interrelated, and are sometimes difficult to differentiate. The lymphocytic infiltration is often dense, sometimes sparse, and occasionally follicular. The appearance of true follicles with germinal centres is most remarkable in an area which normally contains no lymphoid tissue at all.

The lymphocytic infiltrates are composed of mature, fully-developed cells, occasionally with other inflammatory cells intermixed. The infiltrates are most often present in the connective and

adipose tissue. We have to remember, on the other hand, that these are the most frequently biopsied areas (Fig. 1).



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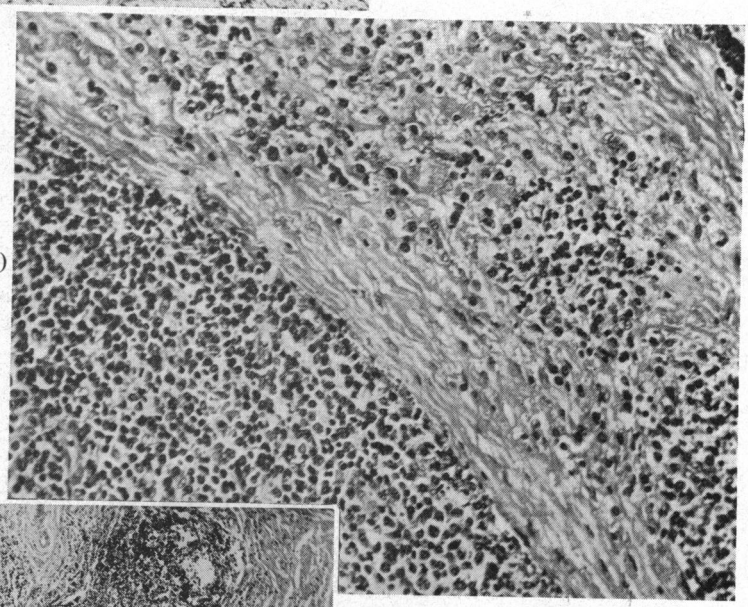

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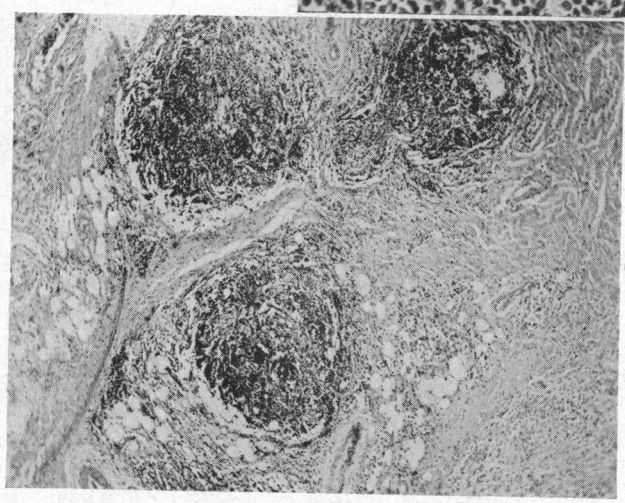


(*c*)

FIG. 1.—(*a*) Lymphocytic infiltration of orbital connective and adipose tissue. ×98.

(*b*) Lymphocytes invading and surrounding a tendon. ×196.

(*c*) Lymph follicles in orbital tissue. ×38.

Benign lymphocytic hyperplasia is frequently observed in specimens from orbital pseudotumours (Moro and Tosi, 1964), where we find a dense and diffuse cellular infiltration (Fig. 2).

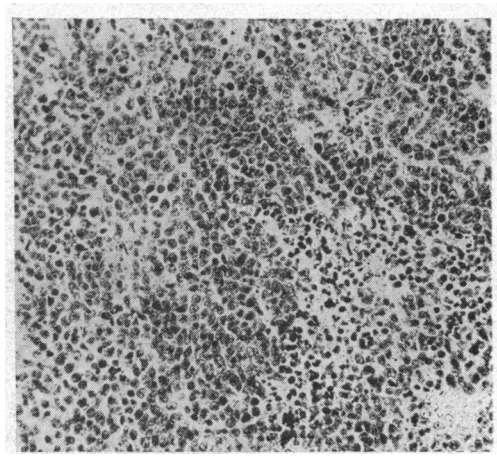


FIG. 2.—Benign lymphocytic hyperplasia. Lymphocytes, reticulum cells, and plasma cells replacing orbital tissues. ×150.

The infiltration is so massive that the underlying tissue, whether adipose or connective tissue, can no longer be appreciated; this feature differentiates the benign lymphocytic hyperplasia from lymphocytic and follicular infiltration, but there is no sharp demarcation. The cells are mainly lymphocytes and reticulum cells. Numerous other types are also present, such as polymorphonuclear leucocytes, eosinophilic leucocytes, plasma cells, and macrophages. This is definitely a reactive inflammatory lesion and not a neoplastic one. Lymph follicles appear often and the blood vessels are frequently affected. This lesion should not be confused with the malignant orbital lymphoma characterized by highly anaplastic and poorly differentiated cells. These two extremes are easy to differentiate histologically, but some examples of lymphocytic proliferation in the orbit are difficult to classify; they fall between the two groups described above, but in general behave like a benign lesion and are not the first symptom of a malignant neoplasm.

Group 4.—In eleven cases (8 per cent.) a true granulomatous lesion was found, usually in areas of adipose tissue (Fig. 3). It is reasonable to assume that these granulomata are caused by fat necrosis and the term "lipogranuloma" has been suggested by Coop (1961), but in our series the relative frequency of this histological picture does not warrant the use of this term for the entire group of orbital pseudotumours, though other authors have been impressed by the frequency of a true granulomatous process in this orbital condition (Jackson, 1958).

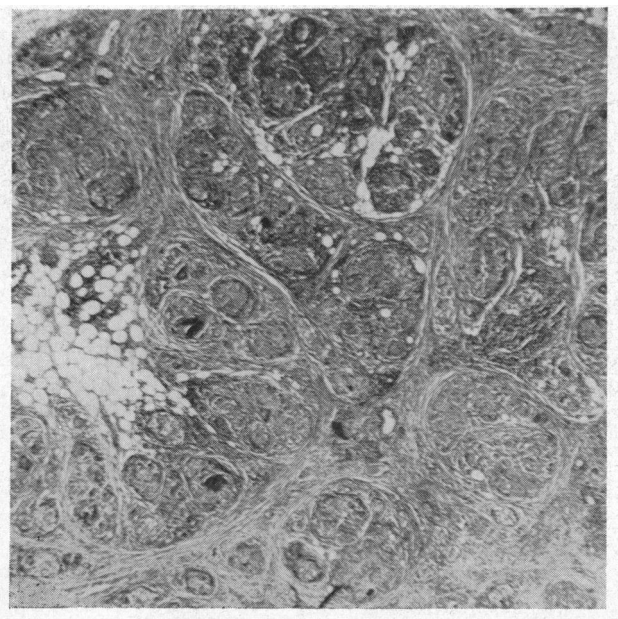
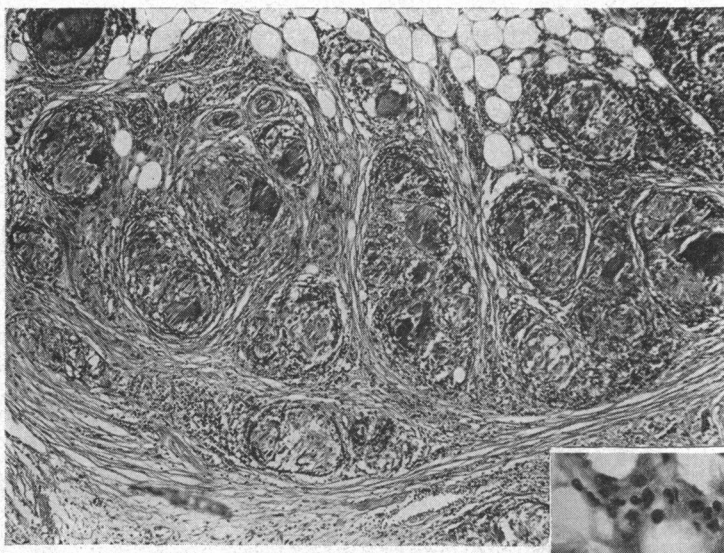


FIG. 3.—Granulomatous inflammation of the orbit

(*a*) Low-power view resembles sarcoidosis. ×25.



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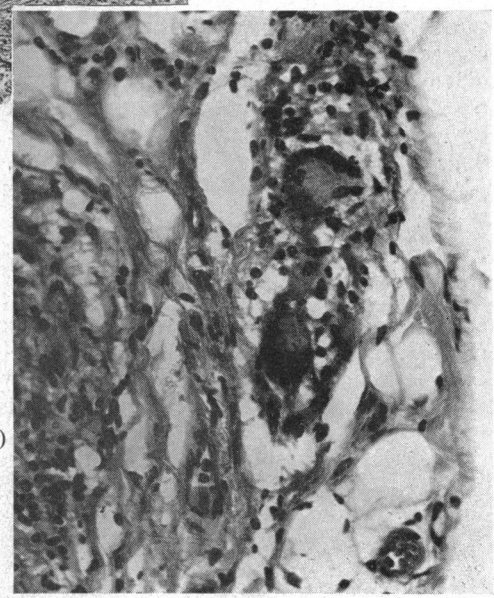

(*c*)

FIG. 3. (*b*) In higher magnification individual granulomata and giant cells can be recognized. ×64.

(*c*) Lipid granuloma in high magnification. Note foamy cytoplasm in giant cells. ×250.

In two cases the granulomatous reaction centred not around adipose tissue, but around striated muscle (Fig. 4, opposite). This site is unusual and has not hitherto been described. In some instances these granulomatous reactions in the muscle are accompanied by a marked eosinophilic infiltration. These cases may, at least in part, be due to an allergic phenomenon.

These granulomatous lesions sometimes resemble sarcoidosis. While it is unquestionably true that a sarcoid infiltrate may appear in the orbit, this occurs as part of a systemic Boeck's disease. It is quite likely that most reported cases of a so-called solitary, orbital sarcoidosis (Stein and Henderson, 1956) are instances of the granulomatous type of orbital pseudotumour. Most cases of true orbital sarcoidosis occur in the area of the lacrimal gland, and in these patients a systemic involvement can usually be diagnosed.

Group 5.—Thirteen cases were characterized by the formation of dense, collagenous, connective tissue frequently containing hyaline (Fig. 5, opposite). On clinical examination these specimens are quite hard, sometimes nearly bony-hard, and tend to become closely adherent to neighbouring structures such as the periosteum of the orbital wall, the sheaths of the optic nerve, the sclera, or the extra-ocular muscles (Fig. 6, overleaf). The suggestion that this picture is the end-stage of the preceding three, more acute, lesions is a likely explanation, though direct proof is lacking.

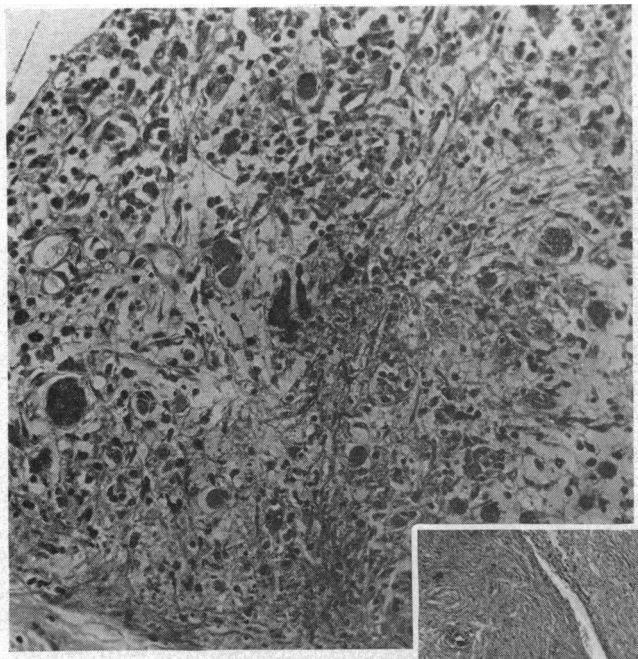

FIG. 4.—Granulomatous myositis. ×225.

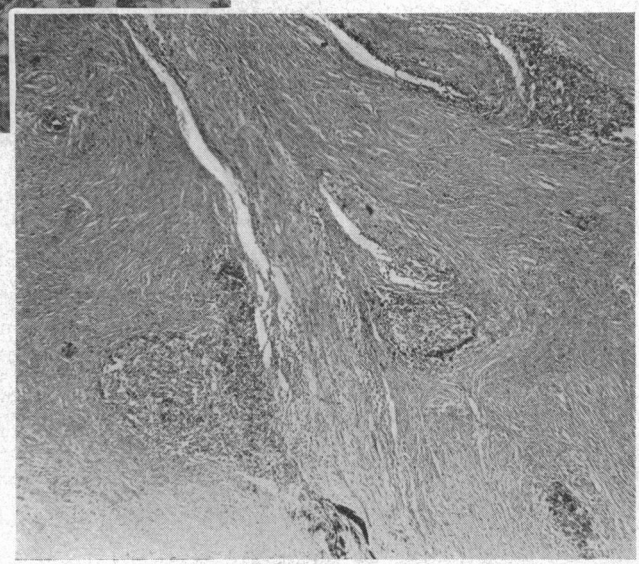

FIG. 5.—Foci of lymphocytes embedded in dense hyalinized connective tissue. ×64.

Group 6.—Inflammation predominantly affecting the orbital vessels was seen in only two cases (Fig. 7, overleaf).

Group 7.—In the past attempts have been made to distinguish chronic orbital myositis (6 cases) from other orbital pseudotumours (François, Rabaey, and Evans, 1956). It is true that occasionally the extra-ocular muscles are predominantly affected, but we always find some spilling over of the inflammatory process into the adipose and connective tissue of the surrounding structures. It is also quite possible that infiltrations of the muscle would be found more often if the muscle were biopsied instead of less differentiated orbital tissues. The cellular infiltration of the muscles resembles that occurring in other areas of the orbit (Fig. 8, overleaf). In exenteration specimens, in which the pseudotumour was radically extirpated, we found the extra-ocular muscles invariably affected if the main lesion lay in the connective or the adipose tissue.

The histological picture of this chronic myositis resembles that of the muscular changes in endocrine exophthalmos, but the latter usually gives rise to more oedema and swelling of the extra-ocular muscles. In endocrine myopathy there is also a large accumulation of acid mucopolysaccharides in these muscles and the inflammatory reaction is confined to them.

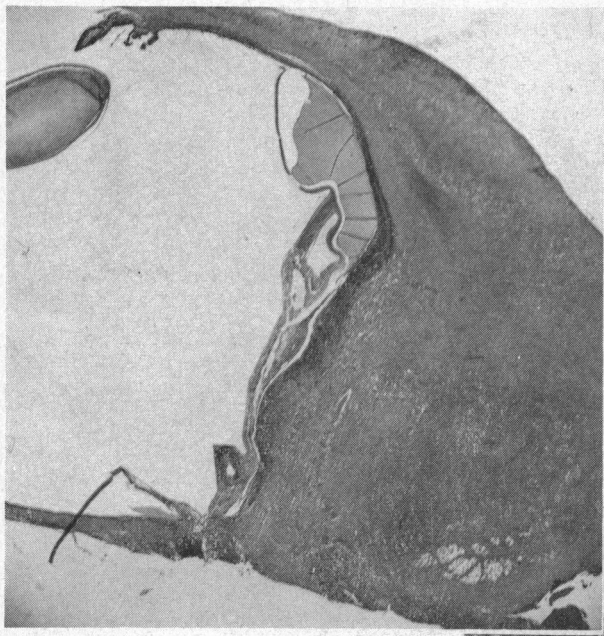

FIG. 6.—Dense hyalinized connective tissue in the orbit involving sclera and optic nerve (down and right) There is choroiditis and retinal detachment. ×4.

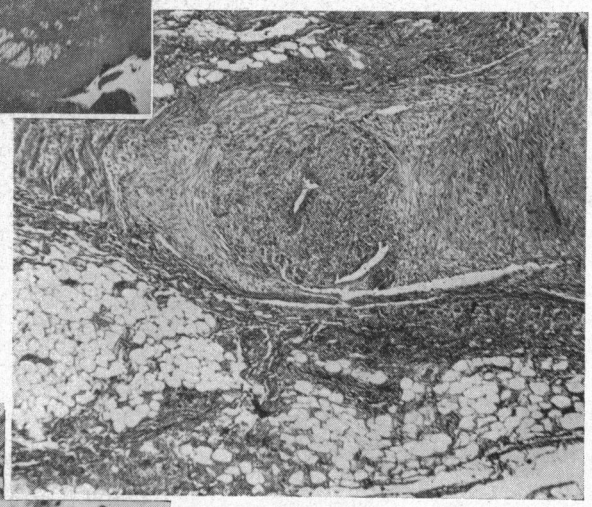

FIG. 7.—Thrombosed vein in inflamed orbital tissue. ×40.

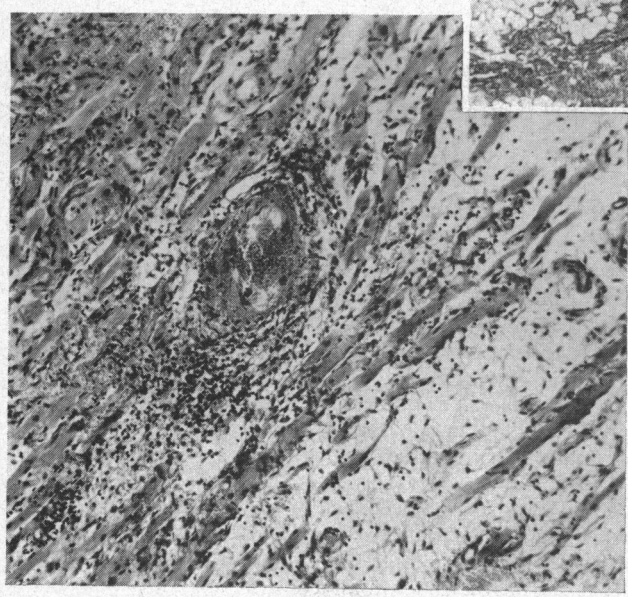

FIG. 8.—Lymphocytic infiltration and severe oedema of an extra-ocular muscle in a case of inflammatory pseudotumour of the orbit. ×60.

Group 8.—The lacrimal gland was quite often affected, but in the nine cases listed dacryoadenitis predominated. This entails not only a severe lymphocytic infiltration of the gland, but also extensive destruction and atrophy of the acini and ducts with secondary replacement fibrosis (Fig. 9).

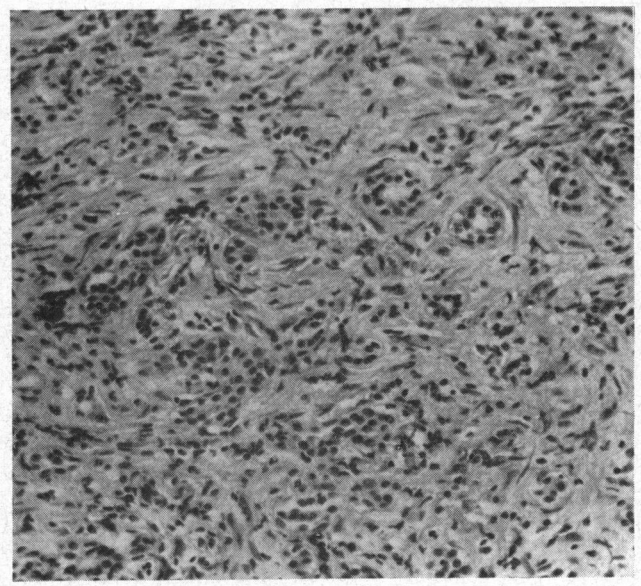

FIG. 9.—Chronic dacryoadenitis with lymphocytic infiltration and destruction of glandular elements. Only a few acini are visible in the centre of the photomicrograph. ×195.

Group 9.—In the miscellaneous group we found instances of plasma-cellular infiltration, with necrosis or polymorphonuclear leucocytes or other unusual properties which made it impossible to classify them elsewhere.

The bilateral cases (shown in brackets in Table II) were found to be evenly distributed, being absent only in the smallest groups.

FOLLOW-UP (Table III).—Ninety cases were followed for from 1 to more than 10 years.

In general, the prognosis of this condition is excellent, and most of the patients will remain cured or improved. All the deaths were due to completely unrelated conditions.

TABLE III
FOLLOW-UP OF NINETY CASES

No. of Years		1–2	2–3	3–5	5–10	More than 10
Result	Healed	4	19	12	4	5
	Improved	0	13	9	5	1
	Unchanged or Worse	1	2	2	0	0
Died		4	4	1	1	3

In Table IV (overleaf) the final results in 72 patients are arranged according to the histological classification. No clear-cut trend is apparent and the ultimate result does not appear to depend upon the histological features of the lesion.

RECURRENCE.—In only six patients did the history or follow-up study reveal a recurrence of the lesion on the same side. In five of them this occurred within 6 months and may have been due to fluctuation of the original condition. In one patient the condition recurred 2 years after the original onset.

TABLE IV

RESULTS IN 72 CASES RELATED TO HISTOLOGICAL FINDINGS

Histological Findings	Healed	Improved	Unchanged	Total
Lymph follicles	9	5	0	14
Diffuse lymphocytic infiltration	11	9	2	22
Benign lymphocytic hyperplasia	6	3	1	10
Granuloma	3	3	0	6
Dense collagen	6	2	0	8
Vasculitis	0	0	0	0
Myositis	2	1	0	3
Dacryoadenitis	1	2	1	4
Miscellaneous	2	3	0	5
Total	40	28	4	72

INVOLVEMENT OF THE EYE.—In about 5 per cent. of cases the eye was severely involved and permanent visual loss or damage will result, as observed by Schulte (1955). It has been claimed (Badtke, 1954) that the reverse process, namely an orbital pseudotumour secondary to an intra-ocular inflammation, may also occur.

In four cases the eye was enucleated and in seventeen the orbit was exenterated; most of these were operated on many years ago (some of them by neurosurgeons) when this diagnosis was not so well appreciated. Occasionally the coats of the eye become involved in the inflammatory process, and severe uveitis, retinal detachment, or optic neuritis result (Fig. 10).

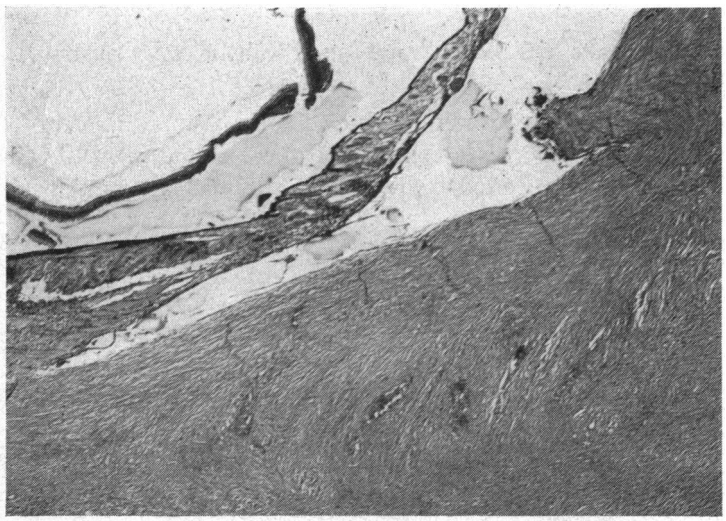

FIG. 10.—The eye is encased in a dense inflammatory tissue. The sclera is indistinguishable. There is severe choroiditis with retinal detachment. ×10·5.

SYSTEMIC DISEASE.—In twelve patients (five affected bilaterally) a definite systemic disease* became apparent soon after the orbital biopsy was obtained. A retrospective review of the orbital biopsy could not reveal the true nature of the condition, though the course of the disease was known to the examiner. Five bilateral cases (out of the thirteen included in the study) went on to develop a systemic disease.

* Wegener's granulomatosis (6), lethal midline granuloma (1), lymphoma (2), Hodgkin's disease (1), leukaemia (1), endocrine disorder (1).

Differential Diagnosis

"Inflammatory orbital pseudotumour" has to be differentiated from orbital inflammations in which the cause is known or detectable:

(1) A chronic inflammatory reaction may occur in the orbit after an injury in which the orbital walls have been opened (Fig. 11), especially if a foreign body remains in the orbit. If the history is vague and if the foreign body is small and cannot be found, a diagnosis of orbital pseudotumour is likely to be made. A detailed history is, therefore, indispensable.

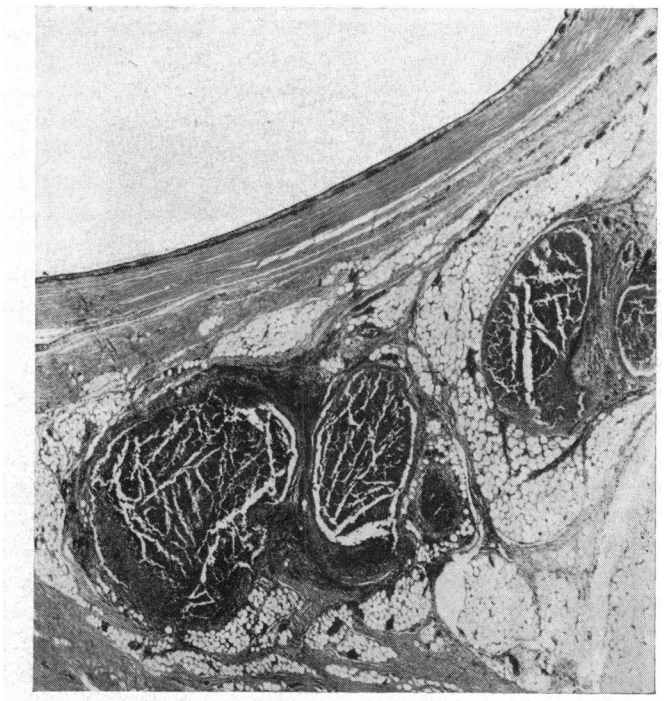

FIG. 11.—Purulent orbital cellulitis due to an exogenous infection. ×12.

(2) The orbit may be the site of a specific infection, though such instances are probably rare.

Sarcoidosis of the lacrimal gland must be borne in mind when true granulomatous lesions are discussed. We have never seen a patient with a localized sarcoid-like orbital granuloma go on to develop systemic sarcoidosis.

Tuberculosis and syphilis of the orbit are nowadays museum pieces. A true tuberculous inflammation used to be observed in the lacrimal gland and is one of the causes of the Mikulicz syndrome. Another type of tuberculous infection arose from the bone and periosteum. A gumma of the orbit has occasionally been observed.

An occasional fungal or parasitic infection may occur in the orbit. Most of these are rare in the U.S.A. Somewhat more common are hydatid cysts of *Echinococcus* infestation, and mucomycosis of the orbit and the optic nerve in cases of severe acidosis, especially in diabetic coma, is characteristic.

(3) An orbital dermoid cyst will occasionally rupture spontaneously or through trauma, and the fatty contents may produce a granulomatous reaction in its immediate neighbourhood (Fig. 12, overleaf). More peripherally a non-granulomatous chronic inflammatory reaction may give a misleading impression when the biopsy does not include the cyst wall.

(4) An orbital haemangioma may undergo spontaneous regression through occlusion of the blood vessels and blood spaces; this may lead to an inflammatory reaction around the occluded vessels

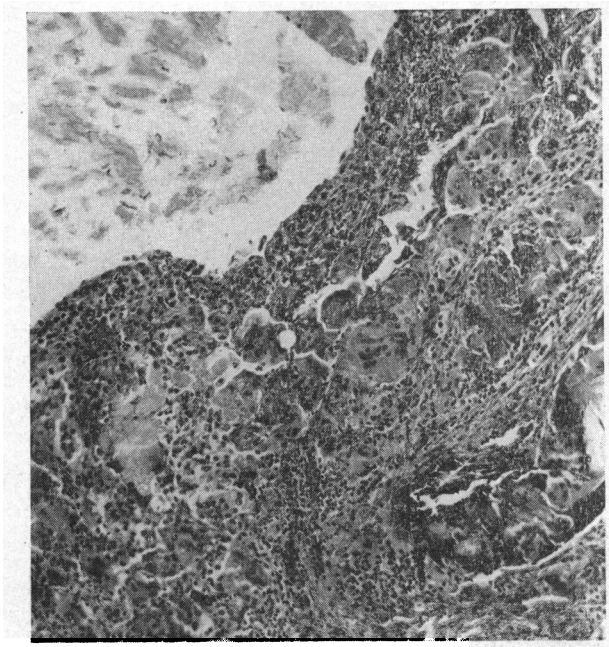

FIG. 12.—Granulomatous reaction around broken wall of an orbital dermoid. The fatty contents of cyst are seen in right upper corner. ×98.

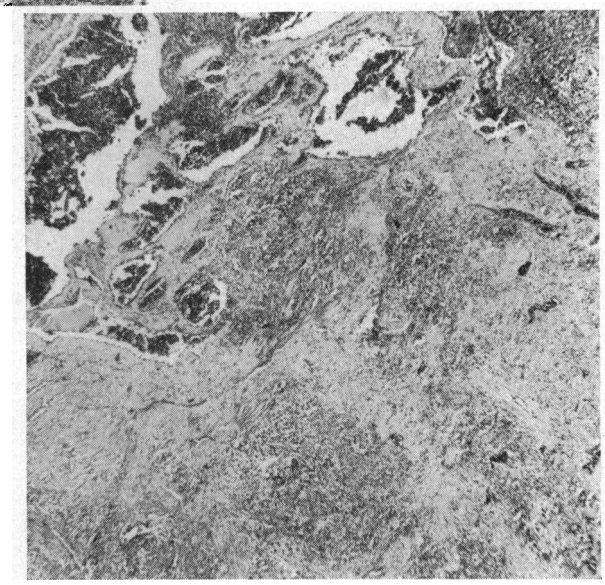

FIG. 13.—Sclerosing orbital haemangioma. ×25·5.

and finally a replacement fibrosis (Fig. 13). Biopsy of such a lesion may be misleading especially if the blood vessels and spaces have all but disappeared (Niessen, 1956). The age at onset should assist in differential diagnosis, as most of these haemangiomata are congenital malformations and become manifest early in life. They will develop slowly and enlarge the bony orbit and a biopsy will usually be necessary only after many years of minor difficulties. If a biopsy is done early in life the true nature of the condition will be revealed.

(5) Chronic inflammatory reaction around a neoplasm may be misleading if an inadequate biopsy is taken. This seems to be especially true for malignant tumours of the lacrimal gland; Reese (1963) has justly emphasized that a deep wedge-shaped biopsy is necessary to recognize the true nature of the neoplasm.

(6) The orbital inflammation may be part of a systemic inflammatory process, as in Wegener's granulomatosis (Foulds and Wear, 1960; Straatsmaa, 1957), (Fig. 14). Similar lesions can also be observed in such conditions as periarteritis nodosa and panniculitis.

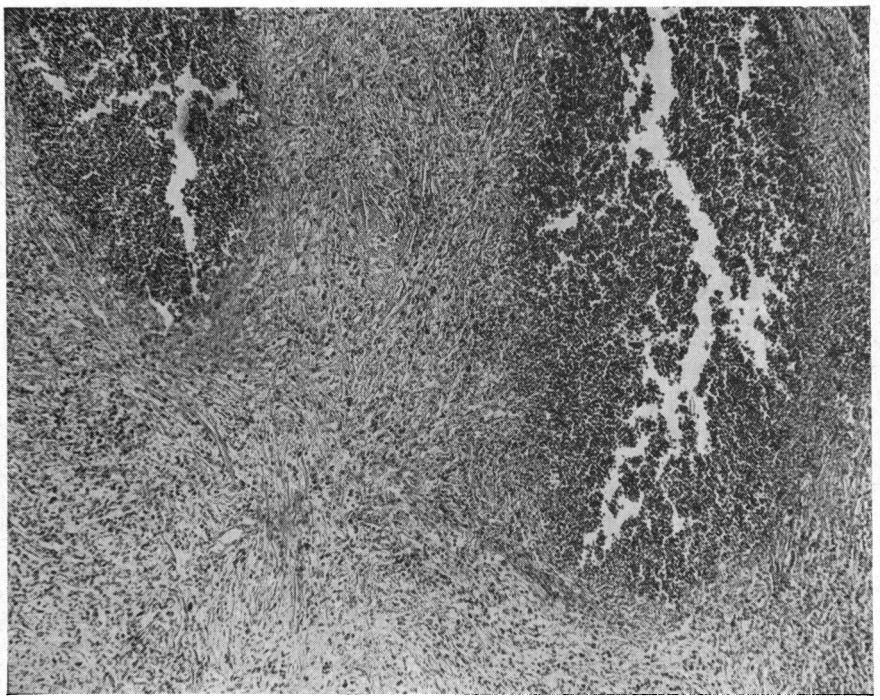

FIG. 14.—Acute orbital cellulitis with abscess formation (right) in a patient with Wegener's granulomatosis. ×66.

Aetiology

The cause of the condition remains unknown. Only three of our patients had a paranasal sinusitis, and none showed evidence that the two conditions were related. Chronic inflammation of the orbit may sometimes be due to sinusitis, but this produces acute orbital cellulitis (Herrmann, 1958; Szepessy, 1951; Williamson-Noble, 1954).

Pseudotumours of the orbit have been observed with diffuse vascular diseases (Harcourt, 1964), and especially with periarteritis nodosa (van Wien and Merz, 1963; Walton, 1959).

Cases of Wegener's granulomatosis form a special group. We have included only the six patients in whom the orbital pseudotumour preceded the systemic manifestations. A retrospective review of the biopsy specimens showed that five out of six belonged to our "miscellaneous" group and were characterized by the presence of polymorphonuclear leucocytes.

The close histological resemblance between endocrine exophthalmos and myositic orbital pseudotumour has already been mentioned. Bilateral cases especially should be investigated for an endocrine dysfunction. The clinical and histological picture of orbital pseudotumour may not only be simulated by hyperthyroidism, but may also occur in hypothyroidism (Hogan and Dickson, 1950) and with thyroiditis (Andersen, Seedorff, and Halberg, 1963; Arnott and Greaves, 1965). The clinical picture may be mimicked by thyroid myo-

pathy and although all tests for a thyroid disorder give normal results in the initial stages the patient will later develop definite evidence of thyroid dysfunction.

Only occasionally will an orbital tumour be the first sign of systemic disease. The diagnosis may not be apparent from the first biopsy specimen, but the subsequent systemic disease may be lethal.

Discussion

There is no clear-cut difference among our nine histological types as regards clinical history, signs and symptoms, incidence of bilateral cases, or prognosis. We have, therefore, to assume that we are dealing with a single entity, the histological appearance of which may vary with the stage of the disease and the nature of the tissue excised.

Moro (1966) suggested that there are two main types of orbital pseudotumour: one in which the granulomatous reaction dominates the histological picture and one in which there is a benign lymphocytic reaction. Chronic orbital myositis would then be excluded from the pseudotumour group.

Summary

We have studied 140 cases of inflammatory pseudotumour of the orbit in an attempt to elucidate its clinical course and prognosis and, if possible, to establish subtypes according to a histological classification.

The lesion is of sudden onset, and presents with exophthalmos, swelling of the lids, conjunctival oedema, and inflammation. It often produces a decrease in ocular motility. Recurrences are extremely rare.

The condition is only exceptionally bilateral. If it occurs in both orbits (simultaneously or consecutively) a systemic disease (lymphoma, endocrine disorder, etc.) may appear later. The prognosis is good.

The histological picture varies between lymphocytic developments, true granulomatous infiltration, dense hyalinization, and the involvement of a particular orbital structure. No difference can be established between the histological groups as far as clinical course, symptomatology, or prognosis is concerned.

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