THE EYES IN SARCOIDOSIS*

BY

R. PITTS CRICK, CLIFFORD HOYLE, AND HUGH SMELLIE

From the Eye Department and Medical Unit, King's College Hospital, London

The importance of ocular lesions in sarcoidosis was not recognized until recently, although they have been known for much longer (Bloch, 1914; Mylius and Schürmann, 1929; Schaumann, 1934). Most of the early literature was preoccupied with Heerfordt's syndrome and Bruins Slot (1936) eventually identified this as a form of sarcoidosis. Osterberg (1939) made the first attempt to study how sarcoidosis affects the eyes, but he found only 27 reports of it among 500 patients in the European literature to that time. Soon afterwards, however, Levitt (1941) collected 100 patients from recent literature, of whom 43 had had their eyes affected; 28 had uveitis and ten were blind. In the following years Woods and Guyton (1944) described uveitis in fifteen of 29 patients, Gifford and Krause (1949) reported ocular lesions in ten others, and Ricker and Clark (1949) and Longcope and Freiman (1952) recorded briefly the ocular findings in their series of patients with sarcoidosis, concluding that the eyes were more often affected in the Negro. It was evident from these American accounts that ocular sarcoidosis was an important part of the disease.

Within the last decade treatment with corticosteroids has been shown to cause regression of the lesions of sarcoidosis, especially those of the eyes and lungs. The advent of effective treatment drew attention to the need for further study of the eyes so that early lesions may be recognized, their significance assessed, and indications for treatment defined. Crick gave a precursory review of our patients in 1955 and Ainslie and James (1956) and James (1959) reported the ocular findings in their series of 100 and 200 patients respectively. The present paper is based on a detailed study of the eyes of 185 patients with sarcoidosis by the same group of observers using a standard examination technique.

Patients Investigated and Methods

The series includes all patients found to have ocular sarcoidosis at the ophthalmic clinics of one of us in the 5 years 1954 to 1958, those referred by colleagues during that time, and a few first seen many years ago. Most patients, however, attended

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a medical clinic initially, between 1954 and 1958, for some other feature due to sarcoidosis. With few exceptions the ophthalmic examinations were made to standard criteria so that subjective errors were reduced as far as possible. Inspection with the slit-lamp microscope was carried out at each visit. Rose bengal and Schirmer’s tests for lacrimal secretion were frequently made: Schirmer’s test on a selected group of thirty patients, and both tests on control groups of subjects. The techniques were as follows:

A drop of 1 per cent. rose bengal stain was instilled into each conjunctival sac and the conjunctiva and cornea were examined with the slit-lamp microscope for any staining of degenerate epithelial cells due to kerato-conjunctivitis sicca. Excess tears and stain were absorbed by cotton wool. Schirmer’s test was done after rose bengal staining by the usual technique. A strip of Whatman No. 41 filter paper, 5 mm. in width, was bent so that it hung over the lower lid and the opening of the punctum of the lower canalculus. The length of the strip wetted by the pink tears was measured after five minutes.

The degree of rose bengal staining was classified in four groups: nil, slight, moderate, and severe; only moderate and severe staining were regarded as significant.

When conjunctival follicles could be identified by the slit-lamp microscope, a biopsy was taken as described by Crick, Hoyle, and Mather (1955):

Three drops of 4 per cent. cocaine solution were instilled into the conjunctival sac at 2-minute intervals. A small fold of fornix conjunctiva about 2 mm. long containing follicles was grasped with forceps and snapped off with one cut of the scissors. Usually this was painless, though occasionally a momentary prick was felt. A suture was unnecessary as there was little haemorrhage, at the most slight capillary oozing. Chloramphenicol ointment 1 per cent. was applied, but a dressing was not required and the site of the biopsy healed completely in a few days. Neither infection nor symblepharon occurred in our series of biopsies. The specimen was fixed in formol saline and fifty serial sections were cut and examined.

Biopsies of a lacrimal gland were also taken on three occasions.

All patients were investigated for sarcoidosis as recorded in previous papers (Hoyle, Dawson, and Mather, 1954, 1955; Mather, Dawson and Hoyle, 1955; Crick, Hoyle, and Mather, 1955; Smellie and Hoyle, 1957, 1960). The age and sex distribution and tuberculin sensitivity of these patients conformed to the usual pattern. All were Europeans; there were no Negroes. Most of them came from urban areas and none had been exposed to occupational hazard likely to confuse diagnosis. Whenever possible diagnosis was based upon the presence of epithelioid cell follicles in biopsied tissue taken usually from the liver, skin, lymph nodes, or conjunctiva. Histological support was found in 115 of the 185 patients. In the remaining seventy the diagnosis rested upon the presence of characteristic radiographic changes in the lungs, a low tuberculin sensitivity, and hypergamma-globulinaemia; a negative occupational history; the absence of M. tuberculosis from cultures of biopsy material, sputum, gastric washings, and urine; and also upon their failure to show a rapid or severe loss of health. These patients are included for comparison because the diagnosis was not in doubt and because their exclusion would have biased some of our evidence since they are probably a group with less florid sarcoidosis than those with lesions readily accessible to biopsy.
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After investigation most patients have attended a special clinic regularly. With few exceptions, including three who died from progressive pulmonary sarcoidosis after a course of many years, they have all been observed to date. Treatment with topical corticosteroids consisted of cortisone, hydrocortisone, or prednisolone drops or ointment instilled from twice to four times daily. Subconjunctival injections were given occasionally. Systemic treatment was given orally, as cortisone, 100 to 150 mg., or prednisone, 20 to 40 mg., daily in divided doses. When the maximum effect was reached the daily amount was reduced gradually by steps of 25 mg. for cortisone and 5 mg. for prednisone. Usually we allowed an interval of several weeks between each successive reduction in dosage, aiming eventually at a minimal effective maintenance dose if treatment could not be discontinued without relapse. Neither troublesome side-effects nor serious withdrawal symptoms were seen. The few patients with hypercalcaemia took a low calcium diet containing not more than 200 mg. daily. The effects of treatment were assessed weekly or more often when necessary, until progress was satisfactory.

Results

Incidence of Ocular Sarcoidosis

Surveying the records of 300 patients with sarcoidosis, Ricker and Clark (1949) found the eyes involved in 9 per cent. although no special search was made. Longcope and Freiman (1952) reported 48 per cent. of their 124 patients with the eyes affected and in Great Britain Crick (1955) found 33 per cent., Ainslie and James (1956) 28 per cent., and James (1959) 25 per cent. In the present series (Table I), where search was very thorough, the incidence was distinctly higher among the 115 patients with a positive biopsy, the eyes being affected in 73 (63 per cent.). Among the 49 patients with a negative biopsy, however, the incidence fell to eighteen (37 per cent.), a figure probably reflecting a less severe and widespread form of the disease. Taking the series as a whole, 93 of 185 patients (50 per cent.) had some form of ocular disorder as part of their sarcoidosis. This high proportion we attribute to the recognition of kerato-conjunctivitis sicca and of uveitis by routine examination with the slit-lamp microscope. Eye symptoms were the presenting feature in 29 of the 185 (16 per cent.).

<table>
<thead>
<tr>
<th>Clinical Sarcoidosis</th>
<th>Number of Patients</th>
<th>Patients with Ocular Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Biopsy positive</td>
<td>115</td>
<td>73</td>
</tr>
<tr>
<td>Biopsy negative</td>
<td>49</td>
<td>18</td>
</tr>
<tr>
<td>Not biopsed</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>185</td>
<td>93</td>
</tr>
</tbody>
</table>
Clinical Forms of Ocular Sarcoidosis

Table II (overleaf) shows the incidence of the various forms of ocular sarcoidosis and its associated lesions.

Uveitis

This is the chief ocular lesion in sarcoidosis, being present in 46 of the 115 patients (40 per cent.) in whom the diagnosis was confirmed by biopsy; and in fifteen of the seventy (21 per cent.) without histological confirmation, an overall incidence of 33 per cent. Conversely, the incidence of sarcoidosis in 653 patients with uveitis investigated recently at the Institute of Ophthalmology was only 2.1 per cent. (Perkins, 1958).

Anterior uveitis was found in 42 of the 46 patients with uveitis in whom sarcoidosis was confirmed histologically (Table II), and in 26 of them there was posterior uveitis as well. The condition may be acute or subacute and presents with the usual aching, photophobia, and watering of the affected eye, although these symptoms are less severe than would be expected from the degree of inflammation observed. Keratic precipitates are characteristically semitranslucent, often slightly pigmented and disposed irregularly in assorted sizes (Fig. 1, opposite). The inflammatory exudate may be considerable and may then cause acute secondary glaucoma. Occasionally even this condition may be present with surprisingly mild symptoms. Nodules of sarcoid tissue form on the iris in about a quarter of these patients (Fig. 2 and Table II overleaf). Though suggestive of sarcoidosis, nodules are also not infrequent in non-specific uveitis.

When resolution is delayed, posterior synechiae (Fig. 1) and fibrous scarring of nodules in the angle may lead to chronic secondary glaucoma which may require operation (Fig. 3). In the absence of intensive treatment, severe uveitis can lead to rapid disorganization of the eye (Fig. 4). Even lesser degrees, particularly when posterior synechiae have formed, predispose to cataract formation (Fig. 3).

Fig. 1.—Case A, male, aged 29, severe untreated sarcoid uveitis (Group 1) of 2 years' duration. Numerous keratic precipitates, moderate rose bengal staining, and posterior synechiae. In addition he had generalized lymphadenopathy, including the hilar nodes, and diffuse pulmonary infiltration. A lymph node biopsy showed epithelioid cell follicles.

Fig. 3.—Case C, female, aged 56, late results of sarcoid uveitis. Broad peripheral anterior synechiae. Tridectomy for secondary glaucoma. A secondary cataract has formed. 5 years before she had had bilateral hilar lymph node enlargement, pulmonary infiltration, and active anterior uveitis.

Fig. 4.—Case D, male, aged 21, late severe untreated sarcoid uveitis. This patient lost his sight within a month of the onset of symptoms. He had massively enlarged hilar lymph nodes and some pulmonary infiltration at this time, with epithelioid cell follicles in a liver biopsy and a negative Mantoux reaction at 1/100.
FIG. 1.

FIG. 3.

FIG. 4.

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Fig. 2.—Case B, female, aged 29, recent sarcoid uveitis with large iris nodules and keratic precipitates. She also had enlarged hilar lymph nodes and diffuse pulmonary infiltration, with a negative Mantoux reaction at 1/100 although one of six cultures of gastric washings showed a growth of M. tuberculosis.

TABLE II

CLINICAL FORMS OF OCULAR AND ASSOCIATED LESIONS IN 185 PATIENTS WITH SARCOIDOSIS

<table>
<thead>
<tr>
<th>Ocular Lesions</th>
<th>In 73 of 115 Patients with Biopsy Confirmation</th>
<th>In 20 of 70 Patients without Biopsy Confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uveitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>46 (40 per cent.)</td>
<td>15 (21 per cent.)</td>
</tr>
<tr>
<td>Anterior uveitis alone</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Anterior and posterior uveitis</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>Posterior uveitis alone</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Nodular uveitis</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Glaucoma secondary to uveitis</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Secondary cataract</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Perivasculitis Retinae</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Conjunctival Follicles, i.e. with sarcoid histology in forty tested (9 inaccessible; 24 had no follicles)</strong></td>
<td>20 (31 per cent. of 64 accessible)</td>
<td></td>
</tr>
<tr>
<td><strong>Ocular Lesions due to Disturbance of Calcium Metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7 (6 per cent.)</td>
<td>0</td>
</tr>
<tr>
<td>Corneal band opacity</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctival chalky deposits</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Lacrimal Gland Involvement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>48 (70 per cent. of 69 patients tested)</td>
<td>10 (53 per cent. of 19 patients tested)</td>
</tr>
<tr>
<td>Palpable swelling</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Kerato-conjunctivitis sicca</td>
<td>48</td>
<td>10</td>
</tr>
<tr>
<td><strong>Salivary Gland Enlargement (i.e. palpable parotid swelling)</strong></td>
<td>7 (6 per cent.)</td>
<td>2 (3 per cent.)</td>
</tr>
<tr>
<td><strong>Facial Palsy</strong></td>
<td>7 (6 per cent.)</td>
<td>0</td>
</tr>
</tbody>
</table>

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Sarcoid anterior uveitis may be so insidious that it is discovered only on routine examination. This occult form is usually due to the mildness of the inflammatory changes at the time, but it can be a deceptive phase as a severe inflammation may follow. We have not seen iris nodules in the absence of cells or keratic precipitates. Of three patients with iris neo-plasms, referred because these were thought to be sarcoid nodules, two had no signs of inflammation while the third had a transient coincidental anterior uveitis.

Posterior uveitis was seen in thirty of the 46 patients with uveitis in whom sarcoidosis was confirmed histologically. Evidence of former posterior uveitis alone was found in four (Table II). Posterior uveitis gives the usual symptoms of blurred sight and floating black specks in the field of vision and is seen as rounded white patches of choroido-retinal exudate (Fig. 5). When the inflammation is active, extension of the exudate into the adjacent vitreous humour surrounds them in a mist. More commonly the vitreous humour shows discrete fluffy "snow-ball" opacities (Fig. 6) mainly in the lower vitreous. Fibrosis transforms the lesions later into discrete white scars with retinal and choroidal pigment irregularly deposited in and around them (Fig. 7).

RETINITIS

The retina, though frequently sharing in the subjacent choroidal inflammation, may apparently be affected alone. One retinal lesion was observed to appear close to the macula as a blurred white patch with surrounding oedema (Fig. 6). The vision, though impaired, recovered gradually in the course of 2 months as the lesion subsided and finally disappeared. Round vitreous opacities are sometimes seen in the lower vitreous where they may lie in relation to whitish superficial patches in the retina (Fig. 6 and Fig. 8). It seems likely that these opacities arise elsewhere than in the retina, probably in the ciliary body, and gravitate through the vitreous, causing lesions in the lower retina when they come into contact with it.

Fig. 5.—Case A (same as Fig. 1), choroido-retinitis seen after resolution of massive vitreous haemorrhage.

Fig. 6.—Case E, female, aged 20 (Case 7 in Table IV), active retinal lesion near the macula due to sarcoidosis, also vitreous "snow-ball" opacity and superficial retinal lesions in lower fundus. This patient had had a right facial palsy with the onset of symptoms of uveitis 2 months before, and was found to have enlarged hilar lymph nodes, a negative Mantoux reaction at 1/100, and epithelioid cell follicles in a liver biopsy.

Fig. 7.—Case F, female, aged 47, widespread choroido-retinal scarring due to sarcoid uveitis of 4 years' known duration. She had had pulmonary sarcoidosis for 11 years, and had diffuse fibrosis when first seen, a negative Mantoux reaction at 1/100, and epithelioid cell follicles in a liver biopsy.

Fig. 8.—Case G, female, aged 60 (Case 6 in Table IV), foci of retinal scarring in the lower part of the fundus in a woman with 5 months' history of impaired vision, followed by uveo-dacryoparotitis and sarcoidosis of the skin confirmed histologically.
PERIVASCULITIS RETINAE

Patches of diffuse retinal exudate were seen in relation to slightly dilated retinal veins of varying calibre in one patient with sarcoidosis and uveitis since this series closed. The appearances resembled those illustrated by Ferguson and Paris (1958). Vitreous haemorrhage did not occur in this case and the exudates absorbed rapidly on treatment with systemic corticosteroids.

Perivasculitis retinae of the type seen in cases usually described as Eales's disease was not encountered in any of the 185 patients reviewed in this paper. One patient with multiple foci of choroido-retinitis suffered a massive vitreous haemorrhage which gradually cleared revealing the picture shown in Fig. 5. It seems probable that the chance involvement of vessels in patches of choroido-retinal sarcoid inflammation, as was likely in this patient, has accounted for some of the appearances which have been ascribed to perivasculitis in the past (Walsh, 1939; Levitt, 1941; Dressler and Wagner, 1941; Ainslie and James, 1956; James, 1959). During the present investigation six patients with perivasculitis retinae have been seen. All had the typical perivascular cuffing with newly formed vessels in the periphery of the retina (Fig. 9, overleaf) and vitreous haemorrhage eventually. But none of them showed any evidence of sarcoidosis as the cause.

LACRIMAL GLANDS AND KERATO-CONJUNCTIVITIS SICCA

Palpable enlargement of the lacrimal glands was found in only one patient in the entire series, and here lacrimal biopsy showed sarcoid follicles (Fig. 10, overleaf).

One other patient whose lacrimal glands were not palpable also showed sarcoid follicles in a biopsy. Many patients complained at some time of dryness, soreness, and redness of the eyes due to kerato-conjunctivitis sicca. This results from tear deficiency causing hyaline degeneration of the epithelial cells of the conjunctiva and cornea, particularly where they are exposed in the palpebral aperture. The degenerate cells can be detected by slit-lamp microscopy after instilling a drop of 1 per cent. rose bengal solution, as they take up the dye whereas healthy epithelial cells do not (see Fig. 1 (Plate I) and Fig. 11 (Plate III)).

This evidence of kerato-conjunctivitis sicca was found in 48 of 69 patients with histologically confirmed sarcoidosis (70 per cent.) (Table III), and in 58 of 88 tested (66 per cent.) in the whole series (Table II). Similar significant rose bengal staining from causes other than sarcoidosis was found in only 6 per cent. of fifty control subjects (Table III). This difference is even more striking if the mean ages of the sarcoid and control groups are taken into account: most control patients were in the fifth to eighth decade, and most of those with sarcoidosis in the third to sixth decade. As the incidence of kerato-conjunctivitis sicca increases with age, chance liability to
FIG. 9.—Case H, male, aged 23, perivasculitis retinae (Eales's disease) with vascular cuffing, haemorrhages, exudates, and new-vessel formation, particularly in the periphery of the retina. No evidence of sarcoidosis.

FIG. 10.—Case 1, male, aged 32 (Case 2 in Table IV), biopsy of lacrimal gland showing epithelioid cell follicles. (Haematoxylin and eosin ×150.)
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It among the patients with sarcoidosis was probably less than the 6 per cent. of the controls.

**TABLE III**

INCIDENCE OF KERATO-CONJUNCTIVITIS SICCA IN SARCOIDOSIS

<table>
<thead>
<tr>
<th>Rose Bengal Staining</th>
<th>69 Patients (with histologically confirmed sarcoidosis)</th>
<th>50 Control Patients (mainly with cataract, glaucoma, and squint)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nil</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>Slight</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Moderate</td>
<td>34 (70 per cent.)</td>
<td>3 (6 per cent.)</td>
</tr>
<tr>
<td>Severe</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

The tear secretion of another group of thirty patients was measured by Schirmer’s test and correlated closely with the results of the rose bengal test. Thus an eye with a Schirmer test of less than 10 mm. showed severe rose bengal staining, if the measurement was 10 to 20 mm. the conjunctiva was moderately stained, and if it was more than 20 mm. there was no more than mild staining. Both tests revealed kerato-conjunctivitis sicca to be much commoner in sarcoidosis than has been hitherto supposed. No evidence was found in this series that its presence was related to hepatic damage as judged by abnormal serum globulin values or raised turbidities.

**UVEO-PAROTITIS**

Longcope and Freiman (1952) comparatively recently entitled the section of their monograph on ocular sarcoidosis “Uveo-parotid Fever”. Though still the most memorable feature, uveo-parotitis (Heerfordt’s syndrome) is less important as a feature of sarcoidosis than the numerous reports of isolated examples suggest. Only thirteen of our 185 patients had evidence of it at any time (Table IV) and none of these showed the complete syndrome.

**TABLE IV**

UVEO-PAROTITIS IN THIRTEEN PATIENTS WITH SARCOIDOSIS

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>moderate</td>
<td>normal</td>
<td>severe</td>
<td>normal</td>
<td>present</td>
</tr>
<tr>
<td>2</td>
<td>normal</td>
<td>present</td>
<td>severe</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>3</td>
<td>normal</td>
<td>normal</td>
<td>moderate</td>
<td>not tested</td>
<td>present</td>
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<tr>
<td>4</td>
<td>severe</td>
<td>normal</td>
<td>not tested</td>
<td>present</td>
<td>normal</td>
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<td>5</td>
<td>severe</td>
<td>normal</td>
<td>not tested</td>
<td>present</td>
<td>normal</td>
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<tr>
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<td>severe</td>
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<td>moderate</td>
<td>present</td>
<td>normal</td>
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<td>7</td>
<td>severe</td>
<td>normal</td>
<td>not tested</td>
<td>normal</td>
<td>present</td>
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<tr>
<td>8</td>
<td>severe</td>
<td>normal</td>
<td>severe</td>
<td>normal</td>
<td>normal</td>
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<tr>
<td>9</td>
<td>severe</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>present</td>
</tr>
<tr>
<td>10</td>
<td>severe</td>
<td>normal</td>
<td>slight</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>11</td>
<td>normal</td>
<td>normal</td>
<td>not tested</td>
<td>normal</td>
<td>present</td>
</tr>
<tr>
<td>12</td>
<td>slight</td>
<td>normal</td>
<td>moderate</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>13</td>
<td>severe</td>
<td>normal</td>
<td></td>
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</table>
As already mentioned palpable enlargement of the lacrimal glands was rare. Two patients combined with uveitis a facial palsy and parotid swelling, four had uveitis and parotid swelling alone, and three others had uveitis and facial palsy without parotid swelling. Uveitis and defective tear secretion, though surprisingly absent on occasion, were the most uniform features. The uveitis (ten patients out of thirteen) was usually severe, as was keratoconjunctivitis sicca in this group, and it was often persistent or recurrent. Facial palsy and parotid swelling were transient as a rule and did not recur.

A characteristic feature of the syndrome was that it occurred at or near the onset of the disorder. It was the first evidence of sarcoidosis in twelve of the thirteen patients, all of whom came to be investigated because of symptoms due to it. The remaining patient had had erythema nodosum a few months before the onset of a facial palsy and uveitis. In keeping with this, the pulmonary lesions when present (ten out of thirteen) confirmed that the disorder was recent (Smellie and Hoyle, 1960); seven had hilar lymph node enlargement, three with pulmonary infiltration as well, and three had pulmonary infiltration alone. None of them showed any radiographic evidence of pulmonary fibrosis at the time, though five subsequently developed progressive pulmonary sarcoidosis with severe fibrosis, from which three have died and one other is a respiratory cripple. This incidence of five out of thirteen for progressive pulmonary sarcoidosis among our patients with uveo-parotitis contrasts with only six others in the rest of this series, i.e. six out of 172.

**Corneal and Conjunctival Calcium Deposits**

Seven patients, all with histological confirmation of their sarcoidosis, were found to have deposits of calcium salts beneath the corneal epithelium or in the conjunctiva. Four of them had both features, two others a band opacity, and one conjunctival deposits only.

Band opacities were situated in the middle and lower zones of the cornea, being a little higher towards the limbus on either side. The opacities were not uniform, having small circular clear areas within them which gave an appearance like Gruyère cheese. They were also seen to be denser near the limbus, from which they were usually separated by a narrow zone of clear cornea. Acute calcification was observed in one patient who had at the time a serum calcium value of 14.7 mg. per cent. accompanied by photophobia, aching, and redness of the eyes. Both corneae showed fine close punctate fluorescein staining in the area of opacity, and beneath the disturbed epithelium a fine haze of white deposit was seen (Fig. 12, opposite), more marked near the corneo-scleral junction. The bulbar conjunctiva adjacent to the band opacities contained small translucent follicles with chalky granules in them. On treatment with a low calcium diet the
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Fig. 12.—Case J, male, aged 21, acute corneal band opacity from hypercalcaemia (serum calcium 14.7 mg. per cent.) due to sarcoidosis. This led to aching pain and photophobia and the affected part of the cornea stained with fluorescein. This patient also had bilateral hilar lymph node enlargement with pulmonary infiltration, generalized lymphadenopathy, and renal calculi with albuminuria, casts, and a reduced urea clearance. Biopsies of liver and a lymph node showed numerous epithelioid cell follicles.

Fig. 13.—Case J. (same as Fig. 12), after treatment with a low calcium diet. The band opacity is no longer seen but there is residual marginal calcification.

symptoms were soon relieved. The central parts of the corneal opacities cleared but the juxta-limbal parts remained. At the same time the bulbar conjunctival follicles subsided leaving, however, small flecks of chalk-like deposit which have persisted (Fig. 13).

The other corneal band opacities (Fig. 14, see Plate III) have had a less dramatic onset and have been similar to those seen in degenerate corneas or in eyes with severe chronic uveitis in the absence of hypercalcaemia. Only one of the seven patients had severe chronic iridocyclitis of the type which predisposes to band opacities and three were entirely free of uveitis.

All seven patients were known to have had sarcoidosis for more than 3 years. Five of them had taken large doses of calciferol, three shortly before their ocular calcification was discovered on coming under our care for the resultant symptoms. Five were hypercalcaemic at this time. One other had a normal serum calcium with persistent band opacity and conjunctival calcification 4 years after receiving a short course of calciferol which was discontinued because of toxic effects. None of the patients showed radiographic calcification in the kidneys, though two had renal calculi, six of the seven had evidence of renal damage, and four were uraemic.
CONJUNCTIVAL SARCOIDOSIS

Isolated examples of conjunctival sarcoidosis have been reported in the literature. Our attention was drawn to it by a patient seen early in this series, who had large confluent follicles in the conjunctival fold of the lower fornix (Fig. 15).

![Image of conjunctival biopsy showing numerous epithelioid cell follicles. (Haematoxylin and eosin ×100.)](image-url)

They were the presenting feature of her illness and had the characteristic histology (Fig. 16).
Routine examination of patients with the slit-lamp microscope soon revealed the frequent presence of similar but smaller aggregations of follicles. It seemed that conjunctival biopsies might therefore provide a simple and rapid means of distinguishing uveitis due to sarcoidosis from other forms, and also of confirming a diagnosis of sarcoidosis when biopsies elsewhere failed to do so or could not be done (Crick, Hoyle, and Mather, 1955; Crick, 1955, 1956). From some comments in the literature certain limitations of the method have not always been appreciated. James (1959) remarked that, in their original account, Crick, Hoyle, and Mather (1955) advocated blind conjunctival biopsy, but this is not so. They emphasized that it was always necessary to identify follicle-bearing conjunctiva (Fig. 17, see Plate III) with the slit-lamp microscope and to take this tissue only for histological examination. Failure to observe this precaution renders the method valueless, as has been our experience in five patients with biopsy confirmation from other sites. It is, of course, true that follicles of lymphoid tissue with germinal centres (Fig. 18), which are common in the conjunctiva, cannot with certainty be distinguished from true sarcoid follicles by their naked-eye appearance though the latter are often larger and tend to be less evenly distributed, with a characteristic disposition to the confluence of adjacent follicles. It has been suggested that a subconjunctival foreign body may lead to error by producing a local ‘sarcoid’ reaction similar to those found elsewhere from other causes, but this would not appear to present any practical difficulty. Elevations in the bulbar conjunctiva which are indistinguishable histologically from sarcoid tissue occur in acne rosacea. They were, however, limited to the bulbar conjunctiva in three patients investigated and we have not found them in the fornix conjunctiva. Conversely, true sarcoid follicles have not been found to be limited to the

Fig. 18.—Lymphoid follicles in the conjunctiva. (Haematoxylin and eosin x150.)
bulbar conjunctiva; all those confirmed histologically (Table V) were situated in the lower fornix.

**TABLE V**

RESULTS OF CONJUNCTIVAL BIOPSY IN 79 PATIENTS WITH SARCOIDOSIS AND 48 CONTROLS

<table>
<thead>
<tr>
<th>Type of Case</th>
<th>Number of Patients</th>
<th>Number of Patients Available for Biopsy</th>
<th>Number of Patients with Conjunctival Follicles</th>
<th>Histological Sarcoïdosis in Conjunctival Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoïdosis with histological confirmation other than conjunctival</td>
<td>111</td>
<td>80</td>
<td>43</td>
<td>16 (i.e. 20 per cent. of patients available for biopsy; 37 per cent. of patients with conjunctival follicles)</td>
</tr>
<tr>
<td>Sarcoïdosis without histological confirmation other than conjunctival</td>
<td>74</td>
<td>59</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total Number of Patients with Sarcoïdosis</strong></td>
<td><strong>185</strong></td>
<td><strong>139</strong></td>
<td><strong>79</strong></td>
<td><strong>20 (i.e. 14 per cent. of patients available for biopsy; 25 per cent. of patients with conjunctival follicles)</strong></td>
</tr>
<tr>
<td>Control Patients</td>
<td><strong>48</strong></td>
<td><strong>48</strong></td>
<td><strong>48</strong></td>
<td><strong>0</strong></td>
</tr>
</tbody>
</table>

Table V gives the results of 146 conjunctival biopsies; 48 of these were control biopsies taken mainly from patients attending the eye clinics for uveitis (other than sarcoïd) or various conditions of the conjunctiva. All these control patients had negative biopsies. The other 98 biopsies were done on 79 patients with sarcoïdosis. Of the 115 patients with biopsy-confirmed sarcoïdosis, 111 were shown to have sarcoïd histology in tissue other than the conjunctiva. Of these, 31 were not available for conjunctival biopsy. Of the remaining eighty patients, 43 showed conjunctival follicles; in 25 these were of typical appearance and in eighteen atypical. Sarcoïd histology was found in conjunctival biopsies of sixteen, only two of these showing atypical follicles. Thus, in sarcoïdosis confirmed otherwise by biopsy, conjunctival involvement was found in sixteen (20 per cent.) of the eighty patients biopsied or in 37 per cent. of those showing follicles.

For various reasons, 46 of the 185 patients in the whole series were not able to have a conjunctival biopsy taken. Conjunctival follicles were present, however, in 79 of the remaining 139 patients; they were of typical appearance in 43 and atypical in 36. Conjunctival biopsy showed sarcoïd histology in twenty, only two of these having atypical follicles. In four patients conjunctival biopsy was the only histological confirmation of the disease. Thus, in all 139 patients with clinical sarcoïdosis in this series who
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were available for conjunctival biopsy, the result was positive in twenty (14 per cent.) of all patients biopsied and in 25 per cent. of those showing follicles. When, however, the conjunctival follicles were judged to be of typical appearance, 42 per cent. of the biopsies showed sarcoid histology. Conjunctival biopsy is much more frequently positive in patients having biopsy confirmation from other tissues than in those in whom this is not the case. Probably this reflects a difference in the degree of generalization of the disorder similar to the respective incidences of kerato-conjunctivitis sicca and of uveitis among patients with and without confirmation of their sarcoidosis histologically.

Phlyctenular conjunctivitis, recorded by some authors, has not been seen in our patients. We also failed to find any close concurrence between the three main ocular lesions—uveitis, kerato-conjunctivitis sicca, and conjunctival follicles.

**Course and Treatment**

The chief problem in treatment is the management of the uveitis which is responsible for most of the symptoms and is the main danger to the eyes in sarcoidosis. This requires at least local treatment by corticosteroid drops or ointment as well as routine mydriatics; and in addition it has to be decided whether systemic corticosteroids are essential to prevent complications and serious loss of vision. Most of the literature has been concerned with these problems only in individual patients, though there are a few papers dealing with small groups (Ainslie and James, 1956; James and Thomson, 1959; James, 1959).

The effects of treatment were observed systematically in 35 of our 46 patients with uveitis in whom sarcoidosis was confirmed histologically. Because of the potential dangers we rejected the opportunity of a strictly-controlled trial of their treatment. Instead, we selected treatment for each patient initially according to criteria which at the time seemed likely to decide the probable outcome: the most important of these were the severity, extent, and duration of the uveitis when first seen. In this way three groups were defined:

1. Patients seen in the pre-corticosteroid era and also those treated with mydriatics before they were referred to our care. They were treated initially by local mydriatics only.

2. Those in Group 1 whose uveitis failed to improve or deteriorated and also those seen initially with mild or moderate anterior uveitis after corticosteroids were available. Patients in this group were treated with local corticosteroids as well as mydriatics.

3. Those in Group 2 who failed to improve and patients who had severe uveitis, especially when nodules were present and when the inflammation was generalized throughout the uveal tract. These were treated with systemic corticosteroids.
Table VI gives the results of treatment. In Group 1 uveitis improved spontaneously while using mydriatics in eight of 23 patients, only four of these eight achieving complete clearing and a quiet eye. Seven patients in the group were left with persistent uveitis and in eight others the condition deteriorated, all eventually needing either local or systemic corticosteroids.

Thirteen of twenty patients whose uveitis was treated with local corticosteroids (Group 2) were improved, though only five achieved complete clearing; in the rest the uveitis failed to respond, and in two it deteriorated.

All twelve patients in Group 3 responded to systemic corticosteroids, four with complete resolution of the lesions and the remainder to the point where they were left with minimal changes.

### TABLE VI

<table>
<thead>
<tr>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Mydriatics</td>
<td>Local Corticosteroids</td>
<td>Systemic Corticosteroids</td>
</tr>
<tr>
<td>State of Uveitis</td>
<td>Clear</td>
<td>Improved</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>20</td>
<td>12</td>
</tr>
</tbody>
</table>

Nodular uveitis in particular responds much more rapidly and more often to systemic than to local treatment with corticosteroids. One severe example in which local treatment failed is shown in Fig. 19; the iris nodules virtually disappeared within 3 weeks when systemic cortisone was given (Fig. 20). Three patients in whom the uveitis occurred before systemic treatment had bilateral hilar lymph node enlargement and pulmonary infiltration, a negative Mantoux reaction at 1/100, and epithelioid cell follicles in a liver biopsy. Two further lymph node biopsies taken 6 and 7 years after the first one still showed active epithelioid cell follicles. This patient did not have uveitis.

Fig. 11.—Case E (same as Fig. 6), kerato-conjunctivitis sicca due to sarcoidosis, showing rose bengal staining of the conjunctiva.

Fig. 14.—Case K, female, aged 45, corneal and conjunctival calcification due to hypercalcaemia (serum calcium 15.2 mg. per cent.) from sarcoidosis, 3 months after treatment with large doses of calciferol for one month. Blood pressure 190/110, blood urea 65 mg. per cent. 7 years previously she had been found to have generalized lymphadenopathy, and biopsy of a node had shown epithelioid cell follicles. The abdominal lymph nodes became massively enlarged and later splenomegaly and skin sarcoïds were found. Two further lymph node biopsies taken 6 and 7 years after the first one still showed active epithelioid cell follicles. This patient did not have uveitis.

Fig. 17.—Case M, male, aged 23, sarcoïd conjunctival follicles, typically confluent in the lower fornix and confirmed histologically. This patient also had recurrent uveitis, enlarged hilar lymph nodes, and pulmonary infiltration, a negative Mantoux reaction at 1/100, and epithelioid cell follicles in a liver biopsy.

Fig. 19.—Case N, female, aged 25, nodular anterior uveitis before treatment with systemic cortisone. This patient was found to have bilateral hilar lymph node enlargement and pulmonary infiltration 8 months previously, followed 5 months later by bilateral uveitis. Liver and conjunctival biopsies showed numerous epithelioid cell follicles.

Fig. 20.—Case N (same as Fig. 19), resolution of nodules 3 weeks after starting treatment with systemic cortisone.
corticosteroids were available were left with severe damage, including secondary glaucoma.

A number of patients still require treatment with local or systemic corticosteroids to suppress a mild uveitis which recurs if therapy is discontinued. It is, however, encouraging to find that visual acuity has been reduced below 6/9 in either eye in only eleven of the 185 patients. Six of these eleven patients have had severe uveo-parotitis, two with subacute secondary glaucoma; one had a massive disorganizing uveitis; and one other developed chronic secondary glaucoma. All eleven were first treated in the pre-corticosteroid era. One other patient (Figs 1 and 5) failed to attend for treatment for 6 months and sustained a vitreous haemorrhage, but this has since resolved during treatment with corticosteroids. The remaining two have had the sight of one eye reduced to 6/18 by general uveitic impairment. Three equally severe examples of uveo-parotitis have since responded well to early and prolonged treatment with systemic prednisone and vision has been maintained.

Subacute and chronic uveitis are regarded by James (1959) as distinct from the prognostic point of view. Our experience with the 35 patients in whom the type and progress of anterior uveitis was followed does not support this claim. The onset was chronic in eleven and subacute in twenty-four. Of the eleven with a chronic onset, six did well and one badly, while the uveitis in the other four, though much improved, tended to persist in a mild form. Of the twenty-four with a subacute onset, seven did well and seven badly. In the remaining ten patients, the uveitis improved greatly though slowly in four, the other six being left with a chronic mild uveitis. There is no justification for considering that subacute uveitis has a particularly favourable prognosis. The severity of the condition, whether subacute or chronic, and the adequacy of early treatment decide the outlook rather than the mode of onset.

All seven patients who had calcium deposits in the cornea or conjunctiva were treated by low calcium diet and four who were uraemic were given systemic corticosteroids as well. Of the six patients with evidence of renal damage, this was limited in one to proteinuria, casts, and a reduced urea clearance, all of which improved rapidly on a low calcium diet with disappearance of the ocular calcification and hypercalcaemia in six weeks and no subsequent recurrence in the last 6 years. One other patient who had a persistent band opacity and corneal calcification 4 years after a short course of calciferol had severe renal failure and hypertension, but here the problem was complicated by long-standing diabetes to which the renal damage may have been partly attributable, though she is still alive 10 years after the discovery of her eye lesions which have been unaffected by prolonged treatment with topical cortisone. Of the other four patients with renal damage one had two calculi removed from the left kidney after attacks of renal colic, but she died subsequently from pulmonary fibrosis with cor pulmonale.
The other three recovered rapidly from their hypercalcaemia and renal failure when given a low calcium diet and systemic cortisone: in all of them the ocular calcification resolved within a few months. Mather (1957) has already reported one of these patients in detail, with the results of calcium balance studies and a review of the literature.

Compared with uveitis and the effects of hypercalcaemia, the other features of ocular sarcoidosis are less important and their treatment rarely calls for more than symptomatic measures. Discomfort from keratoconjunctivitis sicca may be partially relieved by artificial tear drops (gelatin 1 per cent., chlorbutol 0·8 per cent., Ringer Locke’s solution to 100 per cent.) until improvement occurs either spontaneously or during treatment with a corticosteroid. Seriously persistent keratoconjunctivitis is rare from sarcoidosis and we have not found it necessary to use corticosteroid treatment for this alone. Florid conjunctival nodules occasionally require systemic corticosteroids if local applications fail. An example of their suppressive effect was seen in one patient who had a large conjunctival nodule (Fig. 15) which healed within a year when systemic cortisone was given after local cortisone injections and applications for 3 years had failed to do any permanent good.

Discussion

The eyes were found to be affected much more commonly in our patients with sarcoidosis than has been reported hitherto. The high figure of 63 per cent. for those confirmed histologically was due mainly to recognition of early uveitis and keratoconjunctivitis sicca by routine inspection with the slit-lamp microscope, and this emphasizes the need for this examination as part of the search required to establish the extent of the disorder. Moreover, it places ocular sarcoidosis alongside hilar lymph node enlargement and pulmonary infiltration as one of the three commonest forms. The ocular condition more often causes symptoms than either hilar lymph node enlargement or pulmonary infiltration. Smellie and Hoyle (1960), reporting 125 patients with hilar lymph node and pulmonary sarcoidosis, found that the commonest complaints were due to coincident uveitis in eighteen of 41 cases with symptoms referable to sarcoidosis at the time it was discovered.

The most frequent lesion, keratoconjunctivitis sicca, was found about as often (70 per cent.) as hepatic follicles are found by biopsy (63 per cent.: Mather, Dawson, and Hoyle, 1955), indicating that the lacrimal glands and the liver are similarly involved by the disorder. Conjunctival sarcoidosis was less common, being present in 14 per cent. of the whole series and in 25 per cent. of patients with conjunctival follicles. Conjunctival biopsy is, however, of value in that its affords a rapid and easy out-patient method of biopsy confirmation with a minimum of discomfort or preparation. Though it is only applicable to patients showing follicles, these were present in
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57 per cent., and when they had the typical macroscopic appearance, which is seen in 31 per cent., histological confirmation of sarcoidosis was obtained in 42 per cent. of those examined.

Uveitis was the principal feature among our patients. It was found in 46 of 115 (40 per cent.) in whom the diagnosis was supported histologically. Although its appearance is not diagnostic, sarcoid uveitis shows two features which may point to this aetiology: the presence of nodules in a minority (12 in 46), and scattered small patches of exudate in a semicircular distribution along the lower margin of the fundus as part of a posterior uveitis and retinitis (Fig. 6). Nodules were once regarded as a frequent and distinctive feature of sarcoid uveitis (Blegvad, 1938; Levitt, 1941; Woods and Guyton, 1944), an opinion based upon selective experience much of which related to Negroes. This was not found to be true of the present group of patients.

Frequent reports of Heerfordt's syndrome in isolation from any large series of patients with sarcoidosis have led to the belief that it is a cardinal part of the disorder. On the contrary its classical form is exceptional (thirteen in 185 patients), at any rate in Great Britain. Moreover, in all of our thirteen patients so affected, the syndrome was partial. The commonest combinations were uveitis with parotid gland enlargement (6 of 13) or keratoconjunctivitis sicca (6 of 13), with one or other additional features in a minority (Table IV). As the high incidence of keratoconjunctivitis sicca in our series as a whole shows that the lacrimal glands are commonly involved, the same may well apply to the salivary glands. Though occult forms of Heerfordt's syndrome may be common, there is strong evidence that the classical form is always part of an exceptionally florid sarcoidosis. The uveitis occurs early in the course of the disorder, is severe as a rule (8 in 13), often becomes chronic or recurrent, and has a worse prognosis unless treated with systemic corticosteroids (6 in 11 with reduced visual acuity). Progressive pulmonary sarcoidosis is commoner also among these patients (5 in 13) than among others whose sarcoidosis is not complicated in this way (6 in 172).

Perivasculitis retinae (Eales's disease) has not infrequently been ascribed to sarcoidosis: Donders (1958) reviewed the subject very fully, reporting on 100 examples followed at Utrecht since 1938. In this group there were only three with concurrent sarcoidosis. Ainslie and James (1956) and James (1959) have reported another. We have not seen the diffuse form, with its characteristic perivascular cuffing by exudate and leashes of new vessels in the periphery of the retina, in any of our patients with sarcoidosis, though one patient had mist-like patches of exudate near veins of varying calibre consistent with periphlebitis. It also seems likely that a vitreous haemorrhage may occur when a focus of choroido-retinal inflammation happens to involve a vessel (Fig. 5). Six patients with diffuse perivasculitis, seen during the course of this study failed to show any evidence of sarcoidosis. We
regard diffuse perivasculitis as an entirely separate disorder and unrelated to sarcoidosis.

Ocular sarcoidosis differs in its course from the pulmonary form in one important respect which Smellie and Hoyle (1960) have recently pointed out. The difference is the liability for uveitis to persist or recur after enlarged hilar lymph nodes have regressed or after infiltration in the lungs has become quiescent or has cleared radiographically. Such lesions frequently remit spontaneously within 2 years. After that they are unlikely to do so and the duration of the active sarcoid process is then often much longer. In keeping, hilar node enlargement and pulmonary infiltration which resolves spontaneously within 2 years of discovery are not found to recur. In both groups, however, uveitis is liable to relapse after spontaneous improvement.

Although anterior uveitis due to sarcoidosis may improve spontaneously, only four of 23 patients treated expectantly with mydriatics (Group 1) achieved complete clearing. Topical treatment with corticosteroids in Group 2 was equally disappointing, only five out of twenty achieving resolution. It had no effect upon posterior uveitis, and one patient in this series went totally blind within a few weeks of the onset of symptoms. Unfortunately, there was no opportunity of using systemic corticosteroids until both eyes were severely damaged, and from then onwards treatment was ineffective. It is likely that immediate use of full doses of systemic corticosteroids in these severe examples will prevent such catastrophes. Judging from the results in Group 3, which included all the severest examples as well as failures from Groups 1 and 2, this is the safest and most effective treatment for most patients with sarcoid uveitis. Although the condition of the eyes at the time is the chief concern, one other factor also needs to be taken into account. This is the risk of chronic uveitis to patients with uveo-parotitis or with extensive, severe, or chronic sarcoid lesions elsewhere. If this is given due weight the strength of the case for using systemic corticosteroids for many patients with sarcoid uveitis becomes even more impressive.

Summary

185 patients with sarcoidosis have been studied to determine the ways in which the eyes are affected. There was some ocular abnormality in 73 of 115 (63 per cent.) where the diagnosis was histologically supported. Keratoconjunctivitis sicca (48 in 69) and uveitis (46 in 73) were the main ones and conjunctival sarcoidosis less commonly (20 in 64). Conjunctival biopsy is a ready and useful source of support for a diagnosis of sarcoidosis when follicle-bearing conjunctiva is present.

Uveal sarcoidosis is an early feature of the disorder and the commonest cause of symptoms at this time. It is prone to relapse, even when hilar lymph node and pulmonary sarcoidosis have cleared radiographically and
do not recur. Nodular uveitis (12 in 46) is infrequent. Classical uveo-parotitis (Heerfordt's syndrome) is rare in sarcoidosis (13 in 185) and is as a rule partial when it does occur. It is usually associated with a severe uveitis and with a pulmonary infiltration which leads to fibrosis more often (5 in 13) than in patients in whom it does not occur (6 in 172). Diffuse perivasculitis retinae was not seen in this series, and six patients with perivasculitis did not have any evidence of sarcoidosis.

The course and treatment of ocular sarcoidosis including uveitis in 35 patients, are reviewed. Treatment of the uveitis with mydriatics alone is not justified. Topical corticosteroids are effective in only a minority, though useful to suppress residual chronic inflammation. Systemic corticosteroids are therefore often needed and are essential for severe progressive anterior uveitis and for posterior uveitis of any degree. Although a low calcium diet may be effective for hypercalcaemia with corneal or conjunctival calcium deposits, systemic corticosteroids are needed when there is renal damage.

We wish to thank Mr. L. H. Savin and the many other colleagues who have helped this investigation by referring patients or in other ways, especially Prof. H. A. Magnus, Dr. B. S. Cardell, and Dr. M. E. A. Powell for the histology. We are indebted to Mr. E. R. Alexander for many of the illustrations, and to Mr. W. Smith and Mr. G. Harwood for the photomicrographs. We are grateful also to the Research Committee of King's College Hospital for a grant to one of us (C. H.) for secretarial expenses and to Mr. A. J. Shrosbery and Dr. Maurice Davidson, F.R.C.P., for their generous gifts towards the cost of the coloured illustrations.

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