

COMMUNICATIONS

OCULAR SARCOIDOSIS*

BY

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WHEREAS sarcoidosis is responsible for only about 4 per cent. of cases of uveitis, eye involvement, predominantly uveitis, occurs in about one-quarter of patients with sarcoidosis. Although the ocular lesion is but an incident in a generalized disease, it is the most troublesome and incapacitating. Its early recognition and treatment may prevent both protracted suffering and blindness.

Patients and Methods

The 442 patients, who have been personally studied, showed clinical or radiological features of sarcoidosis always supported by histological evidence of sarcoid tissue. Patients with clinical, radiological, and immunological features of sarcoidosis were excluded from this analysis if there was no histological confirmation. This series includes 123 (27·8 per cent.) with ophthalmic involvement.

Routine clinical examination included chest radiography, ophthalmoscopy, and slit-lamp examination of the uveal tract. Mantoux tests were done in all cases, and Kveim tests were performed in 380 patients. Electrophoresis of serum proteins and estimations of serum albumin and globulin levels by the biuret method were carried out in 266 cases. Serum globulin levels above 3·5 g. per 100 ml. or an electrophoretic pattern showing a relative preponderance of α , β , or γ globulin were considered abnormal. Serum calcium levels were determined in 256 and 24-hour urine calcium levels in 65 patients.

Histological evidence of sarcoid tissue was obtained from various sources by biopsy and at necropsy. All histological sections were examined for acid-fast bacilli, and were scrutinized by polarized light for doubly-refractile material.

Results

Ocular Lesions

123 of the 442 (27·8 per cent.) patients presented with various ocular manifestations of sarcoidosis (Table I, overleaf). By far the commonest mode of presentation was acute or chronic iridocyclitis (in 89 patients), followed in frequency by some form of conjunctival involvement in almost all others. Whereas anterior uveitis was a common presenting feature of ocular sarcoidosis, posterior uveitis almost never drew attention to the eye involvement; the latter was nevertheless present in twelve patients, but it was overshadowed by concomitant anterior uveitis in almost all of them.

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TABLE I
PRESENTING FEATURES IN 123 PATIENTS WITH OCULAR SARCOIDOSIS, SHOWING SEX DISTRIBUTION, AND INVOLVEMENT OF ONE OR BOTH EYES

Presenting Features	No. of Patients	No. of Females	Degree of Involvement	
			Bilateral	Unilateral
Iridocyclitis	89	59	76	13
Acute	34	20	24	10
Chronic	55	39	52	3
Conjunctivitis	14	9	10	4
Phlyctenular	6	5	2	4
Non-specific	8	4	8	0
Kerato-conjunctivitis Sicca	10	7	10	0
Conjunctival Follicles	5	4	4	1
Scleral Plaques	3	2	1	2
Cataract	1	1	1	0
Retinitis Proliferans	1	1	0	1
Total	123	83	102	21

Acute Iridocyclitis.—This was noted in 34 patients; it was bilateral in 24 and unilateral in ten. It was slightly commoner in females (20 females; 14 males), thereby following the trend shown by all types of ocular sarcoidosis. The onset was sudden with pain and mistiness of vision, and the affected eyes showed ciliary congestion, turbidity of the aqueous humour with occasional cells circulating in the anterior chamber, and fine keratic precipitates.

Evidence of involvement of other tissue systems was widespread (Table II), their most characteristic feature being their transience. Thus, intrathoracic involvement, present in 29 of the 34 patients with acute iridocyclitis, was always observed to subside completely sooner or later (Table III, opposite). Likewise, the skin lesions (Table II) almost always took the form of erythema nodosum which disappeared in

TABLE II
INVOLVEMENT OF OTHER TISSUES IN OCULAR SARCOIDOSIS

Type of Ocular Lesion	No. of Patients	Other Tissues Involved							
		Skin		Lymph Nodes	Spleen	Bone Cysts	Glands		Bell's Palsy
		Erythema Nodosum	Other				Lac-rimal	Salivary	
Iridocyclitis	89	15	26	32	14	9	1	8	6
Acute	34	12	2	15	3	0	0	1	4
Chronic	55	3	24	17	11	9	1	7	2
Conjunctivitis	14	8	4	3	2	0	1	0	0
Kerato-conjunctivitis Sicca	10	3	4	6	3	0	5	5	0
Conjunctival Follicles	5	3	1	2	1	1	0	0	0
Scleral Plaques	3	1	0	1	0	0	0	0	0
Cataract	1	0	0	1	1	0	0	0	0
Retinitis Proliferans	1	0	1	1	1	1	0	0	0
Total	123	30	36	46	22	11	7	13	6
Per cent.	100	54		38	18	9	6	10	5

TABLE III
INTRATHORACIC RADIOLOGICAL CHANGES

Type of Ocular Lesion	No. of Patients	Chest X-ray Stage*				Subsequent Complete Clearing	
		0	1	2	3	No.	Per cent.
Iridocyclitis	89	26	30	19	14	36	57
Acute	34	5	18	9	2	29	100
Chronic	55	21	12	10	12	7	20
Conjunctivitis	14	3	10	1	0	11	100
Kerato-conjunctivitis Sicca	10	1	5	1	3	4	44
Conjunctival Follicles	5	1	2	1	1	2	50
Scleral Plaques	3	1	1	1	0	2	100
Cataract	1	0	0	1	0	0	0
Retinitis Proliferans	1	0	0	1	0	1	100
Total	123	32	48	25	18	56	61

* STAGE 0=Clear chest radiograph
 STAGE 1=Bilateral hilar lymphadenopathy
 STAGE 2=Hilar lymphadenopathy and pulmonary mottling
 STAGE 3=Diffuse pulmonary mottling

the course of one month. Bone cysts, the hall-mark of chronicity in sarcoidosis, were never associated with acute iridocyclitis.

Apart from these clinical associations, other features supported the diagnosis of active, acute, generalized sarcoidosis in this group. The Kveim test was positive in 24 of 39 (83 per cent.), the Mantoux test was negative in thirteen of 29 (45 per cent.), and abnormal serum globulins were noted in four of seventeen (24 per cent.) patients (Table IV).

TABLE IV

RESULTS OF KVEIM AND MANTOUX SKIN TESTS AND SERUM GLOBULIN AND SERUM CALCIUM LEVELS IN PATIENTS WITH OCULAR SARCOIDOSIS, BY TYPE OF OCULAR LESION

Type of Ocular Lesion	Kveim Test			Mantoux Test			Serum Globulin			Serum Calcium		
	No. Done	Positive		No. Done	Negative		No. Done	Abnormal		No. Done	Elevated	
		No.	Per cent.		No.	Per cent.		No.	Per cent.		No.	Per cent.
Iridocyclitis	66	54	82	80	49	61	55	18	33	46	6	13
Acute	29	24	83	29	13	45	17	4	24	14	1	7
Chronic	37	30	81	51	36	71	38	14	37	32	5	16
Conjunctivitis	14	12	85	12	5	41	8	3	37	9	1	11
Kerato-conjunctivitis Sicca	7	6	86	8	6	75	9	4	44	10	2	20
Conjunctival Follicles	4	2	50	4	4		5	3	60	5	0	
Scleral Plaques	3	3	100	2	2		1	1		1	0	
Cataract	1	0	0	1	1		1	1		1	0	
Retinitis Proliferans	0	0	0	1	1		1	0		0		
Total	95	77	81	108	68	63	80	30	38	72	9	12

In this group, lymph node biopsy revealed sarcoid tissue in all instances in which it was undertaken, whereas aspiration liver biopsy was positive in three of five and skin biopsy in three of seven instances in which it was carried out.

Chronic Iridocyclitis.—55 patients (39 females) had anterior uveal tract abnormalities, of at least one year's duration, on presentation. In all but three, the changes were bilateral. The onset had been insidious with some pain and blurring of vision in the majority, but signs of active inflammation were minimal. Instead of a pink eye and ciliary congestion, there were keratic precipitates, posterior adhesions of iris to lens, iris nodules, lens opacities, cataracts, or secondary glaucoma.

Accompanying clinical manifestations of sarcoidosis were also long-standing (Table II); lupus pernio and bone cysts in nine patients reflected the chronicity and persistence of sarcoidosis associated with chronic uveitis. Intrathoracic changes (Table III) likewise proved to be persistent, for resolution of the radiological abnormalities occurred in only seven of 34 (20 per cent.) patients with initially abnormal chest radiographs.

Despite the chronicity of the sarcoidosis, it was nevertheless active, for the Kveim test was positive in thirty of 37 (81 per cent.); the Mantoux test was negative in 36 of 51 (71 per cent.); there were abnormal serum globulins in fourteen of 38 (37 per cent.); and the serum calcium level was elevated in five of 32 (16 per cent.) of patients in this group (Table IV).

Apart from positive Kveim tests, histological confirmation was obtained by aspiration liver biopsy in five of ten (50 per cent.) patients, by lymph node biopsy in all but one of nine patients, and by skin biopsy in thirteen of fifteen (86 per cent.) patients with chronic anterior uveitis.

Acute Conjunctivitis.—There were fourteen patients in whom phlyctenular or non-specific conjunctivitis appeared at the same time as other manifestations of sarcoidosis. It was bilateral in all but four patients (Table I). Since it was a troublesome affliction, early medical advice was sought. In eight instances it coincided with both erythema nodosum and bilateral hilar lymphadenopathy. Chest x-ray abnormalities, observed in eleven of the fourteen patients, always subsided (Table III). The Kveim test was present in all but two patients in this group; the Mantoux test was negative in seven of twelve (58 per cent.); abnormal serum globulins were noted in three of eight (37 per cent.); and one patient amongst nine tested showed hypercalcaemia (Table IV). Sarcoid tissue was noted, one in a lymph node biopsy, in three of four skin biopsies, and in two of three aspiration liver biopsies.

Kerato-conjunctivitis Sicca.—This occurred in seven females and three men. It was always bilateral (Table I). Dryness of the eyes was often a distressing symptom, and some showed corneal staining and degenerative changes. Corneal ulceration was an infrequent complication. The commonest clinical accompaniments were enlarged lacrimal and salivary glands (5) erythema nodosum (3) or other skin lesions (4), lymphadenopathy (6) or splenomegaly (3) (Table II). Intrathoracic changes were noted in all but one, and these abnormalities resolved in only four (44 per cent.) patients (Table III). The Kveim and Mantoux tests were almost always positive, abnormal serum globulins were noted in four of nine (44 per cent.) patients; and hypercalcaemia in two of the group (Table IV). Sarcoid tissue was found in lymph nodes in three, by liver biopsy in two of three, and in the skin in four of five instances.

Conjunctival Follicles.—Five patients, all but one female, exhibited nodular collections in the conjunctival folds of the lower eyelids. They were associated with erythema nodosum in three patients, and with lupus pernio and bone cysts once. Abnormalities in chest radiographs were observed to clear in two of four patients (Table III). The Kveim test was positive in two of four and the Mantoux test was negative in all four patients; abnormal serum globulins were noted in three of five patients (Table IV). Sarcoid tissue was found by liver or lymph node biopsy in two instances apiece, and by skin biopsy once.

Cataracts.—Cataract formation was sometimes observed as an end-result of chronic iridocyclitis or following prolonged corticosteroid therapy. However, in one instance, bilateral cataracts were the earliest presenting features in a 55-year-old woman, who also had generalized lymphadenopathy, splenomegaly and extensive persistent pulmonary mottling.

Scleral Plaques.—These were observed in one eye twice, and in both eyes once, in two women and one man. It was associated with erythema nodosum, generalized lymphadenopathy, bilateral hilar lymphadenopathy or pulmonary mottling with hilar adenopathy once apiece. The Kveim test was always positive and the Mantoux test always negative (Table IV).

Posterior Uveitis is difficult to detect in the presence of anterior uveitis and may resolve with the latter. It does not figure (except for the one instance of retinitis proliferans) in Table I because it is not a presenting feature of ocular sarcoidosis. In this respect it is overshadowed by iridocyclitis. It was nonetheless perceived by ophthalmoscopy in eleven patients, and also noted in the retina of 2 excised eyes submitted for histology. Six women and five men had choroiditis, occurring in both eyes in five, in the right eye in five, and in the left eye in one. Almost all of these patients had overlying anterior uveitis obscuring the choroiditis. There was associated pulmonary sarcoidosis in six patients, bilateral parotid gland enlargement in three, and Bell's palsy, splenomegaly, and erythema nodosum in one apiece.

The choroidal nodules were usually scattered discrete off-white waxy exudates sometimes causing venous constriction and periphlebitis. One of these cases has already been admirably described in detail (Gould and Kaufman, 1961). In one instance, non-specific periphlebitis retinae was observed (Ainslie and James 1956). It was not distinctive and could have been coincidental to the generalized sarcoidosis.

Relationship of Ocular to Generalized Sarcoidosis

Age and Sex Incidence.—Acute iridocyclitis predominated in the third decade and chronic iridocyclitis in the fifth decade, and this difference probably accounts for the fairly even overall distribution of all types of eye lesions in the third, fourth, and fifth decades (Figs 1 and 2, overleaf). The age range is similar to that observed with skin lesions; both are older groups than those without eye lesions where the peak incidence of onset is in the twenty to thirty decade.

Sarcoidosis affects both sexes to about the same extent but in those patients with ocular lesions (and again like those with skin lesions) there was a conspicuous preponderance of females (Table I).

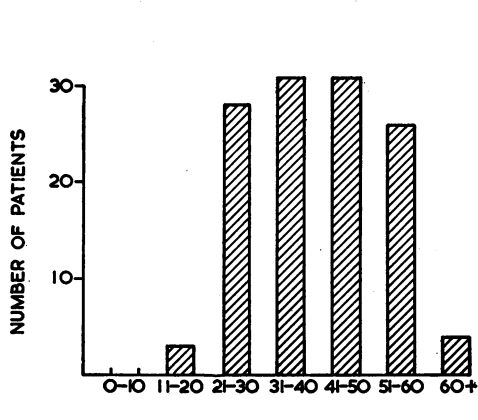


FIG. 1.—Age at apparent onset of all eye lesions in 123 patients.

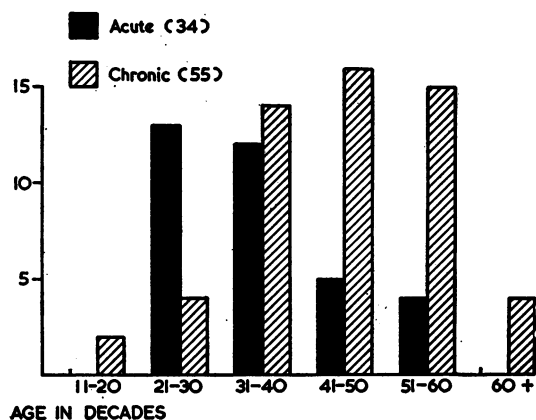


FIG. 2.—Age at apparent onset of acute and chronic iridocyclitis.

Intrathoracic Involvement.—This occurred in 91 of 123 (74 per cent.) patients with ocular disease, the changes ranging from the early stage of bilateral hilar lymphadenopathy to the oldest stage of diffuse pulmonary mottling without hilar adenopathy (Table III). Those with long-standing ocular disease had intrathoracic changes at the older stage of development. The chronicity of the eye lesions was matched by irreversibility of lung lesions. Thus, intrathoracic abnormalities resolved in all patients with acute iridocyclitis and acute conjunctivitis, but only in seven of 34 (20 per cent.) patients with chronic iridocyclitis. Complete radiological clearing was achieved in 56 of 91 (61 per cent.) patients with all types of ocular sarcoidosis.

Skin Lesions.—These included lupus pernio, maculo-papular eruptions, persistent plaques, scars, or erythema nodosum (James, 1959). They occurred in 66 of the 123 (54 per cent.) eye patients, comprising thirty with erythema nodosum and 33 with various other more chronic skin lesions. The simultaneous occurrence of skin plaques or erythema nodosum with uveitis should always arouse the suspicion of sarcoidosis.

Lymphadenopathy.—Enlarged palpable lymph nodes were present at some stage of the disease in 38 per cent. of patients with ocular disease, compared with 31 per cent. of the group without eye manifestations or 33 per cent. of the whole series.

Splenomegaly.—A spleen was palpable in 22 of 123 (18 per cent.) with eye lesions, compared with 9 per cent. without ocular disease or 12 per cent. for the whole series.

Bone Cysts.—Cystic changes in bones of the hands or feet were found radiologically in eleven patients, nine of whom had chronic anterior uveitis. All had accompanying skin lesions, so that the detection of bone changes did not provide diagnostic information not already afforded by examination of the skin.

Lacrimal and Salivary Gland Enlargement.—Enlarged lacrimal glands were observed in seven patients and salivary gland enlargement (principally parotid glands) in thirteen. Five patients had the distressing combination of lacrimal and salivary gland enlargement with kerato-conjunctivitis sicca, so resembling Sjögren's syndrome.

Serum Globulin Levels.—Raised or abnormal serum globulin levels were noted in thirty of eighty (38 per cent.) patients in whom they were determined. There was no significant difference whether ocular lesions were present or absent.

Serum and Urine Calcium Levels.—Hypercalcaemia was found in nine of 72 (12 per cent.) with ocular disease, the same incidence as thirty of 256 (12 per cent.) in the whole series. Hypercalciuria, as judged by repeated 24-hr urine determinations, was noted in five of eighteen (28 per cent.) ophthalmic patients and in nineteen of 65 (29 per cent.) of all patients.

Skin Tests

Mantoux Reaction.—68 of 108 (63 per cent.) with ocular involvement gave negative results with 100 tuberculin units, compared with 61 per cent. with skin lesions or 54 per cent. for the whole series. Positive reactors almost always gave negative results at higher dilutions and 100 tuberculin units were necessary to elicit a positive response (Table IV).

Kveim Tests.—These provided histological confirmation in 77 of 95 (81 per cent.) ophthalmic patients, or 329 of 380 (86 per cent.) in the whole series of patients with histological proof.

Histology

Apart from the results of the Kveim test, histological evidence of sarcoid tissue was also found in various tissues by biopsy of skin (27), lymph node (22), liver (16), excised eye (6), bone (2), tonsil (2), nasal mucosa (1), parotid gland (1), lacrimal gland (1) palate (1), breast (1), lung (1), larynx (1), and at necropsy (1). Biopsy of conjunctiva yielded sarcoid tissue on three occasions when conjunctival follicles were visible. On the other hand, blind conjunctival biopsies (that is, done without visible conjunctival involvement) were negative in ten instances at a time when sarcoid tissue was obtained from other sites.

Treatment

Within a few weeks of the onset of symptoms most of the patients with acute iridocyclitis had received intensive local corticosteroid therapy, eye-drops sometimes being preceded or accompanied by subconjunctival hydrocortisone. They provided relief of symptoms and subsidence of the signs of ocular inflammation, and it was not usually necessary to prescribe additional oral corticosteroids. Interestingly, clinical and radiological features of sarcoidosis also cleared within one year, irrespective of whether or not corticosteroid therapy had been systemic.

The results of treatment of chronic anterior uveitis were disappointing because of the presence of irreversible ocular fibrosis. In the majority, iridocyclitis had preceded the advent of cortisone, and these patients had been subjected to the various regimes in vogue at that time—dental extractions, maxillary antrum lavage, tonsillectomy, cholecystectomy, autogenous vaccines, provocative tuberculin and typhoid vaccine injections, and antituberculous chemotherapy. These regimens were later followed by extraction of cataracts, iridectomy, or even enucleation of the eye.

Posterior uveitis was clearly seen by ophthalmoscopy when vigorous corticosteroid therapy had overcome the signs of anterior chamber activity. Perivenous nodules and peripherally-situated waxy plaques are more persistent, and prolonged vigorous oral corticosteroid therapy is indicated when there are changes in the fundus oculi.

Conjunctivitis subsided without special treatment, and combined oral and topical corticosteroids helped to resolve conjunctival follicles and scleral plaques.

Kerato-conjunctivitis sicca causes distressing symptoms which may be relieved somewhat by steroids, but are liable to recur when steroids are discontinued. It is usually necessary to continue prolonged courses of treatment with the smallest maintenance dose which relieves symptoms. There is no reason for giving anti-tuberculous chemotherapy in any form of ocular sarcoidosis.

Discussion

The commonest presentation of ocular sarcoidosis is anterior uveitis, which may be acute or chronic. There appear to be clear-cut differences between the two types, not only in the eyes but also in other systems (Table V). Acute iridocyclitis presents suddenly in young people in the third decade. There is evidence of acute inflammation which can be expected to subside without complications. Sarcoid lesions in

TABLE V
A COMPARISON OF ACUTE AND CHRONIC UVEITIS IN 89 PATIENTS WITH ANTERIOR UVEITIS DUE TO SARCOIDOSIS

Uveitis	Acute	Chronic
No. of Patients	34	55
No. Bilateral Mode of Onset Decade of Onset (yrs)	24 Sudden 20-30	52 Insidious 40-50
Signs	Ciliary congestion Turbid aqueous K.P.*	Fatty Nodules Synechiae Iris Lens
Sequelae	None	Lens Opacities Glaucoma Cataract Blindness
Chest x-ray Resolution	29/29 (100 per cent.)	7/34 (20 per cent.)
Skin Lesions { Erythema nodosum Other	12 2	3 24
Bone Cysts	0	9
Spleen	3 (9 per cent.)	11 (20 per cent.)
Bell's Palsy	4 (11 per cent.)	2 (4 per cent.)
Lacrimal Gland Involvement	0	1
Parotid Gland Enlargement	1	7
Duration before Cortisone (yrs)	Nil	1-14

* K.P. = Keratic precipitates

other systems also appear to be benign and self-limiting. In our series the intrathoracic abnormalities always cleared, and skin lesions were almost always of the transient type such as erythema nodosum. By contrast, chronic iridocyclitis developed insidiously and was more usually observed for the first time in patients in the fifth decade. Rather than acute inflammation, the signs were those of granuloma formation and fibrosis with synechiae sticking iris to lens. Sequelae included glaucoma, cataract formation, and even ultimate blindness. Chronic iridocyclitis was usually accompanied by indolent skin lesions (such as lupus pernio) and bone cysts, both of which constitute the hallmark of chronicity in sarcoidosis. Intrathoracic changes persisted and a clear chest radiograph was achieved in only seven of 34 (20 per cent.) patients with initially abnormal x rays. The early recognition and treatment of iridocyclitis with corticosteroids undoubtedly leads to a favourable outcome and less residual ocular disability. Such therapy has almost certainly changed the natural history of sarcoid iridocyclitis. But this cannot be the complete explanation, for acute iridocyclitis may resolve without the benefit of corticosteroids and the accompanying extra-ocular lesions (erythema nodosum, lung changes, lymphadenopathy) are also seen to subside without treatment. The favourable outcome of acute compared with chronic uveitis must be related to spontaneous remission as well as to corticosteroid therapy (James, 1961).

Other well-defined syndromes of ocular sarcoidosis include Bell's palsy associated with acute or chronic uveitis, and kerato-conjunctivitis sicca with or without parotid and lacrimal gland involvement.

There are no pathognomonic distinguishing features of sarcoid uveitis and conjunctivitis, so that it is necessary to formulate a routine which may help segregate those cases due to sarcoidosis. In addition to slit-lamp examination, it is useful to perform a chest radiograph which is abnormal in three-quarters of instances of ocular sarcoidosis, and to assess the serum calcium level for this was elevated in one-eighth of the current series. The clinical diagnosis should be confirmed, whenever possible, by histological proof. This is best achieved by the Kveim test; by biopsy of conjunctival follicles, (Crick, 1956; Crick, Hoyle, and Smellie, 1961) skin lesions or enlarged lymph nodes; or by blind biopsy of liver, gastrocnemius, or the right scalene node.

The natural history of sarcoidosis tends towards spontaneous healing by fibrosis. In the eye, this may cause devastating complications, so that ocular involvement is an indication for careful serial observation and energetic corticosteroid therapy. This should always be administered topically and, if necessary, supplemented by oral administration. Posterior uveitis is a pressing indication for vigorous and prolonged systemic corticosteroid therapy.

Summary

Ocular lesions were observed in 123 of 442 (27.8 per cent.) patients with histologically confirmed generalized sarcoidosis. They included acute and chronic anterior uveitis, conjunctivitis, kerato-conjunctivitis sicca, and conjunctival follicles. The striking difference between acute and chronic anterior uveitis also extended to extra-ocular systems, including the lungs, skin lesions, bone cysts, and splenomegaly. The difference in the natural history of the two conditions was only partly explained by

early corticosteroid therapy. Acute iridocyclitis, like acute sarcoidosis elsewhere, also tends towards spontaneous remission.

Ocular sarcoidosis is commonly accompanied by intrathoracic and cutaneous lesions, lymphadenopathy, and splenomegaly. Lacrimal gland and parotid gland involvement may lead to reduced secretions and to kerato-conjunctivitis sicca, superficially resembling Sjögren's syndrome.

The clinical diagnosis should always be confirmed by histological evidence of sarcoid tissue either by biopsy of the affected tissues (skin, lymph node, or conjunctival follicles); by blind biopsy of liver or the right scalene lymph node; or by means of the Kveim test.

The natural history of sarcoidosis tends towards spontaneous healing by fibrosis. In the eye this may cause serious disability, which is best avoided by corticosteroid therapy. There is no indication for antituberculous chemotherapy or for a witch-hunt for focal sepsis in ocular sarcoidosis.

REFERENCES

- AINSLIE, D., and JAMES, D. G. (1956). *Brit. med. J.*, **1**, 954.
 CRICK, R. PITTS (1956). *Trans. ophthal. Soc. U.K.*, **76**, 403.
 ———, HOYLE, C., and SMELLIE, H. (1961). *Brit. J. Ophthal.*, **45**, 461.
 GOULD, H. L., and KAUFMAN, H. E. (1961). *Amer. J. Ophthal.*, **52**, 633.
 JAMES, D. G. (1959). *Quart. J. Med.*, **28**, 109.
 ——— (1961). *Amer. Rev. resp. Dis.*, **84**, Suppl. p. 66.