Sarcoid Heart Disease

HUGH A. FLEMING, MD FRCP

Cardiologist, East Anglian Regional Health Authority, Cardiac Unit, Papworth Hospital, and Addenbrooke's Hospital, Cambridge.

SHEILA M. BAILEY, MB,

Research Assistant, Papworth Hospital Cambridge.

Sarcoidosis is a not uncommon systemic disease that can affect many organs. A brief definition[1] characterises it as 'the presence in all of several affected organs or tissues of epithelial cell tubercles without caseation'. The aetiology has been widely discussed but is really unknown[2].

The recognition of sarcoid heart disease has been slow, for sarcoidosis was first described in 1889 by Besnier[3] and the first description of heart involvement was in 1929[4]; the first death from this cause was reported in 1937[5]. Thereafter there were occasional reports of small numbers of cases, frequently in negroes in the southern states of the USA. The suggestion long persisted that cardiac sarcoidosis was rare, and by 1971 Gozo *et al.*[6], searching the entire literature, found a total of only 70 cases. The varied clinical and pathological features of the disease were soon established and well reviewed[7]. Japanese workers[8, 9] have made particularly valuable contributions to our knowledge of this condition. Pathological studies at Johns Hopkins[10] have demonstrated the high incidence of cardiac involvement in patients dying with sarcoidosis.

The recognition of sarcoid heart disease in the UK is of interest and suggests that many of us have had, and may indeed still have, a blind spot for this diagnosis. In 1962, Forbes and Usher[11] described a classical fatal case in a 44-year-old man with massive cardiac involvement but minimal involvement elsewhere. This remained the sole British case until 1972, when six cases were reported from Cambridge[12]. Subsequent enquiries led to the report of 50 United Kingdom cases, 20 with necropsy confirmation[13]. These studies continue[14] and the present paper reports 197 cases notified to us in the 10 years of this study up to the end of 1980. The vast majority have presented with cardiac problems and have not resulted from cardiac screening of patients already known to have sarcoidosis[15].

Criteria for Inclusion in Series

All cases have a cardiac condition compatible with sarcoid involvement of the heart; there is a definite clinical diagnosis of sarcoidosis which, in most, is confirmed by histological examination of some tissue in life (119 cases). The only final proof can be at necropsy (62 cases) or by myocardial biopsy. Many submitted cases are rejected, as the evidence is considered to be inadequate for a definite diagnosis of sarcoidosis.

Sarcoid heart disease may precede other manifestations of sarcoidosis by as long as three years. In other cases the reverse is true; one woman developed sarcoidosis at the age of 26, but was 38 before heart block appeared.

Distribution of Cases

The map (Fig. 1) shows the distribution of cases known to us. The lack of cases in the northern part of the country is striking. As colleagues there diligently supply progress reports of the few known cases this does not seem to be explained by poor communication. In contrast, there is a great concentration of cases in East Anglia (total 78), and the City of Ely, population 10,000, has three cases of sudden death in men aged 25 to 40 years. This matter obviously merits continuing study[14].

Clinical Presentation

The vast majority of the 197 cases presented with cardiac problems. There were 106 men and 91 women and, of the patients, 185 were white and 12 were coloured. The age range was 18-88 years (mean 44.7). There was no particular emphasis on any age group. This is at variance with the Japanese observation[9] that there is an especially high incidence in middle-aged women. The white dominance dispels the idea that in the UK, at least, sarcoid heart disease has a predilection for coloured people.

Thirty-four cases died suddenly and the diagnosis was first made at necropsy. Even then, the pathologists did not always find the aetiological diagnosis easy. Macroscopic findings were frequently described as tumour[16] and it was only on microscopic examination that the true pathology was evident. Another common feature was to describe 'ischaemic fibrosis' of the myocardium with normal coronary arteries—obviously without thinking of the possibility of sarcoid[17].

Fig. 1. *Map of the UK showing distribution of the cases of sarcoid heart disease, 1971-80 (197 cases, of which 23 were single cases from places other than those named).*

Clinical Aspects of Cardiac Sarcoidosis

Table 1 lists the cardiac features when the patients presented. This list adds up to more than the 197 patients, as any one case frequently showed more than one feature—indeed, bizarre forms of heart disease, often with varying rhythms, difficult to control, were characteristic of the condition and this combination should always bring the diagnosis to mind. As sarcoidosis may be inconspicuous in other organs it must be diligently sought[11, 13].

Heart Block

Complete heart block has developed in 42 patients whose ages range from 20 to 78 years (average 51.1). Sarcoid should be suspected in younger than average patients developing heart block. Lesser forms of heart block are common and right bundle branch block is particularly frequent. Considering the frequent intensive involvement of the conducting system, these conduction disturbances are not surprising. Of those with complete heart block, there were equal numbers of men and women. Thirty-one patients were paced and seven reverted to sinus rhythm; four died without being paced.

The prognosis of this heart block, indeed of sarcoid heart disease, is very difficult to determine in the individual patient, and this is illustrated by the following two contrasting female cases.

D. W. (Fig. 2) has already been reported[13]. The varied arrhythmias are characteristic. The complete heart block of 8.9.66. reverted to sinus rhythm without treat-

Table 1. Cardiac features at time of presentation.

Cardiac features	No. of cases
Ventricular ectopics, ventricular tachycardia	77
First degree heart block and BBB (especially RBBB)	71
Complete heart block	42
Supraventricular arrhythmias	47
Sudden death	34
Myocardial disease	31
Simulating myocardial infarction	13
Pericarditis	4
Road traffic accident	3
(Valve involvement infrequent)	

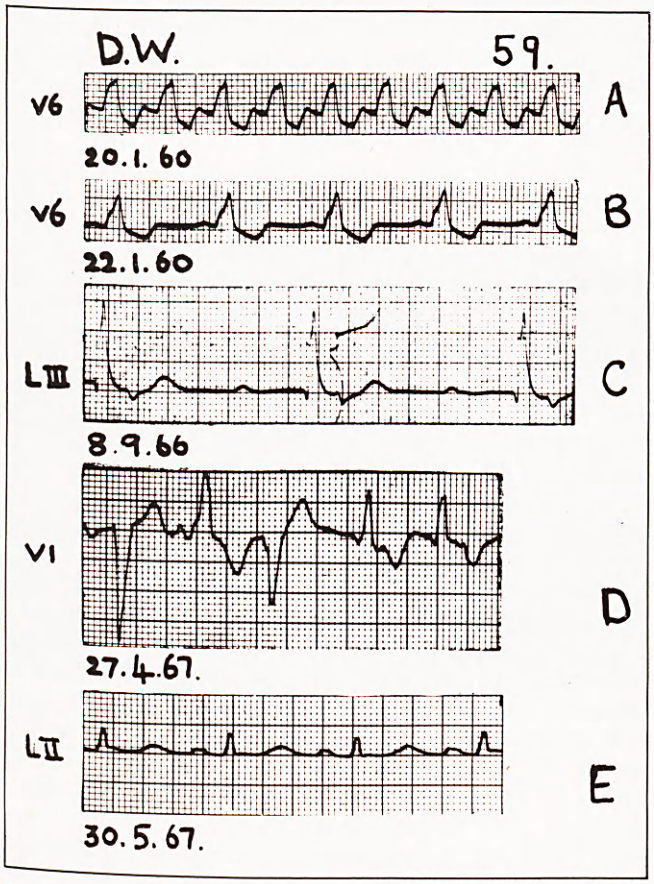


Fig. 2. *These ECGs are taken from the file of a woman (D. W.) aged 59 at the time of death, and show the characteristic variable arrhythmia, starting in 1960 with a supraventricular tachycardia with bundle branch block* (A), *then sinus rhythm with LBB* (B), *complete heart block* (C), *multifocal ventricular ectopic beats* (D) *and* (E) *sinus rhythm with slight prolongation of the PR interval and the QT interval but otherwise normal ventricular complexes, shortly before death. (Courtesy* British Heart Journal.*)*

ment and her last ECG was her most 'normal' showing only slight prolongation of the PR interval. It might have been reasonable to feel that the prognosis was then good, but when she died shortly afterwards[12] the myocardium was severely involved in fibrous and active granulomatous tissue.

C. P., born in 1943, is unusual in this series in that she presented with very severe pulmonary sarcoidosis in 1969 and this was followed by conjunctivitis. The Kveim test was positive and she was treated with steroids which caused very severe adverse effects. In 1975 she was noted to have a slow pulse (40 per minute), and ECG confirmed complete heart block. She was referred for pacing but was so disenchanted with medicine as a result of the steroids (which had been stopped) that she refused this. She has been given no treatment but has been followed carefully with 24-hour ECG tapes and has remained well. In April 1976 she reverted to sinus rhythm with a PR interval of 0.4 of a second, which has subsequently shortened and has been stable at 0.28 of a second for the last two years. Tapes have been satisfactory and one hopes that the prognosis is good.

The oldest patient in the series (S. C.) was 88 when she died following an operation on a fractured femur after a fall. She had first degree heart block, left bundle branch block, and at necropsy a very large heart with extensive sarcoid involvement of the myocardium and also of other organs. Review of her old notes showed that four years previously, when she had had a cholecystectomy, she had an even worse conduction defect, and an astute pathologist had reported sarcoidosis in a lymph node attached to the gallbladder.

Sudden Death

Sudden death is regrettably frequent and occurred in 48 patients, being the presenting symptom in 34. The pathology of cases who have died during follow-up invariably showed severe disease and it would be optimistic to think that any treatment would have had much effect on reversing the pathology. However, in fatal cases it is remarkable how grossly abnormal hearts have been able to support a normal life until the sudden death has taken place[13].

F. A. was a 27-year-old police sergeant who worked normally until he died suddenly at home after a meal. At necropsy all chambers of the heart were extensively involved with sarcoid tissue and the full thickness of the left ventricle (Fig. 3) was largely replaced by granulomatous tissue with some scarring. This tissue also appeared on the epicardium and the endocardium and involved the smaller branches of the coronary arteries. Lymph nodes, lung, spleen and liver were also affected.

G. G. was a 25-year-old man who once complained to his doctor of transient palpitations and a long time later died at home while washing dishes. At necropsy the heart weighed 550 g. At the apex (Fig. 4) there was an aneurysm where the muscle was totally replaced by fibrotic and granulomatous tissue. The interventricular septum was grossly thickened and the rest of the myocardium was severely affected. Fig. 5 shows the histology of the aneurysm wall; the myocardium is almost replaced by granulomatous and fibrous tissue. The coronary arteries were normal and sarcoid was present in lymph nodes, lungs, spleen and liver. Dr P. G. I. Stovin made detailed studies of the conducting system which was totally replaced by sarcoid tissue (Figs. 6, 7).

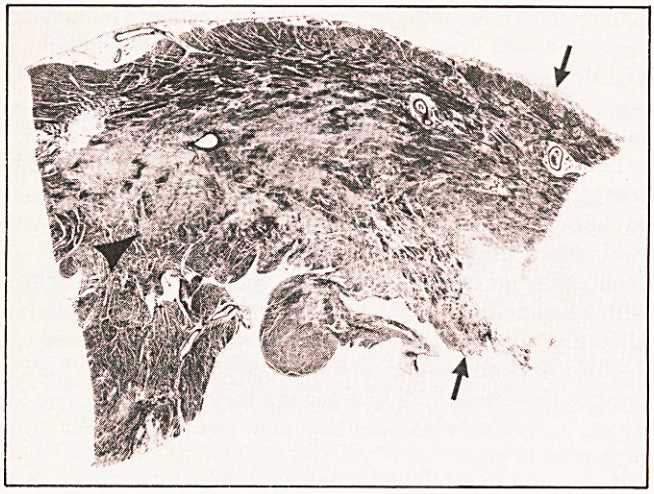
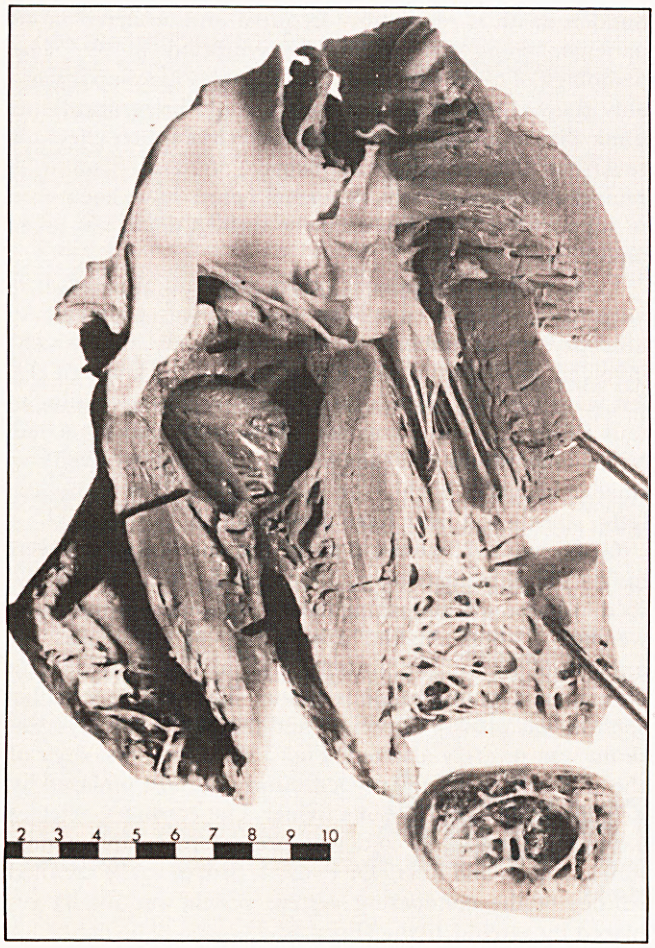


Fig. 3. *(S. A.) Full thickness section of the left ventricular wall showing the granulomatous replacement of most of the myocardium and also pericardial and endocardial involvement. The arrows indicate the edge of the major lesions (epicardium superior). The area within the arrows is largely granulation tissue.*

Fig. 4. *(G. G.) A 24-year-old man dying suddenly. Massive involvement of the myocardium by granulomatous and fibrous tissue. Thinning of the apex of the left ventricle with aneurysm formation is clearly seen.*



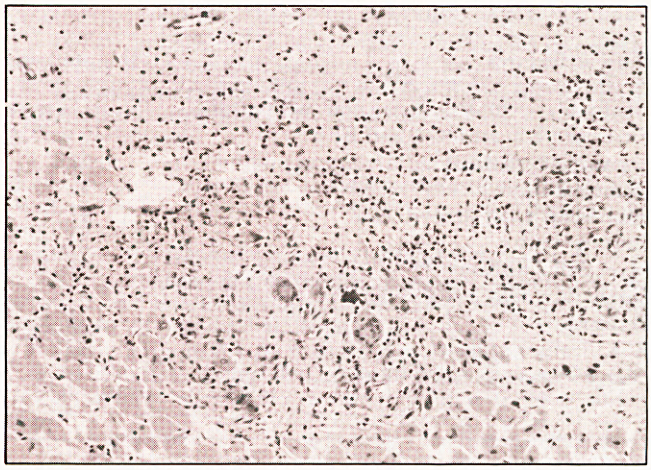


Fig. 5. *(G. G.) Photomicrograph of the wall of the left ventricle in the region of the aneurysm. The myocardium is almost entirely replaced by fibrosis and granulomatous tissue.*

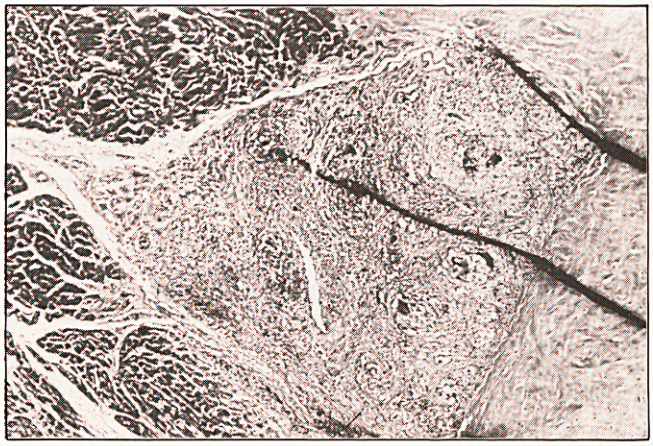
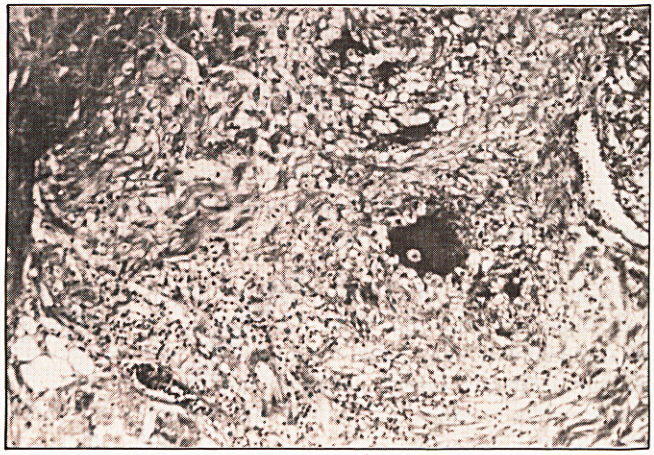


Fig. 6. *(G. G.) Right bundle entirely replaced by granulomatous tissue.*

Fig. 7. *(G. G.) Higher magnification of right bundle showing giant cell with asteroid body.*



Cardiomyopathy

An example of cardiomyopathy was provided by a 39-year-old man who, unusually in this series, was a West Indian. He had a past history of uveitis and bilateral hilar lymphadenopathy and presented in gross congestive cardiac failure with mitral incompetence and gross cardiomegaly. The ECG showed sinus rhythm, atrial ectopic beats, right bundle branch block and frequent multifocal ventricular ectopic beats. Sarcoidosis was diagnosed but despite full treatment, including steroids, he went into ventricular fibrillation and died.

At necropsy the heart weighed 590 g and the entire myocardium was flabby and abnormal with numerous areas of infiltration. The papillary muscles of the mitral valve were replaced by yellow material which was sarcoid granuloma. The conducting tissue was largely replaced by sarcoid tissue, and the lymph nodes, lungs, spleen and liver were also involved.

Simulation of Myocardial Infarction

Where there is full thickness replacement of the myocardium by fibro-granulomatous tissue, the electrocardiographic appearances are those of transmural myocardial infarction. Chest pain and arrhythmia further suggest this diagnosis and may be very convincing[13].

Valve Involvement

Valve involvement of important degree is infrequent and is rarely a presenting feature. Six cases have been noted to have early aortic diastolic murmurs and in one case, where a congenitally stenotic aortic valve was replaced, sarcoid granulomata were found on the excised valve[12]. Sarcoidosis was incidental in this valve and none of the diastolic aortic murmurs were accompanied by haemodynamic disturbance.

Mitral valve involvement appears more common and mitral systolic murmurs have been noted in 46 cases. These are frequently transient or recurrent but often become permanent. It seems likely that they are due to papillary muscle involvement. We know of only two cases who have had mitral valve replacement. One valve was damaged by a mixture of rheumatic heart disease and sarcoidosis and in the other (V. H.), a congenitally cleft mitral valve was found at operation to be associated with complete destruction of the papillary muscles by a granulomatous sarcoid that had exaggerated the initial regurgitation. Similar findings at necropsy are not uncommon, and for this reason we recommend a careful clinical and echocardiographic examination of the mitral valve. Awdeh *et al.*[18] reported a case in which systolic anterior movement of the mitral valve suggesting HOCM proved at necropsy to be due to massive sarcoid involvement of the ventricular septum.

The following case shows many interesting features which include long delay in diagnosis, unusual findings at mitral valve replacement, a positive histology of the papillary muscles but a negative Kveim test and endomyocardial biopsy.

V. H. is a woman now aged 68. In 1953 a mitral systolic murmur was noted. In 1960 she had multifocal ventricular ectopic beats. Thereafter she was admitted to different hospitals on numerous occasions with varied serious rhythm problems—often needing DC version. She was extensively investigated as a 'cardiomyopathy' but the Kveim test was not done. In 1980 she was referred back to us with gross mitral regurgitation confirmed by investigation. The left ventricular angiogram showed a very curious 'aneurysm' of the inferior surface just below the mitral valve. At operation for mitral valve replacement, the surgeon reported appearances he had not previously seen. The left ventricular myocardium was extensively replaced by 'fatty material' and the interior of the left ventricle was seen to be much involved in a similar fashion. There was a congenital cleft of the anterior leaflet of the mitral valve. The papillary muscles were yellow and attenuated due to complete replacement by sarcoid granulomatous tissue, and the correct diagnosis was made for the first time. Endomyocardial biopsy of the right ventricle was carried out, as it was thought it might be helpful in assessing the response to treatment, but it was negative, as was the Kveim test. She recovered satisfactorily and continues on steroids.

Diagnosis

Diagnosis is usually made on the basis of a cardiac condition compatible with sarcoidosis for which there is no other available explanation. Then evidence of sarcoid is sought and may lie in any of the systems mentioned. Whenever possible, histological confirmation of the diagnosis is sought from any available biopsy material such as lymph glands, skin, mucosa or conjunctiva. The Kveim test is useful when positive, but it may be negative in histologically proven cases of sarcoidosis. Bronchial or transbronchial lung biopsy can be useful.

Some clinicians still make the diagnosis solely on clinical grounds and do not feel it necessary to pursue histological evidence in such cases. To include these cases in our series we would need the strongest possible clinical indications.

Endomyocardial biopsy is diagnostic when positive but of no value if negative[19]. This is not surprising when one considers the patchy distribution of the disease and the fact that the deep layers of the myocardium, especially the ventricular septum, are most commonly involved. Sekiguchi and his colleagues[9] examined seven hearts involved in fatal sarcoidosis and simulated myocardial biopsy at 10 separate sites in both the right and the left ventricle. Even in these grossly involved hearts a considerable percentage of biopsies were negative—37 per cent in the right ventricle and 53 per cent in the left ventricle. These findings indicate that cardiac biopsy is not a helpful method of assessing treatment, as has been suggested[20].

Other Organs

Sarcoidosis is a systemic disorder and, although there may be a heavy emphasis on the involvement of the heart, the other organs affected by classical sarcoidosis are similarly affected in this series. However, the involve-

ment may be inconspicuous—certainly clinically—and even at necropsy a careful search may be necessary.

Clinical or necropsy features of sarcoidosis occurred with the usual frequency in other organs, most commonly bilateral hilar lymphadenopathy, lungs, eyes, lymph nodes, skin, spleen and liver, and less commonly in brain, nerve, pituitary, parotid, bone, uterus, kidney, thyroid and vulva.

Deaths

Cardiac sarcoidosis is often a fatal condition which no cardiologist can enjoy diagnosing. Eighty patients have died (average age 50.7 years), the diagnosis being confirmed by necropsy in 62. In 48, death was sudden and in 34 it was the presenting symptom, neither heart disease nor sarcoidosis having been previously suspected.

In our earlier report[13], three fatal cases had been involved in road traffic accidents—one, a man of 49, died at the wheel of his car while on holiday in Cambridge. This prompted one of us (H. A. F.) to raise in discussion at the European Congress of Cardiology in 1976 the possible importance of sarcoidosis in cardiological aspects of flying. At that time no one present had experience of a case, but there have subsequently been unpublished reports of a number of Services incidents in different parts of the world, in which sarcoid heart disease was strongly implicated. The matter has been discussed in two publications[21, 22]. Silverman *et al.*, in a necropsy study of 84 patients dying with sarcoidosis[10], found myocardial granulomata in 27 per cent, and the figure could well be higher[23]. It is our view that no one with sarcoidosis should fly single-handed and, as the clinical cardiac involvement may follow many years after other manifestations, this prohibition should probably be indefinite.

Further Investigations

When the diagnosis has been made, more detailed assessment of the patient should follow. Echocardiography should look in particular for abnormal mitral valve movement and abnormality of the ventricular septum and the left ventricular function and its free walls. A 24-hour ECG tape with exercise testing is reassuring if it excludes significant arrhythmia. If it reveals arrhythmia, treatment may be necessary. Radio-nucleide myocardial imaging[24, 25] may reveal lesions—but, to be detected, they would need to be of 1 cm or more in diameter. Angiotensin-converting enzymes may be of assistance in assessing the activity of sarcoid granulomatous tissue[14].

Any suspected case should be followed closely for any further developments—24 hour ECG tapes are particularly important in this and any change should be regarded as an indication for aggressive treatment. Follow-up should be life-long.

Treatment

It will be obvious that heart block should be treated by pacing; congestive heart failure and rhythm changes require routine treatment. The arrhythmias can be very varied and difficult to treat; the list of the drugs used includes every possible cardiac drug.

Steroids should not be withheld if there is any reason to suppose that they can be helpful. Such a decision is easy in the sick patient but less easy in one who is well. The decision about when to start and when to stop must depend on fine clinical judgement. Steroids have been used in 80 patients in this series. There are reports of myocardial biopsy[20] and electrophysiological studies[26] being used to assess the effect of treatment but, for reasons already stated, these will be of little assistance. The extremely variable history of sarcoidosis without treatment compounds the difficulty of assessment.

Our present advice is: 'If in doubt, try steroids—you can't afford not to.'

Surviving Patients

One hundred and sixteen patients survive and are being followed. It is our hope that from this study we will build up a better knowledge of the natural history of this disease and the effects of treatment. The numbers of men and women are again nearly equal; the average age at presentation is 43 years.

Twelve patients have survived for more than 10 years since presentation and four for more than 20 years. These are a varied series, but they all had serious heart disease. Some are still treated with steroids and anti-arrhythmic drugs, some are paced, and others are well without treatment.

S. H. (female, born 1936) is an example of long survival in spite of severe disease. In 1964 she presented with uveitis and developed cranial nerve lesions and hypercalcaemia. Cervical lymph node biopsy was positive for sarcoidosis. She was treated with steroids for eight months. In 1965 she developed erythema nodosum and in 1968 heart failure with ventricular tachycardia needing DC version and procaine amide. In 1969 she had first degree heart block and a mitral systolic murmur. In 1970 there was a further severe attack of heart failure and ventricular tachycardia and these were both a problem in 1974. In 1975 she was well but the mitral systolic murmur persisted. In 1977 she was well but had first degree heart block, left bundle branch block, multifocal ventricular ectopic beats and considerable cardiomegaly. Yet in 1980 she was still well and her ECG was normal.

Pathology

The cardiac pathology found in our series is similar to that recorded by other pathologists[8, 9, 27-29]. We would only point out that aneurysm can occur without steroid treatment.

The salient features are infiltration, to a varying degree of the myocardium, of any or all of the cardiac chambers, with frequent involvement of the pericardial and epicardial surfaces. The interventricular septum is often involved, as are the papillary muscles, and at times the conducting tissue is extensively replaced. The valves themselves are rarely involved. The small coronary arteries are sometimes affected. In the less gross case a

very careful necropsy is necessary and patient microscopic examination of the myocardium may be needed if the diagnosis is not to be overlooked; the ventricular septum should be searched with special care.

Summary

Myocardial sarcoidosis is not a rare disease in the UK and it is still probably under-diagnosed. A high index of suspicion is necessary for diagnosis of myocardial sarcoidosis, which should be thought of in any unusual form of heart disease for which there is no adequate explanation, particularly if there are serious rhythm changes or unexplained heart failure. Mitral systolic murmurs occur frequently. Histological proof of the aetiology should be sought. The heart is frequently massively involved when other organs have little involvement.

Most of these patients present with cardiac symptoms or signs and the high incidence of sudden death is disturbing. The high rate of occurrence in East Anglia is noted, and merits further study.

Treatment should be energetic where indicated—but its effects are difficult to assess.

This study, representing the largest single source of information on this topic, continues in the hope of shedding more light on a sinister disease.

Acknowledgements

This study is supported by the East Anglian RHA Research Fund.

Grateful thanks are due to a multitude of colleagues for notifying details of cases and continuing to provide information. Many pathologists, too numerous to mention by name, have been generous in the donation of pathological material, some of which is illustrated here. Without the continued co-operation of these colleagues and their secretaries the study would not be possible.

This article is based on a paper read at the Cardiology Conference held at the Royal College of Physicians in November 1980.

References

1. Scadding, J. G. (1967) *Sarcoidosis,* p. 291. London: Eyre & Spottiswoode.
2. Mitchell, D. N. and Scadding, J. G. (1974) *American Review of Respiratory Disease,* **110,** 774.
3. Besnier, E. (1889) *Annales de Dermatologie et de Syphilologie, Paris,* **10,** 333.
4. Bernstein, M., Konzellman, F. W. and Sidlick, D. M. (1929) *Archives of Internal Medicine,* **44,** 721.
5. Gentzen, G. (1937) *Beitrage zur pathologischen Anatomie,* **98,** 375.
6. Gozo, E. G., Cosnow, I., Cohen, H. C. and Okun, L. (1971) *Chest,* **60,** 379.
7. Porter, G. H. (1960) *New England Journal of Medicine,* **263,** 1350.
8. Matsui, Y., Iwai, K., Tachibana, T., Furuie, T., Shigematsu, N., Izumi, T., Homma, A. H., Mikami, R., Hongo, O., Hiraga, Y. and Yamamoto, M. (1976) *Annals of the New York Academy of Science,* **278,** 455.
9. Sekiguchi, M., Numao, Y., Imai, M., Furuie, T. and Mikami, R. (1980) *Japanese Circulation Journal,* **44,** 249.
10. Silverman, K. J., Hutchins, G. M. and Bulkley, B. H. (1978) *Circulation,* **58,** 1204.
11. Forbes, G. and Usher, A. (1962) *British Medical Journal,* **2,** 771.
12. Ghosh, P., Fleming, H. A., Gresham, G. A. and Stovin, P. G. I. (1972) *British Heart Journal,* **34,** 769.
13. Fleming, H. A. (1974) ibid., **35,** 54.
14. Fleming, H. A. (1980) *Thorax,* **35,** 641.
15. Mikhail, J. R., Mitchell, D. N. and Ball, K. P. (1974) *Proceedings VI International Conference on Sarcoidosis,* University of Tokyo Press.
16. Fawcett, F. J. and Goldberg, M. J. (1974) *British Heart J.,* **36,** 220.
17. Fleming, H. A. (1979) *British Medical Journal,* **2,** 1146.
18. Awdeh, M. R., Erwin, S., Young, J. M. and Nunn, S. (1978) *Southern Medical Journal,* **71,** 969.
19. Fleming, H. A. (1980) *British Heart Journal,* **43,** 366.
20. Lorell, B., Alderman, E. L. and Mason, J. W. (1978) *American Journal of Cardiology,* **42,** 143.
21. Hill, I. R. (1977) *Aviation, Space, and Environmental Medicine,* p. 953.
22. Pettyjohn, F. S., Spoor, D. H. and Buckendorf, W. A. (1977) *Aviation, Space, and Environmental Medicine,* p. 955.
23. Fleming, H. A. (1979) *Circulation,* **59,** 1336.
24. Bulkley, B. H., Rouleau, J. R., Whitaker, J. Q., Strauss, H. W. and Pitt, B. (1977) *Chest,* **72,** 27.
25. Kinney, E. L., Jackson, G. L., Reeves, W. L. and Zelis, R. (1980) *American Journal of Medicine,* **68,** 497.
26. Friedman, H. S., Parikh, N. K., Chander, N. and Claderon, J. (1976) *European Journal of Cardiology,* **4,** 141.
27. Bashour, F. A., McConnell, T., Skinner, W. and Hanson, M. (1968) *Diseases of the Chest,* **53,** 413.
28. Morales, A. R., Levy, S., Davis, J. and Fine, G. (1974) *Pathology Annual,* **9,** 139. (ed S. C. Sommers.) New York: Appleton-Century-Crofts.
29. Roberts, W. C., McAllister, H. A. and Ferrans, V. J. (1977) *American Journal of Medicine,* **63,** 86.