The treatment of sarcoidosis

HAROLD L. ISRAEL

Sarcoidosis Clinic, Thomas Jefferson University School of Medicine, Philadelphia

Summary

A discouraging conclusion to many years of study of the natural history of sarcoidosis is the realization that the proper word for the course of sarcoidosis is ‘unpredictable’. An impressive lesson of a controlled study was the frequency with which unexpected and dramatic improvement occurred in the placebo group. Although patients with pulmonary infiltration, uveitis and cutaneous sarcoid have a worse prognosis than the asymptomatic patient with hilar adenopathy, many patients in the former category will recover and some in the latter will go on to death.

A trial of prednisone therapy in a small number of patients with disease restricted to the mediastinal and hilar nodes (Stage I) suggests that prednisone treatment in this form of sarcoidosis may minimize dissemination and progression. An extended trial in Stage I sarcoidosis appears warranted. In more disseminated forms of the disease, the effects of corticosteroids seem to be merely palliative: there is no persuasive evidence that their use in pulmonary sarcoidosis averts fibrosis.

Occasionally corticosteroid therapy is contraindicated, poorly tolerated, or ineffective. In such circumstances chlorambucil or methotrexate may be given a trial. It is clear that both drugs exert an anti-inflammatory action similar to that of the corticosteroids; in a few instances these agents appear to surpass corticosteroids in effectiveness.

Corticosteroid treatment was introduced shortly after sarcoidosis became commonly recognized. Few observations are as a result available regarding the natural history of the disease. The therapeutic effects of corticosteroids are so well established in ocular, myocardial, CNS and endocrine forms of sarcoidosis that their use cannot be withheld for purposes of therapeutic trials. Prednisone therapy, in most series, has been given to approximately a third of patients indicating that clinicians in all countries usually find that two-thirds of patients have benign disease not requiring treatment.

The course and prognosis of sarcoidosis appear to be influenced by many factors. Progressive and fatal disease is somewhat more frequent in American studies than in European ones, in part because of the predominance of Negro patients in the former. The differences are merely ones of degree, however: advanced pulmonary fibrosis is by no means infrequent among white American patients and the lesser likelihood of a fatal end in this race may largely reflect educational and economic advantages which result in earlier and more constant medical care. Even greater than these effects, however, is the influence of selection. Physicians chiefly involved in hospital practice, whether in Norway, Great Britain or the United States, report a high frequency of progressive and malignant disease while physicians dealing with asymptomatic patients whose sarcoidosis was detected in radiographic surveys will describe a disease that is usually benign.

The one major difference in behaviour of sarcoidosis between the United States and Europe, is that of the course of Stage I disease. Most English and Scandinavian studies indicate an almost invariably benign course in patients free of pulmonary infiltration at the time of diagnosis, although Scadding notes that a third of his patients with hilar adenopathy developed pulmonary infiltration under observation. This experience resembles that of American investigators where the prognosis in Stage I is not significantly better than in Stages II and III. In a recent Philadelphia study, improvement was observed in 63% of patients who had entered with hilar adenopathy alone, and 52% of those who had had pulmonary invasion when first observed. But although asymptomatic patients detected in routine surveys have a greater likelihood of quick recovery than patients ill with breathlessness, uveitis, or other extrapulmonary manifestations, the prognosis in the individual case is unpredictable. Some patients discovered with Stage I disease clear completely, others have massive adenopathy for years, and others develop pulmonary infiltration which in turn may be transient or progressive. Spontaneous clearing may occur in a few months, or only after several years. It is a question whether the most remarkable feature of sarcoidosis is the spontaneous clearing of dense infiltrates or the insidious development of diffuse fibrosis and cysts.
Pulmonary physiologists have tended to study symptomatic patients and have been impressed by the frequency of respiratory impairment even in patients with minimal radiologic evidence of damage. Physicians with this experience are likely to urge the wide use of steroid therapy in the hope of averting fibrosis. Physicians in outpatient clinics see patients whose course is as a rule favourable, so that treatment of all patients with hazardous drugs appears unjustifiable. Physicians whose experience encompasses both groups are likely to conclude that corticosteroids suppress the manifestations of sarcoidosis without altering the eventual outcome (Scadding, 1967; Israel, Sones & Harrell, 1954). Although the immediate effects of corticosteroids on the lesions of sarcoidosis, as demonstrated by pathologic (Sones et al., 1951), physiologic (Sharma, Colp & Williams, 1966) and clinical studies (Hoyle, 1967) are quite consistent and often striking, the long term effects are less impressive. It might be anticipated that the symptomatic effects of prednisone would make this drug a popular one with patients. On the contrary, many patients are dismayed by enormous weight gain; this is a frequent cause of cessation of treatment, in women especially.

Trial-and-error experience has taught some generally accepted lessons:

Indications for treatment: the readily demonstrable value of steroids for ocular, myocardial and neural involvement and for hypercalcaemia makes their use essential in these circumstances. It has generally been considered obvious that therapy is not indicated for the asymptomatic patient whose only abnormality is hilar adenopathy.

Difference in practice actually exists chiefly in the case of patients with pulmonary infiltrates, few or no symptoms and minimal functional impairment. Opinions differ sharply as to whether corticosteroid therapy should be used to reduce the inflammatory reaction observed on radiographic examination.

Dosage: Unless a patient is acutely ill there is no need for high doses of prednisone. Institution of therapy with daily dosage of 15 mg is adequate for the majority of patients. If higher doses appear necessary to obtain the desired effects, alternate-day administration is a useful method of reducing adrenal gland suppression. Whatever level is used at the outset, the dosage is gradually reduced to the smallest level which maintains the improvement which has been obtained. One of the remarkable aspects of the prednisone therapy of sarcoidosis is the effect of small doses; in many cases, gradual reduction in daily dosage from 20 to 5 mg has maintained clinical and radiologic improvement, while cessation of this minute maintenance dose has been followed by prompt relapse.

Duration of therapy: This is the aspect of treat-
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The suggestion that all patients with Stage I disease should receive treatment with prednisone may appear inappropriate in Europe where most patients presenting with sarcoidosis in this stage clear without treatment. In the United States, however, the prognosis in Stage I is not significantly better than in Stages II and III (Sones & Israel, 1960; Israel & Beggs, 1969).

The long-term results in patients with pulmonary disease (Stages II and III) on entry to the trial were unaffected by prednisone. No difference was observed by clinical, radiologic or laboratory criteria at the end of approximately 3-5 years of observation. A 3-months’ course of prednisone in daily dosage of 15 mg is clearly insufficient to influence the eventual outcome of pulmonary sarcoidosis. It is of interest that the 6-months’ courses employed by Hapke (1969) were no more effective.

The reason for the apparent effectiveness of prednisone in Stage I sarcoidosis and the lack of effect in more advanced disease may be merely quantitative. Patients with Stage I disease have often been shown on lung biopsy to have pulmonary granulomas. The short course of modest doses of prednisone may exert a therapeutic effect on small granulomas but not on larger, roentgenographically demonstrable lesions. Alternatively, the effect in Stage I may be a more fundamental one, reflecting an immunologic difference between disease grossly confined to the mediastinum and disease which has disseminated. It is probable that the primary lesion of sarcoidosis is in the mediastinal lymph nodes; and the hypothesis that treatment at this stage may minimize dissemination and thereby influence the eventual outcome of the disease is a plausible one.

Although corticosteroids exert fairly consistent suppressive and symptomatic effects, patients are encountered in whom prednisone is contraindicated. poorly tolerated, or ineffective. Oxyphenbutazole and chloroquine have been reported in controlled trials to be effective in sarcoidosis but our clinical experience with these agents has been disappointing. Use of oxyphenbutazone in many fresh cases has failed to yield symptomatic benefit in any, while chloroquine has proved occasionally useful in patients in whom corticosteroids were poorly tolerated or contraindicated.

More promising in our experience have been chlorambucil and methotrexate. Use of these agents appeared justifiable only in patients whose disease was inadequately controlled by adrenal steroids, or patients by whom corticosteroids could not be tolerated. Fourteen patients have been given chlorambucil, nine methotrexate and six additional patients received both. In half the cases there was symptomatic improvement with little radiologic change; suppression of uveitis was noted in four...
patients. In seven patients, clinical and radiologic improvement was dramatic but relapse occurred 3 to 12 months after cessation of treatment. The rapidity with which improvement occurred, the impermanence of the effects, and the inconstant reduction observed in serum immunoglobulin levels indicate that the effects of these drugs is an anti-inflammatory one similar to that of corticosteroids, rather than an immuno-suppressive one. No ill effects were noted from use of these drugs, but they are infrequently more effective than corticosteroids; their use should be limited to occasional cases of progressive sarcoidosis in which corticosteroids are ineffective or contraindicated.

References
