Editorial

Sarcoidosis—a gleam of light?

As we approach the centenary of Besnier's description of sarcoidosis,¹ the enigma of sarcoidosis remains unresolved. That the challenge of the disease is still being faced is amply confirmed by three recent publications.²⁻⁴

Of all the recent major advances in our understanding of sarcoidosis, the recognition that it is not an anergic disease is probably the most important.⁵ The idea that the bronchoalveolar immune response may be separate from any systemic immune response has allowed clarification of many of the seemingly bizarre responses found in sarcoidosis.⁶⁻⁸ The systemic immune responses are characterised by low numbers of circulating lymphocytes, a low percentage of circulating thymus-processed lymphocytes (T cells), hypergammaglobulinaemia, and a correlation with *in vivo* anergy to skin-test antigens, particularly tuberculin.^{9,10} That the reduction in circulating T cells is reversible has been shown *in vitro* by incubation with levamisole.¹⁰ In addition, analysis of the subpopulations of circulating T lymphocytes has suggested an imbalance between the controlling T cells—"suppressor" in function—and the helper T cells, which are usually present in normal numbers.¹¹ Probably the increased activity of T suppressor cells is mediated by circulating immune complexes present in 60% of sera from patients with sarcoidosis.¹²

The contrast between the systemic immune response and the local pulmonary response is striking, for both the proportion and the number of T lymphocytes in bronchoalveolar lavage fluid are significantly greater than in controls.^{13,14} On average, there are 10 times more lymphocytes in the bronchoalveolar lavage fluid of patients with sarcoidosis than in that of normal controls. There is also an increase in the number of alveolar macrophages but there is now a lower ratio of alveolar macrophages to lymphocytes.¹⁵

These observations have led to comparisons between lavage yields, radiographic staging, and the clinical course of the disease. There appears to be little relation between the cellular content of lavage fluid and radiographic stage (stage I—bilateral hilar lymphadenopathy; stage II—bilateral hilar lymphadenopathy and pulmonary infiltrates; stage III—pulmonary infiltrates), but French workers

have convincingly shown a relation between alveolar lymphocytosis and clinical pattern.¹⁵ Symptomless patients have a lesser lymphocytosis in their lavage fluid than those with respiratory or systemic symptoms; extrathoracic disease is also associated with increased lymphocytosis. Those with erythema nodosum lie in the middle range of stage I patients.

More controversial are the observations from Crystal's group suggesting that the proportion of alveolar lymphocytes is a guide to the clinical course.¹⁴ Describing a subgroup of patients with "high-intensity" alveolitis (those with 28% or more lymphocytes in the lavage fluid), they have suggested that this group of patients do badly and that steroid treatment should be considered. This proportion of lymphocytes is not universally accepted as defining such a subgroup, although healed patients often return to a normal proportion in parallel with their clinical and radiological improvement; further studies on prognosis are required. In stage III patients with pulmonary fibrosis, the importance of an excess of polymorphonuclear leucocytes in lavage fluid still remains to be established, although French studies do suggest that steroid treatment may be indicated.¹⁵

A more disappointing aspect of the use of bronchoalveolar lavage has been its meagre contribution to understanding of the aetiology of sarcoidosis. Research into the contribution of infective particles, such as viruses or obligate bacteria, using lavage fluid, has been disappointing. Recent studies on spleen granulomas, however, have indicated potential areas that could be investigated with the use of monoclonal antibodies to granuloma fractions.¹⁶ As well as offering attractive potential for diagnosis, this should enable us to raise specific antibodies to granulomas arising from different causes and to compare granulomas in different patients suffering from sarcoidosis from the point of view of cytological and antigenic identity. Perhaps we will then be able to answer the vexed question of whether sarcoidosis is one disease with a single cause or a syndrome arising as a non-specific response in an immunologically disturbed host.

Considerable difficulties arise in establishing the activity of sarcoidosis. Conventional assessment using clinical severity, radiographic staging, and physiological measurement is unreliable.¹⁷ Interest in the development of simple *in vivo* or *in vitro*

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techniques to assess activity has grown in recent years. Two recent in vitro developments have been studied in sarcoidosis. The activity of angiotensin-converting enzyme (ACE) was hailed as a specific diagnostic test and moreover one which correlated with disease activity.^{18,19} Sadly, more recent evidence suggests that it is neither specific nor sensitive in practice. False-positive increases in activity have been reported in tuberculosis, chronic active hepatitis, berylliosis, asbestosis, and other diseases; and changes in angiotensin-converting enzyme activity seem to reflect steroid treatment rather than changes in disease activity.^{20,21} The source of enzyme in sarcoidosis does, however, seem to be the alveolar macrophage.²² Serum levels of β_2 -microglobulin, a small protein released particularly by immunologically active cells, especially the lymphocyte, do not offer specificity of diagnosis but should reflect the activity of the total mass of pulmonary immunocompetent cells. Levels of this protein, however, fail to reflect clinical activity adequately.²¹ In vivo, measurement of gallium-67 uptake has become fashionable as an index of pulmonary inflammation. In some centres positive results are associated with clinical and lavage fluid indices of disease activity,²³ but others have reported a poor correlation with the presence of granulomas in biopsy material.²⁴

A further vexed topic in sarcoidosis is the role of corticosteroid treatment in controlling the activity of sarcoidosis. The patient with prolonged radiographic shadowing, little clinical disability, and mildly abnormal physiological findings is all too common in clinical practice. Two recent studies lend further weight to the belief that corticosteroid treatment is ineffective. A large study by Eule *et al*²⁵ showed that in symptomless patients with stage II disease prednisolone in a daily dose of 40 mg initially, reducing to maintenance doses of 5-10 mg for 6-12 months, was not effective in altering the natural history of the disease. A smaller but better documented study has confirmed these observations.²⁶

Many other aspects of sarcoidosis are becoming clear as a result of modern research protocols. Genetic susceptibility, for example, seems to have no pivotal role;²⁷ epidemiological studies confirm the worldwide occurrence of the disease;²⁸ and airways obstruction is a common feature of chronic disease.²⁹ The current progress in sarcoidosis is encouraging, and perhaps by the centenary of Besnier's historic description the aetiology of sarcoidosis will be established.

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