THE EARLY DIAGNOSIS OF SARCOIDOSIS

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The recognition of sarcoidosis is much easier at the early acute phase than during the late chronic fibrotic stage of the disease. The early manifestations in young adults fall into set patterns in which the differential diagnosis is limited, whereas late fibrotic sarcoidosis in middle age may present an indistinct or bewildering picture which may mimic a variety of unrelated conditions. Furthermore, the search for histological confirmation is rewarding in the early active disease but disappointing at the late stage of non-specific fibrosis. Nevertheless, and paradoxical though it may seem, the diagnosis of sarcoidosis is often missed at an early stage but entertained too often later on.

If the diagnosis is made early, the natural history of the disease is anticipated and devastating sequelae may be avoided. Moreover, early establishment of the diagnosis may save the patient unnecessary anguish and loss of working-time from over-hospitalisation, sanatorium regimes, radiotherapy, toxic drugs and other fashions of treatment, which are largely unnecessary.

Clinical Features

Sarcoidosis rarely commences below the age of 20 years and it is uncommon for active disease to be present after 50 years. It is, of course, commonly seen later, but by middle life it has usually reached an irreversible stage; symptoms are then more frequently attributable to the fibrosis and its effect on the system concerned.

History

It is necessary to make a detailed enquiry of previous illnesses, for only in this way may it be possible to gauge the duration of the disease. He may present for the first time with diffuse pulmonary mottling, but an inquisitive history may reveal episodes of iridocyclitis or 'atypical' mumps several years earlier. The length of history is significant in assessing both the prognosis and the expected response to corticosteroid therapy.

Direct questioning of old and recent occupations should include possible risk of exposure to beryllium. This is fortunately rare in Great Britain, and I have only encountered one possible example in nearly 300 patients with other types of sarcoidosis. Nevertheless, beryllium is widely used in many industries and many examples may remain undetected. It is extracted from ores, principally beryl, and processed into various alloys, particularly with copper. It is employed in such dissimilar industries as fluorescent lamp, ceramics, crystal and radio tube manufacture. Brass foundry workers and those employed in atomic energy development are exposed to it (Hardy, 1955).

The history should also record the results of any previous tuberculin tests and the response to BCG vaccination. The development of sarcoidosis following BCG vaccination is probably coincidental, but the previous history may reveal failure to convert following vaccination. This information is significant, for patients with sarcoidosis are unable to develop and maintain skin sensitivity to tuberculin following BCG vaccination (Israel et al., 1950).

Erythema nodosum due to sarcoidosis is commoner in women, and it may coincide with lactation. Rural migrants to London seem to be peculiarly vulnerable to this variant of sarcoidosis.

Clinical Examination (Fig. 1)

Examination of the patient must be thorough and general to avoid overlooking less obvious skin lesions, unsuspected lymphadenopathy or splenomegaly, and low-grade uveitis or nasal lesions.

Apart from surveying the whole skin surface, special attention should be paid to old scars or to inoculation sites. Just before or with the onset of erythema nodosum, old childhood scars on the knees or face or even operation scars may become purple and livid. Biopsy of these scars at this time reveals an active sarcoid reaction as distinct from inactive scar tissue. There is no explanation for this phenomenon in which the sarcoid process seems to creep into and light up these scars, but it suggests a hypersensitivity reaction like the erythema nodosum itself. Inoculation sites may also contain sarcoid tissue, similar to a Kveim test. The commonest inoculation site in a patient with
suspected sarcoidosis is that of the intradermal Mantoux test for this is repeated at frequent intervals. Although the reaction at this site is studiously read two or three days later, it is rarely observed one month later when a nodule of sarcoid tissue may have developed. This Kveim-like reaction is too infrequent to be adopted as a practical test, but its occurrence is significant. It appears to be specific, since large tuberculin-testing surveys have not disclosed this phenomenon in tuberculosis or other diseases.

These cutaneous manifestations have been stressed, because, at some stage of the disease, skin lesions occur in one-half of patients, and they provide a readily accessible source of biopsy material.

Enlarged lymph nodes are nearly as frequent and these are also accessible for biopsy. Epitrochlear nodes should be palpated as well as the commonly involved glands behind the inner end of the right clavicle. Accompanying erythema nodosum, they are early and may be transient so that the search must be made as soon as possible.

Clinical examination is incomplete unless it is accompanied by chest radiography, slit-lamp examination of the uveal tract, detection of hypercalciuria by the qualitative Sulkowitch method and also serum calcium estimations. Abnormalities may be anticipated in 80 per cent. of chest radiographs and in approximately one-third of the ophthalmic examinations (James, 1956). Disorders of calcium metabolism are rarely encountered, unless the patient has at some time calciferol therapy. Nevertheless, serum and urinary calcium determinations should be routine if only to identify the 1 per cent. who may otherwise progress undetected to nephrocalcinosis.

**Differential Diagnosis**

There are a comparatively few well-defined clinical syndromes of early sarcoidosis, as distinct from the protean manifestations of the later disease (Table 1):

(a) **Erythema Nodosum.** The combination of arthralgia, erythema nodosum and bilateral hilar lymphadenopathy in young adults, particularly women, is a common early manifestation of sarcoidosis (James et al., 1956). If the fleeting pains in the ankles, knees and elbows precede erythema nodosum, the initial diagnosis of acute rheumatism may be inescapable. This is supported by the fever and markedly raised sedimenta-
tion. However, duration may be of short order, with flitting pains. The frequency of erythema nodosum itself may be the hypersensitivity response to primary tuberculous or streptococcal infection or following drugs, especially sulphanilamide. In most instances, there is no difficulty in ascertaining which of these is responsible for erythema nodosum (Table 3), but there may be many other aetiological factors of which we are at present ignorant.

(b) **Uveitis.** Disturbances of vision and photophobia due to iridocyclitis force the patient to seek medical advice at an early stage of the disease. The frequency of sarcoidosis as a cause of uveitis is unknown, but the converse, the incidence of these ophthalmic changes in sarcoidosis is well recognised to be high, probably in about one-third of cases at some time or another (Ainslie and James, 1956). When uveitis develops, it does so early in the course of the disease. It may subside and recur, but it does not present for the first time in acute form at the stage of long-standing sarcoidosis. It may accompany the erythema nodosum syndrome or be associated with hilar lymphadenopathy, pulmonary mottling, parotid and lacrimal gland involvement. Finally, uveitis may be the sole presentation of early sarcoidosis and involvement of other systems may not become obvious until later in the disease. Thus, sarcoidosis should always be included in the differential diagnosis of granulomatous uveitis.

(c) **Glandular Involvement.** Enlargement of the parotid and lacrimal glands may occur separately or together. When a dry mouth due to salivary gland involvement is accompanied by keratoconjunctivitis sicca due to lacrimal gland involvement, the clinical picture may be confused with Sjögren’s disease. This confusion may be enhanced by diffuse pulmonary changes which occur in both. However, these similarities are superficial for, in sarcoidosis, other mucosal surfaces are not uniformly dry and arthritis is not persistent.

(d) **Reticulo-endothelial Involvement.** Lymphadenopathy and splenomegaly may occur early in the disease. Enlarged lymph nodes tend to be transient but an enlarged spleen may persist and be accompanied by hypersplenism. These manifestations should not provide diagnostic difficulty, for biopsy of the enlarged lymph node will reveal suggestive histological changes.

### Histological Confirmation

Radiography of the chest or digits, Mantoux testing and serum protein electrophoresis may support the clinical diagnosis of sarcoidosis, but histological evidence of sarcoid tissue is the most satisfactory confirmation of the disease. The granuloma consists of a well-defined follicle of epithelioid cells with occasional giant cells and inconspicuous or no necrosis. Since the granuloma are widely disseminated in various tissues, there is an extensive choice of sites for biopsy. When obviously involved tissues are accessible, they provide the most rewarding sources for histological proof. Skin and lymph nodes are common sites, but conjunctiva, nasal mucosa,
palate, tonsil and scars should not be overlooked. In the absence of such involvement, blind biopsy of certain tissues may provide evidence of miliary granulomata consistent with sarcoid tissue. The claims made for different sites for blind biopsy have varied with the interests of the investigator; they include liver, scalene lymph node, conjunctiva, muscle, bronchial mucosa and lung. The most uniformly successful are aspiration liver biopsy (Mather et al., 1955) and scalene lymph node biopsy (Norviit et al., 1952), since two-thirds of patients with sarcoidosis will provide positive results by either means. Aspiration liver biopsy suffers certain disadvantages. Miliary granulomata may be overlooked in the small cylinder of tissue submitted for examination. Furthermore, they are not specific for sarcoidosis, since similar or indistinguishable granulomata may be seen in brucellosis, tuberculosis, following BCG vaccination, and in certain other infections. Scalene lymph node biopsy may also prove inconclusive or frankly confusing if the gland is draining a pulmonary tuberculous focus.

In patients with active sarcoidosis, a dusky-red nodule develops insidiously at the injection site during the ensuing four to six weeks. Histological examination of the nodule reveals sarcoid tissue. This test is positive in three-quarters of patients with the disease; it is negative in patients with tuberculosis, berylliosis and other diseases. Apart from histological proof, it provides a valuable index of activity of the early disease. Serial observation and biopsy are useful for assessing progress and the response to treatment (James and Thomson, 1955).

It is far more difficult to obtain histological confirmation at a late stage of sarcoidosis, for many of the accessible and obviously involved tissues have regressed, blind biopsy may only provide evidence of non-specific fibrosis and the Kveim test is more likely to be negative.

### Kveim Test

The Kveim test is an alternative to the above methods of blind biopsy in providing histological confirmation. It is needless to consider it if biopsy of obviously involved and accessible sarcoid tissue is possible. It has the added attraction that it is a simple out-patient technique, safe, specific and provides an index of activity of the disease. It consists of the intradermal injection of a saline suspension of sarcoid tissue obtained from a sarcoid lymph node or spleen.

### Table 3.—DIFFERENTIAL DIAGNOSIS OF ERYTHEMA NODOSUM

<table>
<thead>
<tr>
<th>Known Causes of Erythema Nodosum</th>
<th>Age-group</th>
<th>Clinical Features</th>
<th>Other Suggestive Evidence</th>
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<tr>
<td>Primary tuberculosis</td>
<td>Childhood adolescence</td>
<td>Close contact with open tuberculosis. Primary complex Post-primary dissemination in throat, lung or abdomen. (e.g. meningitis, choroidal tubercles)</td>
<td>Mantoux conversion. High degree of tuberculin hypersensitivity. Ghon focus in chest X-ray. Isolation of tubercle bacillus.</td>
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<tr>
<td>Streptococcal infection</td>
<td>Any group. Predominantly closed communities such as the Services</td>
<td>Preceding upper respiratory tract infection.</td>
<td>Isolation of haemolytic streptococci from throat. Significant rise in antistreptolysin O titre.</td>
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It might be argued that all patients with sarcoidosis should receive oral prednisolone, since there is no way of selecting those liable to develop disabling complications. Without controlled long-term therapeutic trials, this point of view cannot be refuted. It would, however, expose many patients, who might otherwise have remained trouble-free, to the risk of unnecessary drug intolerance. In our present state of knowledge, it is better to compromise by treating only those patients who have more than transient symptoms and signs or those who show radiological evidence of worsening pulmonary lesions. All patients with ophthalmic involvement or persistent hypercalcaemia should be given the benefit of steroid therapy. Anterior uveitis is treated with an initial subconjunctival injection of hydrocortisone followed by hydrocortisone eye drops at frequent intervals. If there is evidence of posterior uveitis, local hydrocortisone is insufficiently penetrative and must be supplemented by oral prednisolone. Treatment with a daily dose of 20 mg. prednisolone is continued for three months. It is then gradually reduced and discontinued to observe whether remission has been achieved. Relapse is an indication for a further more prolonged course of treatment. At present, it is uncertain whether early and adequate steroid therapy prevents progression to the troublesome fibrotic stage, although preliminary evidence suggests that this is so. Early diagnosis and treatment may well obviate prolonged steroid therapy for purely symptomatic relief of chronic fibrotic sarcoidosis.

BIBLIOGRAPHY
