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SESSION I

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The definition of sarcoidosis

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Summary

The concept of sarcoidosis as a systemic disease arose from the recognition that certain clinical phenomena which were at first described as 'diseases' affecting a number of different organs and tissues had in common (i) a histological pattern which can be described in general terms as a non-caseating tuberculoid granuloma and (ii) possible concurrence in the same patient in various combinations. These two features constitute the basis for a workable definition:

Sarcoidosis is a disease characterized by the presence in all of several affected organs or tissues of epithelioid cell tubercles, without caseation though some fibrinoid necrosis may be present at the centres of a few tubercles, proceeding either to resolution or to hyaline fibrosis.

Because knowledge of the causation of sarcoidosis is fragmentary, investigators must be left free to examine every possible aetiological hypothesis. For this reason, the definition should contain no reference to aetiology.

Before we can usefully consider the definition of sarcoidosis, or of any other disease, we must consider a curiously neglected topic, that of the definition of 'a disease', the basic concept of clinical medicine. Views on this are often implied, rather than explicitly stated, so that the observer must deduce them from the tenor of a discussion. Formulated or unformulated, they fall into two main groups, whose differences parallel in a general way those between the realist and the nominalist doctrines of the scholastic philosophers. One, the realist view, regards diseases as existing independently in some sense, each with its unique clinical syndrome, morbid anatomy, aetiology and other features, and thus logically homologous with each other. On this view, diseases should be mutually exclusive and classifiable in a single taxonomic scheme. The other, the nominalist view, regards the concept 'a disease' as a convenient logical device by which we can refer meaningfully and clearly to defined groups of patients. For reasons I have discussed elsewhere (Scadding, 1967a), I think the second is the only tenable viewpoint. The concept 'a disease' is not logically homogeneous; to say that a patient suffers from a named disease may be a claim to no more than recognition of a previously described combination of symptoms and signs, or to knowledge that a specified anatomical abnormality or a specified disorder of function underlies these symptoms, or to knowledge of their cause. Accordingly, I define 'a disease' as the sum of the abnormal phenomena displayed by a group of living organisms in association with a specified common characteristic or set of characteristics by which they differ from the norm for their species in such a way as to place them at a biological disadvantage.

We may refer to the characteristics which define the group of patients upon the study of whom the description of a disease is based as the defining characteristics of the disease. It is important to recognize that logically they are, and in practice they may be, distinct from diagnostic criteria. Defining characteristics are those that would convince an informed observer able to make every possible relevant observation that a given case belongs to the defined category. These observations might include some that would be inapplicable to the practical clinical situation of a physician faced with a patient. Clinical diagnostic criteria, on the other hand, are selected features, which can be sought conveniently in the living patient and which have been found, by study of cases in which the defining characteristic is known to be present, to be associated closely with it; they are therefore useful

in practical clinical diagnosis, though they may not offer certainty. If defining characteristics are conveniently detectable during life, they may of course be included in possible diagnostic criteria, and then offer a near approach to certainty in diagnosis. But where a defining characteristic cannot be demonstrated conveniently during life, so that only the indirect evidence of other diagnostic criteria is available, diagnosis is inevitably based on probability.

In seeking a definition of sarcoidosis, we must first decide what are its defining characteristics. What features distinguish the group of patients whom we categorize as suffering from sarcoidosis? This question can be answered only when we have considered from a historical standpoint how the concept of sarcoidosis as a systemic disease developed.

The earliest reports of cases that would now be categorized as sarcoidosis related to patients presenting with skin lesions of various types. Besnier reported a single case of lupus pernio in 1889, the histology of another being reported by Tenneson & Quinquaud in 1892. Hutchinson in 1898 gave a clinical description of two cases of 'Mortimer's malady', which, in spite of the absence of histology, can be accepted as similar to Boeck's 'miliary benign sarkoid', described, with histology, in 1899. Boeck at first misinterpreted the histology as indicating a tumour of connective tissue: it is ironic that the name by which the disease is now generally known is derived from this misinterpretation. However, Boeck later recognized that the histological pattern was that of a tuberculoid granuloma. In a series of papers extending to 1916, he described involvement of lymph-nodes, nasal mucosa, lungs, spleen, bones (involvement of which was first reported by Kreibich in 1904) and conjunctiva in patients with lupus pernio or miliary benign sarcoids of the skin, and recognized that these were to be regarded as variants of the same disease, since they might occur together in the same patients and their histology was similar. Schaumann in a series of papers from 1914 onwards confirmed these observations, and showed for the first time that systemic changes having the same histological pattern frequently occurred without skin lesions. The occasional involvement of the eye was mentioned sporadically, and it became evident that Heerfordt's (1909) 'subchronic uveoparotid fever', characterized by chronic uveitis, parotid gland enlargement and facial palsy, was to be regarded as belonging to the same nosological group. The evidence for this, advanced by Bruins Slot (1936) and Pautrier (1937), was that various combinations of skin sarcoids, involvement of internal organs and one, two or all three features of Heerfordt's syndrome could be observed in individual patients, all these manifestations having a common histological pattern, a non-caseating epithelioid granuloma. Löfgren, starting from a study of erythema nodosum, demonstrated that bilateral hilar lymph-node enlargement, either accompanying erythema nodosum or febrile arthralgia, or occurring in patients with trivial or no symptoms, is to be regarded as an early manifestation of sarcoidosis (Löfgren, 1946, 1953); the evidence again being that patients with BHL often show or later develop other evidence of sarcoidosis, and that when the opportunity occurs, the enlarged nodes are found to contain non-caseating epithelioid cell granulomas.

The characteristics that distinguish sarcoidosis are shown by this historic survey to be (i) a common histological pattern and (ii) the concurrence in the same patient of various combinations of the possible manifestations.

Hence, the definition of sarcoidosis must be (Scadding, 1967b):

Sarcoidosis is a disease characterized by the presence in all of several affected organs or tissues of epithelioid cell tubercles, without caseation though some fibrinoid necrosis may be present at the centres of a few tubercles, proceeding either to resolution or to hyaline fibrosis.

No mention of aetiology is made in this definition. Several suggested definitions of sarcoidosis include unknown aetiology as a defining characteristic. For instance, that suggested by the International Conference on Sarcoidosis in Washington, D.C., in 1960 (Proceedings, 1961) starts with the statement 'Sarcoidosis is a . . . . disease of undetermined aetiology and pathogenesis', and later states that 'tuberculosis and fungal infections must be excluded'. This is illogical. It is, of course, proper to note, as an addendum to the definition but not as an integral part of it, that knowledge of the factors concerned in the causation of this disease is fragmentary. But this very lack of knowledge makes it essential to leave the investigator free to examine every possible aetiological hypothesis. Several tenable hypotheses include a role, not necessarily direct, for mycobacteria or other infective agents normally causing granulomatous inflammation; and these must not be excluded from consideration *a priori* by the insertion of an arbitrary veto in a definition.

The definition that I have suggested implies that a diagnosis of sarcoidosis is a statement of knowledge or belief that non-caseating epithelioid granulomas or their hyalinized remnants are present in a number of affected organs or tissues. Because a large number of cases conforming to this definition have been studied for prolonged periods, this belief justifies certain inferences. From the practical viewpoint, judgments about prognosis and management can be based upon it. We know from experience that it is

unlikely that an aetiological agent will be isolated by a currently used technique. Nevertheless, if an agent that might be a factor in pathogenesis is isolated from an individual case, it is illegitimate to exclude this evidence from discussions of aetiology by refusing to admit the case into the category sarcoidosis, though we may well admit uncertainty or suspend judgment about the exact role of the agent isolated.

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