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MYCOBACTERIUM TUBERCULOSIS IN THE AETIOLOGY OF SARCOIDOSIS*

BY

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[WITH SPECIAL PLATE]

In spite of the great interest which has been shown in sarcoidosis in the past 20 years, leading to the recognition of increasing numbers of cases in many parts of the world, controversy concerning its aetiology continues. The validity of a contribution to this controversy depends in large measure upon the definition of sarcoidosis adopted by the person advancing it; for sarcoidosis, like any other disease whose aetiology is not generally agreed, must be so defined that any theory whatever about its aetiology can be discussed intelligibly and with logical propriety (Scadding, 1950, 1956). Any definition which includes the statement, "Sarcoidosis is a disease of unknown aetiology"—for example, that quoted by Ricker and Clark (1949)—is self-stultifying in this respect. An investigator who adheres to such a definition must exclude from the category "sarcoidosis" any case in which a causative agent can be identified, and thus his definition closes his mind to some tenable views concerning aetiology. Important among these is the hypothesis that sarcoidosis may be a reaction to an agent or agents already known, but difficult to demonstrate in this particular manifestation. For if in a given case a probable causative agent has been demonstrated, the definition demands either that the case be excluded from the category "sarcoidosis" or that the presence of this agent be ignored as incidental and unrelated to sarcoidosis. Clearly we must adopt a definition which imposes no *a priori* limitation on our investigation of aetiology.

Definition of Sarcoidosis

Definition of diseases is admittedly difficult. Before we can define an individual disease, we must have a clear definition of the general concept "a disease." I use the term "a disease" to refer to those abnormal phenomena which are common to a group of living organisms with disturbed structure or function, the group being defined in a stated way (Scadding, 1959). The definition of a particular disease must refer to the essential features upon which, in principle (though not necessarily always in practice), it can be decided beyond doubt whether an individual case should be placed in the defined category. These features, which constitute the defining characteristics, may belong to one of several groups, of which the principal can be described in general terms as clinical-descriptive, pathological, and aetiological. The defining characteristics should all belong to one only of these groups, and should be as few as possible and capable of being expressed unequivocally. In sarcoidosis histological features are the essential ones, and therefore they alone should form the basis of the definition. I suggest the following: sarcoidosis is a disease characterized by the presence in all affected organs of epithelioid-cell tubercles without caseation, the older lesions tending to become converted into hyalinized fibrous tissue. An explanatory note may be added to this definition, but not as part of it, that at present the majority of cases conforming to this definition remain of unknown, or at least doubtful, cause. There is a small group associated with exposure to beryllium, which may properly be termed beryllium sarcoidosis. Similarly, if any other cases, either individually or as a group, are found to be associated with a detectable causative agent, it will be permissible to add a term indicative of aetiology to the word "sarcoidosis" to identify them precisely, both by morbid anatomy and by aetiology.

Diagnosis of Sarcoidosis

It can be decided beyond doubt that a case belongs to the category "sarcoidosis" only by a complete necropsy—or by an impossibly large number of biopsies. In practice, in this as in many other diseases, diagnosis is made upon criteria derived from the total description of the disease which results from study of the defined group by all conveniently available methods—clinical, radiological, and immunological—as well as that which forms the basis of the definition. In some instances combinations of clinical features and radiographic changes known to be characteristic of sarcoidosis are sufficient alone to establish a diagnosis with little margin for error. Such combinations of features include symptomless bilateral hilar lymph-node enlargement followed by widespread mottled shadowing in the lungs with spontaneous resolution, and erythema nodosum accompanied by bilateral hilar lymph-node enlargement with low or absent tuberculin sensitivity. These have been shown with sufficient frequency in the past to be associated specifically with non-caseating epithelioid-cell accumulations in the tissues to warrant the diagnosis of sarcoidosis without the need for histological evidence. In some cases showing less characteristic features, biopsy from a single site, even though it shows the typical histological appearance, may be insufficient to establish the diagnosis beyond doubt. In general, it may be said that the need for histological evidence varies inversely with the confidence with which the clinical picture in the individual case is recognized.

In my personally observed series of cases, numbering 230 in all by the end of 1959, histological evidence was obtained from one or more sites in 67%. In the

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remainder the diagnosis was made on clinical and radiological grounds. No case with any unusual feature was accepted unless other features were typical and confirmatory histological appearances had been observed from at least one site. It is my purpose here to examine the evidence available from this series of 230 cases concerning the relationship between infection with *Mycobacterium tuberculosis* and sarcoidosis. This, of course, has been one of the most disputed points in the controversy about the cause of sarcoidosis.

Caseating Tuberculosis Following or Preceding Sarcoidosis

Most investigators have agreed that a notably high proportion of those cases of sarcoidosis which reach a chronic stage develop overt tuberculosis, though the reported incidence of this event varies greatly. At one extreme, Riley (1950) reported the development of overt tuberculosis in 13 out of 52 cases of sarcoidosis in negroes in New York, and Ustvedt (1948), reviewing 59 reported necropsies in cases of sarcoidosis, found that tuberculosis was the cause of death in 11; at the other, a few authors have considered that in their series the incidence of overt tuberculosis was no higher than would be expected in the general populations from which their cases were drawn. The development of sarcoidosis after bacteriologically proved tuberculosis has been less frequently recorded, but is nevertheless well documented (Lindig, 1954; Kerbrat and Cellerier, 1954; Refvem, 1954; Emerson and Young, 1956; Lees, 1958; Taylor, 1958).

In my series of 230 cases tubercle bacilli were isolated at some stage in 29, or 13%. In 5 cases they were first found at the time of a change from the clinical picture of sarcoidosis to one of caseating tuberculosis. In 18 cases tubercle bacilli were found without any change being observed in the clinical picture, which remained that associated with sarcoidosis. In the other 6 the bacilli were isolated before the appearance of manifestations of sarcoidosis, at a time when the clinical picture was one of overt tuberculosis—that is, they were examples of sarcoidosis following overt tuberculosis. In 5 additional cases, although no documentary record of the isolation of tubercle bacilli was available, there was an undoubted history of tuberculosis in the past. Thus there were 11 cases in which various overt forms of tuberculosis preceded sarcoidosis, and later I shall consider these 11 cases together.

The separation of the cases in which tubercle bacilli were discovered into these three groups is convenient for purposes of description, but cannot be regarded as precise, for in some cases the transition from a "tuberculous" to a "sarcoid" type of clinical picture was rather indefinite; and some of those which I have placed in the group "sarcoidosis followed by caseating tuberculosis" might possibly have been placed with equal justification in the group "tubercle bacilli found in sarcoidosis." In order to avoid circumlocution I will refer hereafter to the stages of the clinical history in the patients in whom both overt tuberculosis and sarcoidosis were observed as "caseating" and "sarcoid" phases.

Sarcoidosis from which Tubercle Bacilli were Isolated (18 Cases)

The 18 cases in which tubercle bacilli were found in the sarcoid phase merit special attention, since this conflicts most with widely held ideas. The methods by which the bacilli were found are shown in Table I. In one case two cultures proved positive; in the rest the positive cultures were single findings in a series of examinations. No exceptional efforts were made to obtain positive cultures by the examination of large numbers of specimens. In all of 5 cases in which the tubercle bacilli isolated were appropriately examined they were found to be of human strain and normal virulence for the guinea-pig. The bacilli were found at all stages of sarcoidosis (Table II), and at various periods from the apparent onset of the disease (Table III).

The justification for continuing to regard these as cases of sarcoidosis after the finding of tubercle bacilli is that their course and response to treatment remained that usually associated with sarcoidosis. When they were first observed, 17 of them failed to give a skin reaction to 100 tuberculin units (t.u.); 15 of these remained insensitive to tuberculin, and 2 developed moderate reactions to 100 t.u. and 10 t.u. respectively. One reacted to 10 t.u. throughout. The period of observation after the finding of tubercle bacilli varied from 6 months to 8 years, with a mean of 4½ years.

TABLE I.—*Methods by Which M. tuberculosis was Found in 18 Patients with Sarcoidosis Remaining in Sarcoid Phase*

	No. of Cases
Culture of sputum or gastric contents	13
Culture and microscopy	3
Microscopy of sputum during life; culture from lung *post mortem*	1
,, only	4

TABLE II.—*Stage of Pulmonary Sarcoidosis at Time of Isolation of M. tuberculosis in 18 Patients who Remained in Sarcoid Phase, with Their Condition after Periods of Observation Varying from 6 Months to 8 Years (Mean 4½ Years)*

Condition when First Seen	No. of Cases	Present Condition			
		A	B	C	D
Hilar lymph-node enlargement	3	3			
,, ,, ,, + lung infiltration:					
Little or no fibrosis	2	2			
Fibrosis	4			4	
Lung infiltration only:					
Little or no fibrosis	5	1	1	3	
Fibrosis	4			3	1

A=normal chest radiograph; B=abnormal radiograph, no symptoms; C=abnormal radiograph, symptoms; D=dead.

TABLE III.—*Estimated Duration of Sarcoidosis at Time of Isolation of M. tuberculosis in 18 Patients who Remained in Sarcoid Phase*

Years	No. of Cases
½	6
½–2	4
2–5	6
>5	2

No significant response to antituberculosis drugs was observed. Of 17 patients who received such treatment, 4 were not assessable, 2 because the disease was at a stage at which it might be expected to resolve spontaneously and 2 because it was in an irreversible fibrotic stage. Of the remaining 13, 3 showed an apparent slow response and 10 no response, though the quality of the radiographic changes in the lungs suggested potential reversibility. Of this failure to respond to antituberculosis drugs I shall say more later. Corticosteroids were administered to 11 patients, with no response in 3; temporary suppression, followed by relapse on withdrawal of the hormone and later spontaneous partial or complete resolution, in 3; and suppression of symptoms and signs on prolonged treatment in 5, moderate in 3 and slight in 2. Both these results are in accord with experience, both my own and that of others, in the general run of cases of sarcoidosis. The present state in relation to the condition at first

observation of the 18 patients in whom tubercle bacilli were found in the sarcoid phase is shown in Table II. This also is entirely comparable with the course of the disease in the rest of my 230 cases.

Thus, in 18 (8%) of 230 cases of sarcoidosis, tubercle bacilli were found without the clinical course, response to treatment, or prognosis deviating in any way from that observed in the rest of the series, and without the appearance of any other evidence of caseating tuberculosis. Three possible explanations for this can be advanced: (1) that in some cases at least sarcoidosis is an unusual reaction to a tuberculous infection; (2) that patients with sarcoidosis due to some unknown cause are liable to superinfection with tubercle bacilli, but that the manifestations of such infection may be so modified that they are both undetectable clinically and do not affect the course of the patient's illness; and (3) that the findings were the result of errors in or on the way to the laboratory. I shall discuss the first two possibilities later. With regard to the third, though of course error is always possible, I know of no group of cases in which I have received erroneous reports of the finding of tubercle bacilli in such a high proportion as 8%; and while I might be prepared to explain an unexpected finding in a much smaller proportion of cases on this basis, I do not think it reasonable to do so in relation to an observation made with such frequency.

Tuberculosis Preceding Sarcoidosis (11 Cases)

I will now turn to the 11 patients in whom overt tuberculosis preceded sarcoidosis. As already indicated, there was a record of the isolation of tubercle bacilli in the caseating phase in 6 of these. The types of tuberculosis are summarized in Table IV. Tuberculin sensitivity was recorded in only one of them in the caseating phase, when there was a positive reaction to 10 t.u., changing in the sarcoid phase to a negative reaction to 100 t.u. In the sarcoid phase 7 (64%) of these 11 patients did not react to 100 t.u., 3 (27%) reacted to 100 t.u., and one (9%) to 10 t.u. This is very similar to the distribution of reactions to graded doses of tuberculin in my total series of 230 cases (Table V), in which 64% did not react to 100 t.u., 21% reacted to 100 t.u., 11% to 10 t.u., and 4% to 1 t.u.

TABLE IV.—*Types of Caseating Tuberculosis which Preceded Sarcoidosis in 11 Patients*

	No. of Patients	No. in which Isolation of T.B. was Recorded
Primary complex	1	1
Pulmonary	6	2
Cervical adenitis	1	1
Abscess of chest wall	2	2
Peritonitis	1	

TABLE V.—*Sensitivity to Graded Intradermal Doses of Tuberculin in 230 Cases of Sarcoidosis. Percentages Given are Related to the Number with Complete Records*

	No. of Cases
Total number of cases	230
Record incomplete (stated to be "negative")	9
,, complete	221
Negative to 100 t.u.	141 (64%)
Positive ,, 100 ,,	47 (21%)
,, ,, 10 ,,	25 (11%)
,, ,, 1 ,,	8 (4%)

In 7 of the 11 patients an interval ranging from 18 months to 27 years elapsed between the caseating and the sarcoid phases; in 4 there was no such interval, and the sarcoid phase developed imperceptibly from the initial caseating phase. I will quote cases with and without an interval.

Case 1

In 1945 a man, then aged 22, had tuberculous adenitis in the left side of his neck; this softened and was aspirated, tubercle bacilli being cultured from the pus. Towards the end of 1949 he developed a generalized enlargement of lymph-nodes, affecting cervical, axillary, and inguinal groups; a node removed for biopsy showed non-caseating epithelioid-cell tubercles. The spleen was easily palpable. In January, 1950, he developed iridocyclitis in the right eye. A chest radiograph showed bilateral hilar lymph-node enlargement, with diffuse fine mottling mainly in the middle zones of both lungs. A tuberculin test gave a moderate reaction to 100 t.u. Over the next six months all these manifestations gradually subsided, so that by March, 1951, the lymph-nodes and the spleen were no longer palpable, the eye was free from inflammatory changes, and the chest radiograph was clear. He remained quite well until early in 1955, when a lymph-node swelling appeared again in the left side of the neck. The skin now reacted to 10 t.u. with an area of induration 20 × 20 mm. He was treated with isoniazid and *p*-aminosalicylic acid (P.A.S.). The lymph-node softened and sterile pus was aspirated from it; after this the adenitis subsided completely, and the patient has remained well since. Culture of the pus failed to grow tubercle bacilli, but the specimen was taken after 18 months' antibacterial treatment.

In this case there was a change from a caseating to a sarcoid and back again to a caseating phase.

The next case illustrates the group of 4 in which the sarcoid phase developed insidiously from the caseating phase.

Case 2

A woman, born in 1931, was observed at a chest clinic from 1949 to 1953 as a contact of her husband, who had been found in 1949 to be suffering from pulmonary tuberculosis. Her chest radiograph remained clear during this time, but their son, born in 1950, was found to have skin sensitivity to tuberculin at the age of 1 year. She was first seen at the Brompton Hospital in January, 1956, because a small area of faint mottling had been found in the upper zone of the right lung in a chest radiograph (Special Plate, Fig. 1). Sputum examined at this time produced tubercle bacilli on culture. In May, 1956, she was admitted to hospital. Her skin reacted to 10 t.u. Tubercle bacilli were again found on culture, this time from a gastric-lavage specimen. Treatment with isoniazid and P.A.S. was started, but the lung shadows slowly and steadily spread (Special Plate, Fig. 2). She was readmitted in May, 1958. The skin now failed to react even to 1,000 t.u. Liver biopsy showed non-caseating tubercles (Special Plate, Fig. 3). Prednisolone was added to the antituberculosis drugs in June, 1958, and resulted in rapid clearing of the radiographic shadows. However, after the prednisolone was gradually withdrawn and stopped in July, 1959, she started to feel tired, and in October, 1959, a radiograph showed some recurrence of the abnormal shadows.

In this case the sequence of events is striking; there was a steady and uninterrupted progression from exposure to tuberculous infection, through the development of a localized lung lesion with tuberculin sensitivity and tubercle bacilli in the sputum, to a state typical of sarcoidosis, clinically, histologically, and in response to treatment.

Caseating Tuberculosis Following Sarcoidosis (5 Cases)

Turning now to the 5 cases in which the transition from sarcoidosis to caseating tuberculosis was observed, I must emphasize once again the absence of an absolute distinction between them and the group of 18 which I have classed as "sarcoidosis in which tubercle bacilli

were found." Though in 3 of them the transition was marked by an obvious clinical change, in 2 the change was less definite. Specifically " sarcoid " features which disappeared at the transition included skin lesions in 2 and a generalized adenopathy with scattered lung shadows in one. In 2 of them an iritis of sarcoid type had resolved earlier. In all 5 cases the skin had failed to react to 100 t.u. in the sarcoid phase, and reacted to 10 t.u. or 1 t.u. in the caseating phase. The duration of sarcoidosis at the transition ranged from 2 to 12 years. One patient, observed before chemotherapy for tuberculosis was available, died with progressive disease and right ventricular failure; the other 4 received prolonged treatment with antibacterial drugs, with apparent cure of active tuberculosis, but more or less residual fibrosis in the lungs.

Case 3 is typical of those in which there was a sharp transition from the sarcoid to the caseating phase.

Case 3

In 1946 a man, then aged 33, noticed breathlessness on exertion and cough, and one episode of pain in the right side of the chest. A radiograph (Special Plate, Fig. 4) then showed widespread fine mottling in the lungs with a localized opacity in the region of the right middle lobe. In July, 1948, lymph-nodes on both sides of the neck enlarged, and biopsy showed many non-caseating epithelioid-cell tubercles. In June, 1949, he was admitted to hospital for investigation. At this time he was breathless on moderate exertion, and lymph-nodes were easily palpable in the neck, axillae, and groins. The shadowing in the chest radiograph had become much denser, still affecting the right lung more than the left (Special Plate, Fig. 5). Tomography showed evidence of air-containing spaces in the densely affected middle zones of the lungs. Biopsy of a lymph-node again showed many discrete epithelioid-cell tubercles, with some areas of hyaline fibrosis. The skin failed to react to 1,000 t.u. Specimens of sputum were taken for culture at this time. When he was seen as an out-patient in September, 1949, several important events had occurred. A report was received that *M. tuberculosis* had been cultured from the sputum taken when the skin had failed to react to tuberculin; a painful swelling over the left tibia had appeared, and was shown to be a cold abscess associated with an area of rarefaction in the tibia, from which *M. tuberculosis* was later cultured. The skin now reacted briskly to 10 t.u.; there was considerable clearing of the scattered mottling in the lungs (Special Plate, Fig. 6), though the more localized shadows suggestive of fibrosis persisted; and the vital capacity had increased by 1 litre. Tubercle bacilli were now discoverable in the sputum in moderate numbers on microscopy. He was treated for six months with streptomycin and P.A.S., with disappearance of the tubercle bacilli from the sputum and subsidence of the cold abscess. He suffered a minor relapse of the tuberculosis in 1957, with reappearance of tubercle bacilli in the sputum. This has been satisfactorily dealt with by two years of treatment with isoniazid and P.A.S., but he is now left with permanent lung damage causing considerable respiratory disability.

I will now give an example of a gradual transition from a sarcoid to a caseating phase.

Case 4

A woman born in 1920. During her first pregnancy in 1948 she became breathless on exertion. In October, 1950, a chest radiograph showed enlargement of hilar lymph-nodes and some scattered opacities in the lungs (Special Plate, Fig. 7). When I saw her in February, 1952, she easily became breathless on exertion; there were palpable lymph-nodes above both clavicles, and the scar of a minor abrasion of the left shin nearly three years previously was red with a raised nodular rim around a flat atrophic centre. Biopsy of this scar showed the typical histology of sarcoidosis (Special Plate, Fig. 8). A chest radiograph showed denser mottling in the upper zone of the right and middle zone of the left lung and persistently enlarged hilar lymph-nodes (Special Plate, Fig. 9). The skin failed to react to 1,000 t.u. Temporary remission of symptoms and clearing of the skin lesion followed the administration of cortisone for three weeks, but was not maintained when this was withdrawn. B.C.G. vaccination later in 1952 caused a local nodule, which developed and disappeared within nine days, and after this the skin gave a small reaction to 100 t.u. Over the next two years she slowly improved without treatment, but in April, 1955, she had a febrile illness accompanied by a localized shadow in the middle zone of the left lung. She was treated with streptomycin and isoniazid for a short time and improved. In December, 1955, she had another febrile attack, with little change in radiographic appearance, but the skin now reacted to 10 t.u., and one sputum specimen out of three grew human-type tubercle bacilli on culture. After this, efforts were made to maintain prolonged treatment with antituberculosis drugs. Though no further isolation of tubercle bacilli has been recorded, the progress of the disease from this time onwards is compatible with caseating tuberculosis. The shadow in the middle zone of the left lung resolved; new shadows appeared in the right lung in October, 1957, and in the left lung in January, 1958, and resolved; calcification gradually developed at both hila and in the right lung; and stenosis of the anterior segmental bronchus of the right upper lobe, apparently in association with the lymph-node calcification, has been confirmed bronchographically. This stenosis was complicated by transient abscess-formation in the obstructed segment in October, 1958 (Special Plate, Fig. 10). In October, 1959, she was well, with only slight dyspnoea on exertion; radiographically there was evidence of atelectasis of the obstructed segment of the right upper lobe, extensive calcification at the hila, especially the left, but little residual abnormality in the lung fields.

Calcification Developing in the Late Stage of Pulmonary Sarcoidosis

In several other cases I have observed calcification of the type usually associated with caseous residues of pulmonary tuberculosis developing in patients whose cases otherwise conformed to all accepted concepts of sarcoidosis. These I have perhaps arbitrarily regarded as remaining in the sarcoid phase.

Case 5

A farmer, then aged 41, was first seen by me in November, 1950. He had been becoming gradually more breathless on exertion for four years. Examination revealed moderate enlargement of the liver and considerable enlargement of the spleen. The chest radiograph (Special Plate, Fig. 11) showed coarse mottling throughout both lungs. The skin failed to react to 1,000 t.u. Biopsy of an axillary lymph-node showed many non-caseating tubercles. There was no response to three months' treatment with streptomycin and P.A.S.; but immediate diminution in the size of the liver and spleen, considerable subjective improvement, and slight resolution of the lung shadows were observed during three weeks' administration of cortisone, 100 mg. daily, in July, 1951. This improvement was partially maintained after cessation of treatment, the liver and spleen not returning to their former size. Over the years these organs have become impalpable. The mottled shadowing in the chest radiograph has gradually given place to an irregular linear pattern suggestive of fibrosis and emphysema; and calcification has appeared at the apex of the right lung and at both hila, first becoming evident in September, 1952. By April, 1960, it was very obvious, and of a type normally associated with healed pulmonary tuberculosis (Special Plate, Fig. 12).

Tuberculosis with Low Tuberculin Sensitivity and Poor Response to Chemotherapy

Just as the separation of those of my cases of sarcoidosis in which tubercle bacilli were isolated into

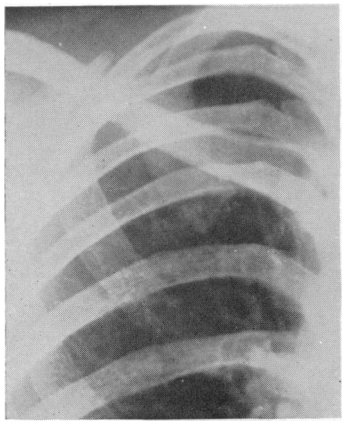

FIG. 1.—Case 2. Radiograph of upper zone of right lung, January, 1956, showing localized tuberculosis.

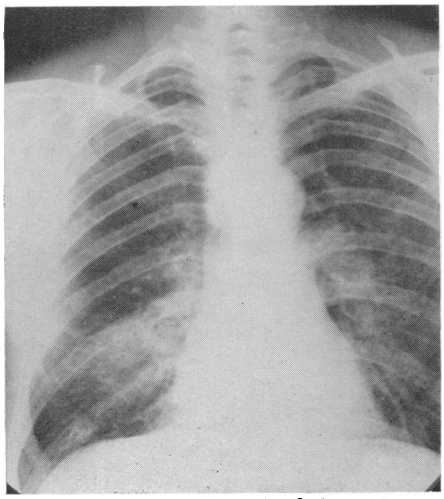

FIG. 4.—Case 3. Radiograph of chest, November, 1946.

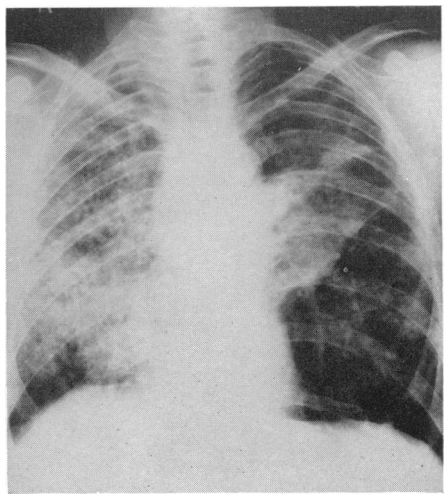

FIG. 5.—Case 3. Radiograph of chest, May, 1949.

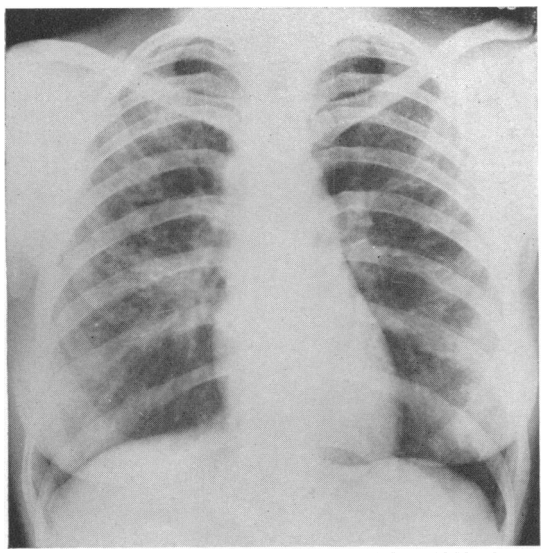

FIG. 2.—Case 2. Radiograph of chest, May, 1958, showing spread of mottled shadowing in both lungs during antituberculosis chemotherapy.

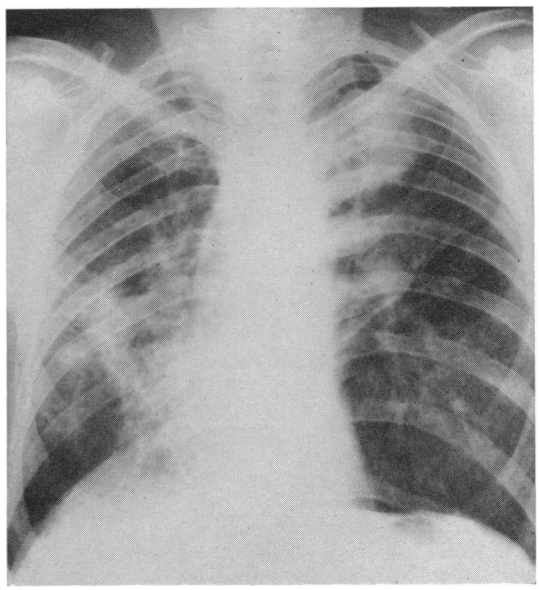

FIG. 6.—Case 3. Radiograph of chest, November, 1949, showing clearing of mottled shadows at time of appearance of tuberculin sensitivity and of tubercle bacilli in sputum.

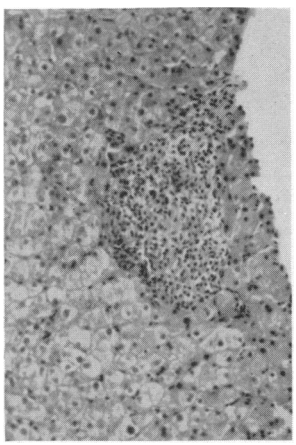

FIG. 3.—Case 2. Liver biopsy, May, 1958. (H. and E. ×188.)

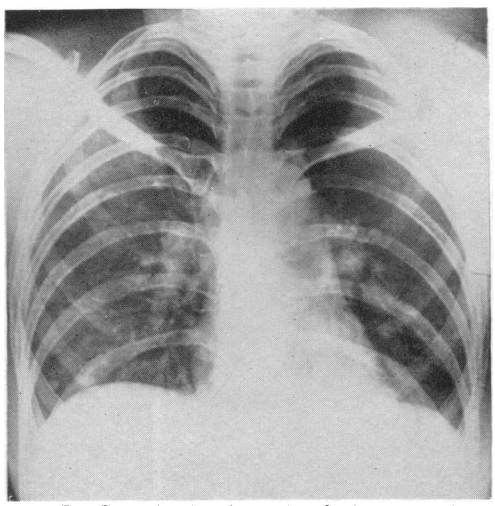

FIG. 7.—Case 4. Radiograph of chest, October, 1950.

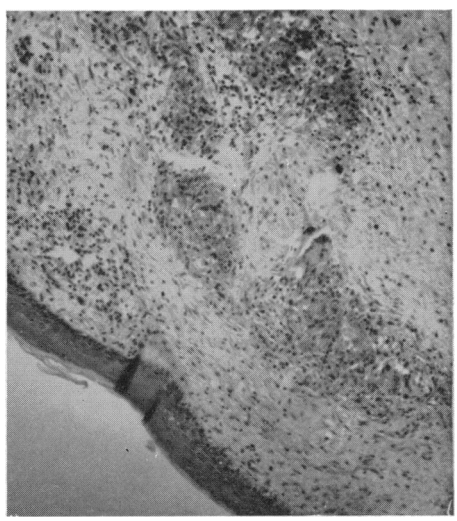

FIG. 8.—Case 4. Biopsy of infiltrated scar on left shin, February, 1952. (H. and E. ×168.)

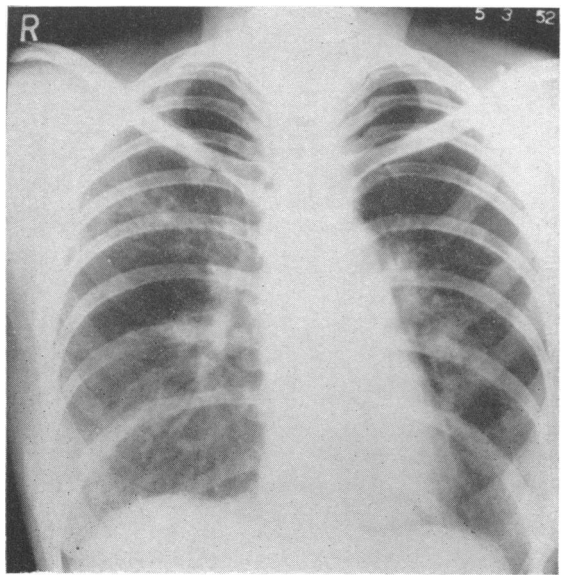

FIG. 9.—Case 4. Radiograph of chest, March, 1952.

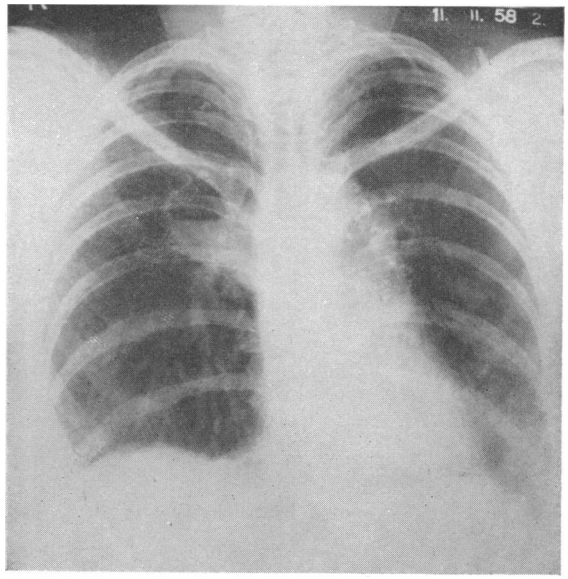

FIG. 10.—Case 4. Radiograph of chest, November, 1958.

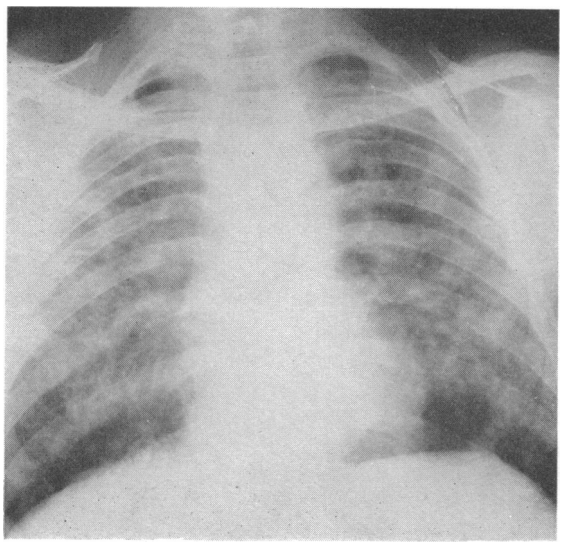

FIG. 11.—Case 5. Radiograph of chest, November, 1950.

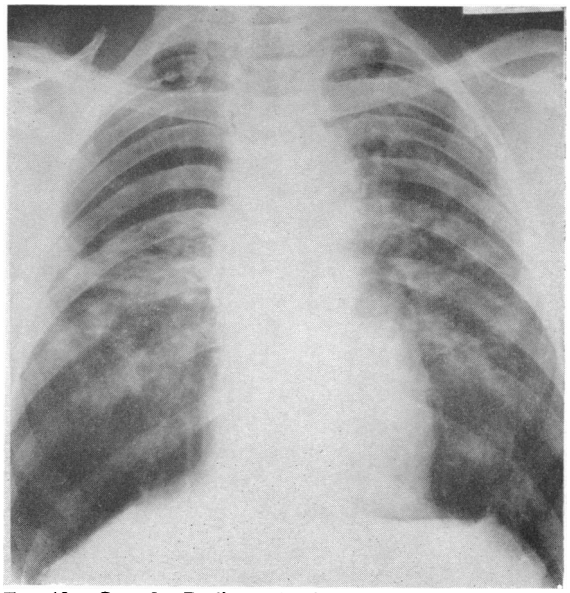

FIG. 12.—Case 5. Radiograph of chest, April, 1960. Note calcification at right apex and at both hila.

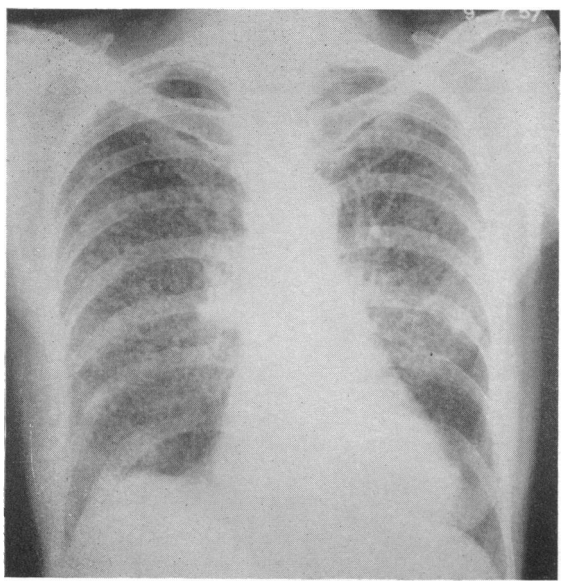

FIG. 13.—Case 6. Radiograph of chest, July 9, 1957.

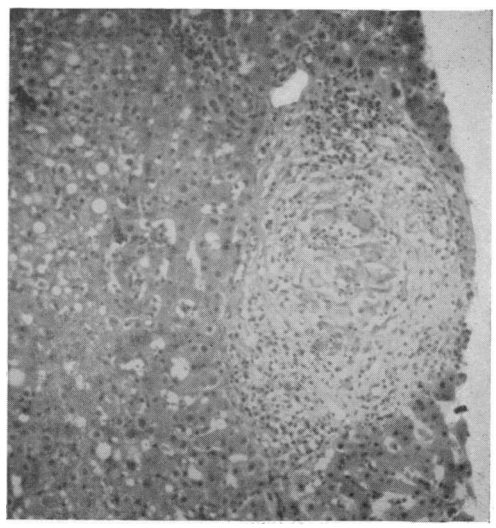

FIG. 14.—Case 6. Liver biopsy. (H. and E. ×200.)

various groups for purposes of description is artificial and seems to me to correspond to no real difference between them, so I believe that no clear line of demarcation can be drawn between sarcoidosis and certain cases which would be accepted without question as indolent tuberculosis with low tuberculin sensitivity. In 1956 I described a group of four cases of tuberculin-negative pulmonary tuberculosis, and drew attention to the difficulty of distinguishing sharply between such cases and some of the cases of sarcoidosis in which tubercle bacilli had been found (Scadding, 1956). A similar conclusion was reached by Zettergren (1954) in relation to the histology of lymph-nodes. He compared 54 lymph-nodes from cases of sarcoidosis with 49 lymph-nodes affected by chronic hyperplastic tuberculosis, distinguished by the microscopic identification of acid-fast bacilli in them ; and concluded that the two groups could not be distinguished histologically. Where there is such difficulty in deciding into which of two categories such cases should be placed, we may well consider whether the two categories may not in fact overlap ; and I have already shown that logically there is no reason why the categories " tuberculosis " and " sarcoidosis " should be mutually exclusive.

In relation to the hypothesis that sarcoidosis may be an unusual reaction to a tuberculous infection, cases of undoubted pulmonary tuberculosis which show features, such as insensitivity to tuberculin, normally associated with sarcoidosis but not with caseating tuberculosis are highly significant in spite of their rarity. Another even rarer type of case with significant atypical features is that in which tuberculosis, bacteriologically proved, fails to respond to antibacterial drugs though the bacilli are sensitive to the drugs used, and there are none of the features, such as overwhelming infection, usually associated with such failure. I will quote two such cases.

Case 6

A woman aged 61 had been feeling tired for a year, had become breathless on exertion, lost weight for six months, and been feverish for two months, when she was admitted to hospital in May, 1957. She looked moderately ill and was febrile. A chest radiograph showed faint miliary shadowing, though a film taken a month previously had been clear. Full doses of streptomycin, isoniazid, and P.A.S. were given, but the fever persisted and the shadows in the radiograph became denser (Special Plate, Fig. 13). No tubercle bacilli were found on culture of two laryngeal swabs and three gastric-lavage specimens. She was transferred to the Brompton Hospital on July 8. Fever swinging up to 101° F. (38.3° C.) persisted. The Mantoux test showed a moderate reaction to 10 t.u. Continuation of full doses of the three antibacterial drugs produced no change in the fever or the general condition, and the radiographic shadows grew denser. On August 6 a liver biopsy (Special Plate, Fig. 14) showed many non-caseating tubercles. On August 21 prednisolone, 40 mg. daily, was added to the treatment, with immediate fall in temperature and erythrocyte sedimentation rate to normal and clearing of shadows from the chest radiograph. On August 28 a lesion resembling a choroidal tubercle was seen in the right fundus oculi. About this time reports were received that cultures of two sputa taken in July had produced tubercle bacilli sensitive to all three drugs. The prednisolone was very gradually reduced, and finally stopped in March, 1958 ; she continued taking isoniazid and P.A.S. until January, 1959, and when last seen in May, 1960, was well, with faint residual mottling in the lungs but no important symptoms.

This patient was clearly suffering from subacute miliary tuberculosis and was not critically ill. Nevertheless the disease progressed in spite of prolonged treatment with antibacterial drugs to which her bacilli were sensitive, and responded rapidly to corticosteroid treatment. Though no explanation can as yet be advanced for this peculiar response to treatment, the occurrence of even a single case of this sort disposes effectively of the argument that, because sarcoidosis does not respond to antituberculosis drugs and may show remissions under corticosteroid treatment, the tubercle bacillus can play no part in its causation.

The following case could be used alternatively either to illustrate this theme once more, or as another example of the group in which sarcoidosis followed caseating tuberculosis. I have not at present grouped it as a case of sarcoidosis, because we have not yet detected any manifestations outside the lungs, and the distribution of the disease as first shown radiographically was that usually associated with caseating tuberculosis rather than with sarcoidosis.

Case 7

A woman aged 36 was found in January, 1958, on routine radiography, to have fine mottled opacities at the apices of both lungs, especially the left. She had no symptoms. Her skin reacted to 10 t.u. From one out of seven laryngeal swabs tubercle bacilli were grown, sensitive to streptomycin, ioniazid, and P.A.S. She was treated for two years with isoniazid and P.A.S., and with streptomycin as well for the first month. There was no change in the radiographic shadows during this time. Tomographic appearances of the apices of the lungs in February, 1958, and in February, 1959, after one year of treatment, were identical. The treatment was stopped in January, 1960. In April, 1960, the fine mottling was observed to have spread into the middle zones of the lungs, and the radiographic appearances were more like those usually associated with sarcoidosis.

Cases in which features diagnostic or suggestive of overt tuberculosis and others more usually associated with sarcoidosis are inextricably mixed are far from uncommon. In 1957, with my colleague, Dr. K. M. Citron, I published three cases under the title " Stenosing Non-caseating Tuberculosis (Sarcoidosis) of the Bronchi " (Citron and Scadding, 1957a). These were clinically very similar to each other ; all had, in addition to the bronchial changes, sarcoid-type histological changes in one or more sites outside the thorax. In one the skin persistently showed low or absent sensitivity to tuberculin, and no tubercle bacilli were isolated ; in the second the skin showed moderate sensitivity to tuberculin, and no tubercle bacilli were found ; and in the third the skin was persistently insensitive to tuberculin, but tubercle bacilli were found on two occasions, and the histology of mediastinal lymph-nodes was thought suggestive of very chronic caseating tuberculosis. There is no diagnostic category with a generally agreed name into which can be placed cases in which, individually or as a group, there is evidence that sarcoidosis has developed as a result of infection by *M. tuberculosis*. I suspect that lack of a convenient name for such cases leads to their being left out of consideration, so that a sharp distinction between the clinical concepts of " tuberculosis " and " sarcoidosis " is maintained simply by our verbal habits. I suggest that these cases can properly be termed " mycobacterial sarcoidosis."

Tuberculin Sensitivity in Sarcoidosis

One of the few facts about sarcoidosis which is generally agreed is that skin sensitivity to tuberculin and to other substances producing similar delayed reactions is depressed as compared with that of unselected control groups. This can be explained on one of two

hypotheses. One of these is that sarcoidosis, caused by some unidentified agent, depresses this sort of sensitivity non-specifically just as do Hodgkin's disease and some other diseases affecting the reticulo-endothelial system (Hoyle *et al.*, 1954). On this hypothesis it would be expected that those patients with sarcoidosis, in whom evidence of past or present tuberculosis can be found, would show a generally higher level of tuberculin sensitivity than those in whom no such evidence is available; but, as I have already shown, in my series this is not so, the distributions of sensitivity to various doses of tuberculin in these two groups being the same. A similar observation was made in the course of an investigation of the effect of cortisone on tuberculin reactions in sarcoidosis. Pyke and Scadding (1952) found that in about 50% of patients with sarcoidosis who were insensitive to tuberculin the addition of cortisone to the tuberculin would cause a reaction. Citron and Scadding (1957b) confirmed this observation in 28 further patients, who all failed to react to 100 t.u., but of whom 14 reacted and 14 did not react to tuberculin plus cortisone. Twelve of them had clear evidence of previous tuberculous infection, either in the form of calcified foci in the lungs or hilar lymph-nodes or of the previous finding of tubercle bacilli. If sarcoidosis is due to an unknown agent which incidentally depresses tuberculin-type reactions, it would be expected that, since these 12 patients presumably had at one time reacted to tuberculin, they would be found predominantly in the group who in the sarcoid phase reacted to tuberculin when cortisone was added to it. In fact, rather less than half of them fell into this group, 5 reacting and 7 not reacting to tuberculin plus cortisone; while of the 16 patients in whom no positive evidence of earlier tuberculosis was found, 9 reacted and 7 did not react.*

These observations support the second possible explanation of the low sensitivity of patients with sarcoidosis to agents producing tuberculin-type reactions—namely, that the depression of the capacity to react in this way is one aspect of the peculiarity of the tissue reactivity of these patients which determines that they develop sarcoidosis in response to an agent or agents more commonly associated with changes of another type. The other observations which I have described on the evidences of tuberculous infection found in some patients with sarcoidosis seem to me to lead to the conclusion that the tubercle bacillus is among these agents. I am impressed by the way in which what I have called the sarcoid and the caseating phases are inextricably intermingled; and also by the arbitrariness of the distinction between sarcoidosis and indolent tuberculosis with low tuberculin sensitivity, as shown by certain cases which could with equal propriety be placed in either of these categories.

External Agents and Host Reactivity in Sarcoidosis

It is my opinion that, both in the patients in whom tubercle bacilli were found in the sarcoid phase and in those in whom there was evidence of caseating tuberculosis before or after the sarcoid phase, the entire illness was attributable to the tubercle bacilli. On this supposition, the reason for the development of sarcoidosis rather than caseating tuberculosis rests in a peculiarity of the tissue reactivity of the patient. In those patients in whom a change from caseating to sarcoid phases or vice versa was observed this peculiar tissue reactivity must be supposed to have developed or disappeared during the observed course. This seems much more plausible than the alternative hypothesis that the disease in these cases is due to two agents, the tubercle bacillus and an unidentified agent causing sarcoidosis. This would imply a most curious mutual antagonism between the two agents; for the whole variety of interrelationships between sarcoidosis and tuberculosis could be explained only by postulating, first, that the unknown agent alleged to cause sarcoidosis is able not only to depress tuberculin sensitivity but also actually to suppress the activity of tuberculous infection; and, secondly, that if tuberculous infection escapes from this suppression it in turn can suppress the hypothetical agent of sarcoidosis.

Thus I accept the proposition that at least some cases of sarcoidosis are a manifestation of a tuberculous infection; or, to express the same proposition from another viewpoint, that the tubercle bacillus can cause sarcoidosis in some subjects. This implies that only a minority of individuals whose reactivity to the infection is or has become peculiar in the appropriate way will develop sarcoidosis. It follows, further, that there are no grounds for denying the possibility that other known or as yet unknown agents, besides the tubercle bacillus, may also be capable of causing sarcoidosis in such individuals. There is at least one report of a patient with sarcoidosis who later developed overt histoplasmosis (Israel *et al.*, 1952), rather as some have proceeded to caseating tuberculosis, suggesting the possibility that *Histoplasma capsulatum* might be considered in endemic areas as one among these possible other infections. This view of the aetiology of sarcoidosis suggests an analogy with erythema nodosum, in which a well-defined clinical syndrome, with equally well-defined and constant histology, can be caused by a variety of external agents, but depends for its production upon the appropriate reactivity of the host.

Thus, in sarcoidosis the study of the peculiar reactivity of the host may be as important as the search for external causative agents. Much work has been done on the ways in which the immune mechanisms of patients with sarcoidosis differed from those of normal persons. It is generally agreed that they show a poor response to antigens causing delayed tuberculin-type responses, including trichophytin, mumps virus, and pertussis agglutinogen (Sones and Israel, 1954), and *Candida albicans* antigen (Citron, 1957). They fail to react to, and do not become tuberculin-sensitive after, B.C.G. vaccination (Lemming, 1940)—an observation which has been confirmed in five cases in my series. On the other hand, they may suffer from diseases associated with sensitivity to antigens producing immediate reactions; several of my patients have also had asthma or eczema. They also produce agglutinins normally after typhoid vaccine (Sones and Israel, 1954), and have been reported to produce higher titres of isoagglutinins in response to mismatched blood than normal individuals (Sands *et al.*, 1955). The hyperglobulinaemia first described by Harrell and Fisher (1939) and

*Since this lecture was delivered Fairley and Matthias (1960) have filled a gap in these arguments. Investigating the effects of cortisone upon skin sensitivity to tuberculin in reticuloses, they found that 62 (45%) of 138 patients failed to react to 100 t.u. The addition of cortisone produced small "positive" reactions in only 5 (8%) of these 62 patients, and in a similar proportion (one out of 14) of tuberculin-negative controls. They compared these proportions with the 50% of tuberculin-negative sarcoidosis patients of Pyke and Scadding (1952) and Citron and Scadding (1957) in whom positive reactions were produced by the addition of cortisone, and concluded that "the mechanism of suppression of tuberculin sensitivity in sarcoidosis is different from that in the reticuloses"

subsequently generally confirmed as occurring in a varying proportion of cases of sarcoidosis may be explicable on the basis of hyperactivity of some aspects of the immune mechanisms. In summary, the altered reactivity of patients with sarcoidosis is complicated, the diminution in sensitivity to antigens producing delayed-type reactions being accompanied by normal or even increased immunological reactivity in some other respects.

I have evidence in one patient that the unusual reactivity preceded the development of sarcoidosis. This was a student nurse who developed clinical signs of sarcoidosis one year after B.C.G. vaccination had twice failed to produce skin sensitivity to tuberculin.

As to the factors which cause patients to develop the unusual reactivity we remain in ignorance. Recently Cummings and Hudgins (1958) have suggested that pine pollens may have some relation to the development of sarcoidosis. This is on the basis of a correlation between the geographic distribution of a large series of cases of sarcoidosis in the United States with that of forests (Michael *et al.*, 1950; Gentry *et al.*, 1955; Cummings *et al.*, 1956); of the finding of acid-fast lipid and an amino-acid resembling diaminopimelic acid in pine pollen; and of the production in animals of epithelioid-cell granulomata by pine pollen and by a phosphatide fraction of pine pollen. If a correlation between exposure to pine pollens and increased liability to sarcoidosis is confirmed, I would suggest, speculatively, that it may be explicable on the hypothesis that contact with pine pollens may be a factor in causing the altered reactivity which determines the development of sarcoidosis in response to infection with *M. tuberculosis* and possibly some other agents.

Summary

To summarize the general view I have tried to put forward on the aetiology of sarcoidosis:

1. Free discussion of aetiology demands a descriptive definition based upon morbid histology.

2. Such a definition will include some cases in which there is good evidence that sarcoidosis is a manifestation of tuberculous infection. The evidence for this in my series of 230 cases consists in the finding of tubercle bacilli in the sarcoid phase in 18; in preceding caseating tuberculosis in 11; and in the change from a sarcoid to a caseating phase, with the appearance of tubercle bacilli, in 5.

3. Indirect evidence leads me to the tentative opinion that most of the cases of sarcoidosis I see in England are of the same aetiological group. The evidence for this is their similarity to those in which direct evidence was obtained; the impossibility of detecting any clear distinction between indolent tuberculosis with low tuberculin sensitivity and sarcoidosis; and the similar distribution of reactions to graded doses of tuberculin in those patients with sarcoidosis who have and have not detectable direct evidence of present or past infection with *M. tuberculosis*.

4. The objection that *M. tuberculosis* cannot be aetiologically related to sarcoidosis because sarcoidosis does not respond to antituberculosis drugs and may be suppressed by corticosteroids is met by the observation that some, admittedly very rare, cases of undoubted tuberculosis behave in the same way in relation to these agents.

5. The cause of sarcoidosis must be sought as much in the altered reactivity of the host as in external causative agents.

6. There may well be other agents, known and as yet unknown, besides the tubercle bacillus which can cause sarcoidosis in a susceptible individual. If such a multiplicity of agents exists, the proportion of cases of sarcoidosis associated with each of them may be expected to vary from one part of the world to another. Hence statements about aetiological agents in sarcoidosis can be accepted as valid only for the population from which the cases on which they are based are derived.

I am much indebted to the many colleagues, both at Brompton and Hammersmith Hospitals, and in chest clinics throughout the country, who, knowing my interest in the subject, have referred to me cases of sarcoidosis and have co-operated in following their progress.

REFERENCES

Citron, K. M. (1957). *Tubercle (Lond.)*, **38**, 33.
—— and Scadding, J. G. (1957a). *Thorax*, **12**, 10.
—— —— (1957b). *Quart. J. Med.*, **26**, 277.
Cummings, M. M., Dunner, E., Schmidt, R. H., jun., and Barnwell, J. B. (1956). *Postgrad. Med.*, **19**, 437.
—— and Hudgins, P. C. (1958). *Amer. J. med. Sci.*, **236**, 311.
Emerson, P. A., and Young, F. H. (1956). *Tubercle (Lond.)*, **37**, 116.
Fairley, G. H., and Matthias, J. Q. (1960). *Brit. med. J.*, **2**, 433.
Gentry, J. T., Nitowsky, H. M., and Michael, M., jun. (1955). *J. clin. Invest.*, **34**, 1839.
Harrell, G. T., and Fisher, S. (1939). Ibid., **18**, 687.
Hoyle, C., Dawson, J., and Mather, G. (1954). *Lancet*, **2**, 164.
Israel, H. L., De Lamater, E., Sones, M., Willis, W. D., and Mirmelstein, A. (1952). *Amer. J. Med.*, **12**, 252.
Kerbrat, G., and Cellerier, R. (1954). *J. Franç. Méd. Chir. thorac.*, **8**, 266.
Lees, A. W. (1958). *Amer. Rev. Tuberc.*, **78**, 769.
Lemming, R. (1940). *Acta med. scand.*, **103**, 400.
Lindig, W. (1954). *Beitr. Klin. Tuberk.*, **110**, 555.
Michael, M., jun., Cole, R. M., Beeson, P. B., and Olson, B. J. (1950). *Amer. Rev. Tuberc.*, **62**, 403.
Pyke, D. A., and Scadding, J. G. (1952). *Brit. med. J.*, **2**, 1126.
Refvem, O. (1954). *Acta med. scand.*, Suppl. 294, p. 128.
Ricker, W., and Clark, M. (1949). *Amer. J. clin. Path.*, **19**, 725.
Riley, E. A. (1950). *Amer. Rev. Tuberc.*, **62**, 231.
Sands, J. H., Palmer, P. P., Mayock, R. L., and Creger, W. P. (1955). *Amer. J. Med.*, **19**, 401.
Scadding, J. G. (1950). *Brit. med. J.*, **1**, 745.
—— (1956). *Tubercle (Lond.)*, **37**, 371.
—— (1959). *Lancet*, **1**, 323.
Sones, M., and Israel, H. L. (1954). *Ann. intern. Med.*, **40**, 260.
Taylor, A. J. (1958). *Brit. J. Tuberc.*, **52**, 70.
Ustvedt, H. J. (1948). *Tubercle (Lond.)*, **29**, 107.
Zettergren, L. (1954). *Acta Soc. Med. upsalien.*, **59**, Suppl. 5.

"The Division of Medical Research has no laboratories of its own; its activities are confined almost entirely to the support of extramural research in the universities and their affiliated institutions. . . . The policy of providing increased support to scientific personnel working in the universities has been continued. In 1959, the number of Medical Research Associates was increased by four, thus bringing to 16 the number of highly qualified medical scientists supported in universities on a continuing full-time basis. . . . Forty-five Graduate Medical Research Fellowships were awarded to enable young medical graduates to take research training in the basic medical sciences. A limited number of postdoctoral Medical Research Assistants were also employed under grants-in-aid to senior investigators. . . . Allocation of Divisional funds was as follows: grants-in-aid of research supported on an annual year-to-year basis $627,485 (32%); 1959 instalments of research grants for terms of three years or longer $847,036 (43%); non-recurring equipment grants $222,968 (11%); Medical Research Associateships $134,751 (7%); Graduate Medical Research Fellowships $147,100 (7%)." (*Forty-third Annual Report of the National Research Council of Canada, 1959–60.*)