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SARCOIDOSIS, WITH SPECIAL REFERENCE TO LUNG CHANGES*

BY

J. G. SCADDING, M.D., F.R.C.P.

Assistant Physician, Brompton Hospital; Dean, Institute of Diseases of the Chest; Physician, Postgraduate Medical School of London

[WITH PHOTOGRAVURE PLATE]

The syndrome to which the name sarcoidosis has come to be generally applied in the Anglo-American literature may seem at first to be of rather rare occurrence and too specialized to form the subject of this lecture. Yet there are few subjects whose study leads into more varied fields of investigation. The more frequent manifestations of the syndrome have led to clinical interest in it by dermatologists, by ophthalmologists, and by physicians concerned with diseases of the respiratory system; while occasional manifestations have aroused the interest also of neurologists and endocrinologists. A study of its peculiar immunological aspects involves a study of the vast field of the immunology of tuberculosis; the study of its pathology and morbid histology cannot be dissociated from studies of similar aspects of tuberculosis, of the reticuloses, of tissue reactions to other infections such as brucellosis, and of foreign-body reactions; and the similarity of the clinical and pathological changes induced by exposure to certain beryllium salts to those of sarcoidosis leads into the field of industrial disease. Thus no subject could better illustrate the essential unity of medicine.

Clear definition of terms is essential to clear thought. Medical literature contains many examples of the fallacy which springs from neglect of this principle: the fallacy introduced by failure to start with a clear definition of terms, and consequent failure to perceive that the same term has been used with different meanings in different parts of the argument. For instance, in the controversy about the relation of sarcoidosis to tuberculosis it is not uncommon to find that the argument has been started as if in the definition the question of the relation to tuberculosis had been left open; while, in collecting the data, cases which show all features of the syndrome but in which tubercle bacilli happened to have been found have been excluded. The failure to start with clear definition also leads to a number of circular arguments in the various controversies about the disease. For instance, many physicians include in their concept of sarcoidosis, whether specifically formulated or not, the idea that in this syndrome tuberculin sensitivity must be either absent or slight. To such physicians questions about the tuberculin test in sarcoidosis will clearly be not factual but purely verbal; the answer to them will require no examination of data but simply elucidation and examination of definitions. This is a fallacy into which physicians studying the pulmonary and other systemic manifestations of the syndrome have fallen, rather than the dermatologists. The latter can use the equivalent of an ostensive definition, involving no proviso stated or implied about the tuberculin test; they simply say that by the various forms of sarcoid of the skin they mean lesions like others which they have observed, and which they describe either in words or, better, by illustration or demonstration. Thus the statements of dermatologists about the proportion of their cases showing a positive tuberculin reaction are more likely to have factual content than the statements of chest physicians.

*The Bradshaw Lecture delivered at the Royal College of Physicians of London on November 10, 1949.

Definition of Sarcoidosis

Having said this I must admit that clear definition of the syndrome is very difficult. It is significant that very many papers and reviews on this subject start with a fairly extensive historical survey mentioning the contributions of Hutchinson (1877), Besnier (1889), Boeck (1899, 1905), Schaumann (1914, 1936), Jüngling (1919), and others to our concept of the syndrome. This procedure avoids the difficulty of formal definition; it answers the question, "What disease are you talking about?" by saying, "The disease that has been described in these classical papers." It leaves as the sole criterion of whether a given case should be classified in the group under discussion its similarity to the classical descriptions. It leaves open the question which part of the classical descriptions should be regarded as essential and which incidental, and has made way for much unfortunate wrangling about priority of description and for a confusing variety of eponyms. As well as the eponyms, several other names have been used; among these I favour "sarcoidosis," because, although the word could be reduced to nonsense by strict etymological examination, it could also be interpreted rather more freely as denoting that group of cases in which there are generalized changes having a similar histology to that of the skin lesions which the dermatologists have named sarcoids. It also has the advantage of being free from aetiological implications.

In general it has been agreed that the most important common distinguishing feature of the group is a histological pattern, consisting of epithelioid cell tubercles, as a rule clearly defined within the affected tissue, with only slight round-cell infiltration in their vicinity, without central caseation, with or without Langhans-type giant cells, and with or without the peculiar inclusion bodies within these cells described by Schaumann (1941), proceeding in the older lesions to conversion into a peculiar hyaline type of fibrous connective tissue. The striking uniformity of these appearances in the most characteristic cases has

suggested to some the possibility of correlation of the histological changes with a specific aetiology.

This appearance, however, cannot be regarded as specific to any one aetiological agent. Although typical sarcoid lesions are easily distinguishable from those of classical tuberculosis, individual lesions can be found in cases of classical tuberculosis which resemble in every respect sarcoid tubercles. In erythema nodosum, presumably of tuberculous origin, van Beek and Haex (1948) state that tubercles, some having all the characteristics of sarcoid tubercles, can be found in a high proportion of cases in liver tissue obtained by aspiration biopsy. In chronic brucellosis, lesions have been found in the liver and in the bone marrow, both by biopsy and at necropsy, which very closely resemble sarcoid tubercles, though from the published reports (Spink and Sundberg, 1947; Spink *et al.*, 1949) it seems to me that there is more round-cell infiltration in and around the lesions, and the lesions are less clearly circumscribed in the tissue, than is present in typical sarcoids; and the granulomatous lesions following chronic exposure to beryllium may resemble the non-caseating tubercle of sarcoidosis very closely (Hardy and Tabershaw, 1946; Dutra, 1948; Grier *et al.*, 1948; Pascucci, 1948; Martland *et al.*, 1948). Hence, although a histological appearance must be described as an essential part of the definition of sarcoidosis, it does not provide the criterion of an aetiologically distinct group. Yet any other criteria that may be added are likely to be permissive and thus blur rather than sharpen the definition. Let us consider the definition of sarcoidosis by the conference on sarcoid of the U.S. National Research Council (quoted by Ricker and Clark, 1949).

"Sarcoidosis is a disease of unknown aetiology. Pathologically it is characterized by the presence in any organ or tissue of epithelioid cell tubercles with inconspicuous or no necrosis and by the frequent presence of refractile or apparently calcified bodies in the giant cells of the tubercles. The characteristic lesions may be replaced by fibrosis, hyalinization, or both. Clinically, the lesions may be widely disseminated. The tissues most frequently involved are lymph nodes, lungs, skin, eyes, and bones, particularly of the extremities. The clinical course usually is chronic with minimal or no constitutional symptoms; however, there may be acute phases, characterized by a general reaction with malaise and fever. There may be signs and symptoms referable to the tissues and organs involved. The intracutaneous tuberculin test is frequently negative; the plasma globulins are often increased. The outcome may be clinical recovery with radiographic evidence of residue, or impairment of function of organs involved, or a continued chronic course of the disease."

The many permissive phrases at the end of this definition ("there may be acute phases" . . . "the tuberculin test is frequently negative; the plasma globulins are often increased. The outcome may be clinical recovery") leave the door wide open to difference of clinical opinion about which cases should be classified under the heading "sarcoidosis." Moreover, the definition as it stands would include cases of chronic beryllium granulomatosis, since these satisfy all its criteria—unless these cases be taken to be excluded by the preliminary statement that sarcoidosis is a disease of unknown aetiology. However, this phrase carries its own difficulties with it, especially for those who believe that sarcoidosis, at least in some cases, is a manifestation of tuberculosis; since, as soon as in any given case they have succeeded in proving their contention, this interpretation of the definition logically excludes the case from the category of sarcoidosis. I consider that the only way out of these dilemmas is to adhere strictly to a careful histological definition. It will be necessary to add to the description of the characteristic histological appearances the proviso that they must be present in all affected tissues; the finding of a few isolated lesions presenting these characteristics accompanying more extensive lesions with different characteristics should not be allowed to bring the case as a whole in the category of sarcoidosis. This proviso would exclude the occasional sarcoid-like lesion in a case of classical tuberculosis and the sarcoid-like lesions which have been found to occur in certain situations in chronic brucellosis. Adopting this definition, it will be perfectly proper logically to speak of tuberculous sarcoidosis, of beryllium sarcoidosis, of sarcoidosis due to any other agent that may possibly in future be shown to cause it, and of sarcoidosis of undetermined cause. We can then hope that the number of cases relegated to the latter group will steadily diminish as our knowledge of the condition and our methods of investigating it advance.

Incidence of Pulmonary Sarcoidosis

My purpose is to review, mainly from a clinical point of view, the pulmonary disorders associated with this disease process. The frequency of cases in which the lungs are involved in sarcoidosis in the general population is difficult to estimate, since the only figures likely to be available are those from mass radiography, and the diagnosis by this means is only presumptive. Schönholzer (1947) stated that in 67 out of 516,879 mass radiographic examinations in the Swiss Army appearances suggesting a diagnosis of pulmonary sarcoidosis were found, an incidence of 0.13 per 1,000.

The incidence of sarcoidosis varies with race. In all large series from the United States there is evidence of a higher incidence in the negro section of the population of that country. Ricker and Clark (1949), who examined the records of the United States Army Institute of Pathology, found that 174 of 300 cases were in negroes; since negroes constituted 10% of the United States Army, they estimated that the disease must have been about 17 times as frequent in the negroes as in the whites. Similarly McCort *et al.* (1947) found that, of 28 patients referred to a United States Army centre for radiotherapy on account of lymphadenopathy who were found to be suffering from sarcoidosis, 15 were negroes. Twenty-three of Longcope's (1941) 31 patients were negroes. Harrell (1940) found that of 11 cases in North Carolina 9 were in negroes. Fourteen of the 36 cases reported by Garland (1947) in California were in negroes. Thirty of the 35 cases which Reisner (1944) observed in New York were in negroes.

In a series of cases diagnosed clinically as sarcoidosis the incidence of involvement of individual organs varies, as would be expected, according to the source of the cases. A high proportion of cases coming under the care of dermatologists on account of skin lesions show intrathoracic changes. Kissmeyer (1932) found that of 24 cases of skin sarcoidosis 19 showed intrathoracic changes on radioscopy. Vosbein and Bonnevie (1940) found intrathoracic changes in 10 out of 16 cases showing typical skin lesions. Nielsen (1934) found lung changes in 37 out of 39 cases of cutaneous sarcoidosis. Reisner (1944) found that 33 out of 35 cases coming under observation in chest clinics showed lung lesions, and 30 enlarged intrathoracic lymph nodes. McCort *et al.* (1947) reported 28 cases seen in an Army Hospital centre for radiotherapy, and therefore coming under observation primarily because of enlarged hilar or peripheral lymph nodes; 15 of these had radiological evidence of lung involvement. Ricker

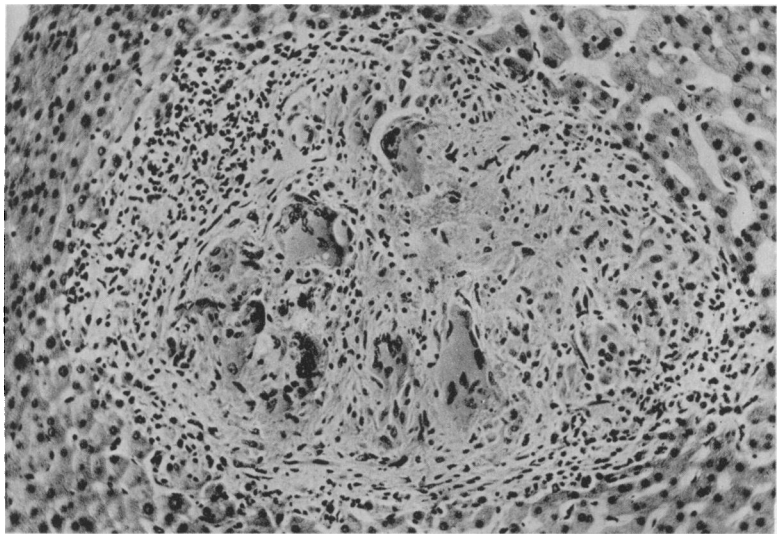

FIG. 1.—Case 4. Liver biopsy. (× 160.)

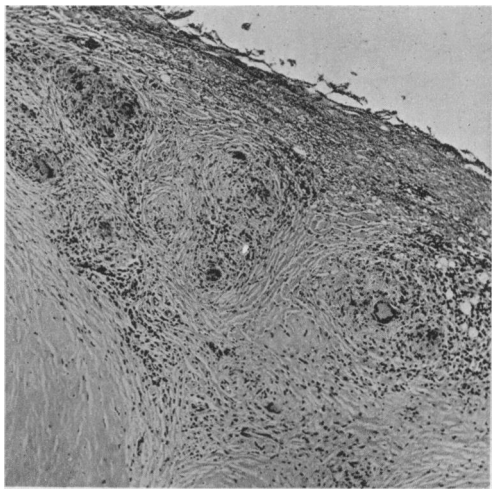

FIG. 2.—Case 16. Biopsy of supraclavicular lymph node. (× 55.)

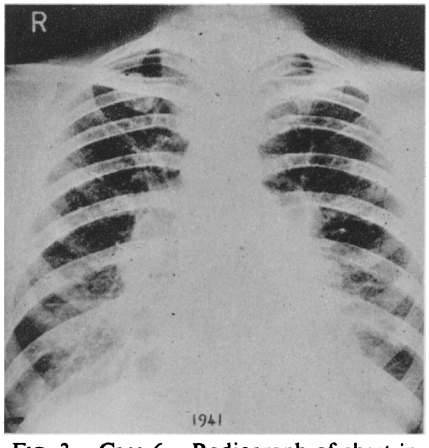

FIG. 3.—Case 6. Radiograph of chest in 1941.

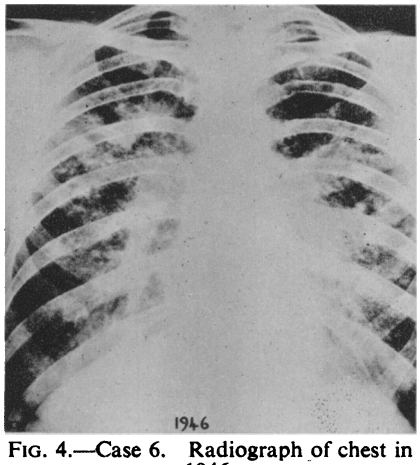

FIG. 4.—Case 6. Radiograph of chest in 1946.

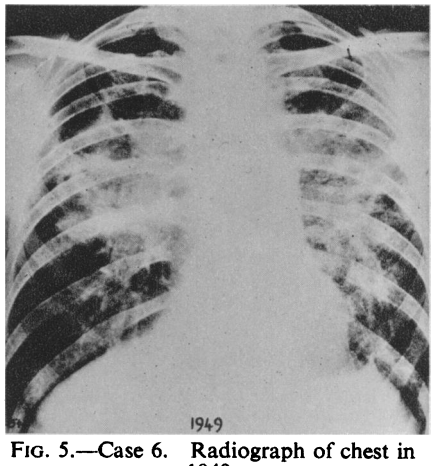

FIG. 5.—Case 6. Radiograph of chest in 1949.

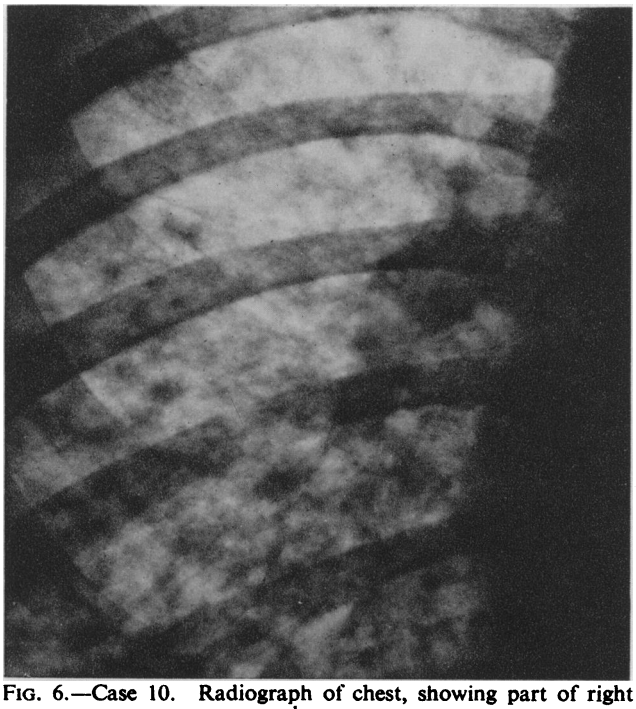

FIG. 6.—Case 10. Radiograph of chest, showing part of right lung.

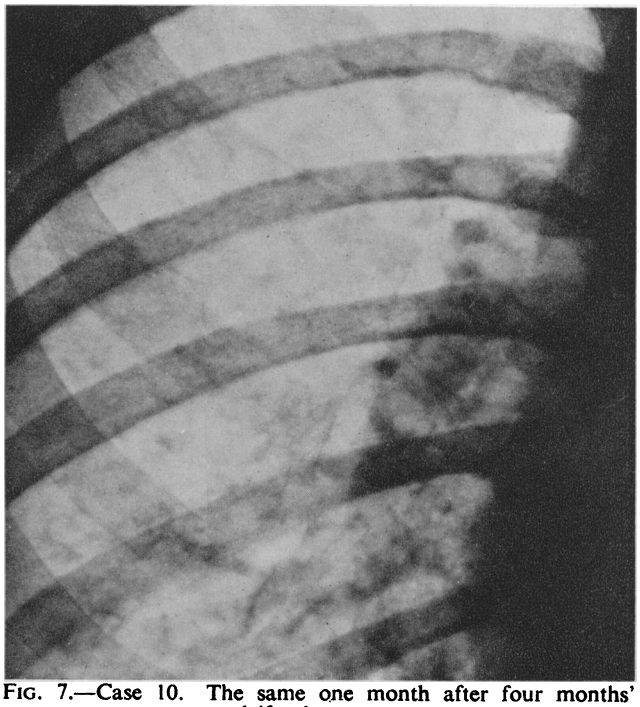

FIG. 7.—Case 10. The same one month after four months' calciferol treatment.

J. G. SCADDING: SARCOIDOSIS, WITH SPECIAL REFERENCE TO LUNG CHANGES

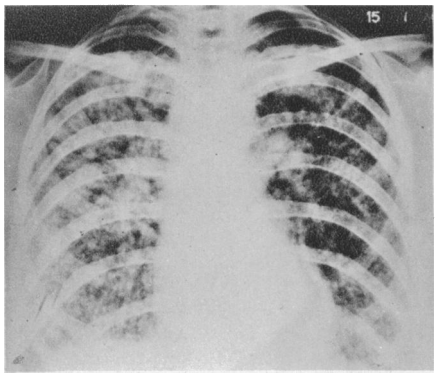

FIG. 8.—Case 11. Radiograph of chest; January, 1948.

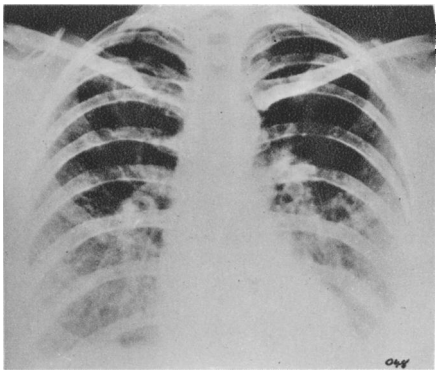

FIG. 9.—Case 11. Radiograph of chest; April, 1949.

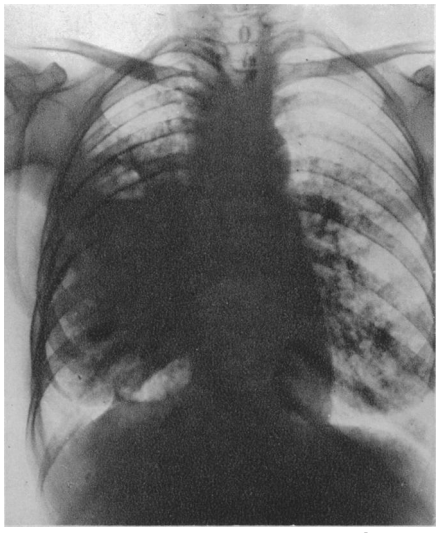

FIG. 10.—Case 16. Radiograph of chest; June, 1949.

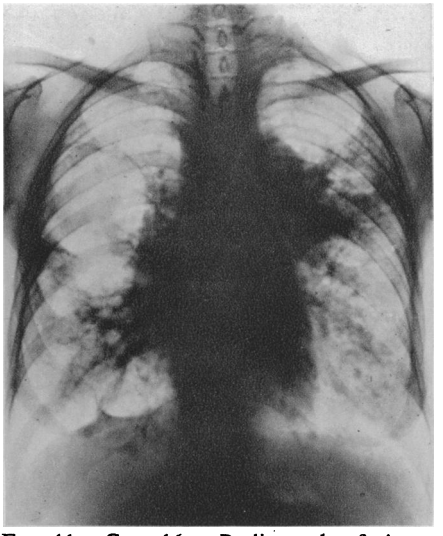

FIG. 11.—Case 16. Radiograph of chest; August, 1949.

H. C. McLAREN: CANCER OF UTERUS IN ADRENOGENITALISM

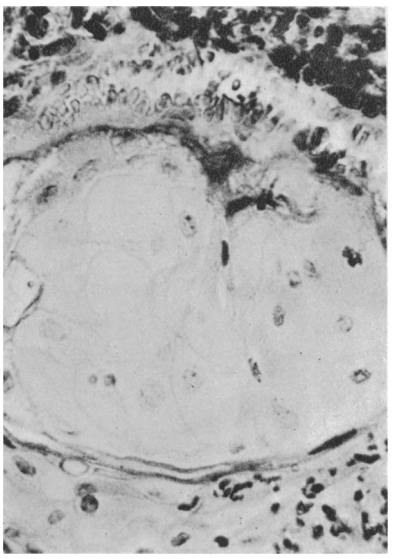

FIG. 1.—Adeno-acanthoma with circumscribed pale area. (× 480.)

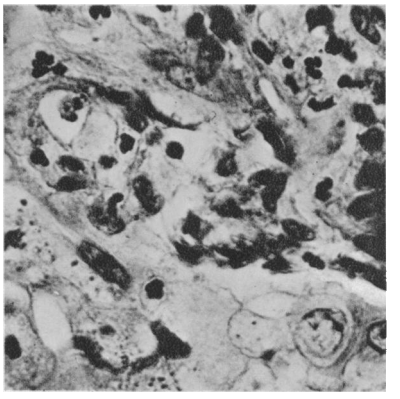

FIG. 2.—Metaplasia. Cytoplasm of irregularly shaped epithelial cells is pale staining with hæmatoxylin-eosin; some of the nuclei are fragmented. (× 480.)

G. H. JENNINGS: AMYLOIDOSIS IN RHEUMATOID ARTHRITIS

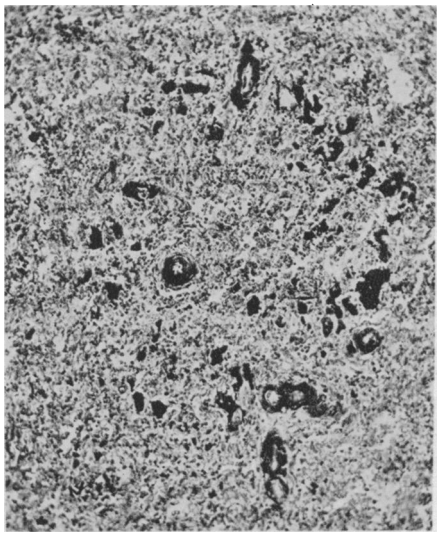

FIG. 1.—Case 2. Spleen (× 85). Methyl violet stain shows amyloid in central arteriole of Malpighian corpuscle and in smaller arteriolar branches around periphery.

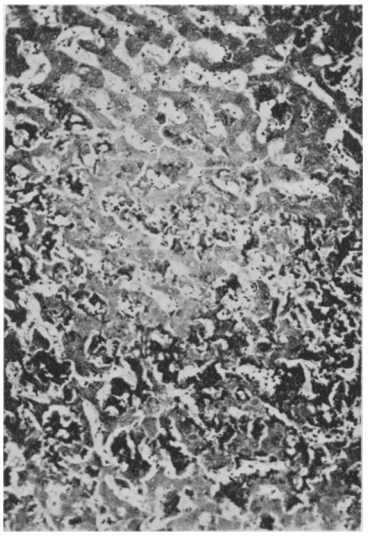

FIG. 2.—Case 2. Liver (× 85). Dark-staining amyloid material between sinus endothelium and compressed, degenerated liver cells.

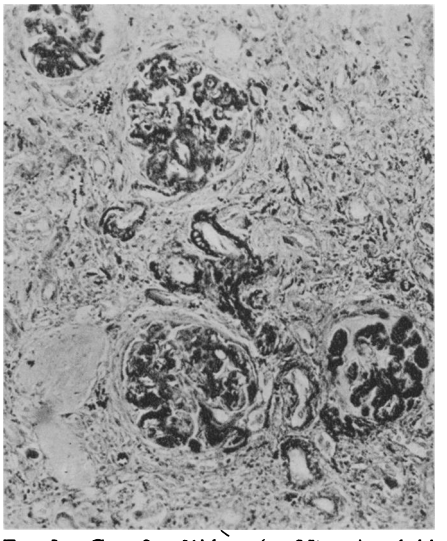

FIG. 3.—Case 2. Kidney (× 85). Amyloid changes in glomeruli and afferent arterioles; tubular degeneration; replacement fibrosis.

Illustrations printed in Collogravure by HARRISON & SONS, LTD., Printers to His Majesty The King, London, Hayes (Middx.) and High Wycombe.

and Clark (1949) found evidence of involvement of the lungs in 36% of 300 cases from which pathological material, either biopsy or necropsy, had been examined at the United States Army Institute of Pathology. Of the 13 cases reported by Snapper from a general medical clinic in 1938, 9 showed lung lesions. In my own 16 cases the lungs were involved in 15 and there was gross enlargement of hilar glands in the other; this finding is of course largely a reflection of my interest in diseases of the chest.

Types of Change in the Chest Radiograph in Sarcoidosis

In the 12 years since I first became interested in this syndrome, interrupted by the war years, I have observed 16 cases in which I made a diagnosis of sarcoidosis. In 13 of these the diagnosis was supported by histological evidence; in the remaining three no suitable tissue was obtained for histological examination, and the diagnosis therefore remained one of clinical probability. I propose to describe briefly the changes in the chest radiographs in these cases; and in an attempt to elucidate the natural history of the lung changes I will classify the cases into groups according to the changes evident in the first available radiograph. In several instances this was made several years before I first saw the patient. In the following description, enlargement of hilar lymph nodes indicates enlargement sufficient to be evident in a plain postero-anterior radiograph. In all cases examination of sputa or other material (e.g., stomach contents) for tubercle bacilli, usually including culture or guinea-pig inoculation, has been performed and yielded negative results, except where otherwise stated.

1. Enlargement of Hilar Lymph Nodes Without Detectable Lung Change

Three cases presented enlargement of the hilar lymph nodes without detectable lung change in the first available chest radiograph; the enlargement was unilateral in one and bilateral in two.

Case 1 (Case 2 of Scadding and Sherlock, 1948).—A man aged 24 had had recurrent bilateral chronic iridocyclitis for 18 months. The spleen was enlarged. The Mantoux test was positive to 0.1 mg. old tuberculin. There were no superficial lymph nodes available for biopsy, but liver biopsy showed typical non-caseating tubercles without giant cells. The first chest radiograph showed enlargement of the right hilar lymph nodes. After treatment with calciferol the ocular condition became quiescent and the lymph nodes subsided in about a year.

Case 2.—A woman aged 35 had been treated in 1937 for an apical tuberculous lesion, though no bacilli had been found. In 1939 she developed grossly enlarged bilateral hilar lymph nodes without symptoms. The only abnormality found on physical examination was slight enlargement of lymph nodes above the inner ends of both clavicles, biopsy of one of which showed characteristic non-caseating tubercles. The Mantoux reaction was persistently negative to 10 mg. O.T. After about a year a diffuse infiltration developed in both lungs, again without symptoms, and both it and the enlarged lymph nodes disappeared gradually over the course of the next two or three years. In 1946, shortly after the birth of a healthy child, the Mantoux reaction was found to be positive to 0.1 mg. O.T. Seen recently, she remained well, and the chest radiograph showed only the old apical scar.

Case 3.—In 1931 a woman then aged 24 developed skin lesions first on the legs and then on the arms (Fig. A). Biopsy of the skin showed characteristic sarcoid lesions. Soon after the appearance of the skin lesions she developed chronic iridocyclitis. This subsided in about two years. In 1936 she complained of cough, substernal discomfort, dyspnoea, and loss of weight, and was found to have enlarged hilar lymph nodes. She was treated in a sanatorium. Pulmonary infiltration developed

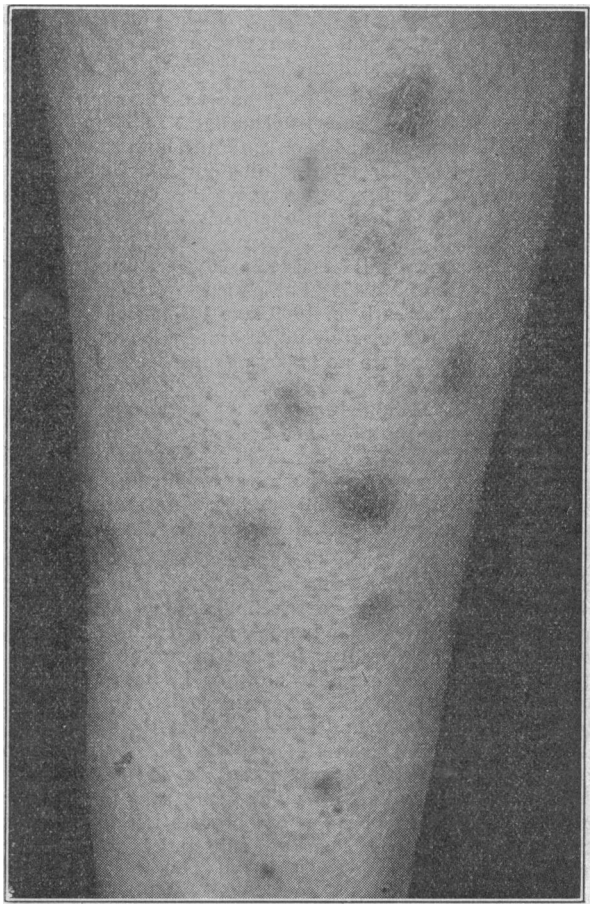

FIG. A.—Case 3. Skin lesions on leg. Similar lesions were present on arms and forearms.

while she was there. When I saw her in 1938 the hilar nodes had diminished considerably in size, but there was diffuse mottling, densest in the middle zones, of a quality suggesting some fibrosis. The skin lesions were still present. The subsequent course of this patient has been briefly reported by Hoyle (1947). Tubercle bacilli appeared in the sputum shortly before death from right heart failure in 1946.

2. Bilateral Enlarged Lymph Nodes With Diffuse Mottling in the Lungs

In four cases the first available chest radiograph showed gross bilateral hilar-lymph-node enlargement with diffuse infiltrations in the lungs of various sorts.

Case 4.—A man aged 32 complained of pain in the left side of the chest for about five weeks followed by some dyspnoea and loss of over a stone (6.35 kg.) in weight. A radiograph showed bilateral hilar-lymph-node enlargement with some faint fine mottling in the lower zones of the lungs. There were no enlarged superficial lymph nodes. The Mantoux test was positive to 0.1 mg. O.T. Liver biopsy showed one small non-caseating epithelioid-cell tubercle with giant cells (Plate, Fig. 1). The symptoms disappeared within three months, and the chest radiograph became normal within nine months without any special treatment.

Case 5.—A man aged 27 was referred to hospital in 1943 on account of progressive enlargement of the cervical lymph nodes for 14 months, followed by swelling of the inguinal lymph nodes. On physical examination generalized enlargement of lymph nodes in all superficial groups was found. The Mantoux test (dose not recorded) was reported negative. Biopsy of a cervical node showed characteristic epithelioid-cell tubercles with some giant cells but not caseation. A chest radiograph showed some enlargement of hilar lymph nodes together with a diffuse mottling in the lung fields. Shortly after this the

superficial nodes started to subside, and when he was next seen in 1949 no enlargement of them was evident and the chest radiograph was within normal limits.

Case 6.—A woman aged 28 came under observation first with a history of two years' cough. The chest radiograph at this time showed enlarged hilar lymph nodes on both sides, together with an irregular rather fine mottling in both lungs (Fig. 3). In the course of the next seven years this condition steadily progressed to fibrosis in both lung fields with gross emphysematous changes in the rest of the lungs, where, however, some miliary-type shadows still persisted. Fig. 4 shows the radiographic appearance in 1946. The patient was in this condition when I first saw her early in 1949, and to clinical examination presented a picture of severe chronic bronchitis with spasm and emphysema. There were no enlarged superficial lymph nodes. The chest radiograph (Fig. 5) showed gross fibrotic changes in the middle zones of both lungs, on a background of the old-standing diffuse fine mottling, and emphysema with large bullae especially in the middle zones, well shown by tomography. The Mantoux reaction was negative to 10 mg. O.T. Liver biopsy showed several small non-caseating epithelioid-cell tubercles without caseation and without giant cells.

Case 7.—A woman aged 38 complained of two years' lassitude, breathlessness, cough, and loss of weight. There were moderately enlarged soft lymph nodes in both axillae. A chest radiograph showed enlarged hilar lymph nodes (confirmed by tomography), together with diffuse increase in striations throughout both lungs and some irregular mottling in both lower zones. Tomography also revealed a small cavity-like appearance, probably an emphysematous bulla, at the right apex. The Mantoux test was negative to 0.1 mg. but positive to 1 mg. O.T. Biopsy of an axillary lymph node showed many discrete epithelioid-cell tubercles with a few giant cells and no caseation. The patient has been under observation for only eight months and there has been no substantial change in her condition.

3. Diffuse Pulmonary Infiltration Without Gross Evidence of Hilar-Lymph-Node Enlargement

In the first available chest radiograph seven cases showed diffuse pulmonary infiltrations without gross enlargement of the hilar lymph nodes. The infiltrations varied from a fine approximately miliary type to an irregular coarser type, and were in some cases followed by irregular fibrotic changes.

Case 8.—A man aged 19 was found on radiography, undertaken because when he was medically examined for the Army he complained of two months' dry cough, to have a diffuse fine mottling throughout both lung fields. On examination there were no abnormal physical signs. The Mantoux test was positive to 0.01 mg. O.T. There were no superficial lymph nodes for biopsy, and liver biopsy showed no abnormality. In this case a diagnosis of sarcoidosis was made by exclusion. His condition has remained unchanged in one year's observation.

Case 9.—A man aged 19 complained of cough, slight dyspnoea, and some loss of weight. On physical examination the spleen was just palpable and there were a few not very notably enlarged lymph nodes palpable in both axillae. A radiograph of the chest showed diffuse fine rather reticular mottling. The Mantoux reaction was negative to 10 mg. O.T. Biopsy of an axillary lymph node showed no specific changes, and an attempt at liver biopsy was unsuccessful in obtaining tissue. The diagnosis of sarcoidosis was made on clinical grounds. After four months' treatment with calciferol, 150,000 units a day, there was a slight though appreciable diminution in the density of the shadows.

Case 10.—A woman aged 23 complained of four months' cough, pain in the chest, and dyspnoea. There were no abnormal physical signs. A chest radiograph showed a diffuse rather coarse pseudo-miliary infiltration in both lungs (Fig. 6). The Mantoux test was positive to 0.01 mg. O.T. Liver biopsy showed no specific changes. She was treated for four months with calciferol, which was followed by striking resolution of the abnormal shadows (Fig. 7).

Case 11 (Case 1 of Scadding and Sherlock, 1948).—A woman aged 22 was found by mass radiography in November, 1945, to have a coarse diffuse bilateral infiltration of both lungs. She was symptom-free. On physical examination the only abnormality was enlargement of lymph nodes behind the inner ends of both clavicles and in both epitrochlear regions. The Mantoux test was negative to 10 mg. O.T. Biopsy of one of the cervical lymph nodes and of the liver showed typical non-caseating tubercles. Under observation the infiltration became gradually denser, and during 1947 she steadily lost weight and the sedimentation rate rose. At the end of this year new lesions were found in some of the phalanges of the hands and feet. At this stage (Fig. 8) she was treated with calciferol in dosage varying from 50,000 to 100,000 units daily, adjusted according to her tolerance, for five months. This was followed by very striking clearing of the abnormal shadows (Fig. 9) and by a great increase in weight with reversion of the sedimentation rate to a normal level.

Case 12.—A man aged 35 was found on routine radiography to have diffuse irregular mottling in both lungs maximal in the middle zones. Physical examination revealed some soft enlargement of lymph nodes in the left axilla and the liver edge was palpable. The Mantoux test was negative to 10 mg. O.T. Biopsy of an axillary lymph node showed non-caseating epithelioid-cell tubercles with giant cells. After four months' treatment with calciferol, 150,000 units a day, which was well tolerated, there was some diminution in the density of the abnormal shadows in the lungs.

Case 13.—A man aged 31 complained of increasing dyspnoea for five years and cough for six months. On physical examination the only abnormality was slight enlargement of lymph nodes above the left clavicle, in both axillae, and in the groins. A chest radiograph showed widespread coarse mottling throughout both lungs. The Mantoux test was negative to 1 mg. but positive to 10 mg. O.T. Biopsy of a lymph node showed non-caseating epithelioid-cell tubercles with many giant cells. He proved intolerant of calciferol. Six days' administration of 50,000 units daily produced severe toxic symptoms.

Case 14.—A man aged 35 complained of increasing dyspnoea and cough with scanty sputum. Shortly before the first radiograph in 1946 he had had an acute illness with pain in the right side of the chest. This radiograph showed diffuse fine mottling through both lung fields with a more homogeneous shadow indicative of consolidation in the right middle lobe. A year later, in September, 1947, the density of the pulmonary infiltration had increased. In July, 1948, enlargement of lymph nodes on both sides of the neck was noted, and a biopsy showed many epithelioid-cell tubercles without caseation. In November, 1948, when I first saw him, he was noticeably dyspnoeic on slight exertion; there were enlarged lymph nodes in both sides of the neck, in the axillae, and in the groins. In June, 1949, when he was admitted for investigation, the radiographic appearances remained similar to those seen in the previous November. Tomography showed evidence of cavitation or emphysematous bulla formation in both middle zones. The Mantoux test was negative to 10 mg. O.T. Biopsy of a lymph node showed many discrete epithelioid-cell tubercles, with some areas of hyaline fibrosis. He proved intolerant of calciferol. Recently, without any immediate change in his symptoms, tubercle bacilli were found in his sputum for the first time, confirmed by culture; and the Mantoux test has become positive.

4. Fine Reticulation

One patient whose only complaint was of dyspnoea showed a very fine reticulated appearance in the chest radiograph which might quite easily be missed on casual inspection of the film.

Case 15 (Case 3 of Scadding and Sherlock, 1948).—A woman aged 40 complained of increasing dyspnoea, especially over the past 18 months, an almost unproductive cough, some pain across the chest, and loss of weight. On physical examination there

was considerable enlargement of lymph nodes in the left axilla, the spleen was easily palpable, and there were fine scattered rales throughout both lungs. The chest radiograph showed fine diffuse reticulation maximal in the upper and middle zones. The Mantoux test was negative to 1 mg. O.T. Biopsy of a left axillary lymph node showed many epithelioid-cell tubercles with some giant cells but no caseation, and biopsy of the liver revealed a discrete lesion with a hyaline connective-tissue centre, surrounded by epithelioid cells, young fibroblasts, and some round cells, but no giant cells. In 2½ years' observation there has been little change in her condition, although in April, 1949, accompanying an intercurrent respiratory infection, she developed a transient atelectasis of the right middle lobe, which subsequently re-expanded.

5. Fibrosis, Emphysema, and Bulla Formation

One patient first came under observation in the late stage with fibrosis, emphysema, and bulla formation.

Case 16.—A woman aged 41 when first seen in June, 1949, complained that she had not felt well since the birth of her third child in 1946. In June, 1947, she had started to suffer from pain and stiffness in the small joints of the hands, wrists, elbows, shoulders, hips, and knees. Early in 1948 she had an acute illness diagnosed as pneumonia. In the summer of 1948 cough gradually developed with about ½ oz. (14 ml.) of purulent sputum. At this time the rheumatic pains ceased and have not recurred. The cough and sputum, however, gradually became worse. Early in 1949 the cough and sputum became much worse and she was admitted to a hospital for two months. At this time it was reported that acid-fast bacilli had been seen in small numbers in the sputum, but on culture shortly afterwards no tubercle bacilli were grown. When I first saw her in June, 1949, she was thin, with no clubbing of the fingers and no abnormal signs, apart from those in the chest, except for a very firm mobile lymph node behind the inner end of the right clavicle. The chest radiograph (Fig. 10) showed diffuse mottling in the left lung maximal in the middle and lower zones, and in the right lung similar mottling partly obscured by a dense opacity with a cavity and fluid level in the middle zone. The Mantoux test was negative to 1 mg. O.T. Biopsy of the supraclavicular lymph node (Fig. 2) showed a central mass of collagen with a number of small active follicles of epithelioid cells and some giant cells at the periphery. There was no evidence of caseation and no tubercle bacilli were seen on fluorescence microscopy. Inoculation of two guinea-pigs from this lymph node and repeated cultures of the sputum were all negative for tubercle bacilli. The diagnosis of sarcoidosis with either pyogenic infection in an emphysematous bulla or intercurrent abscess was made. An attempt was made to treat the abscess on the right side by postural drainage and penicillin. This unfortunately resulted in secondary abscess formation in the left lung (Fig. 11), and tomograms at the beginning of August demonstrated the cavitation in both lungs very clearly. She has been treated intensively with penicillin for the secondary infection with relatively little success, though some diminution in the pneumonic densities is evident. Recently the spleen has become palpable.

Natural History of the Lung Changes

Correlating my own experience with reports in the literature, I think the earliest intrathoracic lesion of sarcoidosis is usually hilar-lymph-node enlargement, which may be shortly followed or more rarely accompanied by a more or less diffuse pulmonary infiltration varying from a fine micro-nodular type resembling miliary tuberculosis to coarser irregular mottling. Possibly some cases start with the pulmonary infiltration without a preceding stage of hilar-lymph-node enlargement. Infiltrations of either type may either clear completely so far as radiographic appearances are concerned, or persist for a variable time with a variable amount of replacement by fibrosis. This fibrosis most frequently takes the form of irregular coarse strands, usually in the middle zones, with gross emphysematous changes elsewhere; or it may more rarely be of much finer type giving rise to a fine reticulated appearance in the radiograph. This latter appearance may easily be missed on inspection of the radiograph; it is accompanied, however, by a considerable diminution in the patient's vital capacity and correspondingly severe functional disability. In the cases which present the picture of fibrosis and emphysema tubercle bacilli may eventually appear in the sputum, although the radiographic appearances may not show any immediate corresponding change.

The question of cavitation in sarcoidosis without frank tuberculosis merits some attention. Gross and obvious cavity appearances were an important feature in Case 16, which, as stated above, presented with a picture suggesting diffuse fibrotic changes in the lungs with abscess formation. I think that this was probably due to secondary infection in emphysematous bullae. Three other cases have shown gross emphysematous bulla formation, and one case had a small very high apical cavity, detectable with certainty only by tomography.

Pulmonary cavitation without evidence of classical tuberculosis has been reported previously in sarcoidosis by several observers. Ustvedt (1948) reported the necropsy appearances in a woman aged 39 who had suffered from Heerfordt's syndrome for 11 years before death and had had respiratory symptoms for two years. At necropsy there were large cavities at both apices without characteristic histological changes, either tuberculous or sarcoid, in their walls, together with generalized fibrotic and bronchiectatic changes in the lungs. Tice and Sweany (1941) reported the case of a woman aged 45 who had shown a characteristic sequence of changes in the chest radiograph starting with enlargement of the mediastinal shadows and irregular nodular infiltration in the lungs. At necropsy a cavity with a fibrotic "capsule" was found in the right lower lobe. Emphysematous changes, often with gross bullae, have been frequent findings in post-mortem examinations (Pinner, 1938; Rubin and Pinner, 1944): Schaumann (1933) and Hogan (1946) have published clinical and necropsy reports on patients whose lungs presented radiographic appearances closely similar to those observed in cases 6 and 14 of my series. Clinical reports of patients showing radiographic appearances suggesting gross cavitation have been made by Salvesen (1935), by Pruvost and Depierre (1946), and by Bernstein and Sussman (1945).

Diagnosis

Confirmation of the diagnosis of sarcoidosis depends upon histology. It is important to recall that the definition adopted above demands that the characteristic changes should be present in all affected tissues; hence the discovery of such changes in a single biopsy specimen is not absolute proof of the diagnosis, but is evidence to be added to clinical, radiological, and other evidence. In many cases superficial lymph nodes are available for biopsy and provide the most accessible material. When lymph nodes are not available it has been shown that liver biopsy, even though there is no clinical evidence of affection of that organ, often shows characteristic lesions (van Beek and Haex, 1943a, 1943b; van Buchem, 1946; Scadding and Sherlock, 1948). If skin lesions are present these of course offer convenient biopsy material. Some Scandinavian workers have recommended biopsy of tonsils, which, even if they appear normal, often show characteristic changes in sarcoidosis; I have not had occasion to adopt this rather severe method. In my series of 16 cases tissue was obtained by lymph-node biopsy in 10, of which nine

gave positive results; by liver biopsy in seven, of which five gave positive results; and from the skin in one.

Differential Diagnosis

In the cases of my series, classical tuberculosis was the condition from which differentiation was most frequently difficult. Cases 5, 6, 7, 9, and 10 all showed at some stage an appearance which would have been compatible with a diagnosis of chronic miliary tuberculosis. They were regarded as falling into the sarcoid group because of their good general condition, in some cases because of their insensitivity to tuberculin, and because of the clinical course. It must be admitted, however, that the differentiation between chronic miliary tuberculosis and sarcoidosis is in many instances little more than a verbal one. Cases 3, 11, and 13 presented radiological appearances consistent with a diffuse tuberculous infiltration of a coarser type, and again it was consideration of all aspects which led to their being classified in the sarcoid group. Cases 3, 6, 14, and 16 all showed at some stage a picture of pulmonary fibrosis with gross emphysema and either cavity formation or emphysematous bullae. These cases at this stage closely simulated the late stage of chronic indolent fibrotic pulmonary tuberculosis; and in fact in two of them tubercle bacilli appeared eventually in the sputum, and in another in an earlier stage acid fast bacilli were once seen in the sputum, though they could not be cultured, and perhaps too much significance should not be attached to this latter finding.

Difficulty sometimes arises in the differential diagnosis of sarcoidosis from industrial lung disease of varied sorts. This difficulty arose in Case 14. This patient had been employed for many years in a cement works. However, there was no recognized incidence of industrial pulmonary disease in the works, and the typical sequence of radiographic changes together with the generalized lymphadenopathy which showed typical sarcoid changes left no doubt of the diagnosis. It is possible, of course, that the exposure to dust may have had some effect in modifying the radiographic appearances of the sarcoidosis. In the more recent cases specific inquiry was made about possible exposure to beryllium, with negative result; and it is highly improbable that this factor entered into the aetiology of the earlier cases.

My own opinion of the aetiology of the cases in my series is that they fall into the category of tuberculous sarcoidosis. In most of them this opinion is supported by collateral evidence only, and there are admittedly strong arguments which could be advanced against it; but in two cases (Nos. 3 and 14), as noted above, acid-fast bacilli appeared eventually in the sputum, and in one (Case 2) the history suggests that a patient originally suffering from classical tuberculosis went through a "sarcoid" phase. Perhaps if I had the courage of my convictions I should follow the lead of Pinner (1938), which he himself subsequently abandoned, and label my cases "non-caseating tuberculosis."

Treatment

Arsenic (Snapper and Pompen, 1938), tuberculin (Irgang, 1939), and *x*-ray therapy have been tried for the treatment of sarcoidosis, but with no general agreement about their value. Since many clinicians believe most cases of sarcoidosis to be of tuberculous origin, a trial of streptomycin might be expected to have been undertaken. However, it is well recognized that streptomycin is most effective in the acute exudative types of tuberculosis and relatively little, if at all, effective in the most productive types; and the lesions of sarcoidosis are the perfect example of the productive non-exudative reaction. Hence, *a priori*, streptomycin would not be expected to have much effect on them even if they are of tuberculous origin; and in the only reference to the use of streptomycin in sarcoidosis which I can find, Pulaski and White (1948) state that they have treated seven cases of pulmonary sarcoidosis with streptomycin without effect on the pulmonary lesions.

After the success of calciferol in the treatment of lupus vulgaris it would have been surprising if dermatologists had not tried calciferol for cutaneous sarcoids. However, I can find only very scanty reference to this in the literature. Dowling and Prosser Thomas (1946) referred to one case of sarcoid which had proved unresponsive to calciferol. Curtis, Taylor, and Grekin (1947) reported a series of five cases treated with calciferol and dihydrotachysterol with generally satisfactory results; several of their patients showed toxic reactions.

Calciferol treatment has been tried in nine of my patients. At first I attempted to give the dose usually employed in lupus vulgaris—namely, 150,000 units a day. The first patient treated was Case 11. When treatment was begun she had been under observation for over two years, during the last six months of which the pulmonary infiltration had become notably denser, there had been loss of weight and a rise in the sedimentation rate, and fresh lesions had appeared in the bones of the hands. Treatment was started with 150,000 units daily, but she soon developed nausea and anorexia and showed a brisk rise of serum calcium together with a slight rise in blood urea. She was maintained on doses varying between 50,000 and 100,000 units a day, depending upon the blood chemical findings, for five months. At the end of this time there was some improvement in the lung lesions, and one month later a most dramatic clearing was evident; the lungs have remained clear apart from a little scarring in the right upper zone during the 15 months that have elapsed since then.

Of the nine cases in which calciferol treatment has been attempted, three tolerated 150,000 units daily, three tolerated only smaller dosage, and three were completely intolerant. This proportion of intolerant cases is much greater than has been reported in series composed of patients most of whom have been treated for conditions other than sarcoidosis: Anning, Dawson, Dolby, and Ingram (1948) reported that of their 200 patients treated with large doses of calciferol 19% developed toxic symptoms, but apparently not severe enough to prohibit further attempts in therapy in most. In the three completely intolerant cases in my series sensitivity to calciferol was remarkable. The accompanying chart shows briefly the response of one patient (Case 13) to a dose as small as 50,000 units daily for six days. The administration of only 10,000 units a day when the condition appeared to be improving was sufficient to cause a return of symptoms

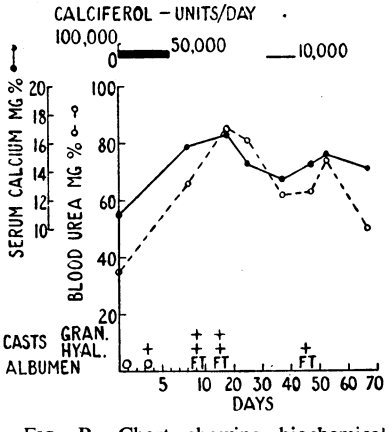

FIG. B.—Chart showing biochemical effects of administration of calciferol. 50,000 units daily, for six days in Case 13 FT = faint trace.

and a relapse in the biochemical changes. The other two patients (Cases 7 and 14) showed equally severe symptomatic and biochemical evidence of toxicity, but after larger doses of calciferol. It is unfortunate that complete investigations of the renal function were not made before treatment was started in these cases, since it is known that sarcoid lesions sometimes occur in the kidneys (Horton, Lincoln, and Pinner, 1939; Cameron and Dawson, 1946), and it is therefore possible that there may have been some preceding impairment of the renal function. The ordinary ward tests had revealed no abnormalities in the urines. In future I shall certainly investigate the renal function before treating any case of sarcoidosis with calciferol. All the six patients who tolerated calciferol showed some degree of improvement. Three tolerated 150,000 units a day for four months. Of these, one (Case 10) showed complete clearing of the lung lesions and two (Cases 9 and 12) showed some improvement. Three (including the one already quoted) tolerated smaller doses varying from 50,000 to 100,000 units daily. Of these, one case (Case 11) showed complete clearing of the lung infiltration, and one (Case 6) diminution in density of miliary type shadows, though established fibrotic and emphysematous changes remained unchanged. In the remaining patient (Case 1) calciferol was given because of persistently active bilateral iridocyclitis, and the only intrathoracic change was enlargement of the right hilar lymph nodes; the iridocyclitis became quiet and the hilar nodes subsided after the calciferol, and there has been no evidence of renewed activity under observation for two years afterwards.

The progress of the patients in whom treatment with calciferol was attempted is summarized in the accompanying Table, together with the progress of the patients not

Progress of Lung Lesions in 16 Cases of Sarcoidosis in Relation to Administration of Calciferol

	Tolerated Daily Dose Units	Progress of Lung Lesion			Worse	Death
		Cleared	Improved	Unchanged		
Treatment attempted (9 cases) ..	150,000	1	2	0	0	0
	50,000–100,000	2	1	0	0	0
	Intolerant	0	0	2	1	0
Treatment not attempted* (7 cases) ..	—	3	0	3	0	1

* This includes the cases with the longest observation periods.

so treated. No conclusion can, of course, be drawn from these data. The average period of observation of the cases in which treatment was attempted is considerably shorter than that for those untreated; and the difference between the progress of the patients intolerant of calciferol and that of those in whom treatment was possible may be explained as well by the hypothesis that patients whose lesions are in an actively progressing phase do not tolerate calciferol as by the hypothesis that calciferol benefited the patients who tolerated it. Nevertheless, I think that the effect of calciferol on the diffuse pulmonary infiltrations of sarcoidosis is well worth further investigation.

Prognosis of the Lung Lesions

Summing up the progress of the 16 cases after periods of observation varying from 8 months to 15 years: one has died in right heart failure with tubercle bacilli in the sputum; six have shown complete clearing of the radiographic abnormality, with or without calciferol treatment; two have shown increase in the extent and severity of the pathological process under observation, and in one of these tubercle bacilli have recently appeared in the sputum; and seven have shown no change, some of them after only short periods of observation. A similarly variable course of the pulmonary lesions has been reported by others. Bruce and Wassen (1940) found that of seven cases showing pulmonary lesions four cleared and three remained unchanged after periods of observation varying from one to three years. King (1941) reported a follow-up of 37 cases, in 23 of which the intrathoracic lesions had cleared or almost cleared in periods varying from seven weeks to three years, with an average of 22 months after first detection; in three there had been some clearing; in eight no change occurred after periods varying from three months to four years; and in three the lesions extended after intervals of seven months, eight months, and four years. Garland (1947) reported that in 36 cases there were two deaths; of 17 followed for periods varying from six months to seven years the lesions regressed in ten, were static in four, and progressed in three. Reisner (1944) followed 27 cases with lung changes and found that the lesion regressed in thirteen, was static in five, and progressed in nine. Six patients developed clinical tuberculosis and two died with generalized tuberculosis. Reisner thought that the disseminated nodular form especially showed a tendency to regression of the lesions. This view is consistent with the findings in my series.

Lung Changes in Tuberculin-negative Cases of Erythema Nodosum

It is now generally agreed that erythema nodosum should be regarded as a cutaneous response which may be elicited by a variety of agents. In respect of several of these, there is good evidence that the response occurs after sensitization to the agent concerned and may therefore be called allergic. This is certainly the case in the common type of erythema nodosum which appears soon after primary tuberculous infection; in these a high degree of tuberculin sensitivity is almost always found. Great interest therefore attaches to a group of cases which present a nodose erythema of typical distribution, with enlargement of hilar lymph nodes, usually bilateral, often with an extensive but transient and symptomless pulmonary infiltration, and in which tuberculin sensitivity, when tested, has been found to be absent or slight. Attention was first directed to these cases by Scandinavian workers (quoted by Forssman, 1946). In this country Kerley (1942, 1943) has recorded 37 cases which appear to belong to this group, though tuberculin tests were performed in only three of them.

Dr. Neville Oswald has recently brought to my notice a case which illustrates this group, and has kindly allowed me to quote it.

Case 17.—A nurse aged 51 noticed an eruption on the legs, later extending to the thighs, but otherwise felt well apart from some slight breathlessness, which, however, did not prevent her carrying out her full day's work. Her general condition was good and no abnormal signs were discoverable on examination apart from about 18 typical erythema nodosum lesions on the legs. The Mantoux test was negative to 1 mg. O.T. A biopsy of one of the lesions on the leg was reported to show a non-specific reaction consistent with erythema nodosum. A radiograph of the chest showed bilateral enlargement of the hilar lymph nodes, well demonstrated in a tomogram, together with a diffuse infiltration throughout both lungs; and in radiographs of the hand small well-defined rarefactions were evident in several of the phalanges.

Skiöld (1945) reviewed 354 cases of erythema nodosum and found that 35 of them had bilateral hilar-lymph-node

enlargement; none of these showed any evidence of frank tuberculosis. Of 91 cases with evidence of tuberculosis all showed unilateral hilar enlargement and none bilateral. Löfgren (1946) reviewed 178 cases of erythema nodosum and found that 102 showed unilateral and 30 bilateral hilar-lymph-node enlargement. Six of those with bilateral enlargement showed a miliary pulmonary infiltration; in two of these, histological appearances suggesting sarcoidosis were discovered—in a lymph node in one and in the skin in the other. Nine of the cases with bilateral hilar-lymph-node enlargement had negative or weak tuberculin reactions. He found the histology of the erythema nodosum the same whether the tuberculin tests were negative or positive. Bjerkelund (1947) reported the case of a woman aged 48 who had erythema nodosum with bilateral hilar-lymph-node enlargement and a Mantoux reaction negative to 1 mg. O.T. Later she developed successively a transient miliary infiltration in the lungs, areas of rarefaction in bones of the fingers, and a subcutaneous nodule which gave a typical histological appearance of sarcoidosis; the biopsy of the original erythema nodosum had shown no specific histological changes.

Thus there is strong evidence that the syndrome of Mantoux-negative erythema nodosum with bilateral hilar-lymph-node enlargement is related to sarcoidosis. Whether this group can be sharply differentiated from the group associated with frank tuberculosis remains doubtful. The difficulty of differentiation is well shown by the work of van Beek and Haex (1948), to which reference has already been made. They performed liver biopsy in 10 cases of erythema nodosum which appeared to be of frankly tuberculous type and found tubercles in seven, and in several of these the tubercles were of the type seen in sarcoidosis; their patients all had positive tuberculin skin reactions. If the hypotheses (*a*) that this particular group of Mantoux-negative erythema nodosum cases is indeed related to sarcoidosis and (*b*) that sarcoidosis is a manifestation of tuberculosis in a subject with a peculiar "anergic" reaction to the infection be accepted, it is surprising that a rash which in frankly tuberculous cases commonly occurs at a time when allergic hypersensitivity is present, and in fact is often regarded as an indication of the presence of such hypersensitivity, should also occur in a phase of the infection characterized by anergy. It is probably this discrepancy which has led some observers to adduce the Mantoux-negative erythema nodosum cases with sarcoid characteristics as evidence for an unidentified agent as the cause of sarcoidosis; Kerley (1943) even suggests that it supports the hypothesis that this agent is a fungus largely by analogy with coccidioidomycosis, in the primary stage of which erythema nodosum is frequent. For those who hold that sarcoidosis is frequently of tuberculous origin Mantoux-negative erythema nodosum with evidence of sarcoidosis presents a fascinating problem, the solution of which may help towards a more complete understanding not only of sarcoidosis and of erythema nodosum but also of immunity and allergy in tuberculosis and other infections.

Conclusion and Summary

In this lecture I have confined my attention to the clinical aspects of the pulmonary manifestations of sarcoidosis. Of the pathology, even of the lung lesions, and of beryllium sarcoidosis, I have had time to say little; manifestations in the skin, the bones, the lymph nodes, the eye, and the kidney have been mentioned only in passing, and of the nervous system, the salivary glands, the endocrine glands, the heart, and the gastro-intestinal tract not at all. I have been unable to deal with the very interesting problems of skin-sensitivity to tuberculin, of procutins and anticutins, of the Kveim reaction, and of the results of B.C.G. vaccination in cases of sarcoidosis.

A definition of sarcoidosis on a strictly histological basis has been suggested in order that it should be logically possible to refer to sarcoidosis of established aetiology—for example, to tuberculous sarcoidosis and to beryllium sarcoidosis.

The lung changes start usually with a diffuse infiltration accompanying or shortly following a bilateral hilar-lymph-node enlargement. This infiltration varies from a fine miliary type to a coarse irregular mottling. In about half the cases this infiltration clears completely. In the rest, slowly progressive fibrosis, usually in coarse strands maximal in the middle zones, replaces the infiltration, and secondary emphysema, often bullous, develops. In patients who have reached this stage tubercle bacilli may appear in the sputum, and the prognosis is then poor.

Calciferol treatment seems worth further trial in the cases with diffuse infiltrations, though many patients tolerate it poorly and it should therefore be given cautiously and with strict biochemical control.

Mantoux-negative erythema nodosum with bilateral hilar-lymph-node enlargement often shows other features suggestive of a relation to sarcoidosis, and may prove a fruitful field of study.

I am indebted to the chest physicians who, knowing my interest in this subject, have referred cases to me, and especially to Drs. G. E. Fearn and H. Broderick for allowing me to use their radiographs in Cases 6 and 14, and to Dr. B. G. Edelston for a complete account of the early history of Case 16; to Dr. H. K. Meller, who referred Case 15 to me and has carried out most of the follow-up; to Dr. Clifford Hoyle, who continued the observation of Case 1 during the war years; to Dr. J. W. Crofton for allowing me to quote Case 5, which was under his care; and to Dr. Neville Oswald for Case 17. I am also indebted to Mr. E. V. Willmott for the photomicrographs, and to him and to Mr. D. F. Kemp for the photographs of the *x*-ray films.

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AMYLOIDOSIS IN RHEUMATOID ARTHRITIS

BY

G. H. JENNINGS, M.D., F.R.C.P.
Senior Physician, Edgware General Hospital

[WITH PHOTOGRAVURE PLATE]

The association of amyloid disease and rheumatoid arthritis was described first by Whitman (1903) in an account of two cases of Still's disease with enlarged liver and spleen: the one of these patients who died was proved to have gross amyloidosis in the liver, spleen, kidneys, and mesenteric glands. This patient, like all those since recorded with associated rheumatoid arthritis and amyloidosis, was emaciated. In 1906 Beattie described four cases in which patients between 19 and 28 years of age had had relapsing acute rheumatism for from seven months to four years. All four patients died, and amyloid disease was found in their liver, spleen, and kidneys. In the three in whom diarrhoea was noted amyloid changes were found in the villi of the small intestine.

No further case of rheumatoid arthritis and amyloidosis was described until 1927, when Carroll and Nelson reported a fatal example in a boy with Still's disease. Since this case fewer than 50 cases have appeared in the literature. By 1944 Trasoff *et al.* had collected 14 cases of amyloidosis in Still's disease and 17 in adult rheumatoid arthritis. In 1947 Yeoman and Wilson referred to 30 adult cases of rheumatoid arthritis with amyloidosis. To this number can be added the two following cases.

Case 1

A female warehouse assistant aged 23 had an attack of tonsillitis during the summer of 1943. This was followed by stiffness and swelling of the knees, ankles, wrists, and fingers. The swelling persisted with fluctuations up to the time of her admission to this hospital five years later. During that time, both in and out of hospital, she had received dental treatment, physiotherapy to the affected joints and neighbouring muscles, vitamin concentrates, iron, one course of auro-calcium, and two courses of sodium aurothiomalate ("myocrisin"). These courses consisted of weekly injections; the first (12 injections) totalled 0.6 g., the second (20 injections) 1 g., and the third (13 injections) 0.95 g. Urine was normal throughout.

The affected joints settled with the first two courses, but chronic deformities were marked in the hands and wrists at the end of the second course. She rested two months, and the E.S.R. was then (June 24, 1947) 38 mm. Slight exercise was allowed and improvement was maintained, though there was occasional pain in the joints, and on September 2, 1947, the E.S.R. was 24 mm. During the third course of gold injections, which then followed, she had occasional attacks of petit mal, but remained fairly well until early March, 1948, and was able to walk, which she could not do from 1945 to 1947. At the beginning of March both knees became painful, hot, and swollen, and she was again unable to walk. She also became generally ill, pale, and febrile (temperature 99.8° F. (37.7° C.), pulse 110). There was loss of weight, but no severe sweating. As the knee-joints did not settle she was admitted to Edgware General Hospital, and was kept under treatment (mostly in bed) for three months.

When admitted on May 5, 1948, she was thin, flushed but anaemic, with marked dental sepsis and gum infection. Severe bilateral chronic deformity of the hands and wrists was present, and neither elbow could be fully extended. There was moderate movement in the wrists, but finger flexion was much impaired. Both knees were swollen, warm, and painful; the left, which was more markedly affected, could not be fully extended. The liver was greatly enlarged and the spleen just palpable (Fig. A). Puncture biopsy (June 2) proved the liver enlargement to be due to amyloid.

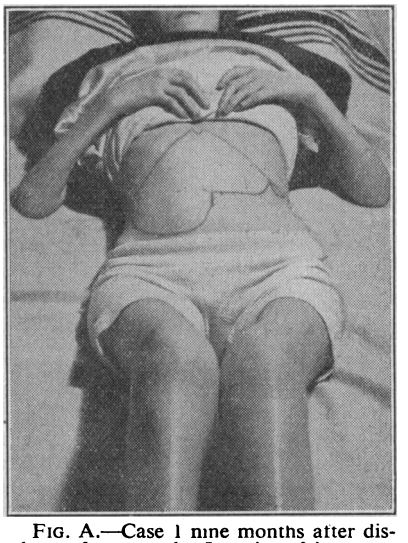

FIG. A.—Case 1 nine months after discharge from ward. In spite of improvement she still shows gross liver and slight splenic enlargement. Rheumatoid changes in knees, wrists, and fingers are present and muscular wasting is still evident.

With physiotherapy (including splinting) and the elimination of dental sepsis the knee swellings settled considerably, and both knees could not only be fully extended but also had a fair degree of flexion. By the time of her discharge she was able to walk with help, and the E.S.R. had by then fallen from 89 to 68 mm. There was a low-grade fever (99–100° F.—37.2–37.8°C.) during the first nine weeks, but this settled gradually to normal during the last four weeks in hospital. A course of systemic penicillin (500,000 units daily) was given for three weeks, and a *Bact. coli* urinary infection was eliminated with sulphonamides. She was also given iron (ferrous sulphate 18 gr. (1.2 g.) daily) and ascorbic acid. Her haemoglobin rose from 50% to 90% (Haldane) and the red blood cells from 4,120,000 to 5,180,000 during her stay in hospital. She was discharged on August 7, 1948.

Since her discharge she has had oral whole liver as well as iron and ascorbic acid, and physiotherapy has been continued. The enlargement of the liver and spleen has persisted unchanged to the time of writing (September 10, 1949). Her knee-joints, elbows, wrists, fingers, and ankles still show chronic rheumatoid deformity (Fig. A), but only the right hip is painful. It is also very stiff, as are the fingers, but all other joints have a satisfactory range of movement, so that she can progress a little on crutches. Her general condition is slightly improved and there is no oedema. Her blood pressure was 110/80.

Investigations During Stay in Hospital.—Radiographs on May 14, 1948, revealed chronic rheumatoid arthritis of long standing in hands and wrists, with moderate osteoporosis and destruction of articular surfaces. The knees showed an early stage of rheumatoid arthritis, with no bone destruction or rarefaction, but with diminished joint spaces. The teeth showed apical rarefaction and sepsis as well as cavitation in places.