SARCOIDOSIS

A REVIEW BASED ON A CASE OF THE DISEASE *

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PART I

CASE HISTORY AND CLINICAL DATA

By Dr CAMERON

Introduction.—The literature and clinical manifestations of sarcoidosis were reviewed in detail by Dr Hutchison at the last meeting of the Tuberculosis Society, and I shall not cover that ground again; but there are certain features of the condition which our patient presented which may be emphasised by a reference to the protean character of the sarcoid manifestations.

The nature of the disease is still in dispute. Tuberculosis as an aetiological basis has not been disproved, and we may be labouring the point in presenting the condition as a diagnostic rarity. Dr Dawson will speak on that with more authority than I can. I shall only say that the disease has not been proved to be of tuberculous origin and that it has many features which are against such a view. The chief of these is the anergy to tuberculin which is practically constant.

Although the disease is commonly associated with his name, Boeck was a comparatively latecomer in the descriptive field. He gave the name of sarcoid to the cutaneous swellings, and when we think of sarcoidosis we are apt to think of a somewhat rare skin disease. In recent years, however, many other clinical entities have been grouped under this diagnostic heading, and it is now recognised that sarcoidosis is a generalised disease of reticulo-endothelial tissue, and many class it with the leucoses and lymphadenoma. Not every part of this widespread system is involved at one, or at any, time, and although skin sarcoiids are common they are estimated to occur only in about 50 per cent. of cases. Involvement of the lungs is a common feature.

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and the eye is a frequent site of the deposits, the uveal tract being the area involved. Splenomegaly is common, as also is lymphadenopathy and secretory adenopathy. Involvement of the hypophysis causing symptoms of diabetes insipidus has been described by several authors.

Diagnosis may be regional if one system, or one organ only, is attacked. Where the distribution is wider the field of possibilities is narrowed and the cutaneous tumours often make the diagnosis certain. In their absence it may be presumptive unless tissue is available for biopsy, and our patient provided that with the immolation of her spleen.

Case History.—In October 1936 Mrs X. Y., 25 years, sustained in a motor accident a fracture of both patellae, and her ill-health dated from that time. A baby was born in January 1937 (by Cæsarean section on account of the stiffness of the knees), and two months later she had an attack of bilateral iritis which subsided after removal of her teeth. Soon after that the right patella was "wired" with catgut. The pressure of a tourniquet led to a sciatic paralysis from which she recovered slowly, but the feelings of ill-health continued. She felt weak and sweated at night and her doctor found her to have slight evening fever. These symptoms persisted, and in November 1938 her chest was X-rayed by Dr J. B. King, who reported that the appearances were those of a diffuse fibrosis of doubtful origin, possibly due to long-standing bronchitis. She had never had bronchitis, and her doctor asked me to see her. I saw her on 29th November 1938, and she made the same complaint of tiredness and slight night-sweating. She had no cough, but she said that she cleared her throat in the morning and brought up a little mucoid sputum. No spit was produced for examination at any time, and she had in fact no real lung symptoms. She was in good general condition and I found no definitely abnormal signs in her lungs; but I detected the presence of a mitral systolic heart murmur with loud intonation of the second sound in the basal areas. The possibility of subacute bacterial endocarditis was discussed, but the clinical picture was unlike that condition and I wrote to Dr King to request an inspection of the X-ray films. Dr Kininmonth replied for him and stated that they had thought that the case was in all probability one of rapidly advancing tubercle, but that the picture was so unusual that they had hesitated to give a categorical diagnosis without some clinical confirmation. There was no clinical confirmation and we marked
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time by keeping her in bed, and she was given small doses of gold by intramuscular injection. I did not see her again until 27th February 1939. She continued to have slight evening fever and to sweat at night. Examination of the chest was negative in its results, but the spleen was now found to be greatly enlarged and to reach the umbilicus. That enlargement was not present three months previously. The liver could not be felt. There were no glandular enlargements and the blood picture was normal. The white cells numbered 5400, the red cells were 4,830,000, and the haemoglobin percentage was 68. A differential white cell count was not made. The blood sedimentation rate (Westergren 1 hour) was 10, and the X-ray film (Fig. 1) showed a partial clearing of the lung shadows. The appearance was essentially that of a bilateral fibrosis and was in no way like miliary tuberculosis. She had no cardiac symptoms. I could not accept a diagnosis of tuberculosis, but I had no better diagnosis to offer, and she was admitted to the Deaconess Hospital under the care of Dr Slater for further investigation.

My next information about her came from Dr King, who wrote on 3rd May 1939 that Mr D. S. Middleton had performed a biopsy on the spleen and that Dr Dawson had reported that the condition was one of miliary tuberculosis. Dr King added that he had found it very difficult to relate the X-ray picture at any time to that of a blood-spread infection or to any diffuse type of pulmonary tuberculosis which he had known. A few days later Mr Middleton informed me that, following the pathological report, he had excised the spleen and that at the operation one or two tiny tubercles were seen under the capsule of the liver. He considered the case to be one of portal miliary tuberculosis, but as the lung condition had preceded the splenic enlargement I could not uphold that view. She recovered quickly from the operation and was admitted to the sanatorium on 3rd June 1939.

She was then in poor condition, thin and pale and mildly fevered (98°-100° F. rectal), and she felt weak and sweated slightly at night. She was, however, bright and cheerful. The X-ray appearances of the lungs were unchanged. She failed to react to a series of Mantoux tests and her blood sedimentation rate was 9. During the second week of July 1939 she complained of thirst, and she began to pass large quantities of urine (up to 112 oz. daily). The urine was of a low specific gravity and contained a trace of albumen. Sugar was not present. The onset of the condition was sudden and the presence of albumen was
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a new development. She had no headache and no cerebral symptoms—nothing, in fact, beyond thirst and polyuria. Almost coincidentally with this she developed bilateral iritis, and towards the end of July attacks of morning nausea and vomiting began. I then discovered (a new development) in the right hypochondrium a big hard fixed nodular mass. The blood picture was unchanged. While I cogitated upon these many things I received on 17th August a letter from Mr Middleton informing me that guinea-pig inoculation with material from the spleen had been entirely negative. As Mr Middleton expressed it, "the possibility arises of the condition being non-tuberculous," and so we were back at the starting-point. Meantime preparations for war were afoot and I had little time for diagnostic puzzles. On 1st September our patients were evacuated and Mrs X. Y. went home.

I heard from her doctor from time to time. She improved at home, and by the beginning of 1942 had become active and well. It was about this time that the possibility of sarcoidosis entered my mind, and I arranged for a further examination. The lung fields radiographically were found to have cleared almost completely (Fig. 2), and she was fat, happy, and fit. Her blood sedimentation rate was 4 and the abdominal mass and the thirst and polyuria had gone. X-ray examination of the hands and feet showed no abnormal bone changes, and similar examination of the abdomen showed no calcification.

**Diagnosis.**—Dr Dawson had reported originally on the splenic tissue, and she very kindly prepared fresh slides from the biopsy material, the original slides having been given to Mr Middleton. Colonel Harvey was unfortunately unable to come to this meeting of the Society, but Dr Dawson, who investigated the case along with him, has agreed to speak from the pathological point of view. The diagnosis rests on that, but the differential diagnosis from chronic miliary tuberculosis presents points of clinical interest. Was this a case of chronic miliary tuberculosis?

This condition is well recognised. A full description of it is given in the work of Hoyle and Vaizey (1937), and authenticated cases of complete recovery are on record. The disseminations may involve lungs, lymph glands, and viscera including the spleen, and an interesting literature on tuberculous splenomegaly has appeared.

The radiographical lung appearances are in the majority of cases of the well-known fine nodular type, but in a minority of
Fig. 1.—X-ray film of lungs showing the coarse bilateral fibrosis, disseminated throughout the right lung and most dense in the lower half of the left. There is emphysema of the upper half of each lung. The fibrosis is of a mixed type, coarse nodules lying in the midst of dense fibrous strands. There is gross enlargement of the hilar glands.

Fig. 2.—Shows a big clearing of the abnormal lung shadows. The right upper interlobe is visible as a thin line and the fibrosis is chiefly confined to the bases. The nodules have become largely absorbed and the hilar glands are smaller.
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cases they are atypical. The miliary nodules may be supplemented, or even replaced, by a network of fine fibrous tissue (Hoyle, 1937) which follows the line of the lymphatics in the sheaths of the bronchi, bronchioles, and the related pulmonary arteries. This condition, described by Pagel as hyperplastic lymphangitis, shows radiographically as a diffuse fibrosis and represents a lymphogenous form of the disease.

The histological basis of the sarcoid is a granuloma, and when the lungs are involved the radiographical picture may be very like that of miliary tuberculosis. On account, however, of the tendency of the sarcoids to undergo fibrotic degeneration they may in time become replaced completely by fibrous tissue and a chronic interstitial fibrosis is the end-result. Sarcoidosis is a self-healing disease, and in time almost complete absorption of the lung shadows may occur. That may happen also in miliary tuberculosis, but some degree of fibrosis must of necessity remain where fibrous transformation has taken place. The radiographical picture of Mrs X. Y.'s lungs might be explained on either of these pathological bases, and I should not like to offer a dogmatic opinion in either direction.

Hoyle lays stress on the frequency of splenic enlargement in chronic miliary tuberculosis, and Howells (1939) in publishing three cases of the condition has recorded the literature. Although in a majority of cases the splenic involvement is of secondary importance to active disease elsewhere, in some cases it may be the major manifestation and may be responsible for distressing symptoms. Hickling (1938) recorded two cases of the condition associated with miliary tuberculosis of the lungs. In both splenectomy was performed, and in both recovery took place. In one the diagnosis was made before operation. In the other it was made at operation for supposed splenic anæmia (this patient's lungs had not been X-rayed). Hoyle and Vaizey (1937) refer to three cases recorded by Bjerim, Cohn, and Klinenstein respectively, where radiographical signs of miliary lung tuberculosis were discovered after removal of spleens found to be tuberculous. The fate of these patients is not recorded, but Hickling expresses the view that the presence of tuberculous disease elsewhere is not a contraindication to the operation—in fact, cure of other tuberculous conditions may, and often does, follow. Here again on clinical grounds there is nothing against a diagnosis of tuberculosis in our patient. Splenomegaly is, however, also a feature of sarcoidosis, and the macroscopic appearance of the miliary

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sarcoids may be indistinguishable from that of miliary tuberculous, particularly when deposits are also present in the liver and are associated with abdominal glandular enlargement.

Iridocyclitis is a common sarcoid manifestation, but it is claimed as an equally common manifestation of chronic tuberculous infection (Brooks et al., 1940), and its presence may provide evidence in either direction.

The sudden onset of polyuria and thirst was suggestive of pituitary involvement, but the urine contained albumen and the cause must remain a matter for speculation. It is interesting that pituitary involvement is described in sarcoidosis, and Hannesson (1941) quotes cases described by Schaumann, Tillgren, and Lesne with symptoms of diabetes insipidus.

The nature of the abdominal mass which accompanied her period of morning nausea and vomiting and which ultimately disappeared can only be guessed.

What significance should be attached to the negative Mantoux reaction? This reaction is often negative in advanced active tuberculous disease in gravely ill patients, but our patient was never gravely ill. Hoyle states that the reaction is positive in the majority of cases of chronic miliary tuberculosis, but that negative results have been found in proved cases of the disease. In sarcoidosis the Mantoux reaction is almost persistently negative. Here at least there was room for doubt.

Miliary tuberculosis when the tubercles are in the fibroid stage is not a disease of tissue destruction, but I have found no reference in the literature to the state of the blood sedimentation rate in this type of disease. Theoretically one might expect a low sedimentation rate. That of our patient was persistently low and it at least provided grounds for contemplation.

Does one expect the guinea-pig inoculated with fibroid tubercle material to develop tuberculosis? I suppose that there is a chance that it may escape the disease, but the failure in this case to infect a guinea-pig called for immediate re-investigation of the diagnosis, and I shall leave the pathological facts in the abler hands of Dr Dawson.

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PART II
A PATHOLOGICAL STUDY OF THE SYSTEMIC DISEASE

By E. K. DAWSON

Introduction.—Sarcoidosis is generally considered a rare disease and has been recognised only within comparatively recent years. Dr Cameron’s patient illustrates well its puzzling and often misleading clinical and pathological features. Its acceptance as a systemic condition has been slow, and there are still few descriptions of its histology outside the dermatological literature. This finds some explanation in the fact that, as the disease is benign and chronic in its course and its varied manifestations tend to appear in succession and regress spontaneously, surgical interference is rarely called for and the pathologist has thus little opportunity to examine tissues and familiarise himself with its characteristic features. Enlarged lymph nodes from neck, axilla, or groin are perhaps the most frequent source of diagnostic material in these cases and the skin may also provide biopsy tissue.

Sarcoidosis has an interesting history which goes back to the latter half of the last century and to the work of a number of distinguished dermatologists—Besnier, Kaposi, Boeck, Darier, Roussy, and others. The clinical picture was recognised by Jonathan Hutchinson in 1867. He described, in a girl of 17 years, the characteristic digital swellings—“last-joint arthritis”—and a chronic iritis, noting in other cases the common concurrence of these two lesions. His patient was alive 9 years later but suffering from advanced phthisis. Hutchinson suggested calling the condition Mabey’s disease, after the patient; it is sometimes called by his own name. He was shown a similar case when he visited Boeck’s clinic in Kristiania in 1869. The term “sarcoid” was given by Kaposi in 1899 to a heterogeneous group of skin diseases usually described as tuberculides, though their relation to tuberculous infection and to each other was ill-defined. Boeck in the same year described a “benign miliary sarcoid,” and Darier in 1910 identified the histological appearances of Boeck’s cutaneous lesion with those of the Darier-Roussy
subcutaneous sarcoid. Enlargement of lymph nodes was observed by Boeck in some of his cases, but the credit for extending the conception of sarcoid as a cutaneous lesion to sarcoidosis as a generalised disease is due to Schaumann of Stockholm. His study of Besnier's lupus pernio in 1914 and later of other allied skin affections, with opportunity to examine biopsy and autopsy material, led him to the conception of an underlying systemic disease of the lymphoid and haemopoietic tissues, the skin itself being a more or less accidental involvement. Schaumann emphasised the affection of lymph nodes and was the first to describe the important lung changes. The name he suggested was benign lymphogranulomatosis, to denote its generalised character and to indicate certain similarities with malignant lymphogranulomatosis or Hodgkin's disease. The condition is often called Schaumann's disease on the continent. The predilection of the disease for the lymphoid and blood-forming apparatus, demonstrated by the involvement of lymph nodes, bone marrow, spleen and liver, suggested its inclusion in the reticulo-endothelioses. Leitner, indeed, describes it as a chronic epithelioid-cell reticuloendotheliosis of tuberculous nature and Robb-Smith discusses its histology in relation to "giant-cell histiocytic sinus reticulosis" in lymph nodes, in his classification of the reticuloses.

Until the relation of the disease to tuberculous infection is more fully established or another etiological factor emerges, there seems little objection on historical grounds to the term sarcoidosis (Schaumann) rather than Besnier-Boeck's disease or Boeck's sarcoidosis.

**Material.**—The following descriptions are based on examination of tissues from Dr Cameron's patient, Mrs X. Y., and from others in the routine reporting material in the Laboratory of the Royal College of Physicians, Edinburgh, and on a study of cases in the literature. Both spleen and liver tissue were available from Mrs X. Y. Biopsy material from the greatly enlarged spleen was initially reported by me as miliary tuberculosis; at the splenectomy operation, the surgeon noticed small scattered nodules under the liver capsule and excised a small piece of tissue. Examination of this supported the previous report. Later, when the favourable condition of the patient suggested reconsideration of the diagnosis, large sections from the splenectomy material (Fig. 1) were prepared and the photomicrographs (Figs. 2-4) were taken from this tissue. I have found no other...
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case in the literature with examination of both spleen and liver in a living subject. Mrs X. Y. had no clinically evident lesions in lymph nodes or bone, and no skin disease.

Sarcoidosis tissue from other sources includes skin (Fig. 7) and lymph nodes (Fig. 8). The clinical pictures and radiographs were kindly lent me by Dr Savatard, Manchester, and show the lesions in one of his patients. Every student of the disease is indebted to Schaumann, who from 1914 onwards produced numerous illustrated studies on the subject which he made largely his own.

The Clinical Picture.—This varies greatly in individual patients and even at different times in the same patient, as lesions tend to appear in succession in one or several organs and then regress. Any description is therefore composite rather than typical. Certain features are, however, characteristic, if only because surprisingly negative. The disease, which starts mainly in early adult life, tends to run a benign and chronic course, with relapses as new tissues are affected but with little if any impairment of general health. There may be fatigue, possibly some loss of weight and slight pyrexia, though the condition is more usually afebrile. Cough with sputum is unusual, and if there is nothing to suggest pulmonary disease the chest may not be X-rayed and one of the most valuable clues to diagnosis is missed. The insignificance or even absence of clinical findings in the lung, associated with pronounced and generalised radiological changes, is indeed one of the most striking features of sarcoidosis. The essential lesions in lymphoid and blood-forming tissues may be difficult to demonstrate, since involvement does not necessarily mean enlargement, but nearly all patients at some stage of the disease show obvious lymphadenopathy, cervical, axillary, inguinal or elsewhere. Thoracic and abdominal nodes may be affected and the enlarged hilar shadow in radiographs of the chest is evidence of the lesion in lymphoid tissue in this area. The spleen and liver may be considerably enlarged, the spleen apparently more frequently than the liver, and the skin, eyes, hands and feet affected as well as other sites. As already mentioned, Jonathan Hutchinson noted the frequent concurrence of eye and digital lesions; his patient Mabey required repeated iridectomy. In other reported cases, bilateral iridocyclitis led to blindness. The eye is said to be affected in about 10 per cent. of cases.
The sequence of the appearance of the lesions in the various sites seems quite arbitrary, and there may be considerable intervals between their detection. Mrs X. Y. is instructive in this respect. The bilateral iritis of March 1937, which subsided on removal of the teeth, may or may not have been evidence of the systemic disease. In February 1939 the lung shadows, so evident fifteen months earlier, were clearing, but the spleen was then greatly enlarged. Soon after splenectomy, the iritis, again bilateral, reappeared with the onset of thirst and polyuria and the appearance of a large, hard, fixed abdominal mass. All symptoms had disappeared 2½ years later and the lung condition was almost resolved. It is interesting to speculate whether there was a transient affection of the hypophysis or hypothalamus and what was the nature of the abdominal mass. Tillgren reported a case with thirst and polyuria, associated with lupus pernio and typical lesions in lungs, lymph nodes, tonsils, hands and feet. The skin lesions disappeared but the spleen enlarged and the lungs became more involved, with general deterioration and death. At autopsy, the middle lobe of the hypophysis showed microscopically the typical folliculoid granulomatous structure of sarcoidosis with much fibrosis and no caseation necrosis. I have found no similar case in the literature. Hardly any tissue or organ of the body seems exempt, and cases have shown the disease in parotid and lachrymal glands, in respiratory mucosa, especially of the upper air passages, in pancreas, intestine, serous surfaces and muscle. Schaumann found lesions in the pericardium and in the kidney capsule without extension into the underlying tissues.

These varied manifestations of the disease explain the frequent difficulty of clinical diagnosis, the greater if the patient's progress cannot be followed for a considerable period. In a number of cases, the condition was only recognised at autopsy when death was due to another cause.

**Diagnosis.**—Radiological and microscopical examinations are required as well as consideration of the clinical picture, especially if the patient has no diagnostic skin condition or digital swellings. The microscopical picture, described later, is more or less characteristic of the lesion wherever it occurs. The unexpected lung shadows suggest *miliary tuberculosis*, but the negative clinical findings exclude the acute type of infection. The chronic infection, however, with the same negative
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tests as in sarcoidosis and with a very similar radiograph, remains the essential diagnostic difficulty, a point discussed later under etiology. The lung shadows might suggest a pulmonary carcinomatosis, but lack of evidence of a primary growth, the usually young age and the comparatively good health would all argue against a bilateral, generalised metastatic pulmonary tumour. Primary carcinoma of the lung, which is initially a localised growth, needs little differential consideration. X-rays are particularly helpful if the hands and feet are affected, even if no swelling is evident, as the site and appearance of the osteoporotic areas are almost pathognomonic. Cases where only one group of lymph nodes showed enlargement have been clinically diagnosed as Hodgkin's disease, but microscopic examination of a node gives the distinctive appearance. The blood picture might be necessary to exclude leukaemia in such cases; it is always helpful in doubtful conditions and, if the affection is sarcoidosis, the differential white cell count frequently shows a relative monocytosis. Simultaneous involvement of eye and parotid gland may suggest uveo-parotitis, and a combination of parotid and lachrymal gland lesions has given a clinical picture similar to that of Mikulicz's disease, but it is highly improbable that the systemic condition would be limited to these locations; in both, biopsy material is available for histological examination. The pre-auricular lymph nodes, however, are sometimes enlarged, in combination with other lymphoid tissue.

Schaumann laid emphasis on the microscopical examination of the tonsils in suspected sarcoidosis, as an easily accessible tissue for biopsy even when they show no obvious affection. They gave him positive evidence of the disease in all of a series of 21 cases. Where no enlarged lymph nodes are present, there seems little objection to diagnostic biopsy or excision of the tonsils. Schaumann found helpful a "diagnostic triad" in suspected cases. This consisted of (a) microscopical examination of tonsillar tissue, (b) X-rays of the hands and feet even if not affected clinically, and (c) the intradermal tuberculin test. He added the differential blood-cell count.

Prognosis.—The disease usually pursues a benign and chronic course, with the health relatively good, though lesions may emerge from time to time in various sites. How far the affected tissues are restored to normal is difficult to assess. Two later developments are possible. The disease may apparently be
maintained in a quiescent form with mild, if any, clinical manifestations, giving a long negative history; or a classical tuberculosis in lung, bone, peritoneum, etc., may appear as the sarcoidosis condition subsides. In “pure sarcoidosis” Schaumann found that death resulted from (a) increasing strain on the heart with hypertrophy and dilatation due to fibrous obstruction in the lung; (b) extensive destruction of haemopoietic tissue; or (c) localisation of the lesion in a vital area. The usual cause of death, however, is probably a classical tuberculosis arising in the course of the benign condition and interpreted either as a superimposition or an exacerbation, according to the view held regarding the etiology of the primary sarcoidosis.

**The Sarcoidosis Lesion in General.**—The histological appearances are essentially similar whatever the tissues affected. The lesion consists of collections of epithelioid cells arranged in follicles, which may be isolated, grouped or in strands. The general character of the follicles is shown at low magnification in Figs. 2 and 3 (spleen), Fig. 5 (liver), Fig. 7 (skin), and Fig. 8 (lymph node), and in some finer detail in Fig. 4 (spleen) and Fig. 6 (liver).

This follicle is often described as differing from the tubercle follicle in showing no caseation necrosis, no multi-nucleated giant-cells and little lymphocytic cell reaction, as well as no demonstrable tubercle bacilli. There may be, however, a slight “blurring” of the central cells, and giant-cells may be fairly numerous before fibrosis and hyalinisation supervene. The absence or paucity of surrounding lymphocytic cell reaction seems a usual finding (cf. Figs. 6 and 7), though it varies considerably in the skin affections. The skin section here (Fig. 7), from a miliary sarcoid of Boeck, shows the stranded arrangement of the epithelioid cells.

Quiescence and regression of the lesion is effected by fibrosis and hyalinisation, an uneven process evident within the follicle itself (Figs. 4 and 6) as well as in the surrounding tissue (Figs. 3 and 5).

It seems curious that so much disorganisation and destruction of tissue by the grouping and coalescence of follicles should occur without necrosis, though hyalinisation may of course be regarded as a form of slow cell destruction. Caseation necrosis in the tubercle follicle—an avascular formation—is associated with a toxic obliteration of small blood vessels and, as the process
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extends, possible erosion of larger ones, as in the lung with haemoptysis, a symptom not observed in sarcoidosis. In the latter condition the initial preservation of blood vessels, as, for example, in the malpighian bodies of the spleen (Fig. 4), is suggestive of a milder injury or a higher immunity with little allergic reaction, and may allow of a slow fibrosis with hyalinisation rather than the destructive necrosis of tissue characteristic of tuberculosis. The reaction in sarcoidosis may be so mild that the tissue or organ affected shows no enlargement even when, as in the tonsil, the characteristic folliculoid formations involve the whole area. Whether clinical enlargement occurred or not, autopsy examination has shown that the proliferated cells of the follicles are gradually replaced by inactive fibro-osed and hyalinised areas. This process explains the emergence and regression of the lesions, well shown radiologically in lung and bone and clinically in other sites.

**Sarcoidosis in Various Organs and Tissues.**—*Lymph nodes and lymphoid tissue* may be involved in any part of the body but are frequently evident in neck, axilla and groin; enlargement of the pre-auricular and submaxillary nodes is recorded and the tonsils seem particularly prone to involvement. Microscopically, the nodes show the typical structure though the lesion seems more evenly diffuse than in other tissues, producing rounded and stranded formations of epithelioid cells over the whole area and suggesting a combination of follicular and sinus proliferation. Later, as elsewhere, the lymphoid structure may be largely replaced by fibrous and hyaline tissue and only discovered at autopsy.

*Spleen* (Figs. 1-4).—The organ may be greatly enlarged and palpable to the umbilicus. The colour of the cut surface is brownish-red, with small grey-white granulations separated by punctate haemorrhages, giving an irregularly mottled appearance. The capsule may be thickened with similar greyish spots. Microscopically, the folliculoid formations of epithelioid cells replace the malpighian bodies, apparently a follicular reticulosis, though the distortion and destruction of normal architecture make identification of structure difficult. The pulp tissue shows extensive hyaline change, much diffuse haemorrhage and, where it remains intact, dilatation of the sinusoids with swelling of the lining cells. The capsule may be involved by closely underlying follicles.
Lung.—Macroscopically, the cut surface shows small greyish-white scattered spots, representing single or grouped epithelioid follicles in the inter-alveolar septa. Strands of epithelioid cells, following the course of blood vessels, bronchi and bronchioles, are seen as fine streaks. These lesions produce the characteristic marbled appearance of the radiological picture, which shows reticular infiltrations with spots and streaks, generalised but denser near the hilum and usually extending more heavily towards the base than to the apex. No calcification is evident. The enlarged hilar shadow is due to enlarged nodes in the area. Microscopically, the picture is similar to that found elsewhere, with few or no giant-cells and a variable surrounding lymphocytic cell reaction, fibrosis and hyalinisation. Followed radiologically, the lung condition in most cases resolves as the active phase of the lesion regresses. In some cases, active phthisis has supervened; rarely, the picture remains stationary.

Liver (Figs. 5, 6).—The lesions are described as being mainly in the portal tracts, but the fibrosis round the follicles, with disorganisation of normal structure, makes the tract difficult to identify. The single follicle in Fig. 6 appeared to be in the mid-zone of a lobule. The subcapsular involvement produces the slightly elevated granulations noticed at operation in Mrs X. Y. Microscopically, the follicles here showed no peculiarity, though compared with the extensive involvement of the spleen, they were not numerous and there was no evident impairment of liver function. Palpable enlargement of the liver may be due, in Schaumann's opinion, to chronic venous congestion associated with pulmonary obstruction and cardiac strain, with fatty degeneration of the liver cells (cf. Fig. 5) rather than to the extent of the hepatic sarcoidosis.

Bone and bone marrow.—The lesion affects almost exclusively the hands and feet, producing osteoporotic areas at the ends of the diaphysis of phalanges, metacarpals and metatarsals. Very rarely, the long bones may be involved. At an early stage, the folliculoid tissue infiltrates the cancellous bone and replaces the bone marrow without modifying the bony structure. Later, the bony trabeculae are absorbed and the process may extend through the periosteum into the surrounding subcutaneous tissues, with the production of the characteristic "spina ventosa," a soft spindle-shaped swelling (Fig. 10). There is apparently no new
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periosteal bone formation. The early lesion, before bone is absorbed, is radiologically negative; later, X-rays show defined rounded areas of rarefaction (Figs. 11 and 12), which are pseudocysts containing folliculoid tissue. Hands and feet may be affected simultaneously or at different times; several or all of the fingers and toes may be involved (cf. Figs. 11 and 12, from the same patient). As in other sites, the lesion becomes fibrous and new bone may be laid down, with reappearance of the negative radiological picture, but this does not occur in all cases. Schaumann records a case, followed for 16 years, with death from pulmonary tuberculosis. Autopsy examination of a toe in which a typical osteoporotic lesion was detected 7 years earlier, showed fibrous tissue arranged like confluent follicles but without deposition of new bone. The hands had been affected 9 years before the feet.

Tuberculous infection of these bones also produces the spina ventosa, but is a more diffuse process in the central part of the diaphysis with new periosteal bone deposition.

Skin.—Sarcoidosis is said to affect the skin in about 50 per cent. of cases and may appear in various forms—lupus pernio, sarcoïd or erythrodermia. These conditions are described in detail in the dermatological textbooks. The face (Fig. 9) and limbs are mainly affected; there is no ulceration and the lesions tend to regress with or without therapy. A curious feature is the occasional transformation of one type into another. Microscopically, the lesions show follicles and strands of epithelioid cells with few or no giant-cells and a variable lymphocytic cell surround. In the miliary sarcoid shown in Fig. 7, the proliferating cells follow the course of the sweat ducts and capillaries; there are no giant cells and few lymphocytes.

Eye.—The eye is said to be involved in about 10 per cent. of cases. The lesion shows folliculoid formations in the iris and ciliary body, an iridocyclitis. The condition may clear up spontaneously, as with Mrs X. Y.; in some cases, it is relieved by iridectomy but may lead to blindness.

The blood.—While some degree of anaemia may be present—Mrs X. Y.'s Hb had fallen to 68 per cent.—the total white cell count shows little change and no abnormal cells. A constant though moderate relative monocytosis is, however, recorded, and Schaumann advocated a differential count for diagnosis in doubtful cases. In his own cases, the monocytosis varied from
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8 to 16 per cent.; Tillgren found a rise from 7 to 14 per cent. during a two years' interval between examinations. The second of Hickling's cases of tuberculous splenomegaly, very suggestive of sarcoidosis, showed a monocyte variation between 12 and 22 per cent. This relative monocytosis suggested to Leitner the possibility of relationship with an aleukaemic form of monocytic leukæmia. Though the histological picture of sarcoidosis in lymphoid tissue does not correspond with that figured by Robb-Smith as monocytic medullary reticulosis, the blood picture strengthens the inclusion of sarcoidosis in the reticulo-endothelioses. The monocytosis is apparently a helpful finding, especially in cases where lymph nodes are enlarged with little systemic disturbance and other blood affections have been excluded.

Etiology.—As with the skin conditions on which the early study of sarcoidosis was based, the important question in etiology, as Dr Cameron has indicated, is the relationship to tuberculous infection. Sarcoidosis has sometimes been described as a non-specific generalised granuloma or reaction because of the similarity of the epithelioid cell proliferation to that seen in various chronic infective conditions. The clinical features, however, suggest in various localities a more specific condition, and these have received different names. The inclusion of the disease in the reticulo-endothelioses and its likeness in some respects to Hodgkin's disease inevitably raises the question of a virus infection. This is, however, still an open question with regard to lymphadenoma and has received little if any serious consideration in sarcoidosis.

The main question is the relationship to tuberculosis, bovine, human or "paratuberculous," and more particularly of possible identity with a chronic type of miliary tuberculosis. Chronic miliary tuberculosis is apparently an accepted form of tuberculous infection. Its histological features in lung and lymph nodes were described by Adami in 1910 as a chronic hyperplastic non-caseating form in which the specific bacilli are detected with difficulty. The clinical features of the two conditions are strikingly similar in recorded cases verified histologically. Hickling's cases, for example, reported as "tuberculous splenomegaly with miliary tuberculosis of the lungs" are very suggestive of sarcoidosis, the clinical, radiological and histological findings in his first case, a man of 35 years, being almost identical with
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those of Mrs X. Y. Bodley-Scott also suggested that these cases may be sarcoidosis. Both conditions show a predominantly young age incidence, insidious onset, marked disproportion between the radiological and clinical aspects, arrest of symptoms and lesions, difficulty in demonstrating the tubercle bacillus and, usually, negative tuberculin and inoculation tests. Hoyle states that half of the chronic miliary tuberculosis patients show involvement of other organs, especially lymph nodes, spleen, joints and eyes, with less frequent cystic lesions in bones. The radiological differences in the lung picture are not easy to define. The great difficulty in the differential diagnosis of the chronic tuberculous disease is from sarcoidosis, a difficulty which disappears if their identity be admitted.

Schaumann's remarks regarding his own attitude to the etiology of sarcoidosis are illuminating. He confessed that a study of the disease usually starts with a "non-tuberculous bias," based on the absence of the laboratory findings associated with accepted forms of the disease. In his early papers, while describing the folliculoid structure of the histological lesion, he regarded the condition as a disease sui generis. When some of his cases showed a terminal definite phthisis, confirmed at autopsy, the lung infection was regarded as an added late complication. There is an analogy in the development of tuberculosis in the fibrosed lung of silicosis. Later, he considered that the disease in the various organs and in the skin was due to infection by the tubercle bacillus, either of bovine or of non-acid-fast type. Latterly, Schaumann emphasised the phenomenon of the development of internal and especially pulmonary tuberculosis concurring with the regression of characteristic sarcoidosis lesions as evidence of the etiological identity of the two conditions, though this sequence may be long delayed and, as far as clinical data are yet available, does not seem to be inevitable. Schaumann claimed to have succeeded in culturing the bovine type of the bacillus from lesions of cutaneous sarcoid and lupus pernio.

The causal relationship of sarcoidosis to tuberculosis may perhaps find added support by a consideration of the benign course, indefinite physical signs, "invariable" resolution of the lung opacity, few or absent tubercle bacilli, and the usual lack of caseation described as cases of pulmonary "epituberculosis." The comparison at least illustrates the wide variation of
individual reaction to tuberculous infection found in the more chronic and benign types in contrast with the more classical forms of the disease. It might give support to the growing weight of opinion that sarcoidosis is probably also a chronic tuberculous condition and possibly identical with the chronic miliary form.

**Summary.**—1. Sarcoidosis is a systemic disease affecting particularly the lympho-haemopoietic apparatus—a reticuloendotheliosis—with the formation of a folliculoid type of granulation tissue.

2. Various organs and tissue are involved in groups and in succession; the lesions tend to regress spontaneously, giving a clinical picture of slow development and benign, protracted course.

3. Characteristic features are (1) multiple lymphadenopathy; (2) extensive radiological lung involvement with little if any clinical disturbance; (3) bone marrow and bone changes, with the production of osteoporotic lesions in the hands and feet; (4) splenomegaly; and (5) iridocyclitis. There may also be a skin affection of the sarcoid type.

4. Histologically, the lesion consists of collections of epithelioid cells arranged in follicles, with no appreciable necrosis, a variable number of multinucleated giant-cells and little surrounding lymphocytic cell reaction. Regression is by fibrosis and hyalinisation.

5. The ordinary laboratory and clinical criteria of tuberculosis—presence of tubercle bacilli in sputum or tissues, positive intradermal tuberculin test and positive animal inoculation—are very rarely demonstrable.

6. There is much against tuberculous infection underlying the disease; there are, however, also sufficient resemblances, clinical, radiological and histological, to suggest a possible causal relationship.

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NOTES ON ILLUSTRATIONS

Fig. 1.—Spleen. Splenectomy tissue. Mrs X. Y. Showing the irregularly mottled surface produced by fine greyish-white granulations, punctate hemorrhages and hyalinisation. \( \times 2/5 \).

Fig. 2.—Spleen. Same tissue. Showing capsule (a), dilated sinusoids (b), and confluent follicles with some giant-cells. \( \times 40 \).

Fig. 3.—Spleen. Same tissue. Showing some single follicles with surrounding hyalinisation (a) and sinusoids (b). \( \times 80 \).

Fig. 4.—Spleen. Same tissue. Showing a follicle unevenly fibrosed (lower part) with some giant-cells. Two small arteries remain unaffected. \( \times 200 \).

Fig. 5.—Liver. Mrs X. Y. Showing a group of follicles under the capsule (c), with intervening hyalinisation (h) and fatty degeneration of surrounding liver cells (d). \( \times 80 \).

Fig. 6.—Liver. Same tissue. Showing a single follicle with several giant-cells, fibrosis, absence of lymphocytic cell surround and no degeneration of liver cells. \( \times 200 \).

Fig. 7.—Skin. Boeck’s sarcoid, miliary type, showing irregular strands of epithelioid cells following the course of sweat ducts (s) and capillaries (c). No giant-cells and no lymphocytic cell reaction evident. \( \times 40 \).

Fig. 8.—Lymph node. Showing follicles with occasional giant-cells but no necrosis. \( \times 80 \).

Figs. 9 to 12 are from a patient of Dr Savatard, Manchester.

Fig. 9.—Sarcoid of Boeck, nodular type, in a young woman.

Fig. 10.—Hands, showing several spindle-shaped swellings, the spina ventosa.

Fig. 11.—Radiograph of the right hand shown in Fig. 10, showing multiple osteoporotic lesions, more marked in first and fourth fingers.

Fig. 12.—Radiograph of the feet, showing very small, defined osteoporotic areas in all the toes. There was no clinical evidence of involvement of the feet in this case.
