# REPORT OF A CASE SUGGESTING THE CLINICAL AND MICROSCOPIC PATHOGENESIS OF SARCOIDOSIS*

HENRY E. MICHELSON, M.D.

Sarcoidosis is a complex subject and such knowledge as has been accumulated consists of heterogeneous facts marshaled from diverse sources. In attempting to systematize and correlate isolated findings, one realizes that the pathogenesis of the disease has not been appraised, nor can reasonable deductions, or even speculations be made. Since in the early stages of the disease there are no symptoms and signs, or at best they are half concealed, therefore studies of its onset are denied the investigator. My purpose in this paper is to report such facts collected as I have been able to confirm and to add some personal observations and studies. I shall not discuss the controversies regarding the etiology of this disease, the matter of tuberculin sensitivity, bacillary findings, the Kveim test, nor any of the matters that remain wholly speculative.

Dermatologists are familiar with individual reports of sarcoidal lesions of the skin, lungs, bones, etc. A synthesis of these individual pictures into a single disease-complex has now been accomplished. If this condition is due to a specific cause, then it must have a natural history of beginning, course, and termination.

In studying this disease which is still of unknown cause it is well to compare it with one of known etiology that most closely resembles it in the nature of the lesions and the pathology. Tuberculosis at once comes to mind because there is much in common between the two conditions. Lesion for lesion, of the skin, hands, lungs, nodes, glands, eyes, etc. sarcoid and tuberculosis are readily comparable, but if we accept the view that sarcoidosis is a systemic and disseminated disease we have difficulty, for only the so-called chronic miliary tuberculosis furnishes us with a disease picture which in its entirety may be compared with sarcoidosis. True, there are other forms of tuberculosis which end in fibrosis which may be compared with sarcoidosis but the important point is that a diffuse miliary or nodular type of tuberculosis exists and that it may begin as the acute miliary type. To be sure it occurs infrequently but sarcoidosis too is not a common disease. It has been stated that ten per cent of cases of miliary tuberculosis heal while thirty per cent become chronic while the rest in pre-antibiotic days succumbed. Chronic tuberculosis most frequently resulted when the acute phase was unusual or atypical. I shall not describe the clinical symptoms, variations or microscopic pathology of chronic miliary tuberculosis; suffice it to say that the roentgenologic and histologic findings are surprisingly similar to those of sarcoidosis.

A minute review of the symptomatology of sarcoidosis, regardless of the extent of the disease sheds no light on its pathogenesis. We must therefore look for a preponderance of involvement of a particular area or organ, for if one organ is more susceptible than any other, we may assume that it might well be the site of primary infection or at least a focus for further dissemination. With this in mind the high percentage of lung involvement is impressive; in fact, regardless of which authority's statistics are examined it must be concluded that of all the internal organs that may be invaded by sarcoidosis, the lungs are the most susceptible. This has been proven by roentgenologic and post-mortem examination. Hartweg attempted clinical appraisal of the genesis of sarcoidosis by analysis of 70 cases. In his series, too, the lungs were most often involved, and he states that he believes the disease has its origin there. He outlines five stages in the pulmonary development and progress of the disease.

I. Hilar enlargement, which may be either unilateral or bilateral. Hilar enlargement is explained however on the theory that the infecting agent enters the lungs. There is no recording of a primary complex in sarcoidosis, but since the pathologic process is purely granulomatosus with no surrounding non-specific exudative reaction, a tiny lesion might exist and not be

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* From the Division of Dermatology, University of Minnesota, Minneapolis, Minn. (Francis W. Lynch, M.D., Director).

demonstrable. [This might well be the case because there is no subsequent calcification in sarcoidosis which would aid in its late identification. Those who wish to explain sarcoidosis on the basis of an altered allergy in tuberculosis point out that sarcoidosis may begin with a tuberculous primary-complex and further development is conditioned by the constitutional peculiarities of the host. This to be sure is merely hypothesis.]

II. Next, miliary dissemination which may be seen in a delicate reticular design or in a number of different patterns, as described so well by Loncope and Freiman.

III. The third stage is regression which follows very slowly as a rule by a process of hyalinosis and fibrosis. This completes the development in the majority of cases.

IV. A stage of infiltrative induration and fibrosis. In a few cases the infiltrates coalesce into large nodular areas.

V. Massive involvement of certain portions of the lungs as the result of the enlargement of the previous large nodular infiltrates. If the disease does not begin in the lungs a gastro-intestinal, cutaneous or tonsilar origin could be proposed, but certainly frequency of involvement indicates the lungs as the most likely site for the first manifestation.

Hartweg concluded that there is no dissemination or appearance of extra pulmonary lesions during his Stage I, but that the lymphatic system (demonstrable nodes), the eyes, and the bones may show lesions during Stage II. However, the majority of his patients who had skin and bone lesions exhibited them during Stage III. Whether or not Hartweg's analysis is correct, it offers a working basis for further studies and it confirms observations that the skin is rarely involved without other demonstrable lesions. The persistence of pulmonary lesions through their final regression allows a very long time for the new manifestations of the disease to appear and I doubt if the stage in the lungs acts as a deterrent to other developments. Moreover lung lesions may appear subsequent to lesions found elsewhere in the body. If or when the disease invades another organ, regardless of the stage of the lung lesions at the time, its development is probably dependent upon the properties of the new tissue attached. Thus we know that skin lesions may have a decidedly varied morphology but they all have about the same natural course

This brings up the possibility that sarcoidosis does not begin in a certain tissue, which acts as a focus, but that lesions develop in various tissues independently much as they do in leukemia. However the frequency of involvement of certain organs and the miliary nodes found in the liver, spleen, marrow cavities and other tissues, which so often also are invaded in miliary tuberculosis (explained by the hematogenous sowing of bacilli) indicate that the pathogenesis of sarcoidosis and of so-called chronic miliary tuberculosis may be similar and that a primary involvement of the lung with subsequent dissemination is at present an acceptable hypothesis.

The question of the transition of sarcoidosis into frank tuberculosis is, to be sure, a controversial one. If this occurs it may be used as an argument in favor of the pulmonal origin of sarcoidosis. There are two explanations for such transition: One is the assumption that sarcoidosis is an atypical tuberculosis whose torpidity and benignity are dependent upon the high resistance of the host, which can be reduced by various means, and thus the epithelioid reaction is transformed into the more destructive one of tuberculosis. The other is that tissues involved with a sarcoidal inflammation are peculiarly susceptible to infection with tuberculosis. Without discussing the pros and cons of either view in detail one fact stands out clearly: that if a transition from sarcoidosis to tuberculosis does occur, as has been repeatedly reported, the change almost invariably is in the lungs; certainly such changes do not occur in the skin. The assumption that lung invasion is the first step in sarcoidosis suggests that searches for a causative agent should be directed toward more intensive bacterial, viral and other studies of secretions, exudates and tissues of the thoracic cavity.

The clinical diagnosis of sarcoidosis is presumptive unless it is verified by histologic examination, but those who are well acquainted with the problem know that at times neither clinical nor histologic findings are sufficient for an exact diagnosis and in such instances too much reliance may be entrusted to the microscopic diagnosis. It must be reiterated that sarcoidal reactions may be produced in many diseases and their number is increasing; for example, tularemia and histoplasmosis have recently been added to the list. Because beryllium and silicates provoke epithelioid reactions, means for experimental production of sarcoidal reactions are available.

Voldet's experiments on the injection of elastic fibers to stimulate production of epithelioid granulomas are very instructive and also point to the need of more intensive studies of the collagenous and fibrous tissues in sarcoidal inflammations for the earliest pathologic changes may appear in the connective tissues. The epithelioid granuloma is the high point in the reaction, not the beginning nor the end of the process. It is much easier to study the end: i.e. the hyalinization and fibrosis, than to obtain specimens which show very early changes.

It must be emphasized that, even though the sarcoidal reaction is similar, if biopsies are taken from, let us say, the skin and a lymph node from the same patient, decided differences may be seen. The propensity of the particular tissue to react decidedly alters the findings. If one inclines to the view that sarcoidosis is a reticulosis, the lymph node offers the best tissue for such a study, while the interstitial tissues of the lung and the cutis afford suitable specimens to observe early connective tissue changes. Lenartowicz and Rothel made observations on sarcoid tubercles found in the brain and stated that the reaction began about the smallest vessels and the development could be followed very well because the surrounding brain tissue did not react. I have examined miliary sarcoids obtained by liver biopsy and found the same naked granulomas with practically no surrounding tissue reaction affording a similar opportunity for study. It should be emphasized that a sarcoidal reaction is purely granulomatous consisting of epithelioid cell formations, but the surrounding tissues may respond which probably accounts for the variance in the number and disposition of lymphocytes which may be present.

The dermatologist would like to correlate an initial morphologic and histologic lesion. With this in mind, it is important to watch for an almost negligible localized erythema in patients with proven sarcoidosis. Bohnstedt and Bauman reported such an occurrence. They observed two patients with erythema nodosum in whom sarcoidosis developed. In one case they were able to observe the transition of a nodose erythema to a plaque of sarcoidance to verify the alteration histologically. They suggested the possibility of erythema nodosum being an initial nonspecific symptom of sarcoidosis or of morphologic erythema nodosum being a phase in the development of a frank sarcoidal lesion. They followed the course of events histologically and noted an actual transition, this does not occur when nodose erythematous lesions are a part of the syndrome of early tuberculosis, so if there were a transition to sarcoid, in the cited cases, it probably was a matter of a continuous development and not an actual metamorphosis.

I had the opportunity recently to observe a similar case. A woman, aged 54, was admitted to the University of Minnesota Hospitals in July 1949 for examination of a breast lesion. During the general examination nothing indicative of sarcoidosis was revealed. She was re-admitted in November 1950 when a fibrotic node was removed from the breast. In January, 1951, she was again admitted because of erythematous plaques on the legs, and fever. The skin lesions disappeared after a few days in bed. Results of the Mantoux test (1:1000) were negative, as were also the results of the chest roentgenograms. The biopsy of a leg lesion will be described later. A diagnosis was made of erythema nodosum of the symptomatic type. The patient recovered and left the hospital in a few days. Three months later she was again admitted stating that the skin lesions had reappeared a few weeks before and had remained visible. Again biopsy of a skin lesion was done. Peripheral vascular examinations disclosed nothing abnormal, but chest X-rays now showed definite hilar shadows, multiple small nodules in the apex of the right lung and an infiltrative process of the left lung. The findings were consistent with those of intrathoracic sarcoidosis. There were slight changes in the small bones of the hands reported as rheumatoid or sarcoidal. The Kveim test (Professor Danbolt's material) done on December 12, 1951 was declared negative as of May 1952. (The same material was injected into a patient with proven sarcoidosis and later the excised papule revealed a characteristic sarcoid reaction.) To summarize, the history was that of nodose erythematous lesions disappearing but quickly reappearing, with histologic changes from banal interstitial inflammation to a sarcoidal reaction, and roentgenologic findings in the thorax diagnosed as sarcoidosis.

The first biopsy specimen (January 1951) showed a reaction of the interstitial tissues of the hypoderm. No granulomas of Miescher were noted, however, there was a marked fibrotic reaction with large multinucleated grant cells. The reaction was mild enough not to be destruc-

tive and there were globular areas in the infiltrate which contained some cells with oblong nuclei, which stained deeply and showed a tendency to whorl formation, but the cells were not densely packed. The fat cells were not altered. The second biopsy specimen (April 1952) also showed marked fibrosis of the interstitial tissues and grant cells but adjacent to this were sharply demarcated, purely epithelioid granulomas. This sarcoidal reaction reached up into the corium, not down into the hypodermis. Although diffuse, the individual tubercles were distinct. There was some lymphocytic infiltrate in the spaces between the tubercules.

The entire picture resembled that of an early sarcoid reaction as found in the lung.

*Chronologic Review of Findings*

| Date | Findings |
|---|---|
| January 17, 1945 | Negative |
| July 25, 1950 | Negative |
| July 28, 1950 | Slightly inceased density of base of right lung |
| January 9, 1951 | Appearance of nodose erthnmatous lesions on legs |
| February 19, 1951 | Bilateral hilar enlargements |
| December 10, 1951 | Definite hilar enlargement. Multiple small nodes right apex of the lung. Infiltrative process of the left lung. Hands—minimal bone change |
| April 4, 1952 | Cutaneous sarcoid lesions on legs. |

There are two possible explanations of the skin lesions in this case. One is that the early (January 1951) lesions were non-specific but symptomatic and if this were the case they might be symptomatic of dissemination, for the chest at that time had lesions of sarcoid. The other is that the skin lesions of sarcoid, especially when on the lower leg and of the deep type, may be recognized as erythematous blotches which represent the surface change of a developing deep lesion.

This case would also corroborate Hartweg's conception of the clinical pathogenesis of sarcoidosis. The disease picture from July 1950 to February 1951 representing his Stage I and that of December 1951 his stage II or stage III. It is very difficult to translate the cutaneous microscopic findings into a formula for the pathogenesis. However, from the many reports of others, and after examination of many skin and lymph node sections, one may infer that in sarcoidosis the epithelioid reaction must take place very early; it seems to have a close affinity for connective tissue and blood vessels and does not produce toxins of irritating substances locally; hence, even in easily irritated tissues there is not much reaction in the surrounding area. The epithelioid reaction, having become established may remain unchanged for ever so long but the process eventually ends in some degree of fibrosis.

SUMMARY

1. The question of the pathogenesis of sarcoidosis is discussed.

2. Hartweg's views on the clinical pathogenesis of sarcoidosis are discussed and a case report is presented which tends to corroborate his theories.

3. The case presented, further, describes the sequence of histologic changes in erythematous nodose lesions eventuating in subcutaneous sarcoidosis.

4. It is concluded that the pathogenesis of sarcoidosis and chronic miliary tuberculosis may be similar in that a primary infection of the lung with subsequent dissemination involves about the same tissues in the two diseases.