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William A. Ingram
*University of Nebraska Medical Center*

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# THE ETIOLOGY OF SARCOIDOSIS

William A. Ingram

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College of Medicine, University of Nebraska

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# INTRODUCTION

Sarcoidosis is a chronic granulomatous disease, protean in nature, and characterized by frequent remissions and exacerbations which seldom produce constitutional symptoms. The lesion seems to spread slowly from organ to organ and is resistant to treatment, although spontaneous recovery may be anticipated in the majority of the cases.

Any organ or tissue in the body may be involved, but there seems to be a predilection for the skin, lymph nodes, lungs, and bones, especially of the hands and feet. The lesion seen grossly is a pearly gray, semitranslucent, spherical or flat nodule, occurring discretely or as confluent masses. Microscopically, there are large, pale-staining, polygonal or spindle-shaped, epithelioid cells arranged irregularly or regularly to form a tubercle. The tubercle of sarcoidosis is very much like the tubercle of tuberculosis with giant cells of the Langhans type, but there typically is no central caseation or peripheral infiltration by lymphocytes as in the tuberculosis tubercle. Growth proceeds apparently by formation of new nodules and not centrifugally. Healing proceeds by resolution or by fibrosis.

Sarcoidosis begins in the early adult life, and affects both sexes. All races seem to be affected, but in certain areas there appears to be a predilection for Negros. The majority of the cases have been reported from the Scandinavian countries, northern Europe,

England and North America. The incidence of the disease does not suggest a familial or communicable basis. Nevertheless, many regard the disorder as infectious in origin, and tuberculosis has been cited as the underlying cause. The evidence for this view is meager, however, and it is of interest that patients with sarcoid are more refractory to tuberculin than are normal persons of comparable age, sex and race.

Patients with sarcoidosis may live for many years without severe symptoms or signs. Death due to sarcoidosis is usually caused by a progressive fibrosis of the lungs leading to right heart failure. Granuloma of the myocardium has been the cause of death in some cases of Boeck's Sarcoid. Other causes of death have been from accumulation of sarcoid tissue in the mediastinum and central nervous system.

As far as etiology of the disease is concerned, opinions are still divided. The similarity of the sarcoid lesion to the lesion of tuberculosis has led many to believe that sarcoidosis is some atypical form of tuberculosis. I have attempted to select the pertinent clinical and experimental evidence for both sides of this concept in order to present a complete and impartial review of the literature for better understanding of this discussion.

## HISTORICAL REVIEW

The disease now generally known as Sarcoid, Sarcoidosis, or Besnier-Boeck-Schaumann's Disease, has attracted considerable attention in the medical world, particularly in the past two decades. It has been the subject of innumerable descriptive articles and several important monographs. Most of the progress in understanding the disease has been limited to clarification of the clinical picture and recognition of some of the pitfalls in diagnosis. As yet, little is known concerning the etiology.

A major division of opinion concerning the etiology has developed over the possible etiologic role of the tubercle bacillus, with most investigators either supporting or condeming the theory. The relation sarcoidosis bears to tuberculosis or possibly to other forms of granulomatous diseases also remains a matter of contention. Conclusive demonstration of its presence rests entirely upon the histological structure of the lesion which it produces.

The early history of sarcoidosis has been thoroughly reviewed by Hunter (31) and others (63, 15, 45). For completeness only the salient historical features of the disease will be presented here. Although Boeck appears to have been the first to describe the histological characteristics of the skin lesions (in 1899), Johnathan Hutchinson had published, as early as 1869, what was probably the first clinical description of sarcoidosis. The lesions were observed involving the extremities. In 1889, Besnier described

a skin lesion which he named lupus pernio, involving the nose, face and fingers. Tenneson, in 1892, reported a similar case and added that the ear lobe could be affected. Caesar Boeck, in the proffessorial chair at Christiania, described, for the first time in 1899, the morbid histology of the skin lesion.

The next contribution came from the roentgenologists. As early as 1902, Keinbock noted on radiological exam, curious "cysts" in the digits and toes of a twenty-seven year old patient who had acquired syphilis five years previously. In those early days of roentgenology, he attributed the lesions to syphilis. Kreibick, in 1904, associated these radiologic findings with lupus pernio. This observation was confirmed by Rieder in 1910.

In 1915, Bittorf and Kuznitzky described the morbid changes in certain viscera (spleen and lymph nodes) confirmed on biopsy to be Boeck's Sarcoid. Schaumann, in 1917, described the microscopic appearance of lymph glands and osseous lesions from both lupus pernio and Boeck's Sarcoid. He found these lesions to be identical histologically. He was the first to associate these findings with the varied reports that sarcoid lesions could be found in various organic systems. He postulated that this was a generalized disease, primarily affecting the lymphohematopoietic apparatus, and only incidently the skin.

Scattered papers depicting either the clinical or histological changes in lymph glands, or in internal organs, began to appear in

the literature in the following ten years. Kischin, Bernstein, Goecherman, Koszleman, Sidlick, Doub and Nenagh all contributed pertinent observations. Between 1931 and 1934, other cases with visceral involvement were recorded by Kirkland, Morton, Funk, Bayer, Bergel and Scharff. In 1932, Kissmeyer summarized the previous contributions in an important monagraph and added many original observations of his own.

In May, 1934, the "R'eunion Dermatologique de Strasbourg" devoted itself entirely to the consideration of "sarcoid". This symposium brought out a number of unique aspects of the malady, with papers being contributed by dermatologists, internists, pathologists, and roentgenologists from Germany, Switzerland, France, Sweden and Denmark. At this meeting the malady was properly called "Hutchinson-Boeck-Sarcoid".

As this disease became more and more familiar to clinicians, the literature on the subject has grown proportionately in volume. This has lead to the recording of many instances of a disease, previously unrecognized, or mistaken most often for tuberculosis. Freiman (15) has estimated that well over on thousand cases had been reported by 1948. One of the largest series has been published by Ricker and Clark (69) who have analyzed three hundred cases occurring in the United States Army.

Cases of sarcoidosis have been reported from practically every country in Europe, but especially the Scandinavian countries.

Other countries reporting this disease include Australia, Japan, Latin-America and there have been an increasing number of reports from the United States and Canada.

## ETIOLOGY OF SARCOIDOSIS

### GENERAL CONSIDERATIONS.

Nothing illustrates the fact that the etiology of sarcoidosis remains so uncertain any better than the multiplicity of theories published at one time or another. These theories implicate practically every agent capable of producing a granulomatous reaction or of diffusely affecting the reticulo-endothelial system. While many different opinions concerning etiology have been presented, no one has been able to prove to his, or to others satisfaction, the true etiology. Thinking has gradually gravitated toward several of many possibilities, such as: (1) the causative agent may be a rare form of noncaseating tuberculosis, in which, presumably, the virulence of the tubercle bacillus is very low; (2) a filterable virus; (3) a reticulo-endotheliosis or pathological tissue. reaction elicited by many infectious micro-organisms, or possibly by some nonliving agents (33).

The concept that sarcoidosis is an altered form of tuberculosis has been a popular one, and after a review of the literature it seems the evidence has been presented principly for or against this theory. The concepts, factual and theoretical, presented by both

sides can best be grouped into four categories: I. Bacteriological; II. Anatomical; III. Immunological; IV. Epidemiological.

## I. BACTERIOLOGICAL CONCEPTS.

Those who hold that sarcoidosis is a form of tuberculosis emphasize the frequently quoted and controversial work of Kyrle (38) who reported the earliest successive observations on a proven case of sarcoidosis. He followed this case over a period of two years and during this time the patient did not ever elicit a positive tuberculin skin test reaction. The patient had three febrile episodes over this period of time which were accompanied by exacerbation of the skin lesions. Biopsies of the skin in the "presarcoid" stage showed only a nonspecific inflammatory reaction with acid-fast bacilli in stained sections on the tenth day of the exacerbation. Guinea-pig inoculation was negative. By the twenty-first day, the infiltrate was composed largely of epithelioid cells accompanied by a few giant cells. The bacilli were reduced in number and guinea-pig inoculation again was negative. After thirty-six days the epithelioid cell foci were free of organisms and the lesion developed a typical sarcoid structure, complete with epithelioid cells and giant cells of the Langhans type with slight perituberecular infiltration of small round cells. By the ninety-fourth day the infiltrate had disappeared. One of two guinea-pigs inoculated during a febrile episode developed tuberculosis. It is difficult to

evaluate this case in view of the fact that this work has not been repeated successfully by other investigators.

According to Koch, the indisputable proof of a tuberculous causation was to find the acid-fast bacillus in the tissue. A strong argument along this line, offered in favor of the tuberculous nature of sarcoidosis, is the occasional finding of tubercle bacilli in microscopic examinations of lesions recovered from animals inoculated with selected tissues from a patient with sarcoidosis. Pinner (65) has listed various positive findings and other referances (81, 59, 89, 92) are also found in the literature. When the evidence is reviewed, the number of positive findings as compared with the number of repeated failures to identify the organism in the lesion or by animal inoculation seems to make this finding inconclusive.

The fact that the acid-fast organisms have been found in early sarcoid lesions occasionally, but are consistantly absent in older lesions, plus the fact that they are rarely recovered by animal inoculation has led to many and diverse explanations of this phenomenon.

Some authors contend that the organisms are in a filterable form or have dissociated into nonacid-fast forms (48, 80, 30). Hollister and Harrell (30) have suggested that the positive animal inoculations might be due to unsuspected tuberculosis in the patient, occurring in conjunction with the sarcoidosis. Others (75, 65, 48) have suggested that sarcoidosis is a phase in the development of a

caseating tuberculosis in certain individuals.

Freiman (15) states that if the lesion is actually due to the usual form of the tubercle bacillus, it might be assumed that the organisms are quickly killed and disentegrated at their points of focalization under local immune forces. Under these circumstances the lipoids of the tubercle bacillus might be capable of inducing a tubercle formation. This has been demonstrated experimentally by Sabin (76), Smithburn and Thomas (78), who have shown that the lipoid fraction of the tubercle bacillus contains maturation factors for mononuclear cells, epithelioid cells and epithelioid giant cells. The stimulus to form tubercles resides in certain fatty acids of high molecular weight, and two exceedingly complex substances (both phosphatides) may be considered as the types of lipoidal substance especially characteristic of the acid-fast strains of the organism. The tuberculo-phosphatides plus phthioic acid are responsible for the formation of the epitheliod cell. The wax is responsible for the acid-fast property of the tubercle bacillus.

When the sarcoid inoculation experiments were reviewed by Rostenberg (73), he came to the conclusion that it was rare for tuberculosis to develop in inoculated animals. He stated that if tuberculosis should develop at all, it was nearly always only after several passages or after a protracted time had elapsed following inoculation. Lindau (42) commented regarding this as follows: A source of error exists in that guinea-pigs are usually kept under

observation for a long time (up to a year) and it is a well known fact that guinea-pigs living for more than three months in a room where tuberculous animals are kept may acquire tuberculosis spontaneously.

Rostenberg (73) grants that the rat gives a sarcoid-like reaction to inoculation with tubercle bacilli but also notes that the rat behaves in a different fashion immunologically from most species toward the tubercle bacillus, He wonders if the findings in the rat are identical with those of patients with sarcoid. A fact admitted by several authors (19, 27, 12,) is that numerous tubercle bacilli can be found in the lesions developed in the rat, but the constant finding of these organisms in the rat lesions has no counterpart in human sarcoidosis. Kallos (35) has produced evidence which indicates that the white rat behaves toward the tubercle bacillus in this rather abnormal fashion due to the presence of a latent Baronella infection, which he believes so stimulates the reticulo-endothelial system of the animal that it is able to withstand other organisms, such as the tubercle bacillus. He demonstrated that once the Bartonella infection was cured and the spleen extirpated, the animal could be inoculated with tubercle bacilli with the usual type of caseation tuberculosis consequently developing.

Finding acid-fast bacilli in sarcoid lesions of a human could mean that sarcoidosis predisposes a person, especially the lungs and lymph nodes, to the development of pulmonary tuberculosis, just

as silicosis predisposes an individ ual to the development of the pulmonary form of tuberculosis (73). Hogan (29) suggests that a sarcoid lesion may impinge on a healed tuberculous lesion in such a way as to destroy the capsule that keeps the bacilli pent up and thus allow for the dissemination of the tubercle bacilli in the lung itself, or through the blood stream to other parts of the body. Vivas and his associates (97) point out that a possible reason tuberculosis is more frequent in persons with sarcoidosis than in the rest of the population may be that sarcoidosis is often mistakenly diagnosed as tuberculosis and the patients than placed in a tuberculous environment, where they are continually exposed to virulent tubercle bacilli. Finally, Snapper (85) stated that a terminal development of tuberculosis in patients with Boeck's Sarcoid can hardly be considered as proof the tuberculous basis of the disease,, since in patients with diabetes mellitus, Hodgkin's disease, and leprosy, a terminal tuberculosis in not infrequent.

It has been suggested by some authors that sarcoidosis may be caused by an atypical form of tubercle bacillus, a variety of bacteria or fungi with nonacid-fast characteristics. Schaumann (79) cultivated nonacid-fast types of bacilli resembling diphtheroid and streptothrix types which gave positive complement fixation tests with Besredk's antigen and he considered these organisms to be bovine in type. Others (16, 34, 72), by successive animal inoculation of tissues removed from proven cases of sarcoidosis have also obtained bacilli of the bovine type. Employing the Hallberg method of straining the tubercle bacillus, Schaumann and Hallberg (80) have

demonstrated a mycotic form of organism in a number of cases of sarcoidosis. In early lesions of this disease Mellon and Beinhouer (48) have isolated a partially nonacid-fast actinomyces-like thread or a bacillary form of the tubercle bacillus. After many transplantations, this organism developed into a strict acid-fast form. culturally indistengueshable from avian and human tubercle bacilli. They showed experimentally that the acid-fast culture, with which the patient had originally been infected, was capable of producing non-caseating lesions of the same general type as those found in the patient. Crawford (19) in another case found both the "actinomycotic" and the "coccal" type of the tubercle bacillus. Miller (48) has succeeded in converting an acid-fast tubercle bacilli into a nonacid-fast type and after transferring it to a suitable media the organism reverted to the acid-fast type. He concluded from this that the nonacid-fast forms of the tubercle bacilli were spacific.

## II. ANATOMICAL CONCEPTS.

There is a histologic resemblence of the sarcoidosis lesion to the "hard tubercle" produced by the tubercle bacillus under certain conditions. In fact, the resemblence of the miliary lesions of sarcoidosis is so close that the former are often called "hard tubercles". This designation is often used to indicate the predominence of cellular proliferation in the sarcoid granuloma as contrasted with the necrotizing tendency of the tuberculous lesions.

The lesion of sarcoidosis, wherever it is found, is character-

ized by focal areas of large mononuclear cells of epithelioid type, with occasional multinucleated giant cells. Neutrophilic leukocytes and caseous necrosis are absent, and reticulin fibers are demonstrable and intact throughout the nodule. This is in contrast to the breakdown and disappearance of these fibers in tuberculous lesions associated with caseation. A few lymphocytes may be present in and around the focal lesion, but comonly are less numerous than in tuberculous lesions.

The focal lesions of sarcoid tend to be sharply circumscribed and are separated from surrounding tissues which are without evidence of inflammatory reaction and appear normal. Although they are variable in size, there is relativly little tendency to become conglomerate. The epithelioid cells and giant cells are essentially similar to those which may be found in tuberculous lesions. However, the epithelioid cells often give the impression of being larger and have more nuclei, which are often distributed evenly throughout the cell rather than having a peripheral arrangement. Acid-fast organisms are not demonstrable in the lesions by the usual staining techniques or by animal inoculation. Various type of inclusions have been found in the giant cells in some cases, but but such inclusions are not pathognomonic of sarcoid lesions (1).

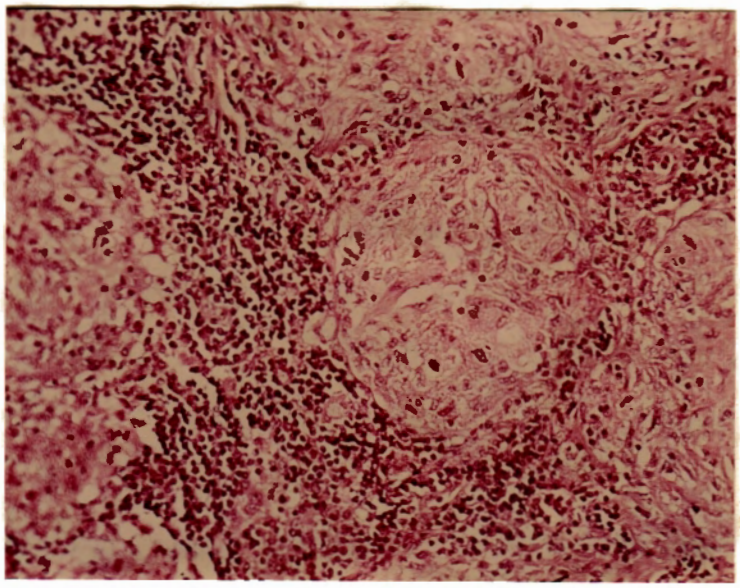

Figure 1.

Sarcoidosis of a lymph node found in the region of the common bile duct. The histological picture is that of a sharply circumscribed lesion, limited by tissue undergoing fibrosis, and containing large mononuclear cells of the epithelioid type. There is no neutrophilic infiltration or caseation seen which one would expect if this were a tuberculous lesion. Surrounding the tuberculoid lesion are many lymphocytes but no evidence of inflammation as would be expected around a typical tubercle of tuberculosis. There is no evidence that the lesion is attempting to unite with like-adjacent tubercles.

Courtesy of J.R. Schenkin, M.D.

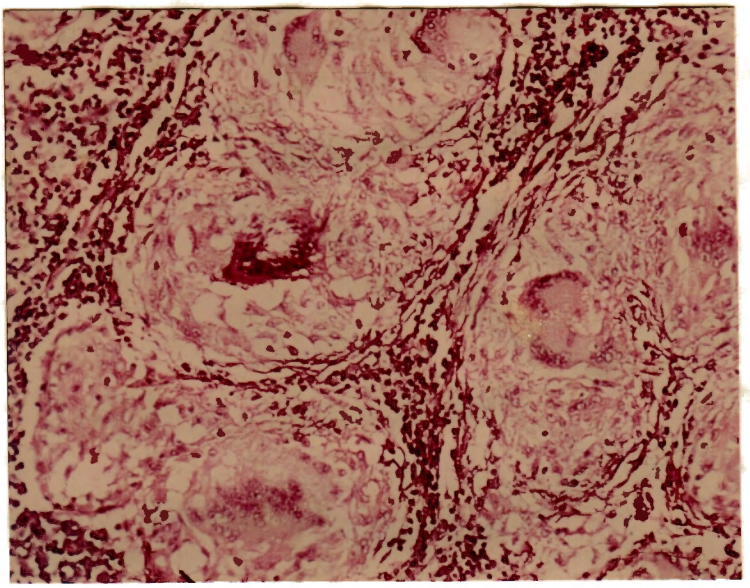

Figure 2.

Sarcoidosis of a lymph node. This is another section through the same lymph node seen in Fig. 1. There is the same histological picture apparent here, but in addition there are several large multinucleated giant cells of the Langhan's type to be seen. The two lesions pictured could be confused with the "hard tubercle" of a noncaseating tuberculosis but for one thing; one would expect to see caseation in a tuberculous lesion before it had attained this size.

Courtesy of J.R. Schenkin, M.D.

There are several points in which the two lesions differ. The tuberculous lesions may apparently persist in recognizable form after the organisms that have formed them have been destroyed (3, 64), and they do not seem to be capable of persisting for long periods of time as do the lesions of sarcoidosis. There is also a lack of correlation in the distribution of the lesions. While the pattern of dissemination in sarcoidosis suggests a hematogenous spread with lymphoid and reticulo-endothelial localization, it is different from miliary tuberculosis. Involvement of the myocardium, not very unusual in patients with sarcoidosis, is rarely seen in those individuals with tuberculosis (90). On the other hand, the serous surfaces of the intestine, meninges, and the adrenal glands, so commonly affected by tuberculosis are rarely involved by sarcoidosis (50, 57, 90, 44, 15).

## III. IMMUNOLOGIC CONCEPTS.

To say that the tubercle bacillus is the cause of sarcoidosis, one must at this point explain the frequent negative tuberculin reaction exhibited by patients with sarcoidosis. One must also formulate an explanation for a specifically altered tissue state whereby organisms can be rapidly destroyed and tubercles formed in the absence of a hypersensitive state.

The question arises whether the suspected dissociations in sarcoidosis are the result of an inherent property of the tubercle bacilli or whether they are the result of immunity in which the

negative tuberculin reaction may be an expression. In 1914, Jadassohn proposed that this state be designated as "positive anergy", and be distinguished from the infected state and the cachetic state by the terms "absolute anergy" and "negative anergy" respectively. He believed the positive anergy was partly the result of anticutins (tuberculin-neutralizing antibody in the serum of some individuals) which he believed to have demonstrated in rats. Pinner and his associates (66) argue that this may be a partial immunity state which is capable of modifying the tuberculous infection until it loses the characteristics of tuberculosis, but if for any reason the immune state is broken down, the process may be transformed into the usual form of tuberculosis. In support of this contention is the fact that the lesions of sarcoidosis are usually regressing or in large part healed at the time the tuberculosis supervenes (68, 75). Lemming's investigation (41), if confirmed, is significant. He vaccinated a number of sarcoid patients with B.C.G., and although the regional lymph nodes showed unmistakable sarcoidosis, the Mantoux reactions, even with as large a dose as 1.0 mgm. remained completely negative.

Cornbleet (8) has reported on a series of six cases with diagnosis of sarcoidosis verified by biopsies of the skin and lymph nodes. They were inoculated with B.C.G. vaccine by the multiple puncture method. Five of these cases gave negative reactions to tuberculin, and the sixth patient was positive to 1:100 material. The vaccination

was considered successful in all cases, in that the characteristic papules were present at the site of the inoculation.

Israel (32) made a study of B.C.G. vaccine under controlled conditions in twenty patients with sarcoidosis which indicated that individuals with this disease were unable to develope and maintain skin sensitivity to tuberculin. He also noted that only one-third of the patients with this disease exhibit a positive tuberculin skin reaction. He commented that the percentage of positive reactors to tuberculin among the young adults in most parts of the country at this time is no greater than this.

Thomas (90) observed fifteen cases of proven sarcoidosis over a period of seven years. He found seven patients to be anergic and seven other patients reacted to 1.0 mgm. or less of tuberculin. There were no anticutins in the serums of four anergic patients, and he could not demonstrate any good correlation between the occurrence of anticutins and the negative tuberculin reaction in his series of cases.

Martenstein (47) has recorded a negative tuberculin reaction in seventy-one percent of the cases of sarcoidosis and seventy-six percent of forty cases of lupus pernio. Longcope (45) had seventy-four cases in the Johns Hopkins Hospital series of which sixty-five percent had negative reactions. Kissmeyer (37) states a negative reaction was obtained in sixty percent of his thirty-five patients with doses of tuberculin up to 1.0 mgm. He concurs with Pinner that positive tuberculin reactions are less common in patients with

sarcoidosis than in the general population of the same age. This was particularly striking since his group of thirty-five patients was made up of thirty negros.

Ricker and Clark (69) in their study of sarcoidosis in the negro have even more striking statistics. Using young soldiers of the United States Army, with the majority of the soldiers being negro, they found that out of eighty-eight cases of sarcoidosis there were only three positive reactions, or about a four percent incidence. In one of these positive cases caseating tuberculosis was found in one of the lymph nodes, and in another the tuberculin reaction, at first negative, become positive after onset of a tuberculous meningitis.

In attempting to explain this phenomenon, Longcope (43) proposes that this generalized deficiency, illustrated by anergy to tuberculin, may be analogous to that which occurs in measles. Also, during the active infection by the causative agent, possibly an unknown virus, the reaction to tuberculin is suppressed and the skin test is negative.

Dubin (11) has shown that this reaction is not specific and states that patients with Hodgkin's disease also are deficient in ability to produce antibodies. He states that this is a generalized deficiency which is demonstrated by a lower incidence of positive serologic tests for syphilis, and an inability to make antibodies against brucella antigens.

Reisner (68) noted a change in the tuberculin reaction from a negative to a positive state, or an increase in the degree of tuberculin sensitivity in several of his cases that developed frank tuberculosis under observation. In some, the altered reactivity to tuberculin was found to have preceded the appearance of clinical manifestations of active tuberculosis for a period of several months or years. This suggested an increased sensitivity to tuberculin, developing in a case of sarcoidosis, that may be more than a fortuitous circumstance and might signify a potential transformation into manifest tuberculosis. This observation has also been made by several other authors (79, 43).

Rubin and Pinner (75) noted a positive tuberculin test in one case with a primary tuberculous infection. Nine years later the patient developed classical evidences of a generalized sarcoidosis. A Mantoux test at the time was negative and a biopsy of a lymph node showed sarcoidosis. Three years later the intracutaneous tuberculin test (O.T. 1:10) was positive and at autopsy a caseous pulmonary tuberculosis was found. Pappenheimer (60) and Carnes(5) have independently reported that it is possible to find typical tubercles and large caseating tuberculous lesions side by side, the former without caseation and without bacilli, the latter teeming with bacilli. Rostenberg (73) finds it difficult to understand how sarcoidosis can be a manifestation of an altered immunologic response to the tubercle bacillus when one has in one area a sarcoid lesion and a

few millimeters away an ordinary tuberculous lesion, since this should indicate a usual type of hypersensitivity reaction on the part of the host to tubercle bacilli.

Heden (26) has reported on two cases of sarcoidosis, one of which had a positive and the other a negative tuberculin reaction. He gave intravenous injections of a lipoid substance, extracted from tubercle bacilli, to both patients. The tuberculin test remained negative in the patient with the original negative reaction, but the other patient developed more discomfort and had a temporary desensitization for the Mantoux test. There was also an increase noted in the volume of the hilar glands.

Warfringe (93) records a case of sarcoidosis who failed to respond to tuberculin, but later developed pulmonary tuberculosis. The tubercle bacilli were cultivated from the sputum, killed, and injected intracutaneously. A lesion like that of sarcoidosis developed and the Mantoux test remained negative. It was concluded that the reaction produced by heat killed bacilli was similar to those porduced by B.C.G.

Tuberculin reactions in sarcoidosis are usually negative, but the incidence of positive reactions is appreciable. Reisner (68) found a positive result in forty percent of his thirty-five cases. However, most of the reactions were weak. Lomholt (46) found a positive result in eighteen percent of his cases with strong reactions in two percent. Bernstein and Oppenheimer (3) found four

positive reactions in their six cases, or a sixty-six percent incidence.

In 1941, Kveim (56) described the production of a cutaneous skin reaction in patients with sarcoidosis following intracutaneous injection of a heated saline suspension of lymph glands obtained from active cases of that disease. The response was described as a small brownish-red, indurated papule at the site of the injection, which was remarkable for its slow evolution and persistence. Characteristically, the reaction required weeks to attain its maximum size and there-after remained visable for many months. The microscopic picture revealed a histological picture similar to that of spontaneously occurring sarcoidosis. Simultaneous injections of O.T. and the Frei antigen in the same patients gave no comparable response. Conversely, the sarcoid material yielded negative results when administered intracutaneously to normal individuals and to persons with syphilis or lupus vulgaris.

Similar reactions have been seen when intracutaneous injections of killed tubercle bacilli were injected in sarcoid cases. Nelson (5) believes that this reaction might be a generalized tissue response to a number of different substances rather than the specific reaction that Kveim believed it was. In experiments with seventeen American negros with sarcoidosis, Nelson found that eleven cases had a positive reaction, but none of the healed or inactive cases gave a positive response. The individuals with positive skin tests to

sarcoid material also gave a characteristic Kveim response to normal spleen tissue. Lemming (41) has also produced this same type of response using normal spleen and leukemic tissues on the skin where B.C.G. vaccine had been made in the case of Schaumann's Disease.

Danbolt (10) has duplicated Kveim's experiment, with similar results. He excised papules from nine cases and on histological examination found granulation tissue made up of epithelioid cells surrounded by lymphocytes and occasional giant cells of the Langhan's type; in other words, a histological picture very similar to the lesion of sarcoidosis. Leider (39) also concurs with Kveim's findings and believes that the test is of distinct diagnostic value. He states the disadvantage of the test lies in the difficulty in processing standardized material and the slow development of the actual reaction. He also believes that the Kveim reaction, as well as the reaction of an individual with sarcoidosis to B.C.G., confirms Jadassohn's concept of specific positive anergy to tuberculin in sarcoidosis.

Investigating the theory that sarcoidosis might be caused by some atypical form of the tubercle bacillus, Brooke and Day (4) prepared a tuberculin vaccine from eighteen different strains of human, bovine and avian strains of the Mycobacterium genus. This included, among others; M. butyricum, M. smegmatis, M. leprae, M. phlei, M. marinum and M. pseudoperlsucht. They injected this vaccine into seven patients with sarcoidosis and into five normal

controls. Three of the seven cases with sarcoidosis and two of the five controls developed sensitivity to O.T. prepared from human tubercle bacilli. The experiments offered no evidence for, and in fact, represent evidence against the view that the etiology of Boeck's Sarcoid Disease is related to any member of the Mycobacterium genus used in this series. Longcope (43), after an examination of the lymph nodes, cultures, inoculation of guinea-pigs, rabbits and pigeons concurs with Brooke and Day in that no evidence could be found to support the claim that the disease was caused by human, bovine or avian tubercle bacilli.

The effect of cortisone on skin sensitivity to tuberculin has been investigated by Pyke and Scadding (69). They found that the sarcoid patients with a negative reaction to tuberculin developed a transient sensitivity lasting one to seventeen days while cortisone was being administered systemically or locally. In a few Mantoux-negative cases, tuberculin plus cortisone administration gave negative results. In several Mantoux-positive cases, the skin hypersensitivity appeared to be either inhibited, diminished or uneffected by cortisone. This last result was also true in three sarcoid patients, as proved clinically and histologically, with positive Mantoux reactions. This phenomenon is of theoretical interest in relation to etiology and may prove to be of practical importance as a diagnostic test.

Carnes and Raffel (6) have made a comparison of sarcoidosis and

tuberculosis with respect to the complement-fixation test using antigens derived from the tubercle bacillus. They used eight different antigens of the Mycobacterium genus on twenty-two cases of sarcoidosis, twenty-six cases of active tuberculosis and thirty controls. There was no clinical or pathological evidence of active tuberculosis among the sarcoid patients, although four of this group had positive tuberculin skin tests. Positive serologies were obtained in five (27.3%) of the cases. In contrast to this, sixteen (61.7%) of twenty-six cases of active tuberculosis gave positive serologic reactions and the average titer was higher in this group than among the cases of sarcoidosis. Ten (33.3%) of the healthy controls, who had positive tuberculin skin tests, gave positive complement-fixation reations with titers similar to that of cases of sarcoidosis. It is believed, therefore, that the positive complement-fixation tests observed among the cases of sarcoid may be due to past tuberculosis infections unrelated to sarcoidosis. Unless patients with sarcoidosis have an impaired ability to develope complement-fixation antibodies to the tubercle bacillus, the considerable difference in serologic reactions between them and cases of active tuberculosis indicates a difference in etiology of the two diseases.

Middlebrook and Dubos (51) have developed a hemagglutination reaction to detect the presence of antibodies to some fractions of the tubercle bacillus in the serum of tuberculous patients. They

take advantage of the reaction between the sheep erythrocytes treated with a component of a polysaccharide fraction of the mammalian tubercle bacilli and the sera of tuberculous patients. Observations show that at least one heat stable component present in a polysaccharide fraction of the tubercle bacilli can be adsorbed onto sheep erythrocytes, rendering them agglutinable by antibodies directed against them. The antibodies responsible circulate in the blood of immunized animals and individuals with active tuberculosis and have a cross reaction with the Wasserman positive sera. The positive tests are considered significant if the titer is 1:8 or higher.

In reviewing the Middlebrook and Dubos hemagglutination test, Smith and Scott (83) repeated the test on eleven cases of sarcoidosis. The diagnosis was based on clinical and historical findings and there was no reaction to the tuberculin test of 1:100 diluted O.T. Seven of the eleven had titers which were positive in the range of tuberculosis and four had negative titers. There was no record given of the titer and the evidence found here was not definite, but adds to the composite picture.

Though the number of reports is small, Longcope and Freiman (44) feel that the hemagglutination test for tuberculosis, which is high in a high percentage of the cases of active tuberculosis, is either negative or demonstrable in such low titers that it is insignificant in the vast majority of cases of sarcoidosis that have been examined.

It has been known for some time that skin sensitivity to tuberculin can be lost, even to the degree whereby a subject may fail to react to large doses. Rothchild, Frieden and Bernstein (74) demonstrated complete desensitization to tubercle bacilli and to tuberculin in guinea-pigs by prolonged and properly graded courses of subcutaneous injections of Koch's O.T. The desensitizing power of purified tubercular-protein was found to be less in proportion to its power to produce allergic reactions than Koch's O.T. The infection in desensitized immune animals does not introduce into the histological picture of tuberculous lesion features that are novel to the pathologic picture of human tuberculosis. Complete desensitization did not deprive the animals of any aspect of their immunity. It has been postulated then that a similar effect may be produced by repeated hematogenous dissemination of the tubercle bacilli as might be the case in sarcoidosis (15).

This theory has been substantiated by animal experimentation. Schwabacker and Wilson (82) found that large infectious doses of tubercle bacilli caused little difference between vaccinated animals and control animals, but the vaccinated animals were protected from small infecting doses by an immunity, evidently of low order. Skin sensitivity took longer to develope and never was so high in B.C.G. vaccinated animals. Wells and Brooke (95) vaccinated guinea-pigs with vole (bacilli causing tuberculosis-like disease in the rodent, Microtus) acid-fast bacilli prior to infecting them with virulent

mammalian tubercle bacilli. They found that it gave a degree of protection which was apparently far greater than has been recorded by other means.

Willis (96) has also demonstrated experimentally that desensitization occurs spontaneously in animals. After injection of tubercle bacilli of low virulence into guinea-pigs he found the guinea-pigs exhibited a gradual declining cutaneous allergy as infection subsided. Some guinea-pigs, after thirty months, were found to be able to call forth a high specific immunity to reinfection with virulent tubercle bacilli.

It has been noted under "anatomic arguments" how active tuberculosis is a frequent terminal complication of sarcoidosis with a negative tuberculin test becoming positive with the development of a caseating tuberculosis. Reisner (63) and others (69, 79, 43) have observed that a positive tuberculin test may precede the clinical manifestations of active tuberculosis by several months. Other observers (41, 32) have noted that vaccination of patients with B.C.G. up to two or three times the usual dose may fail to produce a positive test, or may only produce a delayed or slightly positive reaction.

It is rather obvious that this refractory state is more than a coincidence in individuals with sarcoidosis, and it may even be exaggerated to an unusual degree. It does not seem to be an inherent property of an individual, for it has been shown that when

an active tuberculosis occurs, the refractory condition disappears and gives place to a sensitivity to tuberculin.

## IV. EPIDEMIOLOGICAL CONCEPTS.

If sarcoidosis were on a tuberculous basis, it would be expected that it would originate more frequently in homes where tuberculosis exists than is apparently the case. Longcope and Pierson (45) in this connection state that the disease rarely occurs in tuberculous families. There is no evidence to the effect that sarcoidosis arises more frequently by virtue of contact with persons with known tuberculosis than it does where there is no history of this. Riley (70) states that the incidence of significant tuberculous contacts has been low in this series. Among forty-seven cases in which it was specifically determined, six, or thirteen percent, have a positive history. In several of these the intimacy of the contact was not determined. Most series have shown a similar low incidence, although Hagn-Meincke (21), in a review of twenty-six cases reported a history of contact in one-half of his patients. Similarly, if sarcoidosis were on a tuberculous basis one would expect that either tuberculosis or sarcoidosis would be more frequent in the other inhabitants of the home of a patient with this disease. Sarcoidosis occurring in siblings is sufficiently rare that it warrants reporting (71).

Geographically there are oddities in the distribution of

sarcoidosis which do not correspond to similar data for tuberculosis. Michael and his associates (49) in a study devoted especially to the epidemilogic aspects of sarcoidosis, have shown that in this country the disease occurs in significantly higher proportion in the southeastern corner of the country than elsewhere. Further, a disproportionate percentage of the cases occur in persons born in rural areas. Similarly Lomholt (46) in Denmark found that most of his forty-nine cases came from the rural districts where tuberculosis was least common.

A point often emphasized by the proponents of the tuberculous etiology of sarcoidosis is the apparent frequency with which patients with sarcoidosis contract tuberculosis. Pinner (65) states that ten percent of the sarcoid cases develope ordinary caseating tuberculosis. There are differences of opinion as to how this occurs. After Pinners first estimate, Rubin and Pinner (75) reported that seven of a total of forty-four cases, or about fifteen percent, had developed ordinary caseating tuberculosis. They were able to find small areas of caseation in many cases of sarcoidosis, but could not culture them successfully, even though there were typical organisms seen in the caseated foci. Hogan (29) has reviewed another series of forty-four autopsy examinations and found active tuberculosis in eleven of the cases, or twenty-five percent. Tuberculosis was the cause of death in five, or eleven percent. Moyer and Ackerman (54) report one percent of twenty-five cases had active tuberculosis.

It would seem that the incidence of tuberculosis in autopsied cases varies from one to twenty-five percent. Riley (70) in his study of fifty-two cases of Boeck's Sarcoid estimates there is a mortality of twenty percent due to tuberculosis. An additional thirteen percent develope active tuberculosis at some time or another. He believes that the juxtaposition of the two types of lesions does not necessarily imply a common etiology. Longcope and Freiman (44) report that the incidence of tuberculosis is high in most published series, but such etiologically dissimilar diseases as disseminated lupus erythematosus, Hodgkin's disease and leprosy also frequently terminate with a caseating tuberculosis.

In various families where sarcoidosis has occurred there is some evidence of an incidence of tuberculosis (21, 71), but as Freiman (15) concludes, such cases represent too small a proportion of the total cases reported to permit accurate evaluation. There are, at present, the factors of infection, environment, constitution, and the definite establishment of the incidence of tuberculosis in such groups that differ in any way from other comparable groups to be considered before any conclusion is reached.

SUMMARY OF THE TUBERCULOUS CONCEPTS.

In summary, the case for the tuberculous etiology rests largely on negative, circumstantial evidence and there is no convincing answer to this concept. To date, a definite separation of the two

conditions can not be made and the tubercle bacilli can not yet be excluded as the positive etiologic agent. The few positive bacteriologic findings pointing toward a tuberculous etiology can not be taken as the final answer. The theory that a modified tubercle bacillus may be the causative agent is also a debatable subject, just as the attempts to prove other acid-fast organism of the Mycobacterium genus have failed to be conclusively incriminated. It is possible that the newer methods, such as the Kveim reaction, hemagglutination and complement-fixation tests may eventually prove effective in answering this question.

NON-TUBERCULOUS ETIOLOGIC AGENTS

The resemblence between the lesions of sarcoidosis and other granulomatous diseases of known etiology has been noted by many and there have been innumerable suggestions as to the basis of this similarity.

LEPROSY.

There is a striking resemblence between the lesions of sarcoidosis and the lesion of the tuberculoid type of leprosy (13, 61). There have been suggestions that the same organism might be implicated since the symptoms, clinical picture of osseous and cutaneous changes, as well as changes in lymph glands may be caused by leprosy. The adenopathy has been said to be the same as sarcoidosis in ninety-

five percent of the cases. Culture of leprosy and sarcoid lesions gives the same type of bacteria (streptothrix and grampositive organisms) but few if any acid-fast organisms. Animal inoculation results have almost invariably failed in each disease (13). Cystic bone changes in the phalanges seen in leprosy are very similar to those of sarcoidosis and are easily confused (61).

It seems evident that leprosy can mimic many of the features of sarcoidosis, but there have been other reports which cast doubt on whether leprosy can be a varient or the same disease. Pardo-Castello (61) and Murdock (55) have pointed out that sarcoidosis rarely, if ever, causes the ulnar nerve involvement as seen in the neural type of leprosy.

Weeks and Smith (94) have attempted an immunologic approch to this problem. They skin tested ten proven cases of sarcoidosis with lepromin, but with inconclusive results. The test was negative in seven cases and positive in three. Six of the seven were known to have negative tuberculin tests and two of the three positive tests were in patients with positive tuberculin tests. Two patients with tuberculosis gave false positive skin tests with lepromin. No evidence was obtained to indicate Boeck's Sarcoid was an attenuated or modified form of leprosy.

Harrel and Horne (24) tested five sarcoid patients with injections of lepromin and found that the reactions, when present, were infrequent and indefinite. Of the five cases tested, three had

a one-plus reaction and none gave a two or three-plus reaction.

A review of immune types of leprosy with varying responses to lepromin skin tests made by Pardo-Castello and Tiant (61) demonstrated that almost all healthy adults in Havana, Cuba gave positive lepromin tests and the authors suggested the cases of Boeck's Sarcoid in Cuba might be instances of an atypical leprosy. People of European races, especially in the cold climates, with inherited resistance, develope a systemized disease which could be a modification of leprosy (13). There have been only a few reports in the literature, but the negative reaction to lepromin found in these cases seems to indicate that sarcoidosis is not a modified form of leprosy. There is a possibility that the lepromin test might be useful in the differential diagnosis of the two diseases (24).

BRUCELLOSIS.

The response of tissues to invasion of the brucella organism gives a picture much like that of sarcoidosis. It effects nearly every organ in the body, has a frequent low-grade chronic sourse and has a world wide distribution - all of which has made it a suspect as a possible cause of sarcoidosis. With the invasion of tissues by the brucella organism there is a proliferation of epithelioid cells, with or without the presence of giant cells of the Langhans and foreign body types, and occasionally eosinophilia (87). Necrosis is not a common feature. Pulmonary involvement may resemble that of sarcoidosis. Harvey (25) points out the ease with

which pulmonary brucellosis may be confused with Boeck's Sarcoid, and also tuberculosis. Agglutination tests and skin tests of patients with sarcoidosis have been proved negative (22) as well as cultures of the lesion for brucella organisms.

SYPHILIS.

Schaumann (79) in 1924, reported the clinical picture of Boeck's Sarcoid could be produced by syphilis and at times even direct examination of the lesion could not differentiate sarcoidosis from certain syphilides since the lesion of syphilis was not unlike the tuberculoid lesion at times. Biopsy of the lesion was the only way to differentiate the lesions in many cases. As mentioned previously, Keinbock (31), in 1902, was the first to note curious "cysts" in the digits and toes on radiological examination of a known case of syphilis. The serologic reaction was negative in sarcoidosis (11, 43) and from this it seems unlikely that syphilis can be the responsible agent.

MYCOCES.

Because of similar pulmonary manifestations, various yeasts and fungi have been suggested as etiologic agents of sarcoidosis. King (36) has observed such organisms as aspirgillus and monilia from the sputum of patients with radiographic and clinical evidence of pulmonary involvement like that of sarcoidosis; on the other hand, Harrell (22) found negative skin tests for blastomyces, monilia,

and coccidioides. Histoplasmosis (62) mimics many of the more common diseases of man and effects most of the organs of the body. When the lesion is found within an organ, granulomas occur which resemble miliary tubercles, the centers of which may undergo necrosis. Tornell(92) has reported on the similarity between the radiologic pictures of the lung in sarcoidosis and "threshers lung," a form of moniliasis, or possibly histoplasmosis, due to inhalation of burnt grain. However, such unspecific evidence can not be considered as conclusive evidence of etiology.

VIRUS DISEASES:

The inability to identify organisms in the lesions of most cases has suggested a virus etiology to some authors (15, 43). Attempts to implicate the virus of lymphogranuloma inquinale by means of the Frei test (6), at least have usually been negative.

The Kveim antigen, which was at one time considered strong evidence for a virus etiology was used by Nelson (56) on eleven negros with active sarcoidosis, as noted previously, but the test proved inconclusive. As yet, no virus has been demonstrated as the cause of sarcoidosis.

INORGANIC AGENTS:

Mineral particles and chemical substances causing some form of pneumoconiosis have been suggested as possible causes of the

sarcoid lesion because of the similarity in the granulomatous lesion formed.

SILICA.

Gardner (17) states that a simple inorganic substance such as silicon dioxide ($SiO_2$) is capable of exciting a tubercle formation. The reaction is determined by the number and size of the particles that come to rest in a given focus in the body. German (18) describes a sarcoid lesion in which minute crystals, presumably silica, were found. The lesion resulted from a wound caused by a falling rock. Ayers and Ober (2) reported a series of seven cases with granulomatous lesions associated with traumatically induced crystalline material which was believed to be silica. They also believe many strictly isolated localized sarcoid lesions of the skin following trauma are due to silicosis.

ASBESTOSIS.

Pulmonary asbestosis and sarcoidosis present many clinical and roentgenographic similarities with a like complication, tuberculosis. A pathogenetic relationship has been based on the chronological development of the sarcoid lesion. Shavlem (81) describes a case where asbestos bodies were found in sarcoid tubercles but admits this may be only coincidental.

BERYLLIUM.

Workers who are exposed to compounds of beryllium are occasionally subject to a chronic form of pulmonary disease which resembles sarcoidosis of the lung and has suggested a like etiology to several investigators.

Nichol and Dominquez (58) have reported granulomatous cutaneous lesions in five cases due to zinc-beryllium silicate accidently induced in and under the skin by laceration due to broken flouresecent light bulbs. They found a direct proportion between the amount of beryllium present and the amount of sarcoid-like formations. A biopsy of such a lesion was examined histologically and found to be similar to Boeck's Sarcoid (7).

Higgins (28) reviewed a series of cases in which thirty-three out of eight hundred workers exposed to beryllium phosphor developed a chronic pulmonary disease. He suggests that due to the nature of the lesions there might be an associated sarcoidosis. The lesions developed over a period of three to four years after exposure. Allergy was dismissed as a cause because most of the affected workers were not in contact with the phosphors at the time they developed the pulmonary lesions. The amount of exposure was not proportional to the severity of the disease, so a chemical agent could not be entirely responsible and it was concluded that the physical condition of the worker was an important factor.

In comparing the two diseases, too much emphasis has been placed on individual similarities and the clinical picture has been ignored. Instead of being a relatively asymptomatic disease such as characterizes sarcoidosis, the delayed chemical pneumonitis is frequently progressive to the point of incapacitation, cor pulmonale and right sided heart failure. Bone lesions have not been seen and the raddographic picture is similar only in the early stages. Histological examination of the granulomatous lesion reveals only superficial resemblence to sarcoidosis, often with foci of necrosis resembling caseation (15). The geographic distribution of this disease does not correspond to that of sarcoidosis, and the relatively limited exposure to beryllium compounds makes this an unlikely cause of sarcoidosis.

ALLERGY.

Certain features of sarcoidosis, such as the anergy to tuberculin, eosinophilia and erythema nodosum suggest that hypersensitivity plays an important role in this disease. Crawford (9) has reported two cases of sarcoidosis with positive anergy to tuberculin. One patient become allergic and a fatal pulmonary tuberculosis developed. He concludes that the reaction to tuberculin remains negative during the period of dissemination of mutation forms of the tubercle bacillus. Others (43, 68, 49) have also observed the same phenomenon.

Goddard (20) injected shock antigens, subcutaneously, into specifically sensitized guinea-pigs and induced a local inflammatory reaction which was a granuloma of histiocytic and epithelioid character and was associated with an anaphylactic response. Teilum (89) has also postulated on an allergic basis for sarcoid lesions. He states that hyperglobulinemia is a significant feature of Boeck's Sarcoid, and as a result the reticulo-endothelial system is found to contain precipitates of a homogeneous substance which passes on to hyalinosis. The alterations with regard to pathogenesis, structure and phasic development (proliferation of reticulum cells and precipitate), localization and alteration of the blood (hyperglobulinemia) must be considered analogous to atypical and experimental amyloidosis. The common primary basis is supposed to be an allergic hypoglobulinosis in the reticulo-endothelial system determined by persistant or repeated stimulation of immune mechanisms. He states that this theory explains why Boeck's Sarcoid locates in the reticulo-endothelial system, the morphological features (epithelioid cell granulation without necrosis) of the disease, the hyperglobulinemia and the immunity state or positive anergy.

SUMMARY OF NON-TUBERCULAR ETIOLOGIC AGENTS.

It is known that the local histological changes comparable with sarcoidosis are found in many chronic conditions such as syphilis, tuberculoid leprosy, brucellosis, fungus infections, and can be

experimentally reproduced by injection of lipoid containing extracts of various organisms as well as some oils. The full blown picture of sarcoidosis does not occur with any of these, but the findings suggest a syndrome that may be only a generalized tissue reaction to a number of unrelated substances, possibly a reticulo-endothelial response to various antigenic stimuli. The failure to consider this possibility has led to much confusion in the literature, and many different agents have been suggested as probable etiologic agents.

## GENERAL SUMMARY AND CONCLUSIONS

The etiology of Besnier-Boeck-Schaumann Disease or sarcoidosis has been a constant controversial issue in medical literature, particularly in the past twenty years. The majority of writers, for reasons which are inferential and circumstantial, favor some form of the tubercle bacillus as the etiologic agent. Other students of the disease believe that it may be the result of a number of different causes, and there are others who hold that the etiology is unknown. Many of the arguments offered are highly theoretical, dogmatic, and often based on evidence which has been interpreted and selected to substantiate the writer's preconceived ideas. The identical clinical, laboratory, and anatomic findings have been quoted as evidence for and against the tuberculous etiology.

Probably the strongest argument against a tuberculous etiology has been the failure in an overwhelming majority of cases to recover

tubercle bacilli from biopsy and autopsy specimens of the sarcoid lesion. Culture and animal inoculation procedures have been invaiably disappointing. It has been found that emulsions from sarcoid lesions do not cause tuberculosis when injected into experimental animals, but do produce sarcoid-like reactions in humans with sarcoidosis, a phenomenon which forms the basis for the Kveim test.

Among the leading arguments for the tuberculous etiology is the high incidence of complicating tuberculosis and the frequency of the disease as the cause of death. However, there are many who disagree with this concept and have presented evidence showing the incidence of fatal tuberculosis is no greater in the normal healthy population.

Although the high incidence of the non-reactors to the tuberculin test undoubtedly has some relationship to the etiology, the exact relationship is not clear. The negative reaction to tuberculin by patients with sarcoidosis has been explained in terms of "positive anergy" by Jadassohn, but it has not been established that there is a possibility of an allergic organism that is also tuberculin anergic. Another, and more likely possibility, is that for some reason these individuals are unable to produce circulating antibodies in response to the introduction of a foreign antigen.

Under certain conditions the pathologic response to virulent tubercle bacilli in induced tuberculosis of experimental animals, and also in the naturally occurring disease in humans, may mor-

phologically be indistinguisable from sarcoidosis. Both the caseating and non-caseating tubercles are sometimes found side by side in cases where there is no question about the diagnosis of tuberculosis, but the juxtaposition of the two types of lesions does not necessarily imply a common etiology.

The non-specificity of the histologic response of the tissues to certain foreign antigens has been used as a strong argument by those who believe that the disease may be caused by a variety of etiologic agents. They cite the close histologic similarity between the lesions of sarcoidosis and the lesions produced by syphilis, tuberculoid leprosy, brucellosis, certain fungus diseases, foreign bodies and beryllium granulomatosis. However, the similarity in morphology of the lesions has generally been over-emphasized and the clinical and pathological differences have not been properly stressed.

After analysis of the clinical and experimental evidence at hand, it must be concluded that the etiology of sarcoidosis is unknown. The case for the tuberculous etiology seems to be very strong, but there has been no data presented to date which can irrevocably establish this theory. A definite differentiation between sarcoidosis and tuberculosis can not be made and a flat denial that any relationship exists is yet hardly possible. New methods of approch, as suggested by the Kveim reaction, the hemagglutionation tests, complement-fixation tests, as well as

attempts to discover more subtle and profitable cultural and inoculation techniques, may eventually lead to the solution of the etiology of this disease.

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