PULMONARY SARCOIDOSIS

Lincoln J. Bynum, M. D.

MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

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INTRODUCTION

The disorder most commonly identified today as sarcoidosis has been called many things since the original descriptions in the late nineteenth century by Besnier (1) and Boeck (2). As is the case with many diseases that have widespread manifestations, the nomenclature used to describe sarcoidosis has varied according to the organ systems predominantly involved. The literature on sarcoidosis contains a confusing array of terminology and eponyms, including Boeck's sarcoid, Besnier-Boeck-Shaumann disease, lupus pernio, uveoparotid fever, Heerfordt's disease, lupus vulgaris multiplex nonulcerans et nonserpiginosus, benign lymphogranuloma, and perhaps the most appealing of all, Mortimer's malady. Today the term sarcoidosis is well established and, although the name itself has no real meaning, this is perhaps a desirable feature, since it avoids etiologic or taxonomic commitment and allows the kind of diversity and uncertainty that has come to be associated with this disorder.

The aura of mystery that surrounds sarcoidosis derives from the fact that this is one of the few diseases for which etiology and pathogenesis remain virtually completely unknown. This feature, along with the great variability of its manifestations, have led many to doubt that sarcoidosis should be considered a single disease entity at all. The uncertainty about its cause has also resulted in great difficulty even defining what is meant by the term sarcoidosis; of course, a satisfactory definition is necessary for coherent and meaningful study of such a disorder, in order to ensure that different investigators are describing the same condition.

The difficulty associated with defining sarcoidosis is evident from the variability and, in some cases, the length of definitions offered by some of the most authoritative figures in the field. J.G. Scadding, for instance, gives a pathologist's point of view:

> "A disease characterized by the presence in all of several affected organs and tissues of noncaseating epithelioid-cell granulomas, proceeding either to resolution or to conversion into featureless hyaline connective tissue." (3)

A more clinical definition is offered by D. Geraint James:

> "A multisystem disorder in which well-defined clinicoradiologic patterns are associated with widespread granulomas and with depression of delayed-type hypersensitivity." (4)

A somewhat vague account, in spite of his use of the term "well-defined." In order to achieve greater specificity, the International Conference on Sarcoidosis found it necessary to go to greater lengths:

> "Sarcoidosis is a systemic granulomatous disease of undetermined etiology and pathogenesis. Mediastinal and peripheral lymph nodes, lungs, liver, spleen, skin, eyes, phalangeal bones, and parotid glands are most often involved, but other organs or tissues may be affected. The Kveim reaction is frequently positive, and tuberculin-type hypersensitivities are frequently depressed. Other important laboratory findings are hypercalcuria and increased serum globulins. The characteristic histologic appearance of epithelioid tubercles with little or no necrosis is not pathognomonic, and tuberculosis, fungal infections, beryllium disease, and local sarcoid reactions must be excluded. The diagnosis should be regarded as

established for clinical purposes in patients who have consistent clinical features, together with biopsy evidence of epithelioid tubercles or a positive Kveim test." (5)

EPIDEMIOLOGY

The epidemiology of sarcoidosis is equally difficult to define as most other features of the disorder. Its distribution is world-wide, with reported cases originating from virtually every part of the globe (6). Although a geographic preference for the Southeastern states was previously suggested for cases of sarcoidosis described in this country, this distribution has not been confirmed by more recent studies, which demonstrate a more equal concentration in most regions of North America (6-8). The average age of diagnosis is approximately 30 years, although there is a very wide range, with cases reported in patients from 2 to 80 years of age. In this country, there is a predominance in females, with about two thirds of cases described in women (6,7). In addition, there is a slight racial trend, in that between 50 and 80 per cent of cases have been reported in blacks, depending on the part of the country from which the report originates (6). This racial imbalance is not nearly so strong as was once thought, and in some areas whites outnumber blacks by a considerable margin.

CLINICAL FEATURES

The clinical manifestations of sarcoidosis are incredibly variable. One of the features of this disorder that causes doubt that it is a single entity is the fact that its behavior ranges from a benign, self-limited, asymptomatic involvement of a single organ system to a multi-

system, rapidly progressive, and almost uniformly fatal catastrophe. This review will center on the pulmonary manifestations, but in the interest of completeness and a "whole-patient" approach to internal medicine, Table 1 will list some of the commoner extrapulmonary lesions.

The lung is the most frequently involved organ in sarcoidosis, and abnormalities of the lungs or draining lymphatics occur in over 94% of cases (9). The pulmonary manifestations may also be quite varied, both in appearance and in the course of the disease. Table 2 lists the reported radiographic changes in sarcoidosis. The most commonly observed abnormality is bilateral hilar adenopathy, often associated with right (and occasionally left) paratracheal adenopathy. Although exact incidence figures are hard to find, this pattern without other radiographic abnormalities is the most common presenting picture in sarcoidosis, probably accounting for nearly half the cases (6,10). The next most frequently observed abnormality is parenchymal infiltration of the lungs, which most typically takes the form of diffuse, bilateral, reticulonodular densities, most often described as an "interstitial" pattern. Less commonly, the densities may be fluffy, patchy, or confluent, termed "alveolar" in appearance. A well-described but uncommon pattern is that of single or multiple large nodular shadows, occurring in about 3% of cases (11,12). Cavitation may occur with many of the different kinds of infiltrates (10, 13). Although once considered rare, and even frequently used as an important point in differential diagnosis against sarcoidosis, pleural thickening or effusion has been well described (14,15), occurring in up to 10% of cases (16). A rare manifestation of sarcoidosis is bronchial

TABLE 1

EXTRAPULMONARY MANIFESTATIONS OF SARCOIDOSIS

1. Cardiac
   a. Conduction disturbances
   b. Arrhythmias
   c. Cardiomyopathy
   d. Pericardial effusion
2. Dermatologic
   a. Erythema nodosum
   b. Lupus pernio
   c. Plaques, scars, keloids
   d. Maculopapular eruptions
3. Ophthalmologic
   a. Iridocyclitis
   b. Keratoconjunctivitis sicca
   c. Sjogren's syndrome
   d. Chorioretinitis
   e. Glaucoma
   f. Cataracts
4. Neurologic
   a. Cranial nerve palsy
   b. Neuropathy
   c. Space-occupying lesion
   d. Meningitis
   e. Myopathy
5. Renal
   a. Renal failure
   b. Renal calculi
   c. Nephrocalcinosis
6. Rheumatologic
   a. Polyarthralgias
   b. Polyarthritis
   c. Bone cysts
7. Endocrinologic
   a. Hypopituitarism
   b. Hypercalcemia
   c. Diabetes insipidus
   d. Hypothyroidism
8. Hematologic
   a. Peripheral lymphadenopathy
   b. Splenomegaly
9. Gastrointestinal
   a. Parotid gland enlargement
   b. Hepatic granulomas
   c. Crohn's disease

stenosis, resulting in obstruction with distal atelectasis and infection (17). The most difficult diagnostic problem may be presented by the unusual appearance of local consolidation, which may be lobar and may simulate tuberculosis when seen in the upper lobes (18). Most of these parenchymal abnormalities progress to variable degrees of fibrosis and scarring, which may be minimal or extensive and may involve lung tissue, pleura, and mediastinal structures.

The different radiographic patterns seen in sarcoidosis have been classified into a staging system that has considerable diagnostic and prognostic importance (4,6). These are described in Table 3. Stage 0 refers to those patients without radiographic abnormalities in the chest, a decidedly small fraction of cases. The absence of radiographic changes does not necessarily indicate a lack of pulmonary involvement, however, for unmistakable physiologic and histologic abnormalities may be demonstrated in patients with a normal chest roentgenogram (19). Stage 1, as previously indicated, is the most common variety, occurring in almost half the cases. The prognosis of this type is quite good, with a rate of spontaneous and complete resolution exceeding 60% (6). Stage II is the next most frequently observed pattern, occurring in about a third of the patients. The prognosis of this type is less favorable, with an overall remission rate of about 45%. The remainder of these cases usually progress to Stage III, in which hilar adenopathy has resolved but parenchymal densities persist or advance, observed in about 15% of cases. Only slightly over 10% of these patients show resolution, the remainder progressing more-or-less inexorably to death.

Clinical manifestations correlate rather well with radiographic stages as far as severity and prognosis are concerned (9,20,21). Patients

TABLE 2

RADIOGRAPHIC MANIFESTATIONS OF PULMONARY SARCOIDOSIS

1. Bilateral hilar adenopathy
2. Mediastinal adenopathy
3. Diffuse parenchymal infiltration
4. Nodular densities
5. Cavitation
6. Pleural thickening/effusion
7. Bronchial stenosis
8. Local consolidation
9. Fibrosis/scarring

TABLE 3

RADIOGRAPHIC STAGES OF SARCOIDOSIS

0 - Clear chest

I - Bilateral hilar adenopathy

II - BHA plus pulmonary infiltration

III - Pulmonary infiltrates without BHA

with Stage I radiographic disease are most likely to be asymptomatic or have only mild constitutional symptoms, and have the best prognosis. Erythema nodosum commonly accompanies this form of presentation, but the combination does not worsen the prognosis; this clinical picture is well known as Lofgren's syndrome (22). Other symptoms which are rather non-specific include weakness, weight loss, malaise, easy fatigue, and fever. Thoracic manifestations include cough and dyspnea most commonly, often associated with sputum production, hemoptysis, and chest pain. The presence of any symptom, other than erythmea nodosum, indicates a markedly worse prognosis, and the greater the number of organ systems that have symptomatic manifestations, the grimmer the outlook.

Complications of sarcoidosis include primarily those clinical consequences that are well known to accompany many forms of progressive, destructive pulmonary fibrosis, including hemoptysis, pneumothorax, and cor pulmonale. Infectious complications are also frequent and perhaps more important to consider due to their potential preventability and treatability. The more routine types of bacterial pneumonia are exceedingly common, especially in later stages; in addition, because of the severity of the pulmonary disease, the underlying immunologic deficiencies, and the frequency of steroid therapy, many types of "opportunistic" infections also occur, such as those due to tuberculosis, fungi, viruses, and protozoa. Infections with nocardia and aspergillus are said to be so frequent as to be rather characteristic, and the aspergillus-related fungus ball ("aspergilloma") often complicates cavitary or cystic forms of sarcoidosis (20, 23, 24).

DIAGNOSIS

In general, the diagnosis of sarcoidosis depends upon the histologic demonstration of characteristic pathologic changes in a biopsy specimen. However, the clinical picture which includes bilar hilar adenopathy, in either an asymptomatic patient or one with concomitant erythema nodosum or uveitis, is said by some to be so characteristic as to be diagnostic in the absence of histologic confirmation (25). However, not everybody agrees with this concept, and there is certainly general agreement that tissue biopsy is necessary when the picture includes any other elements, especially evidence of parenchymal pulmonary involvement. Any involved tissue may be the source of diagnostic biopsy material, particularly lymph nodes or skin. A popular technique currently is the use of transbronchial biopsy with the fiberoptic bronchoscope, a relatively benign procedure that is said to yield diagnostic results in over 80% of cases of sarcoidosis (26-28). Our own experience and that of other investigators is that the transbronchial lung biopsy may be diagnostic even when the lungs appear radiographically normal (19,26). In addition, when pleural involvement with effusion can be demonstrated, pleural biopsy may be productive (14, 15, 29).

For many years, the Kveim test has been touted as the most definitive test for sarcoidosis, especially by Dr. Siltzbach in New York and others (21,30,31). This test involves grinding up tissue from a patient with known sarcoidosis, usually the spleen, and suspending it in saline (See Table 5). The suspension is injected intradermally and this

site is then biopsied 4-6 weeks later; the finding of characteristic granulomas is diagnostic of sarcoidosis. The test has been the source of much controversy, since some authors have reported a very high incidence of false-positive reactions in other diseases (32,33). Moreover, there appear to be major differences in response to tests with different lots of the antigen, and this makes interpretation of results very difficult. Currently, the greatest problem is the inability of most centers to obtain reliable test material, thus rendering the Kveim test virtually useless as a diagnostic test for the majority of American physicians (34).

Recently, elevations in serum angiotensin converting enzyme (ACE) were reported in patients with sarcoidosis, and this determination has been proposed as a helpful diagnostic test (35). This finding was confirmed, and elevations of ACE were found to be correlated with disease activity, by other investigators (36). The enzyme has also been found to be elevated in Gaucher's disease and leprosy but not in tuberculosis, lymphoma, or fungal diseases (37,38). Although it may be capable of contributing to the diagnosis in some patients, other authors do not yet have enough confidence in ACE measurements to eliminate the need for a biopsy diagnosis in most patients (34).

It should also be emphasized that sarcoidosis is, to a large extent, a diagnosis of exclusion. The clinical picture, radiographic findings, and even histologic changes are not specific for this disorder and are shared by a number of other diseases. Therefore, the positive diagnosis of sarcoidosis invariably depends upon the successful demonstration of

negative results for tuberculosis, fungal diseases, and other conditions (See Table 4).

PATHOLOGY

The histologic changes that are typical of sarcoidosis have been extensively described and illustrated by a number of sources (4, 7, 21). The most characteristic feature is the sarcoid granuloma, which is classically described as a "non-caseating" epithelioid tubercle, primarily to distinguish it from the granulomatous reaction of tuberculosis, which typically shows caseation necrosis. The granuloma is made up mostly of epithelioid cells, which are large, pale-staining cells varying from polyhedral to fusiform in configuration, with abundant granular cytoplasm and prominent oval nuclei. Other cells frequently seen are giant cells, lymphocytes, plasma cells, and fibroblasts, and various degrees of fibrosis may be present. There is little or no peripheral cuff of inflammatory cells, as is seen in tuberculosis. Several inclusion bodies may be found in the cytoplasm of giant cells: the asteroid body, a star-shaped structure with fine spicules, probably representing crystallized lipid, and the Schaumann body, a concentrically lamellated, darkly staining body that probably represents deposits of mineral salts. Besides the granulomas, sarcoid lung may show an interstitial chronic inflammatory reaction with fibrosis. Granulomas are characteristically found around blood vessels and bronchioles, and are occasionally seen within alveoli, in the submucosa of airways, or in the pleura.

PHYSIOLOGY

In keeping with its character as an interstitial fibrotic and chronic inflammatory process, sarcoidosis has classically been said to result in

TABLE 4

DIFFERENTIAL DIAGNOSIS OF PULMONARY SARCOIDOSIS

1. Tuberculosis, typical and atypical
2. Fungal infection
3. Berylliosis and other pneumoconioses
4. Hypersensitivity pneumonitis (extrinsic allergic alveolitis)
5. Lymphoma
6. Metastatic carcinoma
7. Connective tissue diseases
8. Idiopathic pulmonary fibrosis
9. Histocytosis X

the typical restrictive ventilatory defect. Thus, the physiologic changes described have included a reduction in lung volume (as manifested by decreased total lung capacity and vital capacity), abnormal stiffness of the lungs (manifested as decreased lung compliance), and an abnormality in the tissue barrier between the alveolus and the capillary (measured as a reduction in diffusing capacity for carbon monoxide) (39-42). Decreases in gas diffusion have been shown to relate both to increased thickness of the alveolar-capillary membrane and to a reduction in the number of capillaries due to fibrotic lung destruction (43). Somewhat surprisingly, some of the earlier studies suggested that airway function might also be abnormal in patients with sarcoidosis, in addition to the restrictive defect, as manifested by elevated residual volumes and reduced mid-expiratory flow rates (41, 42). More recently, with the advent of more sophisticated tests of airways function, a number of investigators have described obstruction in small airways in sarcoidosis (44, 45). Most authors have postulated that kinking or distortion of small airways by fibrosis explains the reduction in airflow in these sites. However, very recent data from Rosenblatt and associates (46) has demonstrated that, although the lungs of sarcoidosis patients are stiffer than normal at high lung volumes (as measured by lung elastic recoil), there is actually a reduction in recoil pressures at low lung volumes. Reduced lung elastic recoil is the abnormality typical of emphysema and could explain reduced flow rates in small airways in sarcoidosis. Thus, sarcoidosis is coming to be characterized as a mixture of both restrictive and obstructive lung defects, probably because the granulomatous and

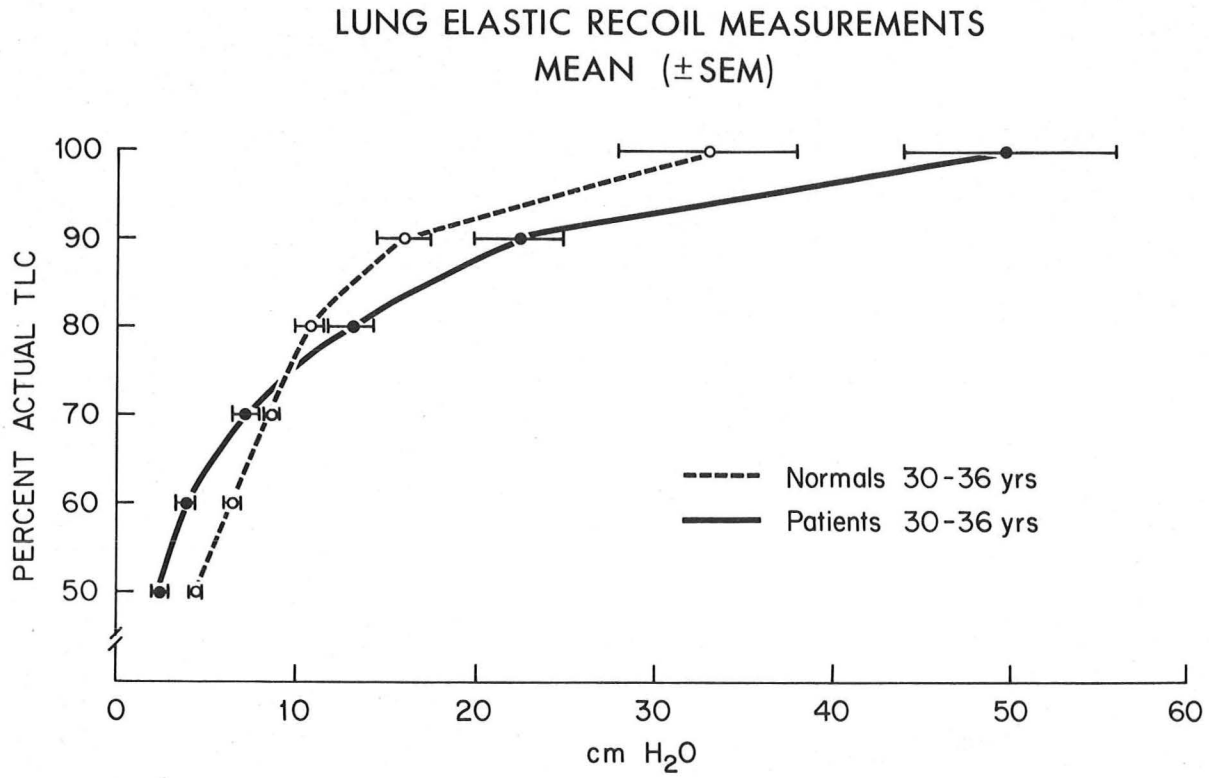

Figure 1. Compliance curves in patients with sarcoidosis and normal subjects. Lung elastic recoil, on the abscissa, is plotted against lung volume, on the ordinate; volume is expressed as a percent of the actual total lung capacity (TLC). At high lung volumes, the compliance curve of sarcoidosis patients is shifted downward and to the right, indicating an increased stiffness of the lungs. Thus, at large volumes, the elastic recoil pressure is greater than normal. However, at volumes below 70% of TLC, the patients' curve is shifted leftward, indicating an increase in compliance. This demonstrates that lung elastic recoil is abnormally low at smaller lung volumes. From Rosenblatt et al (46).

fibrotic reaction not only stiffens the lung and restricts its expansion, but also destroys lung parenchyma and reduces its natural elasticity.

IMMUNOLOGY

The earliest immunologic abnormality described in sarcoidosis was a generalized hyporeactivity to skin tests which produced a delayed, cellular, or Type IV reaction; the depression of delayed hypersensitivity, suggesting thymus-mediated lymphocyte (T cell) anergy and impaired cellular immunity, has been confirmed numerous times (47-50). Subsequently demonstrated was hyper-reactive humoral immunity with lymphoproliferation and overactivity of bursa-dependent (B cell) mononuclear cell activity (47, 50, 51). These abnormalities have been shown to be due to a decrease in the number of circulating T cells, decreased in vitro response of lymphocytes to mitogens, and increased cell binding of immunoglobulins (50, 52). The immunologic dysfunction of cultured lymphocytes correlates well with cutaneous anergy and the severity of disease (48). In addition, leukotactic dysfunction has been described in sarcoid patients, due to a circulating factor which inactivates chemotactic factor (53, 54). Recent data has been reported that suggests a role for circulating immune complexes in sarcoidosis (55). Both the T-cell and B-cell defects may be tied together by the reported evidence for antibodies against T cells in these patients (56). The immunologic derangements in sarcoidosis are summarized in Table 5.

ETIOLOGY

The etiology of sarcoidosis remains a complete mystery in spite of our long experience with the disease. The list of possibilities is long, but none has been established with any degree of certainty. Because of the evidence for immunologic abnormalities presented above, most

TABLE 5

IMMUNOLOGIC ABNORMALITIES

IN SARCOIDOSIS

1) Depression of delayed hypersensitivity
    a) Skin test hyporeactivity
    b) Decreased T cell population
    c) *In vitro* hyporesponse to mitogens
    d) Serum lymphocyte inhibitor
    e) Chemotactic factor inactivation
    f) Anti T cell antibody
2) Hyper-reactive humoral immunity
    a) Elevated immunoglobulins
    b) Antiviral antibodies
    c) False-positive Wasserman
    d) Increased B cell Ig receptors
    e) Increased serum complement
    f) Circulating immune complexes
3) Kveim antigen reactivity
    a) Ground sarcoid tissue
    b) Intradermal injection
    c) Biopsy at 4-6 weeks
    d) Acute: 85% positive
    e) Chronic: 50% positive
    f) Many false positives

investigators feel that sarcoidosis represents some sort of hypersensitivity phenomenon, directed against an unknown antigen or perhaps as a non-specific response to a variety of different antigenic stimuli. A number of rather specific etiologic agents have been proposed to explain this disorder, one of the earliest of which was the group of so-called "anonymous" or atypical mycobacteria (57). Subsequently, a number of other infectious agents have been implicated, including typical tuberculosis, histoplasmosis, blastomycosis, cryptococcus, sporotrichosis, aspergillosis, and mycoplasma (58-60). In addition, many non-infectious etiologies are possible, such as berylliosis, hemosiderosis, and neoplastic processes (58). A familial predisposition to sarcoidosis has been described, suggesting that hereditary factors may also play a role (61). The most reasonable conclusion may be that sarcoidosis, rather than being a single, distinct disease entity, probably represents a somewhat non-specific response (probably mediated immunologically) to a wide variety of stimuli, including both infectious and non-infectious agents. When and if the answer is ever worked out, it will represent the solution of one of the great medical mysteries of history.

THERAPY

The most widely employed therapeutic modality for sarcoidosis has for years been corticosteroids. Although these agents have been used long and often, there remains a great deal of controversy concerning their efficacy. There is some theoretical justification for the use of corticosteroids, considering the possible hypersensitivity basis for the disorder. Most clinicians feel that steroids are effective in

ameliorating many of the clinical and physiologic derangements, at least on a short-term basis, and some uncontrolled series suggest some demonstrable benefit (62, 63). Several controlled studies, however, have shown no substantial advantage in patients given corticosteroids for 3 to 6 months (64, 65). At least one of these studies showed some improvement in pulmonary manifestations, in spite of the lack of overall benefit, in treated patients (64). Because of findings such as these, a large proportion of patients with sarcoidosis are treated with corticosteroids at some point in their course. The list of universally accepted indications for such treatment includes progressive pulmonary dysfunction, ocular involvement, central nervous system manifestations, cardiac disease, other major organ impairment such as hepatic or renal insufficiency, disfiguring skin lesions, and hypercalcemia. As has been well documented in very elegant clinical and physiologic studies by Johnson (66), although highly significant improvements can be demonstrated following corticosteroid therapy, many patients relapse after therapy and, even with long-term treatment, may have an inexorably progressive deterioration in lung function over a number of years. A variety of other therapeutic modalities, including antimalarial drugs and immunosuppressive agents, have been proposed for the treatment of sarcoidosis, but none has been subjected to critical evaluation.

CONCLUSION

In summary, sarcoidosis is an acute or chronic granulomatous process of unknown etiology which may affect virtually any organ and tissue in the body, but pulmonary, lymphatic, and dermal manifestations are most common. The most frequently observed intrathoracic abnormalities

are hilar and mediastinal adenopathy, which may be accompanied by more-or-less diffuse interstitial lung infiltration. The majority of patients with sarcoidosis undergo remission of the disease with or without therapy, but a certain number of cases manifest progressive parenchymal fibrosis and pulmonary insufficiency. A variety of infectious complications may intervene in the course of sarcoidosis, especially fungal and bacterial pneumonias. The diagnosis is established most reliably with tissue biopsy and the demonstration of typical, non-caseating granulomas without other demonstrable etiologies. The physiologic changes that are characteristic of sarcoidosis include those abnormalities associated with a restrictive ventilatory defect, including a reduction in lung volumes, a loss of compliance, and a reduced diffusing capacity; however, abnormal function of small airways and loss of elastic recoil at low lung volumes have also been demonstrated. The immunologic derangements associated with sarcoidosis involve both a hyporeactive delayed hypersensitivity and an apparently hyper-reactive humoral immune system. A wide range of etiologic agents have been suggested to play a role in various cases of sarcoidosis, including tuberculosis, several fungal agents, and different types of inhalational injury to the lung, but none has been established as causative. Treatment of this disorder is controversial, but the most widely used class of therapeutic agents are the corticosteroids; these drugs can be shown to ameliorate many of the pulmonary symptoms and physiologic abnormalities, but whether they have any salutory effect on the long-term prognosis of sarcoidosis is still uncertain.

It is probably a conceptual error to regard sarcoidosis as a single

disease entity. The search for a single etiologic agent, a uniform pattern of physiologic abnormalities, and one universally successful form of therapy has led only to confusion and contradiction in the existing literature. It seems that a more reasonable approach would be to consider sarcoidosis as a more-or-less uniform inflammatory tissue reaction to a large number of different insults, with considerable variation in course, severity, and extent, depending upon a multitude of factors involved in the interaction between host and inciting agent. The real unifying feature in the many potential manifestations of this interaction is the immune system, with humoral and cellular hypersensitivity playing important, yet variable roles in the ultimate clinical, radiographic, and physiologic expressions of the disorder. A framework of ideas such as this might allow a more effective approach toward elucidating the mysteries of one of the most perplexing and fascinating maladies in all of medical science.

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