

## Statement on Sarcoidosis

THIS JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), THE EUROPEAN RESPIRATORY SOCIETY (ERS) AND THE WORLD ASSOCIATION OF SARCOIDOSIS AND OTHER GRANULOMATOUS DISORDERS (WASOG) WAS ADOPTED BY THE ATS BOARD OF DIRECTORS AND BY THE ERS EXECUTIVE COMMITTEE, FEBRUARY 1999

Sarcoidosis is a systemic granulomatous disease that primarily affects the lung and lymphatic systems of the body. A diagnosis of the disorder usually requires the demonstration of typical lesions in more than one organ system and exclusion of other disorders known to cause granulomatous disease. Since sarcoidosis was first described in 1877, it has continued to fascinate both clinicians and scientists. Much progress has been made in terms of understanding the protean clinical and unique immunological and pathological features of the disorder. Less is known about the epidemiology and genetic factors that contribute to the development and expression of the disease. The appropriate therapy for the disorder also has not been well defined for all patients. Most importantly, the cause of the disorder is still unknown.

### Objective

The primary impetus for this consensus statement by the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) was to update clinicians and scientists regarding new advances related to sarcoidosis. It is hoped that this document will improve the care of patients with this disorder and trigger new studies to elucidate further the cause and pathogenesis of the disorder.

### Evidence

Panel members are experts in the care of patients with sarcoidosis. The panel was divided into groups responsible for writing specific sections of the statement. The level of evidence for the recommendations made in this statement is largely that of expert opinion developed by consensus. There is little supportive evidence from well-conducted randomized controlled trials.

The following is the consensus of the state of the art of the understanding of pathogenesis, diagnosis, and treatment of sarcoidosis:

#### What we know:

- The clinical features and syndromes
- How to make a diagnosis
- That corticosteroids are an effective short-term therapy
- The incidence and prevalence of the disease
- That some genetic factors alter expression of the disease
- The immunology characteristic of the initial onset of the disease

#### What we would like to know:

- If there is test to predict disease progression
- If corticosteroids alter the natural history of the disease
- The optimal length of therapy

- If there are less toxic therapies than corticosteroids or cytotoxic agents
- How genetic factors alter expression of the disease
- If genetic factors affect susceptibility to the disease
- The mechanisms of lung injury and fibrosis
- The mechanisms that result in persistent disease
- The cause of sarcoidosis

### DEFINITION

Sarcoidosis is a multisystem disorder of unknown cause(s) (1). It commonly affects young and middle-aged adults and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved.

The diagnosis is established when clinicoradiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas. Granulomas of known causes and local sarcoid reactions must be excluded.

Frequently observed immunological features are depression of cutaneous delayed-type hypersensitivity and a heightened helper T cell type 1 (Th1) immune response at sites of disease. Circulating immune complexes, along with signs of B cell hyperactivity, may also be found.

The course and prognosis may correlate with the mode of the onset and the extent of the disease. An acute onset with erythema nodosum or asymptomatic bilateral hilar lymphadenopathy usually heralds a self-limiting course, whereas an insidious onset, especially with multiple extrapulmonary lesions, may be followed by relentless, progressive fibrosis of the lungs and other organs.

### HISTORY

The following is a chronology of some of the sentinel discoveries and advances in the understanding of sarcoidosis (detailed descriptions have been published elsewhere) (2, 3). The initial description of sarcoidosis is credited to an English physician, Jonathon Hutchinson, who, in 1877, described a patient whose hands and feet had multiple, raised, purplish cutaneous patches that which had developed over 2 yr (4). Hutchinson attributed these lesions to a manifestation of gout. In a subsequent publication (5), he described additional cases and suggested this phenomenon represented a "form of skin disease which has . . . hitherto escaped special recognition." The subsequent reports of the salient histopathological and clinical features of sarcoidosis described primarily dermatological manifestations or limited site involvement (e.g., ocular, parotid glands, bones) and the systemic nature of the disorder were not appreciated. Carl Boeck, a Norwegian dermatologist, provided drawings of skin lesions on the hand of a Norwegian sailor; his illustrations were seen by Hutchinson but never published (3). His nephew, Caesar Boeck, described a case of cutaneous lesions in 1899 resembling Hutchinson's report, and

he termed it “multiple benign sarkoid of the skin”; epithelioid cells and giant cells were noted on histologic examination (7). He used the term *sarkoid* (sarcoid → sarcoidosis) because he felt that the lesions resembled sarcoma, but were benign. The term *sarcoidosis* stemmed from this report. Caesar Boeck subsequently published 24 cases of “miliary lupoids,” with involvement of lung, bone, lymph nodes, spleen, nasal mucosa, or conjunctivae, underscoring the systemic nature of the disease (2). Besnier, of France, first described lupus pernio in 1889 (8). The histological features of lupus pernio were delineated 3 yr later (9).

In 1904, Kreibich, a professor of dermatology in Prague, described sarcoid bone cysts in a patient with lupus pernio (10). Sarcoid bone lesions were often attributed to tuberculosis or other specific diseases (11). In 1909, the Danish ophthalmologist, Heerfordt, described uveo-parotid fever in three patients (characterized by a chronic, febrile course, enlarged parotid glands, and uveitis; two had unilateral facial nerve palsy) (12). At the time, the syndrome was ascribed to mumps.

The involvement of internal organs was appreciated by Kuznitsky and Bittorf, who described a 27-yr-old soldier with multiple skin and subcutaneous nodules, histological confirmation of Boeck’s sarcoid, enlarged hilar nodes, and pulmonary infiltrates on chest radiographs (13). Jorgen Schaumann, a Swedish dermatologist, described patients with involvement of multiple organs including lung, bone, tonsils, gums, spleen, and liver (14). In an article submitted in 1919 (ultimately published in 1934), Schaumann suggested that features previously attributed to separate diseases likely represented a systemic disorder, which he termed “lymphogranulomatose benigne” (15). He and many other investigators believed that sarcoidosis likely represented a variant of tuberculosis (3).

An association between sarcoidosis and hypercalcemia or hypercalciuria was first observed in 1939 (16). In 1941, Ansgar Kveim, a Norwegian dermatologist, observed that intradermal inoculation of sarcoid lymph node tissue elicited a papular eruption in 12 of 13 patients with sarcoidosis (17). He concluded that the papules were caused by an unknown agent distinct from tuberculosis. A similar reaction had been noted earlier by investigators in the United States, but was largely ignored (18). Louis Siltzbach developed a revised test using splenic suspension, affirmed its specificity, and organized an international study (19). The test was termed the Kveim–Siltzbach test, recognizing the contributions of these investigators. Sven Löfgren contributed significant new insights to the clinical features of sarcoidosis and delineated a syndrome that often occurs at the onset of sarcoidosis in Caucasians, characterized by erythema nodosum, bilateral hilar lymphadenopathy, fever, and polyarthritis (20). This constellation of features has since been termed Löfgren’s syndrome. Necropsy studies (21) and a large clinical series (22–30) further defined the clinical spectrum and natural history of sarcoidosis.

In 1951, corticosteroids were first used to treat sarcoidosis, with anecdotal successes (31, 32). Numerous uncontrolled studies affirmed favorable responses in a subset of patients (23, 25, 32–37). Interpretation of efficacy was obscured by the high rate of spontaneous remissions noted, particularly in patients with early disease, Löfgren’s syndrome, or bilateral hilar lymphadenopathy on chest radiographs (22, 23, 25–27). In 1958, Wurm and colleagues proposed a radiographic staging system (38), which was adopted by clinical investigators as a prognostic guide (23, 25, 28, 29) and still remains in widespread clinical use. Using this radiographic schema to stratify patients, several prospective, randomized trials were carried out over the next three decades to evaluate the role of corticosteroids in the treatment of pulmonary sarcoidosis (39–46).

While these diverse studies failed to define the role and impact of corticosteroids in modifying the course of sarcoidosis, they did affirm the heterogeneous clinical course and expression of the disorder. By the mid-1970s, the availability of the fiberoptic bronchoscope enabled the diagnosis of sarcoidosis to be confirmed with minimal morbidity and high sensitivity (47–49). In addition, retrieval of immune effector cells via bronchoalveolar lavage (BAL) at the time of bronchoscopy contributed enormously to the understanding of the pathogenesis of sarcoidosis and other inflammatory lung disorders (50–53).

Until the late 1960s, research efforts and the international scope of sarcoidosis investigations were limited. The first International Meeting on Sarcoidosis was convened by Geraint James in London in 1958, but was attended by only 22 participants (by invitation only) (2). After this first interchange, international meetings were held every 3 yr (2). In 1963, the International Committee on Sarcoidosis was formed to develop a wider base for research and epidemiological studies (3). Research investigations and publications escalated dramatically. At the Seventh International Conference in New York in 1975, immunological aberrations associated with sarcoidosis were defined (52) and serum angiotensin-converting enzyme (ACE) was first recognized as a possible biochemical marker of active sarcoidosis (53). By the late 1970s and early 1980s, a plethora of studies dissected the immunological, biochemical, and pathogenetic mechanisms operative in sarcoidosis (54, 55). Compartmentalization of the immune response and involvement of helper T lymphocytes and activated immune effector cells at sites of disease activity were appreciated (50, 51, 54, 55). Ancillary studies to “stage” disease activity were developed (e.g., gallium-67 citrate scanning [54, 56], and bronchoalveolar lavage [50, 51]); however, the clinical value of these procedures remains controversial. In the past three decades, hundreds of scientific studies have evaluated immunologic, pathogenic, or epidemiologic aspects of sarcoidosis. A MEDLINE search of the English language literature cited more than 6,500 publications since 1965 relevant to sarcoidosis. The number of scientific forums devoted to sarcoidosis has also increased. In 1984, the journal *Sarcoidosis* was started in Milan, by Gianfranco Rizzato (2). In 1987, at the Milan World Congress on Sarcoidosis, the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) was formed, replacing the old International Committee (2). These developments provided an infrastructure for fostering collaborative studies of an enigmatic but fascinating disease.

## EPIDEMIOLOGY

Sarcoidosis occurs throughout the world, affecting both sexes and all races and ages. The epidemiology of sarcoidosis remains problematic for several reasons, including (1) lack of a precise, consistent case definition, (2) variable methods of case ascertainment, (3) variability in disease presentation, (4) lack of sensitive and specific diagnostic tests, resulting in underrecognition and misdiagnosis of the disease, and (5) the paucity of systematic epidemiologic investigations of cause (57).

The disease shows a consistent predilection for adults less than 40 yr of age, peaking in those 20 to 29 yr old (58). In Scandinavian countries and Japan, there is a second peak incidence in women more than 50 yr of age (59–61). Most studies suggest a slightly higher disease rate for women. In the only population-based incidence study of sarcoidosis in the United States, rates were 5.9 per 100,000 person-years for men and 6.3 per 100,000 person-years for women (62). On the basis of cumulative incidence estimates, the lifetime risk of sarcoidosis is 0.85% for U.S. whites and 2.4% for U.S. blacks (63). Esti-

mates of the prevalence of sarcoidosis range from fewer than 1 case to 40 cases per 100,000, with an age-adjusted annual incidence rate in the United States of 35.5 per 100,000 for blacks and 10.9 per 100,000 for whites (62–64). Swedes, Danes, and U.S. blacks appear to have the highest prevalence rates in the world (65). Sarcoidosis is rarely reported in Spain, Portugal, India, Saudi Arabia, or South America (65, 66), partly because of the absence of mass screening programs and also because of the presence of other, more commonly recognized granulomatous diseases (tuberculosis, leprosy, fungal infection) that obscure sarcoidosis recognition.

Significant heterogeneity in disease presentation and severity occurs among different ethnic and racial groups. Several studies suggest that sarcoidosis in blacks is more severe, while whites are more likely to present with asymptomatic disease (22, 25, 63, 67–70). Extrathoracic manifestations are more common in certain populations, such as chronic uveitis in U.S. blacks, lupus pernio in Puerto Ricans, and erythema nodosum (EN) in Europeans. Sarcoid-related EN is uncommon in blacks and Japanese (71). Cardiac and ocular sarcoidosis appear to be more common in Japan, where the most frequent cause of death for sarcoid patients is from myocardial involvement (60, 72, 73). Elsewhere, mortality is due most commonly to respiratory failure (67, 74). Overall mortality from sarcoidosis is 1 to 5%.

Intriguing spatial clusters of illness have suggested person-to-person transmission or shared exposure to an environmental agent. A 1987 case-control study of residents of the Isle of Man observed that 40% of sarcoidosis cases reported prior contact with a person known to have the disease, compared with 1 to 2% of the controls (75, 76). Of these contacts, 14 pairs occurred in the same household, only 9 of whom were blood relatives. Nine pairs came in contact with one another at work, 2 were neighbors, and 14 were noncohabiting friends. Other case reports of husband-wife sarcoidosis fuel speculation of shared environmental or infectious exposure. Some studies have observed a seasonal clustering of sarcoidosis cases in winter and early spring (77, 78). Geographic and spatial clusters of disease have also been described, although problems with disease misclassification and study design hamper interpretation. Early observations of increased disease prevalence in the rural southeastern and middle Atlantic United States led to studies that examined potential etiologic factors in meteorology and soil, plants, pine, pollen, proximity to forests, water supply, use of firewood, proximity to lumbering and wood milling, and exposure to farm animals and pets, among others (79–87). Neither animal experiments nor human studies have yet proven these hypotheses.

Several studies have explored occupational risk factors for sarcoidosis. In the 1940s, cases of "sarcoidosis" in women in the fluorescent light industry in Salem, Massachusetts led to the recognition of beryllium exposure as the cause of "Salem sarcoid." Exposure to other metal dusts, fumes, and organic antigens can cause granulomatous lung diseases that are difficult to distinguish clinically from sarcoidosis, emphasizing the importance of a careful occupational and environmental exposure history (88–90). The Isle of Man study (91) observed that 18.8% of sarcoidosis cases were health care workers (mainly nurses), compared with 4.2% of the controls, an observation that has been made in several other studies (92, 93). This finding may reflect a more frequent use of chest radiographs in this population. A report of three sarcoidosis cases clustered among 57 firefighters who apprenticed together suggests a shared environmental exposure (94). A significant association was identified between increased risk for sarcoidosis and ever having served on U.S. Navy aircraft carriers, perhaps, again, only reflecting increased detection rates arising from more

frequent use of routine chest radiographs in this setting (95). Sarcoidosis appears to occur more commonly in nonsmokers than in smokers (96–98). The extent to which environmental and occupational exposures confer increased risk for sarcoidosis awaits further investigation.

There are numerous reports of familial clustering of sarcoidosis. In the United States, familial clusters occur more commonly among blacks (with a rate of at least 19% in affected black families) than whites (with a rate of 5%) (99). In the Republic of Ireland, there is a high national prevalence of sarcoidosis, and a high prevalence (2.4%) also occurs among siblings (100). An increased prevalence of sarcoidosis has been described in the Furano district of northern Japan, with some evidence of familial clustering (101). HLA analyses of affected families suggest that the mode of inheritance of risk for sarcoidosis is likely polygenic, with the most common genotype frequencies being class I HLA-A1 and -B8 and class II HLA-DR3 (102–104). It is likely that genetically predisposed hosts are exposed to antigens that trigger an exaggerated cellular immune response leading to granuloma formation.

## ETIOLOGY AND PATHOGENESIS OF SARCOIDOSIS

Although the cause(s) of sarcoidosis remain unknown, there are three different lines of evidence supporting the idea that sarcoidosis results from exposure of genetically susceptible hosts to specific environmental agents: (1) the aforementioned epidemiological studies (75–93, 105); (2) the inflammatory response in sarcoidosis, which is characterized by large numbers of activated macrophages and T lymphocytes bearing the CD4 helper phenotype (50, 106), with a pattern of cytokine production in the lungs that is most consistent with a Th1-type immune response triggered by an antigen (107–111); and (3) the implications of studies concerning the T cell receptor (TCR) in patients with sarcoidosis (112–118).

### The Role of Genetic Factors

The recognition of race as an important risk factor clearly suggests a genetic predisposition to develop sarcoidosis (63). Nevertheless, the most compelling argument for a genetic mechanism of acquiring this predisposition is that there is occasional familial clustering of cases (85). In general, genetic differences in candidate genes that could predispose an individual to sarcoidosis may reside in loci that influence T cell function, the regulation of antigen recognition and processing, or the regulation of matrix deposition that favors granuloma formation and progressive fibrosis (119). But it is also likely that genetic factors may be important in defining the pattern of disease presentation and progression as well as its overall prognosis. This is illustrated by an investigation of the relationship between sarcoidosis and HLA phenotypes in two different countries in Europe, the Czech Republic and Italy (120). A common observation for both countries was the association of certain manifestations of sarcoidosis with HLA-A1, -B8, and -DR3; whereas a negative association was observed for the phenotypes HLA-B12 and -DR4. Findings that were restricted to only one of the countries were the association of disseminated systemic disease and HLA-B22, among the Italians, and the association of some specific clinical features and HLA-B13, among the non-Italians. In a study using genomic typing of a homogeneous Scandinavian population, a favorable prognosis was related to the DR17 (119) haplotype, whereas DR15 (112) and DR16 (120) indicated a more protracted disease course (121). DR17 (119), which was overrepresented among Scandinavian patients with sarcoidosis, has also been shown by others to be related to a good outcome

(103, 120). In a totally different ethnic population from Japan, restriction fragment length polymorphism showed several restriction fragments of the DR $\beta$  gene only in DRw52-positive patients (122), and these patients were likely to have limited-stage disease without ophthalmic involvement. In contrast, DR5J-positive Japanese patients often get a poorly resolving disease (123). Analyses of the HLA specificity allow ethnic comparisons, and enable studies of the relationship between the HLA phenotype and the clinical outcome.

### The Role of Environmental Agents

As the cause of sarcoidosis has remained unknown, the list of possible causative agents has continuously expanded since pine tree pollen was suggested. Some of the proposed agents are listed in Table 1.

Already in 1969, Mitchell and Rees (124) suggested a transmissible agent in the etiology of sarcoidosis. Ever since, there have been reports supporting such a notion, including the findings of sarcoidosis in recipients of transplants from patients with sarcoidosis (105).

Several infectious organisms have been implicated as potential causes of sarcoidosis, e.g. viruses, *Borrelia burgdorferi*, and *Propionibacterium acnes* (see Table 1). Also, noninfectious environmental agents can elicit a granulomatous response with many features that are similar to sarcoidosis, e.g., beryllium, aluminum, and zirconium (89, 90, 125). Therefore, the accurate diagnosis of sarcoidosis depends on a stringent inquiry concerning potential exposures to both organic and inorganic antigens. Finally, the host itself has been considered a potential source of granuloma-inducing antigens. However, the possibility that sarcoidosis is an autoimmune disorder is now considered less likely.

Because granulomatous inflammation is the histologic hallmark of sarcoidosis, investigators continue to improve and apply modern diagnostic tools in the search for infectious agents such as mycobacteria, which are known to induce a host granulomatous response (126). Although the techniques are now more sophisticated, this principle has been applied for decades. Using various techniques, different groups have been able to detect antibodies to mycobacteria in patient sera in 50–80% of cases (127, 128), whereas fewer of the controls were positive. In the absence of specific patterns, it is difficult to interpret this type of data because patients with sarcoidosis may exhibit a generalized polyclonal synthesis of immunoglobulins resulting in higher titers than normal against a variety of common antigens. Failure to detect anti-mycobacterial antibodies or to culture mycobacteria does not exclude them in the pathogenesis of the disease, but it highlights the importance of seeking the antigen within the affected tissue. The demonstration of tuberculostearic acid (129) and muramyl dipeptide (130), both components of the mycobacterial cell wall, in sar-

coid nodules has been used as indirect evidence for the presence of mycobacteria, and acid-fast L (mycobacteria cell wall-deficient) forms have been grown from the blood of patients with sarcoidosis (131). To date, there is no evidence that sarcoidosis is caused by an infectious agent.

The evidence for an infective etiology, particularly mycobacterial, is becoming more appealing. Unfortunately, even with the advent of molecular tools, such as the highly sensitive polymerase chain reaction, the debate has not been resolved. The advantages and pitfalls of these techniques were elegantly reviewed by Mangiapan and Hance (126). Their overview elucidates the need for caution in interpreting positive as well as negative findings. Failure to demonstrate mycobacteria may depend on insensitive methods, whereas positive findings may be due to contamination. The latter observation demonstrates the need for sufficient control samples to appreciate the frequency with which false-positive results are occurring. Recent findings of mycobacterial DNA or ribosomal RNA in tissue specimens or BAL cells from patients with sarcoidosis must be interpreted in this context (132, 133). Altogether, these data suggest that if mycobacterial DNA is present in most sarcoid tissue, the amount must be relatively small. Alternatively, some of the patients diagnosed as having sarcoidosis may have a disorder initiated by mycobacterial infection (126), while other antigens trigger the disease in other patients.

### The T Cell Receptor

The majority of T lymphocytes use the  $\alpha/\beta$  TCR to recognize antigenic peptides in the context of MHC molecules, and the variable regions of the TCR are constructed through rearrangement of noncontiguous germline gene segments. It has been proposed that analyses of the TCR may reveal the existence of T cells with a restricted TCR usage, suggesting a specific antigen triggering the development of sarcoidosis (105, 113–118). In addition, it has been shown in animal models that T cells with highly restricted TCR V (variable segment) gene usage can mediate an experimental model of autoimmune disease, and that modulation of these cells can affect the disease.

One potential problem with this strategy for identifying an antigen in sarcoidosis is that the duration of the disease may have an influence on the TCR usage, resulting in a more heterogeneous T cell response later on in the disease process. Further, because the onset of disease in sarcoidosis is relatively insidious, it may be difficult to estimate any possible influence of disease duration on the heterogeneity of the T cell response. In addition, the variations in TCR V gene usage that have been reported from different groups may be affected by differences in the ethnic origin of the populations that have been studied. Although many of the findings in this field of research are intriguing, it is still unclear how helpful they will be in eliciting the etiology of sarcoidosis.

### Immunology

The early sarcoid reaction is characterized by the accumulation of activated T cells and macrophages at sites of ongoing inflammation, notably in the lung (50, 106) (Table 2). Studies of sarcoid T lymphocytes in involved areas have shown that, in most patients, cells bear the helper CD4 phenotype; in rare cases the accumulating cells are predominantly CD8<sup>+</sup> lymphocytes (134). These cells spontaneously release interferon  $\gamma$  (IFN- $\gamma$ ) and interleukin 2 (IL-2) and other cytokines (107, 108). Further, sarcoid alveolar macrophages (AMs) behave as versatile secretory cells that release a great variety of cytokines, including tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), IL-12, IL-15, and growth factors (109–111, 135).

The accumulation of immunocompetent cells likely repre-

TABLE 1  
EXAMPLES OF AGENTS SUGGESTED TO BE  
INVOLVED IN THE ETIOLOGY OF SARCOIDOSIS

| Type of Agent  |            |                  |
|--|------------|------------------|
|  | Inorganic* | Organic          |
| Infectious   |            |                  |
| Viruses (herpes, Epstein-Barr, retrovirus, coxsackie B virus, cytomegalovirus) | Aluminum   | Pine tree pollen |
| <i>Borrelia burgdorferi</i>  | Zirconium  | Clay             |
| <i>Propionibacterium acnes</i>   | Talc       |                  |
| <i>Mycobacterium tuberculosis</i> and other mycobacteria                       |            |                  |
| <i>Mycoplasma</i>  |            |                  |

\*Beryllium, which causes berylliosis and not sarcoidosis, is not included.

TABLE 2  
IMMUNOLOGIC ABNORMALITIES OBSERVED IN PATIENTS WITH SARCOIDOSIS

- Intraalveolar and interstitial accumulation of CD4<sup>+</sup> cells with helper-inducer activity and release of IL-2
- Expansion of T cells bearing a restricted TCR repertoire in involved tissues. This pattern is consistent with a TCR oligoclonality. Expansion of the lung  $\gamma/\beta$  TCR cell pool in a subset of patients
- Increased *in situ* production of Th1 cell-derived cytokines (IL-2 and IFN- $\gamma$ ) during granuloma formation
- Increased expression of members of TNF-ligand and TNF-receptor superfamilies by sarcoid T cells
- B cell hyperactivity and spontaneous *in situ* production of immunoglobulins
- Increased spontaneous rate of proliferation of lung immunocompetent cells
- Accumulation of monocyte-macrophages with antigen-presenting cell capacity and expressing increased levels of activation markers (HLA-DR, HLA-DQ, CD71) and adhesion molecules (CD49a, CD54, CD102)
- Increased release of macrophage-derived cytokines (IL-1, IL-6, IL-8, IL-15, TNF- $\alpha$ , IFN- $\gamma$ , GM-CSF) and chemokines (RANTES, MIP-1 $\alpha$ , IL-16). Most of these cytokines favor granuloma formation and lung damage
- Increased production of macrophage-derived fibrogenic cytokines (TGF- $\beta$  and related cytokines, PDGF, and IGF-I), favoring evolution toward fibrosis

*Definition of abbreviations:* GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN- $\gamma$  = interferon  $\gamma$ ; IGF-I = insulin-like growth factor I; IL-2 = interleukin 2; MIP-1 $\alpha$  = macrophage inflammatory protein 1 $\alpha$ ; PDGF = platelet-derived growth factor; RANTES = regulation on activation, normal T cell expression and secretion; TCR = T cell receptor; TGF- $\beta$  = transforming growth factor  $\beta$ ; Th1 = helper T cell type 1; TNF = tumor necrosis factor.

sents the earliest step in the series of events that leads to granuloma formation, with activated CD45RO<sup>+</sup> Th1-type T lymphocytes as the central cell in this phenomenon. From a pathogenic point of view, two mechanisms account for the increased number of cells in tissues involved by the sarcoid inflammatory process: a cellular redistribution from the peripheral blood to the lung and an *in situ* proliferation (136–138). In the first mechanism, chemoattractant cytokines (including IL-8, IL-15, IL-16, and RANTES [regulation on activation, normal T cell expression and secretion]) cooperate to expand the intraalveolar pool of CD4<sup>+</sup> memory cells within the inflamed area (111, 139–141). The second mechanism responsible for the accumulation of CD4<sup>+</sup> helper T cells at sites of granuloma formation is *in situ* IL-2-mediated proliferation. A large number of BAL lymphocytes from patients with sarcoidosis are CD4<sup>+</sup>/HLA-DR<sup>+</sup> T cells spontaneously releasing IL-2 and expressing a functional IL-2 receptor system (111, 142, 143). Various studies indicate that IL-2 acts as a local growth factor for T lymphocytes infiltrating the lung parenchyma and other involved sarcoid tissues (144, 145). T cells isolated from patients with active sarcoidosis also show elevated mRNA and protein levels of IFN- $\gamma$ , proliferation of activated T cells and are involved in the differentiation of Th0 cells into Th1 cells (110). Thus, a Th1-type T cell response (secreting IL-2, IL-12, IFN- $\gamma$ , and TNF- $\beta$ ) is likely to favor the granulomatous response at sites of disease activity.

No studies have shown why lung disease persists in some patients but not other patients. In addition, no studies have shown how persistent disease results in lung injury and fibrosis. However, the immunological pattern of cells in the sarcoid infiltrate suggests that (1) sarcoid granulomas are formed in response to a persistent and likely poorly degradable antigenic stimulus that induces a local Th1-type T cell-mediated immune response with an oligoclonal pattern; in fact, these cells are biased (113–116) in expression of genes for the  $\alpha$ - and  $\beta$ -chain variable region of the T cell receptor (TCR); and (2) as a consequence of their chronic stimulation, macrophages release mediators of inflammation, locally, leading to accumulation of Th1 cells at sites of ongoing inflammation and contributing to the development of the granuloma structure. Experimental data from the *Schistosoma mansoni* model suggest one mechanism by which fibrosis may develop with persistent disease, i.e., there is a shift in the cytokine pattern from a Th1 to a Th2 phenotype with secretion of IL-4, IL-5, IL-6, IL-9, and IL-10. In the model, this results in a fibroproliferative response with substantial extracellular matrix deposition, and subsequent evolution toward pulmonary fibrosis (146). Alter-

natively, in sarcoidosis, a persistent Th1 response may be associated with fibrosis. Studies of the Th1/Th2 secretory pattern in humans during the various phases of the sarcoid inflammatory process are needed to elucidate the regulatory immune mechanisms that govern matrix modifications in this disease.

In addition to understanding the pathogenesis of sarcoidosis, another goal of the immunological studies includes the identification of discrete markers (surface antigens, cytokine production, etc.) that may aid in the management of patients, not only in terms of prognosis, but also to define the different phases of the disease.

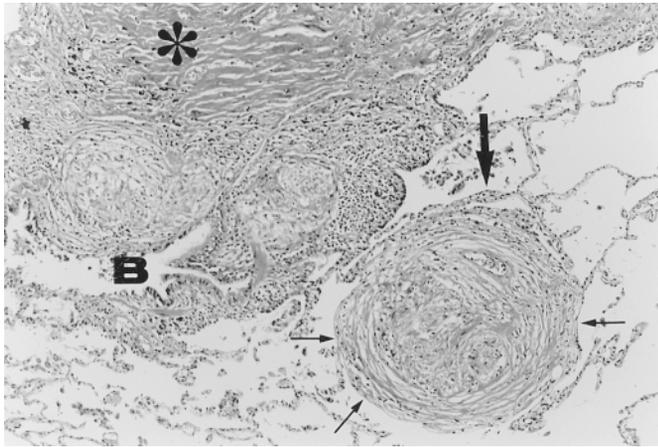
## PATHOLOGY

### Sarcoid Granulomas

*Morphology and the components.* The characteristic lesion of sarcoidosis is a discrete, compact, noncaseating epithelioid cell granuloma. The epithelioid cell granulomas consist of highly differentiated mononuclear phagocytes (epithelioid cells and giant cells) and lymphocytes. Giant cells may contain cytoplasmic inclusions such as asteroid bodies and Schaumann bodies (21, 147–150). The central portion of the granuloma consists of predominantly CD4<sup>+</sup> lymphocytes, whereas CD8<sup>+</sup> lymphocytes are present in the peripheral zone (148, 150). Sarcoid granulomas may develop fibrotic changes that usually begin at the periphery and travel centrally, ending with complete fibrosis and/or hyalinization (Figure 1). Granulomas may occasionally exhibit focal coagulative necrosis (148) (Figure 2). It has been suggested that necrotizing sarcoid granulomatosis (NSG) may be a variant of sarcoidosis (150, 151). On electron microscopy, well developed epithelioid cells show numerous cytoplasmic projections with frequent interdigitations. The morphology suggests a secretory function (148, 149).

*Location and distribution.* Lymph nodes (especially intrathoracic), lungs, liver, spleen, and skin are common sites of sarcoid granulomas, which are of a similar nature when found in any organ (21, 72, 148–150, 152). In the lung, about 75% of the granulomas are located close to or within the connective tissue sheath of bronchioles and subpleural or peribronchovascular spaces (a lymphangitic distribution) (147, 150, 153). Vascular involvement is observed in more than half of the patients with open lung biopsy or autopsy studies (147, 148, 150, 154).

*Course of granulomas.* Sarcoid granulomas either resolve or leave behind fibrotic changes. End-stage sarcoidosis causes parenchymal fibrosis and honey-combing of the lung. Factors that influence the development of fibrosis are not well understood (148, 150).



**Figure 1.** Pulmonary sarcoidosis usually shows nonnecrotizing epithelioid cell granulomas predominantly in the interstitium, such as in the subepithelial layer of a bronchiole (B), the peribronchiolar connective tissues, and the alveolar interstitium. Sarcoid granulomas tend to undergo perigranulomatous fibrotic changes (thin arrow) and are sometimes replaced by hyalinous changes (asterisk) in the chronic stage. Alveolar septa away from the granulomas are essentially normal, except for perigranulomatous alveolar septa, which may show interstitial infiltration mainly of lymphocytes (thick arrow). (Surgical lung biopsy; H&E stain; original magnification,  $\times 25$ .)

#### Histologic Diagnosis of Sarcoidosis

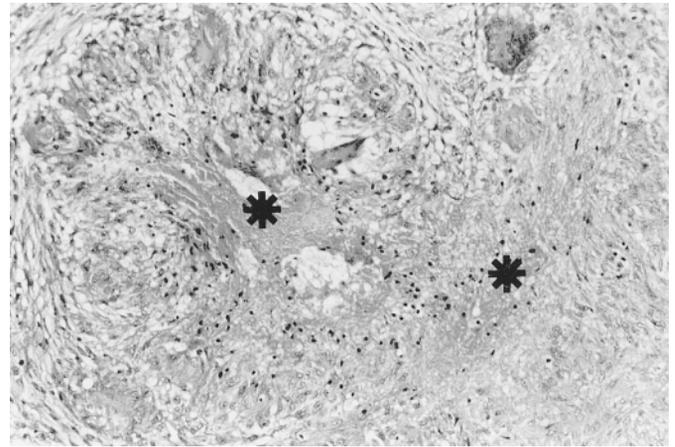
Because of the lack of knowledge about the etiology of sarcoidosis, diagnosis is established when clinicoradiologic findings are supported by histologic evidence of granulomas. Because important differential diagnoses are infectious diseases, the need for microbiologic studies and cultures continues, especially when the patient has fever or when there are necrotic lesions in the biopsy specimens. Special stains for acid-fast bacilli and fungi are justified for the diagnosis, especially when there are atypical features for sarcoidosis such as necrosis or an air-space predominance of granulomas (147–150) (Table 3).

**Diagnosis of pulmonary sarcoidosis.** The morphologic diagnosis of pulmonary sarcoidosis relies on three main findings: the presence of tight, well-formed granulomas and a rim of lymphocytes and fibroblasts in the outer margin of granulomas; perilymphatic interstitial distribution of granulomas (which allows transbronchial biopsies to be used as sensitive diagnostic tools); and exclusion of an alternative cause (147, 155, 156).

**Diagnosis of extrapulmonary sarcoidosis.** The differential diagnosis of sarcoid granulomas varies according to the sites of biopsy, such as lymph node, skin, liver, bone marrow, and spleen (157–166).

**Tumor-related sarcoid reactions.** Regional lymph nodes of carcinomas show noncaseating epithelioid cell granulomas (sarcoid reactions) with an average frequency of 4.4% (167, 168). Biopsy specimens of liver and spleen obtained at laparotomy for the staging of Hodgkin's disease and non-Hodgkin's lymphomas show epithelioid cell granulomas with an average frequency of 13.8 and 7.3%, respectively (167, 168). Three to 7% of patients with carcinoma may show granulomas in the primary tumors (167), as in seminoma and dysgerminoma (169, 170).

**Granulomatous lesions of unknown significance (the GLUS syndrome).** Fifteen to 20% of biopsy samples with granulomatous lesions have an undetermined etiology. These patients have a disease process that has been named the GLUS (granu-



**Figure 2.** A small number of sarcoid granulomas may undergo a mild degree of coagulative necrosis (arrow) in the central portion of granulomas. (Surgical lung biopsy; H&E stain; original magnification,  $\times 50$ .)

lomatous lesions of unknown significance) syndrome (171). Immunohistologically, GLUS syndrome granulomas are B cell positive, as are tumor-related sarcoid reactions and toxoplasmosis. However, granulomas in sarcoidosis and mycobacterial infection are B cell negative (172).

#### CLINICAL PRESENTATION AND ORGAN INVOLVEMENT

Sarcoidosis is a multiorgan disorder. Because of diverse manifestations, patients with sarcoidosis may present to clinicians with different specialties. The clinical picture of the disease depends on ethnicity, duration of the illness, site and extent of organ involvement, and activity of the granulomatous process (60, 173–175).

##### Nonspecific Constitutional Manifestations

Nonspecific constitutional symptoms such as fever, fatigue, malaise, and weight loss may occur in about one-third of patients with sarcoidosis. Fever is generally low grade but temperature elevations of 39 to 40° C may be seen. Weight loss is usually limited to 2 to 6 kg during the 10 to 12 wk before presentation. Fatigue, when present, can be quite disabling. Occasionally, night sweats may occur. The constitutional symptoms are more frequent in African-Americans and Asian Indians than in white individuals and in Asian patients. Sarcoidosis is an important and frequently overlooked cause of fever of unknown origin (FUO) (176). The GLUS syndrome has some of the features of sarcoidosis, including fever and hepatosplenomegaly (171).

##### Findings Related to Specific Organ Involvement

**Lungs.** The lungs are affected in more than 90% of patients with sarcoidosis. Dyspnea, dry cough, and chest pain occur in one-third to one-half of all patients. Although retrosternal in location, chest pain is usually no more than a vague tightness of the thorax, but can occasionally be severe and indistinguishable from cardiac pain (177). Hemoptysis is rare. Clubbing rarely occurs and lung crackles are present in fewer than 20% of patients.

There are five roentgenographic stages of intrathoracic changes (Table 4). Stage 0 describes no visible intrathoracic findings. Stage I is bilateral hilar lymphadenopathy, which

TABLE 3  
MAJOR PATHOLOGIC DIFFERENTIAL DIAGNOSIS OF SARCOIDOSIS  
AT BIOPSY AND SURGICAL PATHOLOGY

| Lung   | Lymph Node   | Skin   | Liver   | Bone Marrow   | Other Biopsy Sites  |
|--|--|--|---|---|---|
| <ul style="list-style-type: none"> <li>• Tuberculosis</li> <li>• Atypical mycobacteriosis</li> <li>• Cryptococcosis</li> <li>• Aspergillosis</li> <li>• Histoplasmosis</li> <li>• Coccidioidomycosis</li> <li>• Blastomycosis</li> <li>• <i>Pneumocystis carinii</i></li> <li>• <i>Mycoplasma</i>, etc.</li> <li>• Hypersensitivity pneumonitis</li> <li>• Pneumoconiosis:               <ul style="list-style-type: none"> <li>beryllium (chronic beryllium disease), titanium, aluminum</li> </ul> </li> <li>• Drug reactions</li> <li>• Aspiration of foreign materials</li> <li>• Wegener's granulomatosis (sarcoid-type granulomas are rare)</li> <li>• Chronic interstitial pneumonia, such as usual and lymphocytic interstitial pneumonia</li> <li>• Necrotizing sarcoid granulomatosis (NSG)</li> </ul> | <ul style="list-style-type: none"> <li>• Tuberculosis</li> <li>• Atypical mycobacteriosis</li> <li>• Brucellosis</li> <li>• Toxoplasmosis</li> <li>• Granulomatous histiocytic necrotizing lymphadenitis (Kikuchi's disease)</li> <li>• Cat-scratch disease</li> <li>• Sarcoid reaction in regional lymph nodes to carcinoma</li> <li>• Hodgkin's disease</li> <li>• Non-Hodgkin's lymphomas</li> <li>• Granulomatous lesions of unknown significance (the GLUS syndrome)</li> </ul> | <ul style="list-style-type: none"> <li>• Tuberculosis</li> <li>• Atypical mycobacteriosis</li> <li>• Fungal infection</li> <li>• Reaction to foreign bodies: beryllium zirconium, tattooing, paraffin, etc.</li> <li>• Rheumatoid nodules</li> </ul> | <ul style="list-style-type: none"> <li>• Tuberculosis</li> <li>• Brucellosis</li> <li>• Schistosomiasis</li> <li>• Primary biliary cirrhosis</li> <li>• Crohn's disease</li> <li>• Hodgkin's disease</li> <li>• Non-Hodgkin's lymphomas</li> <li>• GLUS syndrome</li> </ul> | <ul style="list-style-type: none"> <li>• Tuberculosis</li> <li>• Histoplasmosis</li> <li>• Infectious mononucleosis</li> <li>• Cytomegalovirus</li> <li>• Hodgkin's Disease</li> <li>• Non-Hodgkin's lymphomas</li> <li>• Drugs</li> <li>• GLUS syndrome</li> </ul> | <ul style="list-style-type: none"> <li>• Tuberculosis</li> <li>• Brucellosis</li> <li>• Other infections</li> <li>• Crohn's disease</li> <li>• Giant cell myocarditis</li> <li>• GLUS syndrome</li> </ul> |

may be accompanied by paratracheal adenopathy. Although lung fields are clear of infiltrates, parenchymal granulomas are often found in lung tissue biopsies. Stage II is bilateral hilar adenopathy accompanied by parenchymal infiltration. Stage III is parenchymal infiltration without hilar adenopathy. Stage IV consists of advanced fibrosis with evidence of honey-combing, hilar retraction, bullae, cysts, and emphysema.

Although parenchymal lung disease is more common, the airways (larynx, trachea, and bronchi) may also be involved, leading to airway obstruction and bronchiectasis. Airway hyperactivity has been reported in up to 20% of patients (178). Other uncommon manifestations include pleural effusion, chylothorax, pneumothorax, pleural thickening and calcification, lymph node calcification, and cavity formation (179).

**Lymphoid system.** About one-third of patients with sarcoidosis have palpable peripheral lymph glands. The most frequently involved glands are cervical, axillary, epitrochlear, and inguinal. In the neck, the posterior triangle nodes are more commonly affected than the nodes in the anterior triangle. Enlarged glands are discrete, movable, and nontender. They do not ulcerate and do not form draining sinuses. Splenic enlargement is usually minimal and silent, but it may cause pressure symptoms, anemia, leukopenia, and thrombocytopenia (180).

**Heart.** Clinical evidence of myocardial involvement is present in about 5% of patients with sarcoidosis (60). However, the autopsy incidence may be higher. The course of the disease is variable and ranges from benign arrhythmias or high-degree heart block to sudden death. An electrocardiogram (ECG) may be negative, while 24-h Holter monitoring reveals ventricular tachycardia, heart block, or ventricular ectopic beats. A Doppler echocardiogram can detect diastolic dysfunction but thallium-201 imaging is superior for showing segmental contraction abnormalities (181). Myocardial imaging with thallium-201 may also reveal segmental defects that correspond either to a granulomatous disease or a fibrous scar. The clinical significance of abnormal thallium scans in patients with asymptomatic sarcoidosis is not known. Long-

term studies suggest that the risk of cardiac dysfunction or sudden death in these patients is low (182). Coronary angiography is needed to exclude the possibility of coronary artery disease if the thallium-201 imaging suggests cardiac involvement. Endomyocardial biopsy showing granulomas does confirm the diagnosis of cardiac sarcoidosis, but the diagnostic yield from the procedure is low because of the inhomogeneous distribution of the granulomatous process. Thus, sarcoid patients with cardiac dysfunction, ECG abnormalities, or thallium-201 imaging defects should be presumed to have cardiac sarcoidosis even when endomyocardial biopsy specimens show no granuloma.

**Liver.** Although granulomas are found in as many as 50–80% of liver biopsy specimens, the liver is palpable in less than 20% of patients (22, 183–185). Hepatic involvement rarely causes portal hypertension, hepatic failure, or increased mortality related to liver dysfunction. Abnormalities of liver function tests are common (175, 186). Asymptomatic patients with only hepatic sarcoidosis and mild liver function abnormalities do not require treatment. Corticosteroids may improve severe liver dysfunction (183, 187, 188).

**Skin.** Cutaneous involvement occurs in about 25% of all patients (189). Two clinically important and easily recogniz-

TABLE 4  
CHEST RADIOGRAPHIC STAGING

| Stage* | Finding                               |
|--------|---------------------------------------|
| 0      | Normal chest radiograph               |
| I      | Bilateral hilar lymphadenopathy (BHL) |
| II     | BHL plus pulmonary infiltrations      |
| III    | Pulmonary infiltrations (without BHL) |
| IV     | Pulmonary fibrosis                    |

\* Classification is based on the posteroanterior chest radiograph only. Sometimes a CT scan or <sup>67</sup>Ga lung scan gives information suggesting a different stage. The staging of these patients is presently an open question, but at the moment it is not necessary to change the staging criteria because a CT or <sup>67</sup>Ga scan is indicated in a limited number of patients.

able skin lesions are erythema nodosum and lupus pernio. Erythema nodosum, the hallmark of acute sarcoidosis, is commonly seen in European, Puerto Rican, and Mexican patients, particularly in women of childbearing age. It is rare in Japanese and African-American patients. The lesion consists of raised, red, tender bumps or nodules on the anterior aspects of the legs. Granulomas are not characteristic of these biopsy specimens. Adjacent joints are usually swollen and painful. Erythema nodosum usually remits within 6 to 8 wk. Recurrent episodes of erythema nodosum are rare (190). Löfgren's syndrome consists of fever, bilateral hilar adenopathy, erythema nodosum, and arthralgia (20). Lupus pernio represents chronic sarcoidosis and consists of indurated plaques associated with discoloration of the nose, cheeks, lips, and ears. The lesion is more common in African-American women. The nasal mucosa is frequently involved. Lupus pernio is often associated with bone cysts and pulmonary fibrosis. The course of the disease with lupus pernio is prolonged; spontaneous remissions are rare. Other skin lesions in chronic sarcoidosis include plaques, maculopapular eruptions, subcutaneous nodules, changes in old scars, alopecia, and hypo- and hyperpigmented areas. As a rule, chronic sarcoidosis skin lesions do not cause pain or itch, nor do they ulcerate.

**Ocular lesions.** Ocular involvement may occur in 11 to 83% of patients with sarcoidosis (175). Any part of the eye or orbit may be affected; uveitis is the most common of all sarcoid eye lesions. Acute anterior uveitis clears spontaneously or after local therapy with corticosteroids (eye drops); chronic uveitis may lead to adhesions between the iris and the lens, causing glaucoma, cataract, and blindness. Fluorescence angiography is a sensitive test of microvascular involvement and should be considered if posterior uveitis is suspected (191). Other eye lesions include conjunctival follicles, lacrimal gland enlargement, keratoconjunctivitis sicca, dacryocystitis, and retinal vasculitis.

**Neurosarcoidosis.** Clinically recognizable involvement of the nervous system occurs in less than 10% of patients with sarcoidosis (192, 193). The disease has a predilection for the base of the brain. Cranial nerve involvement, particularly facial palsies and hypothalamic and pituitary lesions, are common. These lesions tend to occur early and respond favorably to treatment (194). Space-occupying masses, peripheral neuropathy, and neuromuscular involvement occur later and portend a chronic course. Serum angiotensin-converting enzyme levels are of limited value. Both computed tomography (CT) and magnetic resonance imaging (MRI) have been used to support the diagnosis of neurosarcoidosis. Gadolinium-enhanced MRI is the preferred test for evaluating brain parenchyma, meninges, and spinal cord. MRI manifestations are, however, nonspecific (195). Whenever possible, an effort should be made to secure histological confirmation. Cerebrospinal fluid (CSF) reveals lymphocytosis and elevated proteins in about 80% of the patients. Other CSF features of neurosarcoidosis include elevated ACE (about half of patients), lysozyme, and  $\beta_2$ -macroglobulins, and an increased CD4/CD8 ratio (175). CSF analysis is also important in excluding tuberculosis and fungal infections.

**Musculoskeletal system.** While joint pains occur in 25 to 39% of patients with sarcoidosis, deforming arthritis is rare (179). The joints most commonly affected are knees, ankles, elbows, wrists, and small joints of the hands and feet. The articular involvement may be acute and transient or chronic and persistent. Symptomatic muscle involvement is rare. Chronic myopathy occurs more commonly in women and may be the sole presentation of the disease. Corticosteroid-induced myopathy should be excluded. Proximal muscle weakness, a com-

mon clinical manifestation, must be distinguished from corticosteroid-induced myopathy. Appropriate synovial or muscle biopsy specimens may reveal noncaseating granulomas (196). Bone cysts occur only in association with chronic skin lesions (189).

**Gastrointestinal tract.** The incidence of gastrointestinal (GI) tract involvement is less than 1.0%. The stomach is the most commonly involved part of the GI tract. Esophagus, appendix, rectum, and pancreas are involved less frequently. Sarcoidosis may mimic Crohn's disease, tuberculosis, fungal infection, or pancreatic neoplasm (197, 198).

**Hematological abnormalities.** Hematologic abnormalities, particularly those involving the red and white cell lines, are frequent but not diagnostic. Anemia (hemoglobin of less than 11 g/dL) occurs in 4 to 20% of patients with sarcoidosis. Hemolytic anemia is rare. Leukopenia occurs in as many as 40% of patients but is rarely severe (186). In the absence of splenomegaly, leukopenia may reflect bone marrow involvement, however, the most common mechanism is a redistribution of blood T cells to sites of disease (22, 51, 199). Leukemoid reaction, eosinophilia, and thrombocytopenia are rare.

**Parotid glands.** The combination of fever, parotid enlargement, facial palsy, and anterior uveitis is called Heerfordt's syndrome. Unilateral or bilateral parotitis with swollen, painful enlargement of the gland occurs in less than 6% of patients. In about 40% of the patients, parotid enlargement is self-limiting.

**Endocrine manifestation.** Hypercalcemia occurs in about 2–10% of patients with sarcoidosis; hypercalciuria is about three times more frequent (200, 201). These abnormalities are due to dysregulated production of 1,25-(OH)<sub>2</sub>-D<sub>3</sub> (calcitriol) by activated macrophages and granulomas (200, 201). Undetected, persistent hypercalcemia and hypercalciuria can cause nephrocalcinosis, renal stones, and renal failure (202). Diabetes insipidus may occur owing to pituitary or hypothalamic involvement. Hypothyroidism, hyperthyroidism, hypothermia, adrenal suppression, and anterior pituitary involvement are rare (203).

**Reproductive organs.** Asymptomatic granulomas may occur in any part of the female reproductive system, including the breast. The uterus is the organ most commonly affected. The male reproductive tract is rarely affected. However, because of concerns about possible testicular malignancy, one-third of male patients with this type of involvement may receive unnecessary orchiectomies (204).

**The kidneys.** Rarely, the granulomatous process may produce interstitial nephritis by directly involving the kidneys. More commonly, renal failure is related to hypercalcemia and nephrocalcinosis. Renal sarcoidosis may mimic a tumor (205, 206).

### Special Situations

**Sarcoidosis in children.** Kendig reviewed 104 cases in which the patients were 15 yr of age or younger and found that the distribution of organs involved in children was similar to that in adults (207). The diagnosis of sarcoidosis should be considered in a child of any age who experiences a skin rash, uveitis, lymphadenopathy, and pulmonary involvement. The prognosis for children is more favorable than for adults (208).

**Sarcoidosis in pregnancy.** Sarcoidosis does not affect pregnancy adversely, but the disease may worsen after parturition; therefore, a chest roentgenogram should be obtained within 6 mo of delivery. The incidence of spontaneous abortion, miscarriage, and congenital fetal abnormalities for patients with sarcoidosis is no different from that found in mothers without sarcoidosis (184, 209).

*Sarcoidosis in the elderly.* Although many patients with sarcoidosis live with the disease through their later years, only a few patients develop it after the age of 65 yr. In managing the disease in the aged, it is important to appreciate that a malignant disease of the lung, stomach, intestine, and even uterus may give rise to a granulomatous reaction in the draining lymph nodes. This local sarcoid reaction must be distinguished from multisystem sarcoidosis (210, 211).

## DIAGNOSTIC APPROACHES

The diagnosis of sarcoidosis needs a compatible clinical picture, histologic demonstration of noncaseating granulomas, and exclusion of other diseases capable of producing a similar histologic or clinical picture. The presence of noncaseating granulomas in a single organ such as skin does not establish a diagnosis of sarcoidosis. The diagnostic work-up for patients with sarcoidosis should attempt to accomplish four goals: (1) provide histologic confirmation of the disease, (2) assess the extent and severity of organ involvement, (3) assess whether the disease is stable or is likely to progress, and (4) determine if therapy will benefit the patient.

### Biopsy

In the presence of a compatible clinical picture, the first step is to choose the site for a proper biopsy. Transbronchial lung biopsy (TLB) is the recommended procedure in most cases. Its diagnostic yield depends largely on the experience of the operator, ranging from 40% to more than 90% when four to five lung biopsies are carried out (212). The risk of the procedure in experienced hands is low.

A careful examination of the patient may disclose other possible sites for biopsy, such as skin, lip, or superficial lymph nodes. A granulomatous scar (a fresh granulomatous reaction on the site of an old scar) may be a very useful site for biopsy. It is not useful to biopsy erythema nodosum lesions because they will not show granulomas. Liver biopsy is rarely indicated, even if there is biochemical or clinical evidence of liver involvement. The use of scalene biopsy also is no longer recommended. In some instances, <sup>67</sup>Ga scans may indicate a site for biopsy (213, 214).

When bronchial or transbronchial biopsies are nondiagnostic, and no other accessible sites for biopsy are identified, surgical lung biopsy may be indicated, if there are readily identified abnormalities on the chest roentgenogram or lung CT scan. The finding of mediastinal adenopathy on the conventional CT scan should prompt biopsy by mediastinoscopy before videoassisted thoracoscopic lung biopsy (VTLB) or open lung biopsy (215, 216). The diagnostic yield of all of these procedures is reported to be more than 90%. The complication rate and hospital stay of patients undergoing mediastinoscopy are significantly lower than for patients undergoing surgical lung biopsy. VTLB has the advantage of permitting biopsy of both lung and lymph nodes.

### The Patient without Histology

Some patients refuse biopsy and in others the pulmonary impairment is too severe for a lung biopsy. Clinical and/or radiological features alone may be diagnostic for patients with Stage I (reliability of 98%) or Stage II (89%) disease, but are less accurate for patients with Stage III (52%) or Stage 0 (23%) disease (217). A patient who presents with a classic Löfgren's syndrome of fever, erythema nodosum, arthralgias, and bilateral hilar lymphadenopathy may not require biopsy proof if resolution of disease is rapid and spontaneous. In some instances, bronchoalveolar lavage (BAL) and studies on

lymphocyte subpopulations are helpful. According to Costabel, a CD4/CD8 ratio greater than 3.5 has a sensitivity of 53%, a specificity of 94%, a positive predictive value of 76%, and a negative predictive value of 85% (218). In other words, a CD4/CD8 ratio > 3.5 provides a diagnosis of sarcoidosis with a specificity of 94% even if the TLB has not been diagnostic. Similar results have been obtained by Winterbauer and co-workers (219). Bronchial mucosal biopsy may be performed during the same procedure; it is positive for noncaseating granulomata in 41–57% of patients with sarcoidosis (220–222). The appearance of a Panda pattern combined with a Lambda pattern on a total body <sup>67</sup>Ga scan may support the diagnosis of sarcoidosis and obviate the need for invasive diagnostic procedures (223). However, these findings are present in only a small number of patients (213). In selected centers, the Kveim-Siltzbach test may be available and helpful for diagnosis (224). It may still be indicated when the chest X-ray and CT scan are normal in cases of uveitis of unknown origin, hypercalciuria, hepatic granulomatous disease, suspected neurosarcoidosis, or recurrent erythema nodosum (225). Transmission of infective agents is possible by this procedure, if the antigen is poorly prepared or controlled. A mildly elevated angiotensin-converting enzyme is never diagnostic because elevations may be seen in many diseases (226). Elevations greater than two times the upper limits of normal are much less common in other diseases but, unfortunately, can occasionally be seen in other granulomatous diseases, such as tuberculosis, Gaucher's disease, and hyperthyroidism.

### Further Investigations

Once the diagnosis is established by history and clinical and radiological features, an additional work-up is recommended for all patients (Table 5). Pulmonary function tests are important to measure initial lung impairment and to provide a baseline to assess improvement or deterioration of the lung disease. Therefore, like the history, physical examination, and chest roentgenograph, they are indicated for all patients. Aberrations in lung function tests are found in only 20% of patients with Stage I disease, compared with 40–70% of patients with Stage II, III, or IV disease. The most common parameters indicating functional impairment are the diffusion capacity and the vital capacity (227–229). Both restrictive and obstructive pulmonary function abnormalities may be found. Other tests that should be routinely performed on all patients are indicated in Table 5.

For some patients, lung CT scans are indicated. The usual indications for lung CT scans are as follows: (1) atypical clinical and/or chest radiograph findings, (2) detection of compli-

TABLE 5  
RECOMMENDED INITIAL EVALUATION OF  
PATIENTS WITH SARCOIDOSIS

|     |   |
|-----|---|
| 1.  | History (occupational and environmental exposure, symptoms)   |
| 2.  | Physical examination  |
| 3.  | Posteroanterior chest radiography   |
| 4.  | Pulmonary function tests: spirometry and $D_{LCO}$  |
| 5.  | Peripheral blood counts: White blood cells, red blood cells, platelets  |
| 6.  | Serum chemistries: calcium, liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), creatinine, BUN |
| 7.  | Urine analysis  |
| 8.  | ECG   |
| 9.  | Routine ophthalmologic examination  |
| 10. | Tuberculin skin test  |

Definition of abbreviations: BUN = blood urea nitrogen;  $D_{LCO}$  = diffusing capacity of the lung for CO; ECG = electrocardiogram.

cations of the lung disease, such as bronchiectasis, aspergilloma, pulmonary fibrosis, traction emphysema, or a superimposed infection or malignancy, and (3) a normal chest radiograph but a clinical suspicion of the disease. In most patients, the classic findings of the disease on lung CT scans are as follows (230): (1) widespread small nodules with a bronchovascular and subpleural distribution, (2) thickened interlobular septae, (3) architectural distortion, and (4) conglomerate masses. Less common findings are: (1) honeycombing, (2) cyst formation and bronchiectasis, and (3) alveolar consolidation.

Extrapulmonary sarcoidosis should be studied with appropriate tests when needed, according to the suggestions given in Table 6. Examples might include Holter monitoring, echocardiography and thallium scans to detect myocardial involvement, and MRI or head CT scans to detect CNS involvement.

Clinical activity is assessed on the basis of onset, worsening, or persistence of symptoms or signs directly related to sarcoidosis. A long list of markers of activity has been suggested as potential diagnostic aids or indices of "activation" (231, 232). Some of these markers are consistent with the ability of the disease to progress in one organ, but they often do not detect progression in other organs. Table 6 describes some commonly used markers.

## NATURAL HISTORY

The clinical expression, natural history, and prognosis of sarcoidosis are highly variable, with a tendency to wax and wane, either spontaneously, or in response to therapy (22, 179, 233). Spontaneous remissions occur in nearly two-thirds of patients, but the course is chronic or progressive in 10 to 30% (23, 25, 28–30, 62, 179, 234). Serious extrapulmonary involvement (e.g., cardiac, central nervous system, hepatic) occurs in 4 to 7% of patients with sarcoidosis *at presentation*; the incidence is higher as the disease evolves (22, 23, 25, 28, 175, 229, 235). Clarification of the *natural* history of the disease is confounded by the influence of corticosteroid therapy, which is usually offered to patients exhibiting significant or progressive pulmonary symptoms or extrapulmonary involvement (229,

233, 236). In most large published series, one-third to one-half of patients with sarcoidosis were treated with corticosteroids (22, 23, 25, 28, 45, 229, 235). Most patients stabilize or improve with treatment, but relapse occurs in 16 to 74% of patients as the amount of drug is tapered or discontinued (22, 23, 25, 28, 36, 74, 229, 235, 237). Assessment of morbidity or death attributable to sarcoidosis is difficult. However, at least 10 to 20% of patients with sarcoidosis sustain permanent sequelae (pulmonary or extrapulmonary).

Fatalities occur in 1 to 5% of patients, typically owing to progressive respiratory insufficiency or central nervous system or myocardial involvement (29, 30, 36, 42, 74, 152, 233, 235, 238–241). Differing mortality rates reflect differences in severity of disease, referral bias, and diverse genetic and epidemiological factors. Studies in nonreferral settings in the United States and Scandinavia comprise predominantly Caucasians, many of whom are asymptomatic (29, 30, 62, 234). In this context, mortality rates are less than 1% and serious morbidity is uncommon. In contrast, published series from referral centers include a disproportionate number of patients with severe or progressive disease, with resultant higher rates of morbidity and mortality (22, 23, 25, 28, 36, 237, 242). Clinical manifestations and attributable causes of death vary in differing geographic regions (which may reflect genetic or environmental differences). In Japan, 77% of deaths ascribed to sarcoidosis were due to cardiac involvement (60). In the United States, most deaths are due to pulmonary complications; 13 to 50% of deaths are attributed to myocardial involvement (74, 152, 241).

## Influence of Ethnicity and Genetic Factors on Prognosis

The clinical course and prognosis of sarcoidosis is influenced by ethnic and genetic factors (237, 242, 243). African-American patients appear to have a higher rate of extrapulmonary involvement, chronic uveitis, lupus pernio, cystic bone lesions, chronic progressive disease, worse long-term prognosis, and higher rate of relapses (28, 36, 237, 242, 244). Several studies have suggested that human leukocyte antigen (HLA) markers reflect prognosis and site(s) of organ involvement (102, 104,

TABLE 6  
MARKERS OF ACTIVITY

| Clinical   | Biochemical or Instrumental                             | Imaging   |
|--|---|---|
| Fever  | Serum ACE   | Progressive changes on chest radiographs or lung CT scans |
| Uveitis  | Hypercalcemia   | Ground-glass attenuation on HRCT scan                     |
| Erythema nodosum                                     |   | Positive <sup>67</sup> Ga uptake                          |
| Lupus pernio   | Worsening lung function                                 | Fluorescein angiography of the eyes                       |
| Changing scar  | BAL fluid: lymphocyte alveolitis and high CD4/CD8 ratio | Brain MRI or CT scan                                      |
| Polyarthralgia                                       |   | Bone cysts  |
| Splenomegaly   |   |   |
| Lymphadenopathy                                      | Abnormal ECG, echocardiogram, or thallium scan          |   |
| Salivary and lacrimal gland enlargement              | Abnormal liver function tests                           |   |
| Myocardial disease                                   |   |   |
| Facial palsy or other neurological symptoms or signs |   |   |
| Progressive respiratory symptoms (dyspnea, cough)    |   |   |

Definition of abbreviations: ACE = angiotensin-converting enzyme; CT = computed tomography; HRCT = high-resolution CT; MRI = magnetic resonance imaging.

120, 121, 123, 243, 245–248). These studies are not definitive and additional studies are required to elucidate the role of HLA markers in the prognosis and clinical expression of sarcoidosis.

#### Clinical Factors of Prognostic Significance

Erythema nodosum and acute inflammatory manifestations (e.g., fever, polyarthritis) are more common among certain racial groups and HLA types and portend an excellent prognosis (25, 120, 121, 190, 237, 244, 245). It is associated with a high rate (> 80%) of spontaneous remissions (20, 26, 78, 121, 196, 249–251). Löfgren's syndrome occurs in 20 to 30% of white individuals (25, 78, 121, 250) and 4% of Asians with sarcoidosis (25). Erythema nodosum and fever usually remit spontaneously within 6 wk; resolution of lymphadenopathy may be delayed for 1 yr or more (179, 190). Corticosteroid therapy is rarely necessary for patients with Löfgren's syndrome.

Several clinical features have been associated with a chronic or progressive course. Adverse prognostic factors include lupus pernio (28, 190), chronic uveitis (28, 190, 202), age at onset greater than 40 yr (29), chronic hypercalcemia (28, 29, 252), nephrocalcinosis (28, 202, 253), black race (25, 28, 237, 242), progressive pulmonary sarcoidosis (26, 78, 184, 196, 249, 254), nasal mucosal involvement (28), cystic bone lesions (28, 255, 256), neurosarcoidosis (193, 257, 258), myocardial involvement (175), and chronic respiratory insufficiency (241).

#### Influence of Chest Radiographic Stage

Numerous studies have affirmed the utility of chest radiographic "stage" as a prognostic guide (23, 25, 28–30, 62, 233, 234). In Stage I disease, chest radiographs usually improve spontaneously or stabilize. Persistence of hilar adenopathy does not imply ongoing active disease or the need for therapy; severe morbidity or late sequelae are rare with Stage I sarcoidosis. In contrast, morbidity and mortality are appreciable among patients with chronic parenchymal infiltrates (radiographic Stages II, III, and IV). Spontaneous remissions occur in 55 to 90% of patients with Stage I disease; in 40 to 70% of patients with Stage II disease; in 10 to 20% of patients with Stage III disease; and in 0% of patients with Stage IV disease (23, 25, 28–30, 62, 233, 234).

How long should patients be followed to determine if spontaneous remissions will occur? In prospective studies, spontaneous remissions have been noted in 16 to 39% of patients within 6 to 12 mo from the onset of symptoms (45, 229, 236). More than 85% of spontaneous remissions occur within 2 yr of presentation (29). Among patients who spontaneously remit or stabilize, late relapses occur in only 2 to 8% of patients (29, 45, 229, 237). Failure to regress spontaneously within 24 mo predicts a chronic or persistent course (29). In various studies (23, 25, 28–30, 45, 62, 229, 233, 234, 237), late sequelae or disease progression was rare among patients (regardless of initial stage) whose radiographs normalized or among Stage I patients with stable bilateral hilar lymphadenopathy (BHL). The prognosis for Stage II or III patients was variable. Some patients with stable infiltrates were symptomatic, with significant pulmonary dysfunction, whereas others were asymptomatic. Chest radiographs do not reliably discriminate active inflammation from fibrosis. The clinical importance of "stabilization" depends on the initial symptoms and functional impairment.

#### Prospective Clinical Trials

Insight into the natural history of sarcoidosis can be gleaned from prospective trials in which patients were randomized to either corticosteroids or no treatment (39, 44). However, patients with severe or progressive disease were excluded from these trials. Enrolled patients typically were asymptomatic or

had minimal symptoms, clinical features associated with a favorable prognosis. Given this significant limitation, these studies failed to detect differences between treatment arms (39, 44). A recent prospective but nonrandomized trial monitored 91 previously untreated patients with sarcoidosis (229). Corticosteroids were administered initially to 36 patients (40%) for progressive loss of lung function or serious extrathoracic disease (229). The remaining 55 patients (60%) were observed without therapy, and of these only 8 (16%) eventually required corticosteroids. At long-term follow-up, 61% of patients (both treated and untreated) were stable; 31% had improved; only 8% had deteriorated from the initial baseline. These latter patients subsequently all responded to therapy. The generally favorable outcome may in part reflect the fact that 85% of patients were white (229). The British Thoracic Society prospectively monitored 149 patients with Stage II or III sarcoidosis (45). Corticosteroids were given to 33 patients at initial presentation for symptomatic disease. The remaining 116 patients were observed without therapy for 6 mo. During that time frame, chest radiographs cleared spontaneously in 58 patients and persisted in 58 patients. Importantly, only one patient who spontaneously remitted required corticosteroids for late relapse.

#### Patient Surveillance

Longitudinal surveillance of sarcoidosis should be most intensive during the first 2 yr after presentation, in order to assess prognosis and determine the need (if any) for therapy. For Stage I disease, initial follow-up every 6 mo is usually adequate. More frequent evaluations (every 3 to 6 mo) are advised for Stage II, III, or IV sarcoidosis. Therapeutic intervention should be considered in patients with severe, active, or progressive disease. All patients (irrespective of radiographic stage) should be monitored for a minimum of 3 yr after therapy is discontinued. Subsequent follow-up is not required unless new or worsening symptoms develop or extrapulmonary sites are involved. Persistent, stable asymptomatic Stage I disease does not require therapy but should be monitored longitudinally (annually). Regardless of whether treatment is offered, patients with persistent Stage II, III, or IV sarcoidosis should be monitored indefinitely (at least annually). As has been pointed out, follow-up needs to be more vigilant among patients with corticosteroid-induced remissions, because of the high rate of relapses in this context (45, 237). In contrast, disease progression or clinical relapse is infrequent among patients who spontaneously remit (45, 229, 237). Patients with serious extrapulmonary involvement require long term follow-up, irrespective of the chest radiographic stage.

During the follow-up period, all patients should have periodic review of their symptoms and repeat physical examinations, chest radiographs, and spirometry. Further studies depend on initial organ involvement or new symptoms or findings. As an example, patients with breathlessness or impaired lung function might require more extensive tests, including exercise testing or lung CT scans.

#### TREATMENT OF SARCOIDOSIS

The symptoms and/or findings that necessitate corticosteroid therapy remain controversial. In patients with mild disease, such as skin lesions, anterior uveitis, or cough, topical steroid therapy may be all that is necessary. In patients with systemic, symptomatic disease, oral corticosteroids are often employed. Systemic therapy is clearly indicated for cardiac disease, neurologic disease, eye disease not responding to topical therapy, and hypercalcemia. The use of systemic therapy in pulmonary

and other, extrapulmonary disease is less clear cut, but most physicians feel that progressive symptomatic disease should be treated (229, 233, 259). A patient with persistent pulmonary infiltrates or progressive loss of lung functions and no symptoms may still require therapy (45). In patients requiring persistent corticosteroid therapy, antimalarial agents and cytotoxic agents should be considered (260). In some refractory cases, transplantation has been performed because of organ failure.

### Corticosteroids

Early studies showed that a short course of adrenocorticotropic hormone (ACTH) or cortisone favorably influenced the pulmonary roentgenographic infiltrates and that prolonged treatment with cortisone resulted in remission of granulomas as seen in repeat biopsy specimens (32). Treatment with oral steroids usually results in relief of respiratory symptoms, improvement in chest roentgenographic findings, and lung function studies (34, 35, 40, 41, 43, 45, 229, 261–263). However, re-appearance of symptoms and roentgenographic infiltrates is frequent after discontinuation of treatment, with some groups finding more than one-third of patients experiencing recurrence within 2 yr of discontinuation of therapy (35, 261).

The optimal dose and duration of corticosteroids has not been studied in randomized, prospective trials. Dose and duration of therapy often must be individualized. For pulmonary sarcoidosis, the initial dosage often is 20–40 mg/d of prednisone or its equivalent on alternate days (259). Higher doses may be necessary for cardiac or neurosarcoidosis. After 1–3 mo, the patient should be evaluated for response. Patients failing to respond by 3 mo are unlikely to respond to a more protracted course of therapy. At this point, other reasons for failure should be evaluated, such as presence of irreversible, fibrotic disease, noncompliance, inadequate dosage, and intrinsic corticosteroid resistance. Among steroid responders, the dose is slowly tapered to 5–10 mg/d or an every other day regimen. Treatment should be continued for a minimum of 12 mo. Occasionally, a patient with minimal disease of recent onset may respond to therapy over a 3- to 6-mo period. Patients with Sjögren's syndrome do not require therapy with corticosteroids, unless a nonsteroidal agent is not effective. Patients need to be monitored for relapse after reduction or discontinuation of therapy. In some patients, recurrent relapses will occur and patients may require long-term, low-dose therapy (35, 261).

Topical therapy with corticosteroids may be used for some patients with skin lesions, iritis/uveitis, nasal polyps, or airway disease (264–269). The potent fluorinated steroids should not

be used on the face. Although never studied in a randomized trial, it is clear that topical therapy, in the form of creams, drops, sprays, and injections, has simplified therapy. Inhaled topical steroids have been administered to patients with pulmonary sarcoidosis. Several studies have demonstrated some benefit of this therapy (264–268, 270, 271), but not all studies have shown clinical efficacy (269).

### Cytotoxic Agents

Several cytotoxic agents have been used to treat sarcoidosis. While these agents clearly are of value in selected patients, there are no studies that have clearly delineated when these drugs should be used for therapy. On the basis of safety and efficacy, methotrexate and azathioprine are the preferred agents for most patients (260). Cyclophosphamide should be reserved for refractory cases.

*Methotrexate.* The original reports of methotrexate were limited to case reports, which described its efficacy in refractory cases (272–275). One center has reported its experience with the use of methotrexate in chronic sarcoidosis. In 33 of 50 patients, there was a response to methotrexate alone and 9 additional patients responded to low-dose prednisone with methotrexate (276, 277). Two other reports found similar response rates in patients with cutaneous sarcoidosis (278, 279). Relapses were frequent after discontinuation of methotrexate, but a favorable response was noted in 26 of 27 patients on re-institution of methotrexate (277). This suggests that methotrexate suppresses but does not cure the disease.

*Azathioprine.* Azathioprine has also been reported to be an effective therapy in a limited number of cases (258, 280, 281). Two series have shown benefit in some patients treated with azathioprine, with or without prednisone (282, 283). In these studies, the drug was used for patients with chronic disease. The efficacy appears similar to that of methotrexate. Experience with azathioprine in patients who have received solid organ transplants and in patients with rheumatoid arthritis has demonstrated that it is a relatively safe and effective immunosuppressive agent.

*Other cytotoxic agents.* Chlorambucil in combination with low-dose prednisone has been used in a limited number of patients. The response rate appears similar to that of methotrexate or azathioprine (284, 285). The risk of malignancy is significantly higher for chlorambucil than for either methotrexate and azathioprine. Thus, the treatment has been abandoned by most physicians. Cyclophosphamide has also been used in a limited number of patients (258, 286–288). Its higher toxicity

TABLE 7  
ALTERNATIVE THERAPY FOR SARCOIDOSIS

|                 | Drug         |              |   |                    |
|-----------------|--------------|--------------|---|--------------------|
|                 | Methotrexate | Azathioprine | Cyclophosphamide  | Hydroxychloroquine |
| Dosage          | 10–25 mg/wk  | 50–200 mg/d  | 50–150 mg/d orally,<br>or 500–2,000 mg<br>every 2 wk intra-<br>venously | 200–400 mg/d       |
| Toxicity        |              |              |   |                    |
| Nausea*         | 1            | 2            | 3   | 1                  |
| Mucositis*      | 2            | 1            | 1   | 0                  |
| Hematologic*    | 1            | 2            | 3   | 0                  |
| Teratogenicity* | 2            | 1            | 3   | 0                  |
| Carcinogenic*   | 0            | 1            | 3   | 0                  |
| Other           | Liver, lung  |              | Bladder   | Retinal            |

\* Scale: 0 = none, 1 = minimal, 2 = occasional problem, 3 = significant problem; it may be necessary to adjust the dosage or to use other agents.

has limited its use to patients with severe disease refractory to other agents. In a small series of patients with neurologic disease failing all prior treatments, some responded to cyclophosphamide (289).

### Toxicity

Table 7 summarizes the toxic effects of cytotoxic drugs used for treatment of sarcoidosis. There are some common features among all of the agents, including hematologic and gastrointestinal toxicity, teratogenicity, and carcinogenicity. Patients should be monitored on a regular basis for evidence of bone marrow toxicity. Nausea and vomiting can occur with any cytotoxic agent, but is usually dose dependent (290–292). All of the cytotoxic agents are teratogenic and both male and female patients should use birth control while on therapy (293, 294). Azathioprine appears less teratogenic. Cyclophosphamide has also been associated with early menopause and aspermia, although any agent can cause this. Postponing pregnancy for at least 6 mo after the last dose of methotrexate is usually sufficient to avoid a teratogenic effect. Many patients have reported having normal children after using cytotoxic therapy, but there is an increased risk of fetal malformations.

Cytotoxic agents are associated with an increased risk of lymphoproliferative disorders and carcinomas. Methotrexate appears to have minimal to no carcinogenicity (295–297). The drug is also associated with hypersensitivity pneumonitis and hepatotoxicity (289, 298–300). Azathioprine has been associated with increased risk in solid organ transplants (301–303), but in rheumatoid arthritis there was no apparent increased risk for malignancy (304). Chlorambucil is known to increase the risk of lymphoproliferative disease. The overall risk of carcinogenicity with cyclophosphamide, including lymphoproliferative tumors and carcinoma, is a significant concern. In addition, there is risk for bladder cancer and hematuria from this agent (305–307). Hematuria is a strong indication to discontinue therapy with this agent.

The toxicity of methotrexate can be minimized by the use of folic or folinic acid (308). Some authors recommend liver biopsy to monitor for hepatotoxicity after each cumulative dose of 1–1.5 g. Methotrexate is cleared by the kidneys and treatment is not recommended for patients with significant renal failure. The active metabolite azathioprine is metabolized by a methyltransferase. A small percentage of the population lacks the active phenotype of this enzyme, leading to excess levels of 6-mercaptopurine and a prolonged effect of the drug (309, 310). Hemorrhagic cystitis caused by cyclophosphamide can be minimized by increased fluid intake. However, urinalysis on a regular basis is necessary to monitor for this toxicity and the associated bladder cancer (306).

### Other Agents

The antimalarial agents most often used to treat sarcoidosis are chloroquine and hydroxychloroquine. Siltzbach and Teirstein treated 43 patients with intrathoracic or cutaneous lesions with chloroquine and reported improvement in more than half of the patients. Patients whose chest roentgenograms indicated advanced lesions were less likely to respond (311). Chloroquine has been particularly helpful for lupus pernio and hypercalcemia (312). In a randomized, double-blind trial, in which patients were treated with chloroquine or placebo for 4 mo, there was clearing of the chest roentgenogram during chloroquine therapy. However, there was no difference in the two groups 8 mo after treatment was stopped (313). Unfortu-

nately, the long-term administration of chloroquine can lead to irreversible retinopathy and blindness; frequent and careful eye examinations are required every 3 to 6 mo. Because of the risk of retinopathy, chloroquine treatment is best limited to a 6-mo period of time (314). Hydroxychloroquine has been used for prolonged periods without retinal damage (314). Hydroxychloroquine causes insulin degradation in the liver, suppresses gluconeogenesis, and increases peripheral tissue utilization of glucose (315). This may be of benefit in diabetics with mild to moderate sarcoidosis. Hydroxychloroquine is preferred to chloroquine, because of the lower risk of ocular toxicity.

Nonsteroidal agents have been shown to be effective for treatment, especially for musculoskeletal symptoms and erythema nodosum (46). The antifungal agent ketoconazole, a known inhibitor of cytochrome *P*-450 steroid oxidases, will lower circulating 1,25-hydroxy vitamin D<sub>3</sub> and serum calcium levels in patients with hypercalcemia due to sarcoidosis (316, 317).

Several other agents have been proposed for refractory cases. Cyclosporine has been shown to have limited (318) to no (319, 320) effectiveness for pulmonary sarcoidosis. The high toxicity of cyclosporine has limited its use. It has been shown to help some patients with refractory neurosarcoidosis, when treatments such as corticosteroids and immunosuppressive agents have failed (258, 321). Radiation therapy has also been used in selected cases with some response (322). Melatonin, thalidomide, and pentoxifylline have also been reported as useful in some cases (323–325).

### Treatment of Associated Conditions or Complications

In patients with fibrotic disease, bronchiectasis often complicates the disease. These patients often require antibiotic therapy. A particular complication of bronchiectasis in sarcoidosis is aspergilloma. Fatal hemoptysis has been noted by many groups. The antifungal agent itraconazole has been used but no clinical trials have demonstrated efficacy. Surgical resection and embolization of the bronchial arteries have been reported as helpful in selected cases.

The issue of osteoporosis is more complicated. Corticosteroid therapy does increase the risk of osteoporosis. However, after discontinuation of corticosteroid therapy, osteoporosis may be reversible, at least for patients less than 50 yr of age (326). Sarcoidosis patients treated with deflazacort, a new bone-sparing corticosteroid, responded clinically and had minimal evidence of osteoporosis (326, 327). Among the agents proposed for osteoporosis prevention are vitamin D and calcium supplementation, nasal calcitonin, and bisphosphonates. Special care must be used if vitamin D or calcium is supplemented in patients with sarcoidosis because the disease may cause hypercalciuria and hypercalcemia by increased endogenous vitamin D. Although hypercalciuria or hypercalcemia may reverse with therapy, patients should be monitored while receiving calcium replacement therapy. Calcitonin and bisphosphonates have also been shown to reverse osteoporosis induced by steroid therapy in patients with sarcoidosis (328).

Patients with sarcoidosis should be evaluated for systemic symptoms such as myalgias and fatigue. Patients with these symptoms and those with significant respiratory insufficiency may benefit from pulmonary rehabilitation. Hypoxemia at rest or with exercise may require supplemental oxygen therapy.

Lung and other organ transplantation has been successfully performed for patients with end-stage sarcoidosis (329). Unfortunately, recurrent sarcoid lesions have been described in the donor organ (330). However, posttransplantation immunosuppression seems to control the sarcoidosis (331).

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