characteristically enlarged, discrete, and sometimes calcified. The tonsils are affected in about one fourth to one third of cases.

The **spleen** is affected in about three fourths of cases, but it is enlarged in only one fifth. On occasion, granulomas may coalesce to form small nodules that are visible macroscopically. The **liver** is affected slightly less often than the spleen. It may be moderately enlarged and typically contains scattered granulomas, more in portal triads than in the lobular parenchyma. Needle biopsy can be diagnostic.

The **bone marrow** is involved in about one fifth of cases. Radiologically visible bone lesions have a particular tendency to involve phalangeal bones of the hands and feet, creating small circumscribed areas of bone resorption within the marrow cavity and a diffuse reticulated pattern throughout the cavity, with widening of the bony shafts or new bone formation on the outer surfaces.

Skin lesions, encountered in one fourth of cases, assume a variety of appearances, including discrete subcutaneous nodules; focal, slightly elevated, erythematous plaques; or flat lesions that are slightly reddened and scaling, resembling those of systemic lupus erythematosus. Lesions may also appear on the mucous membranes of the oral cavity, larynx, and upper respiratory tract. **Ocular involvement**, seen in one fourth of cases, takes the form of iritis or iridocyclitis, either bilaterally or unilaterally. Consequently, corneal opacities, glaucoma, and total loss of vision may occur. These ocular lesions are frequently accompanied by inflammation of the lacrimal glands and suppression of lacrimation. Bilateral sarcoidosis of the parotid, submaxillary, and sublingual glands constitutes the combined uveoparotid involvement designated as Mikulicz syndrome (Chapter 16). **Muscle** involvement is underdiagnosed, since it may be asymptomatic. Muscle weakness, aches, tenderness, and fatigue should prompt consideration of occult sarcoid myositis. which can be diagnosed by muscle biopsy. Sarcoid granulomas occasionally occur in the heart, kidneys, central nervous system (neurosarcoidosis, seen in 5% to15%), and endocrine glands, particularly in the pituitary, as well as in other body tissues.

Clinical Course. Because of its varying severity and inconstant tissue distribution, sarcoidosis may present with diverse features. It may be discovered unexpectedly on routine chest films as bilateral hilar adenopathy or may present with peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly. In the great majority of cases, however, individuals seek medical attention because of the insidious onset of respiratory abnormalities (shortness of breath, cough, chest pain, hemoptysis) or of constitutional signs and symptoms (fever, fatigue, weight loss, anorexia, night sweats).

Sarcoidosis follows an unpredictable course. It may be inexorably progressive, or marked by periods of activity interspersed with remissions, sometimes permanent, that may be spontaneous or induced by steroid therapy. Overall, 65% to 70% of affected patients recover with minimal or no residual manifestations. Twenty percent have permanent loss of some lung function or some permanent visual impairment. Of the remaining 10% to 15%, some die of cardiac or central nervous system damage, but most succumb to progressive pulmonary fibrosis and cor pulmonale.

KEY CONCEPTS

Sarcoidosis

- Sarcoidosis is a multisystem disease of unknown etiology; the diagnostic histopathologic feature is the presence of noncaseating granulomas in various tissues.
- Immunologic abnormalities include high levels of CD4+ T cells in the lung that secrete T_H1-dependent cytokines such as IFN-γ and IL-2 locally.
- Clinical manifestations include lymph node enlargement, eye involvement (sicca syndrome [dry eyes], iritis, or iridocyclitis), skin lesions (erythema nodosum, painless subcutaneous nodules), and visceral (liver, skin, marrow) involvement. Lung involvement occurs in 90% of cases, with formation of granulomas and interstitial fibrosis.

Hypersensitivity Pneumonitis

The term *hypersensitivity pneumonitis* describes a spectrum of immunologically mediated, predominantly interstitial, lung disorders caused by intense, often prolonged exposure to inhaled organic antigens. Affected individuals have an abnormal sensitivity or heightened reactivity to the causative antigen, which, in contrast to asthma, leads to pathologic changes that primarily involve the alveolar walls (thus the synonym "*extrinsic allergic alveolitis*"). It is important to recognize these diseases early in their course because progression to serious chronic fibrotic lung disease can be prevented by removal of the environmental agent.

Most commonly, hypersensitivity results from the inhalation of organic dust containing antigens made up of the spores of thermophilic bacteria, fungi, animal proteins, or bacterial products. Numerous syndromes are described, depending on the occupation or exposure of the individual. *Farmer's lung* results from exposure to dusts generated from humid, warm, newly harvested hay that permits the rapid proliferation of the spores of thermophilic actinomycetes. *Pigeon breeder's lung* (bird fancier's disease) is provoked by proteins from serum, excreta, or feathers of birds. *Humidifier* or *air-conditioner lung* is caused by thermophilic bacteria in heated water reservoirs. Pet birds and moldy basements are easily missed unless asked about specifically.

Several lines of evidence suggest that hypersensitivity pneumonitis is an immunologically mediated disease:

- Bronchoalveolar lavage specimens from the acute phase show increased levels of proinflammatory chemokines such as macrophage inflammatory protein 1α and IL-8.
- Bronchoalveolar lavage specimens also consistently demonstrate increased numbers of both CD4+ and CD8+ T lymphocytes.
- Most patients have specific antibodies against the causative antigen in their serum.
- Complement and immunoglobulins have been demonstrated within vessel walls by immunofluorescence.
- The presence of noncaseating granulomas in two thirds of the patients suggests that T-cell–mediated (type IV) hypersensitivity reactions against the implicated antigens are also common and have a pathogenic role.