and bilateral infiltrates on chest radiographs. The HRCT pattern shows extensive ground-glass infiltrates, and a biopsy is often required for diagnosis. Tissue histologic findings show the accumulation of so-called smoker's macrophages, which contain yellow-brown pigment and fill the alveolar spaces, and some degree of interstitial inflammation and fibrosis.

Treatment of DIP relies on immunosuppressant therapy and the avoidance of tobacco exposure. Prognosis is fair, with some individuals developing progressive lung disease. DIP is considered by some experts to be part of a continuum with RB-ILD, which produces a similar clinical presentation; has a somewhat different pathology, with macrophages centered at the small airways as opposed to the alveolar level; and is associated with tobacco exposure. RB-ILD has a better prognosis. Respiratory bronchiolitis may be found incidentally in asymptomatic smokers, and it does not constitute an ILD if not extensive and associated with clinical symptoms.

AIP is an IIP that manifests acutely. There is no sex predominance in AIP and no association with smoking. Dyspnea and radiographic alveolar lung opacities develop and progress over days to a few weeks, invariably leading to respiratory failure. Patients often have a prior illness suggesting a viral upper respiratory infection with constitutional symptoms such as myalgias, arthralgias, fever, chills, and malaise. The histologic pattern shows diffuse alveolar damage with hyaline membrane formation or with organization. Although a trial of immunosuppressants is recommended (level 3 evidence), this condition is frequently fatal independent of treatment, and relapse may occur even after apparent improvement.

COP manifests over a subacute time course. Patients with COP exhibit dyspnea, cough, and systemic symptoms. Radiographically, patients with COP typically have areas of air space consolidation mimicking a bacterial pneumonia but that do not resolve with antibiotics. The radiographic infiltrates may be unilateral or bilateral and may be migratory. Pulmonary function tests may show restriction or obstruction. Histologically, COP is characterized by distal airway and interstitial inflammation and obliteration of distal small airways and air spaces with plugs of fibroblasts and fibrotic tissue called *Masson bodies*.

Similar to NSIP and DIP, COP is likely to respond to immunosuppressant therapy and is usually treated with prednisone (level 2 evidence). Relapses are typical and may occur when the steroid treatment is tapered. Connective tissue disorders, inhaled irritants, and drugs (e.g., methotrexate) can cause a type of inflammation known as *secondary organizing pneumonia*.

LIP is a rare disease that is seen predominantly in women. Patients have gradual-onset dyspnea and cough and occasionally have fever, weight loss, chest pain, and arthralgias. Cases of apparently idiopathic LIP must be investigated for known causes, such as collagen vascular diseases (especially Sjögren syndrome and rheumatoid arthritis) and immunodeficiency diseases (e.g., acquired immunodeficiency syndrome [AIDS]).

For LIP, HRCT shows interstitial reticulations, centrilobular nodules, ground-glass opacities, and thin-walled cysts. Histologically, infiltration of cells, including lymphocytes, plasma cells, and histiocytes, can be seen within alveolar septa. Type II pneumocyte hyperplasia and an increase in the number of alveolar macrophages can be seen in cases of LIP. Lymphoid follicles are often identified, usually in the distribution of pulmonary lymphatics.

Corticosteroids are used to treat LIP with various degrees of success (level 3 evidence); however, more than one third of patients progress to diffuse fibrosis. It is unclear whether treatment influences the course of the disease or has a significant effect on lung physiology.

GRANULOMATOUS DISORDERS

Interstitial Lung Diseases with Granuloma Formation

Several noninfectious ILDs are characterized by granuloma formation in the lungs, including granulomatosis with polyangiitis, HP, and chronic beryllium disease. These disorders are discussed elsewhere in this chapter. Of the ILDs characterized by granulomatous lung inflammation, sarcoidosis is the most common.

Sarcoidosis

Definition and Epidemiology

Sarcoidosis is a multisystem granulomatous disorder of unknown cause. The lungs and thoracic lymph nodes are frequent sites of involvement. Sarcoidosis is relatively common, with a prevalence of 1 to 40 cases per 100,000 people worldwide. A higher incidence of sarcoidosis is reported among Scandinavian, German, and Irish individuals residing in northern Europe. In the United States, the prevalence rates of sarcoidosis are 10.9 cases per 100,000 whites and 35.5 cases per 100,000 African Americans, with women in both groups being more frequently affected. Because sarcoidosis may be asymptomatic, the true prevalence may be higher. Sarcoidosis typically occurs in individuals between 10 and 40 years old.

Pathology

Sarcoidosis is characterized by the formation in tissues of noncaseating granulomas that organize in an inner core of epithelioid histiocytes, $CD4^+$ T lymphocytes, and giant cells, which are surrounded by a rim of lymphocytes, fibroblasts, and connective tissue (Fig. 17-5). Granulomas are found in the airways or lung parenchyma in more than 90% of patients with sarcoidosis. Granulomatous angiitis may also be found in the lungs. The upper respiratory system, lymph nodes, skin, and eyes are commonly involved. Virtually any other organ may be affected, including the liver, bone marrow, spleen, musculoskeletal system, heart, salivary glands, and nervous system.

The granulomas may be clinically silent or, if extensive, may disrupt normal organ structure and function. The cause of these lesions is unknown, but given the frequency of lung involvement, inhaled antigens ranging from bacteria (especially mycobacteria and *Propionibacterium*) to environmental substances have been hypothesized to trigger the onset of granulomatous inflammation. This inflammation may be self-limited or may be propagated, possibly by repeated exposure to the unknown antigen or because of defective immune regulation.

Familial susceptibility to sarcoidosis exists, and alleles of human leukocyte antigen (HLA) genes involved in antigen