diffuse alveolar damage, including severe atypia of hyperplastic type II cells and fibroblasts. Epithelial cell atypia and foam cells within vessel walls are also characteristic of radiation damage.

Granulomatous Diseases

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown cause that may involve many different tissues and organs. Sarcoidosis presents in many clinical patterns, but bilateral hilar lymphadenopathy or lung involvement is most common, occuring 90% of cases. Eye and skin lesions are next in frequency. Since other diseases, including mycobacterial and fungal infections and berylliosis, can also produce noncaseating granulomas, the diagnosis is one of exclusion.

Sarcoidosis usually occurs in adults younger than 40 years of age, but can affect any age group. The prevalence is higher in women but varies widely in different countries and populations. In the United States the rates are highest in the Southeast and are 10 times higher in blacks than in whites. In contrast, the disease is rare among Chinese and Southeast Asians. Patterns of organ involvement also vary with race.

Pathogenesis. Although the etiology of sarcoidosis remains unknown, several lines of evidence suggest that it is a disease of disordered immune regulation in genetically predisposed individuals. It is not clear whether exposure to any environmental or infectious agent has a role in its pathogenesis.

Immunologic Factors. There are several immunologic abnormalities in the local milieu of sarcoid granulomas that suggest the involvement of a cell-mediated immune response to an unidentified antigen. These abnormalities include:

- Intra-alveolar and interstitial accumulation of CD4+ T cells, resulting in CD4/CD8 T-cell ratios ranging from 5:1 to 15:1, suggesting pathogenic involvement of CD4+ helper T cells. There is oligoclonal expansion of T-cell subsets as determined by analysis of T-cell receptor rearrangement, consistent with an antigen-driven proliferation.
- Increased levels of T cell-derived T_H1 cytokines such as IL-2 and IFN-γ, which may be responsible for T-cell expansion and macrophage activation, respectively.
- Increased levels of several cytokines in the local environment (IL-8, TNF, macrophage inflammatory protein 1α) that favor recruitment of additional T cells and monocytes and contribute to the formation of granulomas. TNF in particular is released at high levels by activated alveolar macrophages, and the TNF concentration in the bronchoalveolar fluid is a marker of disease activity.
- Impaired dendritic cell function.

Additionally, there are systemic immunologic abnormalities in individuals with sarcoidosis:

- Anergy to common skin test antigens such as *Candida* or tuberculosis purified protein derivative (PPD)

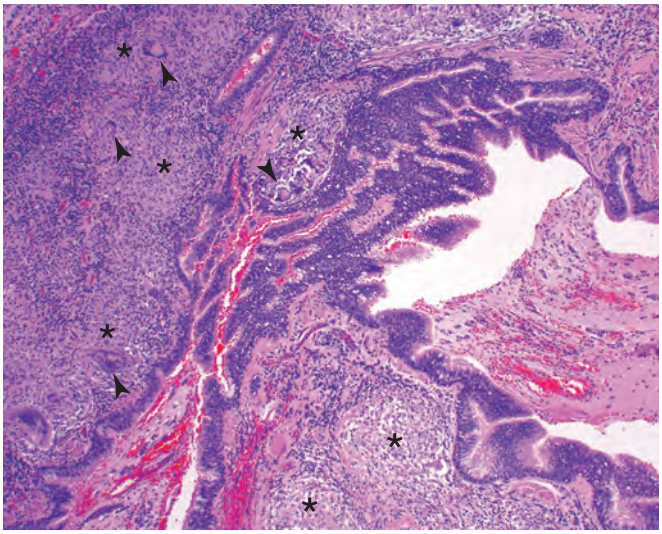

Figure 15-22 Bronchus with characteristic noncaseating sarcoidal granulomas (*asterisks*), with many multinucleated giant cells *(arrowheads).* Note subepithelial location of granulomas.

- Polyclonal hypergammaglobulinemia, another manifestation of helper T-cell dysregulation

Genetic Factors. Evidence of genetic influences include familial and racial clustering of cases and the association with certain HLA genotypes (e.g., HLA-A1 and HLA-B8).

MORPHOLOGY

Virtually every organ in the body has been described as being affected by sarcoidosis, at least on rare occasions. Regardless of the tissue, involved tissues contain well-formed **nonnecrotizing granulomas** (Fig. 15-22) composed of aggregates of tightly clustered epithelioid macrophages, often with giant cells. Central necrosis is unusual. With chronicity the granulomas may become enclosed within fibrous rims or may eventually be replaced by hyaline fibrous scars. Laminated concretions composed of calcium and proteins known as **Schaumann bodies** and stellate inclusions known as **asteroid bodies** are found within giant cells in approximately 60% of the granulomas. Though characteristic, these microscopic features are not pathognomonic of sarcoidosis, because asteroid and Schaumann bodies may be encountered in other granulomatous diseases (e.g., tuberculosis).

The **lungs** are common sites of involvement. Macroscopically there is usually no demonstrable alteration, although in advanced cases the coalescence of granulomas produces small nodules that are palpable or visible as 1 to 2 cm, noncaseating, noncavitated consolidations. The lesions are distributed primarily along the lymphatics around bronchi and blood vessels, although alveolar lesions and pleural involvement are also seen. The relatively high frequency of granulomas in the bronchial submucosa accounts for the high diagnostic yield of bronchoscopic biopsies. There seems to be a strong tendency for lesions to heal in the lungs, so varying stages of fibrosis and hyalinization are often found. **Lymph nodes** are involved in almost all cases, particularly the hilar and mediastinal nodes, but any other node in the body may be involved. Nodes are