T cells to produce cytokines, such as IL-2, which activates other T cells, perpetuating the response, and IFN-γ, which activates the macrophages. It is not established which macrophage-activating cytokines (IL-4 or IFN-γ) transform the cells into epithelioid cells and multinucleate giant cells.

## MORPHOLOGY

In the usual hematoxylin and eosin preparations (Fig. 3-23), the activated macrophages in granulomas have pink granular cytoplasm with indistinct cell boundaries and are called **epithelioid cells** because of their resemblance to epithelia. The aggregates of epithelioid macrophages are surrounded by a collar of lymphocytes. Older granulomas may have a rim of fibroblasts and connective tissue. Frequently, but not invariably, multinucleated **giant cells** 40 to 50 μm in diameter are found in granulomas; these are called Langhans giant cells. They consist of a large mass of cytoplasm and many nuclei, and they derive from the fusion of multiple activated macrophages. In granulomas associated with certain infectious organisms (most classically *Mycobacterium tuberculosis*), a combination of hypoxia and free radical–mediated injury leads to a central zone of necrosis. Grossly, this has a granular, cheesy appearance and is therefore called **caseous necrosis.** Microscopically, this necrotic material appears as amorphous, structureless, eosinophilic, granular debris, with complete loss of cellular details. The granulomas in Crohn disease, sarcoidosis, and foreign body reactions tend to not have necrotic centers and are said to be *noncaseating*. Healing of granulomas is accompanied by fibrosis that may be extensive.

Granulomas are encountered in certain specific pathologic states; recognition of the granulomatous pattern is important because of the limited number of conditions (some life-threatening) that cause it (Table 3-8). In the setting of persistent T-cell responses to certain microbes (e.g., *M. tuberculosis*, *Treponema pallidum*, or fungi), T cell–derived cytokines are responsible for chronic macrophage activation and granuloma formation. Granulomas may also develop in some immune-mediated inflammatory diseases, notably Crohn disease, which is one type of inflammatory bowel disease and an important cause of granulomatous inflammation in the United States, and in a disease of unknown etiology called *sarcoidosis*. **Tuberculosis is the prototype of a granulomatous disease caused by infection and should always be excluded as the cause when granulomas are identified.** In this disease the granuloma is referred to as a *tubercle.* The morphologic patterns in the various granulomatous diseases may be sufficiently different to allow reasonably accurate diagnosis by an experienced pathologist (see Table 3-8); however, there are so many atypical presentations that it is always necessary to identify the specific etiologic agent by special stains for organisms (e.g., acid-fast stains for tubercle bacilli), by culture methods (e.g., in tuberculosis and fungal diseases), by molecular techniques (e.g., the polymerase chain reaction in tuberculosis), and by serologic studies (e.g., in syphilis).

**Table 3-8** Examples of Diseases with Granulomatous Inflammation

| Disease | Cause | Tissue Reaction |
|---|---|---|
| Tuberculosis | *Mycobacterium tuberculosis* | Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli |
| Leprosy | *Mycobacterium leprae* | Acid-fast bacilli in macrophages; noncaseating granulomas |
| Syphilis | *Treponema pallidum* | Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells are necrotic without loss of cellular outline |
| Cat-scratch disease | Gram-negative bacillus | Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon |
| Sarcoidosis | Unknown etiology | Noncaseating granulomas with abundant activated macrophages |
| Crohn disease (inflammatory bowel disease) | Immune reaction against intestinal bacteria, possibly self antigens | Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate |

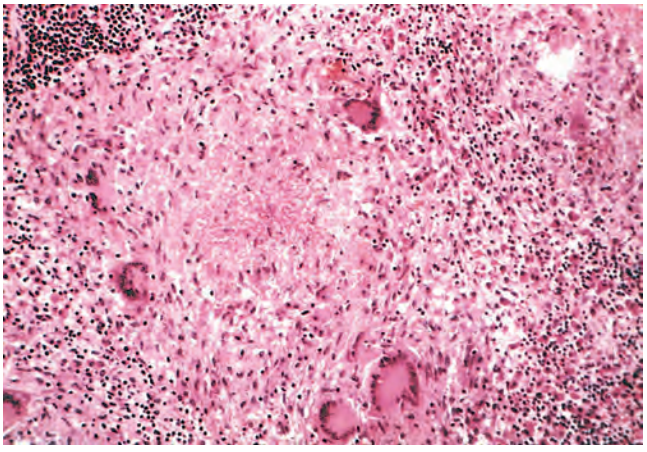

**Figure 3-23** Typical tuberculous granuloma showing an area of central necrosis surrounded by multiple Langhans-type giant cells, epithelioid cells, and lymphocytes.

## KEY CONCEPTS

### Chronic Inflammation

- Chronic inflammation is a prolonged host response to persistent stimuli.
- It is caused by microbes that resist elimination, immune responses against self and environmental antigens, and some toxic substances (e.g., silica); underlies many medically important diseases.
- It is characterized by coexisting inflammation, tissue injury, attempted repair by scarring, and immune response.