node and track to the skin to produce draining sinuses. Healing of such lesions is associated with scarring.

Chronic Nonspecific Lymphadenitis

Chronic immunologic stimuli produce several different patterns of lymph node reaction, as described later.

MORPHOLOGY

Follicular hyperplasia is caused by stimuli that activate humoral immune responses. It is defined by the presence of large oblong germinal centers (secondary follicles), which are surrounded by a collar of small resting naive B cells (the mantle zone) (Fig. 13-3). Germinal centers are normally polarized, consisting of two distinct regions: (1) a dark zone containing proliferating blastlike B cells (centroblasts) and (2) a light zone composed of B cells with irregular or cleaved nuclear contours (centrocytes). Interspersed between the germinal B centers is an inconspicuous network of antigen-presenting follicular dendritic cells and macrophages (often referred to as **tingible-body macrophages**) containing the nuclear debris of B cells, which undergo apoptosis if they fail to produce an antibody with a high affinity for antigen.

Causes of follicular hyperplasia include rheumatoid arthritis, toxoplasmosis, and early stages of infection with HIV. This form of hyperplasia is morphologically similar to follicular lymphoma (discussed later). Features favoring a reactive (nonneoplastic) hyperplasia include (1) preservation of the lymph node architecture, including the interfollicular T-cell zones and the sinusoids; (2) marked variation in the shape and size of the follicles; and (3) the presence of frequent mitotic figures, phagocytic macrophages, and recognizable light and dark zones, all of which tend to be absent from neoplastic follicles.

Paracortical hyperplasia is caused by stimuli that trigger T-cell–mediated immune responses, such as acute viral infections (e.g., infectious mononucleosis). The T-cell regions typically contain immunoblasts, activated T cells three to four times the size of resting lymphocytes that have round nuclei, open chromatin, several prominent nucleoli, and moderate amounts of pale cytoplasm. The expanded T-cell zones encroach on and, in particularly exuberant reactions, efface the B-cell follicles. In such cases immunoblasts may be so numerous that special studies are needed to exclude a lymphoid neoplasm. In addition, there is often a hypertrophy of sinusoidal and vascular endothelial cells, sometimes accompanied by infiltrating macrophages and eosinophils.

Sinus histiocytosis (also called *reticular hyperplasia*) refers to an increase in the number and size of the cells that line lymphatic sinusoids. Although nonspecific, this form of hyperplasia may be particularly prominent in lymph nodes draining cancers such as carcinoma of the breast. The lining lymphatic endothelial cells are markedly hypertrophied and macrophages are greatly increased in numbers, resulting in the expansion and distension of the sinuses.

Characteristically, lymph nodes in chronic reactions are nontender, as nodal enlargement occurs slowly over time and acute inflammation with associated tissue damage is absent. Chronic lymphadenitis is particularly common in inguinal and axillary nodes, which drain relatively large areas of the body and are frequently stimulated by immune reactions to trivial injuries and infections of the extremities.

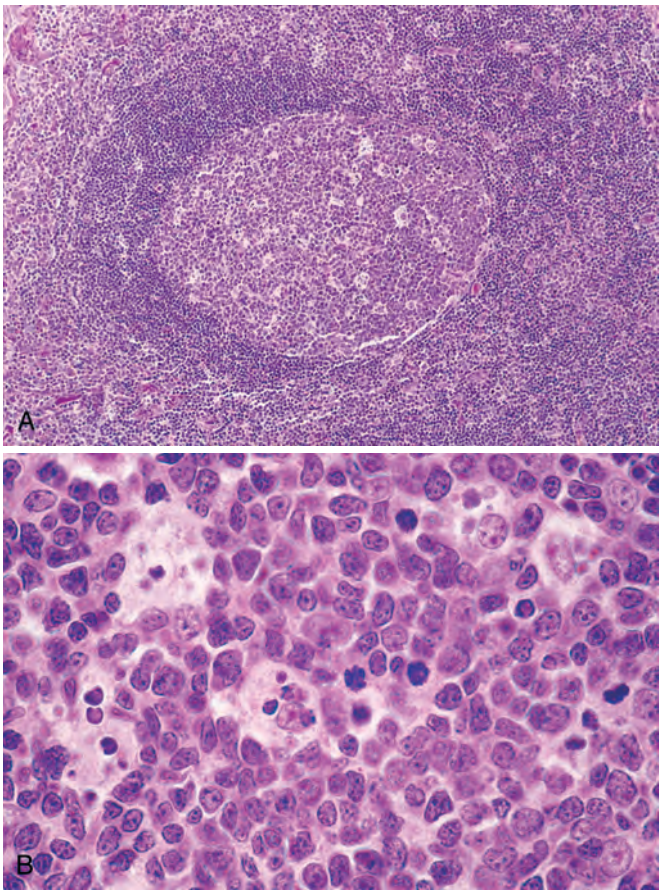

Figure 13-3 Follicular hyperplasia. **A,** Low-power view showing a reactive follicle and surrounding mantle zone. The dark-staining mantle zone is more prominent adjacent to the germinal-center light zone in the left half of the follicle. The right half of the follicle consists of the dark zone. **B,** High-power view of the dark zone shows several mitotic figures and numerous macrophages containing phagocytosed apoptotic cells (tingible bodies).

Furthermore, chronic immune reactions can promote the appearance of organized collections of immune cells in nonlymphoid tissues. These collections are sometimes called tertiary lymphoid organs. A classic example is that of chronic gastritis caused by *Helicobacter pylori*, in which aggregates of mucosal lymphocytes are seen that simulate the appearance of Peyer patches. A similar phenomenon occurs in rheumatoid arthritis, in which B-cell follicles often appear in the inflamed synovium. Lymphotoxin, a cytokine required for the formation of normal Peyer patches, is probably involved in the establishment of these "extranodal" inflammation-induced collections of lymphoid cells.

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a reactive condition marked by cytopenias and signs and symptoms of systemic inflammation related to macrophage activation. For this reason, it is also sometimes referred to as *macrophage activation syndrome*. Some forms are familial and may appear early in life, even in infants, while other forms are sporadic and may affect people of any age.

Pathogenesis. **The common feature of all forms of HLH is systemic activation of macrophages and CD8+ cytotoxic**