antigen; if the activation is sustained, continued inflammation and tissue injury result.

Activated T_H17 cells secrete IL-17, IL-22, chemokines, and several other cytokines. Collectively, these cytokines recruit neutrophils and monocytes to the reaction, thus promoting inflammation. T_H17 cells also produce IL-21, which amplifies the T_H17 response.

Clinical Examples of CD4+ T Cell–Mediated Inflammatory Reactions. The classic example of DTH is the *tuberculin reaction*, which is produced by the intracutaneous injection of purified protein derivative (PPD, also called tuberculin), a protein-containing antigen of the tubercle bacillus. In a previously sensitized individual, reddening and induration of the site appear in 8 to 12 hours, reach a peak in 24 to 72 hours, and thereafter slowly subside. Morphologically, delayed-type hypersensitivity is characterized by the accumulation of mononuclear cells, mainly CD4+ T cells and macrophages, around venules, producing perivascular "cuffing" (Fig. 6-19). In fully developed lesions, the venules show marked endothelial hypertrophy, reflecting cytokine-mediated endothelial activation.

With certain persistent or nondegradable antigens, such as tubercle bacilli colonizing the lungs or other tissues, the infiltrate is dominated by macrophages over a period of 2 or 3 weeks. With sustained activation, macrophages often undergo a morphologic transformation into *epithelioid cells*, large epithelium-like cells with abundant cytoplasm. A microscopic aggregation of epithelioid cells, usually surrounded by a collar of lymphocytes, is referred to as a *granuloma* (Fig. 6-20*A*). This pattern of inflammation, called *granulomatous inflammation* (Chapter 3), is typically associated with strong T_H1-cell activation and high-level production of cytokines such as IFN-γ (Fig. 6-20*B*). It can also be caused by indigestible foreign bodies, which activate macrophages without eliciting an adaptive immune response.

Contact dermatitis is a common example of tissue injury resulting from DTH reactions. It may be evoked by contact

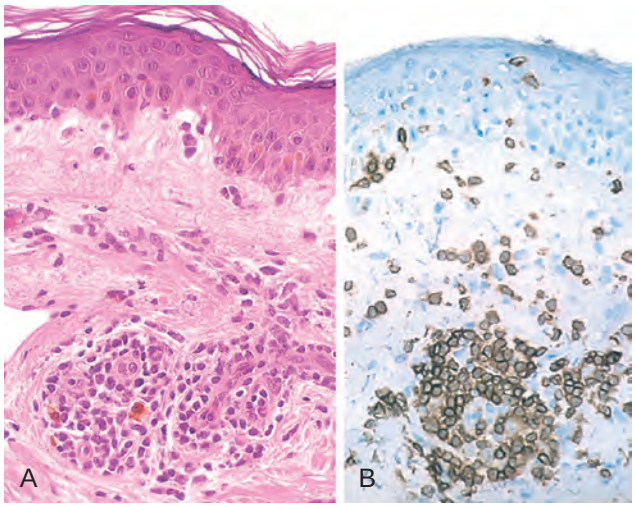
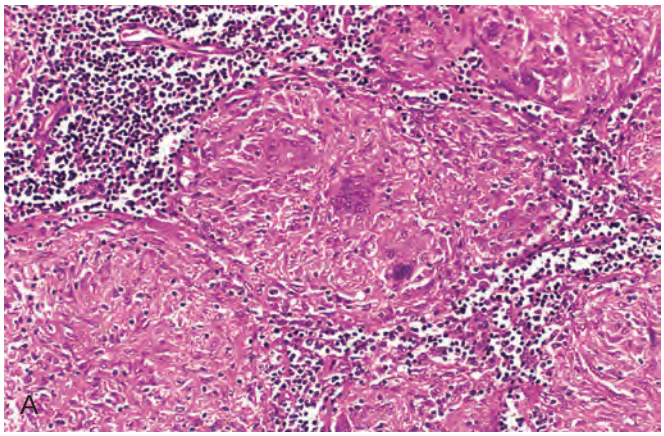


Figure 6-19 Delayed hypersensitivity reaction in the skin. **A,** Perivascular accumulation ("cuffing") of mononuclear inflammatory cells (lymphocytes and macrophages), with associated dermal edema and fibrin deposition. **B,** Immunoperoxidase staining reveals a predominantly perivascular cellular infiltrate that marks positively with anti-CD4 antibodies. (Courtesy Dr. Louis Picker, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)



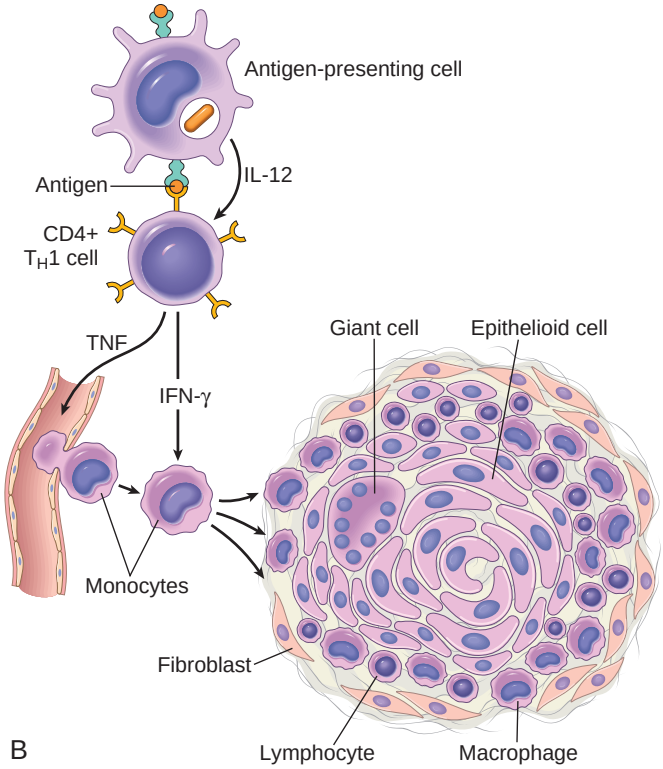


Figure 6-20 Granulomatous inflammation. **A,** A section of a lymph node shows several granulomas, each made up of an aggregate of epithelioid cells and surrounded by lymphocytes. The granuloma in the center shows several multinucleate giant cells. **B,** The events that give rise to the formation of granulomas in type IV hypersensitivity reactions, illustrating the role of T_H1 cytokines. In some granulomas (e.g., in schistosomiasis), T_H2 cells contribute to the lesions. The role of T_H17 cells in granuloma formation is not known. (**A,** Courtesy Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

with urushiol, the antigenic component of poison ivy or poison oak, and presents as a vesicular dermatitis. It is thought that in these reactions, the environmental chemical binds to and structurally modifies some self proteins and peptides derived from these modified proteins are recognized by T cells and elicit the reaction. Chemicals may also modify HLA molecules, making them appear foreign to T cells. The same mechanism is responsible for most *drug reactions*, among the most common immunologic reactions