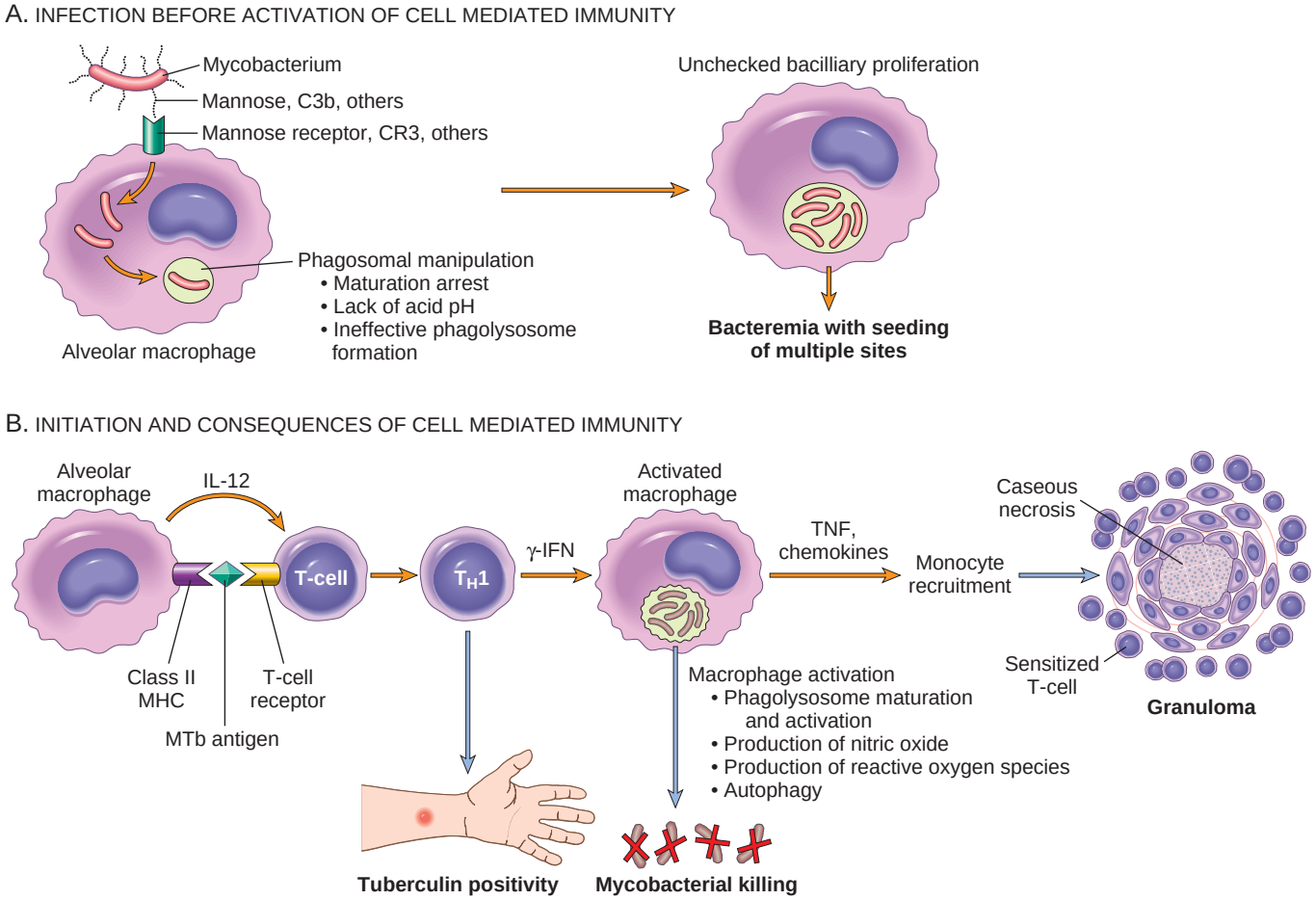

Figure 8-24 The sequence of events in primary pulmonary tuberculosis, commencing with inhalation of virulent *Mycobacterium tuberculosis* organisms and culminating with the development of cell-mediated immunity to the organism. **A,** Events occurring during early infection, before activation of T-cell–mediated immunity. **B,** The initiation and consequences of T-cell–mediated immunity. The development of resistance to the organism is accompanied by the appearance of a positive tuberculin test. γ-IFN, interferon-γ; MHC, major histocompatibility complex; MTB, *M. tuberculosis*; TNF, tumor necrosis factor.

This initiates and enhances the innate and adaptive immune responses to *M. tuberculosis*, as described below.

- *The T_H1 response.* About 3 weeks after infection, a T-helper 1 (T_H1) response is mounted that activates macrophages, enabling them to become bactericidal. The response is initiated by mycobacterial antigens that enter draining lymph nodes and are displayed to T cells. Differentiation of T_H1 cells depends on IL-12, which is produced by antigen-presenting cells that have encountered the mycobacteria. Stimulation of TLR2 by mycobacterial ligands promotes production of IL-12 by dendritic cells.
- *T_H1-mediated macrophage activation and killing of bacteria.* T_H1 cells, both in lymph nodes and in the lung, produce IFN-γ. **IFN-γ is the critical mediator that enables macrophages to contain the *M. tuberculosis* infection.** First, IFN-γ stimulates maturation of the phagolysosome in infected macrophages, exposing the bacteria to a lethal acidic, oxidizing environment. Second, IFN-γ stimulates expression of inducible nitric oxide synthase, which produces nitric oxide (NO). NO combines with other oxidants to create reactive nitrogen intermediates, which appear to be particularly important for killing of mycobacterium. Third, IFN-γ mobilizes antimicrobial peptides (defensins) against the bacteria. Finally, IFN-γ stimulates autophagy, a process that sequesters and then destroys damaged organelles and intracellular bacteria such as *M. tuberculosis*.
- *Granulomatous inflammation and tissue damage.* **In addition to stimulating macrophages to kill mycobacteria, the T_H1 response orchestrates the formation of granulomas and caseous necrosis.** Macrophages activated by IFN-γ differentiate into the "epithelioid histiocytes" that aggregate to form granulomas; some epithelioid cells may fuse to form giant cells. In many people this response halts the infection before significant tissue destruction or illness occur. In other people the infection progresses due to advanced age or immunosuppression, and the ongoing immune response results in caseation necrosis. Activated macrophages also secrete TNF and chemokines, which promote recruitment of more monocytes. The importance of TNF is underscored by the fact that patients with rheumatoid arthritis who are treated with a TNF antagonist have an increased risk of tuberculosis reactivation.