- *Role of other immune cells.* In addition to the T_H1 response, NKT cells that recognize mycobacterial lipid antigens bound to CD1 on antigen-presenting cells, or T cells that express a γδ T-cell receptor, also make IFN-γ. However, it is clear that T_H1 cells have a central role in this process, since defects in any of the steps in generating a T_H1 response result in absence of resistance and disease progression.
- *Host susceptibility to disease.* People with genetic deficiencies in the IL-12 pathway and the IFN-γ pathway, including STAT1 a signal transducer for IFN-γ, are vulnerable to severe mycobacterial infections. Polymorphisms in a large number of genes, including HLA, IFN-γ, IFN-γ receptor, and TLR2 have been found to be associated with susceptibility to tuberculosis, but the contribution of these associations to disease development is still under investigation.
- *Immunological state in active tuberculosis*. It is not entirely clear why some people progress from latent to active tuberculosis. Recent studies demonstrate that neutrophils in the blood of people with active tuberculosis express a group of genes that are upregulated by type I and type II interferons. The expression levels of these interferon-responsive genes correspond to the extent of lung disease as assessed by radiographic analysis. Furthermore, the expression levels of these genes fall in response to treatment for tuberculosis. This type of analysis suggests that an early interferon response is a harbinger of development of active disease, and has potential utility for diagnosis of active tuberculosis or for monitoring the extent of or response to treatment of active disease. A caveat is that while most patients with latent tuberculosis do not have this pattern of gene expression, 10 to 20% of them do.

In summary, immunity to *M. tuberculosis* is primarily mediated by T_H1 cells, which stimulate macrophages to kill the bacteria. This immune response, while largely effective, comes at the cost of accompanying tissue destruction. Reactivation of the infection or re-exposure to the bacilli in a previously sensitized host results in rapid mobilization of a defensive reaction but also increased tissue necrosis. Just as T-cell immunity and resistance are correlated, so, too, the loss of T-cell immunity (indicated by tuberculin negativity in a previously tuberculin-positive individual) may be an ominous sign that resistance to the organism has faded.

Clinical Features. Clinical tuberculosis is separated into two important pathophysiologic types: "primary" tuberculosis, which occurs in the nonimmune host, and "secondary" tuberculosis, which occurs in the host who is immune to *M. tuberculosis*. The many clinical-pathologic patterns of tuberculosis are shown in Figure 8-25.

Primary tuberculosis is the form of disease that develops in a previously unexposed and therefore unsensitized, person. Clinically significant disease develops in about 5% of newly infected people. With primary tuberculosis the source of the organism is exogenous. In most people, the primary infection is contained, but in others, primary tuberculosis is progressive. The diagnosis of progressive primary tuberculosis in adults can be difficult. In contrast to secondary tuberculosis (apical disease with cavitation; see later), progressive primary tuberculosis more often resembles an acute bacterial pneumonia with consolidation of the lobe, hilar adenopathy, and pleural effusion. Lymphohematogenous dissemination following primary infection may result in the development of tuberculous meningitis and miliary tuberculosis (discussed later).

Secondary tuberculosis is the pattern of disease that arises in a previously sensitized host. It may follow shortly after primary tuberculosis, but more commonly it appears many years after the initial infection, usually when host resistance is weakened. It most commonly stems from reactivation of a latent infection, but may also result from exogenous reinfection in the face of waning host immunity or when a large inoculum of virulent bacilli overwhelms the host immune system. Reactivation is more common in low-prevalence areas, while reinfection plays an important role in regions of high contagion.

Secondary pulmonary tuberculosis classically involves the apex of the upper lobes of one or both lungs. Because of the preexistence of hypersensitivity, the bacilli elicit a prompt and marked tissue response that tends to wall off the focus of infection. As a result, the regional lymph nodes are less prominently involved early in secondary disease than they are in primary tuberculosis. On the other hand, cavitation occurs readily in the secondary form. Indeed, cavitation is almost inevitable in neglected secondary tuberculosis, and erosion of the cavities into an airway is an important source of infection because the person now coughs sputum that contains bacteria.

Localized secondary tuberculosis may be asymptomatic. When manifestations appear, they are usually insidious in onset. Systemic symptoms, probably related to cytokines released by activated macrophages (e.g., TNF and IL-1), often appear early in the course and include malaise, anorexia, weight loss, and fever. Commonly, the fever is low grade and remittent (appearing late each afternoon and then subsiding), and night sweats occur. With progressive pulmonary involvement, increasing amounts of sputum, at first mucoid and later purulent, appear. Some degree of hemoptysis is present in about half of all cases of pulmonary tuberculosis. Pleuritic pain may result from extension of the infection to the pleural surfaces. Extrapulmonary manifestations of tuberculosis are legion and depend on the organ system involved.

The diagnosis of pulmonary disease is based in part on the history and on physical and radiographic findings of consolidation or cavitation in the apices of the lungs. Ultimately, however, tubercle bacilli must be identified. Acid-fast smears and cultures of the sputum of patients suspected of having tuberculosis should be performed. Culture on solid agar media show growth at 3 to 6 weeks, but culture in liquid media can provide an answer within 2 weeks. PCR amplification of *M. tuberculosis* DNA allows for even more rapid diagnosis. A PCR test has recently come into use that both identifies the presence of *M. tuberculosis* and, if the organism is detected, whether it is resistant to rifampin. This PCR assay is as sensitive as culture in acid-fast smear-positive samples, but it is slightly less sensitive in smear-negative tuberculosis, and substantially less sensitive in children. Thus, culture remains the gold standard because it also allows testing of drug susceptibility. Multidrug resistance is now seen more commonly than