microorganism and the host. According to recent developments, *latency* may not be an accurate term because bacilli may remain active during this "latent" stage, forming biofilms in necrotic areas within which they temporarily hide. Thus, the term *persister* is probably more accurate to indicate the behavior of the bacilli in this phase. It is important to recognize that latent infection and disease represent not a binary state but rather a continuum along which infection will eventually move in the direction of full containment or disease. The ability to predict, through systemic biomarkers, which affected individuals will progress toward disease would be of immense value in devising prophylactic interventions.

MACROPHAGE-ACTIVATING RESPONSE

CMI is critical at this early stage. In the majority of infected individuals, local macrophages are activated when bacillary antigens processed by macrophages stimulate T lymphocytes to release a variety of lymphokines. These activated macrophages aggregate around the lesion's center and effectively neutralize tubercle bacilli without causing further tissue destruction. In the central part of the lesion, the necrotic material resembles soft cheese (*caseous necrosis*)—a phenomenon that may also be observed in other conditions, such as neoplasms. Even when healing takes place, viable bacilli may remain dormant within macrophages or in the necrotic material for many years. These "healed" lesions in the lung parenchyma and hilar lymph nodes may later undergo calcification.

DELAYED-TYPE HYPERSENSITIVITY

In a minority of cases, the macrophage-activating response is weak, and mycobacterial growth can be inhibited only by intensified DTH reactions, which lead to lung tissue destruction. The lesion tends to enlarge further, and the surrounding tissue is progressively damaged. At the center of the lesion, the caseous material liquefies. Bronchial walls and blood vessels are invaded and destroyed, and cavities are formed. The liquefied caseous material, containing large numbers of bacilli, is drained through bronchi. Within the cavity, tubercle bacilli multiply, spill into the airways, and are discharged into the environment through expiratory maneuvers such as coughing and talking. In the early stages of infection, bacilli are usually transported by macrophages to regional lymph nodes, from which they gain access to the central venous return; from there they reseed the lungs and may also disseminate beyond the pulmonary vasculature throughout the body via the systemic circulation. The resulting extrapulmonary lesions may undergo the same evolution as those in the lungs, although most tend to heal. In young children with poor natural immunity, hematogenous dissemination may result in highly fatal miliary TB or tuberculous meningitis.

ROLE OF MACROPHAGES AND MONOCYTES

While CMI confers partial protection against *M. tuberculosis*, humoral immunity plays a less well-defined role in protection (although evidence is accumulating on the existence of antibodies to lipoarabinomannan, which may prevent dissemination of infection in children). In the case of CMI, two types of cells are essential: macrophages, which directly phagocytose tubercle bacilli, and T cells (mainly CD4+ T lymphocytes), which induce protection through the production of cytokines, especially IFN-γ. After infection with *M. tuberculosis*, alveolar macrophages secrete various cytokines responsible for a number of events (e.g., the formation of granulomas) as well as systemic effects (e.g., fever and weight loss). However, alternatively activated alveolar macrophages may be particularly susceptible to *M. tuberculosis* growth early on, given their more limited proinflammatory and bactericidal activity, which is related in part to being bathed in surfactant. New monocytes and macrophages attracted to the site are key components of the immune response. Their primary mechanism is probably related to production of oxidants (such as reactive oxygen intermediates or nitric oxide) that have antimycobacterial activity and increase the synthesis of cytokines such as TNF-α and IL-1, which in turn regulate the release of reactive oxygen intermediates and reactive nitrogen intermediates. In addition, macrophages can undergo apoptosis—a defensive mechanism to prevent release of cytokines and bacilli via their sequestration in the apoptotic cell. Recent work also describes the involvement of neutrophils in the host response, although the timing of their appearance and their effectiveness remain uncertain.

ROLE OF T LYMPHOCYTES

Alveolar macrophages, monocytes, and dendritic cells are also critical in processing and presenting antigens to T lymphocytes, primarily CD4+ and CD8+ T cells; the result is the activation and proliferation of CD4+ T lymphocytes, which are crucial to the host's defense against *M. tuberculosis*. Qualitative and quantitative defects of CD4+ T cells explain the inability of HIV-infected individuals to contain mycobacterial proliferation. Activated CD4+ T lymphocytes can differentiate into cytokine-producing T_H1 or T_H2 cells. T_H1 cells produce IFN-γ—an activator of macrophages and monocytes—and IL-2. T_H2 cells produce IL-4, IL-5, IL-10, and IL-13 and may also promote humoral immunity. The interplay of these various cytokines and their cross-regulation determine the host's response. The role of cytokines in promoting intracellular killing of mycobacteria, however, has not been entirely elucidated. IFN-γ may induce the generation of reactive nitrogen intermediates and regulate genes involved in bactericidal effects. TNF-α also seems to be important. Observations made originally in transgenic knockout mice and more recently in humans suggest that other T cell subsets, especially CD8+ T cells, may play an important role. CD8+ T cells have been associated with protective activities via cytotoxic responses and lysis of infected cells as well as with production of IFN-γ and TNF-α. Finally, natural killer cells act as co-regulators of CD8+ T cell lytic activities, and γδ T cells are increasingly thought to be involved in protective responses in humans.

MYCOBACTERIAL LIPIDS AND PROTEINS

Lipids have been involved in mycobacterial recognition by the innate immune system, and lipoproteins (such as 19-kDa lipoprotein) have been proven to trigger potent signals through Toll-like receptors present in blood dendritic cells. *M. tuberculosis* possesses various protein antigens. Some are present in the cytoplasm and cell wall; others are secreted. That the latter are more important in eliciting a T lymphocyte response is suggested by experiments documenting the appearance of protective immunity in animals after immunization with live, protein-secreting mycobacteria. Among the antigens that may play a protective role are the 30-kDa (or 85B) and ESAT-6 antigens. Protective immunity is probably the result of reactivity to many different mycobacterial antigens. These antigens are being incorporated into newly designed vaccines on various platforms.

SKIN TEST REACTIVITY

Coincident with the appearance of immunity, DTH to *M. tuberculosis* develops. This reactivity is the basis of the TST, which is used primarily for the detection of *M. tuberculosis* infection in persons without symptoms. The cellular mechanisms responsible for TST reactivity are related mainly to previously sensitized CD4+ T lymphocytes, which are attracted to the skin-test site. There, they proliferate and produce cytokines. Although DTH is associated with protective immunity (TST-positive persons are less susceptible to a new *M. tuberculosis* infection than TST-negative persons), it by no means guarantees protection against reactivation. In fact, cases of active TB are often accompanied by strongly positive skin-test reactions. There is also evidence of reinfection with a new strain of *M. tuberculosis* in patients previously treated for active disease. This evidence underscores the fact that previous latent or active TB may not confer fully protective immunity.

CLINICAL MANIFESTATIONS

TB is classified as pulmonary, extrapulmonary, or both. Depending on several factors linked to different populations and bacterial strains, extrapulmonary TB may occur in 10–40% of patients. Furthermore, up to two-thirds of HIV-infected patients with TB may have both pulmonary and extrapulmonary TB or extrapulmonary TB alone.

PULMONARY TB

Pulmonary TB is conventionally categorized as primary or postprimary (adult-type, secondary). This distinction has been challenged