for all principal outcomes of pericarditis—i.e., no significant impact on resolution of effusion, no significant difference in functional status after treatment, and no significant reduction in the frequency of development of constriction or death. However, in HIV-infected patients, glucocorticoids do improve functional status after treatment.

Caused by direct extension from the pericardium or by retrograde lymphatic extension from affected mediastinal lymph nodes, tuberculous myocarditis is an extremely rare disease. Usually it is fatal and is diagnosed postmortem.

Miliary or Disseminated TB Miliary TB is due to hematogenous spread of tubercle bacilli. Although in children it is often the consequence of primary infection, in adults it may be due to either recent infection or reactivation of old disseminated foci. The lesions are usually yellowish granulomas 1–2 mm in diameter that resemble millet seeds (thus the term *miliary*, coined by nineteenth-century pathologists). Clinical manifestations are nonspecific and protean, depending on the predominant site of involvement. Fever, night sweats, anorexia, weakness, and weight loss are presenting symptoms in the majority of cases. At times, patients have a cough and other respiratory symptoms due to pulmonary involvement as well as abdominal symptoms. Physical findings include hepatomegaly, splenomegaly, and lymphadenopathy. Eye examination may reveal choroidal tubercles, which are pathognomonic of miliary TB, in up to 30% of cases. Meningismus occurs in fewer than 10% of cases.

A high index of suspicion is required for the diagnosis of miliary TB. Frequently, chest radiography (Fig. 202-5) reveals a miliary reticulonodular pattern (more easily seen on underpenetrated film), although no radiographic abnormality may be evident early in the course and among HIV-infected patients. Other radiologic findings include large infiltrates, interstitial infiltrates (especially in HIV-infected patients), and pleural effusion. Sputum-smear microscopy is negative in most cases. Various hematologic abnormalities may be seen, including anemia with leukopenia, lymphopenia, neutrophilic leukocytosis and leukemoid reactions, and polycythemia. Disseminated intravascular coagulation has been reported. Elevation of alkaline phosphatase levels and other abnormal values in liver function tests are detected in patients with severe hepatic involvement. The TST may be negative in up to half of cases, but reactivity may be restored during chemotherapy. Bronchoalveolar lavage and transbronchial biopsy are more likely to provide bacteriologic confirmation, and granulomas are evident in liver or bone-marrow biopsy specimens from many patients. If it goes unrecognized, miliary TB is lethal; with proper early treatment, however, it is amenable to cure. Glucocorticoid therapy has not proved beneficial.

A rare presentation seen in the elderly, *cryptic miliary TB* has a chronic course characterized by mild intermittent fever, anemia, and—ultimately—meningeal involvement preceding death. An acute septicemic form, *nonreactive miliary TB*, occurs very rarely and is due to massive hematogenous dissemination of tubercle bacilli. Pancytopenia is common in this form of disease, which is rapidly fatal. At postmortem examination, multiple necrotic but nongranulomatous ("nonreactive") lesions are detected.

Less Common Extrapulmonary Forms TB may cause chorioretinitis, uveitis, panophthalmitis, and painful hypersensitivity-related phlyctenular conjunctivitis. Tuberculous otitis is rare and presents as hearing loss, otorrhea, and tympanic membrane perforation. In the nasopharynx, TB may simulate granulomatosis with polyangiitis. Cutaneous manifestations of TB include primary infection due to direct inoculation, abscesses and chronic ulcers, scrofuloderma, lupus vulgaris (a smoldering disease with nodules, plaques, and fissures), miliary lesions, and erythema nodosum. Tuberculous mastitis results from retrograde lymphatic spread, often from the axillary lymph nodes. Adrenal TB is a manifestation of disseminated disease presenting rarely as adrenal insufficiency. Finally, congenital TB results from transplacental spread of tubercle bacilli to the fetus or from ingestion of contaminated amniotic fluid. This rare disease affects the liver, spleen, lymph nodes, and various other organs.

Post-TB Complications TB may cause persisting pulmonary damage in patients whose infection has been considered cured on clinical grounds. Chronic impairment of lung functions, bronchiectasis, aspergillomas, and chronic pulmonary aspergillosis (CPA) have been associated with TB. CPA may manifest as simple aspergilloma (fungal ball) or chronic cavitary aspergillosis. Early studies revealed that, especially in the presence of large residual cavities, *Aspergillus fumigatus* may colonize the lesion and produce symptoms such as respiratory impairment, hemoptysis, persistent fatigue, and weight loss, often resulting in the erroneous diagnosis of TB recurrence. The detection of *Aspergillus* precipitins (IgG) in the blood suggests CPA, as do radiographic abnormalities such as thickening of the cavitary walls or the presence of a fungal ball inside the cavity. Treatment is difficult. Recent preliminary studies on the use of itraconazole for 6 months suggest that treatment with this agent may be superior to conservative treatment in improving radiologic and clinical manifestations of CPA. Surgical removal of lesions is risky.

HIV-Associated TB (See also Chap. 226) TB is one of the most common diseases among HIV-infected persons worldwide and a major cause of death in this population; more specifically, it is responsible for an estimated 24% of all HIV-related mortality. In certain urban settings in some African countries, the rate of HIV infection among TB patients reaches 70–80%. A person with a positive TST who acquires HIV infection has a 3–13% annual risk of developing active TB. A new TB infection acquired by an HIV-infected individual may evolve to active disease in a matter of weeks rather than months or years. TB can appear at any stage of HIV infection, and its presentation varies with the stage. When CMI is only partially compromised, pulmonary TB presents in a typical manner (Figs. 202-6 and 202-7), with upper-lobe infiltrates and cavitation and without significant lymphadenopathy or pleural effusion. In late stages of HIV infection, when the CD4+ T cell count is <200/μL, a primary TB–like pattern, with diffuse interstitial and subtle infiltrates, little or no cavitation, pleural effusion, and intrathoracic lymphadenopathy, is more common. However, these forms are becoming less common because of the expanded use of antiretroviral treatment (ART). Overall, sputum smears are less frequently positive among TB patients with HIV infection than among those without; thus, the diagnosis of TB may be difficult, especially in view of the variety of HIV-related pulmonary conditions mimicking TB. Extrapulmonary TB is common among HIV-infected patients. In various series, extrapulmonary TB—alone or in association with pulmonary disease—has been documented in 40–60% of all cases in HIV-co-infected individuals. The most common forms are lymphatic, disseminated, pleural, and pericardial. Mycobacteremia and meningitis are also common, particularly in advanced HIV disease. The diagnosis of TB in HIV-infected patients may be complicated not only by the increased frequency of sputum-smear negativity (up to 40% in culture-proven pulmonary cases) but also by atypical radiographic findings, a lack of classic granuloma formation in the late stages, and a negative TST. The Xpert MTB/RIF assay (see "Nucleic Acid Amplification Technology," below) is the preferred initial diagnostic option, and therapy should be started on the basis of a positive result because treatment delays may be fatal. A negative Xpert MTB/RIF result does not exclude a diagnosis of TB, and culture remains the gold standard.

Exacerbations in systemic (lymphadenopathy) or respiratory symptoms, signs, and laboratory or radiographic manifestations of TB—termed the *immune reconstitution inflammatory syndrome* (IRIS) or *TB immune reconstitution disease* (TB-IRD)—have been associated with the administration of ART and occur in ~10% of HIV-infected TB patients. Usually developing 1–3 months after initiation of ART, IRIS is more common among patients with advanced immunosuppression and extrapulmonary TB. "Unmasking IRIS" may also develop after the initiation of ART in patients with undiagnosed subclinical TB. The earlier ART is started and the lower the baseline CD4+ T cell count, the greater the risk of IRIS. Death due to IRIS is relatively infrequent and occurs mainly among patients who have a high preexisting mortality risk. The presumed pathogenesis of IRIS consists of an immune response that is elicited by antigens released as bacilli are killed during effective chemotherapy and that is temporally associated with improving immune function. There