and the injectable drugs) is mandatory when MDR-TB is found. Susceptibility testing may be conducted directly (with the clinical specimen) or indirectly (with mycobacterial cultures) on solid or liquid medium. Results are obtained rapidly by direct susceptibility testing on liquid medium, with an average reporting time of 3 weeks. With indirect testing on solid medium, results may be unavailable for ≥8 weeks. Highly reliable genotypic methods for the rapid identification of genetic mutations in gene regions known to be associated with resistance to rifampin (such as those in *rpo*B) and isoniazid (such as those in *kat*G and *inh*A) have been developed and are being widely implemented for screening of patients at increased risk of drug-resistant TB. Apart from the Xpert MTB/RIF assay, which, as mentioned above, detects rifampin resistance, the most widely used are molecular line probe assays. After extraction of DNA from *M. tuberculosis* isolates or from clinical specimens, the resistance gene regions are amplified by polymerase chain reaction (PCR), and labeled and probe-hybridized PCR products are detected by colorimetric development. This assay reveals the presence of *M. tuberculosis* as well as mutations in target resistance gene regions. A similar approach has been developed for second-line anti-TB drugs such as the fluoroquinolones, the aminoglycosides kanamycin and amikacin, and capreomycin, but the diagnostic accuracy of the current technology is not yet sufficient to recommend its use in clinical practice. Finally, a few noncommercial, inexpensive culture and drug-susceptibility testing methods (e.g., microscopically observed drug susceptibility, or MODS; nitrate reductase assays; and colorimetric redox indicator assays) may be useful in resource-limited settings. Their use is restricted to national reference laboratories with proven proficiency and adequate external quality control as an interim solution while genotypic or automated liquid culture technology is introduced.

RADIOGRAPHIC PROCEDURES

As noted above, the initial suspicion of pulmonary TB is often based on abnormal chest radiographic findings in a patient with respiratory symptoms. Although the "classic" picture is that of upper-lobe disease with infiltrates and cavities (Fig. 202-6), virtually any radiographic pattern—from a normal film or a solitary pulmonary nodule to diffuse alveolar infiltrates in a patient with adult respiratory distress syndrome—may be seen. In the era of AIDS, no radiographic pattern can be considered pathognomonic. CT (Fig. 202-7) may be useful in interpreting questionable findings on plain chest radiography and may be helpful in diagnosing some forms of extrapulmonary TB (e.g., Pott's disease; Fig. 202-10). MRI is useful in the diagnosis of intracranial TB.

ADDITIONAL DIAGNOSTIC PROCEDURES

Other diagnostic tests may be used when pulmonary TB is suspected. Sputum induction by ultrasonic nebulization of hypertonic saline may be useful for patients who cannot produce a sputum specimen spontaneously. Frequently, patients with radiographic abnormalities that are consistent with other diagnoses (e.g., bronchogenic carcinoma) undergo fiberoptic bronchoscopy with bronchial brushings and endobronchial or transbronchial biopsy of the lesion. Bronchoalveolar lavage of a lung segment containing an abnormality may also be performed. In all cases, it is essential that specimens be submitted for AFB smear, mycobacterial culture, and molecular testing with the Xpert MTB/RIF assay. For the diagnosis of primary pulmonary TB in children, who often do not expectorate sputum, induced sputum specimens and specimens from early-morning gastric lavage may yield positive cultures and/or Xpert MTB/RIF assay results.

Invasive diagnostic procedures are indicated for patients with suspected extrapulmonary TB. In addition to testing of specimens from involved sites (e.g., CSF for tuberculous meningitis, pleural fluid and biopsy samples for pleural disease), biopsy and culture of bone marrow and liver tissue have a good diagnostic yield in disseminated (miliary) TB, particularly in HIV-infected patients, who also have a high frequency of positive blood cultures. In some cases, culture or Xpert MTB/RIF assay results are negative but a clinical diagnosis of TB is supported by consistent epidemiologic evidence (e.g., a history of close contact with an infectious patient) and a compatible clinical and radiographic response to treatment. In the United States and other industrialized countries with low rates of TB, some patients with limited abnormalities on chest radiographs and sputum positive for AFB are infected with nontuberculous mycobacteria, most commonly organisms of the *M. avium* complex or *M. kansasii* (Chap. 204). Factors favoring the diagnosis of nontuberculous mycobacterial disease over TB include an absence of risk factors for TB and the presence of underlying chronic pulmonary disease.

Patients with HIV-associated TB pose several diagnostic problems (see "HIV-Associated TB," above). Moreover, HIV-infected patients with sputum culture–positive, AFB-positive TB may present with a normal chest radiograph. The Xpert MTB/RIF assay is the preferred rapid diagnostic test in this population of patients because of simplicity of use and a sensitivity of ~60% among AFB-negative culture-positive cases and of 97% among AFB-positive cases. With the advent of ART, the occurrence of disseminated *M. avium* complex disease that can be confused with TB has become much less common.

SEROLOGIC AND OTHER DIAGNOSTIC TESTS FOR ACTIVE TB

A number of serologic tests based on detection of antibodies to a variety of mycobacterial antigens are marketed in developing countries but not in the United States. Careful independent assessments of these tests suggest that they are not useful as diagnostic aids—especially in persons with a low probability of TB—because of their low sensitivity and specificity and their poor reproducibility. After a rigorous evaluation of the tests, the WHO issued a "negative" recommendation in 2011 in order to prevent their abuse in the private sector of many resource-limited countries. Various methods aimed at detection of mycobacterial antigens in diagnostic specimens are being investigated but are limited at present by low sensitivity. Determinations of ADA and IFN-γ levels in pleural fluid may be useful adjunctive tests in the diagnosis of pleural TB; their utility in the diagnosis of other forms of extrapulmonary TB (e.g., pericardial, peritoneal, and meningeal) is less clear.

DIAGNOSIS OF LATENT *M. TUBERCULOSIS* INFECTION

Tuberculin Skin Testing In 1891, Robert Koch discovered that components of *M. tuberculosis* in a concentrated liquid culture medium, subsequently named "old tuberculin," were capable of eliciting a skin reaction when injected subcutaneously into patients with TB. In 1932, Seibert and Munday purified this product by ammonium sulfate precipitation to produce an active protein fraction known as *tuberculin purified protein derivative* (PPD). In 1941, PPD-S, developed by Seibert and Glenn, was chosen as the international standard. Later, the WHO and UNICEF sponsored large-scale production of a master batch of PPD (RT23) and made it available for general use. The greatest limitation of PPD is its lack of mycobacterial species specificity, a property due to the large number of proteins in this product that are highly conserved in the various species. In addition, subjectivity of the skin-reaction interpretation, deterioration of the product, and batch-to-batch variations limit the usefulness of PPD.

The skin test with tuberculin PPD (TST) is most widely used in screening for LTBI. It probably measures the response to antigenic stimulation by T cells that reside in the skin rather than the response of recirculating memory T cells. The test is of limited value in the diagnosis of active TB because of its relatively low sensitivity and specificity and its inability to discriminate between LTBI and active disease. False-negative reactions are common in immunosuppressed patients and in those with overwhelming TB. False-positive reactions may be caused by infections with nontuberculous mycobacteria (Chap. 204) and by BCG vaccination. Repeated TST can produce larger reaction sizes due to either boosting or true conversion. The "boosting phenomenon" is a spurious TST conversion resulting from boosting of reactivity on subsequent TST 1–5 weeks after the initial test. Distinguishing boosting from true conversion is difficult yet important and can be based on clinical and epidemiologic considerations. For instance, true conversions are likely after BCG vaccination in a previously TST-negative person or in a close contact of an infectious patient.