2015). A vigorous immune response leads to the paucibacillary or tuberculoid form, in which there are few organisms present in a small number of anesthetic skin lesions, usually associated with swelling or thickening of a peripheral nerve. The spectrum of disease extends through so-called borderline forms to multibacillary or lepromatous leprosy in which there are huge numbers of organisms present in the skin, peripheral nerves, and nasal cavity. The commonly used classification system for clinical disease, which requires both a clinical and pathologic assessment, is the Ridley and Jopling scale (Ridley and Jopling, 1966). This was simplified into a three-part clinical scoring system: a single lesion, paucibacillary disease (two to five lesions), and multibacillary disease (more than five lesions) (Croft *et al.,* 2000). The presence or absence of disease and the form that it takes are dependent on the immune response of the host, which in turn is often genetically determined. This, together with the proximity to active cases, explains the phenomenon that leprosy appears to run in families (Britton and Lockwood, 2004).

Throughout history, there appears not to have been any effective form of treatment for the disease until the recognition by Mouat in 1854 that Chaulmoogra oil, from the Asian tropical tree *Hydnocarpus kurzii,* may have had some effect on the progress of the infection. This unpleasant oil had been fabled in Eastern legend as having miraculous properties against leprosy. Seeds were collected and transported in the late 1800s to Hawaii, where plantations were established. Once a reliable supply had been established, it became a common treatment in leprosariums around the world in the first half of the 20th century. It was either taken orally or injected, and appeared to have an inconsistent effect on the disease, with relapse being commonly described (Schujman, 1947). More recently, Chaulmoogra acids were found to be active against *M. leprae* in the mouse footpad system, lending support to the observations that it appeared to have some clinical effect (Levy, 1975).

The first synthetic antimicrobial agents to be successfully used for bacterial diseases in humans were the sulfonamides, developed initially by the aniline dye industry. Sulfonamides were trialed with only modest success in leprosy (Faget *et al.,* 1942), but were soon overtaken by the sulfones after the recognition of their high level of activity against *M. leprae* in rats (Cowdry and Ruangsiri, 1940).

The first trial of sulfones in leprosy involved dapsone derivatives, because dapsone itself was known to be too toxic at the doses thought to be necessary at the time. Glucosulfone sodium (promin) was evaluated in Carvill, Louisiana in the United States with clearly successful results (Faget *et al.,* 1943). Unfortunately, promin had to be given intravenously, so sulfoxone sodium (Diasone), acetosulfone (Promacetin), and acedapsone were developed as oral alternatives to promin. It was realized late in the 1940s that the dose of dapsone required to inhibit *M. leprae* was considerably lower than initially hypothesized, because the prolonged half-life led to rapid accumulation of the drug and severe methemoglobinemia and hemolysis when given at 1 g/day. This led to trials of less toxic doses being carried out. Lowe (1950) reported a trial of "low-dose" dapsone in 50 patients with lepromatous leprosy. Dapsone was given initially at 100 mg daily for 2 weeks, then 200 mg daily for 2 weeks, and then 300 mg daily, and the results were assessed after an average of 9 months of treatment. Seventy-two percent showed a definite clinical improvement, and 62% showed a definite bacteriologic improvement, with none showing any deterioration. Thirty percent developed a febrile reaction (erythema nodosum leprosum) (Lowe, 1950). Lowe also reported even more striking results of dapsone therapy at 100 or 200 mg/day in 15 patients with the tuberculoid form of the disease. As studies of dapsone's use in leprosy continued to demonstrate its success, the other sulfone preparations gradually fell into disuse. From the time of dapsone's acceptance as the mainstay of treatment in the 1950s, practically all patients diagnosed with leprosy were treated with the drug; however, the dose and duration were by no means constant, with some using a dose as low as 10 mg/day (Gelber *et al.,* 1974). Interruptions in treatment were common because of poor compliance, drug holidays, and cessation during upgrading reactions. These factors were important in the development of secondary dapsone resistance, first suspected in the late 1950s, and proven *in vitro* in 1964 (Ji, 1985). Primary dapsone resistance was reported in the 1970s (Pearson *et al.,* 1977; Jacobson and Hastings, 1978), and because it was by then known that rifampicin had a high level of activity against *M. leprae,* WHO recommended that all patients should receive MDT for all forms of the disease, with the dapsone dose at 100 mg/day with no interruptions (WHO, 1982). This change was introduced without formal trials being performed, although combination therapy with dapsone and rifampicin had been used widely in the United States for multibacillary leprosy since 1971 (Jacobson, 1994). Rifampicin (see Chapter 126, Rifampicin) is the single most potent drug against leprosy. Four days after a single dose of rifampicin 600 mg in a patient with untreated multibacillary disease, it is not possible to isolate the organism after inoculation of lepromatous material in the mouse footpad (Levy *et al.,* 1976). Unfortunately, as with most organisms, a single step mutation allows the development of rifampicin resistance, so in leprosy, treatment with rifampicin alone leads to secondary resistance and subsequent relapse in a high proportion of multibacillary cases (Jacobson and Hastings, 1976). Since the widespread use of MDT, multidrug-resistant *M. leprae* has not arisen. Relapses do occur, however, and the organisms isolated after failure of MDT appear to remain susceptible (Soares *et al.,* 1995).

The reported experience with the WHO MDT regimens for multibacillary disease has, in general, been very favorable. In the 1994 WHO technical report, unpublished WHO data from multiple sites were summarized (WHO, 1994). Between 1981 and 1993, 20,141 patients with multibacillary disease were treated with the WHO regimen. Only 67 were reported to have relapsed (0.74%) after a 9-year follow-up period. There were 306 relapses (1.09%) in 51,553 patients treated for paucibacillary disease. This compares with the expected relapse rate of 10–20% in multibacillary disease when dapsone monotherapy is used.