level, intermediate, and total, as outlined earlier. By the early 1980s, resistance prevalence rates of 10% in many centers around the world were common, and WHO convened a working group that reviewed the data and recommended the cessation of dapsone monotherapy, to be replaced by multidrug therapy (MDT) with dapsone, rifampicin, and clofazimine (WHO, 1982). The US Public Health Service (USPHS) Hansen's Disease Program had changed to MDT for similar reasons some years earlier (Moschella, 2004).

Dapsone resistance in *M. leprae* has now been shown to be due to mutations in the *DHPS* gene (*folP1*). Through use of DNA sequencing of *folP1* extracted from dapsone-resistant and dapsone-susceptible strains grown in mouse footpads, it was demonstrated that two mutations present at positions 53 and 55 were likely to be the cause (Kai *et al.,* 1999; Williams *et al.,* 2000; Nakata *et al.,* 2011). Multidrug resistance has now been widely reported (Cambau *et al.,* 1997), and molecular-based assays have now been developed to detect multidrug resistance in the organism (Williams and Gillis, 2004). Assays are now available that simultaneously detect the presence of the organism and dapsone resistance directly from clinical specimens (Williams *et al.,* 2001). DNA microarrays that detect multidrug resistance have also now been developed (Matsuoka *et al.,* 2008). The current incidence of dapsone resistance worldwide is unknown; however, it is still commonly observed (Roche *et al.,* 2000). The presence of mutations in the *folP1* gene has now been shown in the field to predict dapsone resistance in relapsed cases of *M. leprae* infection (Cambau *et al.,* 2006). A sample of 423 specimens from patients in Vietnam showed high rates of dapsone resistance in those with relapse who had been treated with dapsone monotherapy in the past; however, resistance in new and recent cases of leprosy was low (Kai *et al.,* 2011). Resistance incurred by this gene has now been shown to be transmissible (Li *et al.,* 2011).

PLASMODIUM SPECIES

Resistance to dapsone in *Plasmodium* species is generally thought to result from point mutations in the *DHPS* gene. However, the majority of *in vitro* research on resistance development and DHPS mutation has been directed toward the modification of the action of sulfonamides, and dapsone resistance has been indirectly inferred (Kublin *et al.,* 2002). A large number of mutations have been described, and the general accumulation of these correlate with *in vitro* assays of resistance. This also correlates with field studies that demonstrate clinical failures in the presence of these mutations (Gregson and Plowe, 2005). Differential resistance to combinations of DHFR and DHPS inhibitors has been observed, and resistance in *P. falciparum* to pyrimethamine–sulfadoxine combinations caused by mutations at positions 51, 59, and 108 of *P. falciparum* DHFR did not translate to resistance to the combination of chlorproguanil and dapsone (LapDap) (Roper *et al.,* 2003). In Asia and South America, a fourth mutation of *P. falciparum* DHFR (I164L) has rendered the parasite resistant to chlorproguanil, thereby negating the effectiveness of the combination with dapsone (Nair *et al.,* 2003).

It has been widely hypothesized that the long half-lives of pyrimethamine and sulfadoxine, resulting in prolonged subinhibitory levels of the drugs in plasma, contributed to widespread resistance development, and that the relatively short half-lives of the chlorproguanil–dapsone combination may reduce the pressure for resistance development (Watkins and Mosobo, 1993).

PNEUMOCYSTIS JIROVECI

Mutations in the *P. jiroveci DHPS* gene were first observed in patients who had received prophylaxis with trimethoprim–sulfamethoxazole (TMP–SMX) or dapsone (Kazanjian *et al.,* 1998), and a later study demonstrated that mutations occurred only in the *DHPS* gene and not the *DHFR* gene (Ma *et al.,* 1999). A further study showed that the likelihood of mutations arising in the *DHPS* gene directly correlated with the duration of prophylaxis (Kazanjian *et al.,* 2000). Further work has shown that there appears to be a variation in the prevalence of resistance mutations, depending on the city of origin of specimens taken (Huang *et al.,* 2006). The association of failure of therapy with resistance mutations has not yet been confirmed, although a nonsignificant trend toward an association of DHPS mutations with severity of illness was observed in a large cohort of HIV-infected patients (Crothers *et al.,* 2005). However, there has been a significant association of failure of prophylaxis with pyrimethamine–sulfadoxine and DHPS mutations (Nahimana *et al.,* 2003). The effect of dapsone was not reported.

TOXOPLASMA GONDII

A mutant strain generated *in vitro* with a 330-fold increase in sulfadiazine resistance associated with cross-resistance to dapsone and several other sulfonamides was described in 1992 (Pfefferkorn *et al.,* 1992). This was a result of a mutation of the parasite DHPS enzyme. Further evidence of sulfonamide resistance in wild strains has emerged, showing that the mutant DHPS enzyme was cross-resistant to sulfonamides and dapsone, although dapsone maintained the lowest inhibitory concentration (IC_{50}) of the DHPS inhibitors tested (Aspinall *et al.,* 2002). Evidence is, however, scanty and has not been related to treatment or prophylaxis failure (Menceur *et al.,* 2008).

3. MECHANISM OF DRUG ACTION

Dapsone is a class 1 antifolate that acts on the folic acid synthesis pathway by inhibiting the enzyme DHPS. This enzyme catalyzes *p*-aminobenzoate to form dihydropteroic acid, which in turn is transformed into dihydrofolic acid, which is the substrate for DHFR, the enzyme blocked by pyrimethamine and other DHFR inhibitors (Brunton and Parker, 2008). The inhibition of folate synthesis by inhibitors of these two enzymes leads to decreased levels of fully reduced tetrahydrofolate, an essential cofactor in purine and pyrimidine synthesis. This in turn leads to the cessation of DNA synthesis in the organism (Gregson and Plowe, 2005). The DHPS enzyme is structurally different when the bacterial