that study, the relative risk of developing MAC infection was 0.47 (95% CI: 0.19–1.16), which was not statistically significant (Opravil *et al.,* 1995b). There has been no larger study reported since then, and both had insufficient power to rule out a beta error.

7c. Malaria

Dapsone is only weakly active against *P. falciparum* and less active against non-*falciparum* species. Early trials of dapsone alone demonstrated high failure rates (Rieckmann *et al.,* 1968). Despite this, its use in malaria was pursued in the 1960s and an interesting insight into its introduction as an antimalarial during the Vietnam conflict has been published (Barr, 2011). *In vitro* studies demonstrated considerable synergy with the DHFR inhibitors pyrimethamine (see Chapter 93, Pyrimethamine) and cycloproguanil, and it has been in combination with these agents that dapsone has been found to have a role in the treatment and prophylaxis of *P. falciparum* infection. Early studies of pyrimethamine with dapsone in varying ratios in children in the Gambia with chronic *P. falciparum* infection showed that the combination demonstrated efficacy in suppression of parasitemia (Lucas *et al.,* 1969; Laing, 1970); however, the combination of sulfadoxine with pyrimethamine (Fansidar) rather than the combination of dapsone with pyrimethamine (Maloprim) was found to be more effective (see Chapter 91, Sulfonamides and Chapter 93, Pyrimethamine). Another study of patients with *P. falciparum* in Cambodia who were treated with varying dose levels of dapsone with pyrimethamine demonstrated a disappointing failure rate (Verdrager *et al.,* 1969). The drug combination was re-evaluated in a study in Thailand in which 44 patients aged 15–60 years with symptomatic *P. falciparum* infection were randomized to either a single dose of sulfadoxine 1 g plus pyrimethamine 50 mg, or a single dose of dapsone 200 mg plus pyrimethamine 25 mg. Only 38 patients could be evaluated; however, the patients treated with the dapsone–pyrimethamine combination had a significantly higher relapse rate. There may be a number of reasons for this, in particular the fact that the longer-acting component of the combination (pyrimethamine) was given as a dose half that used in the other combination; however, this was what was commercially available at the time (Segal *et al.,* 1975). The combination of dapsone with pyrimethamine then fell into disuse for treatment as the more effective sulfadoxine plus pyrimethamine (Fansidar) combination gained favor as preferred treatment for chloroquine-resistant *P. falciparum* infection.

Trials of Maloprim (dapsone plus pyrimethamine) for prophylaxis in children in endemic areas were markedly successful. In a trial of over 700 children, an age- and size-adjusted dose of Maloprim administered by village health workers weekly throughout the rainy season over a period of 5 years showed a reduction in overall mortality of 35% in treated children. This was accompanied by significant improvements in hematologic markers and other markers of general health. Side effects of the combination therapy were not apparent (Greenwood *et al.,* 1988). A similar study in infants in Tanzania some years later showed an equally impressive result (Lemnge *et al.,* 1997).

Maloprim was widely used as prophylaxis in travelers to malaria-endemic areas until a significant number of cases of fatal agranulocytosis were reported through the late 1970s and early 1980s (Friman *et al.,* 1983; Hutchinson *et al.,* 1986). Although twice-weekly administration was more strongly associated with the idiosyncratic adverse effect, a significant number of cases were also associated with once-weekly administration. The estimated rate of agranulocytosis ranged from 1:2000 to 1:20,000, a rate far higher than that seen with dapsone alone when used for leprosy (Phillips-Howard and Bjorkmann, 1990). As the cost–benefit balance had significantly changed, recommendations for its use were changed in favor of mefloquine or doxycycline, with Maloprim and Fansidar reserved for use in situations in which the rate of severe malaria far outweighed the rate of potential serious complications. These have subsequently changed again on a number of occasions (Shanks and Edstein, 2005).

Superimposed over the problem of severe adverse effects came that of rapidly developing resistance to DHFRs. Pyrimethamine resistance became apparent in Africa, Southeast Asia, and South America fairly soon after its use became widespread, and the long half-life and persisting low plasma levels of pyrimethamine when administered on a weekly basis were found to be significant factors in the induction of DHFR mutations (see Chapter 93, Pyrimethamine). The significant discordance between the short half-life of dapsone and long half-life of pyrimethamine compared with the longer half-life of sulfadoxine accentuated the situation when Maloprim was compared with Fansidar (Watkins and Mosobo, 1993; Nzila *et al.,* 1998; Nair *et al.,* 2003). The shorter half-life of chlorproguanil, which matches the half-life of dapsone, allowed the combination of the two drugs (LapDap) to be successfully trialed as treatment and prophylaxis in heavily endemic areas in Africa. The presence of the I164L resistance trait in Southeast Asia and South America curtailed its use to Africa. The combination has proven effective in a number of trials in Africa, and has even proven efficacious in Fansidar-resistant disease (Mutabingwa, 2001; Bukirwa *et al.,* 2004). Unfortunately, side effects associated with hemolysis in G6PD-deficient individuals constrained its use significantly, particularly as the trait is common in Africa, and field conditions in resource-poor countries mean that G6PD testing is often impractical. WHO outlined strict guidelines for its use in 2004 (WHO Technical Consultation, 2004).

As the I164L DHFR resistance trait that conferred resistance to chlorproguanil spread gradually in Africa, the WHO principle of MDT was addressed by the trial introduction of a triple combination agent: chlorproguanil, dapsone, and artesunate (Dacart). This combination was investigated in Africa in adults with *P. falciparum* infection and compared in a randomized control trial against artemether–lumefantrine (see Chapter 169, Artemisinins). The results showed that the two combinations appeared to have equivalent efficacy, but