and Briggs, 1974). *In vitro* studies suggest that pyrimethamine may inhibit tolbutamide metabolism, although the *in vivo* relevance of these data is less clear (Karbwang *et al.,* 1988). Phenobarbital therapy appears to be associated with a shortening of the pyrimethamine half-life and reduction in serum pyrimethamine concentrations when the two agents are administered concomitantly to children, compared with children treated solely with pyrimethamine (McLeod *et al.,* 1992). Such an effect may be predicted because phenobarbital induces hepatic enzymes that degrade pyrimethamine.

In vitro and animal studies suggest that zidovudine may reduce the efficacy of pyrimethamine in the treatment of *Toxoplasma* encephalitis, but this has yet to be confirmed in clinical studies (Israelski *et al.,* 1989). Co-administration with zidovudine enhances hematologic toxicity when used for toxoplasmic encephalitis in HIV-infected patients (Freund *et al.,* 2002). An *in vitro* assessment found no interaction between nine antiretroviral drugs and the anti-*Toxoplasma* effect of pyrimethamine and sulfadiazine (Derouin and Santillana-Hayat, 2000).

Artesunate does not appear to have any influence on the pharmacokinetics of pyrimethamine (Minzi *et al.,* 2007), whereas co-administration of artemether with pyrimethamine resulted in a significantly increased C_{max} and reduced the volume of distribution of pyrimethamine (Tan-ariya *et al.,* 1998).

Pyrimethamine inhibits the multidrug and toxin extrusion (MATE) transporter, which mediates the renal elimination of metformin; however, this did not correlate with increased hypoglycemia (Oh *et al.,* 2015).

6. ADVERSE REACTIONS AND TOXICITY

Toxicity associated with pyrimethamine alone and pyrimethamine in combination with dapsone (Maloprim) is discussed later. Toxicity associated with the combination of pyrimethamine and sulfadoxine (Fansidar) is discussed in Chapter 91, Sulfonamides.

6a. Hematologic side effects

Hematological side effects are uncommon with pyrimethamine doses recommended for malaria prophylaxis, although administration for prolonged periods may result in depression of hematopoiesis owing to inhibition of folate metabolism. Use of Maloprim has been associated with significant hematologic toxicity. In a review of adverse reactions to antimalarials, Phillips-Howard and West (1990) identified the rate of serious reactions to Maloprim as 1 per 9100 prescriptions, and for blood dyscrasias as 1 per 20,000 prescriptions with a fatality rate of 1 per 75,000. Such toxicity is possibly dose related because a higher rate of agranulocytosis has been identified in travelers taking twice the usual recommended dose for antimalarial prophylaxis—that is, one Maloprim tablet twice weekly instead of one tablet weekly (Bruce-Chwatt and Hutchinson, 1984; Hutchinson *et al.,* 1986). Hutchinson *et al.* (1986) speculated that this agranulocytosis may be caused by an idiosyncratic reaction to dapsone exacerbated by the concurrent administration of pyrimethamine. In addition to agranulocytosis, Phillips-Howard and West (1990) also noted that three patients developed cyanosis due to methemoglobinemia secondary to the dapsone component of Maloprim.

The higher doses of pyrimethamine administered in the treatment of toxoplasmosis are not infrequently associated with hematologic toxicity, including leukopenia, thrombocytopenia, megaloblastic anemia, and pancytopenia (Kabat *et al.,* 2014). Such toxicity can be reversed by cessation of pyrimethamine therapy or by co-administration of folinic acid (5–20 mg daily), with a mean time to bone marrow recovery of 3.89 days (Kabat *et al.,* 2014). Unlike folinic acid, co-administration of folic acid is likely to reduce the efficacy of pyrimethamine against *T. gondii* because it may result in "bypassing" of the inhibition of dihydrofolate reductase induced by pyrimethamine (Anonymous, 1988; Chute *et al.,* 1995).

Administration of pyrimethamine together with zidovudine in patients with HIV and toxoplasmic encephalitis has been associated with an increased number of deaths, likely associated with increased bone marrow toxicity (Freund *et al.,* 2002).

6b. Rashes

Adverse cutaneous reactions associated with pyrimethamine–sulfadiazine and pyrimethamine–clindamycin can be common in HIV-infected patients with toxoplasmosis, occurring in 75% and 58% cases, respectively (Caumes *et al.,* 1995). However, the role played by pyrimethamine in these reactions is unclear, given the known association between sulfadiazine and clindamycin and cutaneous reactions (see Chapter 85, Clindamycin and lincomycin). Skin hyperpigmentation was present in 60.7% (71/117) of patients affected by pyrimethamine toxicity in Pakistan (Khan Assir *et al.,* 2014). Hyperpigmentation was either diffuse or partial, primarily involving the face, hands, feet, abdomen, axillae, and groin.

6c. Gastrointestinal effects

High doses of pyrimethamine may be associated with atrophic glossitis, anorexia, vomiting, gastritis, abdominal cramps, and diarrhea. Administration of pyrimethamine with meals may reduce the upper gastrointestinal symptoms.

6d. Hepatotoxicity

Hepatotoxicity has been mostly associated with Fansidar at a rate of 1 per 11,000 Fansidar prescriptions. Serious hepatic disorders are less common with Maloprim, occurring at a rate of 1 per 75,000 Maloprim prescriptions (Phillips-Howard and West, 1990).

6e. Neurotoxicity

High dosages of pyrimethamine have been associated with a variety of nervous system side effects, including ataxia,