tremors, and seizures, and occasionally with less specific symptoms such as insomnia, depression, fatigue, malaise, headache, lightheadedness, and irritability. Marked mental obtundation has been associated with hyperammonemia and carnitine deficiency induced by treatment with pyrimethamine and sulfadiazine (see Chapter 91, Sulfonamides).

Seizures have been reported in patients being treated for toxoplasmic encephalitis. Severe confusion, asterixis, and mental obtundation have been associated with hyperammonemia and carnitine deficiency in a patient treated with 75 mg pyrimethamine plus 6 g sulfadiazine daily for cerebral toxoplasmosis. Correction of the carnitine deficiency with L-carnitine 300 mg daily resulted in prompt normalization of the patient's serum ammonia and mental state. The agent responsible for inducing the carnitine deficiency was not definitely identified, but the authors speculated that the deficiency may have been secondary to increased urinary carnitine losses induced by pyrimethamine and/or sulfadiazine, or that the metabolites of these agents may bind with carnitine, similar to some other drugs (Sekas and Paul, 1993).

6f. Eosinophilia and respiratory toxicity

Marked eosinophilia, including pulmonary eosinophilia, has been associated with administration of Maloprim; however, in general this is considered to be due to induction of a "dapsone syndrome" by the dapsone component (Grayson *et al.,* 1988; see Chapter 94, Dapsone). Nevertheless, reports of pulmonary eosinophilia in patients taking Fansidar or pyrimethamine plus chloroquine have raised the possibility that pyrimethamine is responsible for this adverse reaction (Davidson *et al.,* 1988).

6g. Nephrotoxicity

Increases in serum creatinine have been noted in some patients treated with pyrimethamine and dapsone. Opravil *et al.* (1993) studied six healthy volunteers after a single, combined dose of 100 mg pyrimethamine and 200 mg dapsone and noted increases in serum creatinine over a 28-hour period after administration from 81 ± 14 to 102 ± 16 μmol/l ($p = 0.002$), with a corresponding reduction in creatinine clearance from 125 ± 27 to 91 ± 26 ml/min ($p < 0.02$), but no change in inulin clearance, blood urea nitrogen, or beta-2-microglobulin. All changes were reversible within 21 days, and subsequent studies of both pyrimethamine alone and dapsone alone identified pyrimethamine as the agent responsible for the reduction in creatinine clearance. Similar studies in nine HIV-infected males before and after prophylaxis for 1 month with 75 mg pyrimethamine plus 200 mg dapsone weekly (i.e. total of four doses) identified an analogous rise in serum creatinine from 69 ± 17 to 87 ± 32 μmol/l ($p < 0.05$), but both creatinine and inulin clearances were unchanged. Thus pyrimethamine appears to reversibly inhibit renal tubular secretion of creatinine without affecting the GFR (Opravil *et al.,* 1993). Hematuria has been reported rarely with pyrimethamine, although not in the past 3 decades.

6h. Immunosuppression

Subtle forms of immunosuppression may be associated with Maloprim administration. Lee and Lau (1988) identified a 64% higher rate of nonspecific upper respiratory tract infections in military recruits receiving one Maloprim tablet weekly than in those not receiving antimalarial prophylaxis, with the largest monthly differences being recorded during the periods of harder training. They speculated that Maloprim was associated with some degree of immunosuppression, with physical stress possibly having a synergistic effect. It is likely that this effect is related to the dapsone component of Maloprim, because this is a well-known effect of dapsone (see Chapter 94, Dapsone).

6i. Miscellaneous side effects

Rarely, fever, hyperphenylalaninemia, and dryness of the throat have been reported with pyrimethamine therapy (McEnvoy, 1994).

Perinatal exposure to pyrimethamine has been shown to delay testicular development in rats; however, this did not correlate with reduced fertility (Gutiérrez-Pérez *et al.*, 2014). The relevance of this observation to humans is uncertain.

7. CLINICAL USES OF THE DRUG

7a. Toxoplasmosis

Pyrimethamine is the mainstay, and currently the most effective therapy, for all forms of toxoplasmosis in adults and children, when used in combination with other agents such as sulfadiazine or clindamycin (Leport *et al.,* 1988; Cohn *et al.,* 1989; Luft and Hafner, 1990; Dannemann *et al.,* 1992; Luft and Remington, 1992; Luft *et al.,* 1993; Georgiev, 1994; Mariuz *et al.,* 1994; Montoya and Liesenfield, 2004; Montoya *et al.,* 2015). The concentration of pyrimethamine necessary to inhibit or kill *Toxoplasma* tachyzoites has not been clinically established and, important to note, pyrimethamine is inactive against *Toxoplasma* cysts (Luft and Hafner, 1990; Huskinson-Mark *et al.,* 1991; Mariuz *et al.,* 1994). After ingestion of *Toxoplasma* oocytes, the organisms rapidly transform into tachyzoites, which multiply in tissue macrophages and disseminate via blood and the lymphatic system to the brain, heart, and lungs. In the immunocompetent host, the development of immunity is associated with the transformation of tachyzoites into latent cysts (bradyzoites), especially in brain and muscle, which may reactivate at times of reduced host immunity.

In the nonpregnant, immunocompetent host, acute toxoplasmosis does not generally require treatment (McCabe *et al.,* 1987). In such patients, infection is usually asymptomatic, often with lymphadenopathy around the head and neck,