pyrimethamine for treatment of malaria (Ayede *et al.*, 2010; Jansen, 2011; Sagara *et al.*, 2009), and sulfalene has been used with amodiaquine and pyrimethamine (Okafor *et al.*, 2010). However, malarial parasites have become sulfonamide resistant in many regions (see section 7, Clinical uses of the drug).

Sulfadiazine, sulfamethoxazole, and sulfisoxazole are active against *Toxoplasma gondii* both *in vitro* and *in vivo* (Meneceur *et al.*, 2008)—with a synergistic effect observed between sulfadiazine combined with pyrimethamine, trimetrexate–glycuronate, azithromycin (Bosch-Driessen *et al.*, 2002), piritrexim, and novel quinuclidine inhibitor compounds (Martins-Duarte *et al.*, 2006), as well as sulfisoxazole–pyrimethamine and trimethoprim–sulfamethoxazole (Derouin and Chastang, 1988; Harris *et al.*, 1988; Derouin and Chastang, 1989; van der Ven *et al.*, 1996). *In vivo* studies in mice suggest that a combination of sulfadiazine and pyrimethamine results in greater toxoplasma parasite clearance and lower relapse rates than sulfadiazine, pyrimethamine, or clindamycin given alone (Piketty *et al.*, 1990). However, natural resistance to sulfadiazine in *T. gondii* has been observed, and the mechanisms have not been fully elucidated (Doliwa *et al.*, 2013). Experimental dihalogenated sulfanilanilides have demonstrated activity against *T. gondii* and *Pneumocystis carinii* (Chio *et al.*, 1996). These compounds demonstrated inhibitor concentration in which the binding is reduced by half ($IC_{50}$) results 7- to 30-fold lower than sulfadiazine for *T. gondii* as well as 33–95% growth inhibition compared with 9% for sulfamethoxazole against *P. carinii.*

Sulfamoxole, sulfaquinoxaline, and dapsone are inhibitory *in vitro* to *Leishmania major* promastigotes (the insect stage), but the mode of activity may not be by the classic route of inhibition of *de novo* folate synthesis, and the clinical efficacy of sulfa drugs in leishmaniasis has been questioned (Peixoto and Beverley, 1987). Nevertheless, sulfamethoxypyrazine combined with artesunate and pyrimethamine has recently been used for treatment of cutaneous leishmaniasis (Adam and Hagelnur, 2009).

*Pneumocystis jirovecii* (formerly *carinii*) contains dihydropteroate synthetase activity that is inhibited by sulfonamides including sulfamethoxazole, sulfadoxine, dapsone, and least by sulfadiazine and sulfanilamide *in vitro* (Merali *et al.*, 1990). Anti-*Pneumocystis* sulfonamide activity has been confirmed in experimental models of *P. carinii* pneumonia in rats, in which sulfonamides and sulfones appear to be most active (Walzer *et al.*, 1992b; Hughes and Killmar, 1996). Improved efficacy was not demonstrated by the addition of a dihydrofolate reductase inhibitor such as trimethoprim or pyrimethamine in this model (Walzer *et al.*, 1992a; Walzer *et al.*, 1992b; Hughes and Killmar, 1996). In this murine *P. carinii* model sulfamethoxypyridazine was more efficacious than sulfamethoxazole (Bartlett *et al.*, 1998). Concurrent treatment of *T. gondii* and *P. jirovecii* with sulfonamide-containing regimens also occurs, especially in HIV-positive patients (Tsai *et al.*, 2002) (see Chapter 92, Trimethoprim and trimethoprim–sulfamethoxazole [cotrimoxazole], and Chapter 93, Pyrimethamine).

A study demonstrated antischistosomal activity with the antimalarial combination artesunate–sulfamethoxypyrazine–pyrimethamine (Adam *et al.*, 2008); however, it was the activity of the artemisinin derivatives that conferred this benefit, not the sulfamethoxypyrazine–pyrimethamine. In addition this combination has less efficacy for treatment of schistosomiasis compared with praziquantel (Mohamed *et al.*, 2009; Obonyo *et al.*, 2010; Sissoko *et al.*, 2009).

Sulfonamides may also play a role in the treatment of diarrhea caused by *Cyclospora cayetanensis* (trimethoprim–sulfamethoxazole) (Herwaldt, 2000; Kansouzidou *et al.*, 2004; Türk *et al.*, 2004; Sancak *et al.*, 2006) and *Isospora belli* (sulfadiazine–pyrimethamine) (Ebrahimzadeh and Bottone, 1996; Verdier *et al.*, 2000) (see Chapter 92, Trimethoprim and trimethoprim–sulfamethoxazole [cotrimoxazole], and Chapter 93, Pyrimethamine).

## FUNGI

*Paracoccidioides brasiliensis* (causative agent of South American blastomycosis) is usually susceptible to sulfonamides, but resistant strains occur naturally, and strains with acquired resistance may emerge during treatment (Restrepo and Arango, 1980; Hahn *et al.*, 2003). Sulfadiazine has been used most widely, and some authors recommend the combination of trimethoprim and sulfadiazine (cotrimazine) for patients with sulfadiazine-resistant strains (Brummer *et al.*, 1993). Sulfadiazine was equally as effective as itraconazole or ketoconazole in the treatment of moderately severe paracoccidioidomycosis (Shikanai-Yasuda *et al.*, 2002) (see Chapter 152, Ketoconazole, and Chapter 154, Itraconazole).

Sulfonamides have an effect on infections due to *Histoplasma capsulatum* (Goodwin *et al.*, 1980) and have been used in combination with trimethoprim to treat *H. capsulatum* var. *duboisii* (Loyd *et al.*, 1990). Sulfadiazine has no activity against *Exophiala spinifera* when used alone but demonstrates synergy with itraconazole (Vitale *et al.*, 2003).

Sulfonamides have demonstrated antifungal activity *in vitro* against *Aspergillus* species and are synergistic with other agents for *Paracoccidioides brasiliensis, Candida albicans,* and *Exophiala spinifera* (Afeltra *et al.*, 2001; Afeltra and Verweij, 2003; Hanafy *et al.*, 2007). For *A. fumigatus,* MIC values were 64 μg/ml for sulfamonomethoxine, sulfadiazine, sulfamethoxazole, and sulfaphenazole and 128 μg/ml for sulfadimethoxine and sulfisoxazole. No activity was observed with MIC values of ≥ 256 μg/ml for sulfisomidine, sulfamethizole, and sulfamethoxypyridazine. Sulfamethoxazole, alone or in combination with trimethoprim, sulfadiazine, and sulfamethoxypyridazine, demonstrated activity against *A. fumigatus, A. niger, A. flavus, A. oryzae,* and *A. nidulans* (Afeltra *et al.*, 2002; Hida *et al.*, 2005). Trimethoprim alone had no activity. None of the sulfonamides had significant activity against *A. ustus* or *A. terrus.* Prophylactic doses of trimethoprim–sulfamethoxazole at 160–800 mg daily should achieve peak sulfamethoxazole blood levels between 40 and 60 μg/ml, equal to or above the MIC of 19 of 20 *A. fumigatus* isolates (Afeltra *et al.*, 2001). Metal-based complexes with sulfacetamide derivatives have also shown *in vitro* activity