recipients suggested that i.v. sulfadimidine can cause a marked decrease in serum cyclosporine levels (Wallwork *et al.*, 1983; Jones *et al.*, 1986). Furthermore, concomitant administration of cotrimoxazole and cyclosporine has been associated with an increased incidence of nephrotoxicity, independent of the levels of either drug (Sands and Brown, 1989). Sulfapyridine may displace methotrexate from protein binding sites and increase the risk of methotrexate myelotoxicity.

Folate can aid malarial growth *in vitro* and can also antagonize the antimalarial action of sulfadoxine–pyrimethamine, but its role *in vivo* is not well understood. The role of blood folate concentrations and *in vivo* sulfadoxine–pyrimethamine failure was studied in Malawian children with *P. falciparum* malaria in a region with high prevalence of the quintuple mutant conferring sulfadoxine–pyrimethamine resistance (Dzinjalamala *et al.*, 2005). Blood folate concentrations were higher in those children with late treatment failure.

Fosamprenavir shares a sulfonylarylamine structure with sulfamethoxazole and darunavir (Phillips and Mallal, 2007). There is limited information on cross-reactivity between these drugs, and patients with sulfa or sulfonamide antibiotic hypersensitivity were not excluded from darunavir clinical trials.

Fluconazole (CYP2C9/19 and CYP3A4 inhibitor) can inhibit the formation of hydroxylamines (Winter and Unadkat, 2005) and may prove useful in preventing acetylation of sulfadiazine, thus limiting potential adverse reactions.

6. ADVERSE REACTIONS AND TOXICITY

6a. Gastrointestinal side effects

Nausea, vomiting, and diarrhea were common with earlier compounds such as sulfapyridine but are uncommon with the newer sulfonamides. There are at least two reports of toxic megacolon and *C. difficile* colitis associated with extensive use of topical SSD use: one in a patient with 34% total body surface area burns (Jennings and Hanumadass, 1998) and the other in a patient with bullous pemphigus vulgaris (Tan *et al.*, 2012).

6b. Neurotoxicity

Headache and dizziness were commonly reported with the older sulfonamides but are rare with the newer compounds. In the prepenicillin era, toxic psychoses due to sulfonamides were well described (Little, 1942). Other disturbances of the nervous system such as drowsiness, fatigue, insomnia, nightmares, confusion, depression, vertigo, ataxia, and peripheral neuritis have been reported (Weinstein *et al.*, 1960; Floris-Moore *et al.*, 2003). Acute encephalopathy and tremulousness, possibly owing to sulfadiazine, have been described in a patient with AIDS-related complex who was also being treated with pyrimethamine for refractory *I. belli* infection (Young, 1989). Neurotoxicity, manifested by agitation, confusion, hallucinations, and seizures, has also been associated with generalized hypersensitivity reactions in a couple of cases (Smith *et al.*, 1982).

There are case reports of meningoencephalitis associated with sulfonamides, particularly trimethoprim–sulfamethoxazole (Joffe *et al.*, 1989; Tunkel and Starr, 1990; Auxier, 1990) (see Chapter 92, Trimethoprim and trimethoprim–sulfamethoxazole [cotrimoxazole]) but also with sulfamethizole (Barrett and Thier, 1963) and sulfisoxazole (Blumenfeld *et al.*, 1996). Hypercellular pleomorphic CSF with sterile blood and CSF cultures was seen, with prompt resolution of symptoms on drug cessation. Magnetic resonance imaging demonstrated diffuse white matter abnormalities that resolved within months. Aseptic meningitis has also been reported with sulfasalazine (Houitte *et al.*, 2009; Tay *et al.*, 2012).

There is a case report of extrapyramidal symptoms (spasmodic torticollis, trismus, and akathisia) after ingestion of sulfadoxine–pyrimethamine for uncomplicated falciparum malaria (Adam and Elbashir, 2004). Although malaria itself can be associated with neurological manifestations, the symptoms occurred within 50 minutes of the first dose. Sulfasalazine has been associated with a case report of central-variant posterior reversible encephalopathy, with resolution of symptoms within 5 days of cessation of sulfasalazine and normalization of imaging at 30 days (Ocek *et al.*, 2015). There is also a case report of facial palsy associated with sulfasalazine use (Magnus *et al.*, 1993).

6c. Drug fever

Drug fever is rare with commonly used short-acting sulfonamides, such as sulfadimidine and sulfafurazole, although it was frequent with the earlier sulfonamides. Drug fever has been occasionally observed with the long-acting sulfonamide, sulfamethoxypyridazine (Grieble and Jackson, 1958).

6d. Hypersensitivity reactions

The mechanisms of idiosyncratic sulfonamide toxicity have not been clearly defined, although a number of authors have demonstrated an association between sulfonamide toxicity and slow acetylator status (with subsequent reduced ability to detoxify oxidative metabolites) (Shear *et al.*, 1986; Rieder *et al.*, 1989). In an *in vitro* assay, lymphocytes from 6 patients with a history of severe reactions to sulfonamides were compared with those of 20 controls. The lymphocytes of the sulfa-allergic patients demonstrated increased toxicity from sulfonamide metabolites but not from the drugs themselves (Shear *et al.*, 1986). Rieder *et al.* (1989) found that in the case of sulfamethoxazole hypersensitivity, the hydroxylamine derivative of this agent may be one of the reactive metabolites mediating these reactions. Thus, inherited differences in the rate of toxic metabolite production and detoxification, and the rate of acetylation of the parent drug, may contribute to hypersensitivity.

Allergic rashes are fairly frequent complications of sulfonamide therapy. Similar to the penicillins, these usually occur after 1–2 weeks of treatment but may appear earlier with prior sulfonamide sensitization. The most common types of rashes are maculopapular or urticarial, but erythema nodosum,