exfoliative dermatitis, or, rarely, Stevens–Johnson syndrome may occur (Alkadi, 2007). Photosensitivity can also result; these rashes may be accompanied by features of a serum sickness–like illness, such as fever and joint pains (Shear *et al.*, 1986). The risk of adverse cutaneous reactions to sulfadoxine is 40-fold higher when it is taken in regular doses for prophylaxis compared with single-dose treatment (Gimnig *et al.*, 2006). Adverse reactions reported during long-term antibiotic therapy with sulfonamides for recurrent urinary tract infections in children occurred in 10.4% of patients and were mostly cutaneous (Uhari *et al.*, 1996; Karpman and Kurzrock, 2004). None of these were serious or life-threatening, and they were reversible on drug cessation. The rate was higher in children younger than 2 years of age, and fewer than 10% of antibiotic courses were discontinued in children younger than 2 years of age.

Stevens–Johnson syndrome is the most serious form of hypersensitivity reaction to sulfonamides. In its most extensive form, this syndrome consists of erythema multiforme and ulceration of the mucus membranes of the eyes, mouth, and urethra, which can be very severe and sometimes fatal. This complication has been described in association with all sulfonamides, but the long-acting ones, sulfamethoxypyridazine and sulfadimethoxine, have been particularly implicated (Salvaggio and Gonzalez, 1959; Rallison *et al.*, 1961; Claxton, 1963). The FDA collected reports of 116 cases of Stevens–Johnson syndrome associated with long-acting sulfonamide administration from 1957–1965 from all parts of the world. The median time of appearance of this complication was about the 10th day of treatment (Carroll *et al.*, 1966). It was estimated that there had been about one or two cases reported for every 10 million doses of these drugs that had been distributed. The report suggested that this syndrome may be more common in children. Nine cases of Stevens–Johnson syndrome in children, with three fatalities, were reported from one Sydney hospital during the period 1962–1964 (Beveridge *et al.*, 1964). Fatal Stevens–Johnson syndrome occurred in a 26-year-old AIDS patient with cerebral toxoplasmosis who was given sulfadiazine–pyrimethamine after having experienced a previous cutaneous reaction to trimethoprim–sulfamethoxazole (Carrión-Carrión *et al.*, 1999).

The risk of Stevens–Johnson syndrome appears to be the main reason why the long-acting sulfonamides did not become more popular for general use (Pryles, 1970). Some authors used these compounds extensively for the treatment of urinary tract infections and did not encounter this complication (Brumfitt, 1970). Drugs other than sulfonamides may also cause this syndrome, and the underlying infection for which the drugs are given may sometimes be responsible for Stevens–Johnson syndrome. A variety of infectious agents, such as *M. pneumoniae* and herpes simplex virus, have an etiological role in this syndrome. The causative role of the sulfonamides is beyond doubt in many cases. Ström (1962) used provocative tests with suspected drugs (sulfonamides and others) in 29 patients who had had Stevens–Johnson syndrome and obtained positive reactions in 19. Lyell (1982) has also drawn attention to other instances in which this syndrome appeared to be precipitated by sulfonamides. Cases of agranulocytosis, Stevens–Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis with some fatalities have been reported in association with the use of Fansidar (pyrimethamine and sulfadoxine) for malaria (Hornstein and Ruprecht, 1982; Olsen *et al.*, 1982; Whitfield, 1982; CDC, 1985a, CDC, 1985b; Selby *et al.*, 1985) and for prophylaxis against *P. jirovecii* pneumonia in patients with AIDS (Navin *et al.*, 1985). Other adverse reactions associated with Fansidar have included serum sickness–type reaction, urticaria, exfoliative dermatitis, and hepatitis. As a result, indications for the use of this combination were altered, and Fansidar is no longer recommended for prophylaxis against malaria or pneumocystis pneumonia (see Chapter 93, Pyrimethamine). Sulfadiazine has also been associated with hypersensitivity and the drug rash with eosinophilia and systemic symptoms (DRESS) syndrome (McLeod *et al.*, 2006b; Yusuf *et al.*, 2013). There are now multiple reports of DRESS associated with sulfasalazine (Augusto *et al.*, 2009; Cookson *et al.*, 2013; Fathallah *et al.*, 2015; Rosenbaum *et al.*, 2010; Thacker *et al.*, 2015). The HLA-B*13:01 allele is associated with sulfasalazine-induced DRESS in a Chinese Han population (Yang *et al.*, 2014). Linear IgA dermatosis with DRESS has also been associated with sulfasalazine (Hernandez *et al.*, 2013b), as well as a morbilliform eruption as part of a hypersensitivity reaction (Tay *et al.*, 2012). Hypersensitivity associated with reactivation of human herpesvirus 6 and induction of antiphospholipid antibodies has been reported with sulfasalazine use (Tung *et al.*, 2011).

Adverse reactions, including rashes, to cotrimoxazole and sulfadoxine are more common in patients with AIDS (Hughes *et al.*, 1995). Up to 40% of patients with AIDS and toxoplasmic encephalitis are unable to complete a course of therapy with sulfadiazine–pyrimethamine because of adverse reactions to sulfonamides (Leport *et al.*, 1988; Caumes *et al.*, 1995). The rate of serious adverse reactions to cotrimoxazole in HIV-positive infants and children appears to be similar to that among adults (Rieder *et al.*, 1997). Early investigations suggested that the slow acetylator phenotype in HIV-positive individuals was associated with hypersensitivity reactions to cotrimoxazole, regardless of the stage of HIV disease (Carr *et al.*, 1994; Kaufmann *et al.*, 1996; Smith *et al.*, 1997). Contrary to these data, more recent studies have suggested that there may not be an association between slow acetylator genotype and hypersensitivity reactions (Pirmohamed *et al.*, 2000; O'Neil *et al.*, 2002; Alfirevic *et al.*, 2003). This may be due to discordance between methods of phenotype determination (O'Neil *et al.*, 2000). Another mechanism for adverse reactions to sulfonamides in HIV-positive individuals is glutathione deficiency. HIV Tat protein expression is associated with increased intracellular oxidative stress, decreased glutathione biosynthesis, and decreased cellular concentrations of total and reduced glutathione. Glutathione is important in protecting cells from the effects of sulfamethoxazole metabolites by preventing the oxidation of the hydroxylamine to the more toxic nitroso metabolite (Lin *et al.*, 2006).

Desensitization to sulfonamides has been reported in patients both with AIDS and without AIDS, with moderate