sulfonamides (Blum *et al.,* 1992; Carr *et al.,* 1993; Jorde *et al.,* 1993; Holtzer *et al.,* 1998). Successful desensitization with an 18-day oral dose-escalating regimen for a dapsone reaction characterized by rash and fever after a similar reaction to TMP–SMX that failed desensitization with that drug has been reported (Cook and Kossey, 1998).

6g. Dapsone (sulfone) syndrome

A severe hypersensitivity reaction to dapsone (dapsone hypersensitivity syndrome; DHS) has been widely reported but appears to be an uncommon occurrence—although the incidence has been estimated to be between 0.5% and 3.6%, and the mortality rate up to 9.9% (Zhang *et al.,* 2013). In a group of 700 patients with leprosy, there was an incidence of dapsone syndrome of 1.3% occurring within 6 weeks of commencement of the drug (Rege *et al.,* 1994). Dapsone syndrome manifests with fever, malaise, generalized morbilliform or exfoliative rash, hepatitis, generalized lymphadenopathy with or without hepatosplenomegaly, methemoglobinemia, and hemolytic anemia. On average, the syndrome occurs about 4 weeks after commencement of dapsone with a range of 2–6 weeks (Prussick and Shear, 1996; Kumar *et al.,* 1998). The syndrome may occur even 1–2 weeks after cessation of dapsone, explained by hepatic retention and prolonged enterohepatic circulation of the drug. The syndrome does not seem to be related to the dose being taken, because doses ranging from 50 mg to 300 mg daily have been implicated (Lee and Nashed, 2003). Eosinophilia is commonly present, liver involvement may be hepatitic or cholestatic, and liver biopsy usually shows epithelioid granulomas. Liver involvement may be mild or may progress to fulminant liver failure. The syndrome usually resolves after cessation of the drug. The use of prednisolone to hasten the resolution of the syndrome is controversial, with some reporting success and others reporting no effect (Lee and Nashed, 2003). Hypothyroidism has been reported as an occasional late sequela of the syndrome (Gupta *et al.,* 1992).

The syndrome is properly classified as a form of DRESS (drug reaction with eosinophilia and systemic symptoms) and has now been strongly associated with HLA-B*13:1—suggesting that a screening test could be used before commencement of dapsone, thus reducing the chance of development of this severe reaction (Zhang *et al.,* 2013).

6h. Hepatotoxicity

Hepatotoxicity is usually reported in association with the sulfone syndrome, but reactions ranging from mild disturbance of transaminases to fulminant liver failure requiring liver transplantation have been infrequently reported (Johnson *et al.,* 1986; Zhu and Stiller, 2001; Garcia *et al.,* 2014). It has been reported that co-administration of trimethoprim with dapsone in patients with HIV infection markedly increases the incidence of liver damage by up to 40% of one series (Zimmerman, 1999). A recent report of a rat model of dapsone-induced hepatotoxicity found that dapsone-induced oxidative stress was present, the antioxidant systems were impaired, and the *N*-hydroxylamine metabolite of dapsone was the likely mediator (Veggi *et al.,* 2008).

6i. Miscellaneous adverse effects

Numerous miscellaneous adverse effects associated with dapsone use have been reported. In general, they are rare and regarded as idiosyncratic. Neurotoxicity ranging from minor complaints to peripheral neuropathy (Hubler and Solomon, 1972) and acute psychosis (Gawkrodger, 1989; Sheela *et al.,* 1993) has been reported. Rarely, nephrotoxicity may occur, with isolated reports of papillary necrosis (Hoffbrand, 1978) and nephrotic syndrome (Belmont, 1967). Acute renal failure is a well-known sequela of severe acute intravascular hemolysis and therefore may be precipitated by dapsone use. Isolated cases of hypersensitivity pneumonitis have been reported and are regarded as rare idiosyncratic reactions (Jaffuel *et al.,* 1998; Tobin-D'Angelo *et al.,* 2004; Adar *et al.,* 2012). Pancreatitis may also rarely occur (Shivkumar, 2003). Dapsone may also cause falsely low levels of hemoglobin A1c in diabetic patients (Lai *et al.,* 2012)

6j. Carcinogenicity

When dapsone was given to animals in doses far in excess of those used in humans for prolonged periods of time, there was evidence that the drug may be potentially carcinogenic; however, this does not appear to be borne out in practice (Griciute and Tomatis, 1980). A report described 12 patients with leprosy who developed urothelial tumors after many years of dapsone ingestion; however, they were also taking phenacetin, an alternative carcinogenic explanation for their malignancies (Hironaka *et al.,* 1997). A comprehensive review of 1678 patients with leprosy treated between 1936 and 1977 in Carville, Louisiana in the United States found no evidence of an excess of cancer mortality in this large cohort, although they did note an excess of oral, bladder, and renal malignancies (Brinton *et al.,* 1984). An Australian Government study to see if there was an excess of malignancies in soldiers who had taken dapsone as malaria prophylaxis during the Vietnam War assessed 40,207 army personnel, of whom 23,262 received dapsone as part of antimalarial measures. No difference in mortality between the two groups from any cause was identified and, in particular, there was no difference in rates of malignancy as a cause of death (Wilson *et al.,* 2007).

6k. Overdosage

Deliberate or accidental overdose of dapsone may induce life-threatening toxicity, with the most common reaction being acute methemoglobinemia and hemolysis. High levels of methemoglobin lead to symptoms similar to severe hypoxia, including dyspnea, altered mental state, and ultimately death. Acute hemolysis tends to occur some days after ingestion.