and inhibits CYP3A4, and consequently has the potential of increasing dapsone levels, although it may not increase toxicity. Saquinavir inhibits CYP3A and may also increase dapsone levels when administered concurrently. The co-administration of zidovudine may potentiate bone marrow toxicity, and in a study comparing aerosolized pentamidine with oral dapsone, an increased mortality rate was seen in the group randomized to dapsone. The authors hypothesized that the interaction of zidovudine with dapsone decreased the effectiveness of the zidovudine, resulting in lower CD4 counts (Salmon-Ceron *et al.,* 1995). When dapsone given concurrently with zidovudine was investigated further, no change in pharmacokinetic parameters was observed (Lee *et al.,* 1996). The mild hyperbilirubinemia associated with atazanavir may be exacerbated by co-administration with dapsone, with resolution after its cessation (Noda *et al.,* 2012).

6. ADVERSE REACTIONS AND TOXICITY

Patients taking dapsone are subject to both dose-dependent toxicity and idiosyncratic reactions. In general, many millions of patients with leprosy have been successfully treated with dapsone with little, if any, problem with adverse effects, largely because the dose that is required is lower than the dose at which dose-dependent toxicity becomes problematic. When plasma levels remain below 5 μg/ml, dose-dependent toxicity is unlikely (Zuidema *et al.,* 1986); however, when it rises above that level, hematologic problems such as methemoglobinemia begin to rise in incidence. The mechanism of dose-dependent toxicity is thought to be mediated by the hydroxylamine metabolite. Hypersensitivity reactions to dapsone have recently been reviewed, with epidemiologic studies suggesting a prevalence rate of 1.4% (95% confidence interval [CI]: 1.2–1.7%) (Lorenz *et al.,* 2012).

6a. Methemoglobinemia

The most common side effect of dapsone therapy is methemoglobinemia (Coleman, 1993). In normal subjects, less than 1% of hemoglobin is in the form of methemoglobin. When the concentration in erythrocytes rises above 1%, methemoglobinemia is present (Ward and McCarthy, 1998). Administration of dapsone 100 mg/day for even a short period of time in normal patients may result in the development of significant methemoglobinemia (Manfredi *et al.,* 1979). This is caused by the hydroxylamine metabolite of dapsone, which reacts directly with oxyhemoglobin to form methemoglobin and the nitrosoarene dapsone, which is then in turn metabolized by nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase or glutathione back to the hydroxylamine, which can then again react with oxyhemoglobin to form methemoglobin, continuing a cycle of methemoglobin production. This cycle continues until the erythrocyte is depleted of glutathione. There are two erythrocytic electron transport systems that convert methemoglobin back to hemoglobin. One involves a nicotinamide adenine dinucleotide (NADH)–dependent reductase associated with cytochrome b5, and the other is a secondary NADPH-dependent pathway that can be activated by exogenous cofactor molecules such as methylene blue. Glutathione is reduced by NADPH and acts by interfering with the intracellular conversion of oxyhemoglobin to methemoglobin by intracellular oxidizing agents such as dapsone hydroxylamine. Methemoglobin production occurs in most patients receiving dapsone, and levels below 20% are usually asymptomatic, but some patients cannot tolerate even low levels (Manfredi *et al.,* 1979). Patients with a deficiency of the NADPH-dependent methemoglobin reductase are particularly susceptible to the development of symptomatic and often severe methemoglobinemia. Methemoglobin is unable to carry oxygen to the tissues, and symptoms are usually lethargy, headache, dyspnea, tachycardia, and nausea; in extreme cases, deaths have been reported. A characteristic feature is cyanosis, which develops when methemoglobin levels reach 15% and has a characteristic brown hue, labeled "chocolate cyanosis." Blood taken at venesection has a characteristic brown discoloration (Ward and McCarthy, 1998). When methemoglobinemia is suspected (clinically or because of low oxygen saturation meter readings), blood gas determination, blood methemoglobin concentration, complete blood examination, and reticulocyte counts should be performed. Mild symptoms can be managed with supplemental oxygen and cessation of the drug; however, severe cases require the administration of methylene blue intravenously. This rapidly reverses the situation and converts most methemoglobin to hemoglobin within an hour. There have been a number of cases of severe methemoglobinemia reported in the literature, with some the result of accidental or intentional dapsone overdose (Ward and McCarthy, 1998).

The production of the hydroxylamine metabolite is via the CYP450 enzyme complex, and the concurrent administration of cimetidine, which reduces the production of the hydroxylamine metabolite, has been shown to reduce the levels of methemoglobin *in vitro* (Ganesan *et al.,* 2010) and in patients with dermatitis herpetiformis treated with dapsone (Coleman *et al.,* 1990). Ascorbic acid may also be beneficial, but no trials have been reported—although Park *et al.* (2013) reported a case in which, owing to the unavailability of methylene blue, they used intravenous ascorbic acid successfully and suggested its use as an alternative therapy in the event of dapsone overdose (Park *et al.,* 2013).

Symptomatic methemoglobinemia is an uncommon side effect in patients with leprosy (Vieira *et al.,*, 2010) but appears to be more common when dapsone is used in normal doses for PCP prophylaxis in transplant patients. This may be due to interactions with some of the commonly used medicines in transplantation (Malasingam *et al.,* 2014; Mitsides *et al.,* 2014). It also has a greater impact on those who have hematologic malignancies, presumably because of their already compromised hemopoietic systems (Subramaniam *et al.,* 2010).