6b. Hemolysis

Acute and chronic hemolysis is common in patients receiving dapsone. This occurs in patients with normal G6PD activity. A majority of patients with leprosy treated with dapsone were reported to have hemoglobin reductions between 20 and 30 g/l (Byrd and Gelber, 1991). In a cohort of 194 patients receiving MDT for leprosy in Brazil, hemolytic anemia was observed in 48 (24.7%), with the mean fall in hemoglobin ranging from 12.8 to 10.3 g/l (Deps *et al.,* 2012). A high prevalence of hemolysis has been reported in stem cell transplant (SCT) patients receiving dapsone as PCP prophylaxis. Thirty patients who underwent SCT and received dapsone prophylaxis for PCP were compared with 26 SCT patients who received TMP–SMX; none had G6PD deficiency. Among those receiving dapsone, 80% showed laboratory evidence of hemolysis versus none receiving TMP–SMX (Oltenu *et al.,* 2012).

The hemolysis is a result of the oxidative damage sustained by erythrocytes from the action of the dapsone hydroxylamine metabolite, which shortens erythrocyte lifespan and induces premature removal from the circulation (Bordin *et al.,* 2010). Signs of hemolysis in the blood film are common with Heinz body formation and clinically significant anemia. It has been recommended that daily dapsone doses should not exceed 1.5 mg/kg body weight up to a maximum of 100 mg daily to minimize the development of hemolysis (Balakrishnan *et al.,* 1989). Concurrent administration of vitamin E has been proposed as a prophylactic measure to minimize hemolysis, but its use has not been proven to be effective (Smith, 1994).

Hemolysis has been reported in a mother and her breastfed child when the mother was being treated with dapsone for dermatitis herpetiformis (Sanders *et al.,* 1982).

6c. Hemolysis and G6PD deficiency

Patients with G6PD deficiency are subject to a far greater degree of hemolysis if they take dapsone. G6PD deficiency leads to the impairment of NADPH formation in the erythrocyte. This leads to a reduction of the regeneration of the hydroxylamine metabolite in the red cell, but a reduced capacity to protect against the oxidative stress because glutathione is more extensively depleted. This, in turn, leads to an increase in hemolysis. This means that G6PD-deficient patients are less prone to methemoglobinemia and more prone to hemolysis (Zhu and Stiller, 2001). It is recommended that all patients be tested for G6PD deficiency before they are given dapsone and, if it is present, doses should not exceed 50 mg/day. Alternatively, it has been shown that weekly administration of 600 mg of dapsone did not lead to excessive hemolysis in G6PD-deficient patients and that the leprosy that was being treated had an adequate response (Pettit and Chin, 1964). The degree of hemolysis incurred in patients with G6PD deficiency was clearly demonstrated in malaria trials of artemisinin-based combination therapy with some combinations containing artesunate, dapsone, and chlorproguanil. Children with malaria and undiagnosed G6PD deficiency were shown to develop potentially severe hemolysis (Van Malderen *et al.,* 2012; Pamba *et al.,* 2012).

6d. Agranulocytosis

Agranulocytosis is a major problem with dapsone use, although it appears that the patients' underlying condition and the co-administration of other drugs has an impact on its incidence. When dapsone is used in patients with leprosy, the complication is rare; however, when used in patients with dermatitis herpetiformis, the risk has been estimated as being between 1:240 and 1:425 (Hornsten *et al.,* 1990). When the combination of pyrimethamine and dapsone was used in malaria prophylaxis, the observed incidence of 1:2000 was far higher than originally expected (Friman *et al.,* 1983; Hutchinson *et al.,* 1986). Most cases resolve within a week of cessation of the drug; however, fatalities have been reported (Firkin and Mariani, 1977; Hutchinson *et al.,* 1986). The mechanism of damage to the neutrophils is not known but may involve immune-mediated mechanisms. One hypothesis is that hydroxylamine-damaged erythrocytes transport the metabolite to the bone marrow, where it is toxic to granulocyte precursors (Coleman, 2001).

6e. Aplastic anemia

Aplastic anemia is a far less common idiosyncratic reaction to dapsone (Foucauld *et al.,* 1985; Nicholls and Concannon, 1982; Meyerson and Cohen, 1994; Wiholm and Emanuelsson, 1996; Goulart *et al.,* 2005). In contrast to agranulocytosis, aplastic anemia involves the loss of all cell lines from the bone marrow and is generally fatal unless successfully treated with bone marrow transplantation. Occasional cases have been reported in which patients recovered spontaneously after cessation of the drug (Foucauld *et al.,* 1985).

6f. Dermatologic reactions

There have been many reports of various cutaneous reactions to dapsone, including exfoliative dermatitis, erythema multiforme, urticaria, morbilliform eruptions, and erythema nodosum. A case of a photosensitive drug eruption was reported in a patient being treated for dermatitis herpetiformis that was negative on patch testing for the drug but recurred after rechallenge with the oral agent, suggesting that the reaction was related to a metabolite (Vandersteen and Jordan, 1974). A fatal case of toxic epidermal necrolysis was reported in a woman with ovarian cancer who was treated with dapsone for a skin eruption (Tring and Church, 1977). Rash is a not an infrequent side effect of dapsone use in HIV-infected patients using dapsone for *P. jiroveci* prophylaxis. It is usually mild and may resolve despite continuing use. A proportion of patients will exhibit cross-sensitivity with