Treatment involves oxygen, intravenous methylene blue, and oral activated charcoal to stop the enterohepatic circulation and reabsorption of the drug. Other reported measures have included charcoal hemoperfusion, hemodialysis, high-dose vitamin C, and hyperbaric oxygen (Ferguson and Lavery, 1997; Park *et al.,* 2013).

6l. Safety in pregnancy and breastfeeding

Dapsone was not shown to be teratogenic in rats at doses up to 192 mg/kg/day or in rabbits at 200 mg/kg/day (Phillips-Howard and Wood, 1996). Dapsone has been widely used in the treatment of leprosy and malaria in pregnant women and does not appear to pose a risk to the fetus or to the newborn. In one case series, 26 women being treated for leprosy with dapsone had 58 pregnancies analyzed for adverse outcomes. Two infants had congenital abnormalities—one a cleft palate, and the other a dislocated hip. This occurrence was at the expected rate for any group of pregnancies (Maurus, 1978). Other series have also found that MDT for leprosy is also associated with satisfactory outcomes in the mother and child (Bhargava *et al.,* 1996; Lyde, 1997). Dapsone in combination with pyrimethamine (Maloprim) has been extensively used in the prevention of malaria (Greenwood *et al.,* 1988, 1989); however, the drug combination should now not be used owing to the high incidence of agranulocytosis. When it was used, reports of adverse reactions in pregnancy were uncommon, and it was felt that the risks of the treatment were far outweighed by the risks of the disease (Luzzi and Peto, 1993). Newer agents that have a better safety profile are now available. Dapsone in combination with chlorproguanil appears to be relatively safe in pregnancy, with few adverse reactions reported. An extensive review of the literature on dapsone safety in pregnancy and malaria therapy accumulated information on 924 pregnancies in which dapsone was given and found that there was no indication of maternal and fetal toxicity above what would be expected when dapsone was used in nonpregnant individuals; more specific trial evidence is still required (Brabin *et al.,* 2004).

Dapsone can cross the placenta and is excreted in breast milk together with its acetyl metabolite (Edstein *et al.,* 1986; Zuidema *et al.,* 1986). In a case of mild neonatal hemolytic anemia in a breastfed infant whose mother was taking 50 mg of dapsone daily, dapsone levels in breast milk were found to be, on average, 0.67 of the plasma levels in the mother (Sanders *et al.,* 1982). Infants with G6PD deficiency are at particular risk of hemolytic anemia if the breastfeeding mother is taking dapsone; otherwise it is generally safe to use when breastfeeding. In an investigation of excretion of dapsone and pyrimethamine in breast milk, it was found that the amount of both drugs present was insufficient to provide adequate malaria prophylaxis for the infant (Edstein *et al.,* 1986). The estimate of these researchers, based on the testing of three women who were taking 100 mg of dapsone daily, was that 4.6–14.3% of the oral dose was found in the breast milk. This formulation is now not used owing to safety concerns.

7. CLINICAL USES OF THE DRUG

7a. *Mycobacterium leprae* infection (Hansen's disease)

Leprosy is a chronic destructive granulomatous infection, predominately of skin, nerves, and the eye, caused by *M. leprae.* Known since antiquity, its destructive and deforming sequelae have generated great social stigma. Sufferers were stigmatized as "lepers," shunned and driven out from society, and forced to live together in leper colonies, also known as *leprosariums* or *lazarets.* The stigma of the diagnosis of leprosy has led to the widespread use of the term *Hansen's disease* as an alternative name for the condition, particularly in the United States. Gerhard Armauer Hansen, a Norwegian physician and pupil of Robert Koch, discovered that *M. leprae* was the cause of leprosy in Bergen, Norway in the late 19th century. Since that time, research has led to an in-depth understanding of the epidemiology and pathogenesis of the disease. This has led to the development of a cure with antimicrobial agents, of which dapsone was the first of a series of effective agents and has remained the principal drug included in modern multidrug regimens.

The lack of an *in vitro* culture system for the organism has been a major impediment to research; however, the complete sequencing of the organism's genome reported in 2001 (Cole *et al.,* 2001) has led to a surge in the understanding of its biology. It is now known that it is closely related to *M. tuberculosis* and that the two are descended from a common ancestral organism. It is an obligate intracellular parasite and survives within macrophages and Schwann cells. In humans, it prefers the cooler temperatures of the skin and peripheries. It can also replicate in the mouse footpad, and the nine-banded armadillo has provided a useful animal model of infection.

Leprosy is predominately spread via aerosol from the respiratory secretions of patients with the multibacillary or lepromatous form of the disease. The incubation period varies considerably, from as little as a few months to more than 30 years, with the mean incubation period for paucibacillary disease being estimated to be 4 years and the mean incubation period for multibacillary disease estimated at 10 years. Subclinical infection is likely to be common in places where the disease has not been controlled. Up to 5% of people in villages in India and Indonesia where there are untreated cases of multibacillary disease have detectable *M. leprae* DNA on nasal swabs (Hatta *et al.,* 1995; Ramaprasad *et al.,* 1997). The majority of those who develop subclinical infection do not develop the disease. It is thought that approximately 5% of those who have subclinical infection develop the early clinical form of the disease called *indeterminate leprosy.* This manifests as a single skin lesion that usually spontaneously resolves after a period of time. About 25% of those who have had indeterminate leprosy go on to develop the progressive form of the disease.

The clinical manifestations of the disease depend heavily on the host response to the organism (White and Franco-Paredes,