9.1 Introduction

Glutathione (GSH), a tripeptide present in all mammalian cells, takes part in several fundamental biological functions, including handling of reactive oxygen species (ROS), detoxification of xenobiotics and carcinogens, redox reactions, biosynthesis of DNA and leukotrienes, as well as neurotransmission and neuromodulation. Glutathione is metabolised via the γ-glutamyl cycle, which is catalysed by six enzymes. In man, hereditary deficiencies have been found in four of the six enzymes: i.e. γ-glutamylcysteine synthetase, GSH synthetase, γ-glutamyl transpeptidase and 5-oxoprolinase (see Larsson and Anderson 2001). Mutants have not yet been found in γ-glutamyl cyclotransferase and dipeptidase. Most of the mutations are leaky so that many patients have residual enzyme activity. Patients with defects in the biosynthesis of GSH (i.e. γ-glutamylcysteine synthetase and GSH synthetase) have haemolytic anaemia and may also show CNS involvement and metabolic acidosis. The aim of the treatment for these disorders is to avoid haemolytic crises and to support the endogenous defence against reactive oxygen species.

The clinical findings in patients with defects in the degradation of GSH are heterogeneous, more complex and frequently include damage to the CNS. No treatment has been recommended for these disorders.

γ-Glutamylcysteine synthetase deficiency (OMIM 230450) has been described in 8 patients in six families. All have had well-compensated haemolytic anaemia and three have also had neurological symptoms such as spinocerebellar degeneration, neuropathy, myopathy, psychosis and learning disabilities (Richards et al. 1974; Beutler et al. 1999). The recommended treatment is to avoid drugs and foods known to precipitate haemolytic crises in patients with glucose-6-phosphate dehydrogenase deficiency. Early supplementation with the antioxidant vitamins C and E seems to prevent damage to the CNS in patients with GSH synthetase deficiency (Ristoff et al. 2001). In analogy supplementation with vitamins C and E might be worth testing also in patients with γ-glutamylcysteine synthetase deficiency. However, no studies of this treatment have yet been made.

Glutathione synthetase deficiency (OMIM 266130) has been confirmed in more than 70 patients in about 60 families. Approximately 25% of these patients have died in childhood – usually in the neonatal period – of electrolyte
imbalance and infections. Treatment in the neonatal period involves correction of acidosis and electrolyte imbalance, and early treatment with the antioxidants vitamins E and C to prevent damage to the CNS (Ristoff et al. 2001). GSH synthetase deficiency can be classified according to the severity of clinical signs as mild, moderate or severe (Ristoff et al. 2001). The clinical symptoms range from only haemolytic anaemia to metabolic acidosis, 5-oxoprolinuria, progressive neurological symptoms and sometimes also recurrent bacterial infections, due to defective granulocyte function. In some patients with the severe form, the eyes are affected: e.g. retinal pigmentation, crystalline opacities in the lenses, poor adaptation to darkness and pathological electroretinograms (Larsson et al. 1985). Several patients with a deficiency of GSH synthetase have died, but few have been autopsied. The first patient described with GSH synthetase deficiency died at 28 years of age. The autopsy of the CNS showed selective atrophy of the granular cell layer of the cerebellum, focal lesions in the frontoparietal cortex, the visual cortex and thalamus (Skullerud et al. 1980). The lesions in the brain resemble those seen after intoxication with the toxic compound mercury, i.e. Minamata disease, and it has therefore been suggested that treatment of GSH synthetase deficiency with antioxidants may be beneficial (Skullerud et al. 1980). The goal of treatment in patients with GSH synthetase deficiency is to correct the acidosis and to compensate for the lack of antioxidant capacity in the cells. A long-term follow-up study of 28 patients showed that early supplementation with the antioxidant vitamins C and E is useful for preventing damage to the CNS in patients with GSH synthetase deficiency (Ristoff et al. 2001). Recommended treatment does not normalize the elevated excretion of 5-oxoproline in urine.

A pregnancy in one woman with moderate GSH synthetase deficiency has been described and resulted in a healthy infant (Ristoff et al. 1999).