Gaucher’s disease is the most prevalent glycolipid storage disorder. A deficiency in the enzyme, glucocerebrosidase, causes the accumulation of glycolipid in a variety of organs. In many cases, very possibly the majority, manifestations of the disease are so mild as to have a trivial effect on quality and length of life. However, the disease can be devastating, resulting in massive enlargement of the liver and spleen, bone lesions, and in neurological manifestations in the rare type 2 and type 3 forms of the disease.

Alglucerase is a modified glucocerebrosidase preparation that has been found to be effective in the treatment of Gaucher’s disease.

1. Inheritance and Incidence of Gaucher’s Disease

Gaucher’s disease is inherited as an autosomal recessive disorder. It is most common in the Ashkenazi Jewish population, where approximately 6.8% of the population are carriers (heterozygotes) [Beutler et al. 1993b]. In this population, there is an estimated birth frequency of Gaucher’s disease of about 1 in 1000. In the Jewish population, the most common mutation is an adenine to guanine transition at cDNA nucleotide (nt) 1226. This abnormality is carried by 6.4% of the population, which accounts for about 75 to 80% of the mutations found in the Jewish population with Gaucher’s disease.

The second most common mutation is an insertion of a guanine at nt 84; in the Jewish population this mutation accounts for approximately 12% of the disease, and the heterozygote frequency has been estimated at 0.4%. There is also a small isolated population in Norbottnia, Northern Sweden with a high gene frequency of Gaucher’s disease. Here the mutation is at nt 1448.

Apart from the small Swedish group, Gaucher’s disease is rare in the non-Jewish population. No reliable estimates are available, but there is no question that the disease is panethnic, with reports involving such diverse groups as the Japanese (Eto et al. 1993), Africans (Forster et al. 1978; Muguti et al. 1987) and other populations (Beutler & Gelbart 1993). In The Netherlands, virtually none of the population of about 15 million are known to be of Jewish descent, and there are between 100 and 200 known cases of Gaucher’s disease. This incidence of 1 in 100 000 suggests a heterozygote frequency of about 0.6% in this population. Many of the Dutch patients have the nt 1226 guanine mutation, characteristic of the disease in Jews, and thus may have some Jewish ancestry. In non-European countries, such as Japan, the nt 1226 guanine mutation has not been encountered (Beutler & Gelbart 1993). Without this mutation, the overall gene frequency for Gaucher’s disease is probably lower still. This information suggests that some 15 000 individuals...
in the US, and perhaps 40,000 persons worldwide, are affected by this disease.

2. Conventional Treatment

Until 1991, therapy of Gaucher’s disease consisted of a variety of symptomatic measures designed to correct, as far as possible, the various complications of this disorder. Commonly, the spleen was removed to correct the low platelet count that creates a threat to health in those patients in whom bone marrow function has been impaired and the spleen has grown very large. Damage to the head of the thigh bone has been treated with joint replacement. Braces aid patients with collapse of vertebral bodies, and sometimes surgical decompression of the spinal cord has been necessary.

3. Enzyme Replacement Therapy

3.1 History

Gaucher’s disease has long been considered an ideal target for various therapeutic efforts. This is because of the high prevalence of the disease compared with most other genetically determined diseases, and because many of the disease manifestations are reversible.

The possibility that infusion of the missing enzyme could correct the defect in storage diseases was first suggested by de Duve (1964). In 1974, Brady et al. (1974) were the first to infuse partially purified glucocerebrosidase into patients with Gaucher’s disease (n = 2). However, although a decrease in liver glucocerebroside content was reported to have occurred, there was no therapeutic response. Recognising that it would probably be necessary to direct the enzyme to the cells in the body where the glycolipid was stored, we targeted enzyme to the storage cells (macrophages). This was achieved by incorporating the enzyme into red blood cells and coating the cells with immunoglobulin to improve delivery to macrophages. The results demonstrated for the first time a decrease in liver size of a patient being treated with exogenous human glucocerebrosidase (Beutler et al. 1977).

Delivering enzyme to macrophages by incorporation into red blood cells was, however, technically quite cumbersome. In 1978, it was reported that the cells that accumulate glycolipid in Gaucher’s disease had surface sites that bound the common sugar, mannose (Achord et al. 1978). The enzyme glucocerebrosidase contains mannose and can be altered to increase the amount exposed (Doebber et al. 1982; Furbish et al. 1984; Murray et al. 1985). This type of modification led ultimately to the commercial production of glucocerebrosidase from which terminal sugars had been removed enzymatically in order to expose additional mannose. This preparation (alglerase) was found to be effective, first in an anecdotal report of 1 child (Barton et al. 1990) and subsequently in a study of 12 patients (Barton et al. 1991a).

3.2 Mechanism of Action

It is ironic that although alglerase is quite effective in the treatment of Gaucher’s disease, its designation as ‘macrophage-targeted glucocerebrosidase’ is inaccurate. Both in vivo human studies (Beutler 1992) and in vitro models (Sato & Beutler 1993) show that only minimal amounts of the agent are delivered to macrophages. Indeed, most of the enzyme has been shown to bind to a nonspecific receptor that is quite distinct from the classical mannose receptor first described by Achord et al. (1978). This receptor is present on all body cells and diverts the enzyme from cells in which therapeutic effects can occur. Unfortunately, there are only a small number of specific, high-affinity receptors on macrophages and large numbers of low affinity nonspecific receptors for alglerase. This fact, coupled with the very short half-life of alglerase, led to proposals that frequent small doses would be more effective than large doses administered at infrequent intervals.

3.3 Dosage

Barton and colleagues (1991a) selected a large dose of the enzyme preparation to avoid the possibility of an equivocal result due to the need for a larger dose than was administered. They infused alglerase 60 U/kg every 2 weeks to 10 patients and once weekly to 2 additional patients. These