Hereditary anaemias: genetic basis, clinical features, diagnosis, and treatment*

**WHO WORKING GROUP**

The hereditary anaemias present a major genetic health problem that contributes considerably to childhood mortality and morbidity in many developing countries. This article summarizes recent scientific and technical advances in knowledge concerning the genes involved and their interaction to produce major haemoglobinopathies, the clinical pictures of these conditions, and their diagnostic criteria. Though there is no definitive cure, supportive treatment for the haemoglobinopathies has improved significantly, offering better quality of life and improved survival, and should be attempted for all such patients. For sickle cell disease, this comprises a simple set of rules that should be incorporated into existing medical care, whereas for thalassaemia, a regimen of intensive blood transfusion and regular subcutaneous infusion of deferoxamine is recommended. This treatment is stressful and probably too expensive to be applied in many developing countries until the birth rate of patients needing it can be sufficiently reduced by community control programmes.

The hereditary anaemias are among the commonest of the genetically-determined diseases and comprise a group of conditions of considerable complexity. However, because of the easy accessibility of the red blood cell more has been learnt about the genetic and molecular basis of anaemias than about any other inherited human disease. Many hereditary anaemias are rare and are not important as regards public health. However, two groups, the inherited disorders of haemoglobin (haemoglobinopathies) and a deficiency of the red-cell enzyme glucose-6-phosphate dehydrogenase (G6PD), because their heterozygous carrier states appear to provide resistance against *Plasmodium falciparum* malaria, have achieved an extraordinarily high frequency in the world population. In countries where they occur commonly, the haemoglobinopathies are now producing an increasing public health problem.

Because they are so common and have such serious consequences for affected communities, this article will be confined to consideration of the haemoglobinopathies and will not deal further with the problem of G6PD deficiency. This is not to say that the latter

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1 The participants in the Working Group are listed on page 660.
condition is unimportant. There are an estimated 100 million individuals in the world who are G6PD-deficient and who may develop serious neonatal jaundice, severe anaemia when treated with a variety of important drugs, or sensitivity to the fava bean, which produces the clinical syndrome of favism. However, G6PD deficiency is a much less urgent problem than that caused by the common haemoglobinopathies; and wherever the management of haemoglobinopathies is initiated, diagnosis and care for G6PD deficiency may easily be provided.

Of the many inherited disorders of haemoglobin, only two, sickle cell disease and thalassaemia, are a major drain on health resources. Sickle cell disease is common in many parts of tropical Africa and in other parts of the world where 

P. falciparum malaria has been endemic or there are immigrant groups with the sickle cell gene. The thalassaemias are more widespread and occur with high frequency in a line extending through the Mediterranean littoral and islands, south-west Asia, the Indian subcontinent, and throughout South-East Asia, in a region including southern China, Laos, Peninsular Malaysia, Thailand, and many of the islands. The haemoglobinopathies are already a serious public health problem in the above areas, and as infant mortality rates fall with progress in controlling malnutrition and infection, these genetic diseases will pose a major challenge.

This article surveys present knowledge concerning the nature of the more important haemoglobinopathies, with particular emphasis on their diagnosis, clinical features, and treatment. A Memorandum in a subsequent issue of the Bulletin of the World Health Organization (5) will discuss the health burden that these diseases already present, with particular emphasis on measures for controlling them at the community level. The various thalassaemia syndromes have recently been exhaustively reviewed by Bunn et al. (3) and Weatherall & Clegg (20).

GENETIC BASIS

As one of the main objectives of haemoglobinopathy screening programmes is to be able to offer fetal diagnosis, it is necessary to be able to predict the clinical picture arising from different gene combinations as precisely as possible, and this requires a knowledge of the genetic basis of haemoglobin synthesis, the molecular causes of the many haemoglobinopathies, and the clinical syndromes they produce.

All the molecules of human haemoglobin consist of four peptide chains, each associated with one haem group. Four basic types of peptide chain are found (α, β, γ, δ) and each haemoglobin molecule contains one pair of one type and another pair of another type, for example, two α-chains and two β-chains; \( \zeta \) (zeta) and \( \epsilon \) (epsilon) chains are the embryonic counterparts of the adult α- and non-α-chains, respectively. Human haemoglobin is heterogeneous at all stages of development. In adult life, in addition to Hb A (\( \alpha_2\beta_2 \)) there is a minor component Hb A\( _2 \) (\( \alpha_2\delta_2 \)) which normally forms about one-fortieth of the haemoglobin. The major haemoglobin from about the eighth week of gestation until term is Hb F (\( \alpha_2\gamma_2 \)), but the normal fetus also makes about 7% of Hb A: it is this fact that has permitted the antenatal diagnosis of the haemoglobinopathies with present methods. Finally, there are at least three embryonic haemoglobins, Portland (\( \zeta_2\gamma_2 \)), Gower 1 (\( \zeta_2\epsilon_2 \)), and Gower 2 (\( \zeta_2\delta_2 \)).

Each of the different globin chains is controlled by one or more structural genes whose arrangement has been worked out in great detail (Fig. 1). On chromosome 16 there are two α-globin genes per haploid genome linked to two \( \zeta \)-genes. The non-α-genes are clustered on chromosome 11 in the order of activation \( \epsilon-\gamma^-\alpha^-\delta^-\beta \). The genes of these
complexes are activated and switched off sequentially during normal human development with the production of embryonic, fetal, and adult haemoglobins.

There are two main groups of inherited disorders of haemoglobin production. First, there are the structural haemoglobin variants, most importantly represented by the sickling disorders. Second, there are conditions that result from a reduced rate of production of one or more of the globin chains; the general term thalassaemia covers this heterogeneous group of conditions. Both types of genetic disorder of haemoglobin occur together in many populations, so it is quite common for a patient to inherit genes for both a structural haemoglobin variant and a form of thalassaemia. Since both groups of inherited haemoglobin disorders are extremely heterogeneous, the clinical conditions that result from their interactions comprise a complex spectrum of diseases. The major types of hereditary anaemia and their diagnostic and clinical aspects are listed in Tables 1–3 and discussed below.

**DIAGNOSTIC AND CLINICAL ASPECTS**

**The structural haemoglobin variants**

Although several hundred structural haemoglobin variants have been described, the important ones from a public health point of view are haemoglobins S, C, and E. Homozygous Hb S produces sickle cell disease. Haemoglobins C and E are relatively harmless in the homozygous state, but can produce major haemoglobinopathies when combined with Hb S (mainly HbS/C disease, rarely HbS/E disease) or β-thalassaemia (HbS/β-thalassaemia, HbE/β-thalassaemia). Haemoglobin S is thus the constant factor in the major structural haemoglobinopathies. The classical clinical picture of sickle cell disease includes chronic haemolytic anaemia, childhood susceptibility to overwhelming infections, and periodic, painful or haemolytic crises, with progressive damage to vital organs in some cases. However, one of the major difficulties in discussing homozygous sickle cell disease is lack of knowledge about its natural history. The standard textbook picture is based on hospitalized patients who may not be representative, perhaps because they have an unusually severe form of the condition. Some recent information indicates that the disease has a remarkably variable clinical picture in different populations, with a most interesting interplay between heredity and environment. Recent studies in Kenya showed that in some rural parts of Africa 100% of infants with sickle cell anaemia die within the first two years of life. On the other hand, in the Eastern Oasis populations of Saudi
Arabia the disease is extremely mild and seems to be compatible with normal survival. The same may be true for Indian sickle cell disease. Recent cohort studies in Jamaica showed a mortality of about 10% in the first few years of life but thereafter many patients live to middle or old age. In the USA the mortality in childhood is thought to be approximately 2% per year and in a limited study in the United Kingdom the figure was 1.3%. The commonest cause of death in early life is concurrent infection. In Africa this appears to be mainly falciparum malaria, while in the Caribbean it is mainly pneumococcal or other bacterial septicaemia, often associated with the splenic sequestration syndrome. There is increasing evidence of a significant incidence of severe and progressive renal disease in patients who survive into the third or fourth decade.

The Jamaican cohort study is the only wide-scale analysis of the natural history of this disease and the results of this important investigation, together with those of a cooperative study that is currently under way in the USA, will in time provide a better picture of the natural history of sickle cell disease, and the results that can be obtained by modifying the environment.

Though sickle cell anaemia is by far the most important of the sickling conditions, haemoglobin S/C disease is also significant because, though it may go unnoticed during early life, it can present with serious complications in pregnancy or cause progressive blindness or crippling bone disease in later life.

The thalassaemias

The thalassaemias are characterized by a reduced rate of production of one or more of the normal globin chains of haemoglobin, this leading to a relative excess and the consequent precipitation of the unaffected globin chains. These precipitates are largely responsible for the characteristic defects in red cell maturation and survival.

The thalassaemias are classified according to the globin chain that is produced at a reduced rate. The best defined types are the \( \alpha-, \beta-, \delta\beta-, \delta-, \) and \( \gamma\delta\beta- \) thalassaemias. In addition, there is a less well defined group of disorders characterized by the persistence of fetal haemoglobin production into adult life (hereditary persistence of fetal haemoglobin, HPFH). Some of the latter conditions represent extremely mild forms of thalassaemia in which defective \( \beta- \) or \( \delta- \) and \( \beta- \) chain production is largely compensated for by persistent \( \gamma- \) chain synthesis. Most of the thalassaemias can be defined by haematological studies, haemoglobin electrophoresis, and quantification of the haemoglobins F and A2. Occasionally it is necessary to measure the relative rates of \( \alpha-, \beta-, \) and \( \gamma- \) chain synthesis.

The \( \alpha- \) thalassaemias

Before describing the different forms of \( \alpha- \) thalassaemia, it is necessary to review their nomenclature. There are two main forms of \( \alpha- \) thalassaemia; a severe form that produces a typical thalassaemia trait blood picture in heterozygous carriers, and a milder form that is almost completely "silent" in heterozygotes. Until recently, the severe form of the condition was called \( \alpha- \) thalassaemia-1 and the mild form was called \( \alpha- \) thalassaemia-2. However, recent work on the molecular genetics of \( \alpha- \) thalassaemia has provided clear evidence that the \( \alpha- \) thalassaemia-1 determinant causes a complete absence of \( \alpha- \) chain production, whereas \( \alpha- \) thalassaemia-2 results in only a partial deficit of \( \alpha- \) chain production. Thus, it is now more usual to call the severe form of \( \alpha- \) thalassaemia "\( \alpha^0 \) (alpha zero)-thalassaemia" and the milder form "\( \alpha^+ \) (alpha-plus)-thalassaemia", and this nomenclature is adopted here. Both \( \alpha^0 \) and \( \alpha^+ \)-thalassaemia can result from one of several different molecular defects involving the \( \alpha- \) globin gene cluster: the \( \alpha^0 \)-thalas-
saemias result from a series of gene deletions involving both α-globin genes, while the 
α+ -thalassaemias result from deletion of one of the linked pair of α-globin genes or from 
a series of non-deletion defects in which the α-globin genes are present but their output is 
reduced. In some populations, in addition to α0- and α+-thalassaemia determinants, 
there are common structural α-globin variants which, because they are synthesized at a 
reduced rate, produce the clinical phenotype of α+-thalassaemia. The commonest is Hb 
Constant Spring which is found throughout South East Asia; another is Hb Koya Dora 
found in certain parts of India.

A classification and description of the genetic interactions of the α-thalassaemias is 
given in Table 1. The homozygous state for α0-thalassaemia results in the Hb Bart’s 
hydrops syndrome. The compound heterozygous state for both α0-thalassaemia and 
α+-thalassaemia, or α0-thalassaemia and Hb Constant Spring, results in Hb H disease. 
These are the major α-haemoglobinopathies in the sense that they regularly produce 
significant pathology: the common factor is the presence of an α0-thalassaemia gene in 
single or double dosage. The remaining α-thalassaemias, though interesting, are of no 
great clinical importance. Homozygous α+-thalassaemia causes a very mild anaemia with 
hypochromic red cells and no change in the haemoglobin pattern. Homozygous Hb 
Constant Spring is slightly more severe than homozygous α+-thalassaemia, causing mild 
haemolytic anaemia with splenomegaly.

The differential diagnosis of the α-thalassaemias may pose great difficulties, but 
fortunately these are least for the clinically significant conditions, Hb Bart’s haemoglobin 
fetalis, Hb H disease, and α0-thalassaemia trait. In the fetus, α-chain deficiency leads to 
γ-chain excess with the formation of γ4-tetramers (Hb Bart’s); in the adult, α-chain defici-
cy leads to β-chain excess with formation of β4-tetramers (Hb H). Thus the presence of 
Hb Bart’s or Hb H is the hallmark of α-thalassaemia. However, a critical level of

<table>
<thead>
<tr>
<th>Designation</th>
<th>α-gene haplotype</th>
<th>Heterozygous state</th>
<th>Homozygous state</th>
</tr>
</thead>
<tbody>
<tr>
<td>α0-thalassaemia</td>
<td>–</td>
<td>5–10% Hb Bart’s at birth; low MCH and MCV</td>
<td>Hb Bart’s hydrops fetalis</td>
</tr>
<tr>
<td>α+-thalassaemia</td>
<td>–α</td>
<td>0–2% Hb Bart’s at birth; minimal haematological change</td>
<td>as for heterozygous α0-thalassaemia</td>
</tr>
<tr>
<td>deletion</td>
<td>–α</td>
<td>may be similar to above but haematological changes may be more severe</td>
<td>Hb H disease in some cases</td>
</tr>
<tr>
<td>non-deletion α-thalassaemia</td>
<td>αα⁺</td>
<td>0–2% Hb Bart’s at birth 5–6% Hb CS</td>
<td>phenotype slightly more severe than heterozygous α⁺-thalassaemia 5–6% Hb CS</td>
</tr>
<tr>
<td>Hb Constant Spring (CS)</td>
<td>αα⁺CS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Compound interactions**

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Genotype</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>α0-thal/α⁺-thal</td>
<td>– – / – α</td>
<td>Hb H disease</td>
</tr>
<tr>
<td>α⁺-thal/non-deletion α⁺-thal</td>
<td>– – / αα⁺</td>
<td>Hb H disease</td>
</tr>
<tr>
<td>Non-deletion α⁺-thal/non-deletion α⁺-thal</td>
<td>αα⁺/αα⁺</td>
<td>Hb H disease</td>
</tr>
</tbody>
</table>
imbalanced $\alpha$- and $\beta$-chain production appears to be required for the production of detectable amounts of Hb H and Hb Bart's. This is greatly exceeded in individuals with Hb Bart's hydrops fetalis or Hb H disease, so there is little difficulty in diagnosis, but it is not usually reached in heterozygous carriers for the different forms of $\alpha$-thalassaemia. Since there are no significant changes in the haemoglobin pattern, the diagnosis of the carrier states for some $\alpha$-thalassaemias can be very difficult. However, $\alpha^0$-thalassaemia trait, the common denominator of the major $\alpha$-haemoglobinopathies, can be easily identified in the same way as $\beta$-thalassaemia trait by typical thalassaemic microcytosis and increased osmotic resistance; the differential diagnosis can then be established by further investigation. Thus population screening for genetic counselling for the significant $\alpha$-thalassaemia syndromes can be conducted in the same way as for $\beta$-thalassaemia (see below).

The clinical features of the major $\alpha$-thalassaemia syndromes, Hb Bart's hydrops fetalis and haemoglobin H disease, are very different.

Hb Bart's hydrops is observed frequently in south-east Asia and occasionally in the Mediterranean populations and is an important obstetric problem. Toxaemia of pregnancy is usually present and there may be obstructed labour and postpartum haemorrhage. Affected infants are either stillborn between 28 and 40 weeks' gestation, or survive birth for only a short time. They show a typical picture of hydrops fetalis and are anaemic with haemoglobin values in the 60–80 g/l range. The blood film is characterized by hypochromia, marked variation in shape and size of the red cells, a variable reticulocytosis, and the presence of numerous nucleated red cell precursors. The haemoglobin is made up of approximately 80% of Hb Bart’s (Hb$\gamma_4$) with about 20% of Hb Portland (Hb$\zeta_2\gamma_2$); there is no Hb F or Hb A. The condition can be readily diagnosed by electrophoresis of the haemoglobin from lysates prepared from cord blood or blood obtained by cardiac puncture, or by finding that both parents are carriers of $\alpha^0$-thalassaemia.

Hb H disease leads to a variable degree of anaemia and splenomegaly. Patients usually do not require blood transfusions and do not suffer from iron overload. Characteristically, they develop acute haemolysis with infections, and thus pose problems of diagnosis and proper management. Haemoglobin values range between 70 and 100 g/l and the red cells show marked hypochromia and variation in shape and size. There is a reticulocytosis in the 5–10% range. After incubation of the red cells with brilliant cresyl blue, many ragged inclusion bodies are formed, because the redox action of the dye causes precipitation of Hb H. In splenectomized patients some but not all of the red cells contain large, preformed inclusions which can be demonstrated after incubation of the blood with methyl violet. The haemoglobin pattern is extremely variable, consisting of haemoglobins A, H, and A$_2$ with variable amounts of Hb Bart's. The level of Hb H ranges from less than 5% to more than 40%; Hb A$_2$ is nearly always reduced to the 1.5–2% range, and in most cases Hb Bart's can be demonstrated by electrophoresis at pH values of 7.0 or less. There is usually less Hb Bart’s than Hb H. In vitro globin-chain synthesis studies on reticulocytes show a marked degree of chain imbalance, $\alpha/\beta$ globin synthesis ratios ranging between 0.5 and 0.25.

The parents of patients with Hb H disease show variable haematological changes depending on the particular genetic form of the disease. In the common south-east Asian variety, one parent is an $\alpha^+$-thalassaemia carrier and the other carries $\alpha^+$-thalassaemia or Hb Constant Spring; but in some other populations, e.g., in eastern Saudi Arabia, the condition seems to result from the homozygous inheritance of a non-deletional $\alpha$-thalassaemia determinant of severity intermediate between $\alpha^+$- and $\alpha^0$-thalassaemia.

The clinical features of the remaining $\alpha$-thalassaemia syndromes will not be considered here as they do not cause major pathology.
The β-thalassaemias: homozygous states

The β-thalassaemias are more heterogeneous than the α-thalassaemias. Many of them are now well understood at the molecular level and this information is summarized in Table 2. However, for clinical purposes they are broadly divided into β0-thalassaemias, in

<table>
<thead>
<tr>
<th>Number</th>
<th>Type of thalassaemia (or abnormal Hb)</th>
<th>Reference</th>
<th>Frequency</th>
<th>Molecular basis</th>
<th>Molecular identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hereditary persistence of fetal haemoglobin (HPFH)</td>
<td>G, A, type 1 (19) all rare</td>
<td>deletion of β + δ + 4000 base pairs of inter-γ-δ flanking DNA</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>G, A, type 2</td>
<td>deletion of β + δ + 9000 base pairs of inter-γ-δ flanking DNA</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hb Kenya</td>
<td>fusion of Aγ with β</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>δβ-thalassaemia</td>
<td>G, Aγ (9) all rare</td>
<td>deletion of β + 1δ</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gδ</td>
<td>deletion of β, δ and Aγ genes</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gδ</td>
<td>inversion of Aγ to δ segment + 2 deletions</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Hb Lepore</td>
<td>Hollandia (20) all rare</td>
<td>50 δ-β fusion</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baltimore</td>
<td>86 δ-β fusion</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Boston</td>
<td>116 δ-β fusion</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Normal Aβ-β-thalassaemia, mild</td>
<td>(20) uncommon</td>
<td>not known</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Normal Aβ-β-thalassaemia, severe</td>
<td>(20) uncommon</td>
<td>not known</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>β0-thalassaemia mild: Indian</td>
<td>(20) rare</td>
<td>600 base pair deletion end of gene at 5'</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>β0-thalassaemia mild: British</td>
<td>(20) rare</td>
<td>defective initiation of β-mRNA synthesis</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>β0-thalassaemia severe: Italian</td>
<td>(2) common</td>
<td>abolition of splice site at start of large intron</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>β0-thalassaemia severe: Italian, Greek</td>
<td>(15) common</td>
<td>β39 → stop ('non-sense') mutation</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>β0-thalassaemia severe: Chinese, Sardinian</td>
<td>(18) common</td>
<td>β17 Lys → stop ('non-sense') mutation</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>β0-thalassaemia severe: Ferrara</td>
<td>(20) common (locally)</td>
<td>defective protein β-initiation factor</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>β0-thalassaemia severe: Mediterranean</td>
<td>(21) common</td>
<td>additional splice site generated in small intron</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>β4 °-thalassaemia mild: Negro</td>
<td>(4) fairly common</td>
<td>not known</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Hb E</td>
<td>(17) common (locally)</td>
<td>26 β Glu→Lys ( + thalassaemia mutation?)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Hb S</td>
<td>(20) common</td>
<td>6 β Glu→Val</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Hb C</td>
<td>(20) common (locally)</td>
<td>6 β Glu→Lys</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>
which no β-globin chains are synthesized, and the β⁺-thalassaemias in which there is a reduced rate of β-chain production, with a severe Mediterranean form (about 10% of normal β-chain synthesis) and a milder form (up to 50% of normal β-chain production) in some black Americans and Africans (Table 3). There is a further well defined subgroup of both β⁰- and β⁺-thalassaemia in which the Hb A₂ level is normal in heterozygotes. There are also some rare forms of β-thalassaemia which have only been defined in single families or populations; these will not be considered further.

Usually the homozygous or compound heterozygous state for β⁰-thalassaemia and severe β⁺-thalassaemia causes transfusion-dependent anaemia from early life, but some patients run a milder course. They are said to have "thalassaemia intermedia".

**Homozygous β⁰-, homozygous β⁺-, and β⁰/β⁺-thalassaemia.** Classical β-thalassaemia major usually presents with severe anaemia within the first year of life. The typical clinical picture of untreated thalassaemia major is of anaemia with Hb less than 70 g/l, failure to thrive, with anorexia, dark urine, sleeplessness, mild fever, and vomiting. Hepatosplenomegaly may not be present at presentation but develops progressively. Given time, there are also severe bone changes, pathological fractures, and iron overload of gastrointestinal origin. Death in early childhood (1–6 years of age) is usually due to infection or heart failure.

At presentation the haemoglobin is usually less than 80 g/l with marked variation in shape and size of the red cells, hypochromia, nucleated red cells, and a mild reticulocytosis. The bone marrow shows erythroid hyperplasia and many of the normoblasts contain ragged inclusions after incubation of the marrow with methyl violet. The haemoglobin pattern in homozygous β⁰-thalassaemia consists almost entirely of Hb F, with variable Hb A₂ levels which may be reduced, normal, or elevated, while Hb A is completely absent. In typical homozygous β⁺-thalassaemia there may be 10–25% of Hb A, while in β⁰/β⁺-thalassaemia there is a smaller amount. Globin-chain synthesis studies show a marked imbalance of α- and non-α-chain production in the peripheral blood and in the bone marrow. Both parents show the features of heterozygous β-thalassaemia with elevated Hb A₂.

**Homozygous β⁺⁺-thalassaemia** (mild Negro variety). This condition usually produces only a mild anaemia with Hb values varying from 70–110 g/l. The peripheral blood

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**Table 3. Common types of β-thalassaemia**

<table>
<thead>
<tr>
<th>Thalassaemia type</th>
<th>Homozygotes</th>
<th>Heterozygotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>β⁰</td>
<td>thalassaemia major</td>
<td>thalassaemia major</td>
</tr>
<tr>
<td></td>
<td>Hb F, 98%; Hb A₂, 2%</td>
<td>Hb A₂, 3.5–7.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α/β = 2/1</td>
</tr>
<tr>
<td>β⁺ (Mediterranean)</td>
<td>thalassaemia major</td>
<td>thalassaemia minor</td>
</tr>
<tr>
<td></td>
<td>Hb F, 70–95%</td>
<td>Hb A₂, 3.5–7.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α/β = 2/1</td>
</tr>
<tr>
<td>β⁺⁺ (Negro)</td>
<td>thalassaemia intermedia</td>
<td>thalassaemia minor</td>
</tr>
<tr>
<td></td>
<td>Hb F, 20–40%; Hb A₂, 2–5%</td>
<td>Hb A₂, 3.5–7.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α/β = 1.2–2.0/1</td>
</tr>
<tr>
<td>β⁺ (normal Hb A₂, type 1;</td>
<td>mild thalassaemia intermedia</td>
<td>normal</td>
</tr>
<tr>
<td>&quot;silent&quot;)</td>
<td>Hb F, 10–30%; Hb A₂, 5%</td>
<td>a/β = 1.2–1.5/1</td>
</tr>
<tr>
<td>β⁺ or β⁰ (normal Hb A₂, type 2)</td>
<td>probably thalassaemia major</td>
<td>thalassaemia minor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hb A₂, normal</td>
</tr>
<tr>
<td></td>
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changes are typical of those of homozygous \( \beta \)-thalassaemia and the haemoglobin pattern consists of 30–60% Hb F with a normal or elevated Hb A\(_2\) level, the remainder of the haemoglobin being Hb A. Bone changes are slight, gastrointestinal iron absorption may not be significantly increased, and the quality of life and the prognosis are good.

**Thalassaemia intermedia.** This is a clinical term used to describe homozygous \( \beta \)-thalassaemia of a milder kind, where the patient can survive without transfusion. It is not a uniform condition but includes individuals ranging from those with minimal disability to patients who can just survive without transfusion but suffer severe and varied pathology. By far the most common basis for mild homozygous thalassaemia is the coincidence of one or more \( \alpha \)-thalassaemia genes with typical homozygous \( \beta \)-thalassaemia: this reduces the extent of chain imbalance and so ameliorates the disease. In addition, certain thalassaemia genes such as the \( \beta^+ \) Negro type, normal A\(_2\)\( \beta \)-thalassaemia type 1 (see below), and some \( \delta \beta \)-thalassaemias cause only mild disease in the homozygous state, and many patients with HbE/\( \beta \)-thalassaemia have an intermediate syndrome. However, the genetic basis for many cases of milder thalassaemia is still not understood and merits further study.

**Heterozygous \( \beta \)-thalassaemia**

The great heterogeneity of the group precludes characterization by a single method. However, with rare exceptions, all heterozygotes display the following common features:

1. **Haematological**

   (a) Mild anaemia is frequent but not universal and varies with the type of thalassaemia trait. The overlap with the normal range is far too great for this to be helpful in the diagnosis of individual cases.

   (b) Low RBC indices. The MCH gives the best discrimination, MCV is less reliable while MCHC is not reliable at all. It is most unusual to find a \( \beta \)-thalassaemia carrier with an MCH above 25 pg or an MCV above 76 fl, so screening for \( \beta \)-thalassaemia trait using an electronic cell counter is highly effective.

   (c) Mild alterations of RBC morphology.

   (d) Decreased osmotic fragility in a one-tube test with 0.36% normal saline (3.24 g of NaCl per litre). This may give false negative results in about 4% of cases (10), but is a cheap and simple method suitable for use in developing countries.

2. **Biochemical.** The characteristic findings differ according to the molecular defect. They are:

   (a) Increased Hb A\(_2\), which is found in \( \beta^0 \)- and \( \beta^+ \)-thalassaemia, by far the most prevalent types. It may be accompanied by a slight increase in Hb F.

   (b) Increased Hb F with no increase of Hb A\(_2\) occurs in \( \delta \beta^0 \)-thalassaemia.

   (c) Presence of \( \delta \beta \)-crossovers (Hb Lepore), observed on electrophoresis.

3. **Biosynthetic** evidence for decreased \( \beta \)-chain synthesis, but this may be masked by coincidental \( \beta \)-thalassaemia.

4. **Genetic** studies may also be necessary to clarify the genotype in difficult cases.

From the genetic counselling point of view, haemoglobin Lepore trait and \( \delta \beta \)-thalassaemia trait are equivalent to \( \beta \)-thalassaemia trait and must be accurately diagnosed, but the HPFH syndromes are not clinically important. Details of their diagnosis

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\( ^a \) MCH = mean corpuscular haemoglobin; MCV = mean corpuscular volume; MCHC = mean corpuscular haemoglobin concentration; pg = picogram (g x 10\(^{-12}\)); fl = femtolitre (l x 10\(^{-15}\)).
are given by Weatherall & Clegg (20).

The commonest practical problem in screening for haemoglobinopathies is distinguishing heterozygous thalassaemia from simple iron-deficiency anaemia. In communities where both are common this may cause major difficulties, especially as in severe iron deficiency plus \( \beta \)-thalassaemia trait, the Hb A2 level may fall and be restored only after iron therapy. In cases of doubt, iron treatment should be given and the haematological picture and Hb A2 level reassessed when the haemoglobin has risen.

The blood picture of \( \beta \)-thalassaemia heterozygotes who are also heterozygous for \( \alpha^+ \)- or \( \alpha^0 \)-thalassaemia is very similar to that in simple \( \beta \)-thalassaemia trait, except that the MCH and haemoglobin values may be unusually high (e.g., MCH of 24–25 pg) and there is reduced or even no imbalance of globin-chain synthesis. Occasionally the Hb A2 level is intermediate between that in normals and that in typical \( \beta \)-thalassaemia trait, and genetic studies may be required.

There are two forms of \( \beta \)-thalassaemia trait with normal Hb A2 levels. The “mild, normal Hb A2” (type 1) \( \beta \)-thalassaemia trait causes minimal red cell microcytosis, with a normal Hb A2 and \( \alpha/\beta \) globin-chain synthesis ratio of about 1:3. The homozygote has a very mild form of thalassaemia intermedia and the compound heterozygote with classical \( \beta \)-thalassaemia also has thalassaemia intermedia. The fact that these heterozygotes can only rarely be detected prospectively is probably relatively unimportant from the preventive point of view. By contrast, in the “severe, normal Hb A2” (type 2) \( \beta \)-thalassaemia trait there is typical thalassaemic microcytosis but a normal Hb A2 level. Compound heterozygotes with a typical \( \beta \)-thalassaemia gene suffer from severe transfusion-dependent \( \beta \)-thalassaemia major. The differential diagnosis from \( \beta^0 \)-thalassaemia trait is therefore all-important, especially when one of a married couple shows this picture and the other has typical \( \beta \)-thalassaemia trait (or typical \( \alpha^0 \)-thalassaemia trait). At present this can be achieved only by globin-chain synthesis studies. A laboratory strategy for screening for major haemoglobinopathies will be discussed in a subsequent article (5).

**Sickle cell thalassaemia (HbS/\( \beta \)-thalassaemia)**

This occurs frequently in West Africa and less frequently in the Mediterranean. There are three main forms depending on the type of \( \beta \)-thalassaemia involved. HbS/\( \beta^0 \)-thalassaemia closely resembles sickle cell anaemia clinically, but the red cells show a reduced MCH and MCV and there is a slightly elevated Hb A2. The Hb F level is usually around 5%. The condition can be diagnosed for certain by finding \( \beta \)-thalassaemia trait in one parent and sickle cell trait in the other. In some Saudi Arabian populations the Hb F level is much higher while the Hb A2 level may be normal or slightly reduced: these patients have a particularly mild disease. Mediterranean HbS/\( \beta^+ \)-thalassaemia is thought to be similar in severity to sickle cell anaemia, except there are usually fewer sickling crises and hypersplenism with anaemia is more prominent. The red cell changes are characteristic for thalassaemia and haemoglobin analysis indicates the presence of Hb A (5–10%), as well as Hb S and Hb F, and an elevated Hb A2. African HbS/\( \beta^{+-} \)-thalassaemia is much milder, the patients are less anaemic than those with the Mediterranean form, and the quality of life is good. The red cell indices are typically thalassaemic, there is about 25–30% Hb A, the remainder being haemoglobins S and F with an elevated Hb A2 level. Hb F is rarely above 5–10% in any form of sickle cell \( \beta \)-thalassaemia.

As HbC/\( \beta \)-thalassaemia is not common and does not differ greatly from HbS/\( \beta \)-thalassaemia, it will not be discussed separately.

**Haemoglobin E/\( \beta \)-thalassaemia**

This occurs widely throughout south-east Asia. The haematological picture varies
greatly. As in thalassaemia major, the peripheral blood film shows marked variation in shape and size of the red cells with a slightly elevated reticulocyte count. There is marked erythroid hyperplasia in the bone marrow, and many of the red cell precursors contain inclusion bodies which can be seen after incubation with methyl violet. Haemoglobin analysis usually shows only haemoglobins E and F; the level of Hb F ranges from 5–80%. Because the common form of $\beta$-thalassaemia in south-east Asia is the $\beta^0$ variety, it is unusual to find any Hb A, but HbE/$\beta^+$-thalassaemia is found in Bangladesh. The diagnosis is confirmed by finding $\beta$-thalassaemia trait in one parent and HbE-trait in the other.

In south-east Asia, HbE/$\beta$-thalassaemia is more important than homozygous $\beta$-thalassaemia because its incidence is higher and the patients live longer, so it is much more prevalent. Approximately half of the patients have haemoglobin levels lower than 70 g/l. These more severe cases have the typical picture of untreated $\beta$-thalassaemia major, with retardation of growth, anaemia, jaundice, hepatosplenomegaly, bone changes and fractures, iron overload, and death in early childhood from infection and heart failure. The other half are more mildly affected, but develop iron overload through increased intestinal iron absorption and suffer a variety of other problems such as pericarditis, paraplegia due to spinal cord compression from extramedullary haematopoietic masses, and low plasma zinc, folate, vitamin C, and vitamin E levels. A small minority are able to lead a relatively normal life. Despite the broad spectrum of clinical severity, the mean life expectancy is about 20 years.

**Haemoglobin E trait.** Haemoglobin E trait combines some of the features associated with a mildly unstable haemoglobin variant with some of the features of a $\beta$-thalassaemia, since there is microcytosis and imbalance in globin-chain synthesis. It is diagnosed by moderate microcytosis (mean MCH 23 pg, range 17–26 pg) associated with 30–40% of Hb E on electrophoresis. As Hb E cannot be separated from Hb A2, the amount of Hb E present is always somewhat overestimated. Hb E is usually identified by electrophoresis, but there is a much simpler method based on its slight instability ($I$) which may be suitable for use in developing countries. Both homozygous Hb E and Hb E trait are asymptomatic.

### Important areas for future research

This discussion of current knowledge of the haemoglobinopathies leaves many areas of uncertainty, for instance:

1. The reasons for the clinical heterogeneity of homozygous sickle cell disease and the extent to which the provision of adequate primary health care can improve the quality of life for patients with this condition.

2. The genetic reasons for the milder picture in some individuals with homozygous $\beta$-thalassaemia (thalassaemia intermedia); coincidental inheritance of $\alpha$-thalassaemia genes seems to be responsible for many, but not all of these cases.

3. The reasons for the broad clinical spectrum of HbS/$\beta$-thalassaemia and HbC/$\beta$-thalassaemia which vary from very mild to very severe according to the type of $\beta$-thalassaemia gene involved, and possibly other factors.

4. The distribution and clinical spectrum of $\beta^{++}$-thalassaemia (Negro type).

5. The reason for the wide spectrum of severity in HbE/$\beta$-thalassaemia, since unlike thalassaemia intermedia this cannot usually be explained by coincidental inheritance of $\alpha$-thalassaemia genes in different dosage.
TREATMENT

Sickle cell disease

At the moment, the only form of treatment that can be offered to patients with this disease is early treatment of infection, supportive care during painful and aplastic crises, and therapy directed towards particular organ involvement, such as management of the neurological, pulmonary, or renal complications. More recently, regular transfusion programmes have been advocated for the management of recurrent severe crises, cerebral or pulmonary complications, and pregnancy, and to cover major surgery; the value of blood transfusion in pregnancy remains controversial. Trials have been carried out using the new polyvalent pneumococcal vaccine to see if it will be useful for the prevention of pneumococcal infections. This symptomatic management is not complicated and the following preventive steps can greatly improve survival and quality of life:

- Identification of affected individuals as soon as possible after birth so that they can benefit from proper management from the outset. This is most important for the prevention of early death from overwhelming infections.
- Regular visits to a special paediatric clinic at 6–8 week intervals (help with transport often has to be provided)
- Adequate antimalarial chemoprophylaxis
- Folate supplementation
- Treatment of infections (parents must be told to bring the sick child to the clinic for assessment)
- General nutrition (education of the parents about a balanced diet is often more important than their financial ability to provide it)
- Referral to specialist clinics for supervision during pregnancy (management according to WHO Technical Report Series, No. 509 is still current practice).

The requirements are simple and inexpensive, but call for easy access to adequate medical care. This is the limiting factor in providing adequate care in Africa where the benefits of proper management have hitherto been limited to the small fraction of the population with access to centres of excellence. The need in Africa now is to extend these benefits to the population at large, and this can be done only by integrating a simple sickle cell disease programme into existing national medical care.

Because of the high mortality of children with homozygous sickle cell anaemia in most of Africa at present, it is not a chronic disease and its prevalence is relatively low. However, as the measures enumerated above become effective, the prevalence should rise towards 1% in parts of Africa, and the problems presented in terms of chronic disease will increase. This may generate a demand for control by fetal diagnosis, which can now be done using DNA obtained from amniotic fluid fibroblasts (10). Apart from its expense, the main objection to this approach in African populations is that the only option it offers is mid-trimester termination of pregnancy for a condition that often responds so well to basic care. A method for fetal diagnosis in the first trimester of pregnancy has yet to be established, but when it is it may prove acceptable in high-frequency areas.

The thalassaemias

Homzygous $\alpha^0$-thalassaemia (Hb Bart’s hydrops fetalis)

This disease does not present a problem of chronic disease as the prevalence of affected
individuals in a population is zero, even when the prevalence of heterozygotes is high. Instead it presents as an acute obstetric problem with the important complications of toxaemia of pregnancy, obstructed labour, and postpartum haemorrhage. Fetal diagnosis can be done non-invasively during the second trimester of pregnancy by ultrasound monitoring of at-risk pregnancies (DNA analysis of amniotic fluid cells may be used for confirmation), and affected pregnancies should be terminated on straightforward medical grounds to avoid maternal morbidity and distress.

**Haemoglobin H disease**

Hb H requires diagnosis and proper management of haemolytic crises and infections. As the disease may have little effect on life expectancy, the prevalence of affected individuals may be high in populations in which the $\alpha^0$-thalassaemia gene is common.

**$\beta$-thalassaemia major**

Treatment consists of regular blood transfusion, splenectomy when the blood requirement is more than twice basal, and intensive use of an iron-chelating agent to control transfusional iron overload. The most efficient transfusion scheme is one of "super transfusion" where the patient's haemoglobin is not allowed to drop below 120 g/l and is raised regularly to 140 or 150 g/l, so that endogenous marrow activity is completely suppressed. Contrary to expectation, for $\beta^0$-thalassaemia this ultimately calls for no more blood than is needed to maintain the same patient on a lower transfusion scheme (16), though for $\beta^+$-thalassaemia there is a significant increase in the blood requirement (13).

At present the experience gained shows that intensifying the transfusion scheme to give a mean Hb of 140 g/l leads to a 22% increase in blood requirement for the first six months only, after which it returns to the initial value. This is because in low transfused patients the blood volume is expanded to meet the requirements of the grossly hypertrophied bone marrow, but marrow and blood volume return to normal within a year from the initiation of high transfusion. This simple rationalization of the transfusion scheme greatly improves quality of life with no increase in the rate of iron loading; there is evidence that it also suppresses excessive gastrointestinal iron absorption (6) and prevents the development of hypersplenism through clearing abnormal cells from the circulation. It is therefore the recommended scheme of management, but it does require a regular and predictable supply of blood.

It also now appears that regular subcutaneous infusion of the iron-chelating agent deferoxamine hydrochloride, in an average dose of at least 25 mg per kg body weight per day, provides good quality of life and probably improved survival (14). If optimum treatment is started early there is now reason to hope for a good prognosis, including marriage and, possibly, reproduction. However, both transfusion and iron-chelation therapy are stressful and there are often problems of patient compliance. Providing deferoxamine hydrochloride is available, the main threats to life now seem to be:

(a) Non-compliance with iron-chelation therapy, which is particularly common among depressed male adolescents.

(b) Long-term complications of splenectomy. Fatal overwhelming infection occasionally occurs in an older patient whose spleen was removed in early life. Moreover, arterial hypoxaemia and abnormalities of lung function are commonly found in thalassaemia. These have recently been found to occur in splenectomized patients only, as a result of pulmonary microembolism by platelet aggregates. Platelet aggregation can be prevented and the arterial oxygen tension corrected by long-term treatment with aspirin or dipyridamole (12).
(c) Complications of transfusion—namely, accidents at transfusion, and hepatitis. Chronic aggressive hepatitis following infection through transfused blood is very common in Italy but has not been properly studied elsewhere.

The improved prognosis means that increased attention should now be paid to these long-term complications. For instance, once thalassaemia intermedia has been excluded, newly diagnosed patients should be treated by intensive high transfusion from the outset, to avoid splenectomy; arterial hypoxaemia and abnormal lung function need further study and appropriate treatment; and good studies are needed of the value of pneumococcal vaccines and prophylactic antibiotics in avoiding infection in splenectomized patients, and of the possibility of immunization against the hepatitis viruses. Finally, steps should be taken to counteract depression among older patients.

In countries where optimum treatment is available the physical and social needs of the growing cohort of young adults require special attention. As a consequence of ill health and transfusional iron overload in their early years, many have failed to pass through puberty, and many, depending on their country of residence, have difficulty in gaining acceptance for higher educational courses or appropriate work. These patients should be helped to become integrated into adult society. They need hormone replacement therapy and equal opportunities in education, vocational training, and employment.

Once optimum management is initiated, the costs start rising rapidly because not only is the treatment expensive, but the number of patients needing it increases since there are fewer deaths from iron overload. The cost of implementing any form of treatment is extremely high: treatment by transfusion alone as practised in Lebanon (1981) cost about US$ 2000 per patient per year, and in 1978 the optimum treatment, as described above, cost about US$ 7513 per patient per year in the United Kingdom (5) and US$ 5000 in Greece. This high cost is largely due to the price of deferoxamine hydrochloride for which no satisfactory cheaper substitute has yet been found (US$ 6.00 per gram in the United Kingdom, soon to rise to about US$ 7.00 per gram). Consequently, optimal treatment for thalassaemia is available only to patients living in the most prosperous communities, while those born in developing countries are treated only by transfusion, or not at all. The life-expectancy of children with $\beta$-thalassaemia major managed in these 3 ways is summarized in Fig. 2. It shows that even if no treatment is offered, the disease can present a considerable health burden because the affected children who survive an average of 2 years ($\beta^0$-thalassaemia) or even up to 6 years ($\beta^+$-thalassaemia) are chronically sick. If only transfusion is offered, the prognosis is about 17 years, while the prognosis for patients receiving regular intensive treatment with deferoxamine hydrochloride is uncertain.

The need for blood is about 25 units per patient per year, rising with increasing weight of the patient. However, as mentioned, the implementation of the most modern scheme of intensive high transfusion does not greatly increase the total demand for blood but it calls for a high degree of organization, and few of the countries in which thalassaemia is really common are yet able to provide blood in a sufficiently reliable way to support an optimal treatment scheme. This is true even though the present number of surviving patients is small owing to the past high mortality. As more are treated, the prevalence will rise and the problem will become progressively more difficult.

HbE/$\beta$-thalassaemia

Ideally, the more severe cases of this disease should be treated as severe thalassaemia major, while splenectomy, transfusion, and iron-chelation therapy should be available when needed by those with a milder syndrome. Very little treatment is available in southeast Asia where the syndrome is common, but as the mean life expectancy (when
Fig. 2. Survival of patients with thalassaemia major haemoglobinopathies. The first curve shows the survival of untreated children with severe $\beta^A$-thalassaemia, followed in Ferrara in the 1950s (M. Lucci and C. Vullo, unpublished data). The second curve shows the survival of patients (mostly with $\beta$-thalassaemia) treated in the United Kingdom with transfusion only (mean Hb 90–115 g/l). The third curve shows the survival of patients on the same transfusion scheme treated with a minimum of 500 mg of deferoxamine hydrochloride at least 5 days a week for at least 2 years, by the intramuscular or subcutaneous route. The number of older surviving patients in this group is still small and deaths still occur, but these are usually associated primarily with infection rather than iron overload. As many of the older patients will have already sustained considerable organ damage from iron overload, or hepatitis associated with transfusion, they are unlikely to achieve a normal survival; so the top curve will descend on the right. But as the younger patients who have benefited from the outset with such treatment mature, it is to be hoped that the survival curve will be progressively displaced towards the normal. (From: MODELL, B. The management of the improved prognosis in thalassemia major. In: Cao, A. & Rowley, P., ed., Recent advances in thalassemia. New York, Alan R. Liss, for the March of Dimes Birth Defects Foundation, BD: OAS 18(6), 1982).

untreated) is about 20 years, the prevalence of the disease is high and HbE/$\beta$-thalassaemia makes a heavy demand on available health resources.

**Future prospects for treatment**

*Sickle cell disease*

The search for a safe, effective, and cheap anti-sickling agent continues in Africa and in the USA and the hope of finding one appears realistic. However, to date the only really
useful approach seems to be extracorporeal exposure of the red cells to cyanate (7). This is still under investigation, but however effective it proves to be, it is appropriate only in developed countries and even then only for patients with severe problems.

**New iron-chelators for β-thalassaemia**

There is still no definite progress towards developing a cheap, safe, and effective oral iron-chelating agent. There is, however, evidence that the long-known and long-discarded agent diethylenetriaminepentaacete (calcium-DTPA), if given subcutaneously with oral zinc supplements, may be safe and effective and cheap enough for widespread use in developing countries. The requirements for subcutaneous infusion do not necessarily impede its use in developing countries, as cheaper substitutes can be found for the expensive syringe-drivers, disposable syringes, and extension tubes.

**Transfusion of young red cells**

This approach, originally proposed by Dr R. D. Propper, is being worked on in Australia, Greece, the United Kingdom, and the USA, and will probably have some value for both sickle cell disease and thalassaemias. There are two possibilities: (1) preparation of whole units of blood with mean cell age of 12 days or so, from donors who are put on cell-separators (advanced technology); and (2) separation of the younger 50% of red cells from two units of blood, using an IBM cell-washer. This saves discomfort to donors and does not waste any blood because a unit of the younger cells should last almost as long as two units of whole blood. It should even be possible to use the older rejected cells for acute requirements, thus achieving a net economy in blood where it is in short supply. However, for developing countries, the first priority is to obtain sufficient blood donors in the first instance.

**Bone marrow transplantation**

It is not certain whether it will prove possible to ablate the bone marrow in patients with sickle cell disease or thalassaemia, in preparation for donor marrow grafting; furthermore, the problem of graft-versus-host disease is still very intransigent. At present there is no place for unmatched marrow transplantation, and only one in four siblings of an affected child would be suitable donors. These problems are being tackled by such approaches as treating donor marrow with appropriate monoclonal antibodies in an attempt to remove cells responsible for the graft-versus-host reaction, but this is still very much a matter of research and development. Since it is usually possible to give a thalassaemic child or a child with sickle cell disease many years of good and useful life with conservative treatment, it seems too early to start to develop programmes of marrow transplantation for this disorder. Even if marrow transplantation could be made safe and reliable, it would be extremely expensive and difficult to provide on a global basis.

**Specific gene therapy**

There are two theoretical approaches to gene therapy for thalassaemia and sickle cell anaemia. The first would be the replacement of the defective β-gene with a normal β-gene. The second would be to encourage fetal haemoglobin synthesis to persist into adult life. Although much research is going on into the factors which regulate the change from fetal to adult haemoglobin production, there seems no likelihood of being able to manipulate this mechanism in the immediate future. However, the recent advances in molecular biology do offer some promise of being able to replace abnormal β-globin genes in the near future. These genes can be isolated with their regulatory regions intact and there are
several mechanisms now available for inserting them into recipient cells. The major difficulties that have to be overcome are, first, putting them into the correct cell population, i.e., haemopoietic stem cells, and getting them to express themselves in the appropriate progeny in appropriate amounts. This calls for a great deal of work by the molecular and cell biologists but therapeutic gene replacement may become a reality within the foreseeable future. Once again, this form of treatment will require considerable technology and may be difficult to provide on a global basis for many years.

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Annex I

LIST OF PARTICIPANTS

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