MEDICAL PROGRESS

Review Article

Medical Progress

THE β-TALASSEMIAS
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In 1925, Thomas Cooley and Pearl Lee described a form of severe anemia, occurring in children of Italian origin and associated with splenomegaly and characteristic bone changes.1 Over the next decade, a milder form was described independently by several Italian investigators.2-4 Because all early cases were reported in children of Mediterranean origin, the disease was later termed thalassemia, from the Greek word for sea, thalassa.5 Over the next 20 years, it became apparent that Cooley and Lee had described the homozygous or compound heterozygous state for a recessive mendelian disorder not confined to the Mediterranean, but occurring widely throughout tropical countries. In the past 20 years, the two important forms of this disorder, α- and β-thalassemia, resulting from the defective synthesis of the α- and β-globin chains of hemoglobin, respectively, have become recognized as the most common monogenic diseases in humans.6

This article focuses on the β-thalassemias, the severe forms of which are by far the most important of all the thalassemias. The molecular and clinical aspects of the severe α-thalasemia syndromes have been reviewed elsewhere.7,8

DISTRIBUTION AND POPULATION AT RISK

The β-thalassemias are widespread throughout the Mediterranean region, Africa, the Middle East, the Indian subcontinent and Burma, Southeast Asia including southern China, the Malay Peninsula, and Indonesia. Estimates of gene frequencies range from 3 to 10 percent in some areas.9 Within each population at risk for β-thalassemia a small number of common mutations are found, as well as rarer ones; each mutation is in strong linkage disequilibrium with specific arrangements of restriction-fragment–length polymorphisms, or haplotypes, within the β-globin cluster. A limited number of haplotypes are found in each population, so that 80 percent of the mutations are associated with only 20 different haplotypes. This observation has helped demonstrate the independent origin of β-thalassemia in several populations.10 There is evidence that the high frequency of β-thalassemia throughout the tropics reflects an advantage of heterozygotes against Plasmodium falciparum malaria,11 as has already been demonstrated in α-thalassemia.12

MOLECULAR PATHOLOGY

Structure and Synthesis of Hemoglobin

The structure and regulation of the human globin genes have been reviewed elsewhere;13 only aspects with direct relevance to an understanding of the molecular pathology of the β-thalassemias are outlined here.

The β-like globin genes, a linked cluster on chromosome 11, are arranged over approximately 60,000 nucleotide bases (Fig. 1). Promoter elements upstream from the initiation codon of each active gene are involved in the initiation of transcription. The cluster also contains other regulatory elements that interact to promote erythroid-specific gene expression and to coordinate the developmental regulation of each gene.

Hemoglobin Switching

As an adaptation to changing oxygen requirements, different hemoglobins, all composed of two different pairs of globin chains each attached to a heme moiety, are synthesized in the embryo, fetus, and adult.14 Severe β-thalassemia usually becomes manifest as a result of the decline in the synthesis of fetal hemoglobin (α2γ2) during the first year of life (Fig. 1). The precise mechanisms that control the switch from the production of fetal hemoglobin to that of adult hemoglobin (α2β2) (Fig. 1) are not fully understood.15-16

Mutations Causing β-Thalassemia

Nearly 200 different mutations have been described in patients with β-thalassemia and related disorders. Although most are small nucleotide substitutions within the cluster, deletions may also cause β-thalassemia.9 All the mutations result in either the absence of the synthesis of β-globin chains (β0-thalassemia) or a reduction in synthesis (β+-thalassemia) (Fig. 2).

Mutations in or close to the conserved promoter sequences and in the 5' untranslated region down-

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regulate transcription, usually resulting in mild \( \beta^+ \)-thalassemia. Transcription is also affected by deletions in the 5' region, which completely inactivate transcription and result in \( \beta^0 \)-thalassemia.

Both splicing of the messenger RNA (mRNA) precursor and ineffective cleavage of the mRNA transcript result in \( \beta \)-thalassemia. In some mutations, no normal message is produced, whereas other mutations only slightly reduce the amount of normally spliced mRNA. Mutations within invariant dinucleotides at intron–exon junctions, critical to the removal of intervening sequences and the splicing of exons.

Figure 1. The \( \beta \)-Globin Gene Cluster on the Short Arm of Chromosome 11.

In Panel A, the \( \beta \)-globin–like genes are arranged in the order in which they are expressed during development. The \( \alpha \gamma \) and \( \gamma \gamma \) genes are both active genes that produce \( \gamma \)-globin chains that differ only at position 136 (glycine is the product of the \( \alpha \gamma \) gene, and alanine is the product of the \( \gamma \gamma \) gene). The \( \psi \beta \) gene is a pseudogene, an evolutionary remnant of a previously active \( \beta \)-globin–like gene. Areas of nucleotide homology upstream from the initiation codon of each active gene, termed promoter elements, are involved in the initiation of transcription and hence play a vital part in gene regulation. The cluster also contains regulatory elements that interact to promote erythroid-specific gene expression and to coordinate the developmental regulation of each gene, including hemoglobin switching. These include enhancers, distant regulatory elements that increase gene expression, and a master sequence, the cluster’s essential distal regulatory element, the \( \beta \)-globin locus-control region. This is a region that lies 20 kb upstream from the \( \epsilon \)-globin gene. It encompasses five erythroid-lineage–specific nuclease hypersensitive sites (shown in red) that permit expression of the downstream genes. In addition to these elements for up-regulation, several suppressor regions, or silencers, have been defined in the \( \beta \)-globin gene cluster.

Panel B shows the timing of the normal developmental switching of human hemoglobin. Early in fetal life the synthesis of the embryonic \( \alpha \)-globin–like (\( \zeta \)) chains switches to that of \( \alpha \)-globin, which is produced thereafter. At the same time, the synthesis of embryonic beta-like (\( \epsilon \)) chains switches to that of \( \gamma \)-globin chains. The \( \alpha \)-globin and \( \gamma \)-globin chains combine to form fetal hemoglobin (\( \alpha_2 \gamma_2 \)), the main \( \beta \)-globin–like globin during the remainder of fetal life and throughout early postnatal life. As a result of the decline in the synthesis of \( \gamma \)-globin chains in patients with \( \beta \)-thalassemia, fetal hemoglobin production becomes insufficient to compensate for the excess of \( \alpha \)-globin chains, the production of which is unaffected in \( \beta \)-thalassemia.
to produce functional mRNA, result in \(\beta^0\)-thalassemia. Mutations in highly conserved nucleotides flanking these sequences, or in “cryptic” splice sites, which resemble a donor or acceptor splice site, result in severe as well as mild \(\beta^+\)-thalassemia. Substitutions or small deletions affecting the conserved AATAAA sequence in the 3' untranslated region result in ineffective cleavage of the mRNA transcript and cause mild \(\beta^+\)-thalassemia.

Mutations that interfere with translation involve the initiation, elongation, or termination of globin-chain production and result in \(\beta^0\)-thalassemia. Approximately half of all \(\beta\)-thalassemia mutations interfere with translation; these include frame-shift or nonsense mutations, which introduce premature termination codons and result in \(\beta^0\)-thalassemia. A more recently identified family of mutations, usually involving exon 3, results in the production of unstable globin chains of varying lengths that, together with a relative excess of \(\alpha\)-globin chains, precipitate in red-cell precursors and lead to ineffective erythropoiesis, even in the heterozygous state. This is the molecular basis for dominantly inherited (\(\beta^+\)) thalassemia. In addition, missense mutations, resulting in the synthesis of unstable \(\beta\)-globin chains, cause \(\beta\)-thalassemia.

PATHOPHYSIOLOGY
Mechanisms of Anemia

In severe untreated \(\beta\)-thalassemia, erythropoiesis may be increased by a factor of up to 10, more than 95 percent of which may be ineffective. Ineffective erythropoiesis, the hallmark of \(\beta\)-thalassemia, is a result of the myriad deleterious effects of a relative excess of \(\alpha\)-globin chains.\(^{17}\) This relative excess interferes with most stages of normal erythroid maturation: both intramedullary death of red-cell precursors through arrest in the G\(_1\) phase of the cell cycle\(^{18}\) and accelerated intramedullary apoptosis of late erythroid blast\(^{19,20}\) have been demonstrated. Studies of the consequences of the accumulation of excess \(\alpha\)-globin chains and their degradation products within the red-cell membrane and its skeleton\(^{20,22}\) have also demonstrated abnormalities in the ratio of spectrin to band 3 and in the function of band 4.1. This subject has been thoroughly reviewed recently.\(^{20}\) The observa-
tion that the presence of excess membrane iron may aggravate membrane changes has led to interest in the red-cell membrane as a potential therapeutic target in β-thalassemia. In a mouse model, increased cellular rigidity and decreased stability in connection with membrane-associated α-globin chains have reportedly been ameliorated during exposure to agents that bind membrane iron. Further understanding of these processes may guide future therapies.

**Clinical Consequences of Anemia**

The severe ineffective erythropoiesis results in erythroid marrow expansion to as much as 30 times the normal level. Both an increase in plasma volume as a result of shunting through expanded marrow and progressive splenomegaly exacerbate anemia (Fig. 3). Increased erythropoietin synthesis may stimulate the formation of extramedullary erythropoietic tissue, primarily in the thorax and paraspinal region. Marrow expansion also results in characteristic deformities of the skull and face, as well as osteopenia and foci of bone mineralization, and may aggravate a painful periarticular syndrome characterized histologically by microfractures and osteomalacia. Marrow hyperplasia leads ultimately to increased iron absorption and progressive deposition of iron in tissues.

**Cellular Heterogeneity and Fetal Hemoglobin Production**

Although fetal hemoglobin synthesis persists after birth to some degree, its production is insufficient...
to compensate for the reduced synthesis of $\beta$-globin chains and the relative excess of $\alpha$-globin chains. The elevated concentrations of fetal hemoglobin — 2 to 4 g per deciliter — observed in patients with $\beta$-thalassemia reflect a combination of the selection of precursors that produce relatively more fetal hemoglobin and crythroid expansion, which appears to favor the production of $\gamma$-globin chains. Even higher fetal hemoglobin concentrations are associated with specific $\beta$-thalassemia alleles or other genetic determinants within or linked to the $\beta$-globin complex. At least two other determinants may affect the synthesis of fetal hemoglobin, one on chromosome 6 and the other on the X chromosome.

**Clinical Forms**

The $\beta$-thalassemias include four clinical syndromes of increasing severity: two conditions are generally asymptomatic, the silent carrier state and $\beta$-thalassemia trait, and usually result from the inheritance of one mutant $\beta$-globin gene, and two require medical management, thalassemia intermedia and thalassemia major. The more severe forms most often result from homozygosity or compound heterozygosity for a mutant $\beta$-globin allele and, occasionally, from heterozygosity for dominant mutations. Homozygous or compound heterozygous $\beta$-thalassemia usually presents no diagnostic problems. The early onset of anemia, characteristic blood changes, and elevated fetal hemoglobin concentrations are found in no other condition. The diagnosis can be confirmed by the demonstration of the $\beta$-thalassemia trait in both parents. This condition is characterized by mild anemia, reduced mean cell volumes and mean cell hemoglobin concentrations, and elevated concentrations of the normal minor adult component of hemoglobin (usually exceeding 3.5 percent), hemoglobin A$_2$ ($\alpha_2\beta_2$).

Thalassemia major and thalassemia intermedia have no specific molecular correlate but encompass a wide spectrum of clinical and laboratory abnormalities. Patients referred to as having thalassemia major are usually those who come to medical attention in the first year of life and subsequently require regular transfusions to survive. Those who present later or who seldom need transfusions are said to have thalassemia intermedia. After thalassemia is diagnosed, patients who appear not to require immediate transfusion may benefit from a period of observation and folate repletion, particularly if the disease is diagnosed after the age of one year. This approach will allow the identification of patients in whom early growth and development are normal and whose well-compensated anemia may be exacerbated only by infection, folate deficiency, or increasing hypersplenism. With advancing age, even patients with mild forms may have serious complications, including osteopenia, iron loading in tissues, and ectopic marrow expansion. The classic changes of untreated thalassemia major are now regularly seen only in countries without resources to support long-term transfusion programs.

**Relation between Genotype and Phenotype**

Several genetic factors may ameliorate the severity of $\beta$-thalassemia. First, the underlying mutations vary widely in their effect on the synthesis of $\beta$-globin chains. Co-inheritance of $\alpha$-thalassemia may reduce the severity of the globin-chain imbalance. Many different interactions with structural hemoglobin variants may also result in a complex series of clinical phenotypes. The interactions of $\beta$-thalassemia with two of these variants, hemoglobin S and hemoglobin E, are of global importance.

The clinical consequences of the interaction with hemoglobin S depend mainly on the $\beta$-thalassemia allele. If inherited with $\beta^+$-thalassemia or severe $\beta^+$-thalassemia, the resulting clinical disorder may be indistinguishable from sickle cell anemia. By contrast, interactions with mild $\beta^+$-thalassemia alleles produce a milder sickling disorder.

Although hemoglobin E $\beta$-thalassemia is probably the most common serious hemoglobinopathy worldwide, its natural history remains poorly understood. The mutation that produces hemoglobin E activates a cryptic splice site in exon 1 in the $\beta$-globin gene; hence, hemoglobin E is associated with mild $\beta$-thalassemia. For reasons that are not well understood, the interaction of hemoglobin E and $\beta$-thalassemia results in a wide spectrum of clinical disorders: some are indistinguishable from thalassemia major, and some are much milder and not transfusion-dependent. Finally, a number of acquired and environmental factors, including progressive splenomegaly, exposure to infections, socioeconomic factors, and the availability of medical care, may also modify the severity of the disease.

**COMPLICATIONS OF DISEASE**

**Iron Overload**

Iron overload of tissue, which is fatal with or without transfusion if not prevented or adequately treated, is the most important complication of $\beta$-thalassemia and is a major focus of management. In patients who are not receiving transfusions, abnormally regulated iron absorption results in increases in body iron burden ranging from 2 to 5 g per year, depending on the severity of crythroid expansion. Regular transfusions may double this rate of iron accumulation. Although most clinical manifestations of iron loading do not appear until the second decade of life in patients with inadequate chelation, evidence from serial liver biopsies in very young patients indicates that the deleterious effects of iron are initiated much earlier than this. After approximately one year of transfusions, iron begins to be deposited in parenchymal tissues, where it may cause substantial toxicity as compared with that within retic-
As iron loading progresses, the capacity of serum transferrin, the main transport protein of iron, to bind and detoxify iron may be exceeded and a non—transferrin-bound fraction of plasma iron may promote the generation of free hydroxyl radicals, propagators of oxygen-related damage.44,45 The advances in free-radical chemistry that have clarified the toxic properties of these and other oxygen-derived species generated by iron, which may cause widespread tissue damage, have recently been summarized.45 Although the body maintains a number of antioxidant mechanisms against damage induced by free radicals, including superoxide dismutases, catalase, and glutathione peroxidase, in patients with large iron burdens these may not prevent oxidative damage.44,45

In the absence of chelating therapy the accumulation of iron results in progressive dysfunction of the heart, liver, and endocrine glands.40 Within the heart, changes associated with chronic anemia are usually present in patients who are not receiving transfusions and are aggravated by iron deposition. In response to iron loading, human myocytes in vitro increase the transport of non—transferrin-bound iron,46 possibly thereby aggravating cardiac iron loading. Extensive iron deposits are associated with cardiac hypertrophy and dilatation, degeneration of myocardial fibers, and in rare cases fibrosis.47 In patients who are receiving transfusions but not chelating therapy, symptomatic cardiac disease has been reported within 10 years after the start of transfusions48 and may be aggravated by myocarditis49 and pulmonary hypertension.50,51 The survival of patients with β-thalassemia is determined by the magnitude of iron loading within the heart.52,53

Iron-induced liver disease is a common cause of death in older patients54 and is often aggravated by infection with hepatitis C virus. Within two years after the start of transfusions, collagen formation55 and portal fibrosis56 have been reported; in the absence of chelating therapy, cirrhosis may develop in the first decade of life.43,57,58 The extent of these processes may be underestimated if fewer than three cores of liver are sampled at biopsy.59 The risk of hepatic fibrosis is augmented at body iron burdens corresponding to hepatic iron concentrations of more than 7 mg per gram of liver, dry weight (Fig. 4).60 As in cultured heart cells, in cultured hepatocytes the transport of non—transferrin-bound iron is increased,62 possibly aggravating iron loading in vivo.

The striking increases in survival in patients with β-thalassemia over the past decade have focused attention on abnormal endocrine function, now the most prevalent iron-induced complication in older patients. Iron loading within the anterior pituitary is the primary cause of disturbed sexual maturation, reported in 50 percent of both boys and girls with the condition.63 Furthermore, early secondary amenor-

CONTROL AND MANAGEMENT
Prevention Programs and Prenatal Diagnosis

Screening programs, aimed at prevention of the disease, and prenatal diagnosis have resulted in a marked reduction in the birth rate of affected children in Greece, Cyprus, continental Italy, and Sardinia.74 Widespread use of similar programs in other areas of the world has not yet been possible. Screening for carriers is performed most efficiently by measurement of the red-cell indexes and, in samples from persons with reduced mean cell volumes and mean cell hemoglobin concentrations, estimation of the hemoglobin A2 concentration. The practical problems associated with screening for rarer forms of β-thalassemia and the effect of coexistent α-thalassemia on the red-cell indexes have been reviewed recently.29 Prenatal diagnosis, first carried out by fetal-blood sampling and assessment of globin-chain synthesis in fetal blood, more recently has involved direct analysis of fetal DNA obtained by chorionic villus sampling. This approach is associated with a very slightly increased risk of fetal loss and an error rate in experienced laboratories of less than 1 percent. The practical aspects of fetal-DNA analysis have also been recently reviewed.29,74

Medical Therapy

A decision to initiate regular transfusions in patients with β-thalassemia may be difficult and should be based on the presence and severity of the symptoms and signs of anemia, including failure of growth and development. Only rarely is genotyping helpful in this decision. The goals of transfusion include correction of anemia, suppression of erythropoiesis, and inhibition of increased gastrointestinal absorption of iron. “Hypertransfusion” and “supertransfusion”
regimens, which achieve these goals but are associated with substantial iron loading, have been supplanted by regimens in which the hemoglobin concentration before transfusion does not exceed 9.5 g per deciliter. These newer regimens are associated with both adequate marrow suppression and relatively lower rates of iron accumulation.

The beneficial effects of iron-chelating therapy with parenteral deferoxamine, the only chelating agent widely available for clinical use, on the complications of iron loading have recently been reviewed. As a result of programs of deferoxamine therapy, the prognosis for patients in countries able to afford this therapy has greatly improved, in contrast to the prognosis for patients in developing countries, where widespread implementation of this regimen is still awaited.

Adequate deferoxamine therapy prevents early death from cardiac disease: maintenance of body iron burdens corresponding to hepatic iron concentrations of less than 15 mg per gram, dry weight, greatly decrease the risk of clinical disease. Nearly normal concentrations of hepatic iron can be maintained with modern regimens of deferoxamine. Moreover, deferoxamine arrests the progression of hepatic fibrosis to cirrhosis, even when administered in regimens that stabilize, rather than reduce, the body iron burden. The importance of this finding in the seminal study that ushered in the modern era of deferoxamine therapy is highlighted by evidence that in another form of iron overload, hereditary hemochromatosis, progression of hepatic fibrosis is a critical event associated with an increased risk of death.

A favorable effect of a sustained reduction in body iron is also suggested by the relatively low prevalence of thyroid, parathyroid, and adrenal abnormalities in the modern era. In parallel, early and intensive deferoxamine therapy may increase the incidence of normal sexual maturation, but it apparently does not reverse established abnormalities. Similarly, although deferoxamine prevents diabetes mellitus, there is...
no evidence that it can reverse this complication. In
summary, modern regimens of subcutaneous defer-
oxamine may extend survival free of many complica-
tions of iron overload, if body iron is reduced or
maintained below critical concentrations.40,52,53,79

A balance between the effectiveness of deferox-
a mine and its toxicity — the latter observed primarily
in the presence of relatively low body iron burdens80
— can be maintained through regular determina-
tions of body iron burden. In clinical practice, the
serum ferritin concentration is commonly used to
assess the effectiveness of treatment. It is increasing-
ly recognized that reliance on this test may lead to
errors in management; changes in body iron account
for little more than half the variation in serum fer-
ritin concentrations.81 By contrast, the measurement
of hepatic iron stores, whose concentrations are
highly correlated with total body iron stores,82 pro-
vides the most quantitative, specific, and sensitive
method of evaluating iron burden in patients with
thalassemia. Determination of hepatic iron concen-
trations in liver-biopsy specimens obtained with ul-
trasonographic guidance is safe and permits rational
adjustments in iron-chelating therapy.40 Magnetic
susceptometry provides a direct measure of hepatic
iron stores that is quantitatively equivalent to that
determined by biopsy of at least 0.6 mg of liver, dry
weight,83 over a range of iron concentrations.84 Mag-
netic susceptometry is currently available in only
two centers worldwide. By contrast, the more widely
available technique of magnetic resonance imaging
fails to provide accurate quantitation of hepatic iron
concentrations in patients with severe iron overload,
hepatic fibrosis, or both.85

Bone Marrow Transplantation

Bone marrow transplantation from HLA-identical
donors has been successfully performed worldwide in
over 1000 patients with severe β-thalassemia.86 Out-
comes after transplantation are greatly influenced by
the presence of hepatomegaly, portal fibrosis, and in-
effective chelating therapy before transplantation.87
Children without any of these risk factors have rates
of survival and disease-free survival exceeding 90 per-
cent three years after transplantation. In those with
all three risk factors, and in most adults, the rates are
approximately 60 percent. Lower success rates are
reported at smaller centers.87 Complications include a
rate of chronic graft-versus-host-disease ranging from
2 to 8 percent and a variable incidence of mixed chi-
merism.86 Post-transplantation management of preex-
isting hepatic iron overload, iron-induced cardiac dys-
function, and viral hepatitis may prevent progression
of these processes.86 There is interest in experimental
approaches to bone marrow replacement in patients
with thalassemia, including cord-blood transplanta-
tion,88 the use of unrelated phenotypically matched
donors,89 and in utero transplantation.90

Experimental Therapies

Chelators Other Than Deferoxamine

Difficulties associated with deferoxamine therapy
have led to a search for alternatives, including orally
active iron chelators. The administration of one
agent, deferiprone, was reported to have a favorable
short-term effect on body iron in the one study in
which serial systematic determinations of hepatic iron
were obtained.91 Two subsequent long-term studies
have suggested that hepatic iron may stabilize at or
increase to concentrations associated with an in-
creased risk of cardiac disease and early death52 in
approximately half of patients.92 Long-term treatment
has been reported to be associated with progression of hepatic fibrosis; the
odds of progression of fibrosis were estimated to in-
crease by a factor of 5.8 with each additional year of
deferiprone therapy.93 In another study, four deaths
due to cardiac failure were reported during long-term
therapy.92 The results of these clinical trials virtually
 recapitulate those in two animal species, in which
deferiprone and a structurally similar compound were
shown to increase hepatic and cardiac iron loading,
worsen hepatic fibrosis, and induce cardiac and mus-
culoskeletal fibrosis.95,96 Taken together, these data
suggest that deferiprone does not adequately control
body iron in a substantial proportion of patients and
may promote worsening of hepatic fibrosis. These
studies support cautions previously expressed about
the long-term administration of this agent.97

The results of long-term follow-up of the effec-
tiveness of other modes of administration of defer-
oxamine are awaited. These include deferoxamine
attached to high-molecular starch,98 administered in
twice-daily subcutaneous boluses,99 and given in a lip-
id vehicle, permitting slow release.100

Augmentation of Fetal-Hemoglobin Synthesis

Several trials have attempted to augment the syn-
thesis of fetal hemoglobin in an effort to ameliorate
the severity of β-thalassemia.101 Administration of in-
travenous 5-azacytidine was associated with increases
in the hemoglobin concentration in a few patients102;
the potential toxicity of the drug later shifted interest
to less toxic alternatives. Therapy with hydroxyu-
rcac103,104 butyric acid compounds,105 and these agents
in combination106 has reduced or eliminated transfu-
sion requirements in some patients. Other studies
have reported only small increases in fetal and total
hemoglobin concentrations during the administra-
tion of hydroxycurd107,108 and both intravenous109,110
and oral111,112 butyrate compounds.

How can the augmentation of fetal hemoglobin
be optimized? Studies in humans and animal models
of β-thalassemia, including transgenic mice,113 have
suggested that increases in the production of γ-globin chains may be influenced by the degree of erythroid marrow expansion, sequential administration of specific combinations of agents, the degree to which the γ-globin gene is already partially activated, or all of these.113-116 Furthermore, the striking clinical responses observed in patients with mutations104-108 that delete specific sequences within the β-globin gene cluster that may have a key role in the silencing of adjacent genes117 indicate that delineation of some cis sequences may influence the inducibility of the γ-globin gene.

Although they address a highly desirable, cost-effective goal in β-thalassemia, therapies to increase the synthesis of fetal hemoglobin in the disorder have, with few exceptions, proved disappointing to date. Nonetheless, important avenues to be pursued in further studies include the identification of specific mutations that may respond to therapy, particularly with specific combinations of agents.

**Gene Therapy**

Permanent correction of genetic deficit of the hematopoietic system requires the transfer of genes into stem cells and long-term, high-level, lineage-specific expression of these cells after autologous transplantation; mature cells and committed progenitors do not have the proliferative capacity to reconstitute the entire hematopoietic system. Over the past decade, there has been progress in the development of transduction methods and vectors.118 Remaining problems include the identification of all sequences required for stable, high-level expression of the genes and the development of more effective and safe vectors for the transfer of genes.119 Another approach, correction of the defective gene by site-directed recombination, is feasible, but current methods lack the degree of efficiency required.120

**CONCLUSIONS**

Among the first diseases to be studied at the molecular level, the β-thalassemias remain a model for understanding the relation between the molecular pathology of a disease and its clinical diversity. At the same time, these disorders have become an increasingly important part of clinical practice in all countries with large populations from the tropics. The marked increase in survival, to the fifth decade of life, of patients with well-managed β-thalassemia in developed countries represents one of the most dramatic alterations in morbidity and mortality associated with a genetic disease in this century. Still, nearly 75 years after the fascinating initial description of “peculiar bone changes” and other signs and symptoms of the disorder, the β-thalassemias have emerged as a huge public health problem worldwide. They remain a therapeutic challenge for the next millennium.

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