β-Thalassemia

Deborah Rund, M.D., and Eliezer Rachmilewitz, M.D.

THALASSEMIA IS A HEREDITARY ANEMIA RESULTING FROM DEFECTS IN hemoglobin production. β-Thalassemia, which is caused by a decrease in the production of β-globin chains (Fig. 1), affects multiple organs and is associated with considerable morbidity and mortality. Accordingly, lifelong care is required, and financial expenditures for proper treatment are substantial.

Thalassemia is among the most common genetic disorders worldwide; 4.83 percent of the world’s population carry globin variants, including 1.67 percent of the population who are heterozygous for α-thalassemia and β-thalassemia. In addition, 1.92 percent carry sickle hemoglobin, 0.95 percent carry hemoglobin E, and 0.29 percent carry hemoglobin C. Thus, the worldwide birth rate of people who are homozygous or compound heterozygous for symptomatic globin disorders, including α-thalassemia and β-thalassemia, is no less than 2.4 per 1000 births, of which 1.96 have sickle cell disease and 0.44 have thalassemias.

MOLECULAR AND CELLULAR PATHOLOGY

β-Thalassemia is caused by any of more than 200 point mutations and, rarely, by deletions. Thalassemia is clinically heterogeneous because various genetic lesions variably impair globin-chain synthesis. However, genotypic variability at known loci is often insufficient to explain the disparate phenotypes of individual patients with the same genotype. Disparity between genotypes and phenotypes is particularly marked in thalassemia intermedia and hemoglobin E thalassemia (Table 1). However, the known genetic factors are insufficient to account for the marked variability, and other genetic modifiers may exist.

Recently, an α-hemoglobin–stabilizing protein was identified that binds to and stabilizes free α chains, thereby blocking the production of reactive oxygen species and reducing oxidative damage to erythrocytes. This protein appears to modulate the clinical picture of β-thalassemia in a murine model but in human studies has not been found to modify thalassemia.

Hemolysis and ineffective erythropoiesis together cause the anemia that occurs in thalassemia. The relative contributions of these two pathologic processes differ in various forms of thalassemia. Figure 2 illustrates the complex chain of events that occurs in erythrocytes, resulting in their accelerated peripheral destruction.

The bone marrow of patients with thalassemia contains five to six times the number of erythroid precursors as does the bone marrow of healthy controls, with 15 times the number of apoptotic cells in the polychromatophilic and orthochromic stages. Accelerated apoptosis, the major cause of ineffective erythropoiesis, is caused by excess α-chain deposition in erythroid precursors. Although the exact mechanism is not known, a death-receptor–mediated pathway seems to be involved with Fas–Fas ligand interactions. In normal erythropoiesis, apoptotic mechanisms seem to play a regulatory role and are required for normal erythroid maturation. Accelerated apoptosis is
Figure 1. Management of Thalassemia and Treatment-Related Complications.

The anemia that is associated with thalassemia may be severe and is accompanied by ineffective erythropoiesis, with bone expansion and extramedullary hematopoiesis in the liver, spleen, and other sites, such as paravertebral masses. Transfusion therapy, which is the mainstay of treatment, allows for normal growth and development and suppresses ineffective erythropoiesis. Transfusion-transmitted infections (primarily hepatitis B and C) are an important cause of death in countries where proper testing is not available. Iron overload results both from transfusional hemosiderosis and excess gastrointestinal iron absorption. Iron deposition in the heart, liver, and multiple endocrine glands results in severe damage to these organs, with variable endocrine organ failure. The endocrinopathies can be treated with hormone replacement. However, the most serious result of iron overload is life-threatening cardiotoxicity, for which chelation therapy is required.

Thalassemia can be cured by bone marrow transplantation. Experimental therapies to ameliorate the anemia that have been or are currently under investigation include fetal hemoglobin modifiers and antioxidants. In the future, gene therapy or other molecular methods may be feasible.
Table 1. Genetic Basis and Clinical Manifestations of Common β-Thalassemia Syndromes.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Thalassemia Trait</th>
<th>Thalassemia Intermedia</th>
<th>Thalassemia Major</th>
<th>Hemoglobin E Thalassemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic pathology</td>
<td>One β-globin gene carrying a thalassemia mutation</td>
<td>Two β-globin genes carrying a thalassemia mutation, at least one of which is mild; one β-globin thalassemia mutation in combination with excess α-globin genes (less common)</td>
<td>Two β-globin genes carrying a severe thalassemia mutation</td>
<td>One β-globin gene carrying a thalassemia mutation (mild or severe) in combination with a β-globin gene carrying the point mutation encoding hemoglobin E</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td>Mild or no anemia, with variable microcytosis (mean corpuscular volume, 60 to normal); no splenomegaly; no bone disease</td>
<td>Mild to moderate anemia; relative independence from transfusions; prominent splenomegaly and bone deformities; variable degrees of iron overload depending on severity of anemia and transfusion requirement</td>
<td>Severe anemia requiring regular transfusions beginning in infancy; splenomegaly and bone disease depending on the efficacy of transfusion therapy; severe iron overload</td>
<td>Mild to severe anemia; relative dependence on transfusions; splenomegaly and bony deformities; variable degree of iron overload, depending on severity of anemia and transfusion requirement</td>
</tr>
<tr>
<td>Severity</td>
<td>Asymptomatic</td>
<td>From asymptomatic to severely symptomatic</td>
<td>Lifelong supportive care required</td>
<td>From asymptomatic to severely symptomatic</td>
</tr>
<tr>
<td>Ameliorating genetic factors</td>
<td>Presence of concurrent α-thalassemia</td>
<td>Presence of concurrent α-thalassemia; elevated hemoglobin F</td>
<td>Presence of concurrent α-thalassemia; elevated hemoglobin F</td>
<td>Mild β-thalassemia mutation; concurrent α-thalassemia; elevated hemoglobin F</td>
</tr>
<tr>
<td>Exacerbating genetic factors</td>
<td>Excess α-globin genes</td>
<td>Number of excess α-globin genes (five or more)</td>
<td>None known</td>
<td>Severe β-thalassemia mutation</td>
</tr>
</tbody>
</table>

**Clinical Manifestations and Supportive Therapy**

**Anemia and Transfusion Therapy**

Regular transfusion therapy to maintain hemoglobin levels of at least 9 to 10 g per deciliter allows for improved growth and development and also reduces hepatosplenomegaly due to extramedullary hematopoiesis as well as bone deformities.\(^2\)\(^3\) Table 2 summarizes some of the advances in transfusion therapy.

**Endocrinopathies and Bone Disease**

Impairment of growth and endocrinopathies, particularly hypogonadism, are common features of thalassemia.\(^2\)\(^3\)\(^23\)\(^24\) Since these manifestations (Fig. 1) result from chronic anemia as well as from iron overload, they are much more common in older patients or those whose chelation therapy is insufficient (discussed below).\(^2\)\(^3\) Hormonal replacement is indicated for residual endocrine insufficiency.\(^24\) Growth hormone therapy has had variable success.\(^23\) Hypogonadotropic hypogonadism impairs fertility but can be corrected with the use of hormonal replacement in male patients. A small number of female patients, including those with thalassemia major or thalassemia intermedia, have been able to become pregnant, either spontaneously (if they have received adequate chelation therapy) or with assisted reproductive techniques.\(^23\) Pregnancy generally appears safe if baseline cardiac function is good.\(^25\)

Considerable morbidity in older patients results from bone disease due to osteopenia and osteoporosis, which is often accompanied by disabling pain and fractures. The pathogenesis is complex and multifactorial. Bone marrow expansion due to ineffective erythropoiesis, endocrine dysfunction, and complications of treatment all contribute to the condition.\(^26\) Overly vigorous chelation is associated with deferoxamine-induced bone dysplasia, which can slow growth velocity in children and may be only partially reversible.\(^24\) Bone-disease management includes the careful monitoring of chelation, lifestyle adjustments (increased calcium intake and physical activity and refraining from smoking), hormonal therapy, and vitamin D therapy. Osteoclast...
Iron overload causes most of the mortality and morbidity associated with thalassemia. Iron deposition occurs in visceral organs (mainly in the heart, liver, and endocrine glands), causing tissue damage and ultimately organ dysfunction and failure (Fig. 1). Cardiac events due to iron overload are still the primary cause of death. Both transfusional iron overload and excess gastrointestinal absorption are contributory. Paradoxically, excess gastrointestinal iron absorption persists despite massive increases in total body iron load.

Hepcidin is a small peptide that inhibits iron absorption in the small bowel. Hepcidin levels normally increase when iron stores are elevated. Hepcidin levels were found to be inappropriately low in patients with thalassemia intermedia and thalassemia major. Furthermore, serum from patients with thalassemia inhibited hepcidin messenger RNA expression in the HepG2 cell line, which suggests the presence of a humoral factor that downregulates hepcidin. These observations suggest that the administration of hepcidin or agents that increase hepcidin expression may be therapeutically useful for the inhibition of inappropriate iron absorption.

Accurate, preferably noninvasive measurement of iron stores is crucial for the evaluation and management of chelation therapy. Serum ferritin is the most commonly measured as an indicator of iron stores. Ferritin levels below 2500 mg per milliliter are associated with improved survival, free of cardiac disease. However, serum ferritin levels are highly unreliable, particularly when liver disease is present. Liver biopsy has often been used but is invasive. Direct noninvasive measurement of hepatic iron stores is possible with the technique of magnetic susceptometry (with the use of a superconducting quantum-interference device) and is either equivalent to or more accurate than the measurement of hepatic iron by liver biopsy. However, only four centers worldwide currently have this capacity.

It is noteworthy that hepatic iron may not accurately represent iron deposition in other vital organs (such as the heart). Indeed, severe cardiac damage has been observed in a few patients with presumably adequate chelation, and myocardial iron and left ventricular function apparently cannot be predicted from liver iron concentration, ferritin levels, or both. Therefore, noninvasive techniques for the measurement of cardiac iron levels are being developed. Magnetic resonance imaging (MRI) for the measurement of cardiac iron is technically problematic. However, the application of T2 gradient-echo sequencing is more sensitive to hemosiderin deposition and appears to be useful for the measurement of myocardial iron in thalassemia, but this approach requires further validation and long-term studies to determine its usefulness in assessing the effectiveness of chelation therapy.

Elevated tissue iron stores are only one component of the damaging effects of iron overload. A highly toxic form of iron, non–transferrin-bound iron, is formed when the iron-binding capacity of transferrin has been exceeded. Non–transferrin-bound iron is highly toxic because it can catalyze the formation of reactive oxygen species through the Fenton reaction. A fraction of non–transferrin-bound iron, the labile plasma iron, can be measured directly and may serve as a clinically useful test for monitoring iron-chelation therapy.

Iron-chelation therapy is largely responsible for...
doubling the life expectancy of patients with thalassemia major.\textsuperscript{28,32,37} Deferoxamine continues to be the most common iron-chelating agent in use, but it has several limitations: the need for parenteral administration (which is painful and reduces compliance), side effects, and cost (which is prohibitive in underdeveloped countries).\textsuperscript{28}

Much effort has been invested in the development of new orally active chelators. Deferiprone, an orally administered chelator, was initially thought to be an inadequate chelator that might worsen hepatic fibrosis. However, cumulative worldwide experience indicates that the drug is safe and effective.\textsuperscript{38} Long-term administration of deferiprone does not appear to be associated with liver damage.\textsuperscript{39} Adverse effects of deferiprone include arthralgia, nausea and other gastrointestinal symptoms, fluctuating liver enzyme levels, leukopenia, and rarely agranulocytosis and zinc deficiency.\textsuperscript{40} Most of these effects can be monitored and controlled.

Deferiprone has a number of advantages over deferoxamine. It can penetrate the cell membrane and chelate toxic intracellular iron species.\textsuperscript{41} In a preliminary study, hemoglobin levels increased and transfusion requirements decreased in a few patients with hemoglobin E thalassemia who were treated with deferiprone for an average of 50 weeks.\textsuperscript{42} Most important, recent evidence suggests that deferiprone may be more effective than deferoxamine in the removal of myocardial iron.\textsuperscript{34,43,44}

An encouraging new approach to chelation therapy is the sequential combined administration of deferiprone and deferoxamine. Experimental evidence suggests that intracellular iron chelated by deferiprone is transferred in the plasma to the more powerful chelator, deferoxamine (the so-called “shuttle hypothesis”).\textsuperscript{45} As a consequence, more iron is excreted with the use of combined therapy than with the separate administration of each drug. Furthermore, the compliance of patients was improved with the use of combined therapy because fewer painful injections of deferoxamine were required.\textsuperscript{43,46,47}

A number of new oral iron chelators are under development.\textsuperscript{25} Deferasirox (ICL670) is particularly promising for its efficacy, which may be similar to that of deferoxamine.\textsuperscript{44,48} Deferasirox is administered once daily and appears to have an acceptable side-effect profile.\textsuperscript{44,49,50} Toxic effects that have been observed have been related mainly to iron deprivation and transient gastrointestinal symptoms. No cases of agranulocytosis have been reported in several phase 2 trials involving several hundred patients.\textsuperscript{49,50}

In summary, a growing body of evidence suggests that deferiprone is an acceptable alternative for patients who are unable to receive deferox-
The combination of deferiprone and deferoxamine appears very promising but requires further verification. The preliminary data on deferasirox are encouraging, and long-term clinical trials are still required. Finally, improved noninvasive technologies (including imaging and blood tests) for quantitation of iron overload will provide reliable information for the assessment of the efficacy of present and future therapies.

**Hypercoagulability**

Thromboembolic phenomena, both venous and arterial, are not uncommon in patients with thalassemia, particularly in patients who have undergone splenectomy and who undergo transfusion infrequently. Abnormalities in the levels of coagulation factors and their inhibitors have been reported, resulting in what can be defined as a chronic hypercoagulable state.

Erythrocyte-membrane abnormalities contribute to hypercoagulability (Fig. 2). Membrane lipid peroxidation increases the expression of anionic phospholipids such as phosphatidylserine. Exposure of phosphatidylserine on the erythrocyte was highly correlated with the expression of platelet activation markers. Erythrocytes that are exposed to phosphatidylserine may also contribute directly to the vascular damage observed in thalassemia. In addition, erythrocytes and platelets from patients with thalassemia contain higher levels of reactive oxygen species and lower levels of intracellular glutathione than do normal erythrocytes and platelets, and this finding may be attributed to continuous exposure to oxidative insults. Further studies will be required before conclusive recommendations can be made for prophylactic anticoagulation, antiplatelet therapy, or both for patients with thalassemia who are at risk (during pregnancy or in the postoperative period) or on a routine basis, particularly in patients who have undergone splenectomy.

**Hematopoietic Stem-Cell Transplantation**

Although hematopoietic stem-cell transplantation is the only available curative approach for thalassemia, it has been limited by the high cost and the scarcity of HLA-matched, related donors. The past several years have brought progress in the realms of conditioning regimens, donor identification and selection, and the development of alternative sources of hematopoietic stem cells.

Low-risk patients (those with thalassemia termed class 1 or class 2 by the Lucarelli classification, which is used to assess risk factors that predict outcome and prognosis and addresses the degree of hepatomegaly, the presence of portal fibrosis on liver biopsy, and the effectiveness of chelation therapy before transplantation) have had excellent results after bone marrow transplantation; however, patients with class 3 disease (with extensive liver damage from iron overload) have had poor results in the past, primarily because of the 30 percent rate of graft rejection due to attenuated conditioning. A new preparatory regimen (including hydroxyurea, azathioprine, fludarabine, busulfan, and cyclophosphamide) has substantially improved the results in patients with class 3 disease who are younger than 17 years of age. The survival rate among these patients was 93 percent, and the rejection rate fell to 8 percent.

Because of the difficulty of eradicating the endogenous thalassemic bone marrow, it has been considered essential to administer full myeloablative conditioning regimens for transplantation. Nonmyeloablative regimens have rarely been attempted. Follow-up is short, and it is unclear whether this approach will be beneficial. However, in contrast to what may occur after bone marrow transplantation for cancer, long-term mixed chimerism can sometimes result in an acceptable clinical outcome in thalassemia as long as the anemia is corrected.

An increase in the available donor pool for bone marrow transplantation has been achieved by using matched, unrelated donors. Extended haploidentical transplantation has been developed for unrelated donors, and the resulting outcomes were similar to those using matched, related donors. The use of related or unrelated umbilical-cord blood further increases the donor pool. However, cord-blood transplantations have often been unsuccessful in the treatment of thalassemia because large numbers of transplanted cells need to be administered to sustain hematopoiesis and prevent graft rejection. In one study using related cord blood, 7 of 33 pediatric patients rejected grafts and 3 others exhibited stable mixed chimerism. Another study reported a high rate of nonengraftment and secondary rejection: only four of nine children were transfusion-independent at a median follow-up period of 49 months. Rare case reports have described a suc-
cessful outcome with unrelated cord-blood transplantation. In the future, umbilical-cord-blood transplantation may be more successful if stem cells can be expanded ex vivo.

In summary, hematopoietic stem-cell transplantation with the use of related or unrelated donors is a viable alternative that generally results in an excellent outcome for low-risk patients. If transplantation is successful, transfusions, and usually chelation therapy, are no longer necessary. There is a small risk of serious complications (death, graft failure or rejection, and graft-versus-host disease). Furthermore, growth failure and endocrinopathies, particularly gonadal dysfunction, can still occur. All these factors, in addition to the availability of adequate supportive care in various geographical regions, must be considered when deciding whether to perform transplantation in any given patient.

### Experimental Therapies

#### Cellular and Molecular Modifiers

Augmenting the synthesis of fetal hemoglobin should ameliorate the severity of β-thalassemia. Drugs such as 5-azacytidine, hydroxyurea, and various butyrate derivatives have been used for this purpose. Hydroxyurea has shown substantial benefits in a subgroup of patients with sickle cell anemia but has been used less often in thalassemia. In a few pediatric patients with thalassemia, transfusion requirements were eliminated after treatment with hydroxyurea for approximately 20 months. In general, preliminary results among a relatively small number of patients have been inconsistent, and thus the role of hydroxyurea in thalassemia therapy remains uncertain.

One possible explanation for the differential effects of hydroxyurea in sickle cell anemia as compared with thalassemia is that many patients with thalassemia are transfusion-dependent. Hypertransfusion suppresses endogenous erythropoiesis, particularly of hydroxyurea-responsive types of cells. Therefore, despite the beneficial effects of hydroxyurea on erythropoiesis, it will be difficult to correct the anemia associated with thalassemia with the use of hydroxyurea. Moreover, genetic predisposition, such as the presence of XmnI polymorphism, and the type of thalassemia, such as hemoglobin E thalassemia, may determine the response to hydroxyurea treatment.

Recombinant human erythropoietin was shown to provide the benefit of increasing “thalassemic erythropoiesis” without raising fetal hemoglobin. The effect appeared to be dose-dependent and was observed primarily in patients with β-thalassemia intermedia who had undergone splenectomy. Recently, long-acting darbepoetin alfa was shown to increase hemoglobin levels substantially in patients with hemoglobin E–β-thalassemia disease. Two important obstacles to the use of recombinant human erythropoietin are its relatively high cost and its subcutaneous administration route, which restrict its use in developing countries. Appropriate clinical protocols are needed to delineate the role of recombinant human erythropoietin (alone or in combination with the aforementioned drugs) in the treatment of β-thalassemia.

Screening for new compounds that augment fetal hemoglobin production can be performed with the use of cell-culture techniques, and various animal models have been useful in the evaluation of potential fetal hemoglobin inducers. Furthermore, perturbations of growth-related signaling appear to activate tissue-specific fetal genes. Exploration of these signaling pathways may lead to the discovery of new pharmacologic agents for the treatment of thalassemia.

#### Potential Role of Antioxidants

Because reactive oxygen species play an important role in the pathophysiology of thalassemia (Fig. 2), antioxidants may be an effective therapy. Patients with thalassemia have very high plasma levels of malonyldialdehyde, a by-product of lipid peroxidation. Malonyldialdehyde levels correlate positively with serum iron and with non–transferrin-bound iron. Elevated levels of reactive oxygen species tended to normalize in response to oral therapy with vitamin E, with patients exhibiting improvement in the antioxidant–oxide balance in plasma and decreased lipid peroxidation in erythrocytes. Plant flavonoids (including rutin and curcumin) are another group of antioxidants with therapeutic potential in thalassemia. These compounds have salutary effects on erythrocytes that have been damaged by oxidation. Polyphenols (a major component of tea) bind to ferric iron and could also protect thalassemic erythrocytes from oxidation. However, despite their apparent salutary effects on erythrocytes, antioxidants have not yet been shown to ameliorate the anemia of patients with thalassemia.

Antioxidants may be more effective if used in combination — for example, as a lipid antioxidant like vitamin E, together with N-acetylcysteine, which
is a protein antioxidant that improves several measures in oxidized sickle erythrocytes, and an iron chelator such as deferiprone. This approach, if successful, could be particularly useful in countries with limited financial resources.

**EXPERIMENTAL MOLECULAR THERAPIES**

Initial efforts at gene therapy were directed against diseases of the β-globin gene. This therapeutic strategy involves the insertion of a normally functioning γ-globin or β-globin gene into the patient’s autologous hematopoietic stem cells. Although the concept is relatively straightforward, it has met with two decades of seemingly insurmountable hurdles that have been well summarized elsewhere. The major problems with this type of gene therapy have been related to vector construction. The genetic elements of the vector that are necessary for appropriate regulation of the inserted gene have been defined. However, the therapeutic gene must be inserted into a hematopoietic stem cell and must be expressed at high levels, over an extended period, in an erythroid-specific manner. In addition, the vector must be safe from recombination or mutagenesis. Oncoretroviral and adenoviral vectors have been found to be unsuitable for various reasons.

The introduction of lentiviral vectors was an important advance, since these viruses do not require cell division for entry into eukaryotic cells and can stably hold larger DNA inserts without rearrangements. Self-inactivating lentiviral vectors were constructed to address safety issues. Longer locus-control-region elements may abrogate position effects that reduce expression of the therapeutic gene. The problem of gene silencing of the transduced gene has been approached by the use of insulators, which are DNA sequences that can result in diagnostic errors. Preimplantation genetic diagnosis requires a high degree of technical expertise. Furthermore, because pregnancy termination is unacceptable to some persons (even when the fetus is affected), methods were developed, beginning in the early 1990s, to perform diagnostic testing before implantation. Preimplantation genetic diagnosis involves performing conventional in vitro fertilization, followed by removal of one or two cells from the resulting blastomeres on day 3. PCR is then used to detect thalassemia mutations within the cells that have been removed so that unaffected blastomeres may be selected for implantation. Preimplantation genetic diagnosis requires a high degree of technical expertise. Furthermore, the phenomenon of “allele dropout” (failure to amplify one of the two alleles in a heterozygous cell) can result in diagnostic errors. Nonetheless, this technology has been successful, and improvements in outcome have led to its use in many countries.

Recently, preimplantation genetic diagnosis has been extended to HLA typing on embryonic biopsies, which allows the selection of an embryo that is not affected by thalassemia and that may also serve as a stem-cell donor for a previously affected individual.
child within the same family. Recent reports have confirmed that this approach is feasible. However, serious ethical concerns have been raised. Although it is considered ethical not to implant an embryo that is affected with a serious genetic disorder, in certain countries it is forbidden to select an embryo on the basis of its designated role as a potential stem-cell donor.

Future prenatal diagnosis may be performed noninvasively, with the use of maternal blood samples to isolate either fetal cells or fetal DNA for analysis. These techniques are feasible but have not yet been perfected. Furthermore, techniques using DNA in maternal plasma to exclude thalassemia in the fetus are applicable only to couples using DNA in maternal plasma to exclude thalassemia noninvasively, with the use of maternal blood samples to isolate either fetal cells or fetal DNA.

The potential of stem-cell therapy is an important consideration. In certain countries it is forbidden to select an embryo on the basis of its designated role as a potential stem-cell donor. An embryo on the basis of its designated role as a potential stem-cell donor.

Countries emphasize curative forms of therapy, such as bone marrow transplantation and gene therapy, which require compliant patients with access to the newest medications and sophisticated scientific facilities. Western cultures need to develop improved support for patients with thalassemia and their families. Doing so will prevent psychosocial issues from taking their heavy toll due to noncompliance.

In contrast, the treatment of thalassemia is entirely different in less developed countries, where most of the patients with this disease reside. Safe transfusion (with the use of filtration and the viral testing of blood) and chelation are not universally available. Consequently, many patients with thalassemia in underdeveloped nations die in childhood or adolescence. Programs that provide acceptable care, including transfusion of safe blood and supportive therapy including chelation, must be established. Thalassemia-prevention protocols must be developed in these countries, with the use of better education and screening and improved access to prenatal diagnosis.

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