Thalassemia Intermedia
A Regional Conference

Proceedings from a Conference on Thalassemia Intermedia
Sponsored by the New England Thalassemia Program

Boston, MA
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The New England Thalassemia Program, established in 1982, is a collaboration of thalassemia treatment centers at six major hospitals in New England. The program assures optimal care for patients and families affected by or at risk for thalassemia. We offer a network of thalassemia services that include education, diagnosis, culturally sensitive screening, genetic counseling, comprehensive medical care, and psychosocial support. The hospital centers are based at Children's Hospital in Boston, Bay State Medical Center in Springfield, Rhode Island Hasbro Children's Hospital, New England Medical Center, the University of Massachusetts Medical Center in Worcester and Yale New Haven Hospital.

We are directly affiliated with the New England Regional Genetics Group, one of 10 regional networks of the Council of Regional Networks of Genetic Services. We also work closely with both the Asian Thalassemia Screening Project at the South Cove Community Health Center in Boston and the Joint Center for Sickle Cell and Thalassemic Disorders at the Brigham and Women's Hospital.

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Preface

thalassemia intermedia is one of the most challenging and controversial hematologic disorders. This report was assembled from discussions held at a conference in Boston, Massachusetts, on November 14, 1996. The conference brought together leaders and researchers in the fields of hematology and genetics. Presenters included such well-known experts as Drs. Howard Pearson (conference chair), Alan Cohen, George Dover, Ed Forman, Patricia Giardina, Carol Hyman, Haig Kazazian, and Nancy Olivieri.

We offer this material in the hope that our experience will stimulate further thinking about the clinical spectrum of thalassemia intermedia and the genetic correlations. In these proceedings, you will find a history and definition of thalassemia intermedia, a compilation of data from patients in six northeastern medical institutions, a study of the use of sodium phenylbutyrate and hydroxyurea to stimulate fetal hemoglobin, and an analysis of the molecular basis of thalassemia intermedia. There are also presentations on the assessment of iron overload, the use of chelation therapy, splenectomy, and infection control. We close with a lively panel that explores treatment approaches and future questions about the role of fetal hemoglobin enhancement and bone marrow transplant.

As the social worker at the Boston Children's Hospital thalassemia program, I have developed a great respect for patients and their families. Over the past 12 years, I have been impressed by the strength, courage, and perseverance of those who cope with the challenges of this illness. I have seen many patients confront their worst fears and grow to become confident and healthy adults. Because thalassemia intermedia is less common and further complicated by uncertainty and isolation, I am pleased we could devote an entire conference to this topic. With this project, we capture the energy and spirit of the New England Thalassemia Program. I would like to thank the presenters and the planning committee, whose innovative ideas were the foundation of this event. It is an honor to work with so many creative and dedicated professionals.

This conference and publication would not have been possible without the support of the Maternal and Child Health Bureau, the New England Regional Genetics Group, and the Connecticut Campaign Against Cooley's Anemia. We are pleased to make these proceedings available to both the public and professionals.

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Good morning and welcome to the New England Thalassemia Program's second conference on thalassemia intermedia. I want to take this moment to thank all those who have made this meeting possible: the speakers, members of the New England Thalassemia Program, and especially Lauren Berman, our director, and Dr. Howard Pearson, our valued and consistent mentor, who brought this conference into being.

The first thalassemia intermedia conference was held 11 years ago. At its conclusion, we, like Socrates, achieved the wisdom of understanding how little we knew. We knew neither how to predict the natural history of a given patient nor how to manage the patient, nor even how to define this condition (or these conditions). Now, at this second conference, with our panel of esteemed experts, it might not be unrealistic to hope that we can move further toward answering the following questions:

How can we define thalassemia intermedia, perhaps even at a molecular level, such that we can increase understanding of the pathophysiology and enable accurate prediction of the natural history of the condition for a given patient?

How should a patient needing a splenectomy, transfusions, chelation, growth and/or sex hormonal therapy, stimulation of fetal hemoglobin, bone marrow transplantation, etc., be managed?

To start us off, I will give a brief followup report on the original two children who were the focus of the first thalassemia intermedia conference. The photographs of the children are used with their permission and the permission of their family.

Child 1

Child 1 (C1) was noted to be anemic at about 14 months of age, and, upon evaluation, was diagnosed with thalassemia intermedia, probably doubly heterozygous. Aside from dietary recommendations to avoid iron-rich foods and drink tea, no other therapy was given. Over the next few years, she developed progressive splenomegaly and mild thalassemic facial features. Her hemoglobin dropped to 5 g%. She received one transfusion. At age 6, a splenectomy was performed, and thereafter her hemoglobin level has averaged 9 g%. She has not received any further transfusions and has never received chelation therapy. She has short stature, like her family, but has reached a height of 5 feet 1 inch, and achieved puberty, with menarche at 15 years of age. Aside from a possible stress fracture (shin splints in her right tibia), a suspicious test for hepatitis C at one time (not confirmed), pneumonia at age 16, and sinusitis at age 20, she has had no serious complications and has no evidence of diabetes or gallstones. She is currently 22, has been employed, and is now back in college studying for a degree in nursing. Currently, her serum iron is 83 mg%, her total iron binding capacity is 222 mg%, and her ferritin is 152 mg%. A cardiac evalu-
A cardiac evaluation reveals mild cardiomegaly but a normal echocardiogram and electrocardiogram. As you can see from her photograph, she is an attractive young woman who has an active social life and a cheerful disposition.

Child 2

Child 2 (C2), brother of C1, was diagnosed with β-thalassemia intermedia at age 12 months, and the progression of his condition is roughly similar to that of his sister. He developed a worsening anemia, down to 5 g% by the time he was 4 years of age, and progressive splenomegaly and mild thalassemic facies. He received three blood transfusions at around age 4 years without significantly affecting his hemoglobin level. A splenectomy was performed at age 4-1/2, and since that time his hemoglobin level has averaged 8.5 g%. Although he has developed secondary male sexual characteristics (at age 15 years), he was quite short in his preadolescent years—below the 5th percentile—and was put on human growth hormone with a good response (currently in the 25th percentile). He has had one bone fracture (in the wrist at age 11 years) and has undergone cholecystectomy (at 18 years of age) for troublesome gallstones. A side from viral meningitis (4 years of age) and salmonella gastroenteritis (age 9 years), he has not suffered any unusual infections. He does have bony protuberances at his elbows, which are probably secondary to marrow expansion. In 1994, in association with a flu-like syndrome, his hematocrit dropped to 21. He felt severely fatigued, and he received one transfusion. Currently (age 19 years), he is hepatitis C and HIV negative, and his serum iron is 218 mg%, his total iron binding capacity is 244 mg%, and his ferritin is 176 mg%. A cardiac evaluation reveals mild cardiomegaly, but his echocardiogram and electrocardiogram are normal.

As you can see from his photograph, he is a nice-looking, slender but muscular young man with a friendly and cheerful demeanor. He is employed full time, working for his father doing manual labor.

With those case presentations, let us begin the program.

Our first speaker is Dr. Alan Levine, director of the Blood Diseases Program at the National Heart, Lung, and Blood Institute, who will give us an update on the activities of the institute with regard to thalassemia.
At the National Institutes of Health (NIH), hematology research is supported by approximately 12 separate institutes. In fiscal year 1995, funding for such research totaled over $500 million. For nonmalignant hematologic diseases, however, the National Heart, Lung, and Blood Institute (NHLBI) supported the vast majority of hematology research (approximately $263 million). The relative institute expenditures for 1996 are expected to be much the same.

NIH defines an orphan or rare disease as having a prevalence in the United States of fewer than 200,000 patients. β-Thalassemia, with fewer than 1,000 patients, is perhaps the “orphan” of orphan diseases. However, NHLBI by no means treats thalassemia as an orphan. NHLBI support for thalassemia research has almost doubled since 1988, to an estimated $14.7 million in 1996. This amount does not include the substantial support for research in areas that are not specific to thalassemia but nevertheless are extremely important, such as unrelated marrow and stem cell transplantation, including cord blood transplantation, and research on improving the safety of the nation’s blood supply. The research program spans a broad spectrum of research, from the most basic research through applied research to clinical applications, disease prevention, and knowledge dissemination. Specific areas include the following: Red blood cell membrane defects in thalassemia; improved prenatal diagnosis for disease prevention; gene replacement therapy; prenatal treatment and curative therapies; drugs to increase fetal hemoglobin; oral iron chelator development; improving the safety of the nation’s blood supply; bone marrow, umbilical cord blood, and stem cell transplantation; and education and information dissemination.

Most thalassemia research is supported as investigator-initiated research. The NHLBI also utilizes special targeted initiatives to accomplish specific objectives. In the past few years, these have included the following grant- or contract-supported programs: Gene Therapy Strategies for the Treatment of Cooley’s Anemia; Basic Research on Hematopoietic Stem Cell Biology; In Utero Stem Cell Transplantation for Genetic Diseases; Stem Cell Sources and Transplantation Biology; Specialized Centers of Research in Hematopoietic Stem Cell Biology; Human Stem Cell Sources and Transplantation Biology; Herpesvirus Epidemiology Donor Study; Viral Activation Transfusion Study; and Umbilical Cord Blood: Collection, Storage and Transplantation. In addition, the institute has recently
held workshops entitled Butyrate Therapy for Cooley's Anemia, Cooley's Anemia Progress Review, and A Special Emphasis Panel on New Therapies for Thalassemia.

The NHLBI recently published a new booklet for the lay public entitled What is Cooley's Anemia? and a 60-page booklet for professionals, Cooley's Anemia: Progress in Biology and Medicine—1995. The latter contains a chapter discussing recommendations for research, which include: development of safe and effective orally active iron-chelating agents; development of approaches to the accurate, noninvasive assessment of body iron burden; development of new approaches to improving compliance with iron chelation therapy, particularly among adolescents; development of safe and effective therapies to enhance fetal hemoglobin production; development of a consensus regarding the optimal management of thalassemia intermedia; support and expansion of stem cell biology, transplantation, and gene therapy research; enhancement of the safety of the blood supply provided to patients with Cooley's anemia; development of a safe and effective treatment of viral hepatitis; investigation into the psychosocial needs of patients related to increased life expectancy; adaptation of current counseling programs and written materials for multicultural application; investigation of the psychosocial impact of hormone therapy in adolescents and young adults; and establishment of a network of medical centers to enable rapid testing of new clinical modalities.

In 1996, a special emphasis panel on new therapies for thalassemia was convened to focus on the clinically related recommendations mentioned in the preceding paragraph and to reach a consensus on the high priority issues in need of additional research support. The panel recommended clinical studies of more effective iron chelators and drugs to increase fetal hemoglobin; clinical studies of endocrine disturbances (including delayed sexual development, osteoporosis, infertility, and long-term effects of hormone therapy); and research to improve the technology for noninvasive measurement of tissue iron deposits.

NHLBI is committed to continued support of thalassemia research. The outlook for the future for patients with β-thalassemia is bright. Unrelated donor stem cell transplantation is being improved, and new therapies for iron chelation, fetal hemoglobin enhancement, and gene therapy are on the horizon.

References

1. NIDDK. Eighth Annual Report of the Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee NIH, 1996.
Hallasemia was defined as a clinical entity in 1925 when Dr. Thomas B. Cooley and his associate Pearl Lee, pediatricians at the Detroit Children’s Hospital, presented a paper at the annual meeting of the American Pediatric Society describing five young children with severe anemia, splenomegaly, and peculiar bone abnormalities. At that time, children with severe anemia and splenomegaly were classified as having “Von Jaksch’s Anemia.” This was a clinical hodgepodge that included many different diseases: infections, malignancies, benign anemias, and doubtless many others. Two years later, in 1927, Cooley published his classic paper in American Diseases of Childhood that described seven children with distinctive features that indicated they represented a new syndrome. Their common features included a peculiar facies resembling the Mongolian race, with a yellow skin color and thickening of facial bones and malar eminences. The thickening of the calvarial and long bones had a unique and distinctive roentgenographic appearance. Using the limited hematologic tests that were available at the time, Cooley described severe anemia, increased osmotic resistance of the red blood cells (RBCs), and the presence of many nucleated RBCs in the blood. He also observed that his patients were of Italian ethnicity, and he suggested the names erythroblastic or Mediterranean anemia for the disease that was subsequently given his name.

Following Cooley’s epochal descriptions, other similar children were reported in North America and Europe. In 1932, Whipple and Bradford in Rochester, New York, described pathological findings in several children. Apparently wishing to avoid the eponym “Cooley’s anemia,” they coined the term “thalassemia” from the Greek word thalass, meaning “the sea” (i.e., the Mediterranean). Thus, thalassemia became “the sea in the blood” (Table 1).

The characteristic features of Cooley’s anemia are well known. Ninety percent of children develop symptoms of anemia in the first year or two of life. The anemia is so severe that treatment with blood transfusions is necessary. Untreated patients survive only a few years. The RBC morphology of severe thalassemia is extreme and characteristic and includes hypochromia, microcytosis, and target cells, as well as many nucleated RBCs.

Shortly after Cooley’s report was published, a series of related papers appeared in the Italian, Greek, and American medical literature (Table 2). Rietti, Greppi, and Neel described mild, familial disorders resembling Cooley’s Anemia.
and Micheli described individuals with a mild, familial, microcytic anemia with increased RBC osmotic resistance.6–8 Caminopetros in Greece recognized a similar blood condition and showed that it was recessively transmitted.9 A cross the Atlantic, Wintrobe in Baltimore and Dameshek in Boston, apparently unaware of the Italian and Greek literature, described families with a mild inherited anemia. They noted that the red cell morphology of affected individuals resembled that seen in Cooley’s anemia, though not as extreme.10,11

It was shortly thereafter that Gatto in Italy and Valentine and Neel in the United States clearly pointed out the relationship of these mild microcytic anemias to the severe Cooley’s anemia and suggested the clinical terms thalassemia “minor” and “major” for the heterozygous and homozygous conditions.12,13 It is likely that all of these early reports were descriptions of what now is called β-thalassemia, a genetic disorder that results in decreased production of the β chains of adult hemoglobin.

Microcytosis of the RBCs is an important hematologic feature of thalassemia minor. The recognition of microcytosis has been greatly facilitated by the use of electronic cell counters that directly measure the mean corpuscular volume (MCV) of the RBC population. This has been widely and successfully used to screen populations for thalassemia minor.14 Almost all adult patients with heterozygous β-thalassemia have MCVs of less than 75 fL. In infants and children, the microcytosis of thalassemia is superimposed on the “physiologic” microcytosis of infancy and childhood.15

In a patient with microcytic RBCs, a diagnosis of β-thalassemia is usually associated with an increased levels of HbA2. Levels of fetal hemoglobin (HbF) are normal (less than 2.0%) in about 50% of patients, and in the rest rarely exceed 7.0%.

Table 3 lists the salient features of β-thalassemia minor. These include microcytosis and elevations of HbA2, defining what has been called “classical thalassemia trait.” There are other hematologically identifiable variants of β-thalassemia minor. So-called βδ-thalassemia trait is a familial microcytosis with normal levels of HbA2 and HbF levels of 5–10%. The Lepore Hb trait is characterized by a familial microcytosis, normal levels of HbA2, and the presence of a 5–10% electrophoretically abnormal hemoglobin component that migrates in the position of HbS. Finally, some thalassemia pedigrees include individuals who are hematologically normal but transmit a genetic factor that interacts with and intensifies a thalassemia gene. Such individuals are known as “silent carriers.”

We now know that thalassemia is a very heterogeneous genetic condition. More than a hundred different mutations have been associated with thalassemia phenotypes.16 Molecular genetics have been used to diagnose thalassemia prenatally, which has led to a marked reduction in the number of severe homozygous infants born throughout the world.17,18

Almost all patients with β-thalassemia syndromes can be clinically classified as having thalassemia minor or thalassemia major, and the genetic relationship of heterozygous and homozygous genotype to

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Microcytosis (MCV&lt;75 fL)</th>
<th>HbA2</th>
<th>HbF</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Classical”</td>
<td>0 ++</td>
<td>+</td>
<td>&gt;3.5%</td>
<td>1-5%</td>
</tr>
<tr>
<td>βδ</td>
<td>0 ++</td>
<td>+</td>
<td>&lt;3.5%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Lepore</td>
<td>0 ++</td>
<td>+</td>
<td>&lt;3.5%</td>
<td>1-5%</td>
</tr>
<tr>
<td>Silent carrier</td>
<td>0 0</td>
<td>&lt;3.5%</td>
<td>&lt;2%</td>
<td></td>
</tr>
</tbody>
</table>
these clinical conditions is straightforward. In more than 95% of patients, there is a direct correlation of major and minor phenotypes with homozygous and heterozygous genotypes. However, a small number of patients do not fit into this neat dichotomy. Sturgeon first identified this group in the American literature. He suggested the term “thalassemia intermedia” to describe patients who were hematologically too severe to be called “minor” and too mild to be called “major.” Thalassemia intermedia is a clinical designation often used to characterize individuals who are homozygous for β-thalassemia genes but maintain hemoglobins of 6–9 g/dL without regular transfusions. They have more severe RBC morphological abnormalities than the trait, as well as varying degrees of splenomegaly and skeletal changes. In one of my own early thalassemia papers, published in 1964, I described a number of patients with thalassemia intermedia and attempted to reconcile clinical and hematologic findings with genotype (Table 4). Even 30 years later, it doesn’t look too bad! Table 5 shows an expanded summary of the features that define β-thalassemia major, minor, and intermedia.

Thalassemia intermedia has an extraordinarily wide clinical spectrum. Some patients have very few clinical abnormalities. Others experience severe consequences when their erythropoietic systems attempt to compensate for ineffective erythropoiesis and anemia. These compensatory efforts may be associated with massive erythroid marrow hypertrophy in medullary and extramedullary sites. In the long bones, marrow expansion results in cortical thinning and pathologic fractures. The marrow spaces of the cranial vault markedly expand, producing a “hair-on-end” appearance. Expansion of the facial bones and obliteration of the maxillary sinuses result in protrusion of the upper jaw and malocclusion. These changes may result in cosmetic abnormalities that can cause emotional distress. Today in the United States bony and cosmetic abnormalities are seen only in patients with thalassemia intermedia because modern hypertransfusion programs prevent this in thalassemia major. Expanding paravertebral extramedullary hematopoiesis may compress the spinal cord. The spleen enlarges, often requiring a splenectomy to relieve the mechanical burden. These changes are progressive but

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**TABLE 4: THALASSEMAIA**

<table>
<thead>
<tr>
<th></th>
<th>Major</th>
<th>Intermedia</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g %)</td>
<td>&lt;7</td>
<td>7–10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>2–15</td>
<td>2–10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Nucleated RBC</td>
<td>++++</td>
<td>+0</td>
<td>0</td>
</tr>
<tr>
<td>RBC morphology</td>
<td>++++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Jaundice</td>
<td>++</td>
<td>+0</td>
<td>0</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>+++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Skeletal changes</td>
<td>+++-++</td>
<td>-++</td>
<td>0</td>
</tr>
<tr>
<td>Transfusion</td>
<td>+++-+</td>
<td>+0</td>
<td>0</td>
</tr>
</tbody>
</table>

Clinical and genetic characteristics of thalassemia syndromes.
preventable, and are at least partially reversible by adequate transfusion therapy. As a group, patients with thalassemia intermedia live longer than patients with thalassemia major, although many of them develop complications in later life.

The proportion of patients with homozygous thalassemia intermedia is strikingly different among different ethnic groups. About 10% of patients of Mediterranean ethnicity who are homozygous can be classified as intermediates. In contrast, more than 70% of African-American patients who are homozygous may be classified as such. This difference reflects the kinds of thalassemia mutations, especially so-called “mild mutations,” that are prevalent in these ethnic groups.

The purpose of this symposium is to seek the answer to a number of questions concerning the diagnosis and management of patients with thalassemia intermedia. We are fortunate to have the participation of experts from a number of North American centers, where nearly 100 patients are currently being followed.

Before we can begin, we must first define what thalassemia intermedia is. We have decided to use a rather restrictive definition, so we are all talking about the same thing. The definition to be used in this conference is as follows:

The term thalassemia intermedia has been used to describe the clinical and hematologic findings in patients whose illness is not as severe as that which characterizes homozygous β-thalassemia, but is more severe than the heterozygous carrier.

D. Weatherall

For the purposes of this conference, the following, rather arbitrary criteria and exclusions will be used.

**Exclusions:**

1. Only β-thalassemia syndromes will be included. Alpha chain abnormalities (e.g., HbH disease) will not be included. However, if an α chain abnormality interacts with β-thalassemia and modifies the usual phenotype, it can be included.

2. Although there may be similar clinical and hematological features, double heterozygotes for a β-thalassemia and a β-hemoglobinopathy (i.e., HbS-β-thalassemia and especially HbE-β-thalassemia) will not be included.
**Criteria:**

1. Homozygosity for a β-thalassemia gene of any definable sort (β° or β⁴) or a β-thalassemia (β° or β⁺) and a related β⁺ chain production gene (i.e., ββ-thal, Hb Lepore, Swiss type HRFH, etc.) can be indicative of thalassemia intermedia. Homozygosity and double heterozygosity should be established, if possible, by family studies or genotype.

2. Maintenance of a hemoglobin level >7.0 g/dL and no regular transfusions for an extended period of time after 4 years of age can be indicative of thalassemia intermedia. There is a small subset of patients who are homozygous who maintain hemoglobin levels >7.0 during their first few years of life but then have hemoglobins fall lower and require regular transfusions.

3. Patients with thalassemia intermedia who begin regular transfusions because of unacceptable, progressive cosmetic changes or poor growth during the first few years of life despite hemoglobin levels >7.0 g/dL are difficult to categorize. However, for the purposes of this conference, they will be classified as having thalassemia major, unless older affected siblings fulfill criteria 1–3 above.

4. Patients who develop progressively increasingly severe anemia (<7.0 g/dL) and splenomegaly and who, after splenectomy, maintain a hemoglobin level >7.0 g/dL and do not require regular transfusions can be classified as having thalassemia intermedia.

Using the clinical and hematological data from a large number of patients from contemporary North America, we hope at the end of our discussions today to answer a number of questions:

1. How do we define and diagnose thalassemia intermedia?
2. What are the indications for such interventional therapy as splenectomy, transfusions, and chelation?
3. Can we predict early in life how a given patient will fare?
4. In view of the major advances in molecular genetics, can we relate thalassemia genotype to phenotype?

5. What are the long-term complications of thalassemia intermedia, and what is the prognosis of these patients today?

These are the issues I hope we can address, if not answer, today. If we are even partly successful, the lives of these patients and the patients of the future will be better, and the understanding of the physicians caring for them will be increased.

**References**


A retrospective multicenter review of thalassemia intermedia was undertaken by six northeastern medical institutions in the United States: New York Hospital, Cornell University Medical College; Children’s Hospital of Philadelphia, University of Pennsylvania School of Medicine; New Haven Hospital, Yale University School of Medicine; Boston Children’s Hospital, Harvard University School of Medicine; Rhode Island Hasbro Children’s Hospital, Brown University School of Medicine; and Brigham and Women’s Hospital, Harvard University School of Medicine.

The demographics, age, sex, and ethnic origins of the patients were reviewed, as well as their medical histories, including transfusions, alloimmunization, facial appearance, splenectomy, puberty, growth, fractures, bone mineral density, cholecystectomy, cholelithiasis, fractures, iron overload and chelation, infections, β- and α-globin genotypes, miscellaneous conditions, and use of agents to enhance fetal hemoglobin production.

Seventy-one patients (36 females and 35 males) with β-thalassemia intermedia were eligible for the study. Patient data were obtained from medical records, and not all data were available for some patients.

The majority of patients were of Mediterranean ethnic origin. The ethnic origins of the patients were: 48% Italian, 25% Greek, 13% African, 4% Middle Eastern, 3% Armenian, 1% Indian, 4% mixed, and 1% unknown.

The mean age of the population was 26.6 ± 12.3 years (range 3.6–65, median 25.4). During the past two decades, two patients were lost to followup at the ages of 3.6 and 13 years, respectively, and four patients expired at ages 26.7, 27.5, 29.8, and 41.1 years. All those who died suffered from congestive heart failure; related causes of mortality included hepatic cirrhosis in two patients and complications from AIDS in one patient. The median survival extrapolated from a descriptive Kaplan-Meier plot was estimated at 51 years. The mean age at diagnosis in all 71 patients was 3.8 ± 3.2 years (range 0–19, median 3.5).

The mean age at splenectomy was 11.9 ± 8.3 years (range 1.2–41, median 9.0). Fifty-five of 71 patients (77%) underwent splenectomy. All but three patients increased their hemoglobin levels by 0.5–5 g/dL postsplenectomy. The mean hemoglobin levels presplenectomy and postsplenectomy were 6.7 and 8.5 g/dL, respectively, representing a mean rise in hemoglobin of 1.8 g/dL. The mean hemoglobin level of the 16 nonsplenectomized patients was 8.5 g/dL.

Regular transfusions were given to 23 of 71 patients (32%) for indications including severe extramedullary hematopoiesis, chronic fatigue, congestive heart failure, and stunted linear growth or severe cosmetic facial changes. Patients who required regular transfusions were diagnosed for thalassemia intermedia at a mean age of 2.6 ± 3.7 years (range 0.3–5, median 2.5). Splenectomy was performed in 20 of these 23 patients (86%). Patients who ultimately required a regular transfusion program after undergoing splenectomy did so after a 13-year median interval (range 0–38 years) postsplenectomy. Patients on regular transfusions received a mean of 23 units per year postsplenectomy.

Sporadic transfusions were given to 28 of 71 patients (40%) perioperatively, during pregnancy, bouts of illness, and acute episodes of leg ulcers. Patients who received sporadic transfusions or who remained transfusion-independent were diagnosed at a mean age 4.5 ± 3.7 years (range 1–19, median 4). Of those patients who were sporadically transfused, 24 of
28 (86%) underwent splenectomy. Patients who received sporadic transfusions received a mean of two units per year postsplenectomy. Fifty-five percent of patients (11 of 20) who received no transfusions also underwent splenectomy.

Transfusion-related alloimmunization was detected in 6 of 51 patients (12%). This occurred with equal frequency in regularly and sporadically transfused patients. The reported antibodies included E, e, C, c, D, Kell, Co, and Yy. Clinically significant alloimmunization occurred in three patients with autoimmune hemolytic anemias: two who were sporadically transfused and one who had been placed on a regular transfusion program.

Facial manifestations were observed in most patients. As judged by professional staffs, these cosmetic changes were severe in 23 of 71 patients (33%), moderate in 18 of 71 (25%), and minimal in 30 of 71 (42%). Seven patients underwent osteoplasty, radiation therapy, and/or transfusion support in order to ameliorate the thalassemic facies.

Fifteen of 71 patients (21%) had abnormal linear growth (<5% for height), 31 of 71 (44%) had a growth range of >5% and <50%, and 25 of 71 (35%) had above-average linear growth (>50%).

Data for the age of attainment of puberty were available for 45 patients (23 males and 22 females). Spontaneous puberty occurred in 38 of 45 patients (84%), but was delayed in 22 of 45 (49%). Delayed puberty was defined as two standard deviations above the mean age of menarche at ≤13 years and the mean age of male secondary sexual characteristics in males at ≤16 years. Seven patients required hormone therapy to induce puberty (five females and two males). The mean age of menarche in this series was 15.7 ± 2.2 years (range 12.5–22, median 15.0). The mean age of male secondary sexual characteristics corresponding to Tanner stage III was 15.2 ± 1.5 years (range 12–18, median 15.0).

Various endocrinopathies were reported in 21 of 71 patients (30%). Twenty-one percent of patients had poor linear growth (less than the fifth percentile), 10% had primary hypogonadism, 6% had secondary hypogonadism, 4% had hypothyroidism, and 3% had hypoparathyroidism.

Thirty of 71 patients (42%) sustained fractures, with 14 of 30 (47%) sustaining multiple fractures. Of the 60 fractures that occurred, the long bones of the upper and lower extremities were most commonly involved. Fractures occurred at a mean age of 18.7 ± 10.7 years (range 1–60, median 18.0).

Spinal bone mineral densities (S-BMD) were measured in 19 patients with thalassemia intermedia. The mean S-BMD of 10 female patients was 0.79 ± 0.11 g/cm²—slightly lower than age-matched female patients with thalassemia major (0.83 ± 0.15 g/cm²), but significantly lower than normal female controls of comparable age (1.20 ± 0.10 g/cm²). Similarly, the mean S-BMD of nine male patients with thalassemia intermedia was 0.88 g/cm², slightly lower than normal male controls of comparable age (1.26 ± 0.13 g/cm²). All patients with thalassemia intermedia exhibited S-BMD values at or near the fracture threshold of 0.8 g/cm². Five patients with thalassemia intermedia with no fractures were age- and sex-matched with five patients with thalassemia intermedia who had either symptomatic paravertebral extramedullary hematopoiesis or severe facial changes. The mean S-BMD of the fracture-free group was 0.86 ± 0.17 g/cm², versus 0.73 ± 0.14 g/cm² for the group with severe facial changes and/or spinal cord compression.

Cholelithiasis or sludge was demonstrated with ultrasonography or CT scans in 37 of 71 patients (52%) at a mean age of 18.7 ± 7.7 years (range 6–38, median 18.0). Cholecystectomy was performed in 30 of 71 (42%) at a mean age of 20.0 ± 7.9 years (range 6–40, median 20.0).

| β+/β+ | 17/39 | 44% | αα/αα | 25/33 | 76% |
| β+/β0 | 15/39 | 38% | αα/α- | 5/33 | 15% |
| β0/β0 | 7/39 | 18% | αα/αα αα | 2/33 | 6% |
| αα/αα α | 1/33 | 3% |

The beta and alpha globin synthesis analysis demonstrates that 44% of population are compound heterozygous for β+/β0 synthesis and 18% are homozygous for β0/β0 synthesis. 76% have a normal complement of alpha globin genes, 15% have a single alpha gene deletion, and 3% to 6% have alpha globin gene duplications.
Peak ferritin levels were available in 64 patients. The mean peak ferritin level was 2743 ± 2640 ng/mL (range 121–13000, median 2050). Peak levels were reported at a mean age of 20.1 ± 10.0 years (range 3–52, median 18.3). Forty-five patients (70%) had ferritin levels exceeding 1000 ng/mL, and 34 of 45 (76%) received subcutaneous desferrioxamine (SC DFO) therapy at a mean age of 19.8 ± 10.3 years (range 4.3–50, median 17.0). The patients who underwent iron chelation therapy had a mean reduction in their ferritin level of 1966 ± 2505 ng/mL, i.e., from a mean of 3971 ± 2799 ng/mL to a mean of 2005 ± 2212 ng/mL.

Eighteen of 23 regularly transfused patients (78%) were started on SC DFO. Their mean ferritin levels were reduced from a mean of 4711 ± 3334 ng/mL to a mean of 2534 ± 2732 ng/mL (i.e., a mean reduction of 2177 ± 3033 ng/mL). This reduction was accomplished in a mean interval of 12.4 ± 4.9 years from the start of chelation therapy. Similarly, 16 of 28 sporadically transfused patients (57%) were started on SC DFO. Their ferritin levels were reduced from a mean of 3226 ± 1631 ng/mL to a mean of 1473 ± 1207 ng/mL, for a mean reduction of 1753 ± 1419 ng/mL, and this was accomplished in a mean interval of 12.3 ± 5.1 years from the initiation of iron chelation therapy.

Minor, recurrent infections were upper respiratory infections, nasopharyngeal infections, peptic ulcer disease, and thrombotic episodes.

Major infectious complications were reported in 32 of 71 patients (45%). The most common major infections reported were pneumonia (21%), fever with sepsis (15%), and fevers of unknown origin (10%). Minor, recurrent infections were upper respiratory infections, nasopharyngeal infections, and cellulitis.

A host of medical complications were reported in 28 of 69 patients (41%). The most prevalent conditions were cardiac disease, including congestive heart failure, arrhythmia and pericarditis, pulmonary hypertension, severe extramedullary hematopoiesis, leg ulcers, and hyperuricemia. Infrequently reported medical conditions included osteoporosis, hepatic cirrhosis, peptic ulcer disease, and thrombotic episodes.

Fetal hemoglobin enhancement was attempted in 10 of 71 patients (14%). Nine of 10 patients received butyric acid analogs, and 4 of these exhibited an increase in fetal hemoglobin of 1–1.5 g/dL. One patient received hydroxyurea but had no significant change in hemoglobin level.

β-Globin DNA analysis was available in 39 patients. The most prevalent alleles were IVS1,6 in 19 of 39 (23%), β°39 in 19 of 39 (23%), and IVS1,110 in 15 of 39 (18%). With regard to β-globin chain synthesis, 17 of 39 (44%) had homozygous β+β+ alleles and 15 of 39 (38%) had heterozygous β+β° alleles, while only 7 of 39 (18%) had homozygous β°β° globin alleles.

α-Globin gene DNA analysis was available in 33 patients. The majority of these—25 of 33 (76)—had
four α genes, 5 of 33 (15%) had a deletion of a single α gene, and 3 of 33 (9%) had additional α genes (αααα/αα in two and ααα/αα in one).

Complete α-globin and β-globin genotypes were available in 29 patients. In this subset of patients, the most common β genotype was the compound heterozygous IVS1,6/β°39 with a normal α-gene complement, found in 7 of 29 patients (25%). There was the suggestion of a milder phenotype in individuals who had a concurrent α gene deletion, as evidenced by the later age at diagnosis, milder facial cosmetic changes, no requirement of regular transfusion support, and lower ferritin peak levels. There was also a suggestion that mild β mutations may yield a disorder of less severity.

This retrospective series reviews various clinical and laboratory parameters in a limited patient population that is widely distributed over the northeastern United States. To enhance our understanding of phenotypic expression of genotype and optimize the management of patients with thalassemia intermedia, it is recommended that complete DNA analysis of both α and β genotypes be obtained in all patients. This review found suggestions of a milder phenotype resulting from mild β gene mutations and/or concurrent α gene deletions. Regular annual clinical and laboratory evaluations would allow for a prospective evaluation of phenotypic expression and generate a greater data base to identify predictive parameters of disease expression. Management strategies, including the use of splenectomy, transfusion, and chelation therapies, should be optimized. Finally, additional therapeutic options need to be further explored. Can fetal hemoglobin enhancement and effective oral iron chelators improve the clinical outcome of patients with thalassemia intermedia? Should bone marrow transplantation be offered to those who require regular transfusion programs? These questions must be pursued in prospective clinical research studies.
In patients with thalassemia major who are regularly transfused, the most important consequence of life-saving transfusions is the accumulation of iron within tissues, causing progressive organ dysfunction that is fatal without chelating therapy. In patients with thalassemia intermedia, the requirement for transfusions is less regular than with thalassemia major, and iron loading secondary to increased gastrointestinal iron absorption is less accelerated than that associated with transfusional iron overload in thalassemia major. Nevertheless, the clinical consequences of iron loading and the issues relating to iron-chelating therapy encountered in patients with thalassemia major may also apply to patients with thalassemia intermedia. Assessing iron overload, determining the optimal concentrations of body iron, and determining the time to initiate treatment for iron overload are difficult in both patients with thalassemia major and patients with thalassemia intermedia.

Assessment of Iron Overload

In all patients with thalassemia, both direct and indirect means of assessing body iron are available. No single indicator or combination of indicators is ideal for evaluating iron status in all clinical circumstances. Measurement of hepatic iron stores provides the most quantitative means of assessing the body iron burden in patients with thalassemia major, and may be considered the reference method for comparison with other techniques. Data accumulated over the past 10 years permit a quantitative approach to the management of iron overload, providing guidelines for the control of body iron burden.

Indirect. The measurement of plasma or serum ferritin is the most commonly used method for indirectly estimating body iron stores. Normally, ferritin concentrations decrease with depletion of storage iron and increase with storage iron accumulation. A maximum glycosylated plasma ferritin concentration of about 4,000 μg/L may represent the upper physiological limit of the rate of synthesis; higher concentrations are thought to be due to the release of intracellular ferritin from damaged cells. Interpretation of ferritin values may be complicated by a variety of conditions that alter concentrations independently of changes in body iron burden, including ascorbate deficiency, acute infection, chronic inflammation, hemolysis, and ineffective erythropoiesis, all of which are common in patients with thalassemia intermedia. In one study of patients with thalassemia major and sickle cell disease, the 95% prediction intervals for hepatic iron concentration, given the plasma ferritin, were so broad as to make determination of plasma ferritin a poor predictor of body iron stores.

Serum iron, transferrin, transferrin saturation, and transferrin receptor concentration do not quantitatively reflect body iron stores, while chelator-induced urinary iron excretion is also vulnerable to extraneous influences of inflammation, the activity and effectiveness of erythropoiesis, extramedullary hematopoiesis, and ascorbic acid deficiency, all of which are common in patients with thalassemia intermedia. Computed tomography, nuclear resonance scattering from manganese-56, and magnetic resonance imaging have been used to image tissue iron stores in vitro and in vivo, but none of these modalities is clinically available for the accurate measurement of hepatic iron concentrations. Indeed, while many studies demonstrate that magnetic resonance imaging can reflect the presence of and changes in tissue iron in vivo, even this method has not been shown to provide measurements of tissue iron that are quantitatively equivalent to those determined by tissue biopsy.
Direct measurement of hepatic iron concentration is the most quantitative, specific, and sensitive method for determining the body iron burden in patients with thalassemia major. Liver biopsy is the best direct means of assessing iron deposition, permitting chemical measurement of the nonheme (storage) iron concentration and histochemical examination of the pattern of iron accumulation in hepatocytes and Kupffer cells, as well as evaluation of the extent of inflammation, fibrosis, and cirrhosis. Magnetic susceptometry using a superconducting quantum interference device (SQUID) magnetometer provides a direct measure of hepatic storage iron that is based on a fundamental physical property of ferritin and hemosiderin. Only two sites— one in the United States and one in Germany—have the specialized equipment needed for measuring hepatic magnetic susceptibility.

Optimal Body Iron in Patients with Thalassemia Intermedia

Because the magnitude of the body iron burden seems to be the principal determinant of clinical outcome, the prime goal of iron-chelating therapy in patients with thalassemia—both major and intermedia—is optimal control of body iron. The optimal body iron should minimize both the risk of adverse effects from iron-chelating therapy and the risk of complications from iron overload. In a patient treated with deferoxamine, therapy to maintain normal body storage iron— corresponding to a hepatic iron of approximately 0.2–1.6 mg iron per gram liver, dry weight—might abate the likelihood of complications of iron overload, but greatly increases the probability of dose-related drug toxicity. Guidance about the risk of complications associated with slightly higher levels of body iron may be derived from the clinical experience with hereditary hemochromatosis, a condition in which the route and severity of iron loading may be similar to those in thalassemia intermedia. In both these conditions, iron overload is the result of abnormal regulation of iron absorption resulting in an inappropriate increase in iron uptake. The minor degree of iron loading that develops in about one-quarter of patients who are heterozygotic for hereditary hemochromatosis appears to be associated with normal life expectancy. By contrast, patients who are homozygotic for the disorder develop greater iron burdens and have an increased risk of cardiac disease, hepatic fibrosis, diabetes mellitus, endocrine abnormalities, and other complications of iron overload. Finally, body iron burdens corresponding to hepatic iron concentrations at or exceeding 15 mg iron per gram liver, dry weight, greatly increase the risk of cardiac disease and early death. These considerations suggest that a conservative goal for iron-chelating therapy in patients with thalassemia intermedia is maintenance of hepatic iron concentrations of approximately 3.2–7 mg iron per gram liver, dry weight— the range found in patients who are heterozygotic for hereditary hemochromatosis.

Initiation of Chelating Therapy in Thalassemia Intermedia

When should the patient with thalassemia intermedia be treated for iron overload? This decision depends not only on the amount of excess iron but also on the rate of iron accumulation; the duration of exposure to increased iron; the partition of the iron burden between relatively benign sites in the macrophage and more hazardous deposits in parenchymal cells; ascorbate status, which helps determine the allocation of iron between macrophage and parenchymal cells; the presence of other hepatotoxins, including alcohol and viral hepatitis; and other factors in individual patients. Even in patients with thalassemia major, the optimal age for beginning iron-chelating therapy is uncertain. Elevated hepatic iron concentrations associated with hepatic fibrosis, which are not uniformly evident by determinations of serum ferritin or laboratory abnormalities of liver function, have been observed in transfused children with thalassemia under 3 years of age. These data suggest that some modified program of chelating therapy likely is indicated after 1–2 years of regular transfusions in patients with thalassemia major. Because of the imprecision of indirect measurements, initiation of therapy in all patients with thalassemia should be based upon hepatic iron concentration, obtained after approximately 1 year of regular transfusions. Reliance
on serum ferritin measurements alone can lead to inaccurate assessment of body iron burden in individual patients.

**Rate and Severity of Iron Loading in Thalassemia Intermedia**

Only a few studies have attempted to define the extent of iron loading in patients with thalassemia intermedia. One of these examined the absorption and rate of accumulation of iron in 15 patients with homozygous β-thalassemia, ages 4–42 years, not receiving regular transfusions. The severity of iron loading in these patients was assessed from transfusion history, as well as through determinations of serum iron, total iron binding capacity, and serum ferritin concentration. Some patients had never been transfused; the maximum iron load received from transfusions was estimated to be approximately 10 g (equivalent to the iron that might be administered over a 2-year period in a regularly transfused, 50-kg patient with thalassemia major). The absorption of 59-labeled ferrous iron was measured with the Oxford total body counter. After a fast of 2 hours or more, 13 of the patients received a standard dose of 5 mg of 59Fe as a freshly prepared solution of ferrous sulfate to which 50 mg of ascorbic acid was added. Total body radioactivity was measured immediately after the dose and 7–14 days later. The percentage retention of 59Fe was then calculated, with suitable corrections for background and isotope decay. In four subjects, absorption was also measured from a standard meal containing approximately 5 mg iron. In five patients, total iron balance was calculated.

The values for total iron binding capacity in the patients varied from 30% to 100%; in nine patients, transferrin saturation exceeded 75%. Concentrations of serum ferritin increased with the age of the patients, although an increasing scatter of values was noted in the older patients. The absorption of 59Fe from a 5 mg dose was greatly increased in this group of patients, all of whom, as noted above, had evidence of increased body iron burden. Absorption of iron varied between 17% and 89%, compared with a mean of 15% in normal iron-replete individuals. There was a highly significant correlation between the percentage of 59Fe absorbed and the serum iron: The higher the serum iron, the greater the absorption of iron. In normal individuals, the percentage of iron absorbed is inversely proportional to the body iron burden. Therefore, this study indicates that the mechanism(s) regulating iron absorption in the presence of adequate iron stores may be abnormal in patients with thalassemia intermedia.

Supporting these observations was the finding in a balance study of a positive iron balance of 3–9 mg iron per day, or between 3 and 10 times normal absorption of iron. This is the only balance study reported in patients with thalassemia intermedia, and it indicates that iron loading in patients with thalassemia intermedia may be on the order of 2–5 g iron per year. By contrast, in a 50-kg patient with thalassemia major who may receive a yearly volume of 180 mL/kg packed cells, with the hematocrit of transfused blood of about 75%, iron accumulation would be around 6.7 g per year. Clearly, the older patient with thalassemia intermedia might be expected to be at similar risk for iron-induced hepatic, cardiac, and endocrine dysfunction as the patient with thalassemia major. Because the studies by Pippard and colleagues relied upon the use of transferrin saturation and serum ferritin concentrations without direct measurements of tissue iron, iron overload was not quantitated in these patients. Although studies of organ function were not reported in this series, three of these patients were noted to be diabetic or prediabetic, suggesting that loading of tissue iron induces similar changes in patients with thalassemia intermedia as it does in patients with thalassemia major. More recently, striking elevations of hepatic iron concentration have been observed in patients with thalassemia intermedia with only slight increases in serum ferritin concentration. Thus, direct determination of body iron burden is indicated in patients with slightly elevated serum ferritin concentrations.

Iron-chelating therapy in patients with thalassemia intermedia should be initiated if the hepatic iron concentration exceeds 6 mg iron per gram liver, dry weight. Hepatic iron concentration and liver histology should be assessed at intervals every 1–2 years in patients receiving chelating therapy. One report has indicated that short-term therapy with the orally active
iron-chelating agent 1,2-dimethyl-3-hydroxypyrid-4-one (deferiprone; L1) may have been effective in reducing hepatic storage iron in one patient with thalassemia intermedia.23 This agent may prove to be effective in the reduction of tissue iron in conditions such as thalassemia intermedia, which involve less severe degrees of iron overload than thalassemia major.24,25

References


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Homozygous β-thalassemia, a disease in which inadequate production of β-globin leads to severe anemia, affects thousands of individuals worldwide. Current management of this condition includes the use of regular red cell transfusions and iron chelation therapy. The development of an effective therapy to increase hemoglobin levels in patients with homozygous β-thalassemia without the use of red cell transfusions could allow normal growth and development while decreasing or eliminating transfusional iron overload, which remains the major cause of death, reduced life expectancy, and morbidity in individuals with this disease. W hile bone marrow transplantation can achieve these aims, it is not a therapeutic option for the majority of patients.

For some years, there has been interest in increasing γ-globin transcription and fetal hemoglobin (HbF) production in patients with β-hemoglobinopathies. For patients with homozygous β-thalassemia, increased γ-globin production and a reduction in the ratio of α- to non-α-globin could reasonably be expected to ameliorate the severity of the anemia. To this end, trials of chemotherapeutic agents, including 5-azacytidine and hydroxyurea, have been conducted, but myelotoxicity, fears of long-term carcinogenesis, and only modest responses to treatment have limited the clinical usefulness of these agents. Erythropoietin has also been used, but responses to this therapy have been variable.

There is considerable evidence that butyrate analogs induce erythroid differentiation and stimulate HbF production in human erythroid progenitors in vitro. In vivo, these agents have also been shown to reactivate embryonic globin production in an avian model, delay the switch from fetal to adult globin in ovine fetuses, and increase HbF production in adult primates.

In humans, several fatty acids, including α-amino-butyric acid, arginine butyrate, isobutyrylurea, sodium phenylbutyrate, propionic acid, and 2-propylpentanoic (dipropylacetic) acid (unpublished data), have now been demonstrated to stimulate fetal hemoglobin production, suggesting that they may play a role in the treatment of the β-globin disorders. However, previous clinical trials of these agents in β-thalassemia have been limited to relatively short-term trials of the intravenous agent arginine butyrate and oral isobutyramide.

Sodium phenylbutyrate (SPB) is an orally administered agent originally developed to promote waste nitrogen excretion in the treatment of urea cycle disorders and is currently used for this purpose in an FDA-approved Phase III trial. Over 100 patient years of experience have revealed no untoward effects of this drug. The finding of increased HbF levels in these patients stimulated clinical trials of SPB in patients with β-hemoglobinopathies.

We have begun a preliminary trial of oral SPB in patients with homozygous β-thalassemia. This represents the largest clinical trial to date of any hemoglobin switching agent used in patients with thalassemia.

Our preliminary data demonstrate that SPB can safely be administered to patients with homozygous β-thalassemia and is well tolerated by the majority. Problems include the need to take 40 tablets daily, epigastric discomfort, and the body odor experienced by some patients. We expected poor compliance with this regimen based on previous experience with the drug, but surprisingly this was not the case, possibly because many of these patients had prior experience with other cumbersome medical interventions, including transfusion schedules and iron chelation therapy. Oral administration has clear advantages over the intravenous administration required for arginine...
butyrate, particularly as all available evidence suggests that in the management of the β-hemoglobinopathies, these therapies, if effective, will be needed long term.

We found that 36% of all patients (4 of 11) or 50% of patients who were not transfused (4 of 8) responded to SPB. A response was defined as a sustained increase in hemoglobin of more than 1 g/dL over pretreatment values. Clearly, SPB can increase hemoglobin in some patients with homozygous β-thalassemia but is not effective in all. While it seems evident that β-globin mutation alone does not predict response, the fact that two siblings treated in this study both responded to SPB therapy raises the possibility that some other genetic factor is involved. Other genetic factors linked and unlinked to the β-globin locus have been shown to affect HbF levels in normal individuals and patients with β-hemoglobinopathies.

The failure of hemoglobin to increase in patients showing decreased levels of lactate dehydrogenase and indirect bilirubin is disappointing and raises interesting questions about the cause of these changes if they are not related to decreased hemolysis. Similarly, we have observed increased production in F reticulocytes in all patients treated with SPB to date. In some patients, levels of F reticulocytes have remained higher than baseline up to a month or more after the cessation of therapy, even though the agent is known to be rapidly metabolized and excreted. Similar observations have been reported following the use of arginine butyrate. This uniformity of F reticulocyte response, the persistence of response in some patients long after the cessation of therapy, and the lack of correlation between changes in F reticulocytes and increased total hemoglobin or increased absolute HbF production may indicate increases in HbF that are insufficient to decrease ineffective erythropoiesis.

Those patients who did respond to therapy were inconsistent in their response. Decreases in traditional indicators of hemolysis in all nontransfused patients were not predictive of an increase in hemoglobin, and increases in hemoglobin were not entirely explained by increased HbF. This suggests that “classic” hemoglobin switching—an increase in γ-globin production with a resultant decrease in globin chain imbalance—could not explain the increases in hemoglobin. Three possible explanations exist. SPB may have: (1) caused nonspecific induction of all globin production (α, β, and γ) and not just γ alone, (2) caused nonspecific expansion of red cell mass through the release of thalassemic red cells previously sequestered in the marrow or due to an increase in production of thalassemic red cells, or (3) prolonged red cell survival without a change in red cell production. There is evidence to support the first of these explanations (personal communication, G. Stamatoyannopoulos), and the latter two possibilities lead to testable hypotheses in further patients.

A positive correlation between baseline serum erythropoietin level and the potential response to SPB therapy was observed. This observation—together with the fact that erythropoietin levels in patients with homozygous β-thalassemia are generally elevated, but inappropriately so for the degree of anemia—suggests that clinical trials of combination therapy using erythropoietin with SPB may be of value. However, it must be remembered that in these patients erythropoietin levels are related to other factors, such as baseline HbF percent, and therefore erythropoietin may only be a marker of some other factor affecting response.

Both oral hydroxyurea (HU) and subcutaneous/intravenous erythropoietin (EPO) have been shown to increase hemoglobin levels in some patients with thalassemia. Rachmilevitz has shown that combinations of these two drugs also increase hemoglobin levels, but it is not clear whether these drugs taken together are additive. Fibach has shown that SPB and HU in human erythroid cultures have a synergistic effect on increasing HbF. Since not all subjects with thalassemia respond to SPB, we believe initial trials of combination therapy (HU and SPB, EPO and SPB) are warranted.

**Predictors of Increased Hemoglobin in Response to SPB Therapy**

Response to SPB therapy, as defined by a sustained increase in total hemoglobin of more than 1 g/dL above baseline, did not appear to be predicted by β-globin mutation; baseline percent HbF, absolute HbF, or F reticulocyte levels; baseline hemoglobin; or
baseline $\alpha$- to non-$\alpha$-globin ratios. Similarly, significant falls in lactate dehydrogenase and indirect bilirubin—both traditional measures of hemolysis—could be demonstrated in all those nontransfused patients, with no observed differences between responders and nonresponders. Interestingly, those patients with baseline erythropoietin levels greater than 120 mU/mL were significantly ($p<0.05$) more likely to experience an increase in hemoglobin (4 of 6) than those whose baseline erythropoietin level was below 120 mU/mL (0 of 6). A similar trend existed between baseline HbF percent in those patients not receiving regular red cell transfusions and their response to SPB therapy, although this did not reach statistical significance. Of the four patients with a baseline HbF percent of less than 40, none responded to therapy. In contrast, four of the five patients with baseline HbF percent greater than 40 did respond ($p=0.075$).

**Compliance with SPB Therapy**

A 25-day supply of SPB tablets was provided to the patients; a further supply was provided only when the patient specifically requested more tablets. In this way, compliance was calculated for each patient by comparing the number of tablets dispensed to that prescribed. Compliance with therapy was a problem in only one patient (#3), who abruptly discontinued therapy after 100 days, having been 95% compliant up to that time. For the patients as a group, compliance with medication was 97 ± 3%.

**Adverse Events Occurring on Therapy**

The daily dose of 20 g of SPB contributes 2,460 mg (107 mmol) of sodium to the diet, a significant proportion of the recommended daily intake. While in the hospital, one of the 12 patients (#6) developed ankle edema, associated with a 3.5% increase in body weight, which resolved spontaneously with dietary modification. Following discharge from the hospital, one patient (#1) required intermittent treatment with a thiazide diuretic, and one (#8) required an increase in her previous diuretic dose to control peripheral edema. No patient developed hypertension. Epigastric discomfort following the ingestion of the tablets, the most common adverse effect, was reported by 7 of the 12 patients. Two patients, both splenectomized and not on regular penicillin prophylaxis, had nonfatal episodes of bacterial septicemia. Patient #4 developed streptococcus pneumonia on day 71 and plesiomonas shigelloides at day 200, and patient #6 developed staphylococcus epidermidis septicemia at day 24 related to an indwelling central venous catheter. Patient #8 suffered a hemorrhage from a gastric ulcer at day 220, soon after the commencement of aspirin therapy for long-standing pulmonary hypertension. Patient #1, who had spun hemoglobin levels of between 5.1 and 7.5 g/dL associated with marked erythroblastosis, developed spinal cord compression, required irradiation at day 323, and ceased SPB therapy. Patient #10 developed a deep venous thrombosis at day 28, with a hemoglobin level of 5.9 g/dL. Three patients experienced bad body odor while on therapy; in one case, the patient (#12) was unable to tolerate the medication long term even at half the usual dose. These complaints are probably related to the in vivo $\beta$-oxidation of phenylbutyrate to phenylacetate, a compound with an offensive odor secreted as a defense mechanism by the stinkpot turtle.38

**Arginine Butyrate, Then SPB**

In collaboration with Dr. Olivieri at the Hospital for Sick Children in Toronto, we have treated one patient with SPB after she was taken off intravenous arginine butyrate. The patient was treated for 30 days and maintained her hemoglobin level, but was removed from therapy when she had a reoccurrence of neurologic toxicity secondary to expansion of her marrow, which required irradiation. Dr. O livieri does not attribute this side effect to SPB, but more patients will have to be treated to determine whether SPB can safely maintain the hemoglobin levels of patients already treated with arginine butyrate.

**HU and SPB**

We have treated two patients with thalassemia who are transfusion dependent with combinations of HU and SPB. Both patients were maintained on their usual transfusion schedule, and response was moni-
tored by their pretransfusion hemoglobin levels. The first patient showed no response after 60 days and was discontinued. The second patient was treated longer and has shown a steady increase in his pretransfusion hemoglobin level and a decrease in his transfusion requirements.

**Update of SPB/ HU**

To date, we have enrolled 14 patients on SPB/HU protocols: Four were treated through Baltimore/Yale/Penn and 10 through Toronto. All four from Baltimore/Yale/Penn are off-study (three completed SPB/HU trials for more than 200 days, and one stopped therapy without reaching toxicity with HU). The two patients with thalassemia intermedia showed no synergistic effect on SPB/HU, and the patient who was transfusion dependent showed only a questionable effect, according to Dr. A. Cohen.

We originally proposed to treat 10 patients with SPB/HU for more than 200 days. We have completed the evaluation of five and have started two more.

We have treated the Toronto patients for a total of 61 patient months on SPB (18 patient months on SPB/HU) on this protocol and have seen no significant increase in hemoglobin levels. The two Baltimore/Yale/Penn patients were treated for 11 months each on SPB/HU (for a total of 22 patient months).

Only 2 of the present 14 patients treated with SPB who are not transfusion dependent have shown any increase in hemoglobin levels with SPB alone. An additional patient not in the study has had an increase in hemoglobin after over 2 years of SPB, but she does not wish to add HU or EPO.

**References**


The molecular basis of β-thalassemia intermedia is complex and puzzling. The molecular causes of this condition are myriad. Individual variation and genetic modifiers that are poorly understood lead to great variation in genotype-phenotype correlations. For example, some patients who are homozygous for the IVS2, nt 1 mutation have β-thalassemia major, while others have β-thalassemia intermedia. Clearly, one can make generalizations about the molecular basis of β-thalassemia intermedia, but these generalizations fail to hold when one considers the individual patient.

It is still possible, however, to make some sense of the molecular basis of the condition. Thalassemias are due to an imbalance of globin chain synthesis. In the case of β-thalassemia intermedia, the imbalance is greater than that seen in β-thalassemia trait and less than that of β-thalassemia major. In general, most individuals with thalassemia intermedia are homozygotes or compound heterozygotes with either two mild β-thalassemia alleles or two severe alleles plus a modifier such as α-thalassemia. Uncommonly, two severe alleles with no known modifier can unexpectedly lead to the milder intermedia state. Conversely, β-thalassemia intermedia with one defective β-globin gene is usually associated with unusually severe imbalance in globin synthesis due to a very severe β-globin mutation or excess α-globin genes. Very rarely, the genetic modifier altering the phenotype in a patient carrying a single defective β-globin gene is not found.

We begin by discussing patients with two defective β-globin genes. In most instances of β-thalassemia intermedia, both β-globin genes are defective and carry mild mutations. These mild alleles are:

1. Promoter mutations, the most important of which are -101(C-T) in Italians, -88 (C-T) in blacks, -87 (C-G) in Mediterraneans, and -29 (A-G) in blacks;
2. The cap site mutation, +1 (A-C), in Asian Indians;
3. The HbE mutation (codon 26 G-A);
4. The IVS1, nt 6 mutation in Mediterraneans; and
5. Deletion mutations such as those that cause δβ-thalassemia, Hb L epore, or H/PFH.

Homozygosity for these alleles also produces different phenotypes. For example, homozygosity for -101 is extremely mild, for -88 leads to β-thalassemia intermedia, for -29 in blacks can produce a state of wellness indistinguishable from “normal,” for +1 in Asian Indians can appear as mild β-thalassemia trait, for HbE is usually similar to β-thalassemia trait or mild thalassemia intermedia, and for IVS1, nt 6 is usually classic β-thalassemia intermedia. Many individuals who are genetic compounds with one of these mild alleles in combination with a second severe allele, such as a nonsense or frameshift mutation, have β-thalassemia intermedia.

In patients carrying two severe β-globin mutations, the major modifier is concomitant α-globin gene deletion, with loss of either one or two α-globin genes. Since chromosome 16s harboring only a single α-globin gene are fairly common among β-thalassemia populations (including Southeast Asians, blacks, and Mediterraneans), individuals carrying only 2 or 3 α-globin genes and two severe β-globin alleles are not uncommon in many parts of the world. These individuals usually have a β-thalassemia intermedia phenotype. Presumably, since both α- and β-globin defects protect against falciparum malaria in heterozygotes, gene frequencies of these defects increased...
in parallel in malarial-infested regions of the world.

As mentioned above, a minority of patients with intermedia can have two severe β-globin gene defects, no α-globin deletion, and a milder, transfusion-free course. The etiology of this milder phenotype in these patients is unknown.

Occasionally individuals who are merely heterozygous for a severe β-thalassemia allele have a mild thalassemia intermedia phenotype due to either a very severe allele producing an unstable β-globin chain or production of excess α-globin chains. In the first group are individuals who appear to be either new cases without a family history or autosomal dominant cases of the disorder. These patients usually have a mutation in exon 3 of the β-globin gene that produces significant instability of the globin, inclusion bodies in the marrow red cell precursors, and a thalassemia intermedia phenotype. Globin chain imbalance becomes greater than in β-thalassemia trait due to a dominant negative effect of the abnormal β-globin which produces precipitation of normal β-globin chains in the hemoglobin tetramer.

In the second group are a small number of individuals in whom triplicated α-gene clusters have been found along with a single β-globin defect. Two patients with 6 α-globin genes and a single severe β-globin mutation were seen in the Punjab region of India. Two other patients with 5 and 6 α-globin genes were found in Israel. Other isolated cases of individuals carrying 5 α-globin genes and one normal β-globin gene have been seen in Italy. All of the above patients had thalassemia intermedia.

Other individuals heterozygous for a common β-thalassemia allele such as nonsense codon 39 may also have mild thalassemia intermedia. The reason for this variation from the expected β-thalassemia trait in these individuals is unknown. Speculations about the role of sequence variants in the variable region roughly 500 bp 5′ to the β-globin gene and in the second hypersensitivity region (HS2) roughly 10 kb 5′ to the ε-globin gene are still just that—speculations. No definitive proof that these sequences are genetic modifiers of phenotype has been put forward.

Our workup for thalassemia intermedia in the laboratory starts with a family history and, if possible, hematological data on the parents. If both parents appear to have β-thalassemia trait, we expect to find mutations in both β-globin genes of the patient. If one parent looks like a silent carrier with perhaps a HbA₂ that is slightly elevated and an MCV around 78–80, we look for one silent carrier (i.e., mild) allele in the patient, such as -101 or the +1 mutation, depending upon the ethnic group of the patient. If one parent has a phenotype similar to the patient, we look for an autosomal dominant mutation in exon 3. Without any clues from the history or hematology of the parents, we first look for mutations in both β-globin genes. If two mutations are found that explain the phenotype, we often stop the analysis. If two severe alleles are found, we analyze the α-globin genes for deletions. If only a single β-globin defect is found, we look for excess α genes to explain the intermedia phenotype. If after this analysis, only the single β-globin mutation has been observed, we then sequence the β-globin gene and its environs to find any new, rare mutations and carry out Southern blot analysis to determine the presence of a gene deletion involving the β-globin cluster. This complete analysis provides a satisfactory explanation for the thalassemia phenotype in well over 90% of patients.
How clinically useful is genotypic information in practice?

Dr. Giardina: Here is an anecdote of a Greek family whose first child had thalassemia major with an intervening sequence IVS2, nt 745 and a β-39 combination. Their second child was a heterozygote. Prenatal testing was done in Dr. Kazazian’s laboratory, and fortunately that child was an HLA match with the older sibling. A successful bone marrow transplantation took place 2 years ago. The mother became pregnant again, and on this occasion the fetus was found by chorionic villus sampling to have homozygous β-thalassemia. After being informed of this, she decided to keep the pregnancy. The child was born, and the lovely part of the coincidences of good fortune is that this child also has an HLA match with his older middle sibling. That is good fortune, and those lovely things don’t always happen in this world. I presented this anecdote to some geneticists who have been trained in Europe, and they are shocked that I allowed a pregnancy with a homozygous-affect ed fetus to continue. I hope that in the United States we hematologists and geneticists never have to reach that level of withdrawing choice from an affected couple.

Dr. Kazazian: The parent’s freedom to choose is clearly the situation in this country, and everything is voluntary. I don’t personally know of situations where the severity of thalassemia is known from a previous child where in a second pregnancy the couple has decided to carry the unborn affected fetus to term. I do know of times when the fetus’ genotype modifies the counseling. There are children of parents with mild alleles or a combination of one mild allele and one severe allele where we informed the couple that there was a reasonable chance of thalassemia intermedia and the fetus was carried to term. I know of plenty of individuals with other diseases—for instance, sickle cell anemia—where, after prenatal diagnosis of disease, about 40% of pregnancies are terminated and about 60% are carried to term. For factor 8 deficiency, hemophilia, I think it is of the same order of magnitude: something like 50% termination, 50% completion of pregnancy. We try to individualize counseling but believe the decision is up to the couple as to what happens.

Dr. Forman: The mother spoken of earlier knew what she was getting into better than we do, having lived through the first child’s thalassemia. But I am curious as to why people want to be tested if they know ahead of time that they won’t act on the information. Do they change their minds afterwards, or are they doing it to prepare for the future if they plan to carry the affected fetus to term?

Dr. Giardina: I think they are preparing. I think they may not know what they will do for sure in the event of another affected child. They are figuring that there is a three out of four chance that they won’t have an affected child.

Dr. Dover: I was very impressed earlier today with Dr. Giardina’s discussion and the consortium pulling together the thalassemia intermedia data. It has been complemented this afternoon by Dr. Kazazian’s genotyping of patients. However, what is absolutely essential to really interpret this data is to ask those centers who supplied data about these 71 patients with thalassemia intermedia to also randomly send Dr. Kazazian’s lab DNA from patients with thal major. It will not be clear to me that we truly under-
stand the real phenotype/genotype relationship of thalassemia intermedia until I see that there really is a difference between thal intermedia and thal major genotypes. If one is going to make conclusions about disease severity on the basis of these genotypes, it is necessary to demonstrate that the people with thal major in these same centers have different mutations.

**Dr. Kazazian:** Although they weren't randomized, Dr. Giardina has sent us blood from 40 or more other patients, and I don't know whether they had thal major or intermedia. She could easily go back and find out what they had and give you an answer to that question, at least from her series.

**Dr. Dover:** The homogeneity that we see in the different centers in Europe is very different from what we find in the United States. We see so many different mutations here, and my experience was that when I looked at patients who had “thal major” or who were on transfusions and I compared them to the ones with “thal intermedia,” there weren’t major genotypic differences.

**Dr. Kazazian:** We looked at them in Sicily with Dr. Maggio, and clearly they were very different. There was a big difference in the distributions of mutations in those with major versus intermedia. The cases of thalassemia intermedia were loaded with IVS1 nt6, and the majors had very few. In addition, the total number of frequent mutations in the region was small—five or six.

**Dr. Olivieri:** In Milan, it’s not an homogenous population. Milan is a center in northern Italy that gets a lot of referrals, so it has a widespread number of mutations. What they found was (although you worry that physicians don’t uniformly transfuse for the same indications) there weren’t major differences between thal “major” and thal “intermedia” genotypes.

**Dr. Dover:** That’s my point about this analysis. Although it intuitively makes sense to me, genotype/phenotype relationships may not hold up. That’s very important if you are going to start using this information for counseling or if you are going to start asking me to select patients for some form of pharmacologic manipulation of fetal hemoglobin.

**Dr. Kazazian:** I really do think that the thal majors have the severe mutations.
Although thalassemia intermedia does not have a unique association with infectious complications, it shares features with other hematologic disorders that predispose patients who are affected to serious risks of infections. For example, since most patients with thalassemia intermedia undergo splenectomy, the problem of postsplenectomy sepsis is as relevant to the care of patients with this disorder as it is to the care of patients with thalassemia major, sickle cell disease, and idiopathic thrombocytopenic purpura (ITP). Similarly, iron overload and iron chelation therapy are often part of the clinical course of patients with thalassemia intermedia, as well as patients with transfusion-dependent blood disorders, which raises the possibility of infection with organisms that thrive in an environment in which iron or a siderophore is abundant.

Splenectomy

Before discussing the problem of postsplenectomy sepsis, it is important to identify the common indications for splenectomy in thalassemia intermedia. Splenectomy is generally undertaken in patients with thalassemia intermedia who experience weakness or chronic fatigue due to their anemia. In addition, patients with impaired growth or development may benefit from splenectomy. The appearance of early changes in the facial bones or the finding of cortical thinning in the long bones due to expansion of the bone marrow may warrant splenectomy as a means of raising the hemoglobin level, and perhaps decreasing the amount of erythropoietic activity. A similar rationale for splenectomy may apply to patients with massive splenomegaly or extramedullary hematopoiesis. Finally, patients who experience a steadily falling hemoglobin level, particularly in the second or third decade of life, or patients who require repeated red cell transfusions because of frequent decreases in their baseline hemoglobin values may benefit from splenectomy. In each of these instances, splenectomy may only be of partial benefit, and regular blood transfusions similar to those used in thalassemia major may be required.

In a study of 37 patients with thalassemia intermedia in Great Britain, Modell and Berdoukas found that 19 were splenectomized and 18 were nonsplenectomized. The median age at splenectomy was 8 years. The hemoglobin levels rose from a mean value of 7.1 g/dL prior to splenectomy to 8.9 g/dL after surgery. Data collected from 71 North American patients for this conference were remarkably similar to the British data in regard to median age at splenectomy (9 years) and mean presplenectomy and postsplenectomy hemoglobin levels (6.8 and 8.5 g/dL, respectively). Of the 71 patients, 56 underwent splenectomy and 15 had intact spleens.

Postsplenectomy Sepsis

The problem of postsplenectomy sepsis with encapsulated organisms has been recognized for many years. These infections are often abrupt in onset and rapidly fatal. For unknown reasons, patients with thalassemia were believed to be at particular risk for postsplenectomy sepsis compared with patients splenectomized for other reasons. Singer compiled data from 24 series, as well as from his own center, and found that 25% of 109 patients undergoing splenectomy for thalassemia developed postsplenectomy sepsis. In contrast, only 1.4% and 2.0% of patients undergoing splenectomy for trauma and ITP,
respectively, developed postsplenectomy sepsis. Of the 27 patients with thalassemia who developed serious bacterial infections, 12 died.

Subsequent studies have demonstrated a lower but still significant risk of postsplenectomy sepsis in patients with thalassemia. Issaragrisil et al. studied 1,018 patients with hemoglobin E-β-thalassemia in Thailand and found a 4% rate of postsplenectomy sepsis among 228 splenectomized patients. The mortality rate of 89% was unusually high. Among 101 patients with thalassemia major and 18 patients with thalassemia intermedia studied by Modell and Berdoukas, 5 patients had serious bacterial infections, including peritonitis, osteomyelitis, and meningitis. However, no episodes of sepsis were recorded. The lower rates of postsplenectomy sepsis found in more recent studies may reflect the use of prophylactic penicillin, immunization with pneumococcal vaccine, and delay of splenectomy beyond the age of 3 years.

The effectiveness of prophylactic penicillin in preventing serious bacterial infection in patients with absent splenic function has been well demonstrated in sickle cell disease. However, compliance remains an important issue. Borgna-Pignatti et al. studied compliance with prophylactic penicillin in 42 splenectomized patients with thalassemia. These investigators collected five random urine samples at the time of transfusion therapy. In 21% of patients, two or fewer of the five urine samples were indicative of recent penicillin intake. The major risk factor for non-compliance with prophylactic penicillin in the study was a duration of more than 6 years after splenectomy. Patient age and history of previous infection did not predict compliance patterns. Most interestingly, physicians involved in the patients’ care were unable to successfully predict which patients were compliant with penicillin therapy.

Because of the concern about postsplenectomy sepsis, partial splenectomy has been considered as an alternative for patients with thalassemia intermedia. Investigators in Paris reporting on six patients found that the mean hemoglobin level increased in the first year after surgery. However, the results of a single patient with more than 2 years of followup offer a possible warning about the long-term value of this procedure. This patient had an initial increase in hemoglobin level, from 5.0 to 8.0 g/dL. In the second year, the hemoglobin fell to 6.5 g/dL. By the fourth year, the mean hemoglobin was 7.0 g/dL, but the patient required three transfusions. In light of the extraordinarily strong erythropoietic drive found in thalassemia intermedia, regrowth of the spleen remains a distinct possibility, and the long-term benefits of partial splenectomy, both in regard to risk of postsplenectomy sepsis and overall improvement in the hematologic condition, must be carefully assessed.

**Yersinia enterocolitica Infection**

Many bacteria rely on iron as an essential nutrient. Most of these organisms have established methods for retrieving iron from the environment, usually through production of a siderophore. Indeed, chelators developed for human application, including deferoxamine, may be derived from these siderophores. Yersinia enterocolitica does not produce its own siderophore, and it is usually found in environments such as the gut, where it can take advantage of siderophores produced by other bacteria. Experiments in mice have demonstrated the increased lethality of Yersinia enterocolitica when iron, deferoxamine, or a combination of the two is added to the animal. For example, in mice, the LD50 of two of the serogroups of Yersinia enterocolitica that most commonly cause infection in humans is greater than 10. However, when the animals are pretreated with deferoxamine, the LD50 falls as low as 10−1, and pretreatment of the mice with iron followed by deferoxamine reduces the LD50 below 10.

The human counterpart of these animal experiences can be found in patients with iron overload. In an extensive review, Blei et al. found 47 reports of serious infection with Yersinia enterocolitica in patients with thalassemia major. Thirty-five of the 47 patients had septicemia, and an additional 10 patients had abdominal infections, including mesenteric adenitis, peritonitis, or abdominal abscesses. Thirty patients were receiving deferoxamine, 6 were receiving no chelation therapy, and information was unavailable for 11 other patients. These data demonstrate the sig-
significant problem posed by Yersinia enterocolitica in patients with iron overload, particularly those receiving chelation therapy.

Summary

Infections remain a serious problem for patients with thalassemia, as they do for other patients who have undergone splenectomy or who have excessive amounts of iron and require chelation therapy. In assessing the overall risks associated with this surgical procedure, it would be helpful to be able to characterize the risk of postsplenectomy sepsis for patients with thalassemia intermedia receiving presplenectomy immunizations and postsplenectomy prophylactic penicillin. As new iron chelators are developed, their ability to enhance bacterial growth should be carefully monitored. The prevention of infection in patients with thalassemia may become increasingly important as the improved overall management of the disease extends the length and quality of life of affected patients.

References

Dr. Forman: This has been a very interesting conference. I would like to ask the speakers to come up and sit in front. This is the moment for the audience to ask their questions and for the speakers to ask each other questions. We have an additional member of our panel: Dr. Carol Hyman from California, who has considerable expertise in the long-term care of patients, will join Drs. Pearson, Giardina, Cohen, Olivieri, and Kazazian.

Q: I have a question for Dr. Pearson. One of the discussions earlier today dealt with trying to treat patients with transfusion therapy before bony changes become pronounced. I have had the experience recently of being in a situation where the parents want to believe that the child looks normal and it is clear that the child does not. I don’t think that is an unusual situation. It’s very hard not only to be the bad guy who says “I think we need to go to transfusion therapy” (which is something I think most families dread), but on top of it you are saying the reason why you need to do it is that the child looks funny. What do you do with that situation? Have you encountered it? I see some nodding heads, so I doubt we are the only ones.

Dr. Pearson: I think that serial photographs have been most helpful. Ask them to take a photograph of the child at regular intervals. Even a parent who lives with the child’s appearance every day and becomes immune to changes can see the progression. I also found that showing them the x-rays is helpful. If you can show the hair-on-end appearance with a skull that is thick and put it beside a normal skull, even a doubtful person can realize there are differences.

Q: How can we prevent the bone problems associated with bone marrow expansion?

Dr. Olivieri: Dr. Beatrix Wonke has used biphosphonates in thalassemics in the United Kingdom, but I think that her studies were done primarily in adults. Bone disease doesn’t always reverse, and there are pain problems with that. We await the outcome of that interesting study.

Dr. Giardina: We have been impressed that some of the older women with thalassemia intermedia have essentially had secondary amenorrhea and are hypogonadistic. This adds the problem of low estrogen to the already sick bones. I am convinced that this accounts for some of the fractures we have seen, and it is why we have been very aggressive in providing estrogen replacement to adolescent women who need it.

Dr. Olivieri: I agree. We did a survey of 58 adults with thalassemia intermedia. In about 35 of them we looked at calcium bone index, bone indices, as well as quantum digital radiography. The two risk factors for a low bone density were hypogonadism and the irregularity of transfusion. Even people with thalassemia intermedia and good sexual development had a low bone density, but not quite as low as a person with thalassemia major or intermedia and hypogonadism as well.

Q: Can transfusion therapy help prevent fractures in an adult who has severe osteopenia?

Dr. Pearson: I don’t know about adults, but certainly with adolescents transfusions can cause reversal and improvement of the bone structure. I don’t know what the critical age is. If you have a patient with ter-
rible cosmetic problems, can you improve his facial appearance? I know that you can in childhood, perhaps early adolescence, but I am not sure about adults after their bone growth becomes fixed. I have also seen a few patients who had been on transfusions who, when they went off transfusion, had subsequent progression of their cosmetic abnormalities in later life.

Dr. Cohen: A single case may or may not be instructive, but we encountered a gentleman who was probably in his late 20s when he first came to us with debilitating back pain. He had terrible osteopenia, was literally unable to stand up straight, was hunched over and could barely move to get on the examining table. Then he went on chronic transfusions, and he was very, very dramatically improved after about 3 months. It was something of a miracle. I think it is at least worth a shot to see whether there would be symptomatic improvement in adult patients who have severe bone disease.

Q: Did this patient have vertebral compression fractures?

Dr. Cohen: Yes.

Dr. Hyman: We have had a couple of patients with very severe thalassemia intermedia. One young woman as a child had broken many of her bones. She would be in the hospital most of the year with fractures, and every time they would move her from one bed to another she would fracture another bone. A hypertransfusion program was begun for that patient in order to shut off her hematopoiesis. Another of our patients with thalassemia intermedia had the most severe facial changes I have ever seen. It took three major facial surgeries and an aggressive transfusion program to maintain the correction of facial bone growth. Interestingly, once her face looked “normal,” it took her over a year to adjust emotionally to the changes.

Dr. Crocker: There has been no comment yet today from any of the speakers on the issue of self-image or self-identity, especially in this condition that the caregivers are finding hard to define. If you have thal major, you sort of belong to “the club.” Your illness is acknowledged, being maximally challenged, and there is a whole set of precepts required to get through life with the best outcome in terms of survival and control of morbidity. If you are an individual with thal trait, presumably your agonies are minor and this can be incorporated with comfort, particularly in a pedigree where you happen to be a winner. But when you have something in between that is almost as serious but not necessarily, and really isn’t well understood by anyone, and in textbooks it is covered only extremely vaguely and ambivalently, and we are not sure whether it is one disease or six diseases.

Dr. Pearson: Are you referring to my chapter?

Dr. Crocker: This is a little reminiscent of a meeting I just came from, an annual convention of the MPS (Mucopolysaccharidosis Society). There is a sort of strata in which there are very severely affected children, extremely mildly affected ones, and also a group of in-between ones, such as those with delayed onset Hunter syndrome. These children and their families are trying to figure out where they stand: Should they be worried about themselves, or are they really okay, and what’s up? How do you give a person with moderate clinical involvement with thal intermedia a sense of who he is and what’s going on?

Dr. Olivieri: I appreciate what you are saying, and it is something that our thal intermedia patients talk about. In fact, the Diamond Blackman patients that we see in the transfusion clinic say the same things. “We can’t get the oral chelator, we don’t have any real sense of the field moving forward, and there are just 14 of us in the clinic.” In our program, we do see the thal intermedia patients frequently and hover over them more than we do the thal majors, so their connection to us is just as close as the patients with thal major, although perhaps not as frequent. We have tried to make an effort to include them in the program. In fact, many of those patients we worry more about than the standard transfused patient. In our program, we have been making an effort to use Bernadette Modell’s survey of quality of life for thal-
lassemia major, and we apply it to everyone. We are just in the middle of analyzing that now. I don't really have any idea if any of the attempts to involve them closely make a difference.

**Ms. Kurth:** We have a patient in Boston whose parents were told, “Your child has thalassemia intermedia, but your child also needs transfusions.” Now the child is 3 years old after being started on transfusions at about age 2. He is doing well on transfusions, is growing well at the 90th percentile, but has an anxious mother. As I was talking to her the other day, I spoke of him as though he had thalassemia major. And she said, “Dr. Forman told me he has thalassemia intermedia, and now you mean he has thalassemia major. Is he worse?” I had quite a bit of backpedaling to do to try to relieve her anxiety. She is more worried than most, but it shows the dilemma that you have in explaining the diagnosis to families and having them understand what it predicts and what it doesn't predict. I tried to stress that although your child needs transfusions, and that's all we really know, he is doing very well now and is expected to continue to do well.

**Dr. Pearson:** I would be very reluctant to make a definitive diagnosis of thalassemia intermedia under 4 years of age, because there are certain children whose hemoglobin falls gradually, and it isn't clear what is going on until they are 4 or 5 years old.

**Q:** How reliable is ferritin as a measure of iron burden?

**Dr. Olivieri:** What you are asking is, “In the event that you cannot do a quantitative assessment of iron such as a liver biopsy or you are not close to Cleveland and you can't do a SQUID, how effective an estimate of body iron burden is the serum ferritin concentration?” It is certainly true that we have all used the serum ferritin to estimate how a patient is doing. When we have looked within 14 months of a liver biopsy, there is a very good correlation between ferritin and hepatic iron, but the confidence intervals are so wide that a ferritin of 2,000 identifies a liver iron of between 2 and 22 micromoles per gram dry weight. You could be 10 times off using ferritin. So I don't think it is useful for quantitative assessment, and the problem is that if the patient has another problem such as hepatitis C or alcohol use, then you may have a more complicated situation. If we want to make some conclusions from this conference, there are certain important things that kill people with thalassemia intermedia: infections, complications of splenectomy, iron overload. Maybe these things could be addressed by the group of people here so the next conference in less than 11 years could actually answer some prospective questions on this. It is difficult to get liver biopsies, and you really need an infrastructure to do it. We had a lot of trouble with our hepatologists, so we went to our invasive radiologist, and now they do two biopsies under ultrasound guidance on a weekly basis. Physicians really could make more use of the SQUID technology, and hopefully NIH will help to make that more available. A ferritin in Canada costs approximately $33 an assessment, and the biopsy costs us just the radiology time, so we figure if we get that one biopsy every 18 months we are actually saving because we have an exact measure, whereas we are doing a ferritin estimate six times in those 18 months. Dr. Cohen is now going to comment on how he agrees with me.

**Dr. Cohen:** The problem with this question is that Dr. Olivieri knows exactly what I am going to say and I know exactly what she is going to say. My suggestion to Dr. Olivieri to cut her costs down is to stop doing ferritins every 3 months. You have to ask the question with any test you order, which is, “What am I going to do with the information I get, and how important is that versus the risk of the procedure I am about to do?” If it is a venipuncture, it is less of a debate. If it is a liver biopsy, no matter who is doing it, it certainly causes more of a debate, certainly for the families as well as physicians. I am not antibiopsy or antiliver iron, but I do think one has to look at the whole patient and reach a conclusion as to how much information you are going to get. I think there are situations where it is invaluable, and we have seen some, and Dr. Olivieri has gloated when we have. I think there are other situations where we have had very good information based on knowing the family, knowing the ferritin level over time, knowing the
child, and to have subjected that child to a liver biopsy might have been considered inappropriate.

Dr. Olivieri: You can't predict that situation necessarily in advance. Are you saying if you knew this family was compliant, and you knew the relative Desferal consumption and the relative transfusion load, that you could estimate that those patients would have liver iron between 3 and 7? If you don't do the biopsy, you don't know that.

Dr. Giardina: We have all been in this business so long that we have had personal experience with things that were in vogue. Twenty years ago I was doing liver biopsies, and I was measuring serum ferritins, and I recognized the fact then that in a population of 88 patients or so the serum ferritins were all over the place and they would jump around by 500 or 700. In 1984, when I was trying to compare high responders and low responders to chelation therapy (based on ferritin levels), that ferritin just wasn't helpful. I treated my patients as if ferritin didn't exist, but I measured them. And I told my patients, "just use your Desferal, don't worry about your ferritins." I did liver biopsies, and the liver biopsy percents dry weight of iron were all over the place as well. This wonderful man I work with, Bob Grady, said, "Pat, the specimens are too small, your patient population is so variable because there is cirrhosis, and you can't get an accurate measurement." So I stopped looking at liver biopsies, and I told my patients, "just use your Desferal." In close to 20 years, actually, we have achieved something. We see it in the fact that the patients' lives have been prolonged and that they are living healthier lives and better quality lives. I guess I am not being very much of a scientist today, but I have a feeling we are just shifting our horizon. There is something else now in vogue, and it is called a SQUID, but I am not really quite sure that getting SQUID measurements on a yearly basis is going to afford us anything for the patient. We are going to have another parameter to look at in terms of analyzing data, but is it really going to help us? Forgive me. I know that we should be seeking any additional parameter to evaluate iron overload, and maybe the SQUID is it, but maybe it isn't.

Dr. Olivieri: Iron overload is the life-limiting complication of that intermedia. I am not interested in doing SQUID'S because it is in vogue. I happen to live in Toronto, and Cleveland isn't far away by plane, and I am glad I don't have to do a liver biopsy every 18 months. One should use the most accurate determination of body iron burden. I have just told you that the data indicate that a ferritin level can identify a liver iron of between 2 and 22. There is a huge variability, up to 10 fold. The bottom line is that determinant of hepatic iron is not simply "in vogue," it is the best way one can quantitatively assess body iron burden. I have that in mind for the patients—not for studies, but for patients. We have made mistakes with deferoxamine toxicity. We have underdosed patients. We have overdosed patients. I do agree with Dr. Cohen's view that it is difficult to convince families to have biopsies. There's no question he is right, and that's why SQUID technology is useful. I don't view that just going and saying "Do your Desferal" is useful. We still have patient deaths. The important thing in thal intermedia is that there are other complicating factors that may confuse the serum ferritin versus hepatic iron concentration, such as ascorbate deficiency. So we really, really do need a quantitative assessment, and there really isn't another one right now.

Dr. Hyman: First let me thank both Dr. Forman and Lauren Berman for asking me to participate in the panel, especially since I am from the West Coast and have opposite viewpoints—mainly because I don't get a chance to talk to anyone there, so I am sort of by myself. As far as the ferritin is concerned, I have seen numbers of patients who receive ascorbic acid daily and still run serum ferritins of 200, 300, and 400, and they pour out iron when you give them Desferal. My attitude is to beware of the interpretation of low serum ferritins. On the other hand, if you have patients whose ferritins are coming down after starting in the thousands, when you get below 1,000, you have to watch out on the dose that you don't get Desferal toxicity.

Dr. Forman: Let me raise a more benign challenge. I will ask Dr. Hyman to speak first. When should splenectomy be performed?
**Dr. Hyman:** Well, I am being asked the question because everyone here knows that I am a rather anti-splenectomy person. Splenectomy has to be looked at both short-term and long-term for what it does for the patients and also what happens to the patients when they are adults. One of the things that happens as the patients grow older is that they get more hypoxic and require higher pretransfusion hemoglobins as they age because of chronic peripheral hypoxemia. We also know that a lot of them die from cardiac disease, which we say is due to iron overload. There is some evidence from different sources showing that some of the cardiac problems in the thalassemics at least are starting on the right side of the heart, not the left, even though they eventually develop left-sided heart failure. Why is that? Is it just iron? There are a lot of pathology data showing there are chronic frequent thromboemboli all over the lungs and that this is causing some of the AV shunting. It causes little spider hemangiomas under the subendothelium. A large number of patients develop pulmonary hypertension when they get older. Dr. Loukopoulos' group has a paper out where they have shown a large number of people with thalassemia intermedia who developed pulmonary hypertension. The vast majority of them had their spleens out, and he too began wondering if splenectomy is a source of the problem. My objection to splenectomy is that I think it causes problems down the line rather than immediately. Yes, without it you get a little more iron because more transfusions are needed, but I think you get irreversible changes later on which may kill our patients. This is why I am really opposed to splenectomy in most situations. When we have done it in some of our thal intermedia patients, they have had partial splenectomy. I know it is more costly, and I know there is a morbidity to it, but I think one has to consider a way to avoid the late complications of splenectomy. I think partial splenectomy should be thought of as an option.

**Q:** But what's the connection between the emboli and splenectomy and between the pulmonary hypertension and splenectomy?

**Dr. Hyman:** When you take the spleen out you get a higher platelet count. I think we have to consider whether we should give aspirin to our patients with high platelet counts after splenectomy. I am beginning to wonder if we are causing some of the deaths, and whether we should hypertransfuse them instead of taking out their spleen for chronic fatigue and some of these other symptoms of anemia.

**Dr. Pearson:** Speaking of pulmonary hypertension, I have one patient who at age 30 developed right-sided pulmonary hypertension. In talking to the cardiologist at Cornell, they have only two patients with pulmonary hypertension. So it isn’t really common. It appears to be an unusual event.

**Dr. Giardina:** We have three patients, all with thal major, who actually have pulmonary hypertension.

**Dr. Forman:** I wonder how many institutions are now doing partial splenectomy? Could you tell us a little bit about the risk of the procedure and how you assess the patient?

**Dr. Cohen:** While having never done a partial splenectomy myself, I would be delighted to answer your question. Actually Elliot Vichinsky and Lori Styles gave a very beautiful presentation of the technique for doing this. An open laparotomy is performed, and the vascular supply to the spleen is tied off and the edges turn black segmentally. I had to watch it once so I thought I would share it with everybody here. This was continued until 60–80% of the spleen—it might have been 80% of the spleen—was gone (necrotic). The idea is basically to leave what amounts to about half of a normal spleen size behind. At our own institution, with an open splenectomy, the average length of stay is 4–5 days and isn’t a managed care phenomenon. For partial splenectomy, the stay may be longer. There was also a very high incidence of pneumonia postoperatively in that group. That begins to worry me. I think you better be pretty sure you are getting something for your money in order to add to the potential morbidity of the procedure.

**Dr. Hyman:** At L.A. Children’s, radiologists do a number of partial splenectomies by embolectomy technique. With that technique, they sometimes have
to go in more than once. They embolectomize it segmentally, and they try to necrose about 70-80% of the spleen. It does require hospitalization of five days or more. I am personally opposed to complete splenectomy. The partial splenectomy can be done in two ways, by embolectomy or surgically. I think the postop course has to focus on prevention of pneumonia.

Dr. Dover: Let me make just one comment about that. Just to clarify, what Lori Styles and Eliot Vichinsky presented was primarily the use of this technique in patients with sickle cell disease and sequestration crisis. They weren't talking about thalassemia intermedia, and I think one really does have to be worried about the possibility of splenic regrowth in this condition. In sickle cell disease, it is a very different issue altogether, because the spleen undergoes autoinfarction. We don't want to go back to have to do another splenectomy. All the surgeons will say they don't want to have to reoperate, so I think we need some data to prove that they won't have to.

Dr. Pearson: A couple of clinical points. Splenic embolization produces infarction, which can be a very painful event. Second, a child at our hospital some years ago had ligation of his main splenic artery. Apparently there are collateral vessels because six months later he had normal splenic function (low pit count) and a normal radionuclide spleen scan.

Dr. Giardina: Dr. Hyman, your point is very well taken. There is some amount of obstructive lung disease, pulmonary hypertension, and right-sided heart failure in patients with both thal major and thal intermedia, and it should be well studied. There have been sporadic reports of protein C, protein S deficiency in thalassemia patients, and there has been some suggestion that the abnormal erythron mass produces some endothelial damage and might result in the hypercoaguable states. I think that there is a lot of work that we can do on investigating and clarifying possible coagulation disorders that are associated with ineffective erythropoiesis with transfusion and with splenectomy. There may be multiple factors involved here.

Dr. H yman: A another question is whether we should consider transfusing patients with thal intermedia during childhood and early adolescence, and then stopping transfusions to see how they do. Transfusions will help get them through the complications from their bones, growth and development, and endocrine deficiencies. We could transfuse them through the growth spurt and then see what happens off transfusions. We have to think seriously before we take out the spleen. You have to look at the coagulation problems and put them on aspirin, or think of whether you are going to coumadinize them. This seriously has to be thought of and not just forgotten. I think these are real possible complications that are coming along. If you look at the pathology, what are these patients dying of and what are their symptoms? Chronic hypoxia and heart problems.

Dr. Forman: Let's take a case where you know the child has thalassemia intermedia, and the diagnosis is supported by the family history. The child is now 3, 4, or 5; the spleen is getting larger; hemoglobin is falling under 7, under 6; and you know from the family history that if you remove the spleen, the hemoglobin is going to go to 8 and stabilize. What would be your indications for splenectomy, and what would be your options? One option is hypertransfusion, trying to keep that spleen from getting big; another is partial splenectomy; another is splenectomy. Can you think of any other options, and which one would you recommend?

Dr. Hyman: I would recommend partial splenectomy.

Dr. Cohen: I would take out the spleen. I will give a couple of reasons why. I think a partial splenectomy is fine if you do it as an experiment, but I don't think we know enough about the long-term results, which is exactly the point you were getting at with splenectomy. I think to start that child on hypertransfusion is fine if you think that the child was not going to be able to survive without hypertransfusion. I would agree that transfusion is a reasonable option if in fact an older sibling had gone on to transfusion therapy anyway, or you wished that he
or she had gone on to transfusion therapy. But if that older child, as many thal intermedia patients do, is doing very nicely at a hemoglobin of 8 without bony changes or other changes, and you know you can accomplish that by splenectomy, I am not sure quite frankly what the argument would be.

**Dr. Olivieri:** I would agree. We would tell the family exactly that and then most of them, because of the fear of blood, would choose for splenectomy, which is what I would recommend also. Dr. Hyman, if this coagulation problem really exists, then it needs to be looked at, as Dr. Cohen is pointing out. It really needs to be studied. I don’t know how to study the generation of thromboplastic substances or a hypercoagulable state or lung function, but you have a lot of splenectomized thalassemics in this country, in Canada, and everywhere, and you have a lot of non-splenectomized patients. You can do a control and look and see if that’s the clinical impression. I think what Dr. Cohen is really saying is that there is a lot more evidence that splenectomy really does cause a mean hemoglobin rise of at least 2 grams, and you can avoid transfusion. Transfusional iron overload still is going to be the thing that causes mortality. You are quite right that this pulmonary hypertension, right-sided heart failure, and diastolic dysfunction are all observed, but they still haven't been proven to be due to splenectomy.

**Dr. Forman:** Let me respond to that. The young people that I presented this morning benefited tremendously from splenectomy. Early evidence that thromboembolism might be associated with splenectomy would not be sufficient to tilt the balance to move away from splenectomy in general.

**Dr. Hyman:** Well, I still vote for partial splenectomy. You have to look at both short-term and long-term. I really think serious consideration should be given to partial splenectomy, despite its complications and its cost. I think the Thai people may have some data about their patients with hemoglobin E thalassemia, though this is a different form of thalassemia intermedia. Some of them seem to feel strongly about the partial splenectomy, and that there is a splenectomy relationship to their cardiac deaths.

**Dr. Forman:** I want to know if Dr. Pearson would have recommended taking that spleen out.

**Dr. Pearson:** Yes, I would have.

**Dr. Forman:** Would you have recommended transfusions instead?

**Dr. Pearson:** No.

**Q:** I have a question about people who are put on Desferal and then followed longitudinally. Is the urinary iron excretion a helpful measure of chelation? Are there any data on what happens to the urinary excretion iron over time—not when their ferritin drops initially, but when it is high and they are on a stable regimen? After you take one value of iron excretion, can you assume it is going to be the same next year?

**Dr. Olivieri:** Our experience is that when you look at urine iron excretion and correlate it with body iron burden as quantitated by hepatic iron, the correlation is extremely bad. If you calculate urine creatinine and weight and determine if the test reflects a 24-hour collection, only 43% of our outpatient urine samples are correctly collected. I suppose if you did it in hospital it might be much better.

**Q:** In your experience, do you think being able to more precisely define body iron in your patients has been inspiring them to use their Desferal?

**Dr. Olivieri:** Yes, but probably because we are a bit zealous in telling them that the ferritin level is not that useful. I have heard patients tell each other, “Don’t tell me your ferritin, what was your liver iron last time?” So they are very aware that this is not the measurement we use any longer, but we use the liver iron—just as we used to encourage them with serum ferritin. If your physician believes in it and tells you what they think, if you are inspirable, you are going to be inspired. There is nothing different about hepatic
iron versus a serum ferritin. When we used serum ferritin alone to estimate body iron burden, we used to always discuss the value at every visit. Now we discuss the hepatic iron as what we believe is the quantitative assessment.

**Q:** What toxicities are associated with the oral iron chelator, deferiprone (L1)?

**Dr. Olivieri:** In the study we did with patients with thal major, we saw arthropathy in 3 of the 21 patients that were reported. In one, it reversed. In another, it went away after interarticular steroids were given, and the other still has the problem and continues on L1. There has been an incidence of agranulocytosis and neutropenia. There have been 13 reported cases in the literature. It is difficult to know what the denominator of that is. Zinc deficiency was described in four patients by Victor Hofbrand.

**Q:** Have all the incidences of agranulocytosis reversed when they were taken off L1?

**Dr. Olivieri:** Yes.

**Q:** How does cirrhosis affect your interpretation of the liver iron?

**Dr. Olivieri:** If a person has frank cirrhosis, I don’t think the quantitation of liver iron will be accurate, because cirrhosis is a nodular process. If you look at the histology, iron isn’t loaded into the nodules. If a person is frankly cirrhotic, it is difficult to see how iron chelation therapy is going to help this process, because to my knowledge advanced cirrhosis is not reversible. If a person has cirrhosis and hemachromatosis, life expectancy is not extended by iron-chelating therapy. We are already seeing some thalassemia patients who develop hepatoma after cirrhosis has been established. It’s not to say that if you have a good cardiac outlook, and since hepatoma isn’t 100 percent fatal—you certainly want to continue to chelate them. Your question is, “What value of liver iron is recommended?” In those cases, the liver biopsy, I believe, is not quantitative of iron concentration.
The ideas developed and reported in this monograph represent the product of an intense and spirited conference day. It is appropriate to note that the occasion had a gratifying spirit of collegiality, trust, and collaboration. There were also the necessary feelings of passion. As a convener and not as a presenter, I am moved to comment that the nine principal speakers and panelists are very special persons in this field, with a unique history of caring and continuity. We have heard from North America's thalassemia legends.

As conclusions are drawn regarding thalassemia intermedia, it seems reasonable to say that we do not yet have the tiger by the tail. Intermedia is a low incidence situation, but with high stakes. It shares much with the world of thalassemia major. Important areas of study include genotype/phenotype correlations, the pace of transfusion, utility of liver iron measures, the hygiene of splenectomy, control of infection, and oral therapies, all of which have had substantial discussion in these proceedings. Significant new data are available now.
Thalassemia Intermedia Conference
Conference Director: Howard A. Pearson, M.D.
Children's Hospital, Boston, MA
November 14, 1996

8:30–9:00 Registration & Coffee

9:00–9:15 Introduction
Edwin N. Forman, M.D.
Director, Division of Pediatric Hematology/Oncology
Rhode Island Hospital
Professor of Pediatrics
Brown University School of Medicine, Providence, RI

9:15–9:30 Update on Activity of the National Heart, Lung, and Blood Institute
Alan S. Levine, Ph.D.
Director, Blood Diseases Program
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute, Bethesda, MD

9:30–10:00 Thalassemia Intermedia: History and Definition of Thalassemia Intermedia
Howard A. Pearson, M.D.
Professor of Pediatrics
Yale University School of Medicine, New Haven, CT

10:00–11:00 Characterization and Findings in Current American and Canadian Patients with Thalassemia
Patricia J. V. Giardina, M.D.
Associate Professor of Clinical Pediatrics
Chief, Division of Pediatric Hematology/Oncology
The New York Hospital/Cornell Medical Center, New York, NY

11:00–11:15 Break

11:15–11:45 Iron Status in Thalassemia Intermedia
Nancy F. Olivieri, M.D., FRCP (C)
Hospital for Sick Children
Director, Hemoglobinopathy Program
Professor of Pediatrics & Medicine
University of Toronto, Toronto, Canada
11:45–12:15  **Pharmacological Treatment of Thalassemia Intermedia**  
George F. Dover, M.D.  
Professor, Pediatric Oncology and Medicine  
Director, Department of Pediatrics  
Johns Hopkins University School of Medicine, Baltimore, MD

12:15–1:15  **Lunch**

1:15–2:00  **Genetic Basis of Thalassemia Intermedia**  
Haig Kazazian, M.D.  
Professor and Chairman of Genetics  
University of Pennsylvania School of Medicine, Philadelphia, PA

2:00–2:30  **Infections in Thalassemia Intermedia**  
Alan R. Cohen, M.D.  
Professor of Pediatrics  
University of Pennsylvania School of Medicine  
Chief, Division of Hematology  
Children's Hospital of Philadelphia, Philadelphia, PA

2:30–2:45  **Break**

2:45–3:45  **General Panel Discussion & Audience Participation**  
Drs. Pearson, Giardina, Cohen, Oliveri, and Kazazian

3:45–4:15  **Epilogue**  
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