Hemolytic Anemia: Thalassemia Syndromes

By RICHARD DAVID PROPPER, M.D.

The thalassemia syndromes are a group of inherited disorders of hemoglobin synthesis that fall under the classification of the hypochromic microcytic anemias. Since the thalassemias cover a wide spectrum of both specific genetic abnormalities and clinical presentations, there is often a tendency for the nonhematologist to view this complex topic with more than a slight degree of frustration. The complexity is more apparent than real, however, and this article will attempt to clarify the position of the thalassemias within the framework of the hypochromic microcytic anemias.

When one is considering any broad classification of disorders, it is usually easier, and generally more lasting, to grasp a basic understanding of the underlying concepts than to memorize each of the specific causes and the various manifestations of their presentations. This generalization is especially true of the anemias. Therefore, a brief description of the pathophysiology of the hypochromic microcytic anemias will afford the reader an opportunity to look at these disorders from the standpoint of “what went wrong” with the normal homeostatic body mechanism.

Red cells, as seen in the peripheral blood, are the end product of intrinsic erythropoiesis, environmental factors, and reticuloendothelial (primarily splenic) remodeling. An abnormality anywhere in the system may disturb the natural balance and produce microcytosis—i.e., small cells in the peripheral blood.

When considering a red cell, one should think of it as basically a hemoglobin solution, the function of which is to reversibly bind oxygen, packaged in a container—the cell membrane—that gives the cell its structure and protects it from the environment. The normal discoid red cell seen on a peripheral smear has an optimal membrane surface area for the amount of hemoglobin packaged. In other words, there is an adequate amount of membrane to both enclose the contents of the cell and permit the cell to easily squeeze through endothelial channels.

Anything that tends to decrease the amount of hemoglobin packaged per cell more than it decreases the amount of membrane formed will result in a hypochromic microcytic red cell. Disorders that produce such conditions are found at the level of intrinsic erythropoiesis and include the thalassemias (defects in globin-chain production), the sideroblastic anemias (defects in heme production and iron incorporation), and iron-deficiency anemia (a defect in the final path of heme synthesis). On peripheral smear these cells appear smaller than normal and contain a relatively large area of central pallor.

Anything that tends to deplete the cell membrane more than the hemoglobin content will produce an apparently hyperchromic, microcytic red cell. This “microspherocyte” assumes the rounded shape because it is the only shape the cell can assume that will permit the decreased membrane package to enclose all of the cell’s contents without the loss of the cell’s integrity. The conditions that produce these types of changes are peripheral to this article and will not be discussed in detail. Suffice it to say that anything that causes damage to the red-cell membrane might result in the production of the micro-
spherocyte. Whether it is injury, as seen in disseminated intravascular coagulation, or incomplete antibody assault, as in many hemolytic anemias, reticuloendothelial remodeling is the result. Basically, the damaged red cell enters the spleen and emerges as a remodeled microspherocyte. These cells, then, although small, do not fall under the heading of the hypochromic microcytic anemias.

When considering the hypochromic microcytic cell, one is almost exclusively concerned with the conditions that lead to a decrease in mean red cell hemoglobin production. Theoretically, this decreased amount of hemoglobin, in the presence of a normal capacity to produce membrane, will require a smaller package. Decreased hemoglobin, in turn, can be the result of a problem in the synthesis of either heme or globin (Table 1). Underproduction of the heme moiety may be the result of a defect in porphyrin biosynthesis (the sideroblastic anemias and lead poisoning) or of iron availability for heme synthesis (iron-deficiency anemia or, occasionally, the anemia of chronic disease). Underproduction of a globin chain or chains regardless of the cause is referred to as thalassemia, and each specific thalassemia derives its name from the particular globin chain or chains that are missing.

Since the production of normal red cells involves the synthesis of approximately equal numbers of α and non-α (β + γ + δ) globin chains, the resulting imbalance seen in thalassemia has two ramifications. First, there are fewer complementary pairs of globin chains produced per cell, leading to a decrease in intracellular hemoglobin concentration. If the defect is severe enough, the developing red cell destructs while still in the bone marrow, leading to ineffective erythropoiesis. Even cells that have enough hemoglobin to survive intramedullary maturation are still poorly hemoglobinized by normal standards.

Second, these red cells are further handicapped by the unbalanced chain synthesis that has led to a relative excess of one of the globin chains. These excess chains, unable to find complementary chains with which to pair, eventually form aggregates with each other. These aggregates are variably soluble and often produce large intracellular inclusions that are pathologic in and of themselves. They may attach to the cell membrane and cause a decrease in deformability; they may act as an oxidant stress and cause irreversible membrane damage; they may mediate reticuloendothelial destruction of the cell in the spleen. The thalassemias, therefore, are actually anemias with both an ineffective erythropoietic and a hemolytic component (Figure 1).

**TABLE 1**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Defects</th>
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<tbody>
<tr>
<td>Porphyrin biosynthesis</td>
<td>Lead poisoning</td>
</tr>
<tr>
<td>Iron incorporation</td>
<td>Sideroblastic anemias</td>
</tr>
<tr>
<td>Globin-chain production</td>
<td>Iron-deficiency anemias</td>
</tr>
<tr>
<td></td>
<td>Thalassemias</td>
</tr>
</tbody>
</table>

**CLASSIFICATION**

The thalassemias are genetically classified according to the globin chain or chains that are deficient, but their clinical severity is usually related to the specific type of globin-chain defect and the degree of impairment that results from the defect (Table 2). The beta-thalassemias, so named because of the decreased synthesis of the gene product (β⁺) or the complete absence of the gene product (β⁻), are clinically subdivided into the heterozygote state (thalassemia minor) and the homozygous states (thalassemia major and thalassemia intermedia).

The pure alpha-thalassemias—unlike the beta-thalassemias, which cover a wide spectrum of clinical presentations, due basically to the variability of the β⁺ gene output in individuals—seem to fall into four relatively distinct categories (Table 2). These are listed in order of clinical severity: (1) the silent carrier state, (2) α-thalassemia trait, (3) hemoglobin-H disease, and (4) hydrops fetalis. Recent genetic evidence suggesting a duplication of alpha genes on each number-16 chromosome enables ex-
plation of these clinical conditions as 1, 2, 3, and 4 gene-product defects, respectively.
A number of other specific thalassemias have been reported, most of which represent combinations of gene defects. The most significant of these is β-thalassemia, which, in the homozygous state, usually presents as thalassemia intermedia and can be recognized electrophoretically by the presence of 100 percent fetal hemoglobin (α2γ2).

PATHOPHYSIOLOGY
The basic pathophysiology of these disorders is, for the most part, a direct consequence of the interaction of the anemia, the massive ineffective erythropoiesis, and the body’s attempt to maintain homeostasis. Since β-thalassemia major (Cooley’s anemia, Mediterranean anemia) has received the most investigative attention and since it is the most clinically significant thalassemia seen routinely in the United States today, the following discussion will refer primarily to that prototypical form.

Although β-thalassemia can be detected in utero if prenatal diagnosis is carefully performed, the diagnosis of β-thalassemia major is usually not made until the third month of life, when the normal physiologic anemia of the newborn not only fails to resolve but becomes progressively worse. As would be expected by the negligible contribution of the β-globin chain to the total hemoglobin of the fetus, hemoglobin values at birth are usually within the normal range. It is not until normal adult hemoglobin production begins to compensate for the loss of fetal cells that the abnormality becomes apparent. Since the “switch” usually occurs at two to three months of age, detection of the disease on purely clinical grounds before that time is unusual. Actually, in an occasional case, the “switch” from fetal to adult hemoglobin production is delayed, and this results in a coincident delay in diagnosis.

Once the hemoglobin value drops below 7–8 gm./100 ml., the body’s homeostatic mechanisms come into play. The bone marrow is called upon to “crank up” the production of red cells in an attempt to reverse the anemia. Since most of the red cells produced never reach the circulation, the anemia is not corrected and additional sites of potential red-cell production are recruited into action. But the peripheral hemoglobin concentration continues to fall. Eventually, every available hematopoietic region is fully employed in attempting to make enough decent red cells to maintain as high a peripheral hemoglobin concentration as possible.

Often the best the body is able to do is produce a peripheral hemoglobin of 1–2 gm./100 ml. Occa-
### Table 2

**CLINICAL CLASSIFICATION OF THE THALASSEMIAS**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-thalassemias</strong></td>
<td></td>
</tr>
<tr>
<td>Beta-thalassemia trait</td>
<td>Mild anemia with microcytosis and hypochromia</td>
</tr>
<tr>
<td>Severe beta-thalassemia (Cooley’s anemia)</td>
<td>Severe anemia, growth retardation, hepatosplenomegaly, bone-marrow expansion, and bone deformities</td>
</tr>
<tr>
<td>(a). Thalassemia major</td>
<td>Transfusion-dependent</td>
</tr>
<tr>
<td>(b). Thalassemia intermedia</td>
<td>No regular transfusion requirement</td>
</tr>
</tbody>
</table>

| **Alpha-thalassemias**       |                                                                                 |
| Silent carrier (1-locus defect) | Hematologically normal                                                          |
| Alpha-thalassemia trait (2-locus defect) | Mild anemia with microcytosis and hypochromia                                   |
| Hgb-H disease (3-locus defect) | Moderately severe hemolytic anemia, icterus, and splenomegaly                   |
| Hydrops fetalis (4-locus defect) | Death in utero due to severe anemia                                             |

sionally, because of the presence of some ameliorating factor, such as an increase in fetal hemoglobin production or the inheritance of two relatively high-output $\beta^+$ genes, patients are able to stabilize at 6-9 gm./100 ml. (thalassemia intermedia).

Unfortunately, the price the body pays in maintaining a state of chronic maximum hematopoiesis is considerable. Since every possible site for hematopoiesis is utilized, bone marrow expands at the expense of cortical bone. Long bones demonstrate this abnormality most strikingly and become weak and prone to pathologic fracturing (Figure 2). The skull is classically affected in this marrow-expansion process and presents radiologically with a “hair-on-end” appearance (Figure 3). Involvement of the facial bones produces the characteristic thalassemia facies, with prominent orbital separation and maxillary overbite. In addition, the liver and spleen become sites for extramedullary hematopoiesis and enlarge massively.

To support this tumorlike expansion of the bone marrow, blood volume is increased, caloric requirements are enhanced dramatically, and a [continued](#)

![Figure 2](image1.png)  
**Figure 2.** Right arm of patient with Cooley’s anemia.

![Figure 3](image2.png)  
**Figure 3.** Roentgenogram of skull of child with Cooley’s anemia. The diploic spaces are widened, with prominent vertical trabeculae (“hair-on-end” appearance). Note overgrowth of the maxilla.
larger percentage of iron is absorbed from the diet. Classically, untreated patients die in the first few years of life of the consequences of their severe anemia — severe high-output congestive heart failure or massive pulmonary infection brought about by chronic inactivity. Fortunately, since the institution of chronic transfusion regimens, in 1964, this classic pathology is rarely seen today.

In place of the classic pathophysiology, the consequences of chronic transfusion regimens have now become the limiting factors in survival. Specifically, since man has no intrinsic mechanism for excreting excess quantities of iron, the small amount of iron deposited in the body when a red cell dies is retained in the system. The cumulative effect of the iron deposition is generally pan-organ siderosis (Table 3).

Although every tissue in the body is capable of producing small amounts of apoferritin (i.e., molecules that are able to store unneeded, potentially toxic iron), the never-ending deposition of new iron soon overwhelms the system and begins to produce the classic toxic side effects of siderosis. The organs primarily affected are the liver, the endocrine organs, the pituitary gland, and the heart.

The liver is one of the first organs affected by the disease, as it becomes enlarged at an early age. Siderotic and fibrotic changes can be noted in the first decade of life on biopsy, but overt hepatic disease is rare in the absence of intercurrent hepatitis. Death due to cirrhosis, although reported, is extremely rare.

The first evidence of endocrine failure is usually a retardation in growth and development, which manifests between the ages of 10 and 12 years. Delayed pubescence is the rule rather than the exception in females, and puberty is often never attained in males. Extensive endocrinologic study has suggested that the problem is secondary not to end-organ deposition of iron but, rather, to a pituitary failure in luteinizing- and follicle-stimulating-hormone production coupled with a reported decrease in somatomedin production. Other significant endocrine abnormalities are usually limited to the pancreas, where insulin production may be severely impaired. More than 50 percent of patients demonstrate abnormal glucose tolerance curves by the age of 10, and many of these later develop overt insulin-dependent diabetes.

Despite all the peripheral problems discussed above, cardiac dysfunction accounts for more than 90 percent of the deaths reported in this patient population. These dysfunctions may range from the usually annoying yet self-limiting nonrestrictive pericarditis to the more common causes of death — severe arrhythmia and intractable congestive heart failure. Cardiac disease may affect children at any age, but most patients do not succumb to its complications until their late teens or early 20s.

**THERAPY**

Since thalassemia is primarily a disease of globin-chain synthesis, therapy revolves around transfusion regimens. Transfusion programs that constantly maintain near-normal hemoglobin levels will, therefore, restore most of the body's homeostatic mechanisms to normal. Early growth and development, bone structure, blood volume, and organ size will normalize under such conditions. However, maintenance of peripheral hemoglobin values in the "normal" range at all times does require the administration of rather large quantities of packed red-blood cells at routine intervals. This, in turn, leads to an acceleration in the rate of iron deposition and its coincident pathologic. Appropriate therapeutic regimens, therefore, focus on both the maintenance of adequate hemoglobin concentrations by transfusion and the treatment of the severe iron overload with appropriate chelating agents (Table 4).

**Transfusion therapy.** The precise level above which hemoglobin values should be maintained is still controversial. Initial investigations determined that levels above 7.5-9 gm./100 ml. were adequate. Recent evidence, however, suggests that patients be maintained above 10 gm./100 ml. chronically, and some investigators have begun advocating 12 gm./100 ml. as the "trigger point" for transfusion. The latter regimens have the obvious advantages of mimicking the normal physiologic state. It is interesting to note that the very high-transfusion regimens ("supertransfusion regimens") do not require more red cells than do less aggressive regimens because they lead to a decrease in total-body blood volume.

Optimally, each transfusion should consist of 10-15 cc./kg. of compatible washed, frozen, packed red cells, administered over four to six hours on an outpatient basis. Administration of the cells at a rate in excess of that described above runs the risk of precipitating an episode of fluid overload and congestive heart failure. Transfusions usually are required at four-to-five-week intervals to maintain hemoglobin values above the "trigger point."

If, based on theoretic considerations of blood volume and red-cell survival, the administration of a seemingly adequate quantity of packed red cells
TABLE 3

CLINICAL FEATURES OF TYPICAL β-THALASSEMIA-MAJOR PATIENT CHRONICALLY TRANSFUSED

<table>
<thead>
<tr>
<th>Feature</th>
<th>Age at onset</th>
<th>Suspected causative agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>2-3 months</td>
<td>Failure of normal hemoglobin synthesis</td>
</tr>
<tr>
<td>Bone-marrow expansion</td>
<td>6 months</td>
<td>Body's attempt to compensate for chronic anemia</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>3-12 months</td>
<td>Extramedullary hematopoiesis</td>
</tr>
<tr>
<td>Increased iron absorption</td>
<td>36 months</td>
<td>Anemia</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>8-10 years</td>
<td>Somatomedin&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>12-16 years</td>
<td>Folic acid-stimulating hormone and lutenizing-hormone response</td>
</tr>
<tr>
<td>Liver fibrosis</td>
<td>5 years</td>
<td>Iron deposition</td>
</tr>
<tr>
<td>Chemical diabetes</td>
<td>10 years</td>
<td>Iron deposition</td>
</tr>
<tr>
<td>Nonrestrictive pericarditis</td>
<td>Less than 10 years</td>
<td>Iron deposition</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>Less than 10 years</td>
<td>Iron deposition</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Less than 12 years</td>
<td>Iron deposition</td>
</tr>
</tbody>
</table>

does not result in a four-to-five-week interval between transfusions, extensive evaluation is indicated. Among the possible causes of such a situation are (1) the administration of old or somehow defective red cells, (2) the development by the patient of an antibody, (3) hypersplenism, and (4) concurrent gastrointestinal blood loss.

Since further decreasing the rate of iron accumulation should theoretically slow the development of siderosis, attempts at obtaining and administering units of relatively young red cells (“neocytes”) have been made by one investigator. By using a continuous-flow cell separator, he is able to obtain from a normal donor a unit of red cells with a mean cell age of 12 days. These “neocytes” have prolonged chromium survivals and are able to effectively increase the interval between transfusions from four weeks to seven weeks, significantly decreasing the rate of iron accumulation in the recipient.

Chelation therapy. Since the body is unable to excrete excess iron stores, investigators have used a variety of chelating agents in an attempt to effect the specific excretion of significant amounts of iron. Deferoxamine (Desferal), a trihydroxamic acid that has been used successfully in acute iron poisoning, was initially administered intramuscularly on a daily basis in order to determine its chronic efficacy. The results of these trials were somewhat equivocal, because this method of administration did not result in the excretion of sufficient quantities of iron. Recently, however, the method of administration of the deferoxamine has been altered to markedly enhance its effectiveness in removing iron. Deferoxamine, in doses of 20-50 mg./kg./day, is diluted in 3-5 cc. of sterile water and administered as a constant subcutaneous infusion over 10 to 14 hours daily. The medication is placed in a normal 3- or 5-cc. syringe and administered through a 27-gauge connecting set. continued

TABLE 4

THERAPY FOR β-THALASSEMA MAJOR

Transfusion
10-15 cc./kg. of body weight, packed red cells, administered at four week intervals. Goal: to maintain hemoglobin values above 12 gm./100 ml.
Frozen cells decrease the incidence of transfusion reactions.

Neocytes, if available, make it possible to increase interval between transfusions to seven weeks.

Chelation
20-50 mg./kg./day deferoxamine, dissolved in 3-5 cc. sterile water, administered constantly for 12-hour period daily, on outpatient basis (see text). Goal: to achieve excretion of more iron in urine than patient has received.
Supplementary doses of ascorbic acid, administered orally at 2 mg./kg./day, assures maximum possible deferoxamine-induced urinary iron excretion.

Splenectomy
Spleen should be removed without delay after hypersplenism develops.
Polyvalent pneumococcal vaccine administered as precaution.
Prophylactic penicillin administered at 250 mg./day.
whose needle is placed daily by the patient in the subcutaneous tissue of the anterior abdominal wall. The syringe is placed in a small, portable infusion pump, which is usually worn by the patient on a belt. In order to minimize the overall effect on life style, the Auto-Syringe is usually worn from approximately 7 P.M. to 7 A.M. daily (Figure 4).

Under this system, all patients over five years of age studied to date have been shown to excrete more iron in their urine than they accumulate on a mean daily basis. Since deferoxamine also effects a variable but significant excretion of iron from the gastrointestinal tract, iron-excretion measurements underestimate the total amount of iron removed from the body. However, 24-hour urine samples are easy to collect on an intermittent basis and allow approximate calculations of the net rate of iron removal (Figure 5). In this way, comparison of the rate of transfusional iron accumulation (approximately 180 mg. of iron per unit of blood) with the mean daily urinary excretion allows the physician to note changes over time that might reflect growth of the patient and require deferoxamine adjustments. All of the above conclusions are based on the assumption that patients placed on deferoxamine have adequate stores of ascorbic acid. If such stores are not adequate, Desferal-induced urinary iron excretion may be markedly reduced. To assure maximum efficacy of deferoxamine administration, most patients are automatically placed on minimal doses of supplemental oral ascorbic acid (2-3 mg./kg./day).

Figure 4. Portable infusion pump enables this child to receive constant subcutaneous infusion of deferoxamine on an outpatient basis. Device is usually worn from 7 P.M. to 7 A.M.

Splenectomy. The other therapeutic aspects of the disease concern the spleen. Since this organ tends to act as both a filter and a reticuloendothelial depository for iron, it is intimately operative in both red-cell survival and iron storage. Although it is not yet known what role the splenic iron deposits play in the chelation schema, it is apparent that most patients who are chronically transfused develop evidence of hypersplenism within the first five to eight years of life. When this occurs, red-cell survival is decreased below expected values and more frequent transfusions than anticipated are required. This, in turn, leads to an increase in the rate of iron accumulation. Splenectomy is the treatment of choice and should not be unduly delayed. Postoperatively, hematologic values return to their prehypersplenic state in most patients. The risk of this type of surgery is minimal in experienced hands, and most patients are subsequently placed on daily oral penicillin prophylaxis at a dose of 250 mg. In addition, all patients receive the added protection of the recently available polyvalent pneumococcal vaccine, Pneumovax. Initial reports indicate that whether this is administered before or after splenectomy does not seem to affect the resulting antibody titer. As a further precaution, primarily against Hemophilus influenzae infection, fevers are diagnosed as diligently as possible. If there is any significant delay between the onset of fever and the determination by the physician, we advise patients to begin taking readily absorbable oral amoxicillin, 10 mg./kg. three times a day.

Figure 5. Urinary iron excretion possible with various deferoxamine doses.

**MANAGEMENT OF IRON OVERLOAD**

If adequate chelation therapy is instituted too late to prevent some of the complications of iron...
overload or if these complications develop after the institution of therapy, aggressive medical management is indicated. In our experience, the historical bias suggesting that therapy is primarily palliative is not defensible. We have found that aggressive therapy—with digitalis and diuretics in the case of congestive heart failure; digitalis, quinidine, procaïnamide, or disopyramide phosphate (Norpace) in the case of arrhythmia; and insulin in the case of diabetes—is often able to normalize function over a prolonged period.

THALASSEMIA INTERMEDIA

Thalassemia intermedia is clinically described as classic thalassemia major in which the patient is able to produce just enough circulating red cells to maintain hemoglobin concentrations compatible with life. Genetically, these cases usually require the inheritance of two relatively high $\beta^+$-thalassemia genes; the inheritance of a $\delta\beta$-thalassemia gene, which subsequently leads to the production of high levels of fetal hemoglobin; or the concurrent inheritance of both $\beta$-thalassemia and $\alpha$-thalassemia. This combination decreases the relative imbalance in globin chain synthesis and decreases the hemolytic components of the disease.

Historically, these patients presented at an age of six months to three or four years with a severe anemia, jaundice, and some mild degree of growth failure. Under optimal conditions, these patients are able to maintain circulating hemoglobins greater than 6.0 gm./100 ml. without transfusion. However, the price paid in the expansion of available hematopoietic tissue is extensive. Frontal bossing, massive hepatosplenomegaly, and thin long-bone cortices are common and are the result of the tremendous expansion of the erythron. Red cell turnover is so accelerated that patients develop hyperbilirubinemia in the absence of any overt liver damage and often require folic-acid supplementation. Since the bone marrow is barely able to main-

tain a viable circulating red-cell pool, patients must be closely observed for aplastic or hemolytic crises that are often associated with infections. If unattended to, these bouts may accelerate the anemia and lead to congestive failure or death.

Packed—red-cell transfusions during such episodes are not infrequently required to maintain hemoglobin levels above 7 gm./100 ml. Occasionally, patients with thalassemia intermedia will suddenly develop a chronic transfusion requirement. In such cases, overt hypersplenism is often to blame. Usually this is accompanied by a characteristic fall in the platelet count to fewer than 100,000/cu. cm. and a coincident fall in the circulating white-cell count to a normal level from the previously high 12,000-30,000 range. Splenectomy and the acute institution of a transfusion regimen are the treatments of choice. The surgery is usually followed by an abrupt rise in platelet count to 1,000,000 and a coincident rise in white-cell count, nucleated red cells, and reticulocyte count. In addition, such a procedure results in a leveling off of the peripheral hemoglobin values at a slightly higher level than seen presurgically. General postsplenectomy precautions (described above) should be initiated immediately after surgery.

REFERENCES