MANAGEMENT OF SICKLE CELL DISEASE

MARTIN H. STEINBERG, M.D.

One of every 600 black people in the United States has sickle cell anemia. In addition, sickle cell–hemoglobin C disease and sickle cell–β-thalassemia, which are other common genotypes of sickle cell disease, together are as common as sickle cell anemia. Sickle hemoglobin (hemoglobin S, αβ₆) accounts for over half the hemoglobin in patients with these disorders. Eight percent of black Americans are heterozygous carriers of the sickle cell trait; about 40 percent of their hemoglobin is hemoglobin S. They do not have anemia and need neither treatment nor occupational restrictions. About 5 percent have hematuria at some time and most cannot concentrate their urine, but these are clinically unimportant abnormalities.¹²

PATHOPHYSIOLOGY

Sickle hemoglobin has the singular property of forming polymers when deoxygenated. On deoxygenation, there is a delay ranging from milliseconds to seconds before hemoglobin S polymers can be detected, after which they accumulate rapidly. The length of the delay varies among erythrocytes containing hemoglobin S and is exquisitely dependent on the concentration of hemoglobin S. This observation implies that small reductions in the concentration of hemoglobin S might have important clinical benefits.⁴ Sickle cell trait is benign, because the cellular concentration of hemoglobin S is too low for polymerization to occur under most conditions, and it is hemoglobin S polymers that cause the cellular injury responsible for the clinical manifestations of sickle cell disease (Fig. 1).

Among hemolytic anemias, the vaso-occlusive features of sickle cell disease are unique. By occluding small blood vessels and sometimes large ones, sickle cells cause vascular injury. No single mechanism explains the vaso-occlusion; its cause may be different from event to event, and its severity differs among patients. The complexity of the process of vaso-occlusion provides many possibilities for therapeutic intervention (Fig. 1). One reason for the complexity is that in persons with sickle cell disease the erythrocytes contain varying amounts of different types of hemoglobin, especially fetal hemoglobin (hemoglobin F). Vaso-occlusion is initiated and sustained by interactions among sickle cells, endothelial cells, and constituents of plasma. Deoxygenation of sickle cells induces potassium efflux, which increases cell density and the tendency of hemoglobin S to polymerize.⁵⁻⁸ Adhesive interactions between sickle cells and endothelial cells occur as a result of injury to cell membranes.⁹ As sickle cells perturb the endothelium, the balance of vasodilators and vasoconstrictors may be changed to favor vasoconstriction.¹⁰ The adherence of sickle cells to endothelial cells may slow blood flow enough that the successive processes of hemoglobin S polymerization, cell sickling, and vaso-occlusion occur before the passage of blood through the microvessels is completed.

High granulocyte counts are a risk factor for death in sickle cell anemia.¹¹ Granulocytes interact with sickle cells and endothelial cells and are stimulated to release injurious cytokines.¹²⁻¹³ Activated platelets release thrombospondin, which promotes the adherence of sickle cells to endothelial cells.¹⁴ Reticulocytes that are prematurely released from the bone marrow (“stress” reticulocytes) in hemolytic disease display additional adhesive ligands that facilitate interactions between sickle cells and endothelial cells.¹⁴⁻¹⁸

CLINICAL FEATURES

Vaso-occlusion, which is responsible for most of the severe complications of sickle cell disease, can occur wherever blood flows (Table 1). Sickle cell disease is a chronic disease that is punctuated by acute events and that shortens life. Chief among the clinical features of sickle cell disease are acute episodes of severe pain in the chest, back, abdomen, or extremities (crises). Multiple areas are often involved simultaneously, and symmetric involvement of the extremities is common. The episodes last for days or even weeks. The acute chest syndrome, a frequent and sometimes fatal complication of sickle cell disease, affects about 40 percent of all people with sickle cell anemia. It is most common but least severe in children, can occur postoperatively, and when recurrent, can lead to chronic respiratory insufficiency. Its cardinal features are fever, pleuritic chest pain, referred abdominal pain, cough, lung infiltrates, and hypoxia.

The many complications of sickle cell disease (Table 1), which vary widely among patients, are vexing for both the patients and their physicians. Yet there is reason for optimism. In industrialized countries, patients with sickle cell disease now survive into their fifth and sixth decades.¹¹ The widespread use of penicillin for...
prophylaxis, newer transfusion regimens, and possibly, hydroxyurea treatment may further lengthen life.

PRINCIPLES OF TREATMENT

Treatment for sickle cell disease is evolving. The following sections discuss established treatments directed at disease complications, newer treatments that often target disease mechanisms, and emerging treatments.

**General Measures**

The chances of having children with sickle cell disease and the feasibility of antenatal diagnosis should be clearly explained to couples at risk. Neonatal screening can identify infants with sickle cell disease and direct their parents to comprehensive care programs. Early in life, when the risk of infection is highest, counseling parents about the importance of immunizations and penicillin prophylaxis, the detection of an enlarging spleen, and the dangers of fever and increasing pallor may be lifesaving. Periodic visits to the physician should concentrate on education, health maintenance, and control of blood pressure.

Pneumococcal sepsis is a leading cause of death among infants with sickle cell anemia, because a damaged spleen cannot clear pneumococci from the blood. One study found an 84 percent reduction in pneumococcal sepsis among children given 125 mg of penicillin prophylactically twice daily from two or three months to three years of age, followed by 250 mg twice daily until five years of age. Older children and children with sickle cell–hemoglobin C disease who have normal splenic function do not routinely need penicillin prophylaxis. Vaccination against *Streptococcus pneumoniae* with the 23-valent vaccine is recommended for children at two years of age, with booster doses at five years of age. Many reports of infection even after vaccination indicate that protection is imperfect, and the increasing frequency of penicillin resistance heightens the urgent need for an effective vaccine.

Conjugate vaccines are more immunogenic than the standard vaccine, but their clinical effectiveness has not been tested. Even vaccinated children for whom penicillin prophylaxis is prescribed can die of pneumococcal sepsis, perhaps because they do not take their medication faithfully. Splenic atrophy and dysfunction underlie the childhood propensity to infection with encapsulated bacteria. Infection with gram-negative organisms is common among adults. Antibiotics are often

**Figure 1. Pathophysiology of Sickle Cell Disease.**

In hemoglobin S, a substitution of T for A in the sixth codon of the \(\beta\)-globin gene leads to the replacement of a glutamic acid residue by a valine residue. On deoxygenation, hemoglobin S polymers form, causing cell sickling and damage to the membrane. Some sickle cells adhere to endothelial cells, leading to vaso-occlusion.
used in patients with febrile episodes or the acute chest syndrome. Folic acid (1 mg daily) should be prescribed to prevent megaloblastic erythropoiesis.

Military recruits carrying the sickle cell trait who participated in basic training — an especially harsh conditioning experience — had an incidence of sudden, unexplained death 20 times that of recruits with normal hemoglobin. This increase may be due to exertional heat illness. In these subjects, and certainly in persons with sickle cell disease, conditioning should be gradual, with plentiful fluid intake and avoidance of overexertion.

TREATMENT DIRECTED AT THE RELIEF OF SYMPTOMS

Painful Episodes

In a given year, about 60 percent of patients with sickle cell anemia will have an episode of severe pain. A small minority of patients have severe pain almost constantly. These differences are one manifestation of the heterogeneity of this disease, which complicates the choice of treatment. Episodes of pain are sometimes triggered by infection, extreme temperatures, or physical or emotional stress, but more often they are unprovoked and begin with little warning.

Patients with severe pain should be given an opiate parenterally at frequent, fixed intervals, not as needed, until the pain has diminished, at which time the dose of the opiate can be tapered and then stopped and oral analgesic therapy can be instituted. Pain should be assessed frequently with use of pain-measurement scales to guide the intensity of treatment. Some patients, however, prefer patient-controlled analgesia. Management of constant pain is extremely difficult, and expert advice should be obtained. Most patients who have episodes of acute pain are neither drug addicts nor drug seekers. Reliable patients can be given oral analgesic drugs such as acetaminophen with codeine to take at home. There is no standard method for treating episodes of acute pain, but one approach is outlined in Table 2.

Transfusion

Transfusions are not needed for the usual anemia or episodes of pain associated with sickle cell disease. Urgent replacement of blood is often required for sudden severe anemia occurring in children when blood is sequestered in an enlarged spleen or when parvovirus B19 infection causes a transient aplastic crisis. Hy-
oxia accompanying the acute chest syndrome necessitates transfusion and oxygen treatment. Whether exchange transfusion is superior to simple transfusion in patients with hypoxia is not clear. Patients with renal failure, even if it is mild, sometimes have symptomatic anemia requiring transfusion. In some of these patients, treatment with erythropoietin (epoetin) can restore hemoglobin concentrations to levels that were found before the occurrence of renal failure.34

Recent clinical trials have evaluated the efficacy of transfusion in patients with some complications of sickle cell disease (Table 3).35,36 Repeated transfusions reduce the risk of recurrent stroke in children with sickle cell anemia. About 50 percent of children with sickle cell anemia and stroke who do not receive transfusions have another stroke within three years, as compared with about 10 percent of those who receive transfusions.25 The aim of transfusion is to reduce the hemoglobin S concentration rapidly to less than 30 percent of the total hemoglobin concentration and to maintain this percentage for three to five years. Exchange transfusion is the most rapid method. Reducing the frequency of transfusion and permitting the hemoglobin S concentration to rise to 50 percent of the total hemoglobin concentration after four years of intensive transfusion appears to be reasonable.37 Because of vascular damage, intracerebral hemorrhage, which cannot be prevented by prophylactic transfusion, may occur years after the original stroke.

A two-year trial has been completed of prophylactic transfusion in children 2 to 16 years of age who were screened by transcranial Doppler ultrasonography of cerebrovascular blood flow and found to be at high risk for an initial stroke.36 Strokes occurred in 11 of 67 children randomly assigned to receive standard care (16 percent), as compared with 1 of 63 children given prophylactic transfusions to reduce their hemoglobin S concentrations to below 30 percent (2 percent).

Should all children with sickle cell anemia be screened — perhaps twice a year — for abnormalities in cerebrovascular blood flow by transcranial Doppler ultrasonography, and should those with vascular disease that places them at high risk for stroke receive transfusions? It is likely that a hemoglobin S concentration of less than 30 percent of total hemoglobin will prevent not only stroke but also other complications, although the amount of reduction in hemoglobin S that strikes the best balance between therapeutic benefits and complications of transfusion has not been determined. Transfusion is not innocuous. Twenty to 30 percent of patients with sickle cell anemia who receive blood transfusions become alloimmunized.25,38 For this reason, leukocyte-depleted erythrocytes, phenotypically matched for the antigenic determinants that most often elicit an immune response, are preferred for transfusion. Moreover, infections may be transmitted by transfusion, and iron accumulates in vital organs. In the two-year trial of prophylactic transfusion, the mean serum ferritin concentration increased from 164 to 2509 ng per milliliter after two years of transfusions.25,38 Effective iron chelation is arduous, and compliance is generally suboptimal.

The hazards of transfusion, and the fact that the majority of patients at high risk do not have a stroke during a given year, must be weighed against the benefits of transfusion. If transfusions are given, how long should they be continued? When transfusions are stopped, are patients again at risk for stroke? These questions cannot be answered now. Methods of transcranial Doppler ultrasonography must be carefully standardized to determine which patients should receive transfusions and which should not.

For patients undergoing general anesthesia, increasing the hematocrit to about 30 percent by preoperative transfusion prevented postoperative complications as effectively as reducing the fraction of hemoglobin S to 30 percent of total hemoglobin by aggressive exchange transfusion, and was associated with half as many transfusion-related complications (Table 4).38 Routine intrapartum transfusions are not indicated.36

**TREATMENT DIRECTED AT THE PREVENTION OF COMPLICATIONS**

**Hydroxyurea**

Nearly 50 years of clinical and basic research have established that high hemoglobin F concentrations reduce the severity of sickle cell disease by preventing
droxyurea does both. Mia and thus ameliorate their disease clinically. Hy-
tination of hemoglobin F in patients with sickle cell ane-
whether drug treatment could increase the produc-
tion of hemoglobin S–containing erythrocytes became less dense,
and aerobic cardiovascular fitness. In other studies, mostly in chil-
dren, hydroxyurea was associated with mean hemoglo-
in F concentrations of 15 to 20 percent of total hemoglobin.

To some extent, it is possible to predict which pa-
tients will have a response to hydroxyurea. Adults with higher granulocyte and reticulocyte counts and larger treatment-associated decreases in these counts tended to have greater increases in hemoglobin F production. Those with the greatest reduction in the numbers of granulocytes, monocytes, and retic-
ulocytes also had the greatest reduction in the fre-
quency of painful episodes. In patients for whom hydroxyurea was less effective, not only the hemo-
globin F values but also the blood counts changed
little from base line, suggesting that the response to hydroxyurea depends on the capacity of the bone
marrow to withstand moderate doses of the drug. Studies of hydroxyurea in young children or ado-
escents are just beginning, and data from fewer than 200 children with clinically severe sickle cell disease who have been treated with hydroxyurea have been reported. Most were teenagers treated in pilot studies, but 25 patients from 2 to 22 years of age (median, 9) were treated with drug or placebo in a single-blind crossover study.

In other studies, hydroxyurea reduced the adher-
eence of sickle cells to endothelium in vitro and in-
creased the length of time to polymerization. Counts of total reticulocytes and “stress” reticulo-
cytes fell in patients with sickle cell anemia or sickle

In some other studies, the formation of hemoglobin S polymers. The benefi-
cial effects of high hemoglobin F concentrations in sickle cell disease stimulated studies to determine whether drug treatment could increase the produc-
tion of hemoglobin F in patients with sickle cell ane-
mia and thus ameliorate their disease clinically. Hy-
droxyurea does both. Initially, it was thought to act
solely by increasing hemoglobin F concentrations, but further studies suggested that the related reduction in neutrophils, monocytes, and reticulocytes may also be clinically important (Fig. 2). Hydroxyurea also raises
the total hemoglobin concentration slightly.

A double-blind, placebo-controlled trial of hydroxy-
urea in 299 adults with sickle cell anemia, who had had at least three episodes of pain in the year pre-
ceding the study, was terminated early, after an av-
erage of 28 months of treatment, because hydroxy-
urea reduced the frequency of episodes of pain, the
crude chest syndrome, and hospitalization and the
need for blood transfusion. Some patients also had
increases in their anaerobic muscular performance and
acrobic cardiovascular fitness. The hemoglo-
in S–containing erythrocytes became less dense,
and hemolysis was reduced. These changes and the
reduction in painful episodes preceded the increase
in the hemoglobin F concentration.

**Table 4. Perioperative Management of Sickle Cell Disease.**

<table>
<thead>
<tr>
<th>Perioperative period†</th>
</tr>
</thead>
</table>
| Admit to hospital 12 to 24 hr before surgery to allow opti-
| timal hydration with intravenous fluids. |
| Perform pulmonary-function testing and treat any ob-
| structive disease with a bronchodilator. |
| Perform transfusion to increase the hematocrit to 30 per-
| cent before all operations except minor procedures |
| performed under local anesthesia. |
| Intraoperative period |
| Monitor oxygen therapy with pulse oximetry. |
| Maintain hydration. |
| Prevent hypothermia. |
| Monitor blood loss and replace blood when necessary. |
| Postoperative period |
| Perform pulse oximetry until patient is awake. |
| Continue giving fluids for hydration. |
| Perform incentive spirometry. |
| Consider overnight observation.‡ |

*Recommendations apply to patients with sickle cell anemia, sickle cell–hemoglobin C disease, and sickle cell–
β-thalassemia who are scheduled to undergo surgery under general anesthesia or eye surgery (except for laser photo-
coagulation). Data on perioperative complications in pa-
tients with sickle cell–hemoglobin C disease and sickle cell–
β-thalassemia are limited.

†Subjects with the sickle cell trait do not require preoper-
ative transfusions, except possibly before open-heart surgery or extensive lung surgery.

‡Since the acute chest syndrome, a severe postoperative
complication, has its peak occurrence 48 hours after opera-
tion, a prolonged postoperative observation is desirable. In-
traoperative desaturation may cause postoperative acute
chest syndrome.
not yet know the long-term effects of hydroxyurea. Is it mutagenic, carcinogenic, or leukemogenic? To date, no chromosomal breakage, recombination events, or mutations in the p53, N-ras, K-ras, or hypoxanthine phosphoribosyltransferase genes have been identified. Acute leukemia develops in about 5 to 10 percent of patients with polycythemia vera, a neoplastic myeloproliferative disease, who are treated with hydroxyurea. This incidence of leukemic transformation may be greater than that in similar patients treated with phlebotomy alone.58,59 Hydroxyurea has been given for more than five years to 64 children with cyanotic congenital heart disease without any report of tumors.60 To date, leukemia or cancer has not occurred in patients with sickle cell anemia who have been treated with hydroxyurea, but fewer than 300 patients have been treated for five years. We do not know whether this drug has adverse effects on growth and development in children, although none have yet been reported,55 or whether continued treatment starting at a very young age will pose other hazards. If there is a risk of carcinogenesis with hydroxyurea, it is probably a small one. Furthermore, assuming a small risk, the benefits of this treatment in many seriously ill patients may outweigh the risk of tumor development in a few of them.

We hope, but do not currently know, that hydroxyurea will prevent organ damage, restore function to organs that are already injured, and reduce mortality from sickle cell disease, in addition to its hematologic and clinical benefits. Splenic regeneration has been reported in two adults with sickle cell anemia who had hemoglobin F values of about 30 percent during treatment with hydroxyurea.61 Bone marrow transplantation and hypertransfusion may also re-

Figure 2. Mechanisms of Action of Hydroxyurea in Sickle Cell Disease.

By selectively killing cells in the bone marrow, hydroxyurea increases the number of erythroblasts that produce hemoglobin F. It has no known direct effects on gene expression. Bone marrow cellularity may also be diminished. Higher concentrations of hemoglobin F reduce the polymerization of hemoglobin S and the numbers of deformed, dense, and damaged erythrocytes. Cells with a high hemoglobin F content survive longer, attenuating hemolysis and leading to a reduction in reticulocyte counts. The numbers of circulating granulocytes, monocytes, and platelets are diminished. The likelihood of vaso-occlusion is reduced by the reduction in the number of dense, poorly deformable erythrocytes that can adhere to and perturb the endothelium.
Hydroxyurea should be reserved for patients with sickle cell anemia who have complications that are sufficiently severe to justify the burdens of treatment and who can comply with the treatment regimen (Table 5). Therapy should be started with 500 mg of hydroxyurea, or 10 to 15 mg per kilogram of body weight, daily. (About 10 percent of patients cannot tolerate a dose of 10 mg per kilogram, and in such cases the dose must be reduced.) After six to eight weeks of treatment, the dose may be increased to 1000 mg per day if blood counts are stable. Most patients who have a response to hydroxyurea maintain acceptable blood counts at doses between 1000 and 2000 mg daily (20 to 30 mg per kilogram). The recent availability of hydroxyurea in 200-mg, 300-mg, and 400-mg capsules should allow more precise adjustment of doses. The balance between hematologic toxicity (indicated by reductions in the granulocyte or platelet count) and increases in hemoglobin F values determines the optimal dose of hydroxyurea. Increasing values for the mean corpuscular volume parallel the rise in hemoglobin F concentrations, making the mean corpuscular volume a useful, inexpensive surrogate for the hemoglobin F concentration during therapy.

Until a stable dose is achieved, blood counts should be monitored every two weeks. Even when the optimal dose is reached, counts should be checked at four-to-six-week intervals to forestall complications from the occasional, unpredictable fall in the granulocyte or platelet count. In 10 to 25 percent of adult patients, hydroxyurea treatment does not cause an increase in hemoglobin F, perhaps because of abnormal bone marrow, genetic factors, or variations in drug metabolism.43,53,66 When treatment is begun, patients should be counseled that not all patients have a response, that the response differs among patients, that many months may be needed to find the best dose of the drug, that the drug must be taken as directed with frequent blood tests, and that the long-term toxic effects and benefits of treatment are unknown.

Transplantation

Bone marrow transplantation as a treatment for sickle cell anemia was first used in Europe for patients from Africa, on the assumption that the risks of disease in their countries of origin justified the hazards of transplantation.67 These patients did well, and since then additional patients have undergone transplantation in Europe and the United States.68-74 Children and adolescents younger than 16 years of age who have severe complications (stroke, recurrent acute chest syndrome, or refractory pain) and have an HLA-matched donor available are the best candidates for transplantation. About 1 percent of patients with sickle cell anemia meet these requirements.75 About 100 patients with sickle cell anemia

---

**Table 5. Hydroxyurea Therapy in Sickle Cell Anemia.***

<table>
<thead>
<tr>
<th>Indication for treatment</th>
<th>Hydroxyurea is indicated for adolescents or adults with frequent episodes of pain, a history of the acute chest syndrome, other severe vaso-occlusive complications, or severe symptomatic anemia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-line evaluation</td>
<td>Obtain blood counts; measure mean corpuscular volume, hemoglobin F concentration, and serum chemical values; test for pregnancy. Ensure patient’s willingness to follow recommendations for treatment. Determine that patient is not receiving repeated transfusions.</td>
</tr>
<tr>
<td>Initiation of treatment</td>
<td>Administer hydroxyurea at a dose of 500 mg (10 to 15 mg per kilogram of body weight every morning) for 6 to 8 weeks; obtain complete blood count every 2 weeks.</td>
</tr>
<tr>
<td>Continuation of treatment</td>
<td>If blood counts are acceptable, increase dose to 1500 mg every morning in increments of 500 mg every 6 to 8 weeks. Failure of hemoglobin F or mean corpuscular volume to increase Consider biologic inability to respond to treatment or poor compliance with treatment. Increase dose very cautiously to 2000 to 2500 mg daily (maximal dose, approximately 35 mg per kilogram).</td>
</tr>
<tr>
<td>Treatment end points</td>
<td>End adjustments to treatment when there is less pain, an increase in the hemoglobin F concentration (or mean corpuscular volume), an increase in hemoglobin concentration if patient has severe anemia, or acceptable myelotoxicity (granulocyte count, ≥2000 per cubic millimeter; platelet count, ≥80,000 per cubic millimeter).</td>
</tr>
</tbody>
</table>

*Special caution should be exercised in treating patients who have compromised renal or hepatic function or who are habituated to narcotics. Contraception should be practiced by both men and women because the effects of hydroxyurea on pregnancy or fetal outcome are not known. After a stable and nontoxic dose of hydroxyurea has been reached, blood counts may be performed at four-to-six-week intervals. Granulocyte counts should be at least 2000 per cubic millimeter and platelet counts at least 80,000 per cubic millimeter. In most patients who respond to hydroxyurea, the hemoglobin concentration increases slightly. A decrease in the hemoglobin concentration or a decrease in the absolute reticulocyte count to less than 80,000 per cubic millimeter should be carefully evaluated. An initial hemoglobin concentration below 5.5 g per deciliter is not a contraindication to treatment.

---

establish splenic function.62,63 However, because splenic tissue has a propensity to regenerate, regrowth may not be a good indicator of the potential for regeneration of other organs.

Hydroxyurea appears to be as effective in patients with sickle cell–β-thalassemia as in those with sickle cell anemia, but only 40 such patients have been treated and the studies were uncontrolled.64,65 In one trial, hemoglobin F values averaged 23 percent after eight months of treatment.64 In the United States, most patients with sickle cell–β+ thalassemia have 20 to 30 percent hemoglobin A and less severe disease than those with sickle cell anemia, and most do not have symptoms that warrant treatment with hydroxyurea.

In pilot studies of six adults with sickle cell–hemoglobin C disease, 1000 mg of hydroxyurea daily increased the mean corpuscular volume and hemoglobin values and reduced reticulocyte counts, “stress” reticulocyte counts, and serum bilirubin concentrations. The density of erythrocytes was reduced, suggesting improved cell hydration.52
have undergone bone marrow transplantation, as compared with more than 800 patients with β-thalassemia. More than 90 percent of the patients with sickle cell anemia survived, 70 to 85 percent had event-free survival, and 15 percent had graft rejection. Neurologic complications (seizures or intracranial bleeding) were common in the first transplant recipients. Careful control of blood counts, blood pressure, and anticonvulsant-drug prophylaxis may forestall these complications. Follow-up is still short, and the full extent of toxicity is unknown. Whether transplantation can reverse established organ damage is also not known, but early reports suggest some improvement in chronic lung, bone, and central nervous system disease. Transplantation of cord-blood stem cells may obviate the need for bone marrow transplantation.

As more beneficial but potentially hazardous treatments become available, it would be of great value to be able to predict the severity of sickle cell anemia. Low hemoglobin F values and the presence of α-thalassemia may predict a severe clinical course. However, in the absence of predictors of prognosis and with the knowledge that modern supportive care can enable most patients to live into their fifth decade, marrow transplantation, which is associated with a short-term mortality of about 10 percent, should be used with caution. Transplantation should be performed only in the context of a clinical trial.

Controlled trials comparing conventional treatment of symptoms and complications, intensive transfusions, hydroxyurea, and transplantation have not been conducted, and therefore the relative values of these treatments are unknown.

**EXPERIMENTAL THERAPY**

**Induction of Hemoglobin F by Short-Chain Fatty Acids**

Short-chain fatty acids such as butyrate appear to modulate gene expression directly by interacting with transcriptionally active elements of the genes. The initial trials of butyrate in patients with sickle cell disease were disappointing. The trials were small, and although some patients had increases in the total hemoglobin concentration, the number of cells containing hemoglobin F, and the hemoglobin F concentration, it was unclear whether the responses were sustained and clinically beneficial. Recently, a new method of giving arginine butyrate in pulse treatments once or twice monthly resulted in an increase in hemoglobin F values to about 20 percent that was maintained for one to two years in six of eight adults with sickle cell anemia. This regimen deserves further study.

**Membrane-Active Drugs**

Reversing cellular dehydration in sickle cell disease should be beneficial, because hemoglobin S polymerization is highly concentration-dependent.

Several drugs block cation-transport channels in erythrocyte membranes and can shift cellular cation content and cell density toward normal values. Clotrimazole, an antifungal drug, reduced cellular dehydration in vitro in transgenic mice with sickle cell disease and in patients with sickle cell anemia. In a recent study of five patients with sickle cell anemia, cell density decreased with doses of clotrimazole that were one eighth to one fifth of those used to treat patients with systemic mycoses. However, the decrease in cell density was small and less than that achieved during hydroxyurea treatment. Magnesium salts also interfere with cation transport and cause cell rehydration. Whether the cellular changes induced by clotrimazole or magnesium salts are of clinical value is not known.

Combinations of hydroxyurea plus clotrimazole and erythropoietin to prevent sickling have been studied in transgenic mice, and pilot studies of these regimens in patients with sickle cell anemia are starting. A few patients have been treated with hydroxyurea plus erythropoietin, with apparent benefit.

**Other Experimental Treatments**

Recent studies have suggested that low levels of nitric oxide can increase the affinity of hemoglobin S for oxygen, an antipolymerization effect that is potentially useful. A non-ionic surfactant compound has been developed that appears to reduce the length of crises, perhaps by inhibiting the adherence of sickle cells to endothelial cells.

**CONCLUSIONS**

Few would argue that hydroxyurea or bone marrow transplantation, as currently applied, is the final word in the treatment of patients with sickle cell disease. The need to study new applications of current treatments and to devise new treatments directed at disrupting multiple facets of the pathophysiology of the disease remains paramount. Investigators are now focusing on gene therapy to inactivate the hemoglobin S gene or its messenger RNA, increase the expression of the hemoglobin F gene, or introduce genes whose products inhibit hemoglobin S polymerization.

While awaiting new treatments for the underlying disease, we should address several practical problems. For example, how should the acute chest syndrome be managed, and which patients should undergo exchange transfusion? How aggressively should blood pressure be lowered to decrease the risk of stroke? Can we better understand the causes of the striking variability in sickle cell disease, so that hazardous treatments can be directed to the patients who are most likely to have the worst disease complications?

A better and longer life for patients with sickle cell disease in developed countries has resulted from basic
and clinical investigation. Yet the chief burden of this disease lies in Africa, where minimal standards of care are often lacking. In parts of Africa, up to a third of the people carry a gene for hemoglobin S. About 120,000 babies with sickle cell disease are born yearly (as compared with 1000 in the United States), but less than 2 percent survive to the age of five. High-technology treatment will benefit the fortunate few, but to have an important effect, any treatment must be translated into a form that can be applied in the less developed and poorer countries of the world.

Supported in part by the Department of Veterans Affairs.

REFERENCES

14. The sickle cell information center. Atlanta: Emory University School of Medicine, 1998. (See www.emory.edu/PEDS/SICKLE.)
49. Adraga NC, Fonseca P, Laul PK. Hydroxyurea affects cell morphol-
ogy, cation transport, and red blood cell adhesion in cultured vascular en-
52. Steinberg MH, Terrin ML, Brugnara C. Cellular effects of hydroxy-
53. Steinberg MH, Lu Z-H, Barton FB, Terrin ML, Charache S, Dover GJ. Fetal hemoglobin in sickle cell anemia: determinants of response to hy-
54. de Montalembert M, Bellay M, Bernardi F, et al. Clinical and hema-
55. Scott JP, Hillert CA, Brown ER, Misewicz V, Labotka RJ. Hydroxy-
65.
58. Nussenzweig J-D. Treatment of polycythemia vera: use of HU alone or in combination with maintenance therapy using hydroxyurea in 461 pa-
59. Nand S, Stock W, Godwin J, Fisher SG. Leukemogenic risk of hydrox-
yurea therapy in polycythemia vera, essential thrombocythemia, and mye-
60. Triadou P, Maier-Redelsperger M, Krishnamoorthy R, et al. Fetal hae-
moglobin variations following hydroxyurea treatment in patients with cya-
fects the splenic reticuloendothelial dysfunction in sickle cell anemia. Blood 1993;82:100-4.
65. Loukopoulos D. Current status of thalassemia and the sickle cell syn-
67. Vermelyn C, Fernandez Robles E, Ninane J, Correa G. Bone marrow transplantation cor-
fects the splenic reticuloendothelial dysfunction in sickle cell anemia. Blood 1993;82:1102-5.
68. Scott JP, Hillert CA, Brown ER, Misewicz V, Labotka RJ. Hydroxy-
69. Vermylen C, Fernandez Robles E, Ninane J, Correa G. Bone marrow transplantation cor-
fects the splenic reticuloendothelial dysfunction in sickle cell anemia. Blood 1993;82:1102-5.
72. Loukopoulos D. Current status of thalassemia and the sickle cell syn-
73. el-Hazmi MAF, al-Momen A, Kandaswamy S, et al. On the use of hy-
74. Vermelyn C, Fernandez Robles E, Ninane J, Correa G. Bone marrow transplantation cor-
fects the splenic reticuloendothelial dysfunction in sickle cell anemia. Blood 1993;82:1102-5.
77. Loukopoulos D. Current status of thalassemia and the sickle cell syn-