

# Sickle Cell Anemia

## What Is Sickle Cell Anemia?

Sickle cell anemia is an inherited blood disorder, characterized primarily by chronic anemia and periodic episodes of pain.

The underlying problem involves hemoglobin, a component of the red cells in the blood. The hemoglobin molecules in each red blood cell carry oxygen from the lungs to the body organs and tissues and bring back carbon dioxide to the lungs.

In sickle cell anemia, the hemoglobin is defective. After the hemoglobin molecules give up their oxygen, some of them may cluster together and form long, rod-like structures. These structures cause the red blood cells to become stiff and to assume a sickle shape. Unlike normal red cells, which are usually smooth and donut-shaped, the sickled red cells cannot squeeze through small blood vessels. Instead, they stack up and cause blockages that deprive the organs and tissue of oxygen-carrying blood. This process produces the periodic episodes of pain and ultimately can damage the tissues and vital organs and lead to other serious medical problems.

Unlike normal red blood cells, which last about 120 days in the bloodstream, sickled red cells die after only about 10 to 20 days. Because they cannot be replaced fast enough, the blood is chronically short of red blood cells, a condition called anemia

## What Causes Sickle Cell Anemia?

Sickle cell anemia is caused by an error in the gene that tells the body how to make hemoglobin. The defective gene tells the body to make the abnormal hemoglobin that results in deformed red blood cells. Children who inherit copies of the defective gene from both parents will have sickle cell anemia. Children who inherit the defective sickle hemoglobin gene from only one parent will not have the disease, but will carry the sickle cell trait. Individuals with sickle cell trait generally have no symptoms, but they can pass the sickle hemoglobin gene on to their children.

The error in the hemoglobin gene results from a genetic mutation that occurred many thousands of years ago in people in parts of Africa, the Mediterranean basin, the Middle East, and India. A deadly form of malaria was very common at that



time, and malaria epidemics caused the death of great numbers of people.

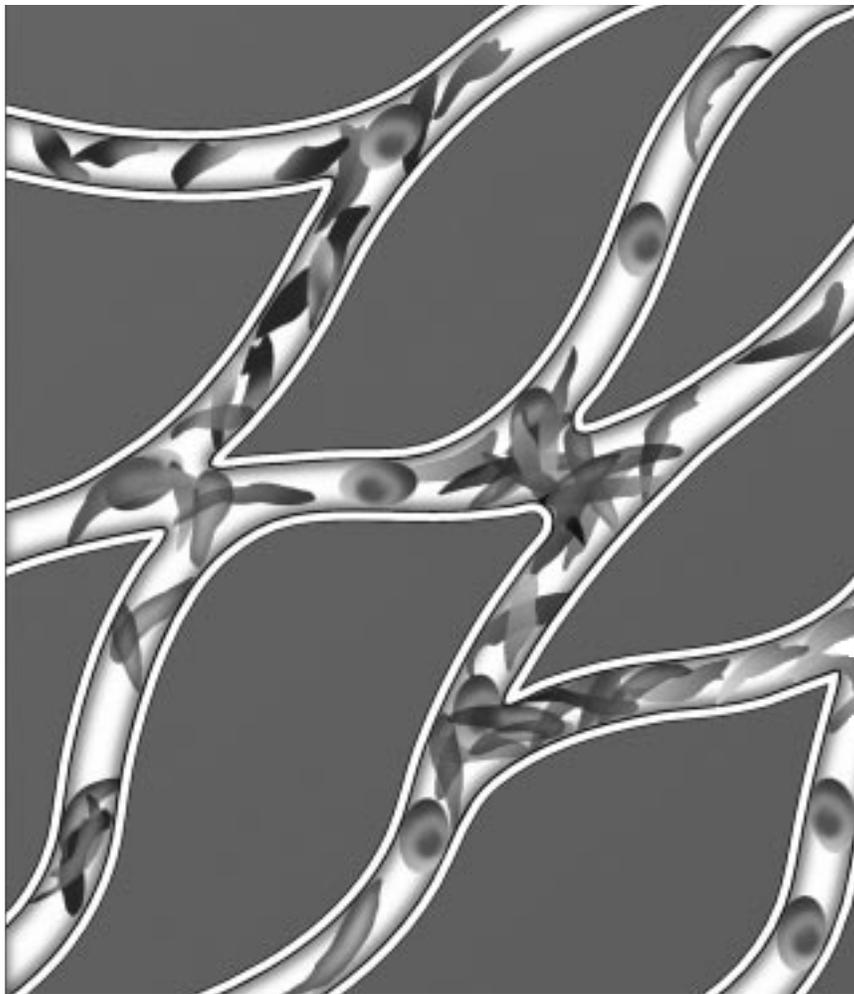
Studies show that in areas where malaria was a problem, children who inherited one sickle hemoglobin gene — and who, therefore, carried the sickle cell trait — had a survival advantage: unlike the children who had normal hemoglobin genes, they survived the malaria epidemics; they grew up, had their own children, and passed on the gene for sickle hemoglobin.

As populations migrated, the sickle cell mutation spread to other Mediterranean areas, further into the Middle East, and eventually into the Western Hemisphere.

In the United States and other countries where malaria is not a problem, the sickle hemoglobin gene no longer provides a survival advantage. Instead, it may be a serious threat to the carrier's children, who may inherit two abnormal sickle hemoglobin genes and have sickle cell anemia.

#### **How Common Is Sickle Cell Anemia?**

Sickle cell anemia affects millions of people throughout the world. It is particularly common among people whose ancestors come from sub-Saharan Africa; Spanish-speaking regions (South America, Cuba, Central America); Saudi Arabia; India; and Mediterranean countries, such as Turkey, Greece, and Italy.



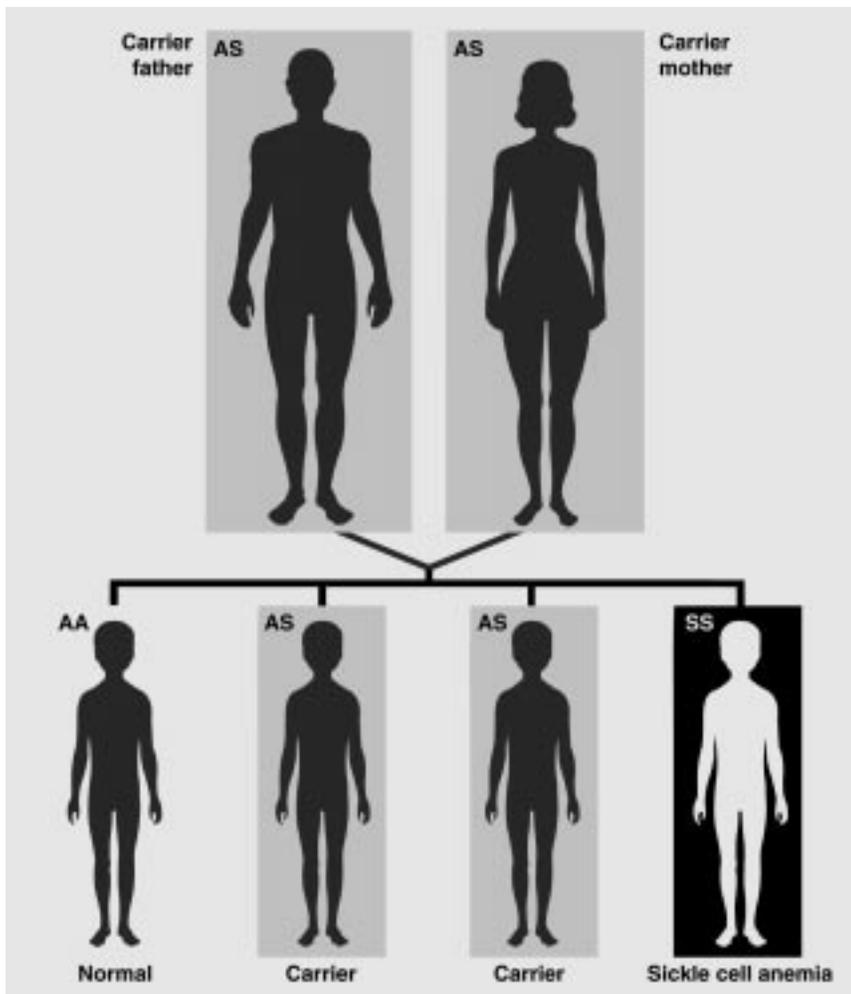
*The sickle-shaped red blood cells tend to get stuck in narrow blood vessels, blocking the flow of blood.*

In this country, it affects approximately 72,000 people, most of whose ancestors come from Africa. The disease occurs in approximately 1 in every 500 African-American births and 1 in every 1,000-1,400 Hispanic-American births.

Approximately 2 million Americans, or 1 in 12 African Americans, carry the sickle cell trait.

#### **What Are the Signs and Symptoms of Sickle Cell Anemia?**

The clinical course of sickle cell anemia does not follow a single pattern; some patients have mild symptoms, and some have very severe symptoms. However, the basic problem is the same — the sickle-shaped red blood cells tend to get stuck in narrow blood vessels, blocking the flow of blood.



*The presence of two defective genes (SS) is needed for sickle cell anemia. If each parent carries one sickle hemoglobin gene (S) and one normal gene (A), with each pregnancy, there is a 25 percent chance of the child's inheriting two defective genes and having sickle cell anemia; a 25 percent chance of inheriting two normal genes and not having the disease; and a 50 percent chance of being an unaffected carrier like the parents.*

This results in the following conditions:

- **Hand-foot syndrome.** When the small blood vessels in the hands or feet are blocked, pain and swelling can result, along with fever. This may be the first symptom of sickle cell anemia in infants.
- **Fatigue, paleness, and shortness of breath** — all symptoms of anemia, or a shortage of red blood cells.

- **Pain that occurs unpredictably** in any body organ or joint, wherever the sickled blood cells block oxygen flow to the tissues. The frequency and amount of pain varies. Some patients have painful episodes (also called crises) less than once a year, and some have as many as 15 or even more episodes in a year. Sometimes the pain lasts only a few hours; sometimes it lasts several weeks. For especially severe, ongoing pain, the patient may have to be hospitalized and treated with painkillers and intra-

venous fluids. Pain is the principal symptom of sickle cell anemia in both children and adults.

- **Eye problems.** When the retina, the "film" at the back of the eye that receives and processes visual images, does not get enough nourishment from circulating red blood cells, it can deteriorate. Damage to the retina can be serious enough to cause blindness.
- **Yellowing of the skin and eyes.** These are signs of jaundice, resulting from the rapid breakdown of red blood cells.
- **Delayed growth and puberty** in children and often a slight build in adults. The slow rate of growth is caused by a shortage of red blood cells.
- **Infections.** In general, both children and adults with sickle cell anemia are more vulnerable to infections and have a harder time fighting them off once they start. This is the result of damage to the spleen from the sickled red cells which prevents the spleen from destroying bacteria in the blood. Infants and young children, especially, are susceptible to bacterial infections that can kill them in as little as 9 hours from onset of fever. Pneumococcal infections used to be the principal cause of death in young children with sickle cell anemia until physicians began routinely giving penicillin on a preventive basis to infants who are identified at birth or in early infancy as having sickle cell anemia.
- **Stroke.** The defective hemoglobin damages the walls of the red blood

cells, causing them to stick to blood vessel walls. This can result in the development of narrowed, or blocked, small blood vessels in the brain, causing a serious, life-threatening stroke. This type of stroke occurs primarily in children.

- **Acute chest syndrome** — a life-threatening complication of sickle cell anemia, similar to pneumonia, that is caused by infection or trapped sickled cells in the lung. This is characterized by chest pain, fever, and an abnormal chest x ray.

### How Is Sickle Cell Anemia Detected?

Early diagnosis of sickle cell anemia is critical so that children who have the disease can receive proper treatment.

More than 40 states now perform a simple, inexpensive blood test for sickle cell disease on all newborn infants. This test is performed at the same time and from the same blood samples as other routine newborn screening tests. Hemoglobin electrophoresis is the most widely used diagnostic test.

If the test shows the presence of sickle hemoglobin, a second blood test is performed to confirm the diagnosis. These tests also tell whether the child carries the sickle cell trait.

### How Is Sickle Cell Anemia Treated?

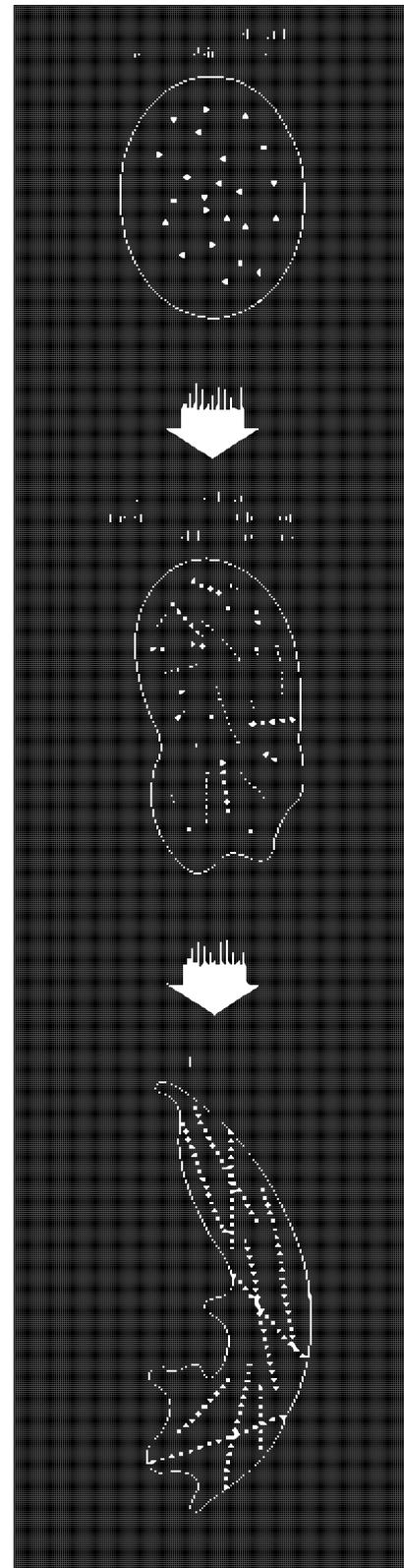
Although there is no cure for sickle cell anemia, doctors can do a great deal to help sickle cell patients, and treatment is constantly being improved.

Basic treatment of painful crises relies heavily on pain-killing drugs and oral and intravenous fluids to reduce pain and prevent complications.

Blood transfusions are used to treat and to prevent some of the complications of sickle cell anemia. Transfusions correct anemia by increasing the number of normal red blood cells in circulation. Transfusions are used to treat spleen enlargement in children before the condition becomes life-threatening. Regular transfusion therapy also can help prevent recurring strokes in children at high risk of crippling nervous system complications.

Giving young children with sickle cell anemia oral penicillin twice a day, beginning when the child is about 2 months old and continuing until the child is at least 5 years old, can prevent pneumococcal infection and early death in these children. Recently, however, several new strains of pneumonia bacteria that are resistant to penicillin have been reported. Since the vaccines for these bacteria are ineffective in young children, studies are being planned to test new vaccines.

The first effective drug treatment for adults with severe sickle cell anemia was reported in early 1995, when a study conducted by the National Heart, Lung, and Blood Institute showed that daily doses of the anticancer drug hydroxyurea reduced the frequency of painful crises and of acute chest syndrome in these patients. Patients taking the drug also needed fewer blood transfusions.



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The long-term side effects of hydroxyurea and its effects in children with sickle cell anemia are still being studied.

Sickle cell anemia patients with severe chest or back pain that prevents them from breathing deeply may be able to avoid potentially serious lung complications associated with acute chest syndrome by using an incentive spirometer. This is a small plastic device, shaped like a tube, with a ball inside. The patient must breathe into it hard enough to force the ball up the tube, so using it helps the patient breathe more deeply.

Most complications of sickle cell anemia are treated as they occur. For example, laser coagulation and other types of eye surgery may be used to prevent further vision loss in patients with eye problems. Surgery may be recommended for certain kinds of organ damage — for example, to remove gallstones or replace a hip joint. Leg ulcers may be treated with cleansing solutions and zinc oxide, or with skin grafts if the condition persists.

Regular health maintenance is critical for people with sickle cell anemia. Proper nutrition, good hygiene, bed rest, protection against infections, and avoidance of other stresses all are important in maintaining good health and preventing complications. Regular visits to a physician or clinic that provides comprehensive care are necessary to identify early changes in the patient's health and ensure that the person receives immediate treatment.

Today, with good health care, many people with sickle cell anemia are in reasonably good health much of the time and living productive lives. In fact, in the past 30 years, the life expectancy of people with sickle cell anemia has increased. Many patients with sickle cell anemia now live into their midforties and beyond.

### **The Future of Sickle Cell Anemia Treatment**

Scientists have learned a great deal about sickle cell anemia during the past 30 years — what causes it, how it affects the patient, and how to treat some of the complications. They also have begun to have success in developing drugs that will prevent the symptoms of sickle cell anemia and procedures that should ultimately provide a cure.

Some researchers are focusing on identifying drugs that will increase the level of fetal hemoglobin in the blood. Fetal hemoglobin is a form of hemoglobin that all humans produce before birth, but most stop making shortly after birth. Most humans have little fetal hemoglobin left in their bloodstream by the time they reach the age of 6 months. However, some people with sickle cell anemia continue to produce large amounts of fetal hemoglobin after birth, and studies have shown that these people have less severe cases of the disease. Fetal hemoglobin seems to prevent sickling of red cells, and cells containing fetal hemoglobin tend to survive longer in the bloodstream.

Hydroxyurea appears to work primarily by stimulating production of fetal hemoglobin. There is some evidence that administering hydroxyurea with erythropoietin, a genetically engineered hormone that stimulates red cell production, may make hydroxyurea work better. This combination approach offers the possibility that lower doses of hydroxyurea can be used to achieve the needed level of fetal hemoglobin. However, both of these drugs may produce serious side effects, so researchers continue to search for safer agents that are just as effective.

Butyrate, a simple fatty acid that is widely used as a food additive, is also being investigated as an agent that may increase fetal hemoglobin production.

Clotrimazole, an over-the-counter medication commonly used to treat fungal infections, is under investigation as a treatment to prevent the loss of water from the red blood cells that contributes to sickling. It is hoped that this medication, used alone or in conjunction with other antisickling agents, may eventually offer an effective long-term therapy for sickle cell anemia patients.

Bone marrow transplantation has been shown to provide a cure for severely affected children with sickle cell disease. Although many of the risks of this procedure have been reduced, it still is not entirely without risk. In addition, the marrow must come from a healthy matched sibling donor, and only about 18 percent of children with sickle cell anemia

are likely to have a matched sibling. Researchers are working on techniques to further reduce some of the risks of bone marrow transplantation for patients with sickle cell disease.

The ultimate cure for sickle cell anemia may be gene therapy. In sickle cell anemia, the gene which switches on production of adult hemoglobin shortly before birth, is defective. Two approaches to gene therapy are being explored. Some scientists are looking into whether correcting this gene and inserting it into the bone marrow of people with sickle cell anemia will result in the production of normal adult hemoglobin. Others are looking at the possibility of turning off the defective gene and simultaneously reactivating another gene that turns on production of fetal hemoglobin. In both cases, the research is at a very early stage. Progress is being made, however, and there is a real possibility of an eventual clinical cure for sickle cell anemia.

Although the genetic defect that causes sickling was identified more than 40 years ago, until very recently, research into the development of treatments for the disease was hampered by the lack of an animal model that could be used to test experimental drugs and gene therapy. Recently, however, scientists were able to genetically engineer a line of mice that exhibit some of the characteristics of sickle cell disease in much the same way humans do. This is an important advance in the search for an effective treatment and eventual cure for sickle cell disease.

### **How Can Patients and Their Families and Friends Be Helped To Cope with Sickle Cell Anemia?**

Sickle cell patients and their families may need help in handling the economic and psychological stresses of coping with this serious chronic disease. Sickle cell centers and clinics can provide information and counseling on handling these problems.

Parents should try to learn as much about the disease as possible so that they can recognize early signs of complications and seek early treatment.

### **Is It Possible To Detect Sickle Cell Anemia in an Unborn Baby?**

Yes. By sampling the amniotic fluid or tissue taken from the placenta, doctors can tell whether a fetus has sickle cell anemia or sickle cell trait. This test can be done as early as the first trimester of pregnancy.

### **What Should Future Parents Know?**

People who are planning to become parents should know whether they are carriers of the sickle cell gene, and, if they are, they may want to seek genetic counseling. The counselor can tell prospective parents what the chances are that their child will have sickle cell trait or sickle cell anemia. Accurate diagnostic tests and information are available from health departments, neighborhood health centers, medical centers and clinics that care for individuals with sickle cell anemia.

### **FOR MORE INFORMATION CONTACT:**

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