Sickle Cell Disease

Milestones in Research and Clinical Progress

National Heart, Lung, and Blood Institute

Blood Diseases & Disorders Education Program

Introduction

In 1910, Chicago physician James B. Herrick published a description of oddly shaped blood cells taken from dental student Walter Clement Noel, providing the first detail in Western medical literature of what has come to be known as sickle cell disease.

We now know that the sickle-shaped cells are caused by a problem in hemoglobin, the protein in red blood cells that carries oxygen throughout the body. A small defect in the gene for hemoglobin changes the way that hemoglobin works.

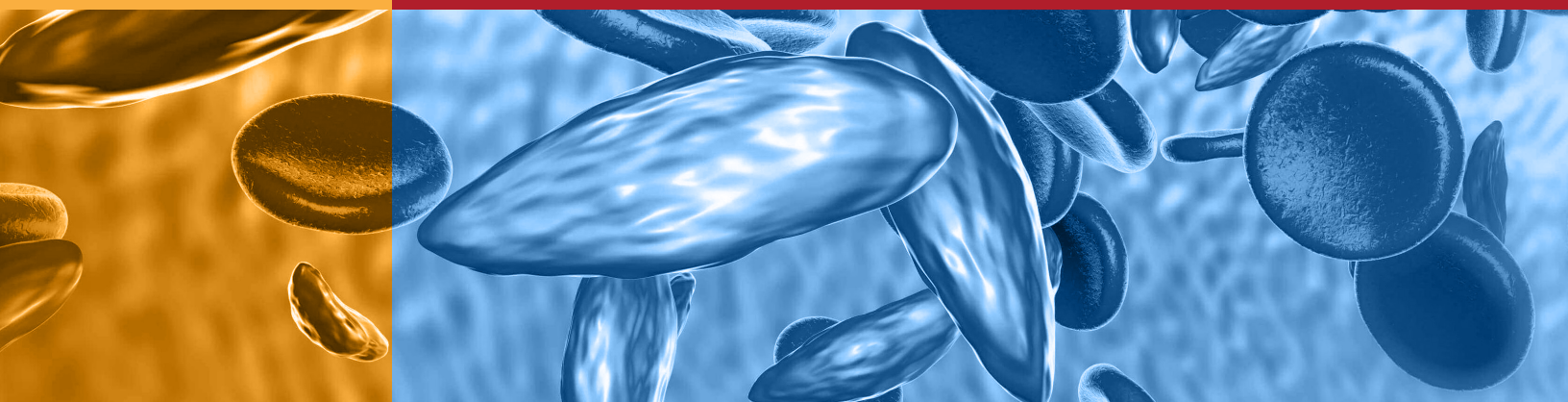
Research supported by the National Heart, Lung, and Blood Institute (NHLBI) has helped make discoveries such as these possible, and, over the years, the NHLBI has continued to advance our understanding of sickle cell disease and improve clinical care.

For example, the NHLBI led an effort to develop evidence-based clinical practice guidelines so that people who have sickle cell disease receive appropriate care. The NHLBI also works with the Department of Health and Human Services (HHS) and other stakeholders to focus nationwide attention on sickle cell disease as a serious public health issue.

Today, the NHLBI is committed to building on its legacy of research excellence to find new treatments, cures, and personalized care for people who have sickle cell disease. Its revitalized research portfolio of basic, clinical, translational, and implementation research addresses the genetic factors affecting disease symptoms, regulation of hemoglobin synthesis, development of medicines to increase a type of normal hemoglobin produced before birth, and the development and application of safe and effective genetic therapies, including gene-editing approaches, in clinical research.

As with all its research endeavors, the NHLBI recognizes that actively engaging patients, families, healthcare professionals, and communities is essential. The NHLBI sponsors many important clinical trials designed to improve existing treatments and find new treatments for sickle cell disease. These studies would not be possible without patients and healthy volunteers who participate in clinical research.

For more information on open and enrolling NHLBI-funded clinical trials, visit **nhlbi.nih.gov/research/clinical-trials**



What Is Sickle Cell Disease?

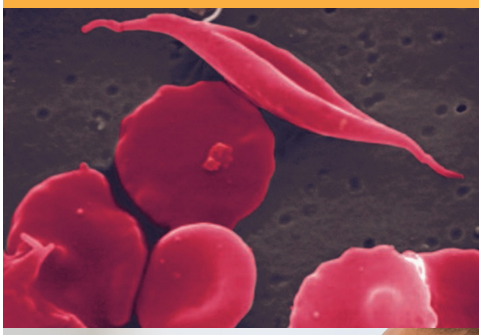
Sickle cell disease is a group of inherited red blood cell disorders. Red blood cells that contain normal hemoglobin are disc-shaped, which allows the cells to be flexible so that they can move through large and small blood vessels to deliver oxygen to the body.

People who have sickle cell disease inherit two abnormal hemoglobin genes, one from each parent. In all types of sickle cell disease, at least one of the two abnormal genes causes a person's body to make hemoglobin S, or sickle hemoglobin. Hemoglobin S can form rigid strands within red blood cells, changing them into a crescent or sickle shape, the hallmark of sickle cell disease. Sickle-shaped red blood cells are stiff and sticky, and tend to form clumps that can block blood flow and lead to episodes of extreme pain, known as crises.

When a person has two hemoglobin S genes, hemoglobin SS, the disease is called sickle cell anemia. This is the most common and often the most severe type of sickle cell disease.

When a person inherits the hemoglobin S gene from one parent and a normal hemoglobin gene from the other parent, the person has sickle cell trait. People who have sickle cell trait are generally healthy. They only rarely have complications like those seen in people who have sickle cell disease. However, because people with sickle cell trait are carriers of the hemoglobin S gene, they can pass it on to a child.

Sickle cell disease is a lifelong illness and can harm a person's spleen, brain, eyes, lungs, liver, heart, kidneys, penis, joints, bones, or skin. The severity of the disease varies widely from person to person. In the early 1970s, the average life span of people with sickle cell disease was only 14 years. Today, people who have sickle cell disease are living into their forties, fifties, and beyond. Research, early diagnosis, and regular medical care are preventing complications and helping people live longer. However, a blood and bone marrow transplant is currently the only cure for sickle cell disease, and only a small number of people who have sickle cell disease are able to have the transplant.



Who Gets Sickle Cell Disease?

In the United States, most people who have sickle cell disease are of African ancestry or identify themselves as Black. Approximately 100,000 Americans have sickle cell disease, and more than 2 million people may have sickle cell trait. About 1 in 13 African American babies are born with sickle cell trait, and about 1 in every 365 African American children are born with sickle cell disease. Many people with this disease also come from Hispanic, southern European, Middle Eastern, or Asian Indian backgrounds.

The National Heart, Lung, and Blood Institute

The NHLBI has funded sickle cell research since 1948, when it was founded as the National Heart Institute at the National Institutes of Health (NIH). The NHLBI has played a crucial role in not only funding basic research but also in developing and implementing large clinical trials and conducting workshops and consensus meetings to guide the research. Research on sickle cell disease and other diseases that affect hemoglobin has played a central role in the advancement of genetics, molecular biology, and other areas of medicine. More importantly, clinical trial participants have been essential for the development of new treatments for sickle cell disease. Because of their contributions, we have gained an understanding of the molecular causes of the disease; developed effective approaches for preventing and treating its complications, including infection, stroke, and lung disease; and even cured a small number of people using blood and bone marrow transplants.

Sickle Cell Disease Milestones

1910

Chicago physician James B. Herrick publishes the first description of sickled cells, which he discovered in the blood samples of a 20-year-old student from Grenada, Walter Clement Noel. The term "sickle cell anemia" is coined.

"The shape of the reds was very irregular, but what especially attracted attention was the large number of thin, elongated, sickle-shaped, and crescent-shaped forms."

— Dr. James B. Herrick

1933

Scientists include 2,500 African Americans in a study that shows sickle cell trait and sickle cell disease are separate conditions.

1934

Research suggests that painful sickle cell "crises" result from blockages of small blood vessels.

1940

Research suggests that the exchange of oxygen for carbon dioxide occurring in small blood vessels may cause red blood cells to sickle and block blood vessels.

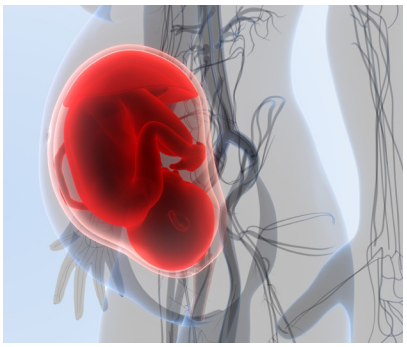
1948

The National Heart Institute is established. The first round of grants includes $8,640 to Dr. James Neel to study how sickle cell disease is passed from parents to their children.

Research suggests that low levels of sickled cells in blood from newborns who have sickle cell disease are due to a high level of fetal hemoglobin in their red blood cells.

"There are many things yet to be learned about sickle cell anemia."

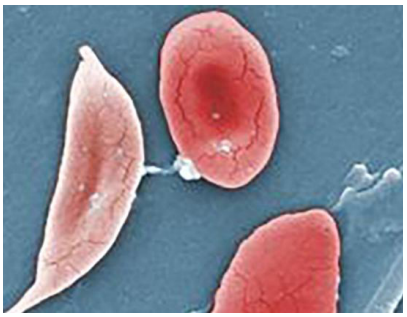
— Editorial, Journal of the National Medical Association



1949

Dr. Linus Pauling and other scientists discover that sickle cell disease is caused by an abnormal hemoglobin protein molecule. The term "molecular disease" is coined.

Two research teams independently find that sickle cell disease can be inherited only when both parents pass sickle cell genes to a child. To produce sickle cell trait in a child, only one parent needs to pass along the gene.

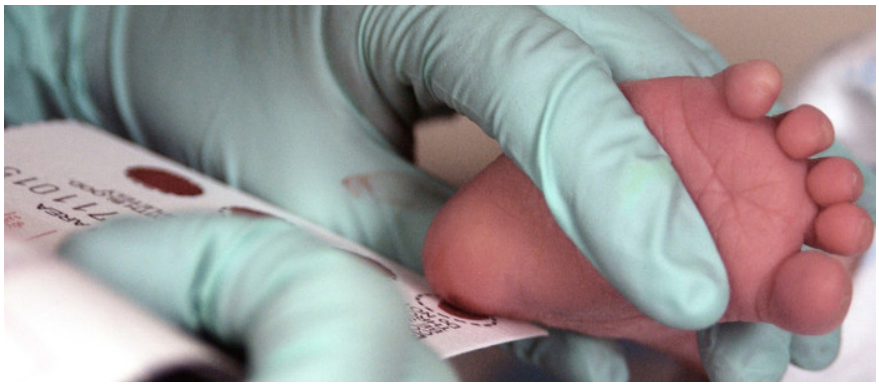


1951

Scientific American publishes an article on Dr. Pauling's discovery of the molecular nature of sickle cell disease, raising public awareness of the condition.

1953

Scientists develop a diagnostic blood test, hemoglobin electrophoresis, that identifies sickle cell disease and other conditions caused by abnormal hemoglobin.



1954

Researchers find that sickle cell trait protects against malaria. The finding explains why the sickle gene is more common in regions of Africa, where malaria is a major cause of death.

1957

Scientists show that the abnormality of sickle hemoglobin is caused by an amino acid substitution in the protein, making sickle cell disease the first genetic disorder with an unknown molecular basis.

1963

Dr. Max Perutz deciphers the three-dimensional structure of the hemoglobin protein using X-ray crystallography. This groundbreaking accomplishment took more than 20 years to complete. Dr. Perutz receives the Nobel Prize for this work in 1967.

1968

Researchers coin the phrase "irreversibly sickled" to describe red blood cells that remain sickled even when oxygen levels are restored in patients with sickle cell disease.

1972

The National Sickle Cell Anemia Control Act provides for the establishment of voluntary sickle cell disease screening, patient counseling, public and professional education, and research and training in diagnosing, treating, and controlling the disease. Howard University's Dr. Roland Scott plays a leading role in advocating for the act.

A milder variation of sickle cell disease found in Saudi Arabia is associated with increased levels of fetal hemoglobin. The finding suggests that increasing fetal hemoglobin levels could help alleviate the disease.

1972–1973

The NHLBI establishes the National Sickle Cell Disease Program. The Institute begins funding comprehensive sickle cell centers and establishes its Sickle Cell Branch.

1973

Scientists develop neonatal screening methods using blood spots on filter paper.

1974

Researchers demonstrate the feasibility of newborn screening for sickle cell disease.

A method for prenatal diagnosis by sampling fetal blood from the umbilical vein is developed.

1975

New York becomes the first state to require newborn screening for sickle cell disease.

1977

The gene for sickle cell disease is sequenced for the first time, leading to an evolution in understanding about sickle cell disease and gene mutations.

1978

Scientists develop a new prenatal method to diagnose sickle cell disease using DNA samples.

The NHLBI launches a multicenter study involving more than 4,000 people who have sickle cell disease, from newborns to 70-year-olds. The Cooperative Study of Sickle Cell Disease is the first to document a clinical course of disease from birth to adulthood.

1979

Researchers discover that red blood cells from patients who have sickle cell disease stick more readily to cells lining blood vessels than normal red blood cells do.

1980

Binding of sickle-shaped red blood cells to the inside of blood vessels is shown to block blood flow. The extent of stickiness is suggested as a possible cause of disease severity.

1982

The compound 5-azacytidine is shown to elevate fetal hemoglobin levels.

1984

The NHLBI first publishes "The Management of Sickle Cell Disease," a guide on diagnosing and counseling, health maintenance, treatment of acute and chronic complications, and special topics.

Several teams independently demonstrate that hydroxyurea increases fetal hemoglobin levels.

A blood and bone marrow transplant is performed to treat a child with leukemia. It also cures the child's sickle cell disease.

1986

The NHLBI's Prophylaxis with Oral Penicillin in Children with Sickle Cell study shows penicillin is effective as a preventive measure in children with sickle cell disease who are between 3 months and 3 years old. The study finds that penicillin can reduce the rate of *Streptococcus pneumoniae* infection, a major cause of childhood death, by 84 percent. The practice becomes widely adopted.

1987

The NIH Consensus Development Panel recommends screening all U.S. newborns for sickle cell disease and giving penicillin to all affected infants by 3 months of age.

Officials require newborn screening for sickle cell disease in 44 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands.

1991

Mice with sickle cell disease are developed to help find treatments. The study shows that even small increases in fetal hemoglobin can result in fewer pain crises.

1995

The NHLBI-sponsored Multicenter Study of Hydroxyurea in Sickle Cell Anemia shows hydroxyurea reduces the number of pain crises and related hospital visits by 50 percent. Treatment increases fetal hemoglobin levels and is the first effective therapy for adults who have severe sickle cell disease.

An NHLBI-sponsored study shows that once a child with sickle cell disease is 5 years old, physicians can stop the penicillin treatment.

1996

Researchers develop a method of using maternal blood samples for prenatal diagnosis of the disease.

A multicenter study of blood and bone marrow transplants in children who have sickle cell disease finds the procedure can cure young sickle cell patients who have siblings with compatible stem cells.

1997

The Stroke Prevention Trial in Sickle Cell Anemia finds that periodic blood transfusions in children who have sickle cell disease and are at high risk of stroke reduce the risk of a first stroke by 90 percent.

1998

The Food and Drug Administration (FDA) approves hydroxyurea for sickle cell disease treatment in adults, based on the NHLBI-sponsored Multicenter Study of Hydroxyurea in Sickle Cell Anemia.

2001

The Collection and Storage of Umbilical Cord Hematopoietic Stem Cells for Sickle Cell Disease Therapy program starts to collect umbilical cord blood from sibling donors in families with children who have sickle cell disease or related blood disorders to aid in future hematopoietic stem cell transplants as needed.

Researchers use a genetic therapy to correct sickle cell disease in mice.

2002

The Health Resources and Services Administration Newborn Screening Program begins to screen for conditions including sickle cell trait or disease.

2003

Researchers find that hydroxyurea therapy improves survival in adults who have severe sickle cell disease.

2004

A study finds that children with sickle cell disease and a high risk for stroke who stop receiving periodic blood transfusions return to high risk of stroke after 30 months.

2005

In 2005, Congress passes the Stem Cell Research and Therapeutic Act to create an inventory of high-quality cord blood samples.

2006

The NHLBI launches the Sickle Cell Disease Clinical Research Network. NHLBI scientists find that a hormone-brain natriuretic peptide detected in a simple blood test can identify people with sickle cell disease who have developed pulmonary hypertension, a life-threatening complication.

The NHLBI launches the Sickle Cell in Focus Conference, a series of annual meetings that bring together researchers and healthcare professionals from around the world to discuss advances and challenges for sickle cell disease clinical care.

All 50 states adopt the requirement of universal newborn screening for sickle cell disease.

2008

The United Nations designates June 19 as World Sickle Cell Day to raise national and international awareness of sickle cell disease every year.

The Newborn Screening Saves Lives Act of 2007 establishes grants to provide for education and outreach about newborn screening and coordinated follow-up care.

The NIH Consensus Development Panel finds hydroxyurea treatment underused and recommends its increased use in adolescents and adults.

"The compelling benefits of hydroxyurea warrant increased adoption of this drug as a frontline therapy in adults with sickle cell disease."

— Dr. Otis Brawley, Conference Panel Chair

The NHLBI realigns the Sickle Cell Disease Research Program by expanding support for basic research and developing a new Clinical Trials Research Network and evidence-based treatment. It also initiates the development of evidence-based clinical practice guidelines.

2009

An NHLBI laboratory study finds that the modified cells in an adult stem-cell transplant reverses sickle cell disease in 9 of 10 adults severely affected by the disease.

The NIH stops a clinical trial testing a treatment for pulmonary hypertension in adults with sickle cell disease due to safety concerns.

The NHLBI convenes a workshop of researchers, healthcare providers, advocacy organizations, patients, and others to discuss key public outreach issues.

2010

"I'm only a patient when I'm in the doctor's office. I'm really a whole person living an active life; I just happen to live with sickle cell disease."

The NHLBI and the Centers for Disease Control and Prevention launch the Registry and Surveillance System for Hemoglobinopathies program to determine the number of people who are diagnosed with inherited blood disorders, including sickle cell disease.

An NHLBI-supported study shows that adults with sickle cell disease may have changes in brain function.

The James B. Herrick Symposium, "Sickle Cell Disease Care and Research: Past, Present, and Future," commemorates the 100th anniversary of Dr. Herrick's paper that first identified sickle cell disease. The symposium brings together researchers, healthcare providers, advocacy groups, patients, and the public.

2012

The NHLBI establishes the Excellence in Hemoglobinopathy Research Awards to foster scientific collaboration and develop new ways to treat sickle cell disease.

2014

A patient with sickle cell disease is treated for the first time in a clinical trial using lentiviral gene therapy, a major step in gene therapies for the disease.

An NHLBI-supported expert panel, Evidence-Based Management of Sickle Cell Disease, offers guidance to healthcare professionals on how best to care for their patients who have sickle cell disease.

The NHLBI-funded study, Transfusions Changing to Hydroxyurea, finds that hydroxyurea is as effective as blood transfusions at reducing transcranial blood flow velocities in children with sickle cell disease. High transcranial blood velocities are a risk factor for stroke in children who have sickle cell disease.

The NHLBI supports NIH-wide efforts leading to the development of a promising new sickle cell disease treatment called Aes-103, which may reduce pain caused by sickle cell disease.

2015

The NHLBI sponsors a Sickle Cell Disease Forum to bring the sickle cell disease community together to chart the future of sickle cell research.

2016

The NHLBI Trans-Omics for Precision Medicine Program includes participants who have sickle cell disease, which may help researchers understand how genes contribute to differences in disease severity and how patients respond to treatment.

Eight clinical sites receive funding as part of the Sickle Cell Disease Implementation Consortium, which aims to identify and remove barriers that limit patient access to consistent, quality care. Although most U.S. children who have sickle cell disease survive to adulthood, the transition from pediatric to adult care is often challenging.

The NHLBI launches a multi-center study, Bone Marrow Transplantation vs. Standard of Care in Patients with Severe Sickle Cell Disease, to identify ways to perform stem cell transplants in adults who have sickle cell disease. Previously, the vast majority of stem cell transplants were performed in children.

The NHLBI Strategic Vision highlights ways that it may support new efforts for sickle cell disease research over the next decade.

2017

The FDA approves L-glutamine for patients 5 years old and older to reduce severe sickle cell-related complications. This is the first approved drug for sickle cell disease in almost 20 years.

The NHLBI holds its first Facebook Live event, with a focus on sickle cell disease.

NIH researchers working on stem cell transplants for sickle cell disease are highlighted in the Discovery Channel's "First in Human" documentary.

The NHLBI expands its research efforts to sub-Saharan Africa, where more than 75 percent of newborns with sickle cell disease are born. Through the Sickle Cell Disease in Sub-Saharan Africa Collaborative Consortium, the NHLBI is improving the use of evidence-based treatments and access to care for patients at home and abroad.

2018

The NHLBI launches the Cure Sickle Cell Initiative to accelerate the development of cures for the disease.

CURE SICKLE CELL.

The NHLBI joins HHS and other partners to create more awareness about the disease and to share information about best practices for management and treatment.

2019

The FDA approves voxelotor for adults and children 12 years old and older to prevent sickling of red blood cells and crizanlizumab-tmca for adults and children 16 years old and older to reduce vaso-occlusive and pain crises.

Results from the NHLBI Realizing Effectiveness Across Continents with Hydroxyurea Program phase I/II open-label hydroxyurea trial among children in sub-Saharan Africa are published in the New England Journal of Medicine. The trial showed that hydroxyurea treatment at a maximum-tolerated dose is feasible and safe. The hydroxyurea treatment also reduced the incidence of vaso-occlusive events, infections, malaria, transfusions, and death, which supports the need for wider access to treatment.

2020

The NHLBI-funded clinical trial Sickle Cell Disease and Cardiovascular Risk-Red Cell Exchange phase 3 trial begins recruiting. The trial looks at the effects of an automated exchange blood transfusion on patient morbidity and mortality and compares them to the standard of care for high-risk adult patients with sickle cell disease.

2021

The NHLBI launches the *Blood Diseases & Disorders Education Program*, a national health education program that aims to bring greater visibility to blood diseases and disorders; their diagnosis, treatment, and management; and blood donation and safety by translating research for patients and professionals. The program establishes the *Blood Health Network*, a broad group of public and private organizations working together to increase awareness about blood diseases, disorders, donation, and safety.

Blood Diseases & Disorders Education Program

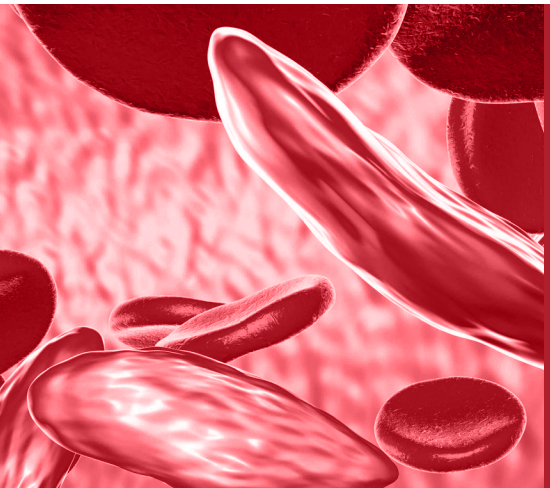
The NHLBI Hope for Sickle Cell Disease Challenge encourages college and graduate students to develop innovative ways to spread evidence-based information about sickle cell disease.

The NHLBI SickleInAfrica Network, which conducts dissemination and implementation research to help increase the provision of care for people with sickle cell disease, is renewed and expanded to include six sites. The registry includes more than 10,000 people living with the disease.

2023

The FDA approves the first cell-based gene therapies, Casgevy and Lyfgenia, for the treatment of sickle cell disease in patients 12 years old and older.

Recruiting for the Sickle Cell Disease Treatment with Arginine Therapy Trial phase 3 trial begins. The trial tests the efficacy and safety of intravenous L-arginine treatment when applied in addition to standard therapy in children who have had acute vaso-occlusive painful events. It also records time to resolve the painful event.



For more information and educational resources, visit **sicklecell.nhlbi.nih.gov**

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