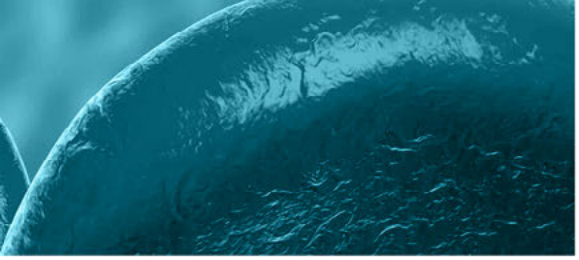
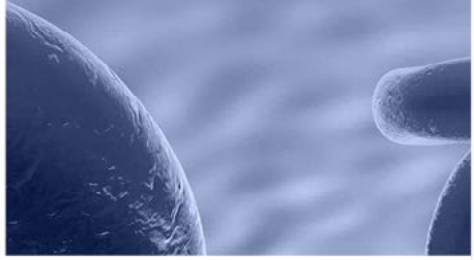
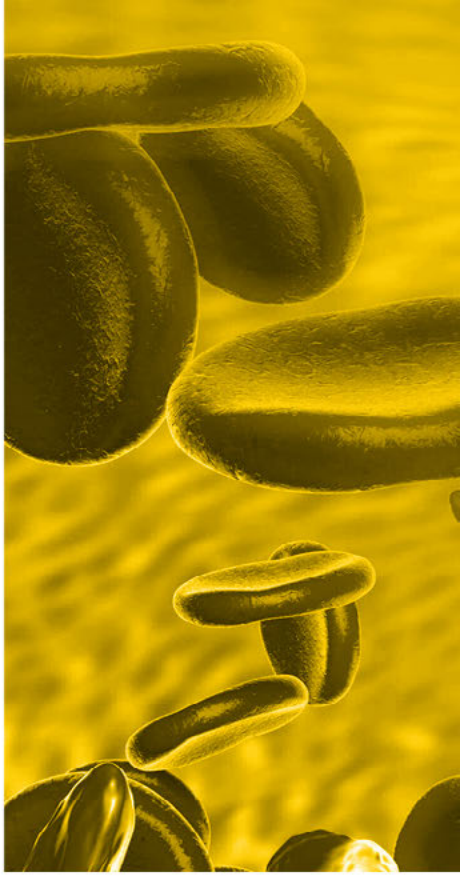
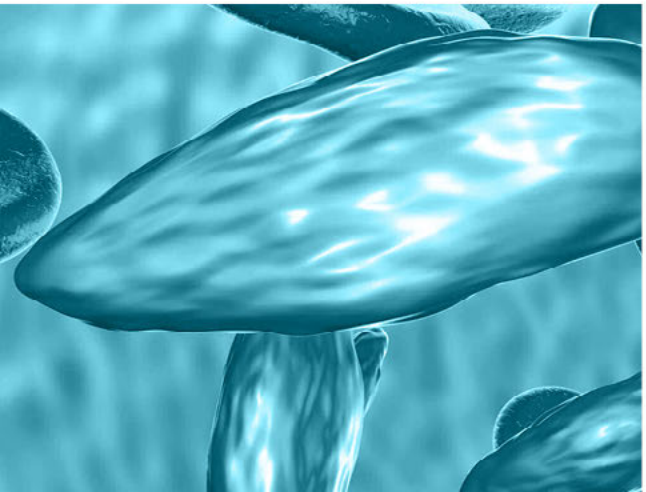




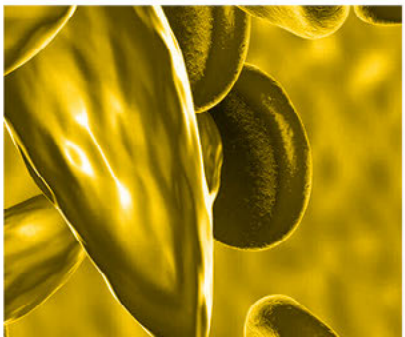


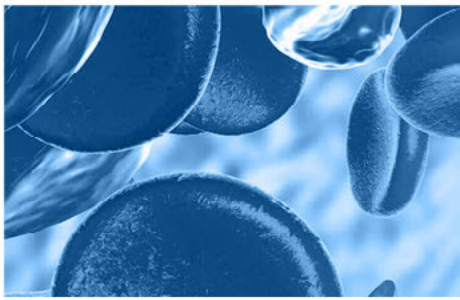
A Century of Progress

Sickle Cell Disease: Milestones in Research and Clinical Progress



NIH National Heart, Lung, and Blood Institute





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.

NHLBI-supported research helped make discoveries such as these possible, and, over the years, the NHLBI has continued to advance the 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 movement of safe and effective genetic therapies, including gene-editing approaches, into clinical research.

As with all its research endeavors, the NHLBI recognizes that actively engaging patients, families, health care 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.

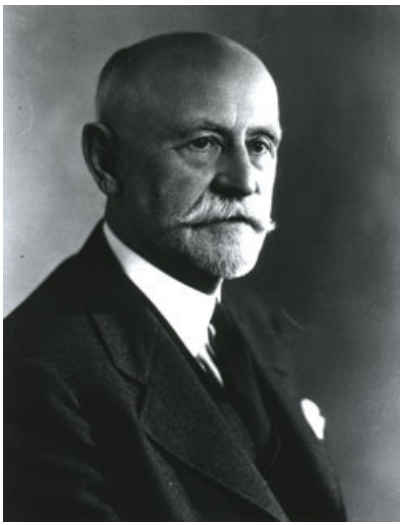
For more information on open and enrolling NHLBI-funded clinical trials, please read *Participate in NHLBI Clinical Trials* in our Sickle Cell Disease Health Topic (www.nhlbi.nih.gov/health-topics/sickle-cell-disease).

1910

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

"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 determined that sickle cell trait and sickle cell disease are separate entities.

1934

- Researchers suggest that painful sickle cell "crises" result from blockages of small blood vessels.

1940

- Researchers suggest exchange of oxygen for carbon dioxide occurring in small blood vessels may cause red blood cells to sickle and block blood vessels.

1945

"There are frequent abdominal crises which may mislead the best surgeon into operating for some acute surgical condition when the real diagnosis is sickle-cell anemia…"

– Dr. John T. Givens,
Journal of the National Medical Association

1948

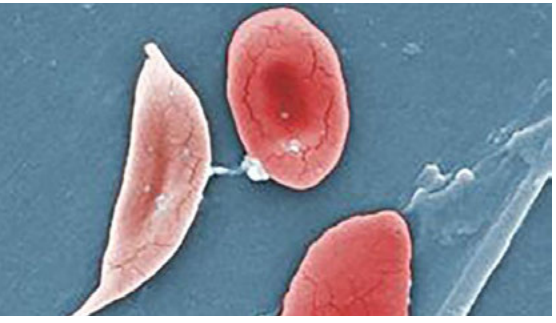
- The National Heart Institute is established. First round of grants includes $8,640 to Dr. James Neel to study how sickle cell disease is passed from parents to their children.
- Research suggests low levels of sickled cells in blood from newborns who have sickle cell disease are due to high levels 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 others discover that sickle cell disease is caused by abnormal hemoglobin protein molecule. Term "molecular disease" coined.



1949–1950

- Two research teams independently find that sickle cell disease can only be inherited 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 a gene.

1951

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

1953

- Scientists develop diagnostic tool that identifies sickle cell disease and other conditions caused by abnormal hemoglobin.

1954

- Sickle cell trait found to protect against malaria. Finding explains why the sickle gene is more common in regions in Africa where malaria is a major cause of death.

1955

- Scientists develop new blood test that identifies abnormal hemoglobin. The test is still used today to diagnose sickle cell disease.

1957

- Scientists show abnormality of sickle hemoglobin is caused by amino acid substitution in protein, making sickle cell disease the first genetic disorder whose molecular basis is known.

1963

- The three-dimensional structure of the hemoglobin protein is deciphered using X-ray crystallography. This groundbreaking accomplishment took over 20 years to complete. Dr. Max 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 of those cells get restored in patients with sickle cell disease.

1970

"What has been little appreciated, despite all this study and interest, is the real importance of the disease as a community health problem."

– Dr. Robert B. Scott, *Journal of the American Medical Association*

1972

- National Sickle Cell Anemia Control Act provides for establishment of voluntary sickle cell disease screening; patient counseling; public and professional education; and research and training in diagnosing, treating, and controlling disease. Howard University's Dr. Roland Scott played a leading role in advocating for the act.
- A milder variation of sickle cell disease found in Saudi Arabia associated with increased levels of fetal hemoglobin. Finding suggests increasing fetal hemoglobin levels could offer treatment target.

1972–1973

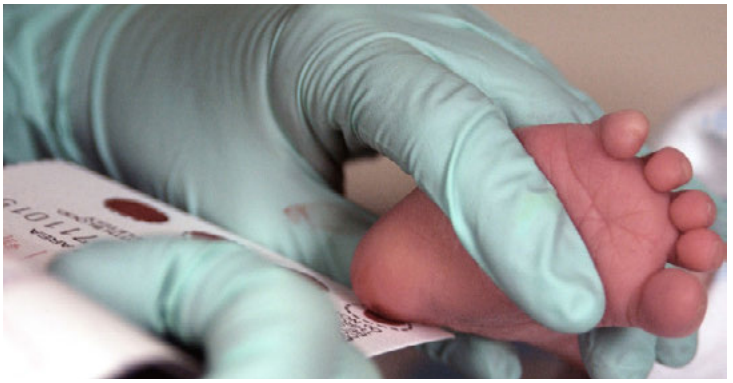
- National Sickle Cell Disease Program established at NHLBI. The Institute begins funding comprehensive sickle cell centers and establishes its Sickle Cell Branch.

1973

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

1974

- Researchers demonstrate feasibility of newborn screening for sickle cell disease.
- Method for prenatal diagnosis by sampling fetal blood from the umbilical vein developed.



1975

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

1978

- Scientists report new prenatal method to diagnose sickle cell disease using DNA samples.
- The NHLBI launches multicenter study involving 4,000-plus people who have sickle cell disease, from newborns to 70-year-olds. The Cooperative Study of Sickle Cell Disease (CSSCD) is the first to document 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 do normal red blood cells.

1980

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

1982

- The NHLBI first publishes "The Management of Sickle Cell Disease."
- The compound 5-azacytidine shown to elevate fetal hemoglobin levels.

1984

- Several teams independently demonstrate that hydroxyurea increases fetal hemoglobin levels.
- Blood and bone marrow transplant performed to treat a child with leukemia. It also cures the child's sickle cell disease.

1986

- 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 3 months to 3 years old. Study finds penicillin can reduce the rate of Streptococcus pneumonia infection, a major cause of childhood death, by 84 percent. Practice later becomes widely adopted.

1987

- 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

- First line of mice that have sickle cell disease developed to help find treatments.
- Study shows even small increases in fetal hemoglobin can result in fewer pain crises.

1995

- NHLBI-sponsored Multicenter Study of Hydroxyurea in Sickle Cell Anemia shows hydroxyurea reduces number of pain crises and related hospital visits by 50 percent. Treatment increases fetal hemoglobin levels and is first effective therapy for adults who have severe sickle cell disease.
- NHLBI-sponsored study shows once a child with sickle cell disease is 5 years old, penicillin treatment can be stopped.

1996

- Researchers develop method to use maternal blood sample for prenatal diagnosis of disease.
- 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 that share a specific protein.

1997

- The Stroke Prevention Trial in Sickle Cell Anemia (STOP) finds periodic blood transfusions in children who have sickle cell disease and are at high risk of stroke reduces risk of first stroke by 90 percent.

"With the completion of [this study], we now know that we can effectively prevent the two leading causes of death in children with sickle cell disease: pneumococcal sepsis and stroke."

– "Sickle Cell Research for Treatment and Cure," NHLBI

1998

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

2001

- Program starts to collect umbilical cord blood from sibling donors in families with children who have sickle cell disease or related blood disorders with the goal of a future transplant.
- Researchers use genetic therapy to correct sickle cell disease in mice.

2002

- The Health Resources and Services Administration Newborn Screening Program begins.

2003

- Hydroxyurea therapy found to improve survival in adults who have severe sickle cell disease.

2004

- Study finds children who have sickle cell disease and a high risk for stroke who stop receiving periodic blood transfusions return to high risk of stroke after 30 months.

2006

- The NHLBI launches Sickle Cell Disease Clinical Research Network. NHLBI scientists find that a hormone—brain natriuretic peptide, or BNP—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 health care professionals from around the world to discuss advances and challenges for sickle cell disease clinical care.

2008

- The Newborn Screening Saves Lives Act of 2007 establishes grants to provide for education and outreach about newborn screening and coordinated follow-up care.
- 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 Sickle Cell Disease Research Program by expanding support for basic research and developing a new Clinical Trials Research Network and evidence-based treatment. Also initiates development of evidence-based clinical practice guidelines.

2009

- Study in NHLBI laboratory finds modified blood adult stem-cell transplant regimen reverses sickle cell disease in 9 of 10 adults severely affected by disease.
- NIH stops a clinical trial early due to safety concerns. Researchers were testing a treatment for pulmonary hypertension in adults who had sickle cell disease.
- The NHLBI convenes workshop of researchers, health care 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."

– Tiffany McCoy, a person who lives with sickle cell disease

- The NHLBI and the Centers for Disease Control and Prevention launch the Registry and Surveillance System for Hemoglobinopathies (RuSH) program to determine the number of people who are diagnosed with inherited blood disorders, including sickle cell disease.
- NHLBI-supported study shows adults with sickle cell disease may have changes in brain function.
- James B. Herrick Symposium—Sickle Cell Disease Care and Research: Past, Present and Future—commemorates 100th anniversary of Herrick's paper that first identified sickle cell disease. Symposium brings together researchers, health care 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

- An NHLBI-supported expert panel, Evidence-Based Management of Sickle Cell Disease, offers guidance to health care professionals on how best to care for their patients who have sickle cell disease.
- The NHLBI-funded study, Transfusions Changing to Hydroxyurea (TWiTCH), 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 trans-NIH 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

- NHLBI's Trans-Omics for Precision Medicine (TOPMed) Program now includes participants who have sickle cell disease, which may help us 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. While 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 (STRIDE), to identify ways to perform stem cell transplants in adults who have sickle cell disease. Previously, the vast majority of stem cell transplants have been performed in children.
- The NHLBI Strategic Vision highlights ways that the NHLBI may support new efforts for sickle cell disease research over the next decade.

2017

- 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 Discovery Channel's First in Human documentary.
- The NHLBI expands its research efforts to sub-Saharan Africa, where more than 75 percent of newborns who have sickle cell disease are born. Through the SCD in Sub-Saharan Africa Collaborative Consortium, the NHLBI is improving the use of proven 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 sickle cell disease.
- The NHLBI joins with HHS and other partners to create more awareness about the disease and share information about best practices for management and treatment.

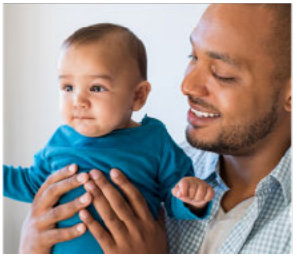
What Is Sickle Cell Disease?

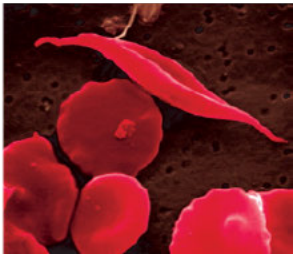
Sickle cell disease is a group of inherited red blood cells disorders. People who have sickle cell disease inherit two abnormal hemoglobin genes, one from each parent. In all types of sickle cell disease, at least one of the two abnormal genes causes a person's body to make hemoglobin S. When a person has two hemoglobin S genes, Hemoglobin SS, the disease is called sickle cell anemia. This is the most common, and often 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. But because people with sickle cell trait are carriers of an abnormal hemoglobin S gene, they can pass it on when they have a child.

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. Hemoglobin S, or sickle hemoglobin, can form rigid strands in the 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. Over a lifetime, sickle cell disease can harm a patient's spleen, brain, eyes, lungs, liver, heart, kidneys, penis, joints, bones, or skin.

Sickle cell disease is a life-long illness, but the severity of the disease varies widely from person to person. In the early 1970s, the average lifespan was only 14 years. Today, patients who have sickle cell disease are living into their forties or fifties, and beyond. Thanks to research, early diagnosis and regular medical care are preventing complications and helping patients 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?

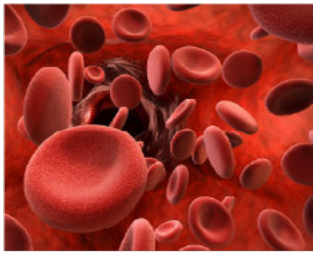
Every state in the United States, the District of Columbia, and the U.S. territories require that all newborn babies be screened for sickle cell disease. In the United States, most people who have sickle cell disease are of African ancestry or identify themselves as black. Approximately 100,000 Americans have sickle cell disease, and more than 2 million people may have sickle cell trait. About 1 in 13 African American babies is born with sickle cell trait, and about 1 in every 365 African American children is born with sickle cell disease. There are also many people with this disease who come from Hispanic, southern European, Middle Eastern, or Asian Indian backgrounds.

The National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI), which is part of the National Institutes of Health, has funded sickle cell research since 1948, when the NHLBI was founded as the National Heart Institute.

The NHLBI has played a crucial role in not only funding basic research but also 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 and molecular biology and has sparked innovations in other areas of medicine.

More important, the contributions of 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.



More information on sickle cell disease is available at sicklecell.nhlbi.nih.gov

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