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.

One hundred years later we know that the sickle-shaped cells are due to a defect in hemoglobin, the protein in red blood cells that carries oxygen throughout the body. A genetic alteration in the hemoglobin molecule causes the body to produce misshapen red blood cells, many of which take the characteristic "C"-shape that is the hallmark of sickle cell disease.

What is Sickle Cell Disease?

Sickle cell disease, also known as sickle cell anemia, is inherited. People who have the disease inherit two copies of the sickle cell gene—one from each parent. The gene codes for production of an abnormal hemoglobin. If a person inherits only one copy of the sickle cell gene, he or she will have sickle cell trait. People who have sickle cell trait do not have the disease, but they carry one of the genes that causes it. Similar to people who have sickle cell disease, people with sickle cell trait can pass the gene to their children.

In the United States, sickle cell disease affects an estimated 70,000 to 100,000 people, the majority of whom are African Americans. All states screen newborns for sickle cell disease. Sickle cell disease occurs in approximately one out of every 500 African American births and one out of every 36,000 Hispanic American births. In addition, about 2 million people in the United States have sickle cell trait.

The symptoms and complications of sickle cell disease vary widely. Some people have mild symptoms while others have very severe symptoms and are hospitalized frequently for treatment. Normal red cells pass smoothly through the blood vessels, but sickled cells are stiff and sticky. Sickled cells tend to form clumps that can block blood flow and lead to episodes of extreme pain, known as crises, as well as chronic damage to vital organs. Persons with sickle cell disease have life-long anemia because their red blood cells survive only about one-tenth as long as cells with normal hemoglobin.

Bone marrow transplants offer a cure to children and adolescents who have a matched bone marrow donor. Because of the limited availability of matched bone marrow donors, however, sickle cell disease has no widely available cure. Treatments are available to address symptoms and complications.

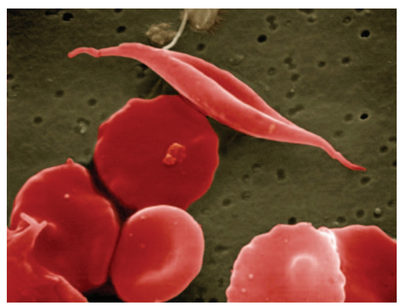
People who have sickle cell disease now lead longer, more productive lives. In the early 1970s, the average lifespan was only 14 years. Today, individuals with sickle cell disease are living into their forties or fifties, and beyond.

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. Since 1972, when the National Sickle Cell Disease Program began, the NHLBI has spent more than $1 billion on sickle cell research.

The NHLBI has played a crucial role in not only funding basic research but also devising and implementing large clinical trials, and conducting workshops and consensus meetings to guide the research agenda. 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 bone marrow transplantation.



Future

The past 100 years of sickle cell research have resulted in landmark discoveries that ushered in the era of molecular genetics.

The NHLBI continues to look ahead to find new and better treatments. Its revitalized research portfolio of basic, clinical, and translational research addresses the genetic factors affecting disease manifestations, regulation of hemoglobin synthesis, development of drugs to increase fetal hemoglobin production, and the development of animal models for preclinical studies. The Institute supports research on transplantation of blood-forming stem cells, gene therapy, a better understanding of and new treatments for pain, optimal uses of blood transfusion, and management of iron overload related to blood transfusions.

The Institute is also leading an effort to develop evidence-based clinical practice guidelines for the care of people who have sickle cell disease, which are expected to be released in 2011. The NHLBI is committed to working with other agencies within the Department of Health and Human Services to disseminate the clinical guidelines with an emphasis on use by primary care practitioners. To ensure that the new guidelines reach their intended audiences, the NHLBI will launch a public awareness and education campaign to focus nationwide attention on sickle cell disease as a serious public health issue.

The NHLBI recognizes that actively engaging patients, families, practitioners, and communities is essential to improving the lives of persons affected by sickle cell disease, and will continue to work with them, community-based groups and scientific organizations to do so.

Sickle Cell Disease and Clinical Trials

The NHLBI sponsors a number of important clinical trials designed to advance the search for better treatments of sickle cell disease. These studies would not be possible without the participation of volunteers who help researchers determine which treatments work. For information on current clinical trials, please visit: http://www.clinicaltrials.gov/.

More information on sickle cell disease is available at http://www.nhlbi.nih.gov/new/sicklecell.htm.

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National Institutes of Health

National Heart Lung and Blood Institute

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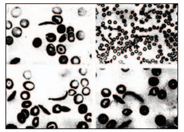
A Century of Progress:
Milestones in Sickle Cell Disease Research and Care

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

1910

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



Sickled cells from 1910 Herrick paper

Dr. James Herrick

"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 test 2,500 African Americans in Memphis; determine sickle cell trait and sickle cell disease are separate entities.

1934

Painful sickle cell "crises" suggested to 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 established. First round of grants includes $8,640 to Dr. James Neel to study inheritance of sickle cell disease.

Dr. James Neel

Research suggests low concentration of sickled cells in blood from newborns with sickle cell disease due to high level of fetal hemoglobin in their red blood cells.

"There are many things yet to be learned about sickle cell anemia. Fame and distinction await the man who can solve the problems of this malady."
– Editorial, Journal of the National Medical Association

1949

Dr. Linus Pauling and others reveal that sickle cell disease due to abnormal hemoglobin protein molecule. Term "molecular disease" coined.

1949–1950

Inheritance of sickle cell disease independently described by two teams. Sickle cell genes needed from both parents to produce sickle cell disease. Receiving gene from one parent produces sickle cell trait.

Public Awareness Poster

1951

Scientific American runs story on Pauling's discovery of molecular nature of sickle cell disease, raising public awareness of the condition.

Dr. Linus Pauling

1953

Diagnostic tool developed to identify sickle cell disease and other conditions due to defective hemoglobin.

1954

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

1955

Blood test developed to identify abnormal hemoglobin, a method still used today to confirm sickle cell disease diagnosis.

1957

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

1959

Marclan A. Walker, a 21-year-old West Virginia college student, describes life with sickle cell disease in the Ebony magazine story, "I'm living on borrowed time." Story was later picked up by Time magazine.

1963

The three-dimensional structure of the hemoglobin protein deciphered using x-ray crystallography. Monumental accomplishment took over 20 years to complete. Dr. Max Perutz received the Nobel Prize for this work in 1967.

1968

Researchers describe red cells from individuals with sickle cell disease that remain sickled even when oxygen levels are restored. Cells termed "irreversibly sickled."

1969

National Heart Institute becomes National Heart and Lung Institute.

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

1971

The National Association for Sickle Cell Disease founded. It becomes the Sickle Cell Disease Association of America, Inc. in 1994.

"It is a sad and shameful fact that the causes of this disease have been largely neglected throughout our history. We cannot rewrite this record of neglect, but we can reverse it. To this end, this administration is increasing its budget for research and treatment of sickle-cell anemia . . ."
– President Richard Nixon, in his "Special Message to the Congress Proposing a National Health Strategy"

1972

National Sickle Cell Anemia Control Act provides for establishment of voluntary sickle cell disease screening; 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.

Dr. Roland Scott

A milder variation of sickle cell disease found in Saudi Arabia associated with increased levels of fetal hemoglobin. Finding suggested increasing fetal hemoglobin levels could offer treatment target.

Bill Cosby stars in TV movie "To All My Friends On Shore," which addresses sickle cell disease.

1972–1973

National Sickle Cell Disease Program established. The National Heart and Lung Institute begins funding comprehensive sickle cell centers and establishes sickle cell branch at Institute.

1973

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

Sidney Poitier directs and stars in movie "A Warm December," which has sickle cell disease as a central theme.

1974

Feasibility of newborn screening for sickle cell disease demonstrated.

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.

1976

National Heart and Lung Institute becomes the National Heart, Lung, and Blood Institute (NHLBI).

1978

Prenatal method to diagnose sickle cell disease using DNA samples reported.

The NHLBI launches multicenter study with 4,000-plus individuals from newborns to age 70. First study to document clinical course of disease from birth to adulthood.

1979

Red blood cells from patients with sickle cell disease shown to stick more readily to cells lining blood vessels than do normal red blood cells.

1980

Binding of sickled red blood cells to the inside of blood vessels shown to block blood flow. Extent of stickiness suggested as possible determinant 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.

Bone marrow transplant performed to treat a child with leukemia. It also cures the child's sickle cell disease.

1986

An NHLBI study shows penicillin as a preventive measure in children with sickle cell disease 3 months to 3 years old can reduce the incidence 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.

NIH Consensus Development Panel Report

Newborn screening for sickle cell disease required 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 aid in finding treatments.

Study shows even small increases in fetal hemoglobin can result in fewer pain crises.

1995

Major NHLBI-sponsored study 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 severely affected adults with sickle cell disease.

NHLBI-sponsored study shows once a child with sickle cell disease is 5 years old, penicillin treatment can be stopped.

1996

Method developed to use maternal blood sample for prenatal diagnosis of disease.

Multicenter study of bone marrow transplantation in children with sickle cell disease finds the procedure can cure young sickle cell patients who have siblings that share a specific protein.

1997

Periodic blood transfusions in children with sickle cell disease who are at high risk for stroke shown to reduce 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 study.

2001

Program starts to collect umbilical cord blood from sibling donors in families with children who have sickle cell disease or thalassemias with the goal of future transplantation.

Researchers use gene therapy to correct sickle cell disease in mice.

2002

The Health Resources and Services Administration Newborn Screening Program starts.

2003

Hydroxyurea therapy found to improve survival in adults most severely affected with disease.

2004

Study finds children with sickle cell disease at high risk for stroke who stop receiving periodic blood transfusions after 30-month minimum return to high risk of stroke.

U.S. Postal Service issues Sickle Cell Disease Awareness postage stamp.

2006

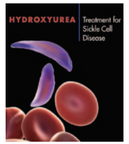
The NHLBI launches Sickle Cell Disease Clinical Research Network.

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.

2008

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

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



NIH Consensus Development Panel Report

"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 nine of 10 adults severely affected by disease.

Clinical trial testing of drug treatment for pulmonary hypertension in adults with disease stopped early due to safety concerns.

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

Tiffany McCoy

The NHLBI and the Centers for Disease Control and Prevention launch program to determine the number of people 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.

For references on studies noted in the timeline, please visit http://www.nhlbi.nih.gov/new/sicklecell.htm.