Can Sickle Cell Anemia be stopped?

Mia Carrington

Global Connections

January 24, 2012

3A

**Abstract**

 Sickle cell is a hereditary disorder that affects roughly one out of 500 African Americans in the United States alone; one can only assume the statistics of those affected outside the U.S.A. Because of the sickled shape of the cells, passing through the veins cause chronic pain and low oxygen levels, making basic activities difficult. Researching methods to relieve these symptoms would positively change the way sickle cell patients live their lives. This investigation required an approach at different angles because one method cannot accomplish such a difficult goal. Angles approached included sickle cell’s relation to other blood diseases in terms of treatments, the symptoms of the disease to find the main problem (red blood cells); after underlying the problem, researching affects and ways to alter the effects on the disease with supporting evidence such as an interview, lab experiments, and scholarly articles. Through investigation, preserving blood from people with sickle cell disease or trait will relieve major symptoms affecting patients. Because sickle cell is hereditary, cures are difficult to discover; as much of the damage has already begun before a person is diagnosed with the disease. The difficulty of the task at hand requires even more in depth research described in this paper. The proposed solution, after modification and testing has the potential to relieve chronic pain, and restore oxygen levels to a healthy level. If proved unsuccessful, it would still provide openings for new experiments and topics to investigate.

The year was 1971. After frustrating travels to Kings Daughters Hospital carrying a constantly crying, aching 3 year old with a 106 degree temperature, the mother, desperate for answers, was led to Portsmouth naval hospital in Portsmouth, Virginia. “What kind of mother are you, letting your child have this high of a temperature?” yelled the internist, making the situation worse. While being held back, the angry mother raged a colorful array of vocabulary to this ignorant internist before the doctor came and suppressed the situation. The doctor took the enraged mother into a room, and asked if she had ever heard of sickle cell anemia. Following the question came a thorough explanation followed by a short film about the disease that was going to affect her and her daughter the rest of their lives. (Interview)

 What the enraged mother came to discover was that her and her husband were carriers of the sickle cell trait, and that her daughter, Cheryl Carrington, had produced the disease. When a person is born with the sickle cell trait, they harbor a recessive gene that contains hemoglobin S. Hemoglobin, located in red blood cells, are proteins that provide both oxygen and iron for the body. Normal hemoglobin A produces healthy, donut shaped red blood cells lasting approximately 120 days; however Hemoglobin S, changes the red blood cell from the healthy, round shape, to an unhealthy sickled or crescent shape, lasting approximately 10-20 days (Sickle Cell Anemia).

 Due to the fact that sickle cell is a hereditary disease, both the trait and the disease are inherited from the parents. When two carriers of sickle cell trait produce a child together, there is a fifty percent chance that each child will either be a carrier of the sickle cell trait, or a perfectly healthy, non carrier. Also, whether carriers of the trait or not, children have a 1 in 4 chance, or twenty-five percent possibility, of being a carrier of the actual disease. Having the trait does not produce many, if any, symptoms of the disease. In some cases, carriers of the trait have endured some small, non severe crisis but this is not usually common unless in extreme conditions such as working out in extreme heat, dehydration, or lack of oxygen in the air --- such as when scuba diving and/or mountain climbing (Sickle Cell Trait).

 Sickle cell anemia and the sickle cell trait, whether affecting the person or not, all share the same problematic commonality. Thus identifying the main problem --- the abnormal hemoglobin S which causing the rapid sickling --- scientist are enabled to legitimately begin researching with a new question produced: How can one prolong the life of a sickled red blood cell long enough for new red blood cells to be produced? If scientist were to prolong the life of a sickle cell, in essence, the amount of oxygen in the body would increase significantly. This alone, would eliminate many of the major, and most severe symptoms such as anemia, oxygen deprivation, and jaundice. The key to the discovery of how to prolong the life of a sickle cell requires solutions in a variety of areas; specifically concentrating in the biological and chemical aspects of a healthy red blood cell and a sickle red blood cell. One or more solutions will be found when scientist research treatments of other blood diseases, in depth analysis of the complications related to sickle cell, and comparing the structure of a normal and abnormal red blood cell thus providing possible solutions to modify the usual patterns that lead to the sickling.

 “Mama I hurt, I hurt. Why do I keep hurting?” (Interview) Carrington cried during one of the many times she complained of the aches and pains throughout her whole body. Accompanied by these aches and pains included low oxygen count, swelled hands and feet, and iron deficiency anemia. She couldn’t walk due to the intense pain as the sickled blood cells would clog the miniscule space in her veins. The blockage in the thousands of veins throughout her body caused a lack of blood flow to essential parts of the body; essentially making her weaker and weaker with every crisis she went through (Interview).

 By taking the time to analyze Carrington and other sickle cell patient’s symptoms, as well as what causes these symptoms, new treatments will be created, leading to scientific breakthroughs to amaze the world and land a mark in history. In order to reach an answer or to analyze ways to go about answering this unanswerable question, other points of understanding must be established; the first point being the symptoms of this disease, and how they relate to the destruction and weakening of the body, misdiagnosis, and treatments used in other blood disorders that may have a positive reaction when used for treating sickle cell.

 At ten years old, Carrington had already received her first blood transfusion. She had 5 to 6 pints of blood in her body compared to the normal 13 pints of blood (Interview). The cause of the unusually low blood count was due to the sickled cells prohibiting the cells from producing oxygen, a key component in blood (Sickle Cell Disease). She was constantly in an out of the hospital receiving blood transfusions. At one point, she had received a blood transfusion due to an enlarged spleen (Interview). Because the spleen is responsible for destroying red blood cells that are unusable or have reached the end of their life cycle, the spleen became overloaded with sickled red blood cells that have died in their 10-20 day life cycle. The large concentration of dead, sickle cells causes the spleen to become enlarged which can cause larger, life threatening problems (Al-Salem H. Ahmed). Blood transfusions normally were capable of relieving her symptoms for a while, but by her early twenties, Carrington had been poked and prodded with so many IVs in her arm that her veins collapsed, making it that much harder to complete blood transfusions. Therefore, doctors inserted first a picc line, then later a metaport due to the picc lines becoming infected (Interview). Picc lines are responsible for acting in place of a vein in which they are usually placed in your arm, close to the heart, and transport fluids and in Carrington’s case, blood (Learning about your health). These symptoms, enlarged spleen and low blood count are just two of the symptoms exhibited in sickle cell anemia.

 If the confused doctors who constantly gave useless answers to an also confused and frustrated mother would have traveled deeper into research and learn more about the effects of the sickling cells, he or she would have discovered the causes for the most common symptoms of sickle cell that Carrington knew about all too well. First of these symptoms was the most common: Sickle Cell Crisis which is described as episodes of intense pain ranging from mild to very severe and having to be hospitalized. Depending on the person, they can last anywhere from minutes to weeks at a time. Carrington unfortunately had her crisis as often as every two months. During these crises, the lack of oxygen being transported to other parts of the body is hindered which causes significant amounts of organ damage. The organ damage then weakens the immune system and, in severe cases, contributes to organ failure. What happens to cause this is that the red blood cells, which have already taken on their sticky, pointy, sickled form, have become stuck inside the veins. The blocked veins, as stated earlier, block other red blood cells from delivering oxygen and blood to other parts of the body. If not taken care of immediately, then the parts of the body will start to painfully swell, and the tissues and organs located in the part of the body being deprived from oxygen start to die (Sickle Cell Disease). Along with Carrington’s constant crisis having her in and out of the hospital, and keeping her away from family school and friends, she also had to endure severe anemia. Shortness of breath, extreme fatigue, and chest pain which is commonly took over her body and continued to keep her running to the hospital just to receive even more medication such as morphine, Vikatin, Tylenol, and Valium. At one point, her pain was so intense from sickle cell crisis, an enlarged spleen, and difficulty breathing she was prescribed dilaudid; a powerful drug, much like the equivalent to morphine and is normally used for severe pain (Interview). The symptoms of sickle cell have the potential to be just as severe as the actual disease itself. Without monitoring these symptoms, there could be a number of other problems that go wrong and lead to other diseases and health issues such as gallstones, stroke, acute chest syndrome, kidney and eye damage, and an increased number of infections (Sickle Cell Disease).

Consequently, symptoms of sickle cell anemia, such as anemia and weak immune systems, are sometimes confused with symptoms in other diseases; slightly due to the fact that sickle cell tends to lead other diseases while at the same time another illness. However, by analyzing symptoms sickle cell have in common with other blood diseases, it is possible to find common treatments that may be beneficial to sickle cell anemia patients.

 Due to the wide range of symptoms sickle cell anemia covers, many times the disease is mistaken for other diseases. Sickle cell anemia, when left untreated, will become lethal to the human body. The many irregular functions this disease causes leads to other diseases and/or complications such as pulmonary hypertension, stroke, and acute chest syndrome. Many sickle cell patients unfortunately fall victims to stroke due to the sickle cells clogging the arteries that lead to the brain (What is Stroke?). Because sickle cell in known for the sickle cells blocking arteries, strokes are common among patients; specifically in children. If the patient is not brought to medical attention in a considerable amount of time, there could be significant brain damage in development, and/or daily activities such as walking, talking, or even lead to death. Blood Transfusions are common treatment for strokes, but as seen in Carrington’s case, blood transfusions can often lead to more harm than good. Blood transfusions are commonly used for sickle cell patients including spleen enlargement and anemia causing the low blood count. Constant blood transfusions cause the veins to become weak, eventually too weak so they are unable to have blood drawn; which often leads to their collapse (Interview). If they collapse, then blood transfusions may be seen as useless because the patient’s veins are too weak to support them. Also, constant blood transfusions can lead to an iron overload which is an over access of iron (**Mir A, Muhammad)**. Even though patients with sickle cell anemia usually suffer from iron deficiency, iron overload can be dangerous just as any other overload of minerals would. Fortunately, another treatment has been used. In an article about sickle cell disease and its relation to stroke, the authors describe an experiment in 1999 by [Russell E. Ware](http://bloodjournal.hematologylibrary.org/search?author1=Russell+E.+Ware&sortspec=date&submit=Submit), [Sherri A. Zimmerman](http://bloodjournal.hematologylibrary.org/search?author1=Sherri+A.+Zimmerman&sortspec=date&submit=Submit) and [William H. Schultz](http://bloodjournal.hematologylibrary.org/search?author1=William+H.+Schultz&sortspec=date&submit=Submit) in which they used hydroxyurea as an alternative for blood transfusions. In the experiment,

 Ware et alexamined 16 children with stroke histories who were on chronic blood transfusions for a mean of 56 months and had their transfusions stopped because of alloimmunization, autoimmune hemolysis, iron overload, or noncompliance. HU therapy and intermittent phlebotomy to remove iron were offered to these patients, beginning 2 weeks after the last transfusion. After a mean of 22 months on HU therapy, the stroke rate was 19%. Although significantly lower compared with historical controls, the stroke rate was almost twice as high as that observed in patients receiving transfusions in the same institution (11%). Notably, the average time to stroke in those who had the complication was only 3 to 4 months. (Nathan, David G; Verduzco, Luis A.)

With new test using hydroxyurea, sickle cell patients are able to rest their veins while receiving a more effective treatment, lasting longer than blood transfusions. However, one would now start to wonder, is there a better treatment out there that has a better effect than hydroxurea?

 Due to increased cardiac output in sickle cell patients, the arteries are required to increase blood flow of deoxygenated blood. Because of the lack of oxygen in this blood, it makes the lungs work harder, which decreases the amount of exercise the sickle cell patient can endure. This increased pressure in the lungs is known as Pulmonary Hypertension, and is a commonly caused in sickle cell patients (Clarke, Melissa E. MD ). Most treatments for pulmonary hypertension include high doses of drugs such as prostacyclin. Prostacyclin has been shown to aggressively attack this disease and significantly increase quality of life, and endurance. Another option less common and for people who will not respond to the medicine is a lung transplant. Lung transplants are a good option for these patients because it reduces the amount of pressure on the lungs and no reports of pulmonary hypertension becoming worse has never been reported. Survival rates for the lung transplant have been over 50 percent, so it looks good as an alternative. However, the wait for this transplant can take years and the life expectancy after diagnosis is approximately 2.8 years in some cases (Nauser, M.D., Trenton D.; Stites, M.D., Steven W.). A sickle cell patient waiting for a lung transplant may not be worth the wait, as new damage to the lungs would occur with each sickle cell crisis they endure. Having both diseases at the same time already reduces life expectancy lower than the average sickle cell patient; therefore, drugs for treatment still stand as the most effective way for treatment.

 During Carrington’s many stays in the hospital, she often had to have aid when breathing, by using the ventilator. Her respiratory system was weak, and the constant sickle cell crises were not making it any better. She would start to complain of chest pains, which were hard to decipher between either a sickle cell crisis or acute chest syndrome. Acute chest syndrome can be caused by an infection and other ways, and the symptoms may sometimes appear as symptoms for other illnesses. It is followed by high white blood cell count, but low oxygen count; severe chest pains, and fever. This can be life threatening if not treated immediately, and most treatments include blood transfusions, high doses of medicine or supplementing the patient with oxygen (Wethers, M.D, Doris L.).

 In terms of misdiagnosis, it is very easy to mix up sickle cell with another disease because of its ability to stretch and conform into other diseases so quickly. Doctors must be able to accurately recognize the symptoms and treat the illnesses correctly otherwise, the patient will become worse. When analyzing the methods of treatment for the three complications listed above, blood transfusion is commonplace, as well as oxygen supplements. These two techniques have seemed to work; however, if continued constantly, they will start to see negative effects. One problem that prohibits scientist from finding an answer is that there is no treatment found that could stop the sickle cells from causing these complications; and this problem ties into the unanswerable question. If the life of a sickle cell were prolonged long enough for new, healthy red blood cells to be made, many of these complications could be avoided. Also, the discovery could be modified to use on other blood disorders with healthy red blood cells instead of having a specific treatment for sickled blood cells.

Concluding understanding of the symptoms of sickle cell and the complications influenced from the disease, the next point of understanding to be investigated is in the area concerning the structure of a red blood cell, also known as an erythrocyte, compared to the structure of a sickle erythrocyte or otherwise stated as: What goes on inside the tiny membranes of red blood cells? To get a closer look and become possibly in reach of a solution to the sickling blood cell; measures such as analyzing the structure of a normal red blood cell vs a sickle red blood cell must be observed for there may be key evidence inside the structure that could be of use. Beginning with the membrane of a normal, healthy erythrocyte, scientist have found that an erythrocyte is structured upon a flexible membrane, constantly bending and conforming to the tiny size of a vein and/or artery before springing back to its normal shape (Ming, Dao). However, in the membrane of sickle cell, the sickle shape is rigid and so far out of its normal shape that it is unable to effectively move through arteries without clogging the vein itself. On a molecular level, the sickling is due to a mutation in the beta globin chain. These results in insoluble polymers forming which in a significant concentration can eventually lead to the sickling of the erythrocyte (Marengo-Rowe, MD, Alain J.). The sickle erythrocyte becomes hard and sticky unlike the characteristics of a normal, healthy blood cell which is round and soft.

 If scientist were to take an approach such as fixing the genetic mutation, there would be at least two large factors to consider. The first factor is that scientist cannot predict when a genetic mutation will occur, no matter what disease there is. In sickle cell anemia, symptoms do not start to show until 4 to 6 months old because of another type of hemoglobin; hemoglobin F, or otherwise known as fetal hemoglobin. Fetal hemoglobin is produced as a child up until about 6 months however the exact time when Hemoglobin F switches to producing adult Hemoglobin A is unknown (Amuzu, Dominic). For this reason only is why the symptoms of sickle cell anemia do not show until at least 6 months after birth. The role of fetal hemoglobin in sickle cell will be later explored throughout this paper. Due to the unknown time where the cells begin to sickle, scientists are at a great disadvantage in preventing this sickling. The second factor to take into consideration concerns the fact that scientist have not found an effective way, if any way at all to revert a genetic mutation. Throughout history and the scientific theory of evolution, and natural selection, mutations in an organism cause that organism to be able to adapt to an environment in a more successful manner than members of their species will in turn benefit them and enable them to live to pass the mutation along to their children. Then the mutation is not seen as a mutation anymore, but an adaptation. Scientist trying to take on the task of changing a genetic mutation adaptation would equate to them, in a sense, trying to revert a physical adaptation; something that has never been proven among any scientists. Therefore, upon reviewing the structure of both a healthy erythrocyte and a sickle erythrocyte, a conclusion drawn is that taking an approach in which a scientist attempts to correct a genetic mutation will most likely result without success.

 The structure of a normal and sickle erythrocyte seems to have taken a dead end however, is one uses the institutive nature in them, this dead end could lead to a secret cave of new questions and topics to explore. Currently, this dead end has led to the secret cave in which a door has opened to our third point of understanding in the journey to answering the unanswerable question. Gaining new knowledge about the structure of the cells allows deeper understanding into the life cycle of both types of cells. By knowing that the Hemoglobin S causes a healthy erythrocyte to sickle and die quicker, one can go into research further and be able to answer the question: What is the life cycle of a normal and sickle red blood cell and how does hemoglobin function in both types of cells?

 According to Union County College in New Jersey, the process to develop new red blood cells takes up to four days and starts in the bone marrow from division of stem cells. From there synthesis of hemoglobin takes places, and at this time large amounts of hemoglobin can be observed. After the hemoglobin is synthesized, the nucleus is extracted and “**These cells exhibit a net-like appearance or reticulum in their cytoplasm when stained. A small number of reticulocytes (only 1 to 3% of the circulating red cells) are found in the circulation.” Next, the cells lose ribosomes and the cells are finally added into the blood stream (Life Cycle of the Erythrocyte). Finally, they are carried to the spleen, land lungs where they are destroyed, and their blood and iron is released to flow and nourish the rest of the body. In a sickle erythrocyte, the process is the same however, due to the mutation in Hemoglobin S, the oxygen in the red blood cell is short lived, as the abnormal hemoglobin uses up all of the oxygen instead of circulating it throughout the body. Because of this, the sickle cell dies in half the time a normal red blood cell would die (**Hemoglobinopathies). At this time, the millions of red blood cells all dying at the same time are sent to the spleen or lungs to be destroyed before the bone marrow can produce new red blood cells. The lack of red blood cells that are alive and bringing oxygen and iron to the body is limited which is often why sickle cell patients such as Carrington suffer from enlarged spleens and iron deficiency anemia.

 The most common way available to replace all of the missing oxygen is to be placed on the ventilator; a place where Carrington had often been for too long. Her doctor gathered her family around to tell them about how due to the early destruction of her red blood cells, there has been a low oxygen count in her body that is getting worse; therefore she has to be put on the ventilator (Interview). At this point she was around 30 years old, pregnant, and had lived ten years longer than her doctors had expected her too. The baby worried doctors, for they had told her not to get pregnant; one reason because the baby would have a higher chance of getting sickle cell anemia, and two, the baby could put Carrington in a worse condition than she was now. Carrington was a free spirit who was not going to let the doctors limit her from what she could do in her limited lifetime; therefore, she carried the baby for the whole 9 months. At points it was almost unbearable because of the individual pains and problems that come along with pregnancy, and also having a severe disease making her weaker and weaker as the weeks dragged on (Interview).

 On December 1, 1997, Carrington gave birth to a healthy baby boy named Jeremiah. Since Jeremiah was just born, doctors were unsure of whether he had the sickle cell trait or the actual disease so he and his mother were on close watch at the hospital for days; meanwhile, Carrington was still on the ventilator. The reason why doctors couldn’t tell Jeremiah’s status on having the trait or the disease was because he was producing fetal hemoglobin, hemoglobin produced only by children up to about 6 months old (Amuzu, Dominic). After these six months, it was found that Jeremiah is a carrier of the sickle cell trait; however that was great new to his mother and family; now they would have a healthy boy ready to take on the world and live for the things his mother isn’t able to do in the hospital. Fortunately for Jeremiah, he was and still is able to live a healthy life with just the sickle cell trait. In reference to the thesis, studying the young red blood cells traveling through Jeremiah’s body could possibly lead to a discovery in which the way red blood cells begin to act in early childhood could contain a key to altering the cells when or before the patients become adults.

 The understanding of theories such as the statement in the previous paragraph is dependent on the final step of understanding: What other ways are there to prevent the sickling of red blood cells? There have been many experiments by scientist to find a way to unsickle cells however at this point in time, scientists are far from reach. In an experiment published in June 20003, Peroxiredoxin II was shown as a possible method for prolonging the life span of red blood cells in mice (Tae-Hoon Lee). The article mainly described an experiment in which the protein peroxiredoxin was used on mice to see if they would have an effect on the life of a red blood cell. “These proteins were characterized to have a number of cellular functions, including cell proliferation and differentiation and protection of specific proteins from oxidative damage” (Tae-Hoon Lee). Oxidative damage is a major setback when trying to preserve cells because it may alter the cells or age them in a way that destroys the cells (Acker, Jason) but if these proteins stop oxidative damage it could be another possible advancement in the discovery of how to increase the life span of the sickle cells. Some experiments have also suggested that Nitric Oxide may be a possibly alternative for stopping the sickling of cells. According to studies from the University of Chicago, Nitric Oxide is a powerful dilator of blood vessels, maybe become useful in halting the sickling of cells. It was found that even the smallest concentration of Nitric Oxide was able to stop sickling of cell; which could serve as a contribution to a large discovery in the treatment or cure to this disease (Nitric Oxide Shows Promise For Treatment Of Sickle Cell Anemia).

 Sickle cell anemia is a frightening disease that has evolved over the years; however as scientist have continued to experiment and make new discoveries, the cure has been traveling closer and closer within reach. Going through this journey of research, the knowledge gathered often feels like too little knowledge and there is always a thirst for more knowledge to be gained. As scientist get closer and closer with experiments, new knowledge will continuously pile together to form a discovery that has changed the world. Also, it could possibly, in modified ways, lead to other discoveries in how other diseases are caused such as stroke, acute chest syndrome, etc. After researching, the author has discovered that though there may not be a possible way to yet prolong the life of a sickle cell, by observing ways around it such as preserving a cell, of using fetal hemoglobin will lead to further discoveries. When talking about fetal hemoglobin, the author has noticed that if scientists concoct a method to extract fetal hemoglobin from infants whom are suspected carriers of the trait or the disease, that same fetal hemoglobin could be used to prevent the sickling of cells. If the infant does not end up inheriting the disease, then the fetal hemoglobin could be preserved and used on another patient with sickle cell anemia. Of course there will be questions still on how to get to the fetal hemoglobin; and also since the inside of a red blood cell is still not a topic completely known by scientists, research seems to be the only way to further progress on the journey to stopping sickle cell anemia.

 Unfortunately, on September 5, 2000, Carrington had lost the fight to sickle cell anemia and passed away. Devastated family members and friends gathered from across the country to pay their respects to this tough woman who spend most of her life in the hospital fighting for her life back; a life she never was fully able to live. Her memory lives on through the hearts of all of whom she touched. Her happy, positive way of life inspired others to do well for themselves, and to never take life for granted. The author wrote this paper as not only advocate for finding a solution to this horrid disease, but also as the niece of Cheryl Carrington. Watching a loved one suffer is not an easy task, however it brings about passion and commitment to find a cure or find a way to improve the lives of people living with that illness that took away that loved one. That same passion and commitment has inspired the author to write this paper has made the author make a promise to one day, make a difference not just for her, but for every child, teenager, and adult that have to suffer this disease just as her aunt did. Writing this paper is just one step into making a difference and fighting for the lives of the sickle cell patients.

**Works Cited**

1. Acker, Jason. Kanias, Tamir. “Biopreservation of red blood cells---the struggle with hemoglobin oxidation.” The FEBS Journal. Vol.227 Issue 2. Pg.343-356.Jan 2010. Wiley Online Library. Oct. 2011. <Onlinelibrary.wiley.com/doi/10.1111/j.1742- 4658.2009.07472.x/full>
2. [Al-Salem](http://www.isrn.com/62101756/), [Ahmed H.](http://www.isrn.com/62101756/) “ Splenic Complications of Sickle Cell Anemia and the Role of Splenectomy.” Department of Pediatric Surgery, Maternity and Children Hospital. Volume 2011 (2011), Article ID 864257. Dec. 14 2011
3. Amuzu, Dominic. Antwi- Bosaiko, Charles. Edoh Dominic. “Fetal hemoglobin during infancy and in sickle cell adults.” Zoology Department, University of Ghana. PMCID: PMC1831961. 6 March 2006.Nov. 30 2011
4. [Brawley](http://www.annals.org/search?author1=Otis+W.+Brawley&sortspec=date&submit=Submit), MD; Otis W. [Cornelius](http://www.annals.org/search?author1=Llewellyn+J.+Cornelius&sortspec=date&submit=Submit), PhD, LCSW; Llewellyn J., [Edwards](http://www.annals.org/search?author1=Linda+R.+Edwards&sortspec=date&submit=Submit), MD; Linda R., [Gamble](http://www.annals.org/search?author1=Vanessa+Northington+Gamble&sortspec=date&submit=Submit), MD, PhD; Vanessa Northington, Green, RN; Bettye L., [Inturrisi](http://www.annals.org/search?author1=Charles+Inturrisi&sortspec=date&submit=Submit), PhD; Charles,  [James](http://www.annals.org/search?author1=Andra+H.+James&sortspec=date&submit=Submit), MD, MPH; Andra H.,  [Laraque](http://www.annals.org/search?author1=Danielle+Laraque&sortspec=date&submit=Submit), MD; Danielle ,[Mendez](http://www.annals.org/search?author1=Magda+Mendez&sortspec=date&submit=Submit), MD; Magda, [Montoya](http://www.annals.org/search?author1=Carolyn+J.+Montoya&sortspec=date&submit=Submit), RN, MSN, CPNP; Carolyn J., [Pollock](http://www.annals.org/search?author1=Brad+H.+Pollock&sortspec=date&submit=Submit), MPH, PhD; Brad H., [Robinson](http://www.annals.org/search?author1=Lawrence+Robinson&sortspec=date&submit=Submit), MD, MPH; Lawrence,  [Scholnik](http://www.annals.org/search?author1=Aaron+P.+Scholnik&sortspec=date&submit=Submit), MD; and Aaron P., [Schori](http://www.annals.org/search?author1=Melissa+Schori&sortspec=date&submit=Submit), MD, MBA; Melissa. “National Institutes of Health Consensus Development Conference Statement: Hydroxyurea Treatment for Sickle Cell Disease.”Annals of Internal Medicine. Vol. 148 No.12 932-938. 17 Jun 2008. Dec. 13 2011
5. Carrington, Louise. Personal Interview. 8 Dec 2011
6. Clarke, MD, Melissa E. “Pulmonary Artery Hypertension in Sickle Cell Disease.” 08 11 2006. Dec.18 2011
7. [Dao](http://www.pnas.org/search?author1=Ming+Dao&sortspec=date&submit=Submit), Ming, Li, Ju, [Lykotrafitis](http://www.pnas.org/search?author1=George+Lykotrafitis&sortspec=date&submit=Submit), George, Suresh, [.](http://www.pnas.org/search?author1=Subra+Suresh&sortspec=date&submit=Submit) “Cytoskeletal dynamics of human erythrocyte.” PNAS. Brown University. 15 Nov. 2006. Dec. 18 2011
8. “Hemoglobin.”Davidson College. Department of Biology.2005. Nov. 29 2011
9. “Hemoglobinopathies.” Harvard University. 17 Apr. 2002. Dec. 22 2011
10. “Hemoglobins- What the Results Mean.” Sickle Cell Information Center. 22 Jun. 2010. Nov. 30 2011
11. “Learning about your Health.” CMPC Sulter Health. 2011. Dec. 14 2011
12. “Life cycle of the erythrocyte.” Union County College. 2011. Dec. 22 2011
13. Marengo-Rowe, MD, Alain J. “Structure-Function Relations of Human Hemoglobins.”PubMed.PMCID: PMC1484532.Baylor University. 19 07 2006. Dec. 22 2011
14. Mir, A Muhammad.“Transfusion-Induced Iron Overload and Treatment.Medscape Reference.WebMD 2012. Jan. 22, 2012
15. Nathan, [David G.](http://bloodjournal.hematologylibrary.org/search?author1=David+G.+Nathan&sortspec=date&submit=Submit), Verduzco, [Luis A](http://bloodjournal.hematologylibrary.org/search?author1=Luis+A.+Verduzco&sortspec=date&submit=Submit). “Sickle Cell Disease and Stroke.”Blood Journal. Hematology Library. Vol 114 no. 25 5117-5125. Dec. 18 2011
16. Nauser, M.D, Trenton D., Stites, M.D., Steven W. Diagnoses and Treatment of Pulmonary Hypertension. AAFP. University of Kansas Medical Center. 01 05 2001. Dec. 18 2011
17. “Nitric Oxide Shows Promise For Treatment Of Sickle Cell Anemia.” Doctor’s Guide.20 Oct. 1997. Dec. 22 2011
18. “Sickle Cell Anemia.” PubMed Health. A.D.A.M. Medical Encyclopedia. U.S. National

 Library of Medicine.28 02 2011. Nov. 30 2011

1. “Scientists Discover Secret Behind Human Red Blood Cell's Amazing Flexibility.”UCSD Jacobs School of Engineering. News Release. 21 10 2005. Nov. 30, 2011
2. “Sickle Cell Trait.” Centers for Disease Control and Prevention. 16 09 2011. Nov. 30 2011
3. Tae-Hoon Lee. Sun-Uk Kim. Seong-Lan Yu. Sue Hee Kim. Do Sim Park. Hyung- Bae Moon. So Hee Dho. Ki-Sun Kwon. Hyuh Jeong Kwon. Ying- Hao Han. Sangkyun Jeong. Sang Won Kang. Hee-Sup Shin. Kyung-Kwang Lee. Sue Goo Rhee. Dae-Yeul Yu. “Peroxiredoxin II is essential for sustaining life span of erythrocytes in mice.: Blood Journal. Vol 101 No 12.pp.5033-5038. 15 June 2011. Blood journal.hematologylibrary.org. Oct. 2011. Bloodjournal.hematologylibrary.org/content/101/12/5033.full.html
4. Wethers, M.D. Doris L., “Sickle Cell Disease in Childhood: Part II. Diagnosis and Treatment of Major Complications and Recent Advances in Treatment” AAFP. St. Luke's–Roosevelt Hospital Center. 15 09 2000. Dec.18 2011
5. “What is Stroke?’ American Stroke Association.2011. Dec. 18 2011