SICKLE CELL TRAIT TESTING IN THE ATHLETE: EXPERIENCE AT THE UNIVERSITY OF PITTSBURGH

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BA, Kenyon College, 2006

Submitted to the Graduate Faculty of

the Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2010

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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It was defended on

April 1, 2010

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There is a general lack of awareness regarding sickle cell trait in the field of athletics. While sickle cell trait is usually considered a benign condition, there have been reports of serious complications during extreme conditions (i.e. high altitude or hot temperatures) among competitive athletes. In June 2009, the National Collegiate Athletic Association (NCAA) recommended that all of its student athletes determine their sickle cell trait status, if unknown. Testing athletes for sickle cell trait has possible undesirable implications, such as stigmatization and discrimination against athletes with sickle cell trait. This project aimed to prevent these negative implications by developing a novel program to provide sickle cell education, testing, and pre/post-test counseling for students in collegiate athletic programs.

The Pediatric Sickle Cell Program at Children's Hospital of Pittsburgh (CHP) collaborated with the University of Pittsburgh in July of 2009 to facilitate voluntary testing of student athletes for sickle cell trait. Our program provided pre-test counseling, testing within the University of Pittsburgh's athletic training facilities for each student athlete, and post-test counseling, regardless of trait status. We met with athletic department staff to provide sickle cell trait education, methods to prevent exercise-related sudden death, and emphasized the importance against stigmatizing student athletes with sickle cell trait.

Testing and education were received well by both coaches and athletes. In total, we tested 79 student athletes; two of which were found to have sickle cell trait. Our program in the

future plans to work with the University of Pittsburgh Athletic Department again and expand testing protocols to other universities in the area. In addition, future studies will assess the student athletes' experience during testing and reasons why some athletes chose not to be tested.

The public health significance of this project is two-fold: to create a testing protocol and educational plan that can be individualized for the needs of a university, while maintaining the autonomy and privacy of the student athletes, and ensuring beneficence and non-malfeasance. In addition, the project raised awareness of sickle cell trait in the field of athletics, which will prevent sudden death among otherwise healthy, young athletes.

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ACKNOWLEDGEMENTS

Finding myself near the commencement of my graduate studies at the University of Pittsburgh, I find it impossible not to look back to where I began nearly two years ago. I have accomplished more personally and academically than I ever though I would, and because of those achievements I am looking forward to the future. The transition from the beginning to the end of the program was not always a smooth path and occasionally I felt like for every step I took, I took two back, but somewhere in the past few months I have made nothing but progress and suddenly find myself miles from where I was.

I need to start at the beginning by thanking Betsy and Robin for their guidance and the depth of knowledge they possess. Because of them, I have learned more than I imagined, both in the field of genetic counseling and about myself. I appreciate that they always had time for a quick talk after class, or a longer one if needed. They believed in me when I did not believe in myself, which helped me see that I was more capable than I realized. I am proud to say that I know them and look forward to joining their profession.

Deep gratitude is necessary for Dr. Lakshmanan Krishnamurti, who was able and kind enough to hire me. I admire his endless enthusiasm for his work and am grateful for the time he took to guide me in this process. The experience and opportunities he has provided for me have been invaluable. Thank you also to Beth Kladny, whose patience, insight and advice on all matters has been much appreciated. I am glad to have worked with you both at Magee Womens

Hospital and Children's Hospital. Additional thanks are necessary to Mary Campbell, for her company and phlebotomy services during testing at the University of Pittsburgh; I very much enjoyed working with her. To Pixie, who helped everything run smoothly and was always available to answer any questions I had or for a quick chat. And to all of the members of the Children's Sickle Cell Program, especially Patti, Regina and Kim, you made me feel welcomed and I enjoyed being part of your team.

To my classmates, whose companionship defined this experience, I appreciate your camaraderie and friendship. To Dan, thank you for your endless support throughout, and sitting through probably one too many genetic counseling stories. Finally, to my family, who have supported me all of my life, regardless of which direction I have taken. Words are not adequate enough to express my appreciation and love for you. It is because of you that I have made it to where I am today and you are the necessary element that makes Pittsburgh, "home."

1.0 INTRODUCTION

Sickle cell trait is present in approximately 1 out of every 12 African-Americans and is generally considered a benign condition.[1] Those with sickle cell trait have one copy of the sickle hemoglobin gene and one copy of the normal hemoglobin gene. Under extreme conditions, namely dehydration and low blood oxygen levels, both of which can be present during periods of intense exertion, sickle red cells can accumulate in the bloodstream, a process referred to as exertional sickling. These sickle red cells can block blood vessels, leading to physical collapse and rapid muscle breakdown, rhabdomyolysis, due to localized oxygen deprivation. In some cases, this process can lead to sudden death in an otherwise young, healthy athlete. There have been nine suspected deaths in middle school, high school, and college athletes over the past seven years alone.[2]

In July of 2009, the National Collegiate Athletic Association (NCAA) strongly recommended that its member universities and colleges screen all athletes for sickle cell trait.[3] As with any genetic testing, it is imperative that sickle cell trait screening be performed in a manner consistent with the hallmarks of genetic testing, autonomy, beneficence, accuracy and privacy. Screening must ensure that student athletes are not stigmatized or otherwise discriminated against as a result of their sickle cell trait status. Additionally, appropriate education to both student athletes and athletic staff needs to be provided so that proper action can

be taken to prevent further deaths from occurring. Merely knowing a student athlete's trait status is inadequate to prevent sudden death.

This project aimed to provide sickle cell trait testing to student athletes at the University of Pittsburgh in a manner that maintained the hallmarks of genetic testing, and ensure that no athletes were discriminated against due to their newly identified trait status. The public health relevance of this effort is in its aims to educate and promote awareness of sickle cell trait in the field of collegiate athletics, a setting in which the importance of knowing a student athlete's trait status has previously been overlooked, and potentially misunderstood.

Services to provide testing for sickle cell trait for the student athletes at the University of Pittsburgh were initiated at the beginning of the Fall 2009 season. Student athletes were offered sickle cell trait testing on a voluntary basis. Those students who elected for testing received pre-test genetic counseling as well as sickle cell education before phlebotomy. Hemoglobinopathy evaluation was performed in the clinical labs at Children's Hospital of Pittsburgh of UPMC. Results were reported to the student athletes via telephone, at which point post-test counseling was provided. A group of coaches, athletic trainers, and athletic staff at the university were given an educational presentation regarding the history of sickle cell disease and trait, the physiological explanation for sudden-death in sickle cell trait carriers, methods to reduce risk of sudden-death in the student athlete, and the appropriate actions to take when an athlete with sickle cell trait collapses suddenly. It is our aim that by promoting responsible sickle cell testing and education at the university level future sudden death due to exertional sickling can be prevented.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 SICKLE CELL DISEASE

Sickle cell disease is an autosomal recessive inherited hematological disorder, most commonly affecting those of African decent. The disorder's name is derived from the presence of abnormally shaped erythrocytes, red blood cells, which instead of being round and soft, are shaped like a sickle and hard. It is defined by the presence of hemoglobin S (Hb S), abnormal hemoglobin resulting from the substitution of valine for glutamic acid at amino acid position six in the ß-hemoglobin chain, produced by the hemoglobin ß gene (*HBB*). Hemoglobin S is much less soluble than normal hemoglobin (Hb A) when deoxygenated, causing polymerization of Hb S in erythrocytes, resulting in the sickle shape.[4] Even when blood is saturated with oxygen, Hb S aggregates may be sufficient to alter the rhologic properties of erythrocytes, which can in turn occlude end arterioles, resulting in chronic hemolysis and microinfarction of a variety of body tissues. This process ultimately leads to vaso-occlusive crisis and irreversible tissue damage.[4] The incidence of sickle cell disease in the United States is one in every 500 African-Americans (compared to one in 2,000-10,000 white Americans). While less prevalent, sickle cell disease can also be found in the Middle East, Greece, India, and occasionally in Caucasians due to admixture over centuries.[5] Sickle cell disease is an umbrella term for a group of disorders characterized by the presence of one Hb S allele and a second, disease-causing allele. Sickle cell

anemia is the most frequent of these disorders and arises when both *HBB* genes have the Hb S mutation.

2.1.1 Molecular and Genetic Basis of Sickle Cell Disease

Sickle cell disease has a long history, starting in 1910 with the discovery of sickled cells by James Herrick in the blood of an anemic African graduate student who experienced recurrent pain; however, the cause was not determined until 1927 that the transformation to sickled cells occurred in response to a lack of oxygen.[6, 7] Earlier, in 1923, sickling was incorrectly classified as an autosomal dominant trait. This assumption was not corrected until 1949, at which point it was determined that heterozygosity for the sickle cell gene resulted in sickle cell trait and homozygosity resulted in sickle cell anemia.[8] Linus Pauling and his colleagues used electrophoresis to demonstrate that hemoglobin from patients with sickle cell anemia showed an abnormally slow rate of migration, and that their parents had both normal and abnormal migrating hemoglobin.[9] It was discovered soon after, that other abnormal hemoglobins could be identified using this method. Eventually, sickle hemoglobin was labeled as Hb S, normal hemoglobin as Hb A and additional variants were assigned letters of the alphabet (e.g. Hb C), until all the letters had been exhausted, at which point they were labeled by the geographic location in which they had been discovered.[10]

Sickle cell disease is a general term to describe the sickling of red blood cells that occur when they are deoxygenated. Sickle cell anemia, the most common, is the specific term for homozygosity of abnormal hemoglobin resulting from the substitution of valine for glutamic acid at amino acid position six in the *HBB* gene.[4] Other sickle cell disorders in which sickling produces a significant clinical phenotype are sickle cell hemoglobin C disease, sickle cell

hemoglobin D disease and sickle cell ß-thalassemia. While there is much overlap between the clinical manifestations and severity of these disorders, sickle cell anemia tends to be the most severe.[10]

While it is estimated that approximately 8% of African-Americans have hemoglobin S trait, the prevalence is much greater in tropical Africa, ranging from 20-40% of the population depending on location within the region.[10] The high prevalence of hemoglobin S trait corresponds to regions of the world where falciparum malaria is common; leading numerous studies to deduce that the trait is protective against the parasite.[11, 12] Studies indicate that this advantage is present only in young children with sickle cell trait. While these children can become infected, the parasite count remains low. The exact mechanism of resistance has yet to be elucidated, however it has been hypothesized that parasitic infection of the erythrocytes with Hb S causes them to sickle, which would lead them to be cleared (destroyed) by the spleen, thereby ridding the body of infected cells.[13]

The role of hemoglobin in the body is to transport oxygen through the bloodstream from the lungs to the various tissues of the body and carbon dioxide from these tissues back to the lungs. Additionally, hemoglobin destroys nitric oxide molecules. Two pairs of polypeptide chains make up each molecule of hemoglobin, two α-chains and ß-chains. The conformation, and therefore oxygen affinity, of the hemoglobin molecule changes as it gains and loses oxygen.[10] When Hb S molecules become deoxygenated, they have a strong tendency to aggregate. Once a few molecules of hemoglobin aggregate, they form a "seed" on which more hemoglobin aggregates on rapidly. This sickling process is characterized by a long delay, which is very dependent on temperature and concentration of aggregates.[14] The deoxygenated Hb S turns into a firm gel, causing the erythrocyte's form to change from round to the characteristic

sickle shape. If a erythrocyte repeatedly changes from a sickle to round shape, the membrane is affected, causing the cell to permanently stay in the sickle formation.[15] Sickled cells have a short intravascular life span of 10 to 20 days, compared to the 120 days of normal erythrocytes, and this reduction in their life span results in anemia.[10]

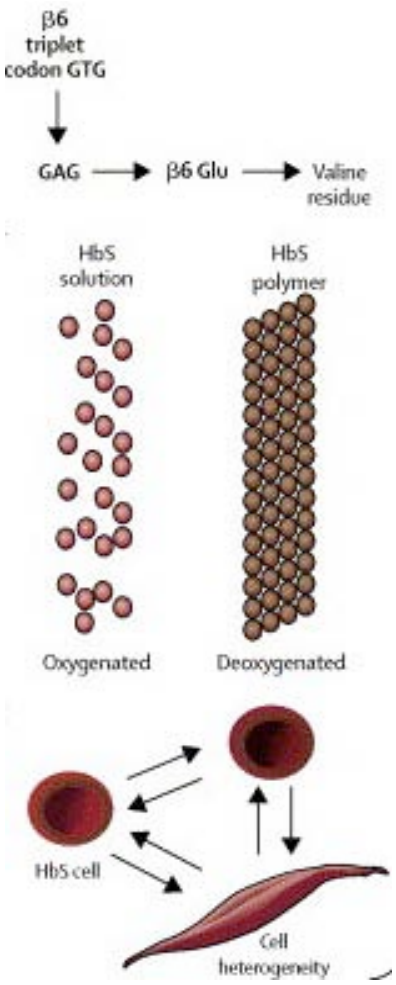


Figure 1: Genetics and Physiology of Erythrocyte Sickling[16]

2.1.2 Factors Which Contribute to Sickling of Erythrocytes

There is wide clinical variety in the presentation of sickle cell disease, and it is thought that this is due to a large number of inherited and acquired factors. Deoxygenation is the most important

factor determining the occurrence of sickling in erythrocytes with Hb S; therefore, situations that decrease oxygen levels in the blood may pose a risk (e.g. decreased cardiac function, higher elevations, exercise, scuba diving).[10] While there have been some reports of pain crises or splenic infarctions in patients with sickle cell anemia while flying aboard a commercial aircraft, there is no evidence that individuals with sickle cell trait are at any risk.[17, 18] Additionally, the speed at which deoxygenation occurs may play a role, as *in vitro* studies suggest that instantaneous deoxygenation can cause more rapid sickling.[19]

Oxygen tension varies throughout the body and is especially low in areas where there is vascular stasis, slowing of the blood flow. While no body site is immune from vaso-occlusion, a blocking of blood vessels as a result of sickling, certain sites are more prone than others; such as the spleen, kidneys and phallus, where hypoxemia occurs and sickling can result. Sickling in erythrocytes is not instantaneous and a period of two to four minutes is needed for the transformation to occur. It is usual for erythrocytes to only spend 10-15 seconds in venous circulation; however, in other areas where vascular stasis is more common sickling can occur.[20] Blood viscosity is increased by sickled cells, resulting in further slowing of the blood circulation and thus more sickling, leading to possible vascular occlusion and infarction. Ultimately, this serious of events can lead to tissue death and pain crisis.[10]

While a causal relationship has not been confirmed, it has been observed that cold temperatures may initiate sickling, possibly due to the vasoconstriction that occurs during cold temperatures.[21] Close to freezing temperatures however *in vitro*, have been shown to inhibit sickling.[22] Increased blood acidity, referred to as acidosis, may precipitate sickling, as it produces conditions which favor the deoxygenated hemoglobin S state.[23] Infection can be a contributor to vaso-occlusive crises due to a combination of potential factors that favor sickling

such as dehydration caused by the associated fever, vomiting and diarrhea, acidosis caused by decreased food intake, and pneumonia resulting in hypoxemia.[10, 24]

2.1.3 Clinical Manifestations of Sickle Cell Disease

While individuals with sickle cell disease are generally healthy much of the time, they can experience intermittent and sudden vaso-occlusion, aplastic, sequestration or hemolytic crises. Vaso-occlusive crisis, referred to as a pain crisis, is characteristic of sickle cell disease and is the most common out of the four crises. Due to the clinical variability of the disease, these pain crises range in frequency from daily to less than one a year, depending on the patient.[25] These crises affect the bones, the chest and the abdomen, but may occur in any tissue. Other manifestations of sickle cell disease may include: sickle cell dactylitis (swelling of the dorsal surfaces of the hands and/or feet) in children (especially under the age of four), splenomegaly and repeated splenic infarctions, jaundice, hepatomegaly, sickle retinopathy, leg ulcers, priapasm, susceptibility to infection, stroke, and later in life, renal failure.[10] With regular and thorough medical care, the current life expectancy for individuals with sickle cell disease is mid-forties.[26]

2.2 SICKLE CELL TRAIT

It is estimated that approximately 8% African-Americans in the United States, and 0.05% of white Americans have sickle cell trait. Individuals with sickle cell trait consistently have a hemoglobin composition of less than 50% HbS.[27] The amount of Hb S varies between

individuals due to genetic and environmental factors, and ranges somewhere between 20-45%.[28, 29] Intracellular polymerization of Hb S in persons with sickle cell trait can not be detected *in vitro*, unless oxygen tensions are decreased to below physiological levels.[30]

2.2.1 Health Implications

In contrast to a sickle cell disorder, sickle cell trait has not been considered a disease, instead being regarded as an asymptomatic condition. There is evidence to support this, including the fact that sickle cell trait does not have a significant impact on life expectancy.[1] As discussed above, sickle cell trait can actually be beneficial, as it confers childhood protection against falciparum malaria. When individuals with sickle cell trait are compared to controls, there is no difference in the age, duration, or pattern of hospital admissions.[31, 32] Despite this evidence, there are reports of definite associations between specific health complications and sickle cell trait.[27, 33-44]

2.2.1.1 Renal and Urinary Tract Complications

Studies indicate that there is an increased prevalence of urinary infections in persons with sickle cell trait, particularly in women during pregnancy.[27, 33] The most frequent complications of sickle cell trait is hematuria, both gross (red blood cells visible in the urine, giving it a red or dark brown appearance), and microscopic (red blood cells visible only under a microscope).[34, 35] There are a variety of causes of hematuria including kidney stones and lower urinary tract neoplasms. In individuals with sickle cell trait the causes of most concern are papillary necrosis and renal medullary carcinoma.

A study released in 1979 observed that among African-American males in Veterans Administration Hospitals, 4% were admitted for hematuria, while only 2% of patients with normal hemoglobin were admitted for the same problem.[31] The authors speculated that among that 4%, it was reasonable to estimate that the cause in half of these cases were unrelated to the patients' sickle cell trait status. Renal papillary necrosis has classically been associated with sickle cell disease, as well as analgesic abuse and diabetic urinary tract infections, and refers to ischemic damage to the renal medulla.[34]

Painless gross hematuria is the common presentation of renal papillary necrosis. The exact mechanism has yet to be elucidated, but physiologically the renal medulla provides a particular environment of dehydration, acidosis, decreased oxygen tension and high osmolarity, which are all well-established triggers of red blood cell sickling. Furthermore, the blood flow is naturally slower in the vasa recta (capillaries of the kidneys) to provide ample time for water to be drawn out of the red blood cells. As a consequence, this process increases intracellular concentration of sickle cell hemoglobin, which can precipitate sickling, thereby increasing the viscosity of the blood. More viscous blood will flow even slower, ultimately leading to the formation of microthrombi, which can cause microinfarctions that damage the vasa reta and may lead to isothenuria, a condition in which the kidneys can no longer dilute or concentrate urine.

The most serious association, although extremely rare, is the occurrence of renal medullary carcinoma, which is a highly aggressive tumor. First described in young patients with sickle cell trait these tumors arise from the epithelium of the distal collecting ducts and mostly form in the right kidney.[36] These tumors are seen nearly exclusively in young individuals with sickle cell trait. While only 120 cases have been reported, 119 of these cases have been in patients with positive sickling status.[35] The median age of diagnosis is 22 years, with a ratio of

3:4 males before the age of 24, and equal gender frequency after age 24. Unfortunately, only 3 patients have reportedly survived the disease and the median survival is 15 weeks, demonstrating the aggressiveness of the tumor.[35]

2.2.1.2 Splenic Infarction

While splenic function is considered normal in sickle cell trait, splenic infarction, an episode in which tissue death occurs due to oxygen shortage, may occur at high altitudes.[37] There have been numerous reported cases amongst persons with sickle cell trait of splenic infarctions in high altitude areas such as the Andes and Rocky Mountains, and less frequently when hypoxemia is not an issue.[17, 38-45] A majority of the cases have occurred in men who were not of African decent.[46] Most cases tend to be mild; however, some patients present with acute splenic syndrome, which can result in splenic rupture requiring an emergency splenectomy. Normally splenic infarction can be managed with adequate hydration, analgesia, rest, oxygen and other necessary supportive measures.[35]

2.2.2 Sickle Cell Trait and Exercise

It has been shown that following exercise, sickle cell trait carriers can experience an increase of sickled cells.[47] The phenomenon is often referred to as exertional sickling. The presence of sickled cells after physical exertion appears especially when higher altitudes are simulated.[48] In 1989, Martin and colleagues demonstrated that the proportion of reversibly sickled cells in venous blood, as measured *in vivo* in a limb, increased during exercise at an altitude of 1270 meters (~4,167 feet) and was even more so pronounced at 4000 meters (~13,124 feet).[48] Hypoxemia caused by increased altitude alone does not always produce sickling in those with

sickle cell trait. Sickling did not occur when four subjects with sickle cell trait were exposed to a simulated altitude of 3250 meters (10,000 feet) or higher for 80-85 minutes, nor did it occur in a study with one subject at simulated 4300 meters (13, 200 feet) 30 minutes. More extreme altitudes of 5000 meters (15000 feet) have been shown to induce sickling in two subjects with "probable sickle cell trait."[27]

The issue of sudden death during exercise in sickle cell trait carriers has been controversial.[49-51] The first cases of sudden death attributed to exertional sickling were identified between March 1968 and February 1969 in U.S. army recruits during basic training at Fort Bliss, Texas.[52] During this time period, four recruits died during or immediately after the strenuous exercise that is characteristic of basic training. Autopsy reports on each recruit concluded that the cause of death was a result of diffuse microvascular obstruction from sickled erythrocytes. The elevation of Fort Bliss is 4,050 feet above sea level and considered a relatively high altitude where modest hypoxemia may occur. Investigators speculated that the combination of altitude and strenuous exercise soon after arrival at basic training caused a decrease in blood oxygen levels leading to lactic acidosis, exertional sickling, and sudden death. They added that other environmental stressors, including dehydration and increased blood viscosity, might have also been contributing factors.

The most convincing data comes from a retrospective study from Kark and colleagues from the Army Medical Corps physicians, which reviewed all deaths amongst active-duty military between the years 1977 and 1981.[53] The comprehensive review of 2 million enlisted recruits concluded that in black recruits with sickle cell trait (*n*=37,000) the risk of sudden unexplained death was estimated to be 30 times greater than that of black recruits without sickle cell trait (*n*=429,000) and 40 times greater than that of non-black recruits without sickle cell trait

(*n*=1,620,000). Among the black recruits with sickle cell trait, the rate of sudden death was 32.2 per 100,000, compared to 1.2 per 100,000 in black recruits without sickle cell trait (n=429,000). As with the Ft. Bliss recruits, deaths tended to occur during the first month of training and were associated with training activities that required a maximal degree of effort. Results similar to Kark's study were demonstrated in a similar study of non-traumatic deaths in the US Air Force between the years 1956 and 1996.[54] Compared to those without sickle cell trait, personnel with sickle cell trait had a relative risk for sudden death of 23.5 (95% CI, 19.5-30.0).

In addition to the military data, there have been over 30 case reports documenting fatal or serious exercise-related complications in young black men with sickle cell trait.[35] Just in the last decade 136 non-traumatic sports deaths were reviewed for high school and college athletes and exertional sickling was the proposed cause in seven (5%) of the cases.[2] On the collegiate level, 13 football players have reportedly died after collapse brought on by exertional sickling, with similar symptoms and settings. The players participated in brief on-field drills, sprinting on average 800-1,600 meters, often early in the season, or in repetitive running of hills/stadium steps. Sickling also occurred when the intensity of exercise increased late in practice or on a rare occasion, during a game. In this scenario there was a sustained, constant action such as sprinting down the field.[55] Reports are not isolated to football as several basketball players have died suddenly as well. Please see Section 2.3.3 for the NCAA response to these deaths.

The explanation of these deaths is not entirely clear. Although the majority of data indicates an association between sickle cell trait and sudden death there is no direct evidence of causation. Autopsies on these individuals revealed sickling; however, Hb S polymerization occurs naturally postmortem and there is no method to discern postmortem and antemortem sickling.[56] It has been suggested that the dehydration, hyperthermia and acidosis associated with

extreme physical exertion can cause Hb S polymerization, exertional sickling, which leads to vaso-occlusion and endothelial damage. The results of these consequences include rhabdomyolysis (muscle break-down), acute renal failure and coronary vasoconstriction.[35]

In response to the sudden death related to exertional heat illness in Army recruits, certain centers participated in an intervention to prevent additional deaths from occurring from 1982-1991.[57] The participating centers measured wet-bulb globe temperature (WBGT) at least hourly at the exercise site. The WBGT is the composite temperature used to estimate the effect of temperature, humidity, wind speed, wind chill, and solar radiation on humans. When the WBGT rose to 90ºF, exercise intensity was decreased and rest cycles were increased. Measures were taken to observe water consumption and increase water intake as needed, as well use of light track clothing in hot weather to keep recruits from overheating. If early symptoms of exertional heat illness presented, immediate cooling and re-hydration was initiated. These precautions were taken for all of the recruits at a participating center.

The number of deaths due to exertional heat illness which occurred at both participating and non-participating centers between 1982 and 1991 were compared to a predicted mortality for those years, based on previous years deaths (1977-1981). Additionally, mortality rates were compared for recruits with and without sickle cell trait. The results of the intervention were dramatic. Observed deaths due to exertional heat illness at non-participating centers were not significantly different, regardless of recruits' sickle cell trait status, when compared to predicted mortality rates. At the participating centers, mortality due to exertional heat illness was reduced from the predicted 18.7 to 11 in recruits without sickle cell trait. Amongst recruits with sickle cell trait 14.9 deaths were predicted; however, there were no reported exertional heat illness deaths in these recruits.[57]

The results of this intervention showed that exertional heat illness is a major preventable factor contributing to exercise-related death of young adults. When these data were published, the authors concluded that there is a strong association between exposure to hot weather within 24-hours of exercise and the risk of exercise-related sudden death, and this risk is even stronger for individuals with sickle cell trait. Furthermore, the basic preventative measures taken during the intervention eliminated the excess risk for exercise-related death for those with sickle cell trait and was able to reduce mortality in those without sickle cell trait.[57]

2.3 HISTORY OF SICKLE CELL TESTING

2.3.1 Methods of Testing for Sickle Cell Disease and Trait

Diagnosis of sickle cell disease and sickle cell trait does not require complex procedures. As illustrated earlier by Pauling's discovery, electrophoresis can distinguish sickle hemoglobin from normal hemoglobin; however, other methods exist which are broadly divided into the following categories: tests for sickle hemoglobin, methods for genotyping, and procedures for pinpointing the genetic sub-division of the major genotypes.[27]

There are two tests that can be used to detect sickle hemoglobin. The sickle test was the first method available for this purpose, in which a drop of blood is prepared on a microscope slide and sealed under a cover slip to isolate the sample from oxygen. Within one hour, if sickle hemoglobin is present, the sickled cells are visible under a microscope.[58] The second, newer method, is the solubility test (a version is marketed under the name Sickledex), which is utilized due to the relative insolubility of deoxygenated Hb S in solutions of high molarity.[59] Using

buffers, lysing and reducing agents, samples with Hb S become cloudy and those without Hb S remain clear. While both methods reliably test for the presence of sickle cells, there is no situation in which a positive sickle cell or solubility test should be reported without follow-up from electrophoresis and complete blood count (CBC) as the major limitations of these earlier tests is their failure to differentiate between sickle cell trait and the clinically significant sickle cell anemia or other sickle cell disorders.[27]

Hemoglobin electrophoresis is the method used to genotype the sickle cell disorders. This is the major technique used for diagnosis of sickle cell disease and trait. It capitalizes on the changes that occur to the charge of the hemoglobin protein when amino acid substitutions occur. Each known hemoglobin variant has a characteristic position movement upon electrophoresis. For example, in conventional alkaline electrophoresis, due to the replacement of neutral valine of Hb A for negatively charged glutamic acid in the hemoglobin ß-chain in Hb S, Hb A moves more slowly than Hb S towards the anode.[27] This method is limited in that it cannot distinguish hemoglobins that have amino acid substitutions resulting in the same charge. To distinguish these changes, genetic mutation analysis or full gene sequencing is necessary.

2.3.2 Sickle Cell Anemia Control Act

In 1972 the Sickle Cell Anemia Control Act (P.L.92–294) was signed by into law by President Richard Nixon. The motion pledged $10 million dollars to expand sickle cell programs for the year 1972 alone, a ten-fold increase from the year before, and $15 million dollars to be spent in 1973. The funds were approved to establish voluntary screening and counseling for sickle cell anemia, development and dissemination of educational materials for both health care personnel

and the general public, in addition to research for the diagnosis, treatment and "control" of sickle cell anemia.[60] Screening was specifically targeted at those people of childbearing age or children under the age of seven. While the act was intended to help increase funding for sickle cell anemia awareness and research, it also stirred controversy. Genetic counseling was triumphed as an effective method to raise awareness and prevent disease; however, some saw it as the new eugenics. Although the act suggested voluntary testing, some states had already or were considering making sickle cell anemia testing mandatory.[61] Allegations were made that the act one of an assault against the African-American community and an effort to curb reproduction.[61]

Sickle cell anemia advocates, patients and experts found themselves in a difficult position. Howard Pearson, a pediatric hematologist, suggested that the controversial hype arose because, "education had been sorely neglected in the rush to run out and stick somebody and take his blood." The screening programs and genetic counseling services that were made available were hastily devised and executed without regard to privacy or awareness of the potential implications. Later in 1972, Pearson went on to write, "Perhaps we should wait until we have more to offer these people before we go around handing out such information [of sickle cell trait status] so casually."[61] Furthermore, often times the sickle cell solubility test was used leading to confusion between sickle cell disease and trait. The controversy has since subsided; however, tensions still remain.

Stemming from the National Sickle Cell Anemia Control Act were advances in research for sickle cell disease, resulting in sickle cell disease no longer being a disease of childhood and extending lifespan for those affected, as well as statewide sickle hemoglobinopathy newborn screening programs.

2.3.3 Newborn Screening

Currently, universal screening for sickle hemoglobinopathies exists in all of the newborn screening programs in the United States (all 50 states and the District of Columbia); however, this was not the case until relatively recently. Although universal screening for sickle hemoglobinopathies was recommended by the National Institutes of Health in 1987, it took nearly 20 years for all screening programs to follow suit.[62] Here in Pennsylvania, sickle hemoglobinopathies were added to the universal newborn screen in September 1992. Shortly after birth a baby's heel is pricked and the blood is collected on a blood filter paper card to create a dried blood spot. This sample can then be used in an electrophoresis based procedure, called isoelectric focusing. This test is used in most newborn screening laboratories, to test for the sickle hemoglobinopathies (another procedure used in some laboratories, similar in result is high performance liquid chromatography). By law, if the result is positive for a sickle hemoglobinopathy, families must be contacted and proper medical measures must be taken. In Western Pennsylvania, families are also notified by telephone and mail if their children are identified to have sickle cell trait.

2.3.4 Military

Each branch of the military maintains its own sickle cell trait screening guidelines and training procedures. After the 1972 National Sickle Cell Anemia Control Act, the U.S. Air Force screened all recruits and restricted those with sickle cell trait from flying, based on the incorrect theory that the high altitude could cause them to go into a pain crisis. This ruling further added to the controversy stemming from the act, with allegations of employment discrimination.

Currently the U.S. Airforce still screens all recruits; however, recruits with sickle cell trait are now given the option to decline service. The Marines and the Navy also screen all recruits. The Marines do not change training regimen for recruits with trait; however, the Navy identifies trait carriers with a red belt and neck tag during strenuous drills. As of now, the Army is the only branch of the military not screening for sickle cell trait.[56]

2.3.5 National Collegiate Athletic Association

On June 29th 2009, the National Collegiate Athletic Association (NCAA) released a statement recommending that member colleges and universities test student athletes to confirm their sickle cell trait status if not already known.[3] The recommendation was adopted by the NCAA committee on Competitive Safeguards and Medical Aspects of Sports, four days prior on June 25th. The action followed guidelines from National Athletic Trainers Association (NATA) and the College of American Pathologists (CAP), and stemmed from the recent resolution of a lawsuit brought against the NCAA by the family of Dale Lloyd II.

Mr. Lloyd, who excelled at football and baseball his entire life, was offered an athletic scholarship as a freshman in 2006 to Rice University, a Division I school in Houston, Texas.[63] In late September, the day after a football game, Mr. Lloyd participated in a practice that included weight lifting and sixteen 100-yard sprints. During the running portion of practice, he collapsed. He died at the hospital the following day; the cause of death was determined to be rhabdomyolysis. After his death, it was determined that he had sickle cell trait. His death was unfortunately not the first of its kind in the field of competitive collegiate athletics. His family stated that they were not aware of the potential dangers of having sickle cell trait and intense exercise, so they never thought it necessary to have their son tested for sickle cell trait. While

they were not aware of the association, they argued that the NCAA was. Legal action against the NCAA was pursued based on officials for not taking any precautionary measures to protect student athletes and promote awareness as to the potential harm associated with sickle cell trait in athletics.[63]

The lawsuit settled in 2009, included a $50,000 donation from the NCAA to the Sickle cell Disease Association in the name of Dale Lloyd II to be used to fund awareness, education, and screening for sickle cell trait in the athletic population, as well as a $10,000 donation to the Dale Lloyd II scholarship fund.[3] As part of the settlement the NCAA agreed to recommend that its participating member colleges and universities screen all athletes for sickle cell trait. The amendment is stated in the NCAA Sports Medicine Handbook Guideline 3c as, "that while sickle cell trait screening is normally performed on all U.S. babies at birth, some student athletes may not know if they have trait. Following recommendations from NATA and CAP, the NCAA recommends athletic departments confirm sickle cell trait status in all student athletes, if not already known, during their required medical examinations." The NCAA also agreed to stress this point during regular media communication during 2009 football preseason and the football rules book (Table 1). Additionally, the NCAA agreed to prepare an educational video about sickle cell trait to be made available on its website and to member schools.[3] Before the lawsuit, 64% of colleges were already screening for sickle cell trait.[63]

Table 1: NCAA Guidelines for Student Athletes With Sickle Cell Trait

Athletes with sickle cell trait should:
• Set their own pace
• Engage in a slow and gradual preseason conditioning regimen to be prepared for sports-specific performance testing and the rigors of competitive intercollegiate athletics
• Build up their intensity slowly while training
• Use adequate rest and recovery between repetitions, especially during "gassers" and intense station or "mat" drills
• Not be urged to perform all-out exertion of any kind beyond 2-3 minutes without a breather • Be excused from performance tests such as serial sprints or timed mile runs, especially if these are not normal sport activities
• Stop activity immediately upon struggling or experiencing symptoms such as muscle pain, abnormal weakness, undue fatigue or breathlessness • Stay well hydrated at all times, especially in hot and humid conditions
• Maintain proper asthma management
• Refrain from extreme exercise during acute illness, if feeling ill, or while experiencing a fever
• Access supplemental oxygen at altitude as needed
• Seek prompt medical care when experiencing unusual distress

2.3.6 Comparison to Other Health Conditions

The leading cause of death in athletes during sport-related activities is sudden cardiac arrest from occult cardiovascular disease.[64] Several congenital or acquired cardiac malformations account for the majority of these deaths in United States athletes aged 35 and younger. Hypertrophic cardiomyopathy is the single most common cause (36%), followed by congenital coronary artery anomalies (17%).[65] In the United States, these deaths occur most commonly in basketball and football, as these sports have the highest levels of participation, as well as including particularly intense levels of physical activity.[66] Similar to sickle cell trait in athletics, sudden cardiac death in a young athlete often generates a high public profile because of the youth or celebrity of

victims and the belief that athletes are amongst the healthiest in our society. As a result, cardiovascular screening for athletes is routinely practiced and performed by most major sporting associations, including the International Olympic Committee and the NCAA.

The NCAA Committee on Competitive Safeguards and Medical Aspects of sports mandates a preparticipation evaluation for all Division I, II, and III athletes before their first practice or competition. Further recommendation is that these evaluations be performed or supervised by a qualified physician, and evaluations is based on gathering a cardiovascular based family history and physical examination.[67] In contrast to sickle cell trait testing, these methods are considerably less invasive, as they are verbal and examination based. The evaluation in the NCAA is based upon American Heart Associations (AHA) Recommendations for Cardiovascular Screening of Competitive Athletes (Table 2), and only omits the medical history question regarding fatigability and Marfan stigmata on examination.[65]

Table 2: The 12 Element AHA Recommendations for Preparticipation Cardiovascular Screening of Competitive Athletes

Medical History
Personal history
1. Exertional chest pain/discomfort
2. Unexplained syncope/near syncope
3. Excessive exertional and unexplained dyspnea/fatigue, associated with exercise
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure
Family History
6. Premature death (sudden and unexpected, or otherwise) before age 50 years due to heart disease, in ≥1 relative
7. Disability from heart disease in a close relative <50 years of age
8. Specific knowledge of certain cardiac conditions in family members: hypertrophic or dilated cardiomyopathy, long QT syndrome or other ion channelopathies, Marfan syndrome, or clinically important arrythmias
Physical Examination
9. Heart murmur
10. Femoral pulses to exclude aortic coarctation
11. Physical stigmata of Marfan syndrome
12. Brachial artery blood pressure (sitting position).

There have been several high profile cases involving cardiac sudden death in basketball, including the untimely on-court deaths Loyola Marymount star Hank Gathers in 1990 and Boston Celtics guard Reggie Lewis in 1993, both of whom collapsed and died, due to undiagnosed hypertrophic cardiomyopathy.[68] In 2005, a controversy brewed over Chicago Bulls player Eddy Curry, who missed several games due to an irregular heart beat. Doctors could not determine the cause. He received clearance from two separate cardiologists to play, but there was still concern that he could be susceptible to hypertrophic cardiomyopathy. The general

manager, John Paxson, offered him a long-term contract to play on the condition that Curry take a DNA test to gauge his susceptibility to HCM. If it was discovered that Curry did have a mutation, then he would be offered $400,000 for 50 years not to play basketball.[68, 69] Curry rejected the deal and refused testing stating that the test would only gauge his susceptibility to sudden cardiac arrest and was not definitive. He was subsequently traded from the Bulls to the New York Knicks, who did not require him to take a genetic test.

While there has not been a similar situation relating to sickle cell trait, lessons need to be learned from the case of Eddy Curry and the controversy stemming from the National Sickle Cell Control Act. Mandatory genetic testing can be very unsettling, especially if it is not approached with the appropriate amount of care and education. It is with this in mind that our team set out to create a methodology to provide adequate education and awareness regarding sickle cell trait amongst student athletes and the athletic staff at the University of Pittsburgh, in addition to voluntary genetic testing that ensured autonomy, beneficence, and protection of health.

3.0 SPECIFIC AIMS

3.1 SPECIFIC AIM 1

Specific Aim 1: To provide voluntary sickle cell trait testing to interested student athletes at the University of Pittsburgh, in concordance with the ethical principles of genetic testing: autonomy, beneficence (non-malfeasance), and protection of health.

Plan: To enable student athlete autonomy and ensure that testing is offered on a voluntary basis. Privacy is provided to the best of our abilities, by reporting the test result only to the athlete; however, as it is part of their medical record, the athletic staff also gains knowledge of their test result. Finally, to provide an environment of non-malfeasance, which ensures that the university will only use this information for the good of the athlete and not discriminate against any athlete who has newly identified sickle cell trait.

3.2 SPECIFIC AIM 2

Specific Aim 2: To educate staff and student athletes about the potential complications of sickle cell trait in athletics, how to avoid these complications and prevent sudden death in the student athlete.

Plan: Provide counseling and education to the student athletes prior to testing, in addition to post-test follow up to answer any remaining questions. For the athletic staff, athletic trainers, and coaches, provide extensive education regarding the historical significance of sickle cell trait; the proposed physiology of exertional sickling; and methods to prevent and treat exertional sickling to avoid sudden death in the student athlete.

4.0 PROGRAM DESIGN

4.1 COLLABORATION WITH THE UNIVERSITY OF PITTSBURGH

In July of 2009, the University of Pittsburgh Department of Athletics contacted The Children's Sickle Cell Program at Children's Hospital of UPMC regarding testing its athletes for sickle cell trait due to the NCAA's recent recommendations to its members to test student athletes for sickle cell trait. The Department of Athletics was seeking information as to how to facilitate and proceed with testing. Before initial contact contact, we were aware of the NCAA's recommendations and were in the process of devising a testing strategy for use in the university setting to ensure that should testing occur it be performed ethically, and abide by the principles of genetic testing; autonomy, beneficence, accuracy and privacy.

We offered our clinical services to the University of Pittsburgh to provide testing services, in addition to pre- and post- test counseling to the student athletes, and education for athletes and athletic staff. We had many discussions with the University of Pittsburgh, specifically with the athletic training coordinator, Mr. Tony Salesi, as to how testing should best be performed to meet the University of Pittsburgh's individualized needs, while maintaining student athletes' privacy, autonomy and preventing any discrimination regarding results of the test. The University of Pittsburgh elected to inform their athletes of the NCAA recommendations and offer testing on a voluntary basis. We worked with them to set up five

separate times over the course of three weeks to come to the athletic training facilities and provide pretest counseling, education, and testing.

The University of Pittsburgh was willing to cover the cost of testing each of its student athletes for sickle cell trait. Our program provided our staff's time at no cost and was able to offer them the test for $12.50 each. This test was billed through each student athlete's insurance plan, provided by and paid for by the University of Pittsburgh. We provided their insurer the current procedural terminology (CPT) code for billing (Table 3). IRB approval was not sought for this project, as being a clinical service, does not meet the definition of research.

Table 3: Explanation of CPT Codes

CPT Codes	Explanation
83021	hemoglobin chromatography
85014	Hematocrit
85018	Hemoglobin
85041	red blood cell count

4.2 ATHLETE PRE-TEST COUNSELING AND EDUCATION

Prior to arriving at the athletic training facilities on the University of Pittsburgh's campus, the athletes had been informed about the availability of voluntary testing either by their coaches or by volunteers during their physical examinations. The athletes were given a form to sign if they elected to be tested for sickle cell trait (Appendix A). Athletes who decided to have testing for sickle cell trait were then informed of the available testing times. Seventy-nine athletes elected to pursue testing (Table 4).

During testing sessions, athletes were given sickle cell disease and trait education, and counseling on an individualized basis (Appendix B). We provided education materials, which included; a handout we created detailing the NCAA's recommendations and the association between sickle cell trait and sudden death in the athlete, NATA's training recommendations regarding SCT and the athlete, and pamphlets explaining sickle cell trait (Appendix B). Explanations of all of these materials were provided at length, and not limited only to sickle cell trait and the athlete, but also included the inheritance of sickle cell trait. Additional materials were on hand regarding other hemoglobinopathies that could be found through testing, such as thalasemia. Approximately five minutes was spent on pre-test counseling and education with each athlete.

Table 4: Composition of Student Athletes Electing Testing for Sickle Cell Trait by Sport

Sport	Number Tested
Football	15
Women's Soccer	15
Women's Basketball	11
Men's Soccer	11
Swimming & Diving	8
Track & Field	5
Men's Basketball	4
Softball	3
Cross Country	3
Cheerleading	2
Other	2

4.3 HEMOGLOBINOPATHY TESTING

All samples were collected on site at the University of Pittsburgh's athletic training facilities, immediately after pre-test genetic counseling and education was completed. We provided a registered nurse to perform phlebotomy services. The nurse performed phlebotomy adhering to sterile standard procedure, and collected 2 mL of blood in a sterile lavender-top EDTA collection vial (BD Vacutainer, 5.4 mg EDTA). The samples were transported back to Children's Hospital of Pittsburgh of UPMC diagnostic laboratories within 2-6 hours of collection. All samples collected underwent standard hemoglobinopathy evaluation via electrophoresis and whole red blood cell count.

4.4 RESULT DISCLOSURE AND POST-TEST COUNSELING

Athletes were notified within two to three weeks of their test date to disclose the result of their hemoglobinopathy evaluation. All results were reported. Each athlete was contacted by telephone for results disclosure and post-test counseling was provided at this time. The athletes were given the option to arrange a meeting time if they desired further counseling or had additional questions. If an athlete was unable to be reached by telephone after three attempts, an e-mail containing the test results were sent to the athlete, with a request for a return e-mail to

confirm that the athlete had received the test result and had no further questions. All positive results were able to be given over the telephone, only negative results were e-mailed if need be.

Once the student athletes had been notified of their test results, the results were given to the University of Pittsburgh's training staff. As student athletes at the University of Pittsburgh, paricipants give the university permission to view all medical information. The athletes were aware that the University of Pittsburgh would also know the results of their hemoglobinopathy evaluation.

4.5 STAFF EDUCATION

Approximately 6 weeks after testing commenced, our program met with members of the coaching, training and athletic staff to provide further education regarding sickle cell disease, sickle cell trait, the NCAA's recommendations, and preventative measures that can be taken to ensure the safety for all athletes, regardless of sickle cell trait status (Appendix C).

5.0 RESULTS

5.1 ATHLETE TESTING AND RESULTS DISCLOSURE

Over the course of the testing sessions, 79 student athletes from the University of Pittsburgh elected to have sickle cell trait testing. Athletes from a diverse group of sports were interested and we had participation from the football, softball, the men's and women's soccer teams, swimming, track and field, cross country and the men's and women's basketball teams. The population of student athletes also varied in terms of gender and race/ethnicity.

All results were reported directly to the student athletes. Two athletes were found to have sickle cell trait. After results disclosure, student athletes were asked if they would like to have a personal counseling session to speak further; however, no student athletes elected to pursue this option. Athletes were given ample time to ask any questions they may have had about their result. In some cases a finding indicated that further testing was needed. Athletes with anemia or microcytic anemia were encouraged to follow-up with their primary care physician for further evaluation. Microcytic anemia can be an indication of alpha-thalassemia trait and requires further evaluation. Abnormal test results were also sent directly to the athletes with a letter explaining the sickle cell trait results and reproductive consequences, including risk and testing options. Athletes were instructed to keep with this letter with their medical records.

5.2 RESPONSE FROM THE ATHLETIC STAFF

We received a positive response from the members of the athletic staff. When coordinating testing, all staff were eager to aid and assist us. They were appreciative of our presence and seemed interested in learning more about sickle cell trait and methods to prevent exertional sickling. During our educational presentation on sickle cell trait, the staff expressed interest and asked thoughtful, pertinent questions. The athletic trainers, in particular, were extremely aware of the needs of their athletes. We discussed at length the WBGT, with which the athletic trainers were familiar with, and they planned to incorporate the WBGT into their standard practice. We also addressed the difficulties of wanting to push students physically to make them better athletes and improve their performance, but at the same time keep them safe.

Our project found that the University of Pittsburgh Department of Athletics understood the potential adverse effects of testing athletes for sickle cell trait and agreed that merely testing student athletes is only a first step. General changes can be made to the training environment to keep all athletes safe, regardless of their sickle cell trait status. In conversations occurring after testing and results disclosure, the athletic training coordinator summed it up well by stating that, “The knowledge has made all individuals within our performance team more aware of potential issues and how we need to address them if a situation would arise.”

6.0 DISCUSSION

6.1 SPECIFIC AIM 1

This project set out to develop a comprehensive method of testing and genetic counseling for student athletes regarding sickle cell trait. The project sought to incorporate the principles of genetic testing to ensure autonomy, beneficence and privacy. We were able to maintain student athlete autonomy as testing was offered on a strictly voluntary basis. The athletes did not appear to be coerced into testing, as not all athletes at the university elected to have testing. It would be beneficial in the future to assess why athletes did not elect to have testing. Possible explanations might include fear of discrimination, awareness of their trait status, lack of knowledge regarding sickle cell trait, or other unforeseen reasons. While all the athletes we spoke to denied any anxiety regarding testing, we were only in contact with those student athletes who elected to have testing and for only a brief period of time.

The results of the sickle cell trait testing did not result in any reported or observed harm to the athletes. When queried, the University of Pittsburgh athletics staff reported that the athletes that were found to have sickle cell trait were still playing for their respective teams and were not being treated differently; however, they did note that they encouraged these athletes to notify the athletic trainers of any fatigue, muscle cramps, or aches during training. Concerns about the possibility that athletes who tested positive for sickle cell trait may see less play time,

face stigmatization, or have scholarships revoked was unfounded. Providing adequate education regarding sickle cell trait should prevent any undesirable implications from occurring, and it appears as if the project succeeded. Again, since this was not a research study, but a clinical service, data were not able to assess or prove this conclusion. In the future, it would be beneficial to survey athletes who are found to have sickle cell trait to discern any changes in how they were treated by athletic staff and regarding the amount of practice or competition time they encounter.

Student athlete health protection and privacy was also a concern. Initially we had planned to only report the test result to the student athlete and then let it be their decision if they wished to inform the athletic staff at the University; however, this was not possible, as the athletes sign a waiver at the beginning of their relationship with the University, allowing the University access to all of the student's medical records. This appears to be a routine collegiate athletics procedure, as the athletic staff is concerned about the well being of their athletes. Athletes were reminded of this agreement prior to testing.

To ensure that the athletes had proper post-test counseling, we contacted them with their test results over the telephone, before releasing their result to the University. While this method worked well, it was very time intensive to contact every student athlete over the telephone. Additionally, leading a student lifestyle, the athletes were not always the easiest to access and multiple telephone messages had to be left for many of the student athletes. In the future, especially if more athletes elect to pursue sickle cell trait testing, perhaps only abnormal results should be called out to facilitate post-test counseling, and normal results could be mailed through the post or electronically.

6.2 SPECIFIC AIM 2

Testing student athletes for sickle cell trait and providing education to the coaches needed to occur in tandem to gain the most from the testing process. We were able to achieve this goal; however, in future initiatives the educational process could be restructured. Education was provided to the athletes after they had already elected to have testing and occurred during pre-test counseling. While the athletes were given some information regarding sickle cell trait from the University of Pittsburgh before opting to have testing, it may be more beneficial for our team to speak with the athletes directly before they have to decide about testing. This approach had been discussed initially with the athletic department, with our suggestion that we could speak for five to ten minutes at the beginning of practice for each team. Our contact at the University of Pittsburgh indicated that while that might be possible, it would be difficult to get that amount of time from each individual coach, as they typically have an agenda at each practice and use every minute. Our inability to meet with the athletes may have partly been due to the short time frame with which we had to work. When planning for the Fall 2010 preseason months in advance, it may be possible to work out a time to meet with the teams individually. If it is still not possible to meet with the teams before they have to decide to elect testing or not, then the University of Pittsburgh Department of Athletics will be provided with comprehensive educational materials to distribute to the teams, which will be reviewed at the time of testing.

Additionally, as this project was not research based, we were not able to quantify or assess if any lasting changes had occurred or if there was a significant gain of knowledge as a result of the project. This is an area that should be targeted in future studies. It would be beneficial to survey the athletes before and after testing in regards to the basics of sickle cell disease/trait (including reproductive risks) and measures that can be taken to prevent exertional

sickling. This method would allow us to determine how much the athletes knew before testing and how much information they retained after testing. A similar assessment of knowledge should also be taken amongst the coaches and athletic trainers; however, with more emphasis on how to prevent and treat an exertional sickling crisis. It would also be interesting to determine if awareness of sickle cell trait in the field of athletics grows from this point forward based on our initiative. By assessing how much knowledge is already known and how much is retained, we can better target educational efforts to provide the maximum benefit in the field of collegiate athletics.

6.3 FUTURE OF SICKLE CELL TRAIT TESTING IN THE NCAA

The NCAA is currently in the process of deciding if it should amend its bylaws to mandate sickle cell trait testing. In a document dated January 26th, 2010 the NCAA Division I Legislation Counsel proposed and amendment to its bylaws that, "prior to participation in any practice, competition or out-of-season conditioning activities (or in Division I, permissible voluntary summer conditioning in basketball and football or voluntary individual workouts pursuant to the safety exception), student athletes who are beginning their initial season of eligibility and students who are trying out for a team shall be required to undergo a medical examination or evaluation administered or supervised by a physician (e.g., family physician, team physician). The examination or evaluation shall include a sickle cell solubility test (SST), unless documented results of a prior test are provided to the institution.[70]" The proposal was submitted for consideration on October 20th, 2009, forwarded for membership comment and received legislative council initial review on January 13th, 2010. A comment period was open from

January 17th, 2010 and closed on March 17th, 2010; there has been no public release at this time as to whether the amendment has passed; however, if passed it will go into effect on August 10th, 2010.[70]

If the NCAA elects to make sickle cell trait screening mandatory, it should proceed with extreme caution, as mandatory genetic testing without consideration of the issues of autonomy, beneficence and privacy can be dangerous. Additionally, the use of the sickle cell solubility test instead of hemoglobin electrophoresis along with complete blood count is concerning. While the sickle cell solubility tests is marginally less expensive that electrophoresis with complete blood count ($10 compared to $12-$15), it does not give the complete picture or most accurate result. If student athletes are administered the test and simply told that they do or do not have sickle cell trait, without further explanation, they may have misconceptions as to their future reproductive risks or carry the trait for other sickle hemoglobinopathies. If they are an undiagnosed carrier, they would have a 25% chance to have a child with sickle cell disease, should their partner also be a carrier of sickle cell trait.

Furthermore, there is no mention of education or genetic counseling in the NCAA's proposed plan. If neither are provided along with the sickle cell trait screening, merely determining if an athlete has sickle cell trait is not sufficient to protect them from potential harm. As the military data suggests, the most effective way to reduce exercise-related death is to follow conditioning guidelines that provide adequate hydration and prevent overheating, to reduce the risk of death for all athletes, regardless of sickle cell trait status. Reassurance that the risk of sudden death is very low should be stressed in all discussions. If a student athlete does not understand the reasoning behind testing the athletic staff may intentionally or unintentionally

discriminate against athletes with trait, resulting in a backlash against testing, doing much more harm than good.

7.0 CONCLUSION

In conclusion, this project was successfully met its specific aims. The project provided a comprehensive testing program for sickle cell trait, one in which education and genetic counseling were both provided, which could be individualized to the needs of a university. Testing was done in concordance with the principles of genetic testing; autonomy, beneficence, and privacy. Within the University of Pittsburgh Department of Athletics we were able to achieve these aims and developed a useful working relationship with the athletic department there. This collaboration represents the beginning of a lasting relationship that should continue to be successful in the future. Additionally our team is currently speaking with other universities in the area to provide testing and education as well. It is encouraging that the universities in the area are motivated to provide the best care for their athletes. By forging additional relationships with area universities and improving our educational efforts, we will be able to better raise awareness regarding sickle cell trait in the field of athletics, hopefully preventing any sudden death in otherwise healthy, young athletes.

APPENDIX A

UNIVERSITY OF PITTSBURGH'S FORM FOR VOLUNTARY SICKLE CELL TRAIT TESTING

University of Pittsburgh

Sickle cell trait Screening Form

TO THE STUDENT ATHLETE: *PLEASE READ THIS CAREFULLY.* IF YOU HAVE ANY QUESTIONS REGARDING THIS FORM, PLEASE ASK AN ATHLETIC TRAINER TO REVIEW IT WITH YOU AND EXPLAIN ITS CONTENTS.

_____

Print Name

I understand that I could be at risk of physical, and potentially life-threatening, problems, if I have an inherited condition known as sickle cell trait and I participate in certain activities as a student athlete. I have read and understood the section titled "The Student athlete with Sickle cell trait" from the 2009-10 NCAA Sports Medicine Handbook, which is attached to this form. I have had the opportunity to ask questions of the University of Pittsburgh's athletics trainers about sickle cell trait, and the screening for sickle cell trait, and all questions I have were answered to my satisfaction and in a way I understand.

I understand a simple blood test is available to determine if I have sickle cell trait. I understand that the University of Pittsburgh STRONGLY RECOMMENDS that I have the test done, and that it is available at no cost to me.

My signature below signifies that (choose one):

A. **I decline** to have the test done at this time in spite of the University's recommendation and in spite of the potential risk to me. I understand the University will continue to make the test available at no cost to me, as long as I am a student athlete at the University, provided I later inform a University athletics trainer that I then wish to be tested.

_____ _____

__ Date

Signature: Student athlete

_____

Date

_____

__

Signature: Parent/Legal Guardian _____

(if under age 18) Date

_____

__

Signature: Witness

B. **I wish to proceed** to have the test done at no cost to me.

_____ _____

__ Date

Signature: Student athlete

_____

_____ Date

__

Signature: Parent/Legal Guardian

(if under age 18) _____

Date

_____

__

Signature: Witness

APPENDIX B

EDUCATIONAL MATERIALS PROVIDED TO STUDENT ATHLETES AT THE UNIVERSITY OF PITTSBURGH PRIOR TO TESTING

Hemoglobin S Trait and YOU, the Athlete
…The importance of getting tested…

New NCAA Recommendations

The National College Athletic Association (NCAA) recently began recommending that all of its athletes be tested for hemoglobin S trait, also known as Sickle cell trait. This recommendation is made due to the fact that "exertional sickling" a complication of sickle cell trait is the leading cause of death among NCAA football players this decade. One can be tested for hemoglobin S trait with a simple blood test.

Where does your hemoglobin come from?

Your hemoglobin type is inherited through family genes. The color of your hair, the color of your eyes, your body build and your hemoglobin type are all examples of things about you that are determined by genes. You receive one gene for hemoglobin type from your mother and on from your father.

Hemoglobin A or normal adult hemoglobin is the most common type. There are more that 500 different types or variations of hemoglobin.

What is Hemoglobin S Trait?

Hemoglobin S is often found in African Americans. It is common in people of African, Mediterranean, Middle Eastern and Indian origin.

Hemoglobin S behaves differently than normal hemoglobin A. Red cells with mostly hemoglobin S can become hard and sickle-shaped. People with hemoglobin S trait inherit a normal hemoglobin gene (HbA) from one parent and a hemoglobin S gene (HbS) from the other parent. This results in hemoglobin AS or hemoglobin S trait.

Hemoglobin S trait is not a disease. It will not turn into a disease. Hemoglobin S trait only causes health problems under extreme conditions, when this happens it is called exertional sickling.

What is exertional sickling?

Under intense exercise, red blood cells with hemoglobin S change from round to quarter-moon shaped, this is called sickling. These sickled cells do not pass through the blood vessels as easily as round cells and can cause the vessels to become jammed, posing a grave risk for the athlete.

How can exertional sickling be prevented?

Although exertional sickling is a serious condition, it can easily be prevented if it is known that one has hemoglobin S trait. It is recommended that athletes with hemoglobin S trait be allowed to acclimate themselves gradually to strenuous drills, set their own pace and drink plenty of water. If these guidelines are followed, exertional sickling can be completely avoided.

Where should I go with more questions?

Doctors, nurses and genetic counselors at Children's Hospital of Pittsburgh of UPMC are available to answer your questions.

For More Information and Testing

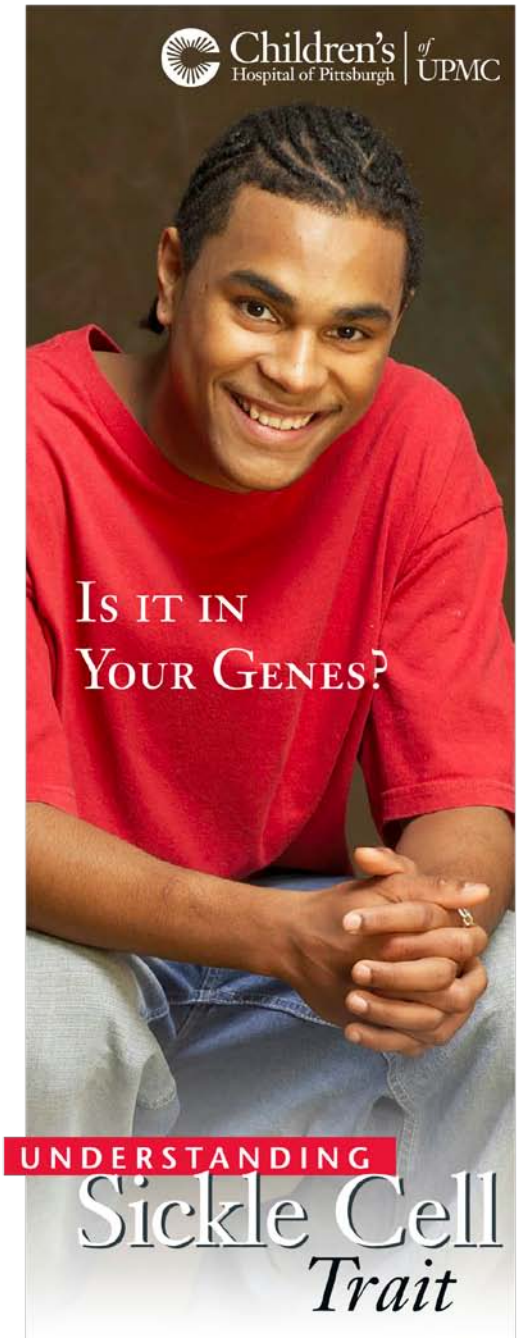
- **Children's Hospital of Pittsburgh of UPMC**
  Division of Pediatric Hematology/
  Sickle Cell Program
  412-692-6059
- **Children's Sickle Cell Foundation Inc.**
  www.cscfkids.org
  412-488-2723
  Gove Business Center
  226 Paul St.
  Pittsburgh, PA 15211
- **Magee-Womens Hospital Medical Genetics**
  412-641-4168 *or*
  1-800-454-8155
- **Sickle Cell Disease Association of America**
  www.sicklecelldisease.org
- **Sickle Cell Society Inc.**
  412-371-0628
  7643 Frankstown Ave
  Pittsburgh, PA 15208

Children's
Hospital of Pittsburgh
of UPMC

www.chp.edu

cscf | Children's Sickle Cell Foundation, Inc.

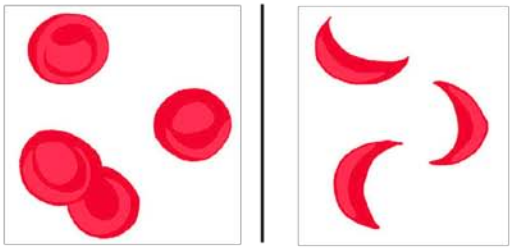
CL/MT 10-061-A PDF



UNDERSTANDING Sickle Cell *Trait*

What is sickle cell disease?

Sickle cell disease is a serious disease of the red blood cells that causes the cells to change their shape. It can be a very painful disease. Sickle cell disease is caused when each of your parents passes to you a non-working gene, before birth. You cannot catch it from being around someone with sickle cell disease.



Normal Red Blood Cells

Sickled Red Blood Cells

What is a gene?

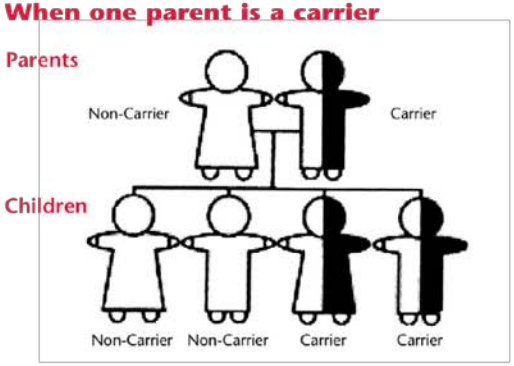
Genes are the instructions that parents pass to their children for different traits such as eye color or diseases such as diabetes. We have two copies of every gene in our body. We receive one copy from our mother and one from our father before birth. There is no way to control which genes are passed from parents to children. The sickle gene (S) affects the red blood cells.

What is sickle cell trait?

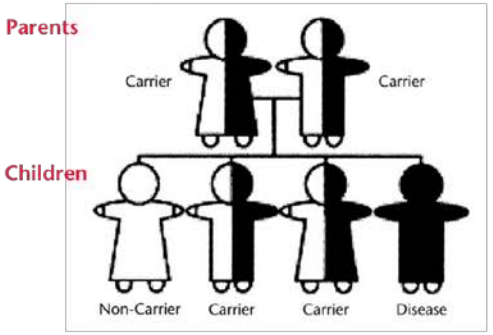
Sickle cell trait occurs when a person inherits a working gene (A) and a nonworking sickle gene (S). People with sickle cell trait are also called "carriers". Sickle cell trait is not a disease. People with sickle cell trait cannot tell they have it without being tested. If two people who have sickle cell trait have a baby, that child is at risk to receive a nonworking sickle (S) gene from each parent, which will cause sickle cell disease.

The most important reason to be aware of sickle cell trait is to find out if you can possibly have a baby with sickle cell disease. The only way to find out is for you and your partner to get tested. The different genes for the disease come from both parents — not just one.

When one parent is a carrier



When both parents are carriers



Who is at risk for sickle cell trait?

Anyone can carry a sickle cell trait; however, some populations are at a higher risk than others are. Sickle cell trait is most common in African Americans. However, people of Mediterranean, Middle Eastern, Indian, Asian and Hispanic backgrounds are also at an increased risk to have sickle cell trait so many people should be tested.

How can you tell if someone has sickle cell trait?

The only way to tell of someone has sickle cell trait is to be tested. Some blood tests are more useful than others. The best tests give detailed results. They can find the (S) gene. But they can also find **other** genes, such as the (C) gene or the Beta thalassemia gene, which can combine with the (S) gene to cause other forms of sickle cell disease.

What can I do if I have sickle cell trait?

If you find out that you have sickle cell trait, your spouse or partner should also be tested. Knowing ahead of time that your future children may be at risk gives you time to prepare for and learn more about caring for a child with a serious illness. Genetic counselors are also available to help explain the risks and discuss prenatal testing, and other options. The most important thing you can do is be responsible for the best health care for your child.

Consensus Statement: Sickle Cell Trait and the Athlete

Purpose
In a recent review of non-traumatic sports deaths in high school and college athletes (1), the top four killers, in order of occurrence, were: cardiovascular conditions, hyperthermia (heatstroke), acute rhabdomyolysis tied to sickle cell trait, and asthma. Acute exertional rhabdomyolysis (explosive muscle breakdown) from sickle cell trait is the least understood of these conditions. The purpose of this Task Force is to raise awareness of this condition and provide measures to reduce the risk of exertional collapse related to sickle cell trait.

Introduction
Sickle cell trait is the inheritance of one gene for sickle hemoglobin and one for normal hemoglobin. During intense or extensive exertion, the sickle hemoglobin can change the shape of red cells from round to quarter-moon, or "sickle." This change, exertional sickling, can pose a grave risk for some athletes. In the past seven years, exertional sickling has killed nine athletes, ages 12 through 19.

Research shows how and why sickle red cells can accumulate in the bloodstream during intense exercise. Sickle cells can "logjam" blood vessels and lead to collapse from ischemic rhabdomyolysis, the rapid breakdown of muscles starved of blood. Major metabolic problems from explosive rhabdomyolysis can threaten life. Sickling can begin in 2-3 minutes of any all-out exertion – and can reach grave levels soon thereafter if the athlete continues to struggle. Heat, dehydration, altitude, and asthma can increase the risk for and worsen sickling, even when exercise is not all-out. Despite telltale features, collapse from exertional sickling in athletes is under-recognized and often misdiagnosed. Sickling collapse is a medical emergency.

We recommend confirming sickle cell trait status in all athletes' preparticipation physical examinations. As all 50 states screen at birth, this marker is a base element of personal health information that should be made readily available to the athlete, the athlete's parents, and the athlete's healthcare provider, including those providers responsible for determination of medical eligibility for participation in sports.

Knowledge of sickle cell trait status can be a gateway to education and simple precautions that may prevent sickling collapse and enable athletes with sickle cell trait to thrive in sport. Nearly all of the 13 deaths in college football have been at institutions that did not screen for sickle cell trait or had a lapse in precautions for it. Small numbers preclude cogent evidence to support screening. All considered, however, we believe that each institution should carefully weigh the decision to screen based on the potential to provide key clinical information and targeted education that can save lives. Irrespective of screening, the institution should educate staff, coaches, and athletes on the potentially lethal nature of this condition.

Background
A condition of inheritance versus race, the sickle gene is common in people whose origin is from areas where malaria is widespread. Over the millennia, carrying one sickle gene fended off death from malaria, leaving one in 12 African-Americans (versus one in 2,000 to one in 10,000 white Americans) with sickle cell trait. The sickle gene is also present in those of Mediterranean, Middle Eastern, Indian, Caribbean and South and Central American ancestry; hence, the required screening of all newborns in the United States.

In the past four decades, exertional sickling has killed at least 15 football players. In the past seven years alone, sickling has killed nine athletes: five college football players in training, two high school athletes (one a 14-year-old female basketball player), and two 12-year-old boys training for football. Of 136 sudden, non-traumatic sports deaths in high school and college athletes over a decade, seven (5%) were from exertional sickling (1).

The U. S. military tied sickle cell trait to sudden death during recruit basic training. The relative risk of exercise-related death in sickle cell trait was about 30 (2). In other words, recruits with sickle cell trait were 30 times more likely to die during basic training. The main cause of death was rhabdomyolysis – and the risk of exertional rhabdomyolysis was about 200 times greater for those with sickle cell trait (3).

In sickle cell trait, strenuous exercise evokes four forces that in concert foster sickling, 1) severe hypoxemia, 2) metabolic acidosis; 3) hyperthermia in muscles, and 4) red-cell dehydration.

Evidence supports this syndrome. Military research shows that, during intense exertion and hypoxemia, sickle cells can accumulate in the blood (4). Recent research also shows that systemic dehydration worsens exertional sickling (5). Field studies in Africa suggest that sickle-trait runners are limited not in single sprints but in middle distance or altitude running (6). The pattern in American athletes is similar.

Sickling Collapse: Football and Other Sports

The first known sickling death in college football was in 1974. A defensive back from Florida ran a conditioning test on the first day of practice at altitude in Colorado. He had collapsed on the first day of practice the year before. This time, near the end of the first long sprint, at about 700 meters, he collapsed again – and died the next day. The most recent sickling death, a freshman defensive back at Rice University in the fall of 2006, is similar. He collapsed after running 16 sprints of 100 yards each – and died the next morning. The cause of death for both athletes was acute exertional rhabdomyolysis associated with sickle cell trait.

Up to 13 college football players have died after a sickling collapse. The setting and syndrome in most are similar:

- Sickling players may be on-field only briefly, sprinting only 800-1,600 meters, often early in the season.
- Sickling can also occur during repetitive running of hills or stadium steps, during intense sustained strength training, if the tempo increases late in intense one-hour drills, or at the end of practice when players run "gassers."
- Sickling can even occur rarely in the game, as when a running back is in constant action during a long, frantic drive downfield (7).

Sickling collapse is not limited to football. It has occurred in distance racing and has killed or nearly killed several college or high school basketball players (two were females) in training, typically during "suicide sprints" on the court, laps on a track, or a long training run.

The harder and faster athletes go, the earlier and greater the sickling, which likely explains why exertional collapse occurs "sooner" in college football players sprinting than in military recruits running longer distances. Sickling can begin in only 2-3 minutes of sprinting – or in any other all-out exertion – and sickling can quickly increase to grave levels if the stricken athlete struggles on or is urged on by the coach.

Sickling Collapse: Telltale Features

Sickling collapse has been mistaken for cardiac collapse or heat collapse. But unlike sickling collapse, cardiac collapse tends to be "instantaneous," has no "cramping" with it, and the athlete (with ventricular fibrillation) who hits the ground no longer talks. Unlike heat collapse, sickling collapse often occurs within the first half hour on-field, as during initial windsprints. Core temperature is not greatly elevated.

Sickling is often confused with heat cramping; but, athletes who have had both syndromes know the difference, as indicated by the following distinctions:

1) Heat cramping often has a prodrome of muscle twinges; whereas, sickling has none;
2) The pain is different – heat-cramping pain is more excruciating;
3) What stops the athlete is different – heat crampers hobble to a halt with "locked-up" muscles, while sickling players slump to the ground with weak muscles;
4) Physical findings are different – heat crampers writhe and yell in pain, with muscles visibly contracted and rock-hard; whereas, sicklers lie fairly still, not yelling in pain, with muscles that look and feel normal;
5) The response is different – sickling players caught early and treated right recover faster than players with major heat cramping (7).

This is not to say that all athletes who sickle present exactly the same way. How they react differs, including some stoic players who just stop, saying "I can't go on." As the player rests, sickle red cells regain oxygen in the lungs and most then revert to normal shape, and the athlete soon feels good again and ready to continue. This self-limiting feature surely saves lives.

Precautions and Treatment

No sickle-trait athlete is ever disqualified, because simple precautions seem to suffice. For the athlete with sickle cell trait, the following guidelines should be adhered to:

1) Build up slowly in training with paced progressions, allowing longer periods of rest and recovery between repetitions.
2) Encourage participation in preseason strength and conditioning programs to enhance the preparedness of athletes for performance testing which should be sports-specific. Athletes with sickle cell trait should be excluded from participation in performance tests such as mile runs, serial sprints, etc., as several deaths have occurred from participation in this setting.
3) Cessation of activity with onset of symptoms [muscle 'cramping', pain, swelling, weakness, tenderness; inability to "catch breath", fatigue].
4) If sickle-trait athletes can set their own pace, they seem to do fine.
5) All athletes should participate in a year-round, periodized strength and conditioning program that is consistent with individual needs, goals, abilities and sport-specific demands. Athletes with sickle cell trait who perform repetitive high speed sprints and/or interval training that induces high levels of lactic acid should be allowed extended recovery between repetitions since this type of conditioning poses special risk to these athletes.
6) Ambient heat stress, dehydration, asthma, illness, and altitude predispose the athlete with sickle trait to an onset of crisis in physical exertion.
    a. Adjust work/rest cycles for environmental heat stress
    b. Emphasize hydration
    c. Control asthma
    d. No workout if an athlete with sickle trait is ill
    e. Watch closely the athlete with sickle cell trait who is new to altitude. Modify training and have supplemental oxygen available for competitions
7) Educate to create an environment that encourages athletes with sickle cell trait to report any symptoms immediately; any signs or symptoms such as fatigue, difficulty breathing, leg or low back pain, or leg or low back cramping in an athlete with sickle cell trait should be assumed to be sickling (7).

In the event of a sickling collapse, treat it as a medical emergency by doing the following:

1) Check vital signs.
2) Administer high-flow oxygen, 15 lpm (if available), with a non-rebreather face mask.
3) Cool the athlete, if necessary.
4) If the athlete is obtunded or as vital signs decline, call 911, attach an AED, start an IV, and get the athlete to the hospital fast.
5) Tell the doctors to expect explosive rhabdomyolysis and grave metabolic complications.
6) Proactively prepare by having an Emergency Action Plan and appropriate emergency equipment for all practices and competitions.

What We Can Do

Though screening is done at birth; many athletes do not know their sickle-trait status, rendering self-report in a questionnaire unreliable. Many institutions have employed screening strategies to rectify this. A recent survey of NCAA Division I-A schools found that 64% (of respondents) screen (8). The NFL Scouting Combine screens for sickle cell trait. All considered, despite no evidence-based proof yet that screening saves lives, each institution should carefully weigh the decision to screen in the absence of documented newborn screen results.

The Consensus of this Task Force is:

1) There is no contraindication to participation in sport for the athlete with sickle cell trait.
2) Red blood cells can sickle during intense exertion, blocking blood vessels and posing a grave risk for athletes with sickle cell trait.
3) Screening and simple precautions may prevent deaths and help athletes with sickle cell trait thrive in their sport.
4) Efforts to document newborn screening results should be made during the PPE.
5) In the absence of newborn screening results, institutions should carefully weigh the decision to screen based on the potential to provide key clinical information and targeted education that may save lives.
6) Irrespective of screening, institutions should educate staff, coaches, and athletes on the potentially lethal nature of this condition.
7) Education and precautions work best when targeted at those athletes who need it most; therefore, institutions should carefully weigh this factor in deciding whether to screen. All told, the case for screening is strong.

Glossary

Acute Ischemic rhabdomyolysis: the rapid breakdown of muscle tissue starved of blood
Acute Rhabdomyolysis: a serious and potentially fatal condition involving the breakdown of skeletal muscle fibers resulting in the release of muscle fiber contents into the circulation
Contraindication: circumstance or condition that makes participation unsafe or inappropriate
Exertional rhabdomyolysis: muscle breakdown triggered by physical activity
Exertional sickling: hemoglobin [red blood cell] sickling due to intense or sustained physical exertion
Hyperthermia: body temperature elevated above the normal range
Hypoxemia: decreased oxygen content of arterial blood
Ischemia: a deficiency of blood flow to tissue
Metabolic acidosis: a condition in which the pH of the blood is too acidic because of the production of certain types of acids
Nontraumatic: not related to a physical injury caused by an external force
Obtunded: having diminished arousal and awareness; mentally dull
Sickling collapse: the collapse of an athlete who shows features consistent with exertional sickling
Ventricular Fibrillation: a condition in which there is uncoordinated contraction of the cardiac muscle of the ventricles in the heart

References

1. Van Camp SP, Bloor CM, Mueller FO, Cantu RC, Olson HG. Nontraumatic sports death in high school and college athletes. *Med Sci Sports Exerc.* 1995;27:641-647.
2. Kark JA, Ward FT. Exercise and hemoglobin S. *Semin in Hematol.* 1994;31:181-225.
3. Gardner JW, Kark JA. Fatal rhabdomyolysis presenting as mild heat illness in military training. *Milit. Med.* 1994;159:160-163.
4. Martin TW, Weisman IM, Zeballos RJ, Stephenson RS. Exercise and hypoxia increase sickling in venous blood from an exercising limb in individuals with sickle cell trait. *Am J Med.* 1989;87:48-56.
5. Bergeron MF, Cannon JG, Hall EL, Kutlar A. Erythrocyte sickling during exercise and thermal stress. *Clin J Sport Med.* 2004;14:354-356.
6. Marlin L, Etienne-Julan M, Le Gallais D, Hue O. Sickle cell trait in French West Indian elite sprint athletes. *Int J Sports Med.* 2005;26:622-625.
7. Eichner ER. Sickle cell trait. *J Sport Rehab*, 2007 (May), in press.
8. Clarke CE, Paul S, Stilson M, Senf J. Sickle cell trait preparticipation screening practices of collegiate physicians. *Clin J Sport Med* 2006;16:440a.

Task Force Participants

The following individuals and associations were members of the Inter-Association Task Force on Sickle Cell Trait and the Athlete. Their participation is not an endorsement of this document. For a complete list of supporting associations, please visit http://www.nata.org/statements/consensus/sct_endorsements.htm.

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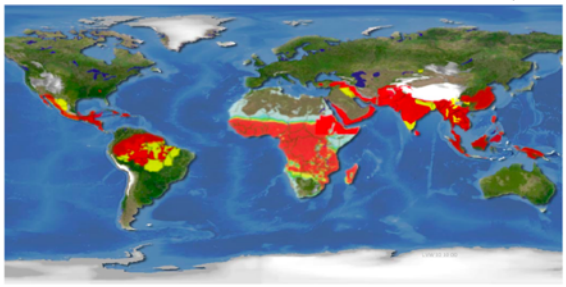
APPENDIX C

PRESENTATION GIVEN TO THE ATHLETIC STAFF AT THE UNIVERSITY OF PITTSBURGH

Sickle Cell Trait and the Athlete

Lakshmanan Krishnamurti, MD
Amy Aloe, BA

Prevalence



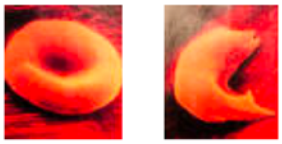
- Those of African, Mediterranean, Middle Eastern, Caribbean, South American and Central American decent are at risk for sickle cell disease

Prevalence of Sickle Cell Disease and Trait

- Sickle Cell Disease
  - 1 in 375 (0.26%) African Americans are born with sickle cell disease
- Sickle Cell Trait
  - 8% of African Americans are carriers
  - 0.046% of nonblack Americans are carriers

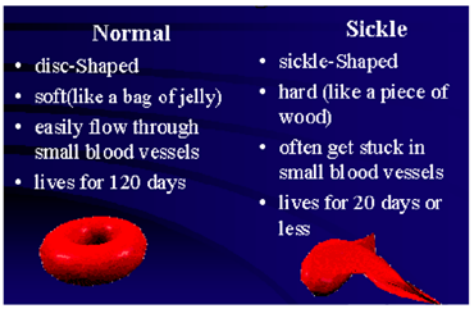
What is sickle cell disease?

- A serious blood disorder, in which a genetic change causes the red blood cells to change shape from round and soft to half-moon shaped



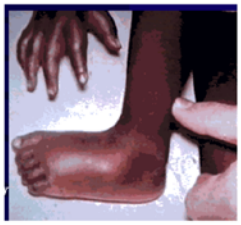
- a person needs to inherit a copy of the nonworking gene from both parents to have disease

Normal vs Sickle Hemoglobin



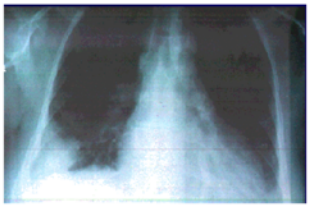
Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
  - Hand Foot Syndrome
    - Painful swelling for hands and feet caused by sickled red blood cells
    - One of the first manifestations, occurring most often between 6mo-2yrs



Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
  - Acute Chest syndrome
    - Caused by sickled cells blocking blood vessels in the lungs
    - Most common cause of childhood death in sickle cell disease



Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
  - Hand Foot Syndrome
  - Acute Chest syndrome
  - Anemia
    - Low number of red blood cells

Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
  - Hand Foot Syndrome
  - Acute Chest syndrome
  - Anemia
  - Jaundice
    - Increased levels of liver enzyme in the blood, due to break down of red blood cells

Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
  - Hand Foot Syndrome
  - Acute Chest syndrome
  - Anemia
  - Jaundice
  - Infection

Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
  - Hand Foot Syndrome
  - Acute Chest syndrome
  - Anemia
  - Jaundice
  - Infection
  - Eye problems

Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
  - Hand Foot Syndrome
  - Acute Chest syndrome
  - Anemia
  - Jaundice
  - Infection
  - Eye problems
  - Stroke

Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
  - Hand Foot Syndrome
  - Acute Chest syndrome
  - Anemia
  - Jaundice
  - Infection
  - Eye problems
  - Stroke
  - Splenic sequestration
    - Sudden pooling of blood in the spleen

Sickle Cell Disease

- Sickle cells can block blood vessels, which cause serious complications such as
  - Hand Foot Syndrome
  - Acute Chest syndrome
  - Anemia
  - Jaundice
  - Infection
  - Eye problems
  - Stroke
  - Splenic sequestration
  - Sickle cell pain crisis

National Sickle Cell Anemia Control Act

- Signed by president Nixon in 1972
- Allocated funds to provide for:
  - voluntary sickle cell trait screening and counseling
  - Sickle cell education for health professionals and the public
  - Research and research training for diagnosis, treatment, and control of sickle cell disease

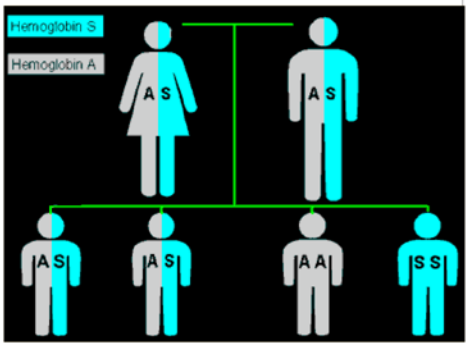
National Sickle Cell Anemia Control Act

- As a result, the outcome for an individual with sickle cell disease is dramatically different
  - Mortality rate dropped 41-52% between 1968 and 1992
  - In 1960, the disease was primarily one of childhood with limited survival to adulthood
  - Now average lifespan for males with sickle cell disease is 42 and for females with sickle cell disease is 48

What is sickle cell trait?

- Sickle cell trait occurs when a person inherits a working gene from one parent and and a nonworking (sickle) gene from the other parent
- Also referred to as being a “carrier”
- Sickle cell trait is <u>not</u> a disease

Autosomal Recessive Inheritance



National Collegiate Athletic Association (NCAA) Recommendation

- On June 25th, the NCAA's Committee on Competitive Safeguards and Medical Aspects of Sports recommended that its member colleges and universities test athletes for Sickle Cell Trait during their required medical examinations, if not already known
- Follows guidelines from the National Athletic Trainers Association and the College of American Pathologists and stems from a recent lawsuit resolution

National Collegiate Athletic Association (NCAA) Recommendation

- The lawsuit was filed against the NCAA by the family of Dale Lloyd II
  - a former football student-athlete at Rice University, who died in 2006 after a practice
  - After his untimely death, testing indicated he was a sickle cell trait carrier and that this had lead to his death

History of Sickle Cell Trait and Death in Athletes & the Military

- In the past 7 years, sickling has been correlated to the death of at least 9 athletes
  - 5 college football players in training
  - 2 high school athletes
  - 2 middle school athletes
- In the U.S. military, sickle cell trait was tied to sudden death during recruit basic training
  - They found that recruits with trait were 30 times more likely to die during basic training, than recruits without sickle cell trait

History of Sickle Cell Trait and Death in Athletes & the Military

- Of the sudden deaths
  - In the athletes
    - Often occurred early in the season, usually after sprinting 800-1600 meters
  - In the army
    - Most occurred during the 1st month of training and associated with exertional activities requiring maximum effort

Debate over cause of sudden death

- There is no direct evidence linking the pathogenesis of exercise-related sickling; however the majority of data shows that sickle cell trait is associated with increased risk of exercise-induced sudden death

Evidence supporting sickling during exercise

- Strenuous exercise may cause sickling, as it causes four changes in the body that foster sickling
  - Severe hypoxemia (low oxygen)
  - Metabolic acidosis
  - Muscle hyperthermia
  - Red-cell dehydration

Evidence supporting sickling during exercise

- Strenuous exercise may cause sickling, as it causes four changes in the body that foster sickling
  - Severe hypoxemia (low oxygen)
  - ↓
  - Metabolic acidosis
  - Muscle hyperthermia
  - } To facilitate oxygen delivery
  - ↓
  - Red-cell dehydration

Evidence supporting sickling during exercise

- When there is low oxygen levels in the blood, the sickle hemoglobin has an increased affinity to bind to the healthy red blood cells
- These collections of blood cells can block blood flow to the muscles, causing rapid muscle breakdown, leading the athlete to collapse

Exertional Sickling

- The sickling that occurs during all-out physical activity, is called "exertional sickling"
- The muscle breakdown that it causes, can be fatal
- Heat, dehydration, high-altitudes and asthma can increase the risk and severity of exertional sickling

Features of Collapse Due to Sickling

- When an athlete collapses from exertional sickling, it may be mistaken for heat or cardiac collapse
- In cardiac collapse, the collapse is "instantaneous," without any cramping, and athletes are unable to talk
- Differences between heat and sickling collapse:

Type	Muscle twinges	Timing in activity	Pain	Muscles
Heat	Yes	Later	More	Locked-up and hard to the touch
Sickling	No	Within first 30 minutes	Less	Weak and feel normal to the touch

Sickle Cell Trait in the Military

- Army
  - Ceased screening for sickle cell trait
- Marines
  - Screen all participants and do not alter training regimens
- Air Force
  - Screen all participants and offers the option to each recruit to decline service if positive for trait
- Navy
  - Screen all recruits and identifies trait carriers with a red belt and neck tag during strenuous exercise drills

Sickle Cell Trait in the Military

- **1982 Intervention for Prevention of Exertional Heat Illness (EHI) During U. S. Armed Forces Basic Training**
  - **Record wet-bulb globe temperature (WBGT) at least hourly at the exercise site**
    - **WBGT composite temperature used to estimate the effect of temperature, humidity, wind speed, wind chill, and solar radiation on humans** (range from $50-$150)
  - **Decrease exercise intensity and increase rest cycles as WBGT rises, to minimal effort at 90°F**
  - **Increase water intake & observe water consumption**
  - **Exercise using light track clothing in hot weather**
  - **Initiate immediate cooling/rehydration with early symptoms**

John W. Gardner, MD, DrPH, COL, MC, FS, USA & John A. Kark, MD
Howard University Hospital

1982 Intervention for Prevention of EHI During U. S. Armed Forces Basic Training

John W. Gardner, MD, DrPH, COL, MC, FS, USA & John A. Kark, MD
Howard University Hospital

1982 Intervention for Prevention of EHI During U. S. Armed Forces Basic Training Conclusions

1. **There is a strong association between exposure to hot weather within 24 hours of exercise and risk of exercise-related sudden death, strongest with sickle cell trait.**
3. **Exertional heat stroke greatly increases the risk for exercise-related threatened or actual sudden death, probably through cardiovascular collapse.**
5. **Intervention to prevent exertional heat illness appears to eliminate the excess risk for exercise-related death with sickle cell trait and to reduce mortality in others.**
4. **Exertional heat illness is a major preventable factor contributing to exercise-related death of young adults.**

John W. Gardner, MD, DrPH, COL, MC, FS, USA & John A. Kark, MD
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Testing for Sickle Cell Trait at the University of Pittsburgh

- We tested 79 athletes from the following teams
  - Football
  - Softball
  - Men's and Women's Soccer
  - Swimming
  - Track & Field
  - Cross Country
  - Men's and Women's Basketball
- Offered on-site education at time of testing and provided results over the phone to athletes

National Athletic Trainers' Association Recommendations to Prevent Exertional Sickling

- Build up slowly in training with pace and progressions, allowing longer periods of rest and recovery
- Encourage participation in preseason strength and conditioning programs to enhance the preparedness of athletes for sport-specific performance testing
  - Athletes with sickle cell trait should be excluded from participation in performance tests, such as mile runs, serial sprints, etc.

National Athletic Trainers' Association Recommendations to Prevent Exertional Sickling

- Cessation of activity with onset of symptoms
  - Muscle "cramping"
  - Pain
  - Swelling
  - Weakness
  - Tenderness
  - Inability to "catch breath"
  - fatigue

National Athletic Trainers' Association Recommendations to Prevent Exertional Sickling

- Let athletes set their own pace
- All athletes should participate in year-round, periodized strength and conditioning program consistent with their individual needs, sport, and abilities
- Educate athletes to create an environment in which they feel comfortable reporting any symptoms immediately

National Athletic Trainers' Association Recommendations to Prevent Exertional Sickling

- More extreme conditions, such as hot temperatures, dehydration, asthma, illness, and higher altitudes predispose the athlete with sickle cell trait to exertional sickling. At these times special care should be taken:
  - Adjust work/rest cycles
  - Emphasize hydration
  - Control asthma
  - If ill, an athlete should not practice
  - In increased altitudes, modify training and have supplemental oxygen available

National Athletic Trainers' Association Recommendations to Treat Exertional Sickling Collapse

- Treat as an emergency
  - Check vital signs
  - Administer high-flow oxygen (15 1pm if available) with a non-rebreather face mask
  - If necessary, cool the athlete
  - If vital signs decline, call 911, attach an AED, start an IV and get the athlete to the hospital ASAP
    - Tell doctors to expect explosive rhabdomyolysis (muscle breakdown) and grave metabolic complications
- Prepare for this scenario by having an emergency plan and appropriate equipment for all practices and competitions

Participation of Athletes with Sickle Cell Trait

- Athletes with sickle cell trait should NOT be excluded from participating in sports, as screening and the simple precautions listed previously may prevent exertional sickling

Genetic Information Nondiscriminatory Act (GINA)

- Signed by president George W. Bush in 2008
- Prevents insurance and employment discrimination based on genetic information
- Genetic information includes:
  - Individual genetic test results
  - Genetic tests of family members or fetuses
  - Manifestation of disease or disorder in family members
  - Any request for, or receipt of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling, or education) by an individual or family member.

Participation of Athletes with Sickle Cell Trait

- Great care should be taken to avoid stigmatization of athletes with sickle cell trait
- If discrimination or stigmatization occurs, it could discourage athletes to be screened for sickle cell trait or take appropriate measures during practice if feeling fatigued
  - This would be to the detriment of the athlete's health and well-being

In closing…

- How can the University of Pittsburgh
  - ensure that it's athletes with sickle cell trait are not discriminated against?
  - foster an environment in which athletes feel comfortable getting tested?
  - run practices to ensure the safety of all athletes? Since testing for sickle cell is voluntary, the trait status of all athletes may not be known.

Thank You

- Thank you to all coaches and administrators for organizing the sickle cell trait screening with your athletes
- Any questions?

BIBLIOGRAPHY

1.Ashcroft MT, Desai P. Mortality and morbidity in Jamaican adults with sickle-cell trait and with normal haemoglobin followed up for twelve years. *Lancet* 1976;2(7989):784-6.

2.Van Camp SP, Bloor CM, Mueller FO, Cantu RC, Olson HG. Nontraumatic sports death in high school and college athletes. *Med Sci Sports Exerc* 1995;27(5):641-7.

3.NCAA. NCAA Recommends Testing to Confirm Sickle Cell Trait Status in Student-Athletes. In: *NCAA News Release*. Indianapolis: NCAA; 2009.

4.Rodgers GP. Overview of pathophysiology and rationale for treatment of sickle cell anemia. *Semin Hematol* 1997;34(3 Suppl 3):2-7.

5.Dunston T, Rowland R, Huntsman RG, Yawson G. Sickle-cell haemolglobin C disease and sickle-cell beta thalassaemia in white South Africans. *S Afr Med J* 1972;46(39):1423-6.

6.Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. 1910. *Yale J Biol Med* 2001;74(3):179-84.

7.Taliaferro WH, Huck JG. The Inheritance of Sickle-Cell Anaemia in Man. *Genetics* 1923;8(6):594-8.

8.Neel JV. The Inheritance of Sickle Cell Anemia. *Science* 1949;110(2846):64-66.

9.Pauling L, Itano HA, et al. Sickle cell anemia a molecular disease. *Science* 1949;110(2865):543-8.

10.Beutler E. Disorders of Hemoglobin: Sickle Cell Anemia and Related Abnormalities. In: Licthmasn Marshall TK, Kenneth Kaushansky, Ernest Beutler, Uri eligsohn, Josef Prschal, ed. *Williams Hematology*. 7th ed. New York: McGraw-Hill 2006:667-700.

11.Allison AC. Protection afforded by sickle-cell trait against subtertian malareal infection. *Br Med J* 1954;1(4857):290-4.

12.Williams TN, Mwangi TW, Wambua S, et al. Sickle cell trait and the risk of Plasmodium falciparum malaria and other childhood diseases. *J Infect Dis* 2005;192(1):178-86.

13.Miller MJ, Neel JV, Livingstone FB. Distribution of parasites in the red cells of sickle-cell trait carriers infected with Plasmodium falciparum. *Trans R Soc Trop Med Hyg* 1956;50(3):294-6.

14.Samuel RE, Salmon ED, Briehl RW. Nucleation and growth of fibres and gel formation in sickle cell haemoglobin. *Nature* 1990;345(6278):833-5.

15.Goodman SR. The irreversibly sickled cell: a perspective. *Cell Mol Biol (Noisy-le-grand)* 2004;50(1):53-8.

16.Stuart MJ, Nagel RL. Sickle-cell disease. *Lancet* 2004;364(9442):1343-60.

17.Lane PA, Githens JH. Splenic syndrome at mountain altitudes in sickle cell trait. Its occurrence in nonblack persons. *JAMA* 1985;253(15):2251-4.

18.Green RL, Huntsman RG, Serjeant GR. The sickle-cell and altitude. *Br Med J* 1971;4(5787):593-5.

19.Coletta M, Hofrichter J, Ferrone FA, Eaton WA. Kinetics of sickle haemoglobin polymerization in single red cells. *Nature* 1982;300(5888):194-7.

20.Mozzarelli A, Hofrichter J, Eaton WA. Delay time of hemoglobin S polymerization prevents most cells from sickling in vivo. *Science* 1987;237(4814):500-6.

21.Smith WR, Coyne P, Smith VS, Mercier B. Temperature changes, temperature extremes, and their relationship to emergency department visits and hospitalizations for sickle cell crisis. *Pain Manag Nurs* 2003;4(3):106-11.

22.Bessis M, Bricka M, Breton-Gorius J, Tabuis J. New observations on sickle cells with special reference to their agglutinability. *Blood* 1954;9(1):39-45.

23.Beutler E. Hypothesis: changes in the O2 dissociation curve and sickling: a general formulation and therapeutic strategy. *Blood* 1974;43(2):297-300.

24.Wong WY. Prevention and management of infection in children with sickle cell anaemia. *Paediatr Drugs* 2001;3(11):793-801.

25.Serjeant GR, Ceulaer CD, Lethbridge R, Morris J, Singhal A, Thomas PW. The painful crisis of homozygous sickle cell disease: clinical features. *Br J Haematol* 1994;87(3):586-91.

26.Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med* 1994;330(23):1639-44.

27.Serjeant GaS, Beryl. Sickle Cell Disease. 3rd ed. New York: Oxford University Press; 2001.

28.Nance WE, Grove J. Genetic determination of phenotypic variation in sickle cell trait. *Science* 1972;177(50):716-8.

29.Levere RD, Lichtman HC, Levine J. Effect of Iron-Deficiency Anaemia on the Metabolism of the Heterogenic Haemoglobins in Sickle Cell Trait. *Nature* 1964;202:499-501.

30.Noguchi CT, Torchia DA, Schechter AN. Polymerization of hemoglobin in sickle trait erythrocytes and lysates. *J Biol Chem* 1981;256(9):4168-71.

31.Heller P, Best WR, Nelson RB, Becktel J. Clinical implications of sickle-cell trait and glucose-6-phosphate dehydrogenase deficiency in hospitalized black male patients. *N Engl J Med* 1979;300(18):1001-5.

32.Hoiberg A, Ernst J, Uddin DE. Sickle cell trait and glucose-6-phosphate dehydrogenase deficiency. Effects on health and military performance in black Navy enlistees. *Arch Intern Med* 1981;141(11):1485-8.

33.Pritchard JA, Scott DE, Whalley PH, Cunningham FG, Mason RA. The effects of maternal sickle cell hemoglobinopathies and sickle cell trait on reproductive performance. *Am J Obstet Gynecol* 1973;117(5):662-70.

34.Kiryluk K, Jadoon A, Gupta M, Radhakrishnan J. Sickle cell trait and gross hematuria. *Kidney Int* 2007;71(7):706-10.

35.Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong Y. Complications associated with sickle cell trait: a brief narrative review. *Am J Med* 2009;122(6):507-12.

36.Davis CJ, Jr., Mostofi FK, Sesterhenn IA. Renal medullary carcinoma. The seventh sickle cell nephropathy. *Am J Surg Pathol* 1995;19(1):1-11.

37.Nuss R, Feyerabend AJ, Lear JL, Lane PA. Splenic function in persons with sickle cell trait at moderately high altitude. *Am J Hematol* 1991;37(2):130-2.

38.Castro O, Finch SC. Letter: Splenic infarction in sickle-cell trait: are whites more susceptible? *N Engl J Med* 1974;291(12):630-1.

39.Diep BN, Scheirman K, Reeves WB, Mask DR, Eichner ER. Splenic infarction in a white man with sickle cell trait. *South Med J* 1979;72(12):1611-3.

40.Gitlin SD, Thompson CB. Non-altitude-related splenic infarction in a patient with sickle cell trait. *Am J Med* 1989;87(6):697-8.

41.Goldberg NM, Dorman JP, Riley CA, Armbruster EJ, Jr. Altitude-related specific infarction in sickle cell trait--case reports of a father and son. *West J Med* 1985;143(5):670-2.

42.King DT, Lindstrom RR, State D, Hirose FM, Schwartz A. Unusual cause of acute abdomen. Sickle cell trait and nonhypoxic splenic infarction. *JAMA* 1977;238(20):2173-4.

43.Magnuson TR, Hunter SW, Bonnabeau RC, Jr. Multiple vascular infarction. A manifestation of sickle cell trait in the absence of hypoxia. *Minn Med* 1980;63(6):381-3.

44.O'Brien RT, Pearson HA, Godley JA, Spencer RP. Splenic infarct and sickle-(cell) trait. *N Engl J Med* 1972;287(14):720.

45.Rywlin AM, Benson J. Massive necrosis of the spleen with formation of a pseudocyst. Report of a case in a white man with sickle cell trait. *Am J Clin Pathol* 1961;36:142-50.

46.Sheikha A. Splenic syndrome in patients at high altitude with unrecognized sickle cell trait: splenectomy is often unnecessary. *Can J Surg* 2005;48(5):377-81.

47.Ramirez A, Hartley LH, Rhodes D, Abelmann WH. Morphological features of red blood cells in subjects with sickle cell trait: changes during exercise. *Arch Intern Med* 1976;136(9):1064-6.

48.Martin TW, Weisman IM, Zeballos RJ, Stephenson SR. Exercise and hypoxia increase sickling in venous blood from an exercising limb in individuals with sickle cell trait. *Am J Med* 1989;87(1):48-56.

49.Baskurt OK, Meiselman HJ, Bergeron MF. Re: Point:Counterpoint: Sickle cell trait should/should not be considered asymptomatic and as a benign condition during physical activity. *J Appl Physiol* 2007;103(6):2142; author reply 2143-4.

50.Connes P, Hardy-Dessources MD, Hue O. Counterpoint: Sickle cell trait should not be considered asymptomatic and as a benign condition during physical activity. *J Appl Physiol* 2007;103(6):2138-40; discussion 2140-1.

51.Le Gallais D, Lonsdorfer J, Bogui P, Fattoum S. Point: Sickle cell trait should be considered asymptomatic and as a benign condition during physical activity. *J Appl Physiol* 2007;103(6):2137-8; discussion 2141.

52.Jones SR, Binder RA, Donowho EM, Jr. Sudden death in sickle-cell trait. *N Engl J Med* 1970;282(6):323-5.

53.Kark JA, Posey DM, Schumacher HR, Ruehle CJ. Sickle-cell trait as a risk factor for sudden death in physical training. *N Engl J Med* 1987;317(13):781-7.

54.Drehner D, Neuhauser KM, Neuhauser TS, Blackwood GV. Death among U.S. Air Force basic trainees, 1956 to 1996. *Mil Med* 1999;164(12):841-7.

55.Eichner ER. Sickle cell trait. *J Sport Rehabil* 2007;16(3):197-203.

56.Mitchell BL. Sickle cell trait and sudden death--bringing it home. *J Natl Med Assoc* 2007;99(3):300-5.

57.Gardner JW, Kark JA. Fatal rhabdomyolysis presenting as mild heat illness in military training. *Mil Med* 1994;159(2):160-3.

58.Daland GA, Castle WB. A simple and rapid method for demonstrating sickling of the red blood cells; the use of reducing agents. *J Lab Clin Med* 1948;33(9):1082-8.

59.Goldberg CA. The ferrohemoglobin solubility test; its accuracy and precision together with values found in the presence of some abnormal hemoglobins. *Clin Chem* 1958;4(2):145-9.

60.National Sickle Cell Anemia Control Act. In: Congress n, ed. *92-294*. Public Libary; May 16th, 1972.

61.Wailoo K. Dying in the city of the blues : sickle cell anemia and the politics of race and health. Chapel Hill, NC: University of North Carolina Press; 2001.

62.Benson JM, Therrell BL, Jr. History and current status of newborn screening for hemoglobinopathies. *Semin Perinatol* 2010;34(2):134-44.

63.Wilson B. NCAA May Force Schools to Test for Sickle Cell Trait. In: *NPR*; 2009.

64.Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. *Circulation* 2009;119(8):1085-92.

65.Maron BJ, Thompson PD, Ackerman MJ, et al. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation* 2007;115(12):1643-455.

66.Maron BJ. Sudden death in young athletes. *N Engl J Med* 2003;349(11):1064-75.

67.Preparticipation Physical Evaluation/The Physician and Sports-Medicine. Minneapolis, Minn: McGraw-Hill 2005.

68.Press A. Bulls deal Curry after DNA test refusal. In: *espn.com*. Deerfield, Ill: Associated Press; 2005.

69.Tell-tale Heart: Is Eddy Curry at risk for cardiac disease? After he refuses a DNA test, the Bulls trade him. In: *Sports Illustrated.com*; October 10, 2005.

70.NCAA. Playing and practice seasons and recruiting-- mandatory medical examination--sickle cell solubility test--documented results prior to test In: NCAA, ed. *2009-75-B*. NCAA Dvision I Legislation; 2010:49-50.