A COMPREHENSIVE STUDY ON SICKLE CELL ANEMIA

BY

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A COMPREHENSIVE STUDY ON SICKLE CELL ANEMIA

A Research Paper

Presented to

the Graduate Council of

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In Partial Fulfillment

of the Requirements for the Degree

Master of Science

in Biology

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by

Patti Jean Mallory Guerard

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To the Graduate Council:

I am submitting herewith a Research Paper written by Patti Mallory Guerard entitled "A Comprehensive Study on Sickle Cell Anemia." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Biology.

Marvin M. Brand
Major Professor

Accepted for the Council:

William D. Ellis
Dean of the Graduate School

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This research paper is dedicated to my parents, Mr. and Mrs. Nathaniel Mallory who aspired for a good and meaningful education for all of their children.

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Chapter I

INTRODUCTION

Sickle cell anemia is an inherited disease. Although it does affect other minority groups, it is predominantly a black man's disease. (Culliton 1972).

Sickle cell anemia was first described by Dr. James B. Herrick, 1910, of Chicago, to be a "thin, elongated, sickle-shaped" red blood corpuscle.

It was not until 1949 that Linus Pauling, a chemist, and three students discovered that the cause of the disease really lay in the structure of the hemoglobin molecule (Spencer 1973).

A Los Angeles physician, Dr. V. R. Masson first named the disease sickle cell anemia.

It is a form of anemia that is so named because of the sickle shape the red blood cells assume whenever an attack occurs. If the oxygen level in the body is reduced, the red blood cells begin to twist and cluster together and assume this abnormal shape.

This disease causes more pain and suffering and affects more people than cystic fibrosis (Culliton 1972) or phenylketonuria (PKU), (Duckett 1971), yet it has been ignored for many years. Sickle cell anemia occurs about 1 per 500 live black births compared to 1 in

1400 live white births for cystic fibrosis (Culliton 1972), and 1 per 10,000 live PKU births (Duckett 1971). Although more than 1,000 infants born in the U. S. each year have sickle cell anemia, it is not as commonly known as muscular dystrophy (a disease which affects fewer children). It has received only a tiny share of the medical research budget: in 1968, for example, volunteer groups raised $50,000 in sickle cell research funds, while $7.2 million was raised in that same year to fight muscular dystrophy (Murata 1971).

An estimated 45,000 Americans suffer from sickle cell anemia, and another 2 million carry the sickle cell trait (ibid).

Sickle cell anemia is an incurable, tragic disease. It will affect many young black Americans, and will kill many of them before they are 20 years old. The average life expectancy of an individual with this disease is 40 years (Cerami et al. 1972). A few individuals survive beyond 40 years and live very productive lives. In this paper are excerpts from Dr. Joseph Phillips' article, "How I Cope With Sickle Cell Anemia", from Ebony, February, 1976. Dr. Phillips is a Professor of Psychiatry at Meharry Medical College, in Nashville, Tennessee and he has lived a very fulfilling life in spite of his illness.

In this paper the history of the disease will be discussed to include the following:

1. the history and background
2. the nature of the disease

3. the symptoms and treatments (there is no cure)
4. the molecular structure of the hemoglobin
5. how the normal red blood cell differs from the sickle cell
6. experiments conducted pertaining to the disease
7. private and governmental support and finances
8. case studies of sickle cell anemia
9. the impact the disease has on the entire family
10. and the community's reaction to the people who have the disease.

Chapter II

METHODS AND MATERIALS

This information has been collected from publications resulting from experiments conducted by research scientists. This paper is basically a summation of their research and findings.

According to Robert Murray of Howard University, Washington, D. C., there are several tests for screening sickle cell anemia, but three predominate. One is the solubility test (two will be discussed: Sickledex and Wolf-Nalbandian versions), another is hemoglobin electrophoresis, and another is direct microscopic observation of the blood (Culliton 1972).

The Wolf-Nalbandian test involves a solution of potassium phosphate, sodium dithionite and saponin. Sickledex is a brand name version of the solubility test manufactured by the Ortho Diagnostics, Raritan, New Jersey. The chemicals in the Sickledex is the rights of the Ortho Diagnostics manufacturing firm. Both solubility tests require only a few drops of the patient's blood.

The hemoglobin electrophoresis test is performed in an alkaline solution at a pH of 8.6.

A compound light microscope is needed for direct observation of the red blood cells. A few drops of sodium metabisulfite will cause

abnormal hemoglobin to sickle, which can be easily observed under a microscope.

A team from the John Hopkins University reported that it is possible to detect sickle hemoglobin in a fetus (Culliton 1972).

There are several chemicals used for treatment of sickle cell anemia. They are urea, cyanate (a constituent of urea), antibiotics and zinc sulfate.

Hyperberic oxygen has also been used as a treatment for sickle cell anemia.

Chapter III

RESULTS

The Wolf-Nalbandian test, named for Dr. Paul Wolf of Sanford University and Robert Nalbandian of Blodgett Memorial Hospital in Grand Rapids, Michigan, is used to detect hemoglobin S (Hb S) and other less harmful sickling substances. This test is based on Dr. Makio Murayama's work of the National Institute of Arthritis and Metabolic Association for the Advancement of Science.

The Wolf-Nalbandian test includes dropping a small sample of blood into a tube containing a solution of potassium phosphate, sodium dithionite and saponin. The test does not distinguish between those who merely carry the sickle cell trait and those that are actually affected by the disease. However, it does provide a fast, inexpensive method of finding individuals who should get further attention (Hinton, Monkmeyer 1971).

With the Wolf-Nalbandian test and most solubility tests, if the solution turns cloudy, one assumes the presence of an abnormal hemoglobin. Follow-up tests are required (Culliton 1972), if the solubility test is positive.

Sickledex is another commonly used brand name version of the solubility test and costs about 2 cents per test for materials (Culliton 1972).

Howard Pearson, a pediatric hematologist at Yale University School of Medicine, says "Sickledex is nondefinitive and of historical interest only. It comes up with wrong answers and is scaring people half to death. Hemoglobin electrophoresis is the only test you can defend" (Culliton 1972).

The most useful method for the preliminary identification of abnormal hemoglobin is that of electrophoresis, a common technique for the separation of proteins (Bowman, Goldwasser 1975).

In order to understand how the electrophoresis test works one must first consider that each person has two genes for this trait, one from each parent. These two genes may be found in the following combinations: AA-normal hemoglobin, AS-trait carrier (one normal gene from one parent, one defective gene from the other parent), SS-sickle cell anemia patient (both genes are defective; received from both parents).

Electrophoresis is the movement of charged particles in an electrical field with appropriate buffers and supporting media. That movement is dependent on the net charge of the molecule.

Electrophoresis of hemoglobin AA, AS and SS is best carried out at a pH of 8.6. In electrophoresis, a blood sample is placed in slots marked ORIGIN, and during an appropriate period of time the hemoglobins move toward the positive (+) pole. The A hemoglobin moves faster than the S hemoglobin (Bowman, Goldwasser 1975). If the

patient has sickle cell anemia (SS), the hemoglobin S molecule will migrate about half-way across the medium from the point marked ORIGIN. If the patient has the trait (AS), hemoglobin A will migrate to the positive pole, hemoglobin S will migrate half-way across the medium. If the patient is normal, the hemoglobin (AA) will migrate to the positive pole.

Electrophoresis costs about 5 cents per test for materials. A technician can run 100 to 150 tests a day. Pearson concedes that he is "very prejudiced in favor of electrophoresis, because it is definitive and picks up sickle cell anemia, sickle cell trait, and other hemoglobin disorders such as C-trait, a related condition of abnormal hemoglobin" (Culliton 1972).

Electrophoresis is no more complicated to perform than the solubility tests. Therefore, programs using electrophoresis can easily be affiliated with medical centers and hospitals that can provide backup support and counseling to persons whose tests are positive for Hb S (Interview with Dr. Davis of Meharry Sickle Cell Anemia Center, Nashville, Tennessee 1977). In my interview with Dr. Davis, he explained the screening, counseling and hospital care that the Center at Meharry Medical provides for a person after an electrophoresis test confirms sickle cell anemia. The Meharry Sickle Cell Anemia Center will be discussed in greater detail later in the paper.

Dr. Makio Murayama gives credit for his diagnosis of Sickle

Cell Anemia in a patient to the compound microscope. The sickle shape of the red blood cells can be easily seen under a microscope. This preliminary research paved the way for work with an electron microscope.

Culliton (1972) describes the work done by Michael Kamback, Moreley Hollenberg, and Haig H. Kazazian, the team from the John Hopkins University, in which it was discovered that it is possible to detect sickle hemoglobin in a fetus. The problem is that in order to perform the test, one needs a drop of fetal blood. Amniocentesis, as it is carried out now, is a procedure in which amniotic fluid is withdrawn and examined for evidence of a disease in the unborn child. Drawing blood from the fetus itself, however, poses additional difficulty.

In the July 6 New England Journal of Medicine, Yuet Wai Kan and his hematology team at the Children's Hospital Medical Center in Boston and obstetrician Frederic D. Frigoletto of the Boston Hospital for women report that they have used a technique similar to that of Kazazian's group to focus on fetal synthesis of sickle cell hemoglobin chains. Again the synthesis was carried out in blood samples taken from aborted fetuses. After the blood samples were collected, radioactively labeled amino acids were placed in them. The blood cells used the amino acids to make new chains of hemoglobin. Since the amino acids were labeled, the chains being made--normal and sickle cell--could be detected. Kan's group also points out that the

assay can be carried out on a sample of fetal blood contaminated with maternal blood cell (Hollenbery et al. 1972).

Kazazian also pointed out that assaying the sickle cell anemia trait or sickle cell anemia in the fetus will not be clinically feasible until blood samples can be drawn from live fetuses. Kaback has said, that it will be necessary to take blood from the heel. In order to do that, one has to be able to see the fetus (Culliton 1972). However, Dr. Davis at the Meharry Sickle Cell Anemia Center states that in his opinion this is now a relatively easy process to perform.

Dr. Makio Murayama of the National Institute of Arthritis and Metabolic Diseases told a symposium at the American Association for the Advancement of Science meeting about his discovery that abnormal hemoglobin molecules stack up to form fibers that cause blood cells to sickle.

The crumpling of sickled erythrocytes is due to aggregation of the hemoglobin molecules into tubules (Murayama 1966). These cells can be made normal under hyperbaric pressure (Murayama et al. 1967).

Dr. M. Murayama was one of the first scientists to discover that, sickled red cells do unsickle reversibly at pressures of about 200 to 300 atmospheres. Atmospheric pressure is being considered not as a cure, but as a temporary relief of pain.

Once when Dr. Richard J. Bing, a Detroit professor, lacked a hyperbaric pressure chamber he used a submarine to alleviate the

pain of a sickle cell anemia crisis in a child patient of his. Although the child was not permanently cured by the pressure aboard the submarine, he was spared the immediate pain and the after effects of a crisis (Murayama et al. 1967).

Sickle cell anemia cannot be cured, though treatment can sometimes control its effect. In the late 1970, Michigan pathologist, Dr. Robert N. Nalbandian reported some success in relieving sickle cell anemia by injecting victims with very large amounts of urea, a constituent of urine (Hinton-Monkmeyer 1971).

Urea, a natural waste substance, produced by the normal liver, breaks some molecular bonds in abnormal hemoglobin. When urea is added to the solution that had shown a positive reaction initially, the liquid clears quickly if hemoglobin S is present. This prevents the abnormal hemoglobin molecules from linking together (Cerami et al. 1972).

The treatment using urea, was based on the research by Dr. Makio Murayama who found how the red cell in sickle cell anemia acquires its peculiar shape, through abnormal hemoglobin bonds stacking together. Work with urea first began when Dr. Raymond L. Henry, of Detroit's Wayne State University, looked for ways to prevent this formation of abnormal hemoglobin bonds. In the test tube the Michigan investigators found urea prevented the abnormal hemoglobin bonds in sickle cells and reversed them to a normal doughnut

shape (Nalbandian et al. 1970).

Working with colleagues in several U. S. medical centers, Nalbandian's team found that intravenous infusions of large doses of urea dissolved in a sugar solution relieved acute sickle cell crisis in all 22 patients. Previously no other therapy, including massive infusions of fluids and narcotics to dull pain, had been effective. More recently, the investigators have explored the possibility of preventing sickle cell crises by administering small amounts of urea orally in a sweet soft drink. Promising results have been obtained in the first three cases. Ultimately, Nalbandian and his colleagues believe victims of sickle cell anemia may lead normal lives through daily drinks of urea, much as diabetics control their disease with insulin (Cerami et al. 1972).

Hb A differs from Hb S in only one site out of 146 amino acids on the B-chain. A valine replaces a glutamic acid (see Figure 1). Valine has an isopropyl side chain, and according to Dr. M. Murayama's theory this encourages formation of hydrophobic bonds between chains at low oxygen concentration. Bonded chains then stick together, forming filaments which eventually thicken and force the cells to assume their twisted shape. The treatment with urea was designed to reverse sickling by breaking those hydrophobic bonds.

Nalbandian applied this technique to a patient who was in severe pain and who had not been helped by other treatments. After intravenous

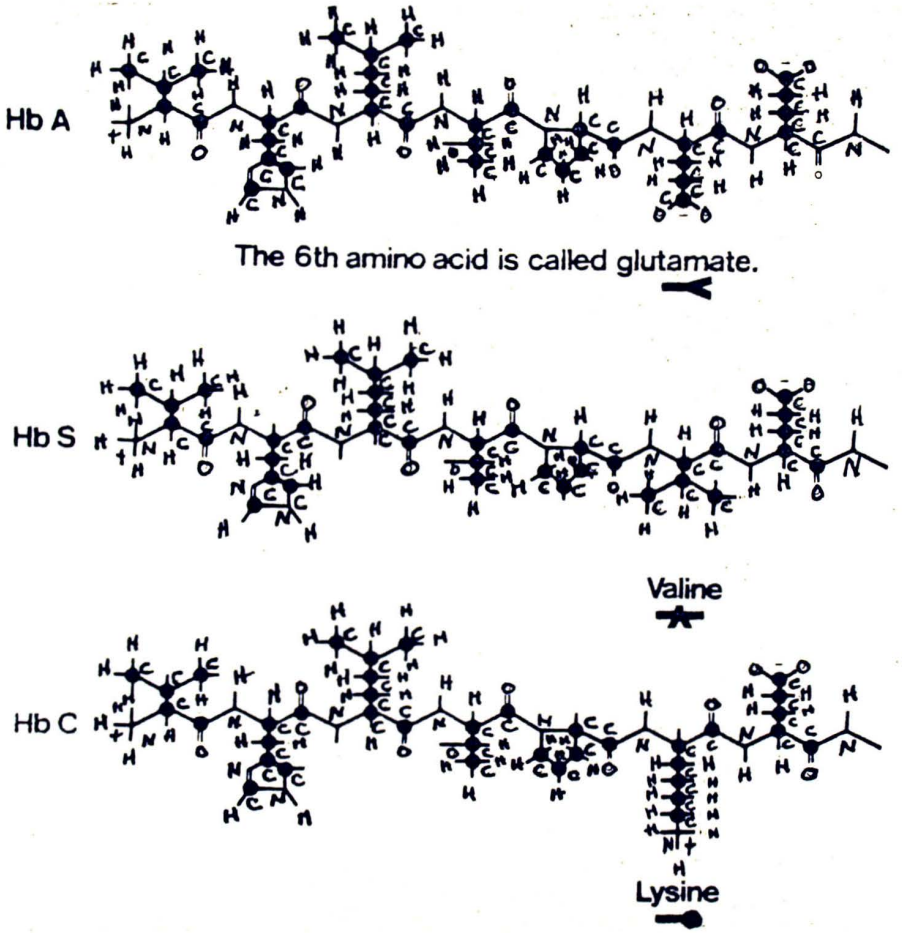

Figure 1. The Beta-Chains of Hemoglobins A, S, and C.

infusion of urea in glucose solution for 24 hours, the symptons disappeared (Kenyo 1971).

Urea can cause severe dehydration, which if unchecked, can cause convulsions and even death. Thus, it is extremely important that this method of treatment is constantly monitored (Kenyo 1971).

Other researchers reasoned that what kept the abnormal hemoglobin molecules apart was not necessarily the urea itself, but one of the impurities regularly found in the compound. The Rockefeller University group, headed by Dr. Anthony Cerami, suggested that this agent might be cyanate (Cerami et al. 1972).

Before clinical trials with cyanate, Cerami and his colleagues tested its toxicity in lower animals. To date, Cerami reported in Atlantic City at the Annual Meeting of the Federation of American Societies for Experimental Biology that studies on mice, rats, dogs and monkeys have turned up no side effects of the chemical (Cerami et al. 1972).

Thus was the stage set for tests of cyanate on blood samples of sickle cell anemia victims. The tests showed that cyanate inhibited sickling just as urea does--and much more effectively. Further the effects of cyanate alone on the sickle cell, unlike that of urea solution appeared to be permanent. Blood cells unsickled by cyanate retained their doughnut shapes even after the cyanate was removed, while cells unsickled by ordinary urea returned to the sickled shape when urea was no longer present. There was also the advantage that only a

small amount of cyanate is required (Cerami et al. 1972)

Dr. Peter N. Gillette, sponsored tests of cyanate in human patients with sickle cell anemia. The object of these trials was to measure the effect of cyanate, consumed in capsule form, on the lifetime of the patients' red blood cells (Cerami et al. 1972).

The cells of sickle cell patients die much sooner than normal cells. Preliminary monitoring of the blood from ten patients on cyanate therapy suggests that the chemical indeed increased the cell life span (Cerami et al. 1972).

Because of the limited scope and short-term nature of the trials, the Rockefeller team refused to speculate on future prospects for cyanate therapy. Nevertheless, Cerami declared, "present indications support our initial findings that cyanate in the amount sufficient to produce clinically measurable effects is well tolerated by man, and have encouraged us to extend our clinical trials and intensify the parallel investigation into the long-term effects of cyanate".

Studies to determine the possibility of the existence of an antibody that is specific for Hb S have been conducted by several researchers.

Anti Hb S antibodies were raised in horses and purified by affinity chromatography. This antibody is used to recognize Hb S. The antibody will bind with Hb S (sickle hemoglobin) while it will not bind with Hb A (normal hemoglobin) nor Hb C (abnormal hemoglobin, not sickled) (Papayannopoulou 1976).

The preparation and characterization of antibodies to specific regions of hemoglobin is of value in developing methods both to identify and to study the conformation of the many forms of hemoglobin (Young et al. 1976).

Peptides purified by the Merrifield procedure and Merrifield method (gel filtration) may be used to fractionate antibodies to the native hemoglobin S, in the characterization of antigen-binding properties of specific antibodies (Eastlake et al. 1976). This method was used to purify antibiotics that was specific for hemoglobin S.

It has been suggested that some patients with sickle cell anemia are zinc deficient (Oelshlegel 1975).

A limited test of zinc therapy was conducted involving daily oral administration of zinc sulfate (660 mg. - more than 20 times the recommended daily allowance for zinc) to seven men and two women with sickle cell anemia. Two 17-year old males gained height during zinc therapy: one gained 5 cm in 49 weeks and the other 7 cm in 42 weeks. Eight of these nine patients also gained weight. Only one patient, a female, lost 0.5 g. Increased growth of body hair in males with sickle cell anemia also occurred during zinc administration (Oelshlegel 1975).

The finding that zinc therapy caused apparent symptomatic improvement in the clinical signs of sickle cell disease suggests that zinc supplementation may be beneficial in treating sickle cell anemia patients (Oelshlegel 1975).

Chapter IV

DISCUSSION AND CONCLUSIONS

Sickle cell anemia is not a communicable disease (Phillips 1976). It is an inherited disease (Culliton 1972).

Persons with sickle cell anemia are characterized by periodic bouts with sickness or crisis, with a variety of symptoms, including a general or localized pain, fever, a drop in the red blood cell count, swelling of the hands and feet, and some associated diseases such as pneumonia, strokes and heart diseases (Phillips 1976).

Almost seventy years has passed since Dr. J. B. Herrick of Chicago first described the thin elongated sickled-shaped cells of a Chicago student as sickled cells.

"Sickle cell anemia is often regarded as a black man's disease," says Dr. Phillips of Meharry Medical Center. However, there are other races which have this condition, such as East Indian and American Indians, Greeks, Italians and Mexicans. The fact that malaria infected areas are associated with the disease gives us a clue as to how it may have originated (Phillips 1976).

Scientists tell us that over many generations in malaria-infested areas the hemoglobin, the oxygen carrying substance in the red blood cells, underwent genetic change. This change in the hemoglobin

developed a resistance in the patient to the malaria parasite which invaded the blood stream. The cell would change shapes making it uncomfortable for the malaria parasite to live. This mutation of the hemoglobin has been passed on and still exists in the sickle cell anemia person.

Sickle cell anemia and trait hemoglobin are inherited from parents with this mutated gene. Sickle cell trait is an inherited condition in which the individual is healthy, but is carrying both Hb A--normal hemoglobin and Hb S--sickle hemoglobin genes (Schaeffer 1976), in his red blood cells. Trait carriers do have different amounts of sickle cells. Venous blood was obtained from 10 sickle cell anemia trait doners. Five had relatively high Hb S concentration--40%, and five with low Hb S levels 25-30% (ibid).

The mutated gene can be passed from one generation to the next in the following manner: if both parents carry the defective gene (AS-AS) both can pass on the defect to the child. Then there is a 1 in 4 chance of a sickle cell anemia victim. If one parent has the trait (AS) and the other parent is normal (AA) then, there is a 2 in 4 chance (or 50%) of having the trait. In a sickle cell anemia person (SS) and a normal person (AA) union, all the children will inherit a defective gene from the sickle cell anemia parent, thus all being trait carriers. In a sickle cell anemia (SS) and a trait carrier (AS) union there is a 2 in 4 chance (or 50%) that there will be trait carriers and a 2 in 4 chance

(or 50%) that there will be sickle cell anemia victims (Interview with Dr. Davis at Meharry Medical Center 1977).

Two genetic sources of variation influence the percentage of sickle cell hemoglobin found in heterozygotes. One factor is strongly related to the percentage of hemoglobin S in the carrier parent and appears to be determined by sickle hemoglobin isoalleles, whereas the other is related to racial background and may well be polygenic (Nance, Grove 1972).

To investigate the causes of individual variation, replicate measurements were made of the proportion of sickle hemoglobin (Hb S) in 272 heterozygous parents and children in 67 families that were segregated for sickle cell trait (Nance, Grove 1972).

"About one in every ten black Americans carries the trait," says Dr. Ronald B. Scott, a Howard University professor who has researched the disease more than 20 years. "Most of these carriers have very little sickling in their blood and have no trouble from it all during their lives".

Most sickle cell anemia hemoglobin defects result from a single amino acid substitution in the Beta-chain, and most are not disadvantageous to the affected individual (Barnhart 1974). Hemoglobin S differs from normal hemoglobin by one amino acid substitution in the Beta-chain, namely a valine in place of a glutamic acid at the number 6 position. This substitution on the external surface results in

abnormal reactions between molecules of Hb S when oxygen tension is lowered. With deoxygenation the valine substitution permits abnormal polymerization or stacking of Hb S molecules, converting Hb S from the sol to gel state.

When the oxygen level is reduced to a low level this triggers an attack or "crisis".

There are different types of crises. One is when the lowering of oxygen in the blood stream causes the cells to clump and clog the capillaries. This obstruction can cause pain in any part of the joints and body. Another type is aplastic crisis--where the blood stops making red blood cells, causing severe anemia. Another type is hemolytic crisis--in this form the red blood cells containing sickle hemoglobin are destroyed in the body in large numbers resulting in severe anemia and jaundice (Interview with Dr. Davis, Meharry Medical Institute, Sickle Cell Anemia Center 1977).

When these crises happen, the sickle cells in the person's blood will hook and stick together in masses that clog the small blood vessels and stop the blood flow through vital areas.

The deformed cells clog narrow capillaries and cause blood clots and symptoms, such as swelling and severe pain in various parts of the body (Fransworth 1970).

The amount of Hb F (fetal hemoglobin) in the blood can influence the number of crises. In a study by Morrison and colleagues it was

found that some patients with low Hb F levels had many crises and others with high amount of Hb F had no crises (Morrison 1976).

Through many years of hardship and deprivation, many families of sickle cell anemia have suffered needlessly because of ignorance and lack of compassion. Many sickle cell anemia families have few friends to help them through the torment of having a sick person in their family.

The average sickle cell anemia patient goes to the hospital 7-12 times a year and has numerous blood transfusions. The cost is enormous--$7,000-$24,000 a year, depending on location of the hospital.

Insurance companies can refuse sickle cell anemia patients coverage after they are 18 or 21 years of age. They can also charge them higher rates, because they are considered high risks. Many employers refuse work to persons with sickle cell anemia (Pierce 1973). This causes many individuals to keep it a secret that they are sickle cell anemia victims. Many refuse to be treated for the disease. This will continue until more understanding of the nature of the disease can be more widespread.

The Hartford, Connecticut screening promoted by WTIC radio and television stations owned by Leonard J. Patrecilli is an example of the interest aroused and concern for the disease now in many communities. Five thousand permission slips were sent out to be signed

by the parents of black children to be screened in grades 7-12. A total of 3,456 children were screened by Sickledex method: 301 tests were positive, and follow-up studies by hemoglobin electrophoresis showed that four children did not carry the trait. No one was notified of the test results until the follow-up electrophoresis, a more precise method, had been done (Culliton 1972).

The Hartford study was conducted with a large measure of community cooperation, which seems to be why so many students and their parents responded. It seems that community concern makes all the difference.

In another study, twelve infants with sickle cell anemia identified in the course of a cord blood screening program were followed up to 3 years of age (O'Brien 1976).

Sickle cell anemia is more common in some parts of the country than leukemia, hemophilia and platelet disease put together. Why does sickle cell anemia receive such lack of attention from both private and governmental organizations? It is also believed to cause more paralysis than polio, and can affect any organ of the body and is a major cause of maternal mortality (Johnson 1966). Yet, many blacks are afraid to submit themselves to even a simple test to detect whether they are carriers or victims, simply because of the stigma attached to the disease.

"The future looks better" says Dr. Roland B. Scott, Professor

of Medicine at Howard University in Washington, D. C., and a long-time leader in sickle cell studies. "Patients are living longer helped by modern therapeutic methods, and if the necessary financial support is provided, a breakthrough may come. Even though sickle cell disease involves mainly a minority group, research on it may eventually help solve other genetic and molecular disease as well" (Spencer 1973).

However, for the time being, the only way you can be sure not to have a child with sickle cell anemia is either to avoid marriage to someone who also carries the trait or to forego having children (Culliton 1972).

Twelve Case Studies of Sickle Cell Anemia Victims

Case #1

Dr. Joseph Phillips, a Psychiastrist and Professor, at Meharry Medical Center in Nashville, Tennessee, is a sickle cell anemia patient. Excerpts have been taken from his article "How I Cope With Sickle Cell Anemia," published in Ebony, in February, 1976 issue. There excerpts will include his personal feelings about having the disease, how he and his family cope with the disease, and how he inherited the disease.

"I was raised in Nashville, where I lived with my parents, brother and a sister between two great ghettos: Black Bottom and Tremble Bottom.

To be born with sickle cell anemia itself (SS) means that a child has inherited a sickle cell gene from each of his parents . . . my father has the trait, is 85, is very active as a minister.

The pains I had were called "rheumatism" by the family doctor who had yet to be exposed to the knowledge, diagnosis and management of a condition called sickle cell anemia.

It was not until high school that the diagnosis was made at a hospital. I had been taken to the clinics because my father decided I needed more treatment for a cold which had lingered for longer than usual.

The episodes of crises did not hinder my progress. . .

College at Tennessee State University was even more rewarding

--scholastically, socially, culturally . . .

I had crises and when hospitalized I had no worries about returning to campus where I studied pre-medicine . . . I suffered a serious crisis complicated with pneumonia . . .

Sure, sickle cell anemia may shorten a life, just as hemophilia, or hypertension or accidental death may do. I turned my attention to a larger goal of helping others. I had a reunion with my family and friends. I also talked with my children--four by this time--helping them to understand my condition. More importantly, my family began to participate directly in the management of my crises.

To my fellow-sufferers, and those who are burdened with other diseases, I would say this: One has to learn to accept such a condition" (Phillips 1976).

Case #2

W. S. was born September 3, 1959. He was the third of five children. There was no known health problems in any other children in the family. Mother and father were in good health and had no significant medical history other than the usual colds and minor complaints. This child had been in good health from the time of birth with normal growth and development until age 29 months at which time he developed acutely swollen hot fingers, hands and feet. The patient was hospitalized with a diagnosis of probable acute septic arthritis, R/O osteomyelytis by his local physician who is a general

practitioner. Subsequent to hospitalization the patient was seen by a pediatrician in consultation who suggested that the process might be sickle cell disease and recommended that appropriate studies be done. Patient subsequently had a sickle prep which was positive and peripheral smears revealing circulating sickled cells. Paper hemoglobin electrophoresis revealed predominantly Hb S hemoglobin with very small amounts of Hb F and Hb A. Patient was given intravenous fluids and the patient was discharged with a diagnosis of sickle cell anemia and polydactylitis.

During the next two years the patient remained relatively asymptomatic but slowly developed increasing anemia and at age 5 he was rehospitalized because of a sudden increase in severity of his anemia and complaining of severe pain in the joints in the arms and legs. The patient was noted on admission to have severe pain in the in the arms and legs. The patient was noted on admission to have a severe upper respiratory infection and pneumonia was present on chest x-ray. Physical findings revealed the patient's spleen to be enlarged. To combat the severe anemia the patient was transfused with packed red cells and treated with antibiotics. His infection responded slowly with use of transfusions and intravenous fluid; patients hematocrit increased and the painful episodes diminished. Some 8 days after admission the patient was discharged with a stable hematocrit level and clear lung fields. Spleen had decreased in size.

Diagnosis at the time of discharge were 1) painful crises, 2) sequestration crises, 3) upper respiratory infection, and 4) bilateral lobar pneumonia.

On the course of the next 5 years the patient experienced recurrent episodes of pneumonia and increased frequency of painful crises. In addition, he had many episodes of severe left flank pain which was finally diagnosed as being secondary to spleenic infarction.

At age 11 the patient was presented to the hospital in a crisis with a swollen hot right leg. He appeared to be septic. X-ray examination of the leg revealed developing osteomylitis. Blood cultures revealed salmonella organisms. Patient was treated aggressively with antibiotics but did not respond. Patient died, two days after admission, of salmonella septicemia (Interview with Dr. Davis, Meharry Medical 1977).

Case #3

This patient of the Children's Hospital of East Bay in Oakland, California was born November 25, 1974. He was seen by the Hematology Service at Children's Hospital for the first time on May 14, 1976. At that time he had been admitted to Children's Hospital to diagnose his failure to thrive. He had been followed by Dr. Quint prior to this decision, who was well aware of his failure to thrive and also the fact that he had sickle cell anemia. Although his growth pattern was increasing, the rate at which he was growing was clearly abnormal.

His medical history revealed that he was a 5 lbs. product of a

39-week gestation. He was born at home. His mother was 22 years of age.

During his hospitalization, he had an extensive workup to rule out metabolic, central nervous system, renal, and endocrine abnormalities. Of the studies that were abnormal, the most significant was a bone age of 2 months when his chronologic age was 17 months. Hematologic evaluation revealed a hemoglobin of 7.6%, reticulocyte count 17%, and a mean corpuscular volume of 92. A cellulose acetate and citrate agar revealed a diagnosis of sickle cell anemia. This child has a severe hemolytic component to his anemia, as his elevated reticulocyte count has been noted on multiple occasions, indicating an increased rate of destruction of red cells peripherally. However, during this hospital stay his weight did increase from 12 pounds 12 ounces to 13 pounds 12 ounces. His weight gain was attributed to adequate calorie intake.

There was moderate muscle weakness, with a question of very mild right hemiplegia.

The patient was examined again in January of 1977. Examination revealed a very small child with minimal spontaneous movement. He was 26 months of age. His weight was 20 pounds and his height 30 inches.

Thorough examination that the child was normal in most aspects. Laboratory examination at that time revealed a hemoglobin

of 8, with a reticulocyte count of 23.3%. The white count was 15,000. There were many sickle forms on the peripheral blood smear.

The extent of hemolysis associated with his sickle cell anemia is sufficient to severely impair his growth in the absence of adequate nutrition (Correspondence - Children's Hospital, Oakland, CA 1977).

Case #4

M. J. was three years old when she was first stricken with sickle cell anemia. It was first diagnosed as leukemia and the patient was given only a few months to live.

M. J. was the second of six children. She and one of her brothers have the disease. For six years neither M. J. nor her brother were allowed to participate in strenous activities.

Both the parents had trouble with health problems. The mother lost sight in her left eye, due to another hereditary trait. The father has a nervous condition that affected his larynx. After a closer look at the parents, tests revealed that both were trait carriers.

During a seven year period M. J. had 100 transfusions.

Of the J.'s children two have sickle cell anemia, three are trait carriers, and one is completely free of the disease.

After two weeks of tests, doctors at the National Institute of Health at Bethesda, Maryland, advised local doctors to discontinue giving blood transfusions to M. J. and her brother because their systems had built up antibodies to the blood (Johnson 1966).

Case #5

On June 2, 1972, this child was examined by the Hematology Clinic in Oakland, California, for problems related to her sickle cell disease.

Since her last visit 3 months before, she had developed pain and swelling of the hands, knees, and ankles; treatment with Darvon controlled these symptoms. This was the first time that she had had significant joint involvement. Two weeks prior to this visit there was a mild crisis manifested by abdominal and back pain, requiring bed rest; these symptoms have subsequently resolved. She also had symptoms of an upper respiratory infection, manifested by marked cervical adenopathy, which resolved in 3 to 4 days on Ampicillin.

This particular young lady was born June 11, 1960. She has been suffering with sickle cell anemia since a very early age and has been examined every 3 months since (Correspondence - Children's Hospital, Oakland, CA 1977).

Case #6

E. S. was born in Grand Rapids, Michigan. He participated in a test program designed to find out whether urea, a substance long known to science, might relieve sickle cell crises and prevent further attacks.

Because of the success of the program, E. S. is gaining weight for the first time (Murata 1971).

Case #7

This patient of the Children's Hospital at Oakland, California, was born July 4, 1963. He has sickle cell disease.

Although the extent of his anemia is very mild, he has suffered a major vaso-occlusive problem in his lungs. This has been localized to his right lower lobe, where he now has extensive fibrosis secondary to a pulmonary infarct. Careful evaluation of the effects of this pulmonary abnormality on his lung functions has been performed at the University of California in San Francisco.

It is evident from these reports that this patient's pulmonary functions are significantly altered as a consequence of his sickle cell disease. It is unlikely that he will have return of function in this area of the lung, as the findings are most compatible with fibrosis which is an irreversible process.

He was also very active physically prior to the development of his pulmonary complications. However, the pulmonary condition has added severity to his sickle cell anemia, which has made him less active (Correspondence - Children's Hospital, Oakland, CA 1977).

Case #8

During the winter of 1972, J. A., a six-year old New York schoolboy, had to drop out of kindergarten because he had suffered a stroke during a sickle cell anemia crisis. A year later, his skinny legs still move with a slow, slightly spastic gait, and he had not yet

regained his strength (Spencer 1973).

Case #9

J. W. was a former student in the Austin Peay State University Prep Program. He did not find out that he had sickle cell anemia until after he was in the Army. (personal knowledge).

According to Culliton 1973, it should be standard procedure to screen recruits for sickle cell anemia.

Case #10

Shelton, the first of five children, woke up one morning in 1949 with hands and feet swollen. The doctors thought he had rheumatic fever. He was treated for rheumatic fever, but the swelling and high temperature continued. His eyes were still jaundiced and his complexion pale, so it had to be more than rheumatic fever.

Rockefeller Institute, now a part of New York University, were the first to diagnose it as sickle cell anemia.

Shelton is always in terrible pain during a crisis. The pain is everywhere he says: bones, joints, ankles, knees, back, chest, arms, and legs. He was given Demerol for the pain. There were times when 150 milligrams of Demerol was given him and absolutely nothing happened. The pain was still there.

Shelton, wasn't expected to live to be older than 21. But at the time of the publication of this article, he was already past 22.

Gregory, Shelton's brother died at the age of five of sickle cell anemia. He died of a blood clot in the brain. He was the second of the five children in the family.

Ramona, Shelton's sister, the third child of the five, has the disease also.

The family has been drained physically, mentally, and financially. Shelton's hospital bills for surgery, blood transfusions, and treatment fluctuated, but have generally been averaging about $7,000 a year.

Shelton, says "If you are here only for a day, the fact is that you lived. You were here" (Pierce 1973).

Case #11

Mrs. S. A., 36, has lived with the constant fear of death since she was eight. During those years she has survived many painful crises as the sickle cells clogged her circulation. "Sometimes I ache so much I just scream with pain," she says. She is hospitalized about 12 times a year, many times for days at a time (Spencer 1973).

Case #12

T. B., age 4, was hospitalized in Milwaukee on Friday night with severe chills and fever. He died during that hospital visit apparently of a heart attack. Mrs. T. B., mother of the boy says, "to watch your child lie there in pain and not be able to do one thing about

it . . . is something you just don't get over" (Spencer 1973).

Chapter V

SUMMARY

Sickle cell anemia is an ethnic disease that was discovered almost seventy years ago in a Chicago student. For many years very little had been done to research and find a possible cure for this disease that occurs more often than cystic fibrosis, muscular dystrophy and PKU. However, more finances are available from both private and public organizations to support finding a cure for this disease than ever before.

There are three tests that predominate for screening sickle cell anemia. They are the solubility test, observation of the blood with a microscope and electrophoresis. They all are relatively inexpensive. But, electrophoresis is more effective in isolating sickling disorders. This method can differentiate between sickle cell anemia, sickle trait, and other sickling disorders. Electrophoresis also provides corroborating evidence for a comprehensive program of screening, education, and counseling to persons with this hereditary disorder.

Some of the treatments used are urea, zinc sulfate, cyanate, atmospheric pressure and antibiotics. But, of the many types used, cyanate has been found to be the most effective in reversing the sickling process for a longer period of time.

Sickle cell anemia is a disease that has been diagnosed at the molecular level. A cure has not been found. However, it is possible that if this mystery can be solved, scientists can begin to understand or even find a cure for some of the other genetic diseases known to man. There may be a link between sickle cell anemia and its relative sickling groups and other genetic disorders.

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INTERVIEWS AND CORRESPONDENCE

Dr. Davis, Meharry Sickle Cell Disease Center, 1005-18th Avenue, North, Nashville, Tennessee 37208.

Children's Hospital at East Bay, Hematology Clinic of the Sickle Cell Disease Center, 51st and Grove Streets, Oakland, California 94609.

APPENDIX

Various Correspondence Regarding Case Studies of

Sickle Cell Anemia

September 26, 1977

Ms. Patti J. Guerard
231 Oak Street
Clarksville, Tennessee 37040

Dear Sir:

My name is Patti J. Guerard. I am a graduate student at Austin Peay State University in Clarksville, Tennessee.

I am having trouble obtaining enough information on actual cases of sickle cell anemia persons, trait carriers or other sickling disorders.

In order to complete my research paper on sickle cell anemia, I need this information desperately. Can you provide any of the above?

Thank you very much for your cooperation.

Sincerely,

Patti J. Guerard

Patti J. Guerard

pjg

W. S. Was born on September 3, 1959. This was the third of five children. There were no known health problems in any other children in the family. Mother and father were in good health and had no significant medical history other than the usual colds and minor complaints. This child had been in perfectly good health from the time of birth with normal growth and development until age 29 months at which time he developed acutely swollen hot fingers, hands and feet. The patient was hospitalized with a diagnosis of probable acute septic arthritis, R/O osteomyelytis by his local physician who is a general practitioner. Subsequent to hospitalization the patient was seen by a pediatrician in consultation who suggested that the process might be sickle cell disease and recommended that appropriate studies be done. Patient subsequently had a sickle prep which was positive and pheripheral smears revealing circulating sickled cells. Paper hemoglobin electrophoresis revealed predominantly S hemoglobin with very small amounts of F and A too. Patient was given intravenous fluids and the process gradually resolved over a period of three or four days at which time the patient was discharged with a diagnosis of sickle cell anemia and polydactilitis.

During the next two years the patient remained relatively asymptomatic but slowly developed increasing anemia and at age 5 he was rehospitalized because of a sudden increase in severity of his anemia and complaining of severe pain in the joints in the arms and legs. The patient was noted on admission to have a severe upper respiratory infection and pneumonia was present on chest x-ray. Physical findings revealed the patients spleen to be enlarged. To combat the severe anemia the patient was transfused with packed red cells and treated with antibiotics. His infection responded slowly with use of transfusions and intravenous fluid; patients hematocrit increased and the painful episodes deminished. Some 8 days after admission the patient was discharged with a stable hematocrit and clear lung fields. Spleen had decreased in size. Diagnosis at the time of discharge were: 1. painful crises 2. Sequestration crises 3. Upper respiratory infection. 4. Bilateral lobar pneumonia.

On the course of the next 5 years the patient experienced recurrent episodes of pneumonia and increased frequency of painful crises. In addition, he had many episodes of severe left flank pain which was finally diagnosed as being secondary to spleenic infarction.

At age 11 the patient presented to hospital in crisis with a swollen extremely hot right leg. He appeared to be septic. X-ray examination of the leg revealed developing osteomyelitis. Blood cultures revealed salmonella organisms. Patient was treated aggressively with antibiotics but did not respond. Died two days after admission of salmonella septicemia.

From: Meharry Medical Center, Sickle Cell Anemia Center,
Nashville, TN

Children's Hospital Medical Center
OF NORTHERN CALIFORNIA

CHILDREN'S HOSPITAL OF THE EAST BAY
BRUCE LYON MEMORIAL RESEARCH LABORATORY
FORD MEMORIAL DIAGNOSTIC AND TREATMENT CENTER

FIFTY-FIRST AND GROVE STREETS
OAKLAND, CALIFORNIA 94609
TELEPHONE 654-5600

October 6, 1977

Ms. Patti Guerard
231 Oak Street
Clarksville, Tennessee 37040

Dear Ms. Guerard,

I hope the enclosed information is sufficient for your research paper on sickle cell anemia. If I can be of further assistance, please feel free to contact me.

Truly yours,

David Nelson

David Nelson
Genetic Counselor
Sickle Cell Screening, Counseling
and Education Clinic

DN/mr

Children's Hospital Medical Center
OF NORTHERN CALIFORNIA

CHILDREN'S HOSPITAL OF THE EAST BAY
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FIFTY-FIRST AND GROVE STREETS
OAKLAND, CALIFORNIA 94609
TELEPHONE 654-5600

January 27, 1977

[redacted]

DOB: 11/25/74

[redacted]

AN # 570-43-8884

Dear Mr. [redacted]

O.C.

I am writing a letter to you in relationship to a request for Supplemental Security Income benefits for [redacted]. This patient was seen by the Hematology Service at Children's Hospital of the East Bay for the first time on 5/14/76. At that time he had been admitted to Children's Hospital to diagnose his failure to thrive. He had been followed by Dr. Quint prior to this decision, who was well aware of his failure to thrive and also the fact that he had sickle cell anemia. His growth failure was disproportionate to his sickle cell disease. Although his growth pattern was increasing, the rate at which he was growing was clearly abnormal.

in Oakl Calif

Patient O.C.'s past medical history revealed that he was a 5-pound product of a 39-week gestation. He was born at home. His mother was 22 years of age, Gravida 2, Para 2. He was breast fed until age 4 months and then placed on vegetables and goat milk. He was assessed for failure to thrive at 5 to 6 months of age. Since then, he has been tried on multiple dietary regimes to enhance his growth. These diets have been suggested to the mother and were to be implemented at home. During his hospitalization, he had an extensive workup to rule out metabolic, central nervous system, renal, and endocrine abnormalities. Of the studies that were abnormal, the most significant was a bone age of 2 months when his chronologic age was 17 months. Endocrine evaluation was normal. Hematologic evaluation revealed a hemoglobin of 7.6 gm%, reticulocyte count 17%, and a mean corpuscular volume of 92. A cellulose acetate and citrate agar revealed a diagnosis of sickle cell anemia. This child has a severe hemolytic component to his anemia, as his elevated reticulocyte count has been noted on multiple occasions, indicating an increased rate of destruction of red cells peripherally. During this hospitalization, [redacted]'s weight increased from 12 pounds 12 ounces to 13 pounds 12 ounces. His weight gain was attributed to adequate calorie intake. A developmental evaluation performed by the Child Development Center at Children's Hospital revealed the following: The child's height and weight were both markedly below the 3rd percentile (see enclosed copy of growth chart). There was moderate muscle weakness, with a question of very mild right hemiplegia. Developmentally, O.C.'s chronologic age was 17-1/2 months, his gross motor coordination was at a 12-month level, his fine motor at a 14-16-month level, his language at a 13-14-

June 14, 1972

B.D. 6/11/60

Hematology Visit--6/2/72

Interval History: This child is being followed in Hematology Clinic at 3-month intervals for problems related to her sickle cell disease.

Since her last visit 3 months ago she has developed pain and swelling of the hands, knees, and ankles; treatment with Darvon controlled these symptoms. This is the first time that she has had significant joint involvement. Two weeks prior to this visit there was a mild crisis manifested by abdominal and back pain, requiring bed rest; these symptoms have subsequently resolved. She also had symptoms of an upper respiratory infection, manifested by marked cervical adenopathy, which resolved in 3 to 4 days on Ampicillin.

Physical Examination: The child appears in no distress. Scleral icterus is noted. The ears, nose, and throat are clear. A grade ii/vi systolic ejection murmur is heard along the left sternal border, radiating to the apex; no thrills or heave are noted; the point of maximum impulse is at the midclavicular line. Abdominal exam is normal; a surgical scar from the previous cholecystectomy is noted. The extremities have a full range of motion at this time, with no notable swelling or tenderness. The neurologic system is intact.

Laboratory Data: Hemoglobin is 6.9 grams% with a PCV of 20% and retic count of 22.8%. White count is 13,400 with 61% polys and 31% lymphs. Total bilirubin is 4.9 mg% with 4.0 indirect and 0.9 direct-reacting.

Impression: Sickle cell disease.

Plan: (1) A return visit is scheduled in 3 months;
(2) CBC, retic count, bilirubin, and sed rate will be obtained at at that time;
(3) Mother is instructed to call prn.

TJL:ljk

cc:

Children's Hospital Medical Center
OF NORTHERN CALIFORNIA

CHILDREN'S HOSPITAL OF THE EAST BAY
BRUCE LYON MEMORIAL RESEARCH LABORATORY
FORD MEMORIAL DIAGNOSTIC AND TREATMENT CENTER

FIFTY-FIRST AND GROVE STREETS
OAKLAND, CALIFORNIA 94609
TELEPHONE 654-5600

May 4, 1977

[redacted]

[redacted]
DOB: 7/4/63

Dear Mr. [redacted]

This letter will summarize my recent evaluation of [redacted]. As you know, this young man has sickle cell disease (sickle cell-beta thalassemia). Although the extent of his anemia is very mild, he has suffered a major vaso-occlusive problem in his lungs. This has been localized to his right lower lobe, where he now has extensive fibrosis secondary to a pulmonary infarct. Careful evaluation of the effects of this pulmonary abnormality on his lung functions has been performed at the University of California in San Francisco by Dr. [redacted]. The reports of these pulmonary functions as well as lung perfusion studies performed at the University of California in San Francisco are included for your review.

It is evident from these reports that [redacted] pulmonary functions are significantly altered as a consequence of his sickle cell disease. It is unlikely that he will have return of function in this area of the lung, as the findings are most compatible with fibrosis which is an irreversible process.

In reviewing his social history since the onset of his pulmonary complications, it is evident that he has suffered extreme consequences. These have been manifested by a marked deterioration in his school performance, as well as significant alterations in his ability to extend himself physically. As significant chest pain has been associated with the development of these pulmonary changes, he missed a great deal of school. The emotional trauma of these events must certainly have had an effect on his ability to perform in school, as his school performance as indicated by his grades has markedly deteriorated since the onset of this process. He was also very active physically prior to the development of his pulmonary complications and is now limited in his activity, as he becomes short of breath upon exertion.

I strongly feel that this complication which has occurred in this child has resulted in significant disability. If I can be of further assistance in evaluating his medical situation, please do not hesitate to contact me.

Yours truly,

[redacted]
Chief, Hematology-Oncology
Director, Sickle Cell Disease
[redacted] Education Clinic