AN ANALYSIS OF THE SIGNIFICANCE OF SICKLE CELL TRAIT IN THREE MICHIGAN POPULATIONS

By

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A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Zoology

1974

ABSTRACT

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OF SICKLE CELL TRAIT IN THREE
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A survey was undertaken to obtain a reliable estimate of the prevalence of sickle cell trait and to gather evidence for its effects on blacks in three Michigan populations.

Laboratory diagnoses of hemoglobinopathies were determined from blood specimens secured from more than 3,500 black Americans in the three sample groupings. Prior to the diagnosis, questionnaires were administered by trained interviewers to ascertain information pertaining to health problems and symptomatology frequently observed among individuals with sickle cell anemia. Comparisons were made between those individuals found to have sickle cell trait and those with normal hemoglobin.

The prevalence of sickle cell trait in the randomly selected sample of Lansing, Michigan was 8.2 per cent, similar to previously reported, but less systematically

sampled populations in the United States. However, comparisons of observed and expected trait children in sibships of trait families were significantly different. Fewer trait children were observed in both the Lansing and Grand Rapids populations.

Prevalences of health problems and symptoms revealed that weakness in legs, pain in bones, sense of exhaustion and epistaxis were significantly associated with sickle cell trait in the Lansing sample, while swollen joints, numbness in legs and epistaxis were more prevalent among trait persons in the Grand Rapids survey. There was no significant difference in the number of symptoms which were more prevalent in either group in the two populations. Further analysis by a single test of association of health problems and sickle cell trait revealed no significant difference between trait and control subjects.

An age trend analysis among trait subjects in the random sample does not show a decrease in the proportion of carriers in the older age groups, providing no evidence that the carrier state is associated with an increased mortality.

Neither of the populations revealed a differential in primary or secondary infertility among females with sickle cell trait. Nor was there any statistical difference between trait and control females of reproductive age for miscarriages or stillbirths or number of children living.

The proportions of trait and normal females using oral contraceptives were similar and no statistical difference in problems resulting from the use of contraceptives was ascertained.

A comparison of means and standard deviations of seven hematological indices between trait and normal subjects sampled in the Michigan State University study revealed no significant differences.

To Norma and Kyle
and my mother and sister

ACKNOWLEDGEMENTS

I wish to express my gratitude to Dr. James V. Higgins, my major professor, for his guidance and counsel throughout my graduate program and especially in the writing of the thesis. A special thanks is extended to Dr. Herman Slatis for his valuable suggestions and critique in the planning and implementation of the study and in the thesis writing. Thanks also are extended Drs. Hiram Kitchen, Emanuel Hackel and Terrell Phenice, members of my graduate committee, for their help, encouragement and confidence.

I am especially grateful to Frankie Brown for her collaboration in conceiving, planning, and, most of all, implementation and follow-up with the study. This vast project demanded our total cooperation and understanding. Special thanks is extended to Dr. Ajovi Scott-Emuakpor for his help, guidance and encouragement during the initial stages of the project and for his genuine friendship throughout our common residence at the University.

I must express my sincere appreciation to the entire faculty and staff of the Department of Epidemiology and Public Health at the University of Miami Medical School. These persons include Dr. John Davies, Chairman; Dr. Charles Hennekens, Dr. Richard Donelson and Janet Cassady. A very special thanks is extended to Dr. William Page who graciously

accepted my plea for help in the analysis of the data and worked with me for many months in advising and implementing the methods of computer analysis and implications of the results.

Special appreciation is extended to Sandra Kasper for typing, re-typing, editing the thesis and listening and encouraging me during moments of depression. Also, thanks to Judy Botana for typing the initial tables.

Further appreciation is extended to the staff that I supervise for continuing with their functions while I neglected them during the writing phase of this project.

This document could not have been completed without the cooperation of black residents of Lansing and Grand Rapids and the black students at Michigan State University who willingly participated in the study.

Most of all, I shall be forever grateful to my wife, Norma, for her encouragement, understanding and confidence through my entire graduate program.

The Grand Rapids study was supported in part by a grant from the Michigan Regional Medical Program, secured through the efforts of Dr. Robert Nalbandian. Also, the subjects in this study were made available by Dr. Nalbandian. The Lansing and University studies were supported by a grant from the Center of Urban Affairs, Michigan State University and the Lansing Demonstration Agency (Model Cities).

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INTRODUCTION

Sickle cell trait, the heterozygous state for the abnormal hemoglobin S, is believed to be a benign condition and asymptomatic unless circumstances are exceptional. The scientific literature abounds with case reports of sudden death of individuals, previously healthy, due to sickle cell trait and there are numerous reports of a variety of nonfatal pathologic concomitants. The few population studies concerned with mortality and morbidity of sickle cell trait under nonmalarious conditions have largely been of hospital admissions.

Because of truncated studies, neither the evidence for mortality nor morbidity is clear. Findings could indicate either a differential death rate or better health for individuals with sickle cell trait. With respect to morbidity, when the carrier state is as common as sickle cell trait, coincidental associations are to be expected. In many of the early reports of associations, techniques did not allow the clear delineation of sickle cell trait or the exclusion of the sickle cell gene in combination with other abnormal hemoglobins or abnormal quantities of other hemoglobins.

With increased public awareness of sickle cell anemia in recent years and the large number of screening programs established, it is important, at least to the black community, that the true state of affairs be known. This becomes especially true when one considers genetic counseling of individuals with the trait. This study was designed to

gather evidence on the effect of sickle cell trait under nonmalarious conditions.

REVIEW OF THE LITERATURE

In 1910 Herrick described "Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia" in a Black West Indian student. Many investigators attempted to find the reason for this phenomenon. Emmel (1917) observed that exclusion of air by the vaseline-sealed cover slip technique resulted in a great increase in the number of sickled cells observed after a short period of time. Huck (1923) "presented evidence that this was a property of the red blood cell itself, inherited by the individual according to the Mendelian Law." Hahn and Gillespie (1927) explained this by showing that sickling would take place only if the hemoglobin within the erythrocytes was in the reduced state. Also, they hypothesized that the only specific cause for active sickle cell anemia was the unique hereditary anomaly of the red corpuscles which predisposed to it. In 1933 Diggs and associates noted that many of the patients who exhibited the sickling phenomenon were asymptomatic while others had a chronic disease beginning in infancy and characterized by chronic anemia, jaundice, leg ulcers, periods of severe abdominal pain, cardiac hypertrophy, hepatomegaly, bone lesions, and decreased longevity. Sherman (1940) attempted to relate the severity of the disease to the sickling tendency. His work supported the theory that sickling is brought about by the lowering of the oxygen tension due to metabolic activity. In 1949 Neel showed that the asymptomatic group was heterozygous for the condition while the symptomatic group was composed of homozygotes. In the

same year, Pauling and co-workers published a paper describing a technique of hemoglobin electrophoresis which identified the abnormal hemoglobin involved and permitted the identification of some other abnormal hemoglobins. This abnormal hemoglobin is called hemoglobin S.

It has been established that the sickling phenomenon occurs when hemoglobin S is present in the red blood cells, regardless of the type of hemoglobin present with it. It occurs when hemoglobin S is combined with normal adult hemoglobin (hemoglobin A), when combined with other abnormal hemoglobins such as hemoglobin C, or when only hemoglobin S is present.

Before the work of Pauling and co-workers, patients were reported who manifested atypical forms of the disease. Usually they were not as ill as those patients who were classified as having sickle cell anemia, nor were they as symptom-free as those patients who were classified as having sickle cell trait. It was not until later that their disease patterns were discovered to be due to combinations of hemoglobin S with other abnormal hemoglobins.

Retrospective studies performed to determine the effects of sickle cell trait on other conditions yielded results which were often contradictory. It is generally agreed that the diagnoses were based on the presence of the sickling phenomenon in vitro in the absence of the classical symptom complex of sickle cell anemia. Obviously, included in this group were individuals with AS hemoglobin as well

as those with hemoglobin S in combination with other abnormal hemoglobins. Consequently, what was previously considered to be a homogeneous group was, in reality, a heterogenous one.

Accurate diagnoses can be made with the use of electrophoretic techniques coupled with solubility tests, as well as hemoglobin A_2 quantitation and alkali denaturation determination for fetal hemoglobin. "Sickle cell trait" denotes the combination of a gene for hemoglobin S with a gene for normal hemoglobin A. "Sickle cell anemia" denotes the homozygous condition of the gene for hemoglobin S.

The only difference between hemoglobin A and hemoglobin S is the substitution of the amino acid valine for glutamic acid at the sixth position of the beta chain in the tetrameric hemoglobin molecule (Ingram, 1957). Apparently any red blood cell containing hemoglobin S can undergo bizzare distortion under certain conditions which decrease the solubility of the hemoglobin and thus favor tactoid (crystal) formation.

Murayama's hypothesis for the mechanism of sickling in Hb S-containing cells is a synthesis of experimental data and theoretical concepts. According to Murayama, in the interior of an intact Hb S red blood cell upon deoxygenation a series of events occur. First, the beta S globin chains are displaced laterally. In the presence of adequate concentrations of a sickling cofactor, hydrophobic bonds are formed between alternate interacting molecules of Hb S and pairs of cofactor molecules which lead to helical aggregations or monofilaments. The monofilaments then

aggregate laterally to form six-membered microcables. Eventually, the entire molecular population within the sickled red cell may participate in these reactions excluding hemoglobin F and stray molecules of methemoglobin (Murayama, 1971). This process results in the "sickling" phenomenon and in turn favors intravascular clumping. These sickled red blood cells have greater mechanical fragility, liability to hemolysis, and a shortened life span. The major factors which determine if sickling will occur are the proportion of hemoglobin S present in the red blood cell and the oxygen tension of the blood. Leukocyte concentration, temperature elevation, bacterial contamination, decreased pH, potassium ions, increased pCO_2, hypothermia and hypotonicity have also been implicated as sickling potentiators (Sherman, 1954: Greenberg and Kass, 1956; Griggs and Harris, 1956; Rubenstein, 1961; Perillie, 1962).

Recognition of the varied clinical manifestations of sickle cell hemoglobin and disorders associated with it has been repeatedly emphasized in the medical literature. Although many clinicians maintain that sickle cell trait is a completely benign condition, there are several reports of cases of mortality which have appeared in the literature due to the complications of sickle cell trait. Moreover, reports of non-fatal complications of sickling in sickle cell trait include bone, joint and abdominal pain, splenic enlargement, hematuria, neurologic disorders, priapism, splenic,

pulmonary and hepatic infarction, retinopathy and other ocular abnormalities, and increased incidence of toxemia and complications during pregnancy, bladder atony and femoral necrosis.

A. Fatal Cases of Sickle Cell Trait

Among the cases of complications published prior to the use of hemoglobin electrophoresis (approximately 1954), many were described as "sicklemia" or as "sickle cell disease without anemia." Also, several case reports since the establishment of electrophoresis as the unequivocal diagnosis of sickle cell trait, do not specifically indicate that this technique was used. For this reason, some cases summarized in Table 1 may have been sickle cell-thalassemia, hemoglobin S/C disease, or any one of several other hemoglobinopathies characterized in part by the presence of hemoglobin S.

This review reveals forty reports of cases in which it is reported that sickle cell trait was a major factor in death. Even though hemoglobin electrophoresis was not performed in 16 of these cases, genetic and clinical histories as well as autopsy findings were typical of sickle cell trait. It is quite possible that among these 16 cases, other genotypes such as hemoglobin S/C disease or sickle cell thalassemia could have been present. In most cases, evidence that sickle cell trait was responsible for the deaths lies with the exclusion of other obvious causes of death, demonstration of massive generalized sickling and demonstration that appropriate circumstances were present to cause sickling.

Table 1

FATAL CASES OF SICKLE CELL TRAIT

	Investigator(s)	Age, Race, Sex	Other Disease	Finding Relative to Sickle cell trait	Hemoglobin Electrophoresis
1.	Bauer & Fisher (1943)	24, B M	Lobar pneumonia	Massive generalized sickling, splenic infarcts and osteosclerosis	None
2.	Bauer & Fisher (1943)	26, B F	Severe back and flank pain and generalized abdominal tenderness	Massive generalized sickling and kidney infarcts	None
3.	Thompson, Wagner & MacLeod (1948)	20, B M	Dizziness, right arm pain and convulsions	Massive generalized sickling	None
4.	Diggs & Jones (1952)	48, B F	Drug-induced coma and hypoxia	Generalized sickling and focal hemorrhage and focal ischemia necrosis	None
5.	Thoma (1953)	34, B M	None	Intense vascular congestion with packed sickle cells	None

Table 1 (Cont'd.)

	Investigators	Age, Race, Sex	Other Disease	Finding Relative to Sickle cell trait	Hemoglobin Electrophoresis
6.	Thoma (1953)	55, B M	Bronchopneumonia	Perifollicular hemorrhage and congestion of the spleen and other organs with masses of packed sickle cells	None
7.	Thoma (1953)	65, B M	Lobar pneumonia, scleral jaundice and acute fibrinous pericarditis	Massive generalized sickling in all organs	None
8.	Thoma (1953)	8, B F	Meningococcemia	No specific indication	None
9.	Thoma (1953)	50, B M	Tuberculosis	"Full blown histologic sickle cell crisis"	None
10.	Thoma (1953)	65, B M	Spinal cord injury and pneumonia	A few scattered sickle cells	None
11.	Thoma (1953)	33, B F	Acute alcoholism	Few congested vessels with some sickle cells and a perifollicular ring of hemorrhage on the spleen	None

Table 1 (Cont'd.)

Investigator(s)	Age, Race, Sex	Other Disease	Finding Relative to Sickle cell trait	Hemoglobin Electrophoresis
12. Thoma (1953)	34, B F	Pulmonary embolus	Scattered sickle cells	None
13. Adams (1957)	25, B F	Coma	Massive generalized sickling and enlarged spleen, focal hemorrhage and necrosis of liver	None
14. Ende, Pizzalato & Zaskino (1955)	46, B M	Death after a period of confusion and disorientation	Extensive sickling pulmonary and renal infarcts and neuronal satellitosis	None
15. Tellem, Rubenstone & Frumin (1957)	35, B M	Fever, vomiting, diarrhea and uremia	Massive generalized sickling, azotemia, focal erosion of bony trabeculae of vertebrae	None
16. Tseng (1959)	56, B F	Marked disorientation and shock	Slightly anemic, sickling blood smear enlarged spleen with focal coagulation. Necrosis, focal liver hemorrhages and sickle cells in glomerular capillary tufts	None

Table 1 (Cont'd.)

Investigator(s)	Age, Race, Sex	Other Disease	Finding Relative to Sickle cell trait	Hemoglobin Electrophoresis
17. Tseng (1959)	86, B M	Projectile vomiting, fever pneumonia and shock	Enlarged spleen with infarct, generalized sickling	None
18. Ober et al. (1960)	15, B M	Severe abdominal pain, nausea and vomiting	Positive S.C. prep. occlusion of right colic artery and intense intra-vascular sickling	AS (post mortem)
19. McCormick (1961)	2 1/2 mo, B M	Pulmonary edema	Massive generalized sickling	AS
20. McCormick (1961)	8 mo., B M	Mild interstitial pneumonitis	Massive generalized sickling	AS
21. McCormick (1961)	4 mo., B M	Mild interstitial pneumonitis	Massive generalized sickling	AS
22. McCormick (1961)	2, B F	Mild diarrhea	Massive generalized sickling	AS
23. McCormick	32, B F	Pulmonary edema, mild	Massive generalized sickling	AS
24. McCormick	2 mo., B F	Whooping cough	Massive sickling	AS
25. McCormick	82, B F	50% 2° body burns	Massive sickling	AS

Table 1 (Cont'd.)

Investigator(s)	Age, Race, Sex	Other Disease	Finding Relative to Sickle cell trait	Hemoglobin electrophoresis
26. McCormick (1961)	70, B M	Post-spinal anesthesia	Massive generalized sickling and multiple infarcts	AS
27. McCormick (1961)	40, B M	Staph, food-poisoning with shock	Massive sickling	AS
28. McCormick (1961)	40, B F	Anemia and congestive heart failure	Massive sickling	AS
29. McCormick (1961)	51, B M	Bronchial asthma	Massive sickling with perifollicular hemorrhages in spleen	AS
30. McCormick (1961)	51, B M	Alcoholism (0.26%)	Generalized massive sickling	AS
31. McCormick (1961)	54, B F	Acute and chronic tracheobronchitis, moderate	Massive sickling and visceral infarcts	AS
32. McCormick (1961)	8 mo., B F	Pillow found over head	Massive sickling	AS
33. McCormick (1961)	2 mo., B F	Otitis media and minimal broncho-pneumonia	Massive sickling	AS

Table 1 (Cont'd.)

Investigator(s)	Age, Race, Sex	Other Disease	Finding Relative to Sickle cell trait	Hemoglobin electrophoresis
34. Mull (1964)	35, B F	Rash, sore throat, stiff neck and fever	Vessels filled with conglutinations of sickled erythrocytes and marked congestion of all viscera	AS
35. Schenck (1964)	12, B M	Tonsillectomy, convulsion, confusion and vomiting	Thrombi of superior longitudinal sinus and many veins emptying into it	AS
36. Jones et al. (1970)	21, B M	Shortness of breath, faintness, epistaxis and absence of deep tendon reflexes, hypotension	Fluid-filled lungs, massive sickling	AS
37. Jones et al. (1970)	19, B M	Complete unresponsiveness and lower gastrointestinal tract hemorrhage, hypotension	Diffuse vascular congestion in all organs. Small foci of perivascular hemorrhage in brain, G.I. tract, lungs and spleen	AS
38. Jones et al. (1970)	21, B M	Faintness and loss of consciousness	Generalized congestion and marked coronary atherosclerosis, massive sickling	AS

Table 1 (Cont'd)

Investigator(s)	Age, Race, Sex	Other Disease	Finding Relative to Sickle cell trait	Hemoglobin electrophoresis
39. Jones et al. (1970)	21, B M	Faintness and numbness of legs; loss of consciousness (apneic)	Generalized congestion of all organs. Massive sickling	AS
40. E.B. Smith (1970) (1)	34, B F	Epigastric and abdominal pain; nausea; post-operative complications of lobar pneumonia and hypertension	Gastro-intestinal infarction	AS

The reviewed cases clearly illustrate that the reported symptoms and organ involvement are as variable in sickle cell trait as in sickle cell anemia. Splenic weights vary markedly from case to case and evidence of prior sickling may be present or absent. The ages ranged from two months to 86 years and sex ratios were not significantly different from 1:1.

B. Nonfatal Complications Due to Sickle Cell Trait

Usually individuals with sickle cell trait do not demonstrate the sickling phenomenon in their peripheral blood. This requires a reduction in the oxygen tension to the range of 10-15 mm Hg which is inconsistent with life. In contrast, sickling will occur in vovo in individuals with sickle cell anemia when the oxygen tension is reduced to only 45-60 mm Hg. At a given partial pressure of oxygen, the amount of hemoglobin S present in a red blood cell influences the degree of sickling. The concentration of sickled cells present, in turn influences the viscosity of the blood (Greenberg and Kass, 1955).

1. Splenic Infarction

Between 1950 and 1968 more than 20 cases have appeared in the literature which have reported the association of splenic infarction, sickle cell trait and airplane flight (Sullivan, 1950; Cooley et al., 1954; Conn, 1954; Harvey, 1954; Smith and Conley, 1955; Rotter et al., 1956; Nichols, 1978). Several of the earlier reports were

based on positive sickle cell tests and clinical symptoms and histories.

Rotter and co-workers in their discussion of this problem noted that an altitude of 10,000 - 15,000 feet is required to reduce the oxygen tension sufficiently for subjects with sickle cell trait to manifest sickling; moreover, this must be maintained for 10-15 minutes. The modern airplane cabin is pressurized to reflect altitudes of 4,000 - 6,000 feet. Assuming normal splenic circulation, no problem should arise. If, however, there is any aberration in splenic circulation, it is possible that even this slight reduction in oxygen tension might be sufficient to produce splenic infarction (Blank and Freedman, 1969).

2. Hematuria and Hyposthenuria

Since Abel and Brown (1948) reported the first case of massive hematuria in sickle cell trait in a 23 year old, previously healthy black soldier, nearly 100 additional cases have appeared in the literature (Goodwin et al., 1950; Harrison and Mostofi, 1957; Bruegge and Diggs, 1957; Myerson et al., 1959). In the largest series among the above reports, diagnosis was made on the finding of sickled cells in the kidney sections and review of clinical data.

Twenty-one papers on this subject covering 97 patients were reviewed by Lucas and Bullock (1960). They found 80 per cent of the patients were male and that the bleeding came from the left kidney four times as often as from the right. In established cases of sickle cell trait

the age of presentation varied from 13 to 46 (mean 28.7). In 37 patients electrophoresis had been performed and 25 were shown to have sickle cell trait. There were three cases of true sickle cell anemia, eight cases of sickle cell hemoglobin-C disease and one case of sickle cell thalassemia. Classification of all 97 patients on clinical grounds showed that 15 had sickle cell anemia and 82 had sickle cell trait.

One additional case of massive unilateral hematuria was reported by Bennett and co-workers (1957). These authors include a review of most reported cases of hematuria associated with sickle cell trait.

In view of the pathological changes occurring in the renal papillae, Harrow, Sloane, and Liebman (1963) paid close attention to these areas in a radiological study of this condition. In five patients they found definite evidence of renal papillary necrosis in pyelography.

The tendency of the massive hematuria of sickle cell trait to originate in the left kidney is striking. Harrow et al. (1963) suggest that the many tributaries of the left renal vein may lead to an elevated venous pressure on that side with resultant stagnation and sickling. There are distinct differences in the pattern of venous drainage between the left and right kidneys, as emphasized by Erlik, Barzilai and Shramek (1965), but the influence of these anatomical differences on the left renal venous pressure is undetermined.

Many authors have attributed the massive hematuria in sickle cell trait to a reduction in oxygen tension in the venous limb of the vasa recta with subsequent localized infarction. However, Harrow et al. (1963) put forward the theory that the graded increase in osmolality from the base of the medulla to the tips of the pyramids resulting from the countercurrent mechnaism of urinary concentration accounts for the distribution of the pathological changes at the papillae. Perillie and Epstein (1963) showed that the renal medulla is the only body structure in which osmolality is normally increased to four times the plasma level in both the interstitial and intravascular structures. Moreover, it has been shown that cells from the inner medulla of the kidney are able to gain their energy from anaerobic as well as aerobic processes. These cells are therefore adapted to survival if oxygen tension should become critical (Ullrich, Kramer and Boylan, 1962). Thus, increased osmolality and low oxygen tension, both of which are factors favorable to sickle cell formation, obtain in the renal medulla.

This peculiarity in the renal architecture also permits explanation of the finding of hyposthenuria in patients with sickle cell disease, clinically detected by finding a persistently low urine specific gravity even after water deprivation (Schlitt and Keitel, 1960). The sickling in the medulla leads to an increase in blood viscosity and a relative decrease in renal medullary

blood flow. There is no significant change in renal cortical blood flow or glomerular filtration rate. The oxygenation of the loop of Henle is decreased and as a result, the metabolic function of its cells is affected. There is a decrease in the ability to reabsorb sodium actively. Hypertonicity of the medullary interstitium results and this, in turn, produces a lowering of the concentration of solutes in the final urine (Blank and Freedman, 1969).

Miller et al. (1969) described the unusual occurrence of massive renal infarction with perirenal hematoma formation secondary to sickle cell trait. Of the 144 cases of sickle cell trait reviewed by McCormick (1961) and Tellem (1957), only four instances of renal infarction were encountered.

Bansbach et al. (1960) found four of 16 patients with sickle cell trait to have sensory paralysis of the urinary bladder without evidence of intravesical obstruction. Hypotonia was thought to result from the overdistension secondary to the sensory loss.

3. Other Nonfatal Trait-associated Dysfunctions

There are numerous reports in the literature of infarction and abnormal function occurring in other organs. Ende and co-workers (1955) reported two cases of electrophoretically proven sickle cell trait associated with priapism and one additional case with pain in the occipital region. Rahimtoola (1960) described three cases of pulmonary

infarction in West Indian Blacks with hemoglobinopathies. Two of these individuals had sickle cell trait and the third had S-C disease. His findings do not prove that the illnesses from which the patients suffered were a consequence of intravascular sickling, but no other cause for pulmonary infarction in these previously healthy men could be found, and there was collateral evidence of activity of the sickling process.

Greer and Schotland (1962) reported the occurrence of neurologic manifestations in 18 per cent of 400 patients with abnormal hemoglobins. These included convulsions, 8%; meningeal signs, 5.75%; cerebral vascular syndromes, 3.75%; impaired visual acuity, 3%; radiculopathy, 1.25%; acute mental disorders, 1%; and vertigo, 0.75%. Among the patients in whom hemoglobin electrophoresis was performed, the incidence of neurologic abnormalities was hemoglobin SS, 34.8%; hemoglobin SC, 24.2%; and hemoglobin AS, 6.4%. There were no fatalities or cerebral vascular syndromes in patients with hemoglobin AS.

These authors indicate that in these disorders, only cerebral infarction can be clearly attributed to the abnormal hemoglobin and even here the pathogenesis is not always clear. However, there is circumstantial evidence that the other neurologic symptoms were also due to vascular lesions related to the abnormal hemoglobin in most cases.

The case histories of two black men with avascular necorsis of the femoral head were described by Ratcliff and Wolf (1962). One patient had avascular necrosis of other bones as well. The lesions these patients demonstrated were found in areas usually involved in sickle cell anemia, the ends of long bones. Both patients were proven to have sickle cell trait by hemoglobin electrophoresis. Other causes for avascular necrosis could not be incriminated.

Konotey-Ahulu (1965) listed 16 well-documented predisposing causes of sickle cell crises. Included in this list is general anesthesia. Konotey-Ahulu (1969) indicates..."Given the appropriate (or rather inappropriate) change in the internal environment, persons with the sickle cell trait may, rarely, have splenic or pulmonary infarcts, priapism, hematuria, polyuria, vitreous haemorrhages, and musculoskeletal/arthritic pains and, not so very rarely, may die from general anaesthesia."

The ocular findings described in sickle cell trait have included retinitis proliferans, a chrioretinal scar resembling a black sunburst, optic atrophy, papilledema (Welch and Goldberg, 1966), chorioretinitis (Isbey, et. al., 1958), acute open angel glaucoma (Shipiro and Baum, 1964), venous tortuosity (Kennedy and Cope, 1957; Lieb et al., 1959), micoraneurysms, edma, and exudates (Lieb et al., 1959). In addition, there have been three reported cases of central retinal artery occlusion (Welch and Goldberg, 1966; Conrad and Penner, 1967; Kabakow et al., 1955).

Isbey et al. (1958) reported four cases of vitreous hemorrhage associated with sickle cell trait. Stein and Gay (1970) reported a six-month old patient who sustained a bilateral retinal artery occlusion and extensive vaso-occlusive disease of the choriod with chorioretinal scarring.

Adams et al. (1953), Whalley et atl (1963), Jenkins and Clark (1960), Anderson et al. (1960), Petrakis et al. (1970) and others, have reported incidence rates of pregnancy patients with sickle cell trait to be approximately the same as found in their general clinic populations. The investigations by Adams and Whalley indicate, in addition, that there is no secondary infertility involved.

Most studies indicate that the spontaneous abortion rate in women with sickle cell trait is no higher than that in a control group with similar socioeconomic background and the number of children previously born (Adams et al. 1953; Whalley et al., 1963; Abrams, 1959; Beacham and Beacham, 1960 and Petrakis et al., 1970). Jenkins and Clark (1962), however, found a much higher incidence among patients with the trait in their series.

Similarly, there has been no evidence to indicate an increase in prematurity or stillbirth rates in patients with the trait.

With the many reported cases of fatal and nonfatal complications associated with sickle cell trait, evidence

strongly supports the belief that it is not a totally benign condition. According to Konetey-Ahulu (1969), "while the difference in hemoglobinopathy, between normal homozygotes and persons with sickle cell trait is qualitative, that between persons with sickle cell trait and those with sickle cell anemia is quantitative; so that the same conditions which would cause crises in patients with sickle cell anemia could, if pushed to a further un-physiological degree, also cause in-vivo sickling in persons with sickle cell trait." That this is true is illustrated by the protean symptoms and problems and organ involvement in these cases with the trait as is seen in those individuals with sickle cell anemia.

These reviewed cases strongly suggest that acute intravascular sickling in persons with sickle cell trait may constitute a serious threat to life, since the sickling crisis may be precipitated by mild illness or physiologic stress in an otherwise healthy person.

Hyposthenuria, an increased tendency to hematuria, and renal infarction appear to be firmly established associations with sickle cell trait. The same is true of an increased frequency of splenic and pulmonary infarction, especially under conditions of low oxygen tension. The increased incidence of pylelonephritis and urinary tract infection reported to occur in women with sickle cell trait (Whalley et al., 1964) may be explained on the basis of susceptibility of a damaged kidney to infection (Neel, 1973).

The other reports of complications in sickle cell trait, though plausible, do not yet have the status of the foregoing.

Despite the many case reports, the question of whether sickle cell trait shortens the average life span has not been satisfactorily answered. In some of the reports in which death was attributed to the trait, other causes have not been excluded. In the present state of knowledge, the clinical significance of this genetic abnormality remains confused. If .001 of all cases had some rare effect (e.g. priapism) not otherwise seen in people, case reports would be a good source of information and a survey would be entirely useless.

All of the foregoing reports provide one kind of evidence for a plausible deleterious effect of sickle cell trait. Another kind of evidence consists of data that raise the possiblilty that sickle cell trait is less frequent in older individuals, presumably on the basis of individual mortality.

With respect to mortality, Neel (1973) has summarized all of the pertinent data to date. The summarization confines its attention to data from temperate climates to avoid the effects of positive selection for the trait by malaria. Three early series from the United States, summarized in 1951 (Neel), all showed a lower frequency of sickling in older individuals. Of five series reported since then (Rucknagel and Neel, 1961; Pollitzer, 1958;

McCormick and Kashgarian, 1965; Heller, 1968; Petrakis et al., 1970) three show less sickling in older persons (McCormick and Kashgarian, Heller and Petrakis et al.). The age trend is not clearly significant in any of these series. Neel (1973) points out that the series are sufficiently heterogeneous that it seems unwise to attempt to combine them.

Most of the series have been assembled from hospital populations and could therefore indicate either a differential death rate or better health for persons with sickle cell trait. A random sampling of a large population of "at risk" individuals would give a more reliable indication of age trends.

METHODS AND MATERIALS

The purpose of this study was to detect the presence of the sickle cell gene in the black population of several metropolitan areas in Michigan and to gather information to ascertain possible deleterious effects of this gene in single dose on health and welfare (morbidity and mortality). Three surveys were conducted.

A. Sampling Procedures

1. Lansing Michigan

A random sampling technique was used in this population. Demographic data were obtained from Tri-County Regional Planning Commission in Lansing, Michigan. These data were part of the 1970 census collection including the greater Lansing community.

The sample was a cluster sample with unequal cluster sizes within two strata. The strata were defined by the amount of clustering of the black population. Stratum one contained all the black population which clustered in groups of one hundred or more persons per block group. Stratum two contained all the black population which clustered in groups of two to ninety-nine persons per block group. Eighty per cent of the sample was drawn from the first stratum and twenty per cent from the second stratum (see Figure 1). The total sample as selected included approximately 3,000 persons (see Table 2).

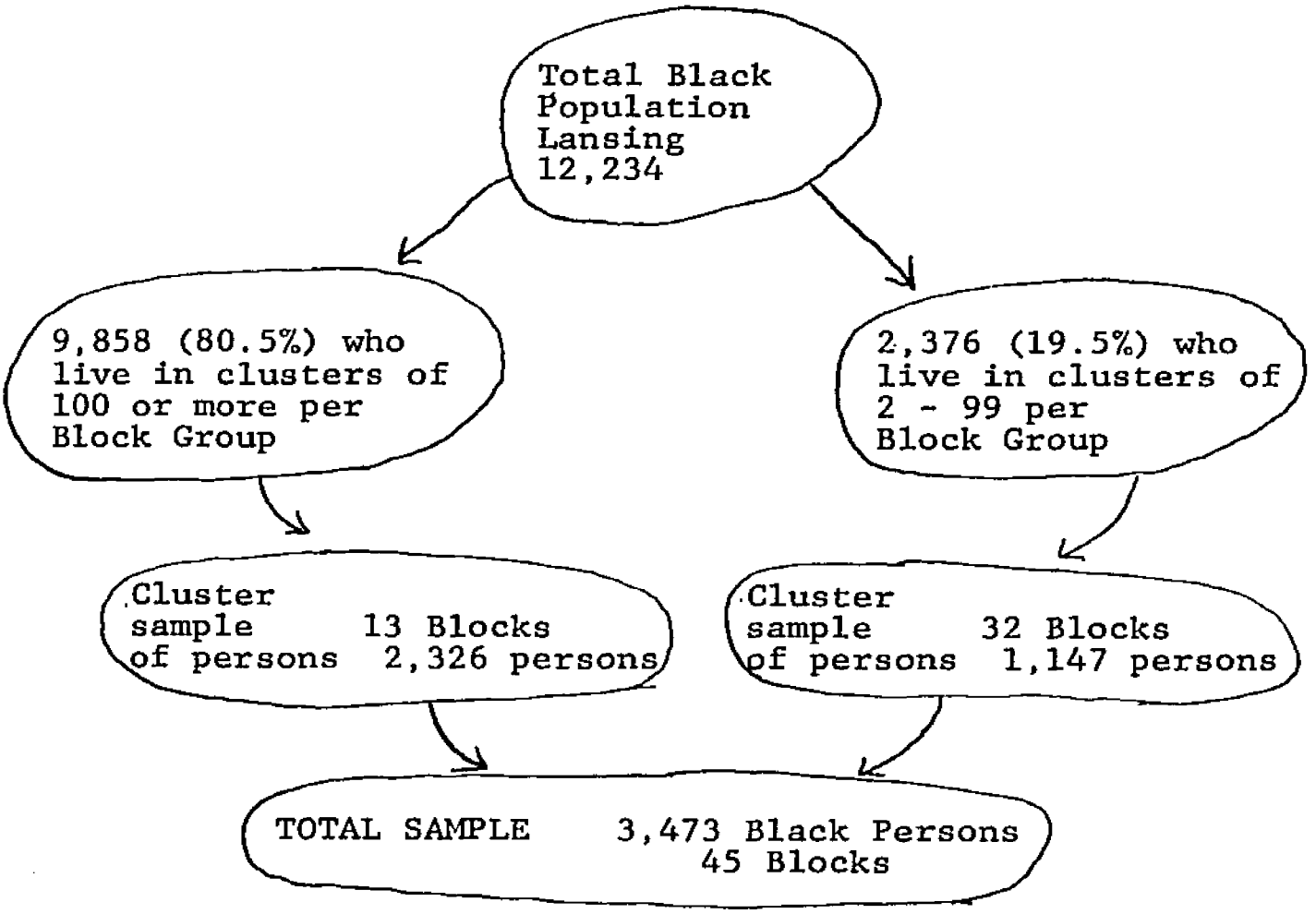

Figure 1. Sampling Scheme for Lansing Survey

Table 2

SAMPLE FOR SICKLE CELL STUDY - Lansing, Michigan

	Census Tract	Block Sampled	Number Black	Cumulative No. Black		Census Tract	Block Sampled	Number Black	Cumulative No. Black
1.	1	116	10	10	24.	16	111	36	1,904
2.	3	404	10	20	25.	16	115	14	1,918
3.	4	306	23	43	26.	16	216	57	1,975
4.	5	302	116	159	27.	18	303	173	2,148
5.	6	303	23	182	28.	18	308	98	2,246
6.	8	404	69	251	29.	18	402	78	2,324
7.	11	101	155	406	30.	18	403	85	2,409
8.	11	404	4	410	31.	18	404	80	2,489
9.	12	304	16	426	32.	18	407	81	2,570
10.	12	404	5	431	33.	18	413	41	2,611
11.	12	408	13	444	34.	18	414	13	2,624
12.	13	314	8	452	35.	19	112	2	2,626
13.	15	203	162	614	36.	20	316	47	2,673
14.	15	204	143	757	37.	21	109	59	2,732
15.	15	206	93	850	38.	21	306	9	2,741
16.	15	304	77	927	39.	27	403	7	2,746
17.	15	307	177	1,104	40.	30	114	17	2,765
18.	15	401	246	1,350	41.	36.02	209	12	2,777
19.	15	402	123	1,473	42.	36.02	213	291	3,068
20.	15	404	164	1,637	43.	37	204	5	3,073
21.	15	405	176	1,813	44.	15	403	233	3,306
22.	16	103	18	1,831	45.	15	407	167	3,473
23.	16	104	37	1,868					

After each block was identified, a physical survey was made and a letter of introduction was sent to each household. (Copy in Appendix A). Shortly thereafter, an interviewer was sent to each household to inform the family about sickle cell anemia and sickle cell trait and to complete a demographic and medical questionnaire with the family or individual. When the questionnaire was completed an appointment was made with the family for the collection of blood specimens for hemoglobinopathy detection.

2. Grand Rapids, Michigan

Dithionite tests for sickling had previously been made on 5,192 students enrolled in several public and parochial schools in the Grand Rapids community by Dr. Robert Nalbandian and his staff at Blodgett Memorial Hospital. Of these students, 309 (5.95 per cent) were found to have sickle cell trait and one had sickle cell anemia.

Demographic information on those students with positive dithionite tests was given to this investigator for the primary purpose of performing more definitive tests and for genetic counseling. The parents of the 309 propositi were informed and the entire family was invited to come to the Franklin Hall Complex, one of several neighborhood health clinics, for testing and genetic counseling. The administrator of Franklin Hall Complex assisted in contacting the families and making appointments for the interview and collection of blood specimens. When families reported, the

health information questionnaire was administered and each family member, including the propositus, received a blood test.

3. Michigan State University, East Lansing, Michigan

The names and addresses of all known black students enrolled at Michigan State University during the Spring term, 1971, were obtained and letters were sent to each, inviting them to Olin Health Center to be tested for sickle cell anemia, trait and other hemoglobinopathies. All of the predominantly black sororities and fraternities were contacted, informed and invited to be tested, and announcements were made in the State News, the student daily newspaper. In addition, teams of authorized and certificated personnel were organized to visit dormitory complexes where black students were housed and additional invitations and information were made available to black students. Black students were further identified through black aids in each dormitory. The testing was begun on April 11, 1971 and continued until June 12, 1971.

In the Michigan State University sample, 40 students tested at Olin Health Center whose blood specimens showed positive turbidity tests, plus 40 selected controls, were tested for additional hematological indices, including hemoglobin levels, hematocrits, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell count and total protein. The purpose of these tests was to collect additional data for

comparisons between those individuals with sickle cell trait and normal controls.

B. Health Survey and Questionnaire

A common health questionnaire was administered by trained interviewers to respondents in the Lansing and Grand Rapids surveys. General objectives, instructions and interviewer responsibilities and behavior in the collection of information, as well as the questionnaire are included in Appendix B. In each instance the interview was completed before the blood test for diagnosis of hemoglobin type was made.

With the exception of basic demographic information, most of the questions pertaining to health were related to those problems of symptoms frequently observed or reported in individuals with hemoglobinopathies. Many of htese questions had to be phrased to assure understanding by the respondents. For example, hyposthenuria is a commonly reported abnormality in sickle cell disease. In questioning, the respondent was asked if he had observed an increased urine flow.

In most instances during the interview, one adult respondent answered questions pertaining to minors in the household and for other adults not present at that time. In the Lansing survey, if the respondent was not knowledgeable enough of the information pertaining to others in the household, the interviewer made arrangements to return at a time when the absent person would be at home.

In Grand Rapids, those questions which could not be answered for an absent member of the family were ascertained when the respondent or the absent family member returned to the clinic for their results and for counseling.

The brief questionnaire used in the Michigan State University survey was self-administered. This form was completed immediately prior to testing, (see Appendix C).

C. Laboratory Procedures

1. Solubility Test

All blood specimens were tested for solubility of their hemoglobins by a method commonly used in screening procedures. The basic principle of this procedure included the placement of whole blood in a buffer, lysing of the red blood cells, and the deoxygenation of the hemoglobins with a reducing agent, causing any sickling hemoglobin to polymerize, thus becoming insoluble in the buffer. Those specimens containing sickling hemoglobins (S, C Harlem, Barts, and I) would appear cloudy when compared to the non-sickling varieties and could thus be qualitatively identified.

a. Sickletest reagent: This reagent contains 2.5 M sodium phosphate buffer, o.15 M sodium dithionite (reducing agent), and 3 per cent saponin (erythrolytic compound). To prepare the reagent, 165.6 grams of monobasic sodium phosphate and 156.2 grams of dibasic sodium phosphate were weighed. These two compounds were dissolved in 500 ml of water in a liter flask. Twenty-six and two-tenths grams of sodium dithionite

and 30 grams of saponin were added and the solution brought to the one liter mark with distilled water. Two ml of sickletest reagent was pipetted into a 12 x 75 mm test tube. To this was added 20 microliters of well mixed whole blood collected in ethylenediaminetetraacetic acid (EDTA). This was mixed by inverting the tube and allowed to sit at room temperature for 3 minutes. After three minutes the tube was held approximately three centimeters from a typewritten page. A positive test was represented by a turbid solution (print behind the tube was not visible). A negative test was represented by a clear, transparent solution.

b. Sickletest-Urea reagent: This reagent contains 2.0 M urea in the sickletest reagent. To prepare the reagent, 120.1 grams of urea was placed in a liter flask and sickle-test reagent added to equal one liter. Two ml of the sickle-test-urea solution was pipetted into a 12 x 75 mm test tube and 20 microliters of whole blood from a positive specimen was added, mixed and allowed to stand at room temperature for three minutes. If the sickletest-urea solution was transparent (print visible), but the same specimen gave a positive sickletest reaction, the hemoglobin present was presumed to be either hemoglobin S or hemoglobin C (Harlem). If the sickletest-urea solution remained turbid and the sickletest reaction was positive, the presence of a non-S sickling hemoglobin was indicated - e.g., hemoglobin C (Georgetown), Bart's, or perhaps Alexandra. For structural reasons, hemoglobin I (also a non-S sickling hemoglobin)

would be expected to be negative.

The theoretical explanation for those specimens that were turbid in the sickletest reagent, but transparent in the sickletest-urea reagent, was interference of urea with the hydrophobic bonds formed within the interlocking tetramers of the sickled hemoglobin S. Once the bonds are broken the microfilaments break down and the solution mimics those of the normal hemoglobins in the first reagent.

2. Hemoglobin Electrophoresis

All blood specimens were subjected to hemoglobin electrophoresis, regardless of solubility test results.

Five to 10 ml of blood were collected in EDTA and refrigerated at 4° C until used, usually within 24 hours. The blood was then centrifuged at 2,000X g for 15 minutes and the plasma removed. The packed red blood cells were then washed three times with 0.85 per cent saline solution to remove serum proteins. After the final wash 0.2 ml of the packed red blood cells was pipetted into a small test tube and lysed by adding six parts hemolysate reagent, a commercial preparation, (V:V).

The hemolysate was then applied to a cellulose acetate plate that had been soaked in buffer for 15 minutes, along with a control, another hemolysate containing a variety of known hemoglobin types. It was then electrophoresed in Supre Heme buffer, pH 8.6, at 1.5 milliamperes per strip. Each strip was then stained for 10 minutes in Ponseau S, a protein stain, washed (de-stained) twice in five per cent

glacial acetic acid for two minutes each, dehydrated in methanol for two minutes each, cleared in glacial acetic acid: methanol (1:3) for two minutes and air dried.

Movement through cellulose acetate depends on the nature of the charged particle, the character of the buffer, and the intensity of the electric field. As protein is amphoteric, it may be charged either positively or negatively, depending upon the pH of the buffer used. Since positively charged proteins usually exhibit greater absorption, negative charges (with less absorption) are usually induced with an alkaline buffer. With respect to hemoglobin S, the charge difference results from the shift from the negative glutamic acid to the neutral valine. When hemoglobin S is placed in the alkaline buffer with hemoglobin A, the two migrate from the cathode to the anode with hemoglobin A moving faster. As molecular weight and shape have negligible effects, the hemoglobins align in an order of (A_2, C, E, O): (D, S); (G, F); and A_1 from cathode to anode, relative to each other's charge difference (Figure 2).

Voltage, or potential difference is the driving force of the proteins. Yet, as voltage is increased or prolonged, amperage and heat also increase. Higher temperature, although leading to greater mobility, leads also to denaturation of the proteins, evaporation of the buffer, and subsequent shifting of the ionic strength as the salts become concentrated.

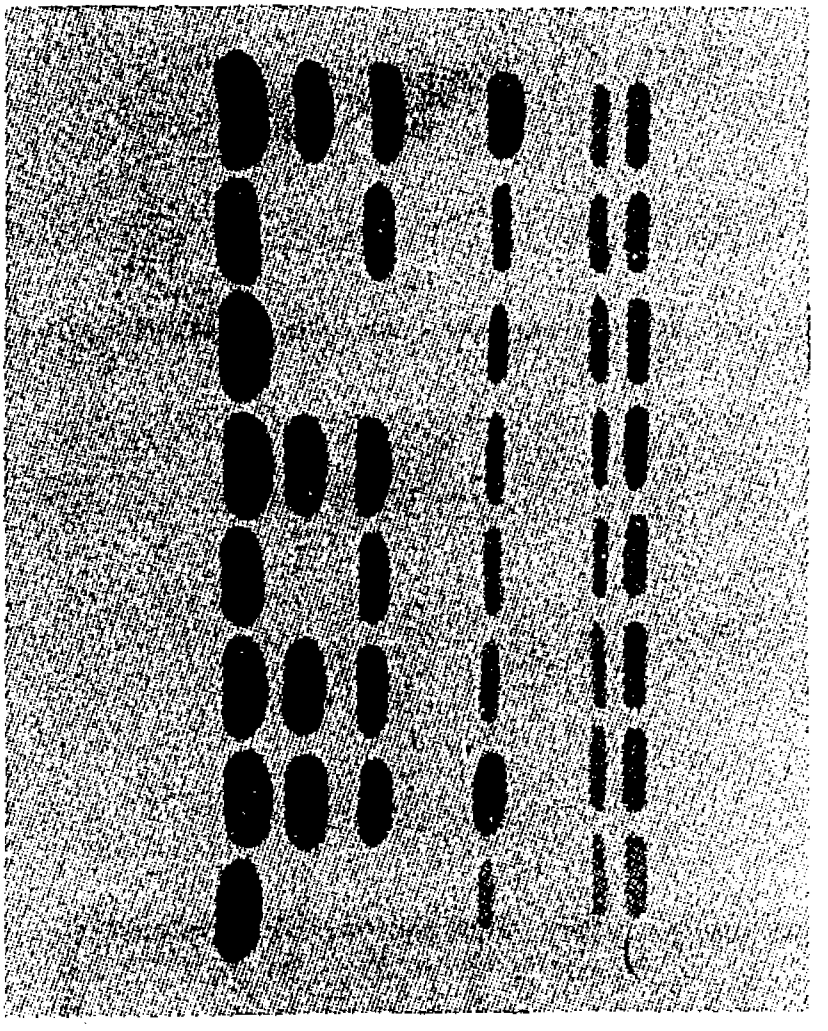

FIGURE 2. Hemoglobin Electrophoresis on Cellulose Acetate: Migratory Pattern at pH 8.6

Lower ionic strength is usually desired in increasing the velocity of the movement of protein. Evaporation is kept to a minimum to maintain a constant ionic strength and to minimize free diffusion.

3. Densitometry

After the strips were dried and a diagnosis made, densitometric readings were made to determine the relative percentages of the various hemoglobins present in each blood specimen. A Densicord Photovolt, Model 542 was used. This machine operates on the principle of a photo-electric cell which measures relative intensities of light. The strip was passed over a light source at a uniform rate and its translucence was plotted on a graph (Figure 3). In calculating percentages, lines were dropped from the low points of the graph (the points at which one hemoglobin stops and another starts) and the area under each curve was calculated from the integrated markings below. The low point between carbonic anhydrase and hemoglobin A_2 was considered ground zero. Thus the integrated areas were counted (the area below ground zero and the full light setting being subtracted from the integration), added, and the percentage of each hemoglobin calculated.

4. Alkali Denaturation

Aliquots of the hemolysates of those specimens that revealed fetal hemoglobin on the electrophoregrams were subjected to alkali denaturation to determine the percentage

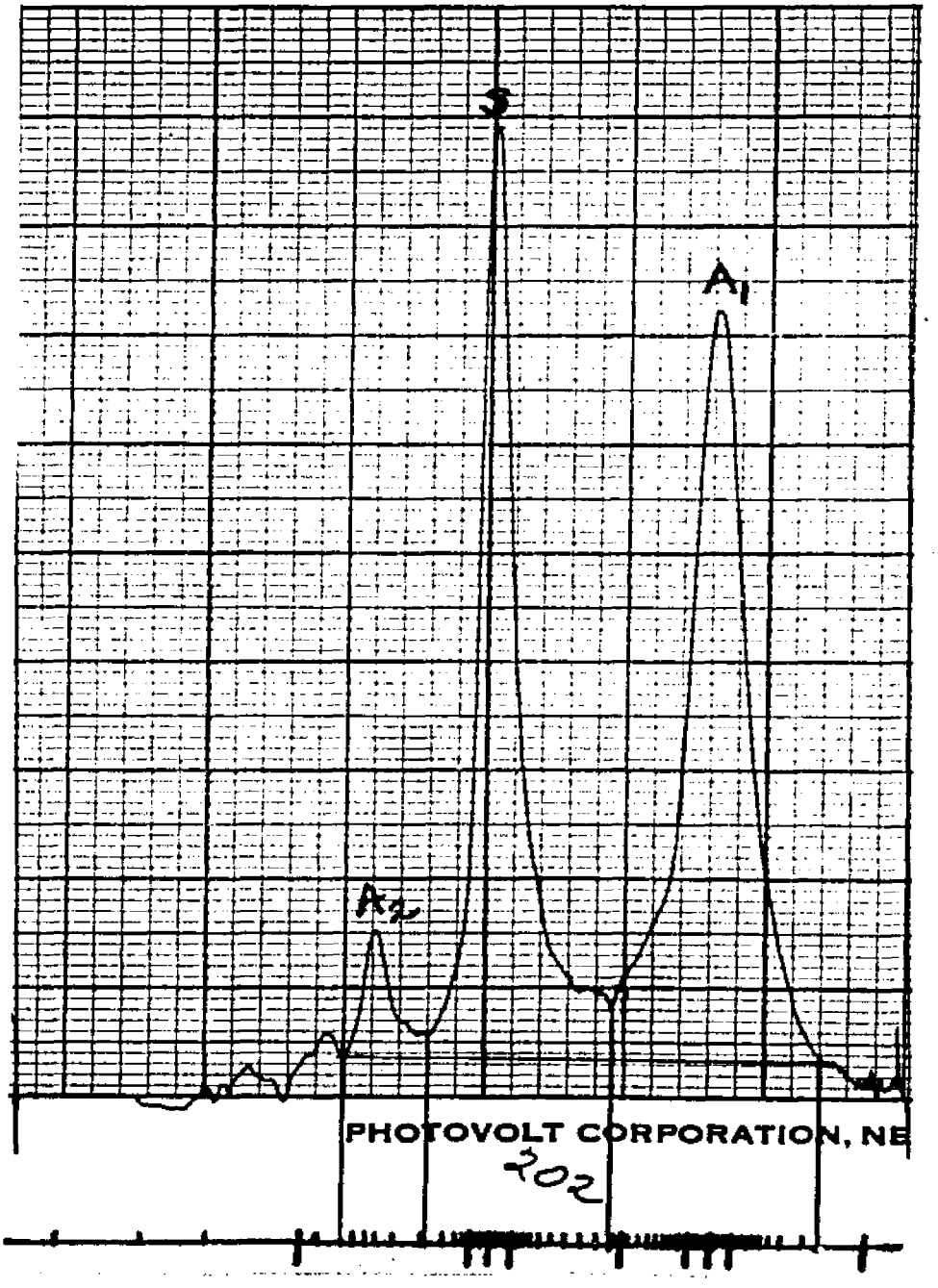

FIGURE 3. An Example of a Densitometric Graph Used for Semi-Quantitation of Hemoglobin Types

of fetal hemoglobin. The one minute denaturation test of Singer was used. In this method potassium hydroxide is added to a solution containing a known amount of hemoglobin and exactly one minute later denaturation is stopped by adding half-saturated ammonium sulfate. The ammonium sulfate lowers the pH and precipitates the denatured hemoglobin. After filtration, the amount of unaltered hemoglobin is measured and expressed as the per cent of alkali-resistant (fetal) hemoglobin.

RESULTS

In Lansing, the sample contained 3,473 individuals, based on the 1970 census data. Of this number, 2,026 individuals representing 538 families were actually interviewed. There were several instances of household refusals, but primarily as a result of an urban renewal project and extensive demolition of houses and relocation of families subsequent to the 1970 census taking, large numbers of houses were no longer in existence or were unoccupied. This was especially evident in those blocks where blacks were numbered 100 or more.

Of the 533 families interviewed, 48 were infants too young for definitive laboratory diagnosis (due to the large percentage of fetal hemoglobin); 56 non-infants refused to allow blood to be drawn for testing and 62 could not be contacted even after numerous visits to the home and several written invitations to visit a nearby clinic for the purpose of having blood drawn for testing. Complete data, consisting of an interview and blood test, were obtained on 1,860 individuals in the Lansing sample frame.

In the Grand Rapids survey, health data were obtained on 769 individuals; blood specimens and complete health data were secured from 643 persons, representing 145 families.

The only data included here concerning the 1,012 students tested in the Michigan State University survey are those comparing hematological indices between 31 students with sickle cell trait and 36 selected controls with normal hemoglobin.

A. Prevalence of Hemoglobin Types in Lansing Survey

Table 3 shows the prevalence of hemoglobin genotypes in the Lansing population. Of the 1,860 individuals tested, 1,642 (88.3 per cent) had only normal adult hemoglobin (AA); 152 (8.2 per cent) had sickle cell trait (AS), 45 (2.4 per cent) had hemoglobin C trait (AC); 9 (.43 per cent) were thalassemia heterozygotes (thalassemia minor); one child was homozygous for hemoglobin C disease (CC), and three (.16 per cent) had sickle cell anemia (SS).

B. Prevalence of Hemoglobin Types in Grand Rapids Survey

The proportions of genotypes in the Grand Rapids study are different from those in the Lansing group. This is due to the difference in method of ascertainment. In the Grand Rapids study 330 individuals (51.3 per cent) had normal adult hemoglobin; 306 (47.6 per cent) had sickle cell trait; three (.47 per cent) were carriers of hemoglobin C disease; two (.31 per cent) were found to have sickle cell hemoglobin C disease and two (.31 per cent) had sickle cell anemia (see Table 4).

C. Awareness of Sickle Cell Anemia

Of the 1,097 adults (18 years of age or older) who were interviewed in the two cities, 437 (39.8 per cent) had never before heard of sickle cell anemia: 329 (38.3 per cent) in the Lansing sample and 130 (45.4 per cent) in Grand Rapids. As expected, the more elderly individuals were least aware of sickle cell anemia (see Table 5). The difference in

Table 3

PREVALENCE OF HEMOGLOBIN TYPES BY AGE GROUPS IN LANSING

Age Group	Number	AA	AS	AC	CC	SS	A/F	Thal. minor
0 - 4	234	200	15	7	1	1	1	0
5 - 8	249	225	13	9	0	1	1	0
9 - 12	221	198	16	6	0	0	1	0
13 - 17	258	221	30	4	0	0	2	1
18 - 25	292	258	27	4	0	0	1	2
26 - 35	214	184	17	10	0	1	2	0
36 - 45	169	148	17	2	0	0	0	2
46 - 55	98	89	6	0	0	0	1	2
56 - 65	76	67	6	3	0	0	0	0
66 +	49	43	5	0	0	0	0	1
Total (All ages)	1,860	1,642	152	45	1	3	9	8

Table 4

PREVALENCE OF HEMOGLOBIN TYPES BY AGE GROUPS IN GRAND RAPIDS

Age Group	Number	AA	AS	AC	SC	SS
0 - 4	67	48	19	0	0	0
5 - 8	111	40	71	0	0	0
9 - 12	141	63	75	2	1	0
13 - 17	112	61	50	0	1	0
18 - 25	48	29	18	0	0	1
26 - 35	74	34	39	0	0	1
36 - 45	61	37	24	0	0	0
46 - 55	24	15	9	0	0	0
56 - 65	0	0	0	0	0	0
66 +	5	3	1	1	0	0
Total (All ages)	642	330	306	3	2	2

Table 5

PERCENTAGE OF INDIVIDUALS AWARE OF SICKLE CELL ANEMIA AMONG BLACK ADULTS SURVEYED IN LANSING AND GRAND RAPIDS

Age Group (Years)	Lansing		Grand Rapids		Combined	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
18 - 25	153	60.9	26	56.5	179	60.3
26 - 35	150	68.2	36	43.4	186	61.4
36 - 45	115	68.9	43	63.2	158	67.2
46 - 55	64	61.5	21	67.7	85	63.0
55 - 65	35	46.0	2	50.0	37	46.2
66 +	13	61.7	2	33.3	15	31.9
Total (All Ages)	530	61.7	130	54.6	660	60.2
N	859		238		1,097	

awareness in the two populations was not statistically significant (Chi square = .3895, d.f. = 1).

Those adults who indicated that they had heard of sickle cell anemia before were asked, "Before being contacted by this group, did you know that sickle cell anemia is an inherited kind of anemia and is passed from parent to offspring?" Eighty-one per cent (430 of 530) in the Lansing group and 99 of 130 (76 per cent) in the Grand Rapids group answered in the affirmative.

An analysis of awareness of sickle cell anemia by educational level (Figure 4) revealed in the combined survey (Lansing and Grand Rapids) that those adults who had previously heard of sickle cell anemia were 61 of 164 (37.2 per cent) who had completed eight years or less of school, 168 of 352 (47.7 per cent) who had completed 9 to 11 years of school, 226 of 369 (61.2 per cent) who had completed 12 years of school and 127 of 174 (73 per cent) of those who had at least one year of college.

D. General Health

Respondents to the health survey were asked to describe their general health as excellent, good, fair or poor. In the Lansing survey (see Table 6) 1,331 of 1,603 individuals (83 per cent) with normal hemoglobin described their health as excellent or good and 272 (17 per cent) considered their general health as fair or poor. Among those individuals diagnosed as sickle cell trait, 116 of 152 (76.3 per cent) were in excellent or good health and the remainder, 23.6 per cent, thought their health was fair or poor.

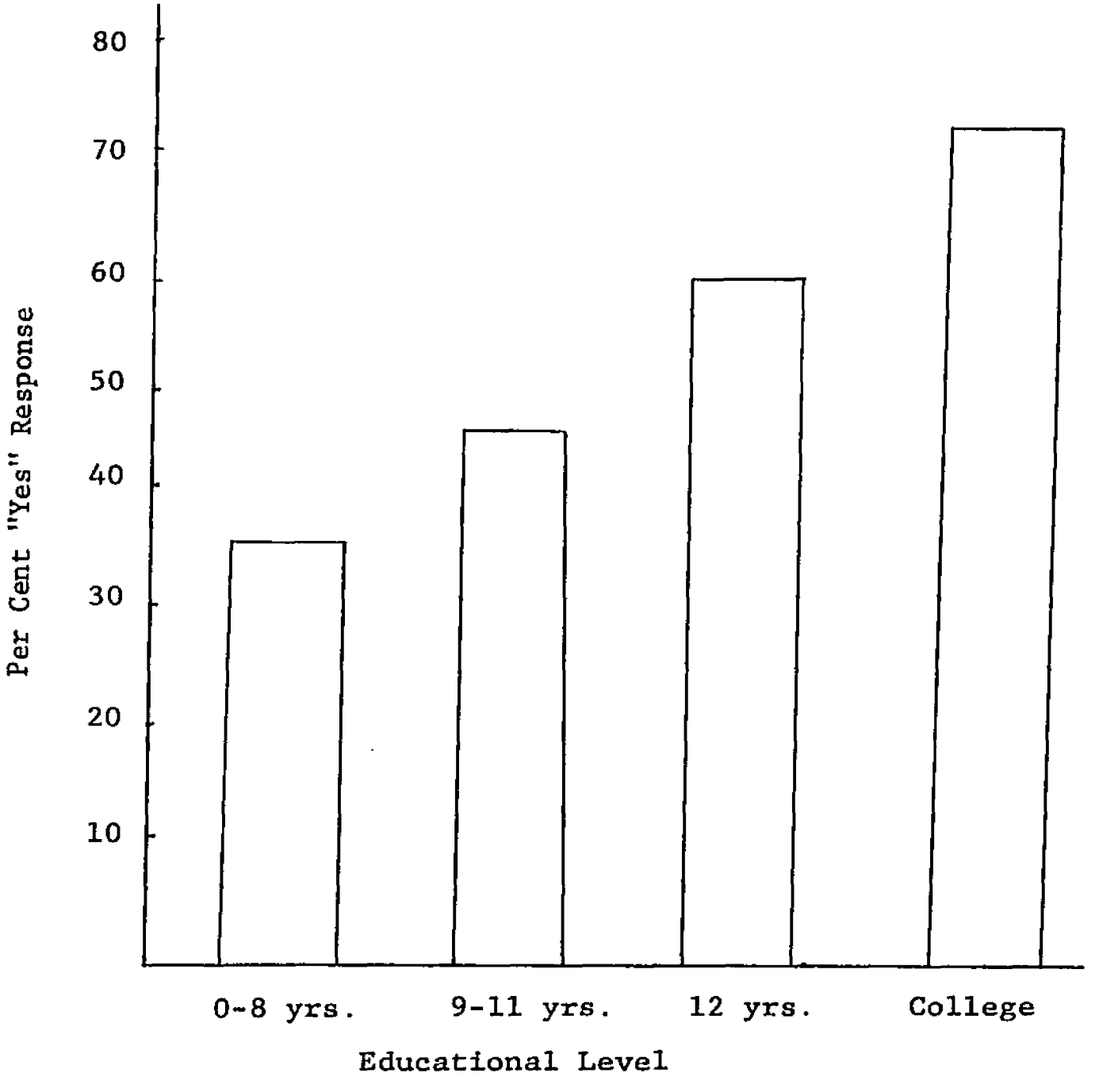

FIGURE 4. Awareness of Sickle Cell Anemia by Educational Level Among Adults with and without Sickle Cell Trait in Lansing and Grand Rapids

Table 6

COMPARISON OF GENERAL HEALTH AS OBTAINED BY QUESTIONNAIRE FROM SUBJECTS WITH AND WITHOUT SICKLE CELL TRAIT IN LANSING SURVEY

Age Group (Years)	Sickle Cell Trait (AS)				Normal Hemoglobin (AA)			
	Excellent or Good	Fair or Poor	Total AS		Excellent or Good	Fair or Poor	Total AA	
			No.	Per Cent			No.	Per Cent
0 - 12	39	8	47	30.9	562	59	621	38.7
13 - 25	46	9	55	36.2	421	53	474	29.6
26 - 45	24	10	34	22.4	242	82	324	20.2
46 - 65	6	6	12	7.9	88	63	151	9.4
66 +	1	3	4	2.6	18	15	33	2.1
Total	116	36	152	100.0	1,331	272	1,603	100.0

Table 6a

General Health by Genotype (Lansing)

	Ex. - Good	Fair - Poor
AS	116	36
AA	1,331	272

Chi square = 4.33, d.f. = 1

Table 7

COMPARISON OF GENERAL HEALTH AS OBTAINED BY QUESTIONNAIRE FROM SUBJECTS WITH AND WITHOUT SICKLE CELL TRAIT IN GRAND RAPIDS SURVEY

Age Group (Years)	Sickle Cell Trait (AS)				Normal Hemoglobin (AA)			
	Excellent or Good	Fair or Poor	Total AS		Excellent or Good	Fair or Poor	Total AA	
			No.	Per Cent			No.	Per Cent
0 - 12	147	18	165	54.1	135	15	150	45.7
13 - 25	58	9	67	22.0	79	10	89	27.1
26 - 45	48	15	63	20.6	55	16	71	21.7
46 - 65	6	3	9	3.0	13	2	15	4.6
66 +	1	0	1	0.3	2	1	3	0.9
Total (All Ages)	260	45	305	100.0	284	44	328	100.0

Table 7a

General Health by Genotype (Grand Rapids)

	Ex. - Good	Fair - Poor
AS	260	45
AA	284	44

Chi Square = 0.234, d.f. = 1

Chi square analysis (see Table 6a) reveals that the difference in general health among all individuals with trait, as compared with all normals, is significant at the five per cent level. This indicates that those respondents with sickle cell trait do not consider themselves in as good a state of health as those with normal hemoglobin (AA).

In the Grand Rapids survey the responses to general state of health were proportionately the same among those persons with and without the trait in all five age groups (see Table 7). Eighty-five per cent of all respondents with sickle cell trait had excellent or good health, compared to 87 per cent of all normals. Chi square analysis with one degree of freedom (see Table 7a) indicates no significant difference between the two groups. The proportions of normals in excellent or good health and in fair or poor health are similar in all age groups.

E. Drug, Tobacco and Alcohol Usage

The prevalences of the use of patent medicines, prescription drugs, tranquilizers, alcohol and cigarettes on most days or everyday among adults (18 years of age or older) are shown in Table 8 for Lansing and Table 9 for Grand Rapids.

Patent medicines are used on a daily basis by 43 of 463 (9 per cent) adult females with normal hemoglobin and four of 45 (9 per cent) with trait in Lansing. Comparable rates among males were 9 per cent of those without the trait and 6 per cent of those with the trait. When the data for both sexes are pooled and tested for association between all

normal adults and all adults with the trait, the difference is not significant at the five per cent level.

Drugs prescribed by the doctor were used daily by 20 per cent of those adults with normal hemoglobin and by 13 per cent of those with sickle cell trait. Chi square analysis reveals no significant difference at the five per cent level.

Nearly 11 per cent of the normal control adults in Lansing consume alcoholic beverages on a daily basis, compared with 20 per cent of those with trait. The difference, by Chi square analysis, is significant at the five per cent level (Chi square = 4.7, d.f. = 1, p. = .03). This difference is reflected in both sexes.

The prevalence of the use of tranquilizers regularly is small in both sexes both among trait and normal adults. Only one of 33 males and two of 45 females with trait use tranquilizers regularly. The percentages among the normal controls are similar. Fisher's exact test of association gives a probability value of 85 per cent.

Cigarette smoking in the Lanising sample is not significantly different between trait and normal adults. Forty-three per cent of normals and 53 per cent of trait adults smoke regularly, but the difference is not statistically significant at the five per cent level.

The prevalence of patent medicines usage in the Grand Rapids survey was very small among male and female adults and among those with and without sickle cell trait;

two (1.7 per cent) normals and four (4.4 per cent) of those with the trait. Fisher's exact test gives a probability value greater than 45 per cent.

Fourteen per cent of the controls in the Grand Rapids survey use prescription drugs daily, compared with 18 per cent of the heterozygotes. The difference between the two groups is not significant at the five per cent level.

None of the adult females in Grand Rapids admitted to regular consumption of alcoholic beverages. Also, only two of 41 male controls and two of 26 males with the trait indicated daily consumption. It is difficult to explain these results, especially when compared to the findings in Lansing. The differences are probably not due to the interviewing technique, as the two most reliable interviewers, who conducted nearly 100 per cent of the Grand Rapids interviews, also administered a relatively large proportion of the interviews in Lansing.

The prevalence of the use of tranquilizers in Grand Rapids was also small. Only two per cent of adult controls and four per cent of trait persons use tranquilizers regularly.

The prevalence of cigarette smoking on a regular basis was not significantly different when comparisons were made between adult controls and heterozygotes. Forty-eight per cent of the controls and 43 per cent of heterozygotes smoke cigarettes regularly. No attempt was made to determine the number consumed per day.

Table 8

PREVALENCE OF DRUG, TOBACCO AND ALCOHOL USAGE AMONG ADULTS IN LANSING ACCORDING TO TYPE OF HEMOGLOBIN

	Patent Medicines						Prescription Drugs					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Females	463	43	9.3	45	4	8.9	463	111	24.0	45	7	15.6
Males	323	29	9.0	33	2	6.1	323	42	13.0	33	3	9.1
Total	786	72	9.2	78	6	7.7	786	153	19.5	78	10	12.8
	Alcoholic Beverages						Tranquilizers					
Females	463	32	6.9	43	7	16.3	463	28	6.0	45	2	4.4
Males	323	52	16.1	33	8	24.2	323	13	4.0	33	1	3.0
Total	786	84	10.7	76	15	19.7	786	41	5.2	78	3	3.8
	Cigarette Smoking											
Females	463	173	37.4	45	22	48.9						
Males	323	168	52.0	33	19	57.6						
Total	786	341	43.4	78	41	52.6						

Table 9

PREVALENCE OF DRUG, TOBACCO AND ALCOHOL USAGE AMONG ADULTS IN GRAND RAPIDS ACCORDING TO TYPE OF HEMOGLOBIN

	Patent Medicines						Prescription Drugs					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Females	76	2	2.6	65	3	4.6	76	14	18.4	65	15	23.1
Males	41	0	0	26	1	3.8	41	2	4.8	26	1	3.8
Total	117	2	1.7	91	4	4.4	117	16	13.7	91	16	17.6

	Alcoholic Beverages						Tranquilizers					
Females	76	0	0	65	0	0	76	2	2.6	65	4	6.2
Males	41	2	4.8	26	2	7.7	41	0	0	26	0	0
Total	117	2	1.7	91	2	2.2	117	2	1.7	91	4	4.4

	Cigarette Smoking					
Females	76	32	42.1	65	25	38.5
Males	41	24	58.5	26	14	53.8
Total	117	56	47.9	91	39	42.9

F. Symptoms of Health Problems

1. Ophthalmologic and Hearing Problems

Among the respondents in the Lansing survey, 20 per cent of trait persons and 22 per cent of normals use glasses or contact lenses regularly (see Table 10). The difference is not statistically significant. There were no children under 9 years of age that use glasses. The distribution among other ages were roughly the same, except that no trait males between the ages of 26 and 55 use glasses or contact lenses. Only 11 of 1,636 "normals" in the Lansing survey reported that they used a hearing aid and none of the 152 trait persons used hearing aid devices.

In Grand Rapids, as shown in Table 11, 16 per cent of "normals" and 15 per cent of trait persons wear glasses or contact lenses regularly. The difference is not significant. Also, in Grand Rapids, no "normals" use hearing aids and only three persons with trait use them. Two of these were females between the ages of 46 and 55 years and the third person was another female between 13 and 17 years of age.

2. Infections

The prevalence of influenza, sore throat, colds, ulcers and earaches are shown in Tables 12 and 13. In the Lansing sample, 284 (17.4 per cent) of 1,636 persons with normal hemoglobin had at least one attack of influenza as compared with 17 (11.2 per cent) of 152 persons with sickle cell trait. In Grand Rapids, 44 of 329 controls (13.4 per cent) and 50 of 306 individuals with trait (16.3 per cent) had encountered at least one episode of influenza in the past year.

Table 10

PREVALENCE OF OPHTHALMOLOGIC AND HEARING PROBLEMS
AMONG SUBJECTS WITH AND WITHOUT SICKLE CELL TRAIT IN THE LANSING SURVEY

	Use of Glasses or Contact Lenses						Use of Hearing Aid					
	AA			AS			AA			AS		
		"Yes" Response			"Yes" Response			"Yes" Response			"Yes" Response	
	Tested	No.	Per Cent	Tested	No.	Per Cent	Tested	No.	Per Cent	Tested	No.	Per Cent
Female	894	227	25.4	77	22	28.6	894	6	0.7	77	0	0
Male	742	130	17.5	75	8	10.6	742	5	0.7	75	0	0
Total	1,636	357	21.8	152	30	19.7	1,636	11	0.7	152	0	0

Table 11

PREVALENCE OF OPHTHALMOLOGIC AND HEARING PROBLEMS
AMONG SUBJECTS WITH AND WITHOUT SICKLE CELL TRAIT IN THE GRAND RAPIDS SURVEY

	Use of Glasses or Contact Lenses						Use of Hearing Aid					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Female	196	42	21.4	174	35	20.1	196	0	0	174	3	1.7
Male	133	11	8.3	132	11	8.3	133	0	0	132	0	0
Total	329	53	16.1	306	46	15.0	329	0	0	306	3	1.98

These differences were not statistically significant at the five per cent level. It is interesting to note that the large majority of reported cases of influenza had been diagnosed by physicians as opposed to self-diagnosis. This was ascertained by asking if a doctor had been seen if an affirmative answer was given to the question pertaining to presence or absence of the symptoms.

In the Lansing population, a significantly larger proportion of controls had a throat infection in the past year than among those with the trait (28.7 per cent controls to 19.1 per cent traits). However, in the Grand Rapids population roughly the same proportion of normal and trait persons had throat infections (27.7 per cent normals to 25.8 per cent traits). In both populations the prevalence of ulcers and earaches was small and not statistically different.

Sixty-five per cent of the controls (1,068 of 1,636 respondents) in Lansing had at least one cold in the past year as compared with 58.5 per cent (89 of 152) of the traits. The difference was not significant at the five per cent level. In Grand Rapids the difference between those with and without the trait with at least one cold was not statistically significant at the five per cent level. Sixty-three per cent of normals and 64 per cent of traits had at least one cold in the past year.

3. Symptoms of Anemia

Prevalences of affirmative responses to symptoms of anemia, such as easy fatigue, sense of exhaustion, faintness and dizziness are shown in Tables 14 and 15. There were no

Table 12

PREVALENCE OF INFECTIONS IN THE LANSING POPULATION ACCORDING TO TYPE OF HEMOGLOBIN

	Influenza						Sore Throat					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Female	894	176	19.7	77	10	13.0	894	292	32.7	77	19	24.7
Male	742	108	14.5	75	7	9.3	742	178	24.0	75	10	12.3
Total	1,636	284	17.4	152	17	11.2	1,636	470	28.7	152	29	19.1
	Ulcers						Earaches					
Female	894	27	3.0	77	1	1.3	894	77	8.6	77	5	6.5
Male	742	23	3.1	75	0	0	742	56	7.5	75	5	6.7
Total	1,636	50	3.0	152	1	0.7	1,636	133	8.1	152	10	6.6
	Colds											
Female	894	570	63.7	77	49	63.6						
Male	742	498	67.1	75	40	53.3						
Total	1,636	1,068	65.3	152	89	58.5						

Table 13

PREVALENCE OF INFECTIONS IN THE GRAND RAPIDS POPULATION ACCORDING TO TYPE OF HEMOGLOBIN

	Influenza						Sore Throat					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Female	196	28	14.3	174	34	19.6	196	65	33.2	174	52	29.9
Male	133	16	12.1	132	16	12.1	133	26	19.5	132	27	20.4
Total	329	44	13.4	306	50	16.3	329	91	27.7	306	79	25.8
	Ulcers						Earaches					
Female	196	5	2.5	174	3	1.7	196	22	11.2	174	9	5.2
Male	133	1	0.7	132	0	0	133	5	3.8	132	8	6.1
Total	329	6	1.8	306	3	1.0	329	27	8.2	306	17	5.5
	Colds											
Female	196	122	62.2	174	118	67.8						
Male	133	84	63.1	132	78	59.1						
Total	329	206	62.6	306	196	64.0						

statistically significant differences in prevalences of any of these symptoms in either population, except sense of exhaustion in the Lansing population. Nineteen of 152 individuals with trait (12.5 per cent) indicated that they frequently experienced a sense of exhaustion as compared with 7.4 per cent among the controls (122 of 1,636). This difference was statistically significant at the five per cent level.

4. Musculoskeletal Symptoms

The musculoskeletal symptoms inquired about in the survey were muscle pain, weakness in legs, pain in bones, swollen and painful joints. The prevalences of these symptoms are included in Table 16 (Lansing and Table 17 (Grand Rapids).

Even though relatively few individuals indicated that they had experienced any of these symptoms, the prevalences of weakness in legs and pain in bones were greater among individuals with the trait in the Lansing survey and the differences in both categories were statistically significant at the five per cent level. In the Grand Rapids survey, the prevalence of swollen joints was the only category among musculoskeletal symptoms where there was a significant difference. The ratio of problems with swollen joints was greater than two to one, when traits are compared to controls.

5. Genitourinary Problems

In the category of genitourinary problems, Tables 18 (Lansing) and 19 (Grand Rapids), it was anticipated that there would be a greater prevalence of problems among individuals with sickle cell trait. This anticipation was based on previous

Table 14

PREVALENCE OF SYMPTOMS OF ANEMIA AMONG BLACKS IN LANSING ACCORDING TO TYPE OF HEMOGLOBIN

	Easy Fatigue						Sense of Exhaustion					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent
Female	894	160	17.9	77	16	20.8	894	91	10.2	77	13	16.9
Male	742	46	6.2	75	7	9.3	742	31	4.2	75	6	8.0
Total	1,636	206	12.6	152	23	15.1	1,636	122	7.4	152	19	12.5

	Faintness						Dizziness					
Female	894	49	5.5	77	7	9.1	894	117	13.1	77	12	15.6
Male	742	16	2.2	75	1	1.3	742	23	3.1	75	2	2.6
Total	1,636	65	4.0	152	8	5.3	1,636	140	8.5	152	14	9.2

Table 15

PREVALENCE OF SYMPTOMS OF ANEMIA AMONG BLACKS IN GRAND RAPIDS ACCORDING TO TYPE OF HEMOGLOBIN

	Easy Fatigue						Sense of Exhaustion					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Female	196	25	12.7	174	18	10.3	196	11	5.6	174	10	5.7
Male	133	7	5.3	132	4	3.0	133	3	2.2	132	3	2.3
Total	329	32	9.7	306	22	7.2	329	14	4.2	306	13	4.2

	Faintness						Dizziness					
Female	196	7	3.6	174	6	3.4	196	12	6.1	174	14	8.0
Male	133	1	0.7	132	4	3.0	133	6	4.5	132	4	3.0
Total	329	8	2.4	306	10	3.3	329	18	5.5	306	18	5.8

Table 16

PREVALENCE OF MUSCULOSKELETAL SYMPTOMS AMONG BLACKS IN LANSING ACCORDING TO TYPE OF HEMOGLOBIN

	Muscle Pain						Weakness in Legs					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent
Female	894	75	8.4	77	9	11.7	894	61	6.8	77	11	14.3
Male	742	40	5.4	75	7	9.3	742	24	3.2	75	4	5.3
Total	1,636	115	7.0	152	16	10.5	1,636	85	5.2	152	15	9.8
	Pain in Bones						Swollen Joints					
Female	894	32	3.6	77	6	7.8	894	78	8.7	77	2	2.6
Male	742	19	2.6	75	4	5.3	742	30	4.0	75	4	5.3
Total	1,636	51	3.1	152	10	6.6	1,636	108	6.6	152	6	3.9
	Painful Joints											
Female	894	73	8.2	77	5	6.5						
Male	742	46	6.2	75	5	6.6						
Total	1,636	119	7.3	152	10	6.6						

Table 17

PREVALENCE OF MUSCULOSKELETAL SYMPTOMS AMONG BLACKS IN GRAND RAPIDS ACCORDING TO TYPE OF HEMOGLOBIN

	Muscle Pain						Weakness in Legs					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent
Female	196	7	3.6	174	10	5.7	196	6	3.1	174	8	4.6
Male	133	6	4.5	132	4	3.0	133	4	3.0	132	4	3.0
Total	329	13	3.9	306	14	4.6	329	10	3.0	306	12	3.9
	Pain in Bones						Swollen Joints					
Female	196	4	2.0	174	1	0.6	196	5	2.5	174	11	6.3
Male	133	3	2.2	132	3	2.2	133	2	1.5	132	6	4.5
Total	329	7	2.1	306	4	1.3	329	7	2.1	306	17	5.5
	Painful Joints											
Female	196	8	4.1	174	7	4.0						
Male	133	3	2.2	132	6	4.5						
Total	329	11	3.3	306	13	4.2						

Table 18

PREVALENCE OF GENITOURINARY PROBLEMS AMONG BLACKS IN LANSING ACCORDING TO TYPE OF HEMOGLOBIN

	Hematuria						Kidney or Bladder Trouble					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Female	894	12	1.3	77	1	1.3	894	93	10.4	77	9	11.7
Male	742	14	1.9	75	0	0	742	27	3.6	75	4	5.3
Total	1,636	26	1.6	152	1	0.7	1,636	120	7.3	152	13	8.5
	Hyposthenuria						Vaginal Discharge					
Female	894	48	5.4	77	5	6.5	894	67	7.5	77	4	5.2
Male	742	15	2.0	75	3	4.0						
Total	1,636	63	3.8	152	8	5.3						
	Priapism											
Male	742	5	0.7	75	2	2.7						

Table 19

PREVALENCE OF GENITOURINARY PROBLEMS AMONG BLACKS IN GRAND RAPIDS ACCORDING TO TYPE OF HEMOGLOBIN

	Hematuria						Kidney or Bladder Trouble					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Female	196	3	1.5	174	0	0	196	18	9.2	174	20	11.5
Male	133	1	0.7	132	0	0	133	0	0	132	1	0.8
Total	329	4	1.2	306	0	0	329	18	5.5	306	21	6.9
	Hyposthenuria						Vaginal Discharge					
Female	196	5	2.5	174	10	5.7	196	8	4.1	174	4	2.3
Male	133	3	2.2	132	4	3.0						
Total	329	8	2.4	306	14	4.6						
	Priapism											
Male	133	1	0.7	132	0	0						

studies and case reports. The specific symptoms queried were hematuria, kidney or bladder trouble, hyposthenuria, vaginal discharge among females and priapism among males. In neither of the two populations was there a significant difference in the prevalences of any of these symptoms.

In the category of vaginal discharge among females in the Lansing survey, 466 of the "normals" were between the ages of 14 and 45 years. Fifty-six of these (12 per cent) reported problems with this condition. Fifty-one of the 77 females with trait who responded were in the same age group (14-45 years) and four (8 per cent) had problems with vaginal discharge.

6. Cardiovascular and Gastrointestinal Problems

High and low blood pressure, pain in chest and shortness of breath were the symptoms included in the category of cardiovascular problems. With respect to high and low blood pressures, the respondents would have to have been informed by a clinician, as it is highly possible that a person could have these conditions and not know it.

No statistically significant differences were discerned in either of the separate populations in any of these symptoms (see Table 20 and 21). When the data pertaining to high and low blood pressures were analyzed by age groups and sex, no differences were seen.

The gastrointestinal problems inquired about in the surveys included jaundice, blood in stool, blood in sputum, liver trouble (cirrhosis, hepatomegaly, etc.), diarrhea and abdominal pain. The relative proportions of the prevalences of these conditions in Lansing, (Table 22) and

Table 20

PREVALENCE OF CARDIOVASCULAR PROBLEMS AMONG BLACKS IN LANSING ACCORDING TO TYPE OF HEMOGLOBIN

	High Blood Pressure						Low Blood Pressure					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Female	894	105	11.7	77	8	10.4	894	81	9.1	77	8	10.4
Male	742	33	4.4	75	3	4.0	742	17	2.3	75	0	0
Total	1,636	138	8.4	152	11	7.2	1,636	98	6.0	152	8	5.3
	Pain in Chest						Shortness of Breath					
Female	894	108	12.1	77	5	6.5	894	104	11.6	77	8	10.4
Male	742	43	5.8	75	4	5.3	742	34	4.6	75	3	4.0
Total	1,636	151	9.2	152	9	5.9	1,636	138	8.4	152	11	7.2

Table 21

PREVALENCE OF CARDIOVASCULAR PROBLEMS AMONG BLACKS IN GRAND RAPIDS ACCORDING TO TYPE OF HEMOGLOBIN

	High Blood Pressure						Low Blood Pressure					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent
Female	196	11	5.6	174	9	5.2	196	11	5.6	174	12	6.9
Male	133	1	0.8	132	0	0	133	3	2.3	132	5	3.8
Total	329	12	3.6	306	9	2.9	329	14	4.3	306	17	5.5
	Pain in Chest						Shortness of Breath					
Female	196	18	9.2	174	10	5.7	196	14	7.1	174	9	5.2
Male	133	7	5.3	132	3	2.3	133	5	3.8	132	5	3.8
Total	329	25	7.6	306	13	4.2	329	19	5.8	306	14	4.6

Grand Rapids, (Table 23) are similar when controls are compared with sickle cell trait subjects. The difference in each case is not statistically significant.

7. Epistaxis

The prevalence of spontaneous nosebleeds was greater among individuals with sickle cell trait in both populations (see Tables 24 and 25). In the Lansing survey, 191 of 1,636 normals (11.7 per cent) reported nosebleeds in the past year as compared with 26 of 152 (17.1 per cent) individuals with the trait. The difference is significant at the five per cent level. In the Grand Rapids survey 31 of 329 controls (9.4 per cent) and 48 of 306 (15.7 per cent) trait individuals reported nosebleeds in the past year.

8. Neurologic Symptoms

Confusion and disorientation, convulsions and numbness in legs were the symptoms included in the neurologic category. In Lansing, there was no significant difference between traits and controls in any of these symptoms (see Table 26). In Grand Rapids (Table 27), 15 of 306 persons with the trait (4.9 per cent) reported problems of numbness in legs, while only six of 329 controls (1.8 per cent) had similar problems.

A second set of analyses was done on the data collected from the Grand Rapids survey. All probands and data concerning them were removed and prevalences of the 34 health problem symptoms were re-calculated. The purpose for doing this was to remove some of the bias inherent in

Table 22

PREVALENCE OF GASTROINTESTINAL PROBLEMS IN LANSING ACCORDING TO TYPE OF HEMOGLOBINS

	Jaundice						Blood in Stool					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent	Tested	"Yes" Response No.	Per Cent
Female	894	11	1.2	77	1	1.3	894	16	1.8	77	3	3.9
Male	742	8	1.1	75	1	1.3	742	20	2.7	75	0	0
Total	1,636	19	1.2	152	2	1.3	1,636	36	2.2	152	3	3.0
	Blood in Sputum						Liver Trouble					
Female	894	27	3.0	77	2	2.6	894	8	0.9	77	1	1.3
Male	742	21	2.8	75	0	0	742	6	0.8	75	0	0
Total	1,636	48	2.9	152	2	1.3	1,636	14	0.8	152	1	0.6
	Diarrhea						Abdominal Pain					
Female	894	64	7.2	77	3	3.9	894	97	10.8	77	10	13.0
Male	742	39	5.2	75	5	6.7	742	40	5.4	75	2	2.7
Total	1,636	103	6.3	152	8	5.3	1,636	137	8.4	152	12	7.9

Table 23

PREVALENCE OF GASTROINTESTINAL PROBLEMS IN GRAND RAPIDS ACCORDING TO TYPES OF HEMOGLOBIN

	Jaundice						Blood in Stool					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Female	196	2	1.0	174	0	0	196	3	1.5	174	3	1.7
Male	133	0	0	132	1	0.8	133	3	2.2	132	3	2.3
Total	329	2	0.6	306	1	0.3	329	6	1.8	306	6	2.0
	Blood in Sputum						Liver Trouble					
Female	196	4	2.0	174	3	1.7	196	2	1.0	174	2	1.1
Male	133	2	1.5	132	2	1.5	133	0	0	132	1	0.7
Total	329	6	1.8	306	5	1.6	329	2	0.6	306	3	1.0
	Diarrhea						Abdominal Pain					
Female	196	22	11.2	174	13	7.5	196	16	8.2	174	11	6.3
Male	133	12	9.0	132	10	7.6	133	9	6.8	132	9	6.8
Total	329	32	10.3	306	23	7.5	329	24	7.6	306	20	6.5

Table 24

PREVALENCE OF EPISTAXIS IN LANSING ACCORDING TO TYPE OF HEMOGLOBIN

	AA			AS		
		"Yes" Response			"Yes" Response	
	Tested	No.	Per Cent	Tested	No.	Per Cent
Female	894	87	9.7	77	14	18.2
Male	742	104	14.0	74	12	16.0
Total	1,636	191	11.7	152	26	17.1

Table 25

PREVALENCE OF EPISTAXIS IN GRAND RAPIDS ACCORDING TO TYPE OF HEMOGLOBIN

	AA			AS		
		"Yes" Response			"Yes" Response	
	Tested	No.	Per Cent	Tested	No.	Per Cent
Female	196	16	8.2	174	20	11.5
Male	133	15	11.3	132	28	21.2
Total	329	31	9.4	306	48	15.7

Table 26

PREVALENCE OF NEUROLOGIC SYMPTOMS IN LANSING ACCORDING TO TYPE OF HEMOGLOBIN

	Confusion and Disorientation						Convulsions					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Female	894	43	4.8	77	3	3.9	894	16	1.8	77	0	0
Male	742	14	1.9	75	1	1.3	742	8	1.1	75	0	0
Total	1,636	57	3.5	152	4	2.6	1,636	24	1.5	152	0	0

	Numbness in Legs					
Female	894	47	5.3	77	6	7.8
Male	742	16	2.2	75	1	1.3
Total	1,636	63	3.8	152	7	4.6

Table 27

PREVALENCE OF NEUROLOGIC SYMPTOMS IN
GRAND RAPIDS ACCORDING TO TYPE OF HEMOGLOBIN

	Confusion and Disorientation						Convulsions					
	AA			AS			AA			AS		
	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent	Tested	"Yes" Response No.	"Yes" Response Per Cent
Female	196	5	2.5	174	6	3.4	196	1	0.5	174	6	3.4
Male	133	2	1.5	132	2	1.5	133	4	3.0	132	5	3.8
Total	329	7	2.1	306	8	2.6	329	5	1.5	306	11	3.6

	Numbness in Legs					
Female	196	5	2.5	174	10	5.7
Male	133	1	0.7	132	5	3.8
Total	329	6	1.8	306	15	4.9

the previous analyses. Specifically, parents may have been prone to remember better any of the problems the probands may have had. This assumption was made, based on the fact that parents knew which of their children had participated in the initial screening program at the schools. As a result of the test findings parents, along with the rest of the family were invited in for definitive testing, education and counseling. Of the 33 symptoms the only one that was significantly different at the five per cent level between trait and normal homozygous individuals was prevalence of swollen joints in the category of musculoskeletal symptoms. Specifically, seven of 329 (2 per cent) of the controls reported problems with this symptom compared to 13 of 160 (8 per cent) persons with sickle cell trait. In the previous calculations pertaining to the Grand Rapids data set, including probands, three of the symptoms were significantly more prevalent among trait persons. These were swollen joints, epistaxis and numbness in legs.

In the Lansing sample, sense of exhaustion, pain in bones, weakness in legs and epistaxis were the only variables significantly associated with sickle cell trait.

Table 27a shows a listing of all of the health problems asked about and indicates the group (trait vs normal) that is less affected. Of the 35 conditions summarized, in the Lansing sample, 21 were less frequently reported among persons with sickle cell trait and 15 were less frequently reported among individuals with normal hemoglobin. In the Grand Rapids survey,

16 of the symptoms were less frequently reported by trait persons, 19 less frequently by the AA group and with one symptom (sense of exhaustion) each group was equally affected. These differences in frequencies are not significantly different in either population.

With respect to the itemized symptoms or conditions, the apparent general health of average trait individuals is about the same as that of average persons with only normal hemoglobin. This is generally true in both populations studied.

G. A Single Test of Association of Health and Sickle Cell Trait

Thirty-four separate symptoms of health problems were ascertained in the two separate populations. In the Lansing sample, five of these were statistically significantly different, all except one, more prevalent among those persons with sickle cell trait. In the Grand Rapids survey, three of the 34 symptoms were significantly different at the five per cent level, all more prevalent among those persons with sickle cell trait. Only one symptom, epistaxis, was significnatly different in both populations. When probands in the Grand Rapids survey were excluded only one symptom was found to be significantly different.

In the utilization of the Chi square test of significance for several separate comparisons, the probability of a false difference is amplified. If one test is performed at the five per cent level, the probability of a type one error is five per cent. The probability of finding at least one false difference by performing 34 independent tests is 82 per cent.

Table 27a

TABULATION OF SYMPTOMS FOR THE 36 HEALTH PROBLEMS INDICATING THE GROUP (AS vs. AA) WITH LOWER FREQUENCY

Condition or Symptom	Lansing					Grand Rapids				
	AA		AS		Group less	AA		AS		Group less
	N	%	N	%	Affected	N	%	N	%	Affected
Fair or Poor Health	1603	17	152	24	AA*	328	13	306	14	AA
Use of Glasses or Contact Lenses	1636	22	152	20	AS	329	16	306	15	AS
Hearing Aid	1636	1	152	0	AS	329	0	306	2	AA
Influenza	1636	17	152	11	AS	329	13	306	16	AA
Sore Throat	1636	28.7	152	19.1	AS*	329	27.7	306	25.8	AS
Ulcers	1636	3	152	1	AS	329	2	306	1	AS
Earaches	1636	8	152	7	AS	329	8	306	6	AS
Colds	1636	65	152	59	AS	329	63	306	64	AA
Easy Fatigue	1636	13	152	15	AA	329	10	306	7	AS
Sense of Exhaust.	1636	7.4	152	12.5	AA*	329	4	306	4	--
Faintness	1636	4	152	5	AA	329	2	306	3	AA
Dizziness	1636	8.5	152	92	AA	329	5.5	306	5.8	AA
Muscle Pain	1636	7.0	152	10.5	AA	329	3.9	306	4.6	AA
Weakness in Legs	1636	5.2	152	9.8	AA*	329	3.0	306	3.9	AA
Pain in Bones	1636	3.1	152	6.6	AA*	329	2.1	306	1.3	AS
Swollen Joints	1636	6.6	152	3.9	AS	329	2.1	306	5.5	AA*
Painful Joints	1636	7.3	152	6.6	AS	329	3.3	306	4.2	AA
Hematuria	1636	1.6	152	0.7	AS	329	1.2	306	0	AS
Kidney/Bladder Trouble	1636	7.3	152	8.5	AA	329	5.5	306	6.9	AA

Table 27a (Cont'd.)

Condition or Symptom	Lansing					Grand Rapids				
	AA		AS		Group less Affected	AA		AS		Group less Affected
	N	%	N	%		N	%	N	%	
Hyposthenuria	1636	3.8	152	5.3	AA	329	2.4	306	4.6	AA
Vaginal Discharge	894	7.5	77	5.2	AS	196	4.1	174	2.3	AS
Priapism	742	0.7	75	2.7	AA	133	0.7	132	0	AS
High Blood Pres.	1636	8.4	152	7.2	AS	329	3.6	306	2.9	AS
Low Blood Pres.	1636	6.0	152	5.3	AS	329	4.3	306	5.5	AA
Pain in Chest	1636	9.2	152	5.9	AS	329	7.6	306	4.2	AS
Shortness of Breath	1636	8.4	152	7.2	AS	329	5.8	306	4.6	AS
Jaundice	1636	1.2	152	1.3	AA	329	0.6	306	0.3	AS
Blood in Stool	1636	2.2	152	3.0	AA	329	1.8	306	2.0	AA
Blood in Sputum	1636	2.9	152	1.3	AS	329	1.8	306	1.6	AS
Liver Trouble	1636	0.8	152	0.6	AS	329	0.6	306	1.0	AA
Diarrhea	1636	6.3	152	5.3	AS	329	10.3	306	7.5	AS
Abdom. Pain	1636	8.4	152	7.9	AS	329	7.6	306	6.5	AS
Epistaxis	1636	11.7	152	17.1	AA*	329	9.4	306	15.7	AA*
Confus. and Disorientation	1636	3.5	152	2.6	AS	329	2.1	306	2.6	AA
Convulsions	1636	1.5	152	0	AS	329	1.5	306	3.6	AA
Numbness in Legs	1636	3.8	152	4.6	AA	329	1.8	306	4.9	AA*

Total Number for Each Group:
AS = 21; AA = 15

Total Number for Each Group:
AS = 16; AA = 19 No Diff = 1

* Denotes Statistically Significant Difference

In an effort to avoid the above difficulty, an attempt was made to devise a single test of association of health and the trait. An analysis was made by categorizing in both traits and normals, those individuals with any symptoms who had seen a doctor as "sick". That is, if a person indicated that he had problems with at least one of the 34 symptoms and reported that he had seen a doctor for it, that person was categorized as "sick". On the other hand, those persons who had no problems with any of the 34 symptoms, along with those who reported that they had one or more of the symptoms, but had not seen a doctor about it, were categorized as "well". An overall Chi square test with one degree of freedom was then computed. As shown in Table 28, the percentage of individuals in the Lansing sample with normal hemoglobin defined as "sick" was 43.7, compared with 44.7 per cent (68 of 152) of those with sickle cell trait. In the Grand Rapids sample, 33.6 per cent of the controls were defined as sick, compared with 36.9 per cent of those with sickle cell trait. A Chi square test of significance shows no difference in either of the two separate samples.

Table 28

A COMPARISON BETWEEN SICK AND WELL INDIVIDUALS WITH AND WITHOUT SICKLE CELL TRAIT FOR THE LANSING AND GRAND RAPIDS SAMPLES

	AA		AS		Relative Odds Ratio
	No.	Per Cent	No.	Per Cent	
Lansing					
Well	925	56.3	84	55.3	1.04
Sick	717	43.7	68	44.7	
Total	1,642	91.5	152	8.5	
Grand Rapids					
Well	219	66.4	193	63.1	1.16
Sick	111	33.6	113	36.9	
Total	330	51.9	306	48.1	

H. Relative Odds Ratios

The kind of crosstabulation shown in Table 28 lends itself to another computation, the relative odds ratio, which gives some indication of the risk of being well or sick among trait individuals compared with controls. Such a computation of the data included in Table 28 reveals that the odds that individuals with the trait are sick is 1.04 times the odds of individuals with normal hemoglobin in Lansing and 1.16 in Grand Rapids.

Table 29 shows age specific relative odds ratios for sickness in the Lansing sample. There is an increasing risk of sickness with increasing age among trait and normal individuals.

In contrast to the implications of data contained in Table 29 of symptomatic health problems, interviewees were asked to characterize their general health as excellent, good, fair or poor (Table 6). Dividing the respondents into two categories: Good Health (those who perceived their general health as excellent or good) and Bad Health (those who indicated that their general health was fair or poor), Table 30 was obtained. It is clear that among trait persons, there is a decrease in bad health with increasing age.

I. Age Trends

The relation between age and sickle cell trait in the Lansing sample is shown in Table 31. The mean frequency for trait in this group is 8.5 per cent. No statistically significant relation to age was seen in the frequency of sickle cell trait when ages were grouped.

Table 29

AGE SPECIFIC RELATIVE ODDS RATIOS FOR SICKNESS IN LANSING

Age Group (Years)		Normal (AA)	Trait (AS)	Relative Odds Ratio
0 - 17	Well	598	49	1.196
	Sick	255	25	
18 - 35	Well	195	24	0.658
	Sick	247	20	
36 - 55	Well	90	6	1.735
	Sick	147	17	
56 +	Well	32	4	0.787
	Sick	61	6	

Table 30

AGE SPECIFIC RELATIVE ODDS RATIOS FOR GOOD OR BAD HEALTH IN LANSING

Age Group (Years)		Good Health	Bad Health	Relative Odds Ratio
0 - 17	Normal	562	59	1.95
	Trait	39	8	
18 - 35	Normal	421	53	1.50
	Trait	46	9	
36 - 55	Normal	292	117	1.34
	Trait	26	14	
56 +	Normal	56	43	1.30
	Trait	5	5	

Table 31

THE RELATION BETWEEN AGE AND SICKLE CELL TRAIT IN THE LANSING SAMPLE

Age Group (Years)	Number	Hemoglobin Types AA	AS	Per Cent With Trait
0-4	224	209	15	6.7
5-8	238	225	13	5.5
9-12	214	198	16	7.5
13-17	251	221	30	11.9
18-25	285	258	27	9.5
26-35	201	184	17	8.5
36-45	165	148	17	10.3
46-55	95	89	6	6.3
56-65	73	67	6	8.2
66 +	48	43	5	10.4
Total	1,794	1,642	152	8.5

$X^2 = 9.8$, d.f. = 9, $p > .35$

In order to facilitate comparison with several previous reports, the subjects were re-grouped into four age periods, zero to four, five to 20, 21 to 49 and 50 years and over, respectively (see Table 32). No statistically significant relation to age was seen in the frequency of sickle cell trait in either sex.

The age trend of sickle cell trait in the Grand Rapids survey (Table 33) shows a decrease in the older age groups. This type of pattern was expected from the outset, due to the method of ascertainment. In this population the study began with propositi with some sickling involvement but no definitive diagnoses as to specific hemoglobin types. Subsequently, the propositi were re-tested for definitive diagnoses along with other family members, including parents, siblings and, in several instances, more distant relatives living in the household. Since the propositi were school-aged and all with sickle positive solubility tests, it would be expected that at least one parent and one-half of the sibs would have sickle cell positive tests. Moreover, a high percentage of the parents would be expected to fall in an age group preceding 55 years. This is true for the most part as implied in Table 33. Those persons in the older age group were usually grandparents or other older relatives who were guardians of the propositi.

Table 32

THE RELATION BETWEEN AGE AND SICKLE CELL TRAIT IN MALES, FEMALES AND COMBINED SAMPLE, LANSING (DIVIDED INTO FOUR AGE GROUPS)

Age Group (Years)	Number	Hemoglobin Types AA	Hemoglobin Types AS	Per Cent With Trait
Males:*				
0-4	111	101	10	9.1
5-20	398	359	39	9.8
21-49	226	208	18	8.0
50 +	74	67	7	9.5
All Ages	809	735	74	9.1
Females:**				
0-4	112	107	5	4.5
5-20	415	379	36	8.7
21-49	353	322	31	8.8
50 +	82	77	5	6.1
All Ages	962	885	77	8.0
Combined:***				
0-4	223	208	15	6.7
5-20	813	738	75	9.2
21-49	579	530	49	8.5
50 +	156	144	12	7.7
Total All Ages	1,771	1,620	151	8.5

*X^2 = .59, d.f. = 3, $p > .5$
**X^2 = 2.8, d.f. = 3, $p > .4$
***X^2 = 1.6, d.f. = 3, $p > .5$

Table 33

THE RELATION BETWEEN AGE AND SICKLE CELL TRAIT IN THE GRAND RAPIDS STUDY

Age Group (Years)	Number	Hemoglobin Types		Per Cent With Trait
		AA	AS	
0-4	67	48	19	28.4
5-8	111	40	71	64.0
9-12	138	63	75	54.3
13-17	111	61	50	45.0
18-25	47	29	18	38.3
25-35	73	34	39	53.4
36-45	61	37	24	39.3
46-55	24	15	9	37.5
56-65	0	0	0	-
66 +	4	3	1	25.0
Total	636	330	306	48.1

J. Pregnancy History

Table 34 contains pregnancy data obtained from 630 females, 14 years of age or older, in the Lansing survey. Of the 573 females with normal hemoglobin, 407 (71 per cent) had at least one pregnancy as compared with 33 of 57 (58 per cent) females with sickle cell trait. When a Chi square test of independence was employed, no significant difference was revealed at the .05 level.

Among those females in the 14-17 age group, 92 per cent of the trait females have never been pregnant, compared with 88 per cent of normal females. The greatest difference is seen among females in the 18-25 age group. Fifty-three per cent of trait females have never been pregnant, compared with 30 per cent of the normals. Twenty-one of the 24 never pregnant trait females are between the ages of 14 and 25 years.

When comparisons are made with respect to the number of pregnancies among those females with at least one pregnancy (see Table 35), no significant difference between trait and normal females is detected.

Among those females who had at least one pregnancy, 124 normals (30.5 per cent) had at least one miscarriage or stillbirth while 13 (43.3 per cent) trait females had at least one miscarriage or stillbirth. The difference is not statistically significant at the .05 level (see Table 36). Further analysis of the numbers and distribution of miscarriages or stillbirths among those females who had a history of at least one pregnancy reveals no significant

Table 34

PREGNANCY HISTORY OBTAINED BY QUESTIONNAIRE FROM 630 FEMALES WITH AND WITHOUT SICKLE CELL TRAIT IN THE LANSING SURVEY

	Trait					Normal				
Age Group	None		At Least One		Total	None		At Least One		Total
(Years)	No.	%	No.	%	No.	No.	%	No.	%	No.
14-17	12	92.3	1	7.7	13	98	87.5	14	12.5	112
18-25	9	52.9	8	47.1	17	46	30.3	106	69.7	152
26-35	1	9.1	10	90.9	11	6	5.4	106	94.6	112
36-45	0	0	9	100	9	4	4.6	83	95.4	87
46-55	1	33.3	2	66.7	3	3	5.7	50	94.3	53
56-65	0	0	3	100	3	4	11.1	32	88.9	36
66 +	1	100	0	0	1	5	23.8	16	76.2	21
Total	24	42.1	33	57.9	57	166	29.0	407	71.0	573

$X^2 = 3.65$, d.f. = 1, p = .056

Table 35

NUMBER OF PREGNANCIES AMONG FEMALES WITH AND WITHOUT SICKLE CELL TRAIT IN LANSING SURVEY

No. of Pregs.	1	2	3	4	5	6+	Total
Normal	81	76	73	45	49	83	407
	19.9%	18.7%	17.9%	11.1%	12%	20.4%	
Trait	10	5	3	3	7	5	33
	30.3%	15.2%	9.1%	9.1%	21.2%	15.2%	
Totals	91	81	76	48	56	88	440
	20.7%	18.4%	17.3%	10.9%	12.7%	20%	

$X^2 = 5.73$, d.f. = 5, p = .33

Table 36

MISCARRIAGE AND STILLBIRTH HISTORY AMONG FEMALES WITH AND WITHOUT SICKLE CELL TRAIT IN THE LANSING SURVEY

	None		At Least One		Total
	No.	Per Cent	No.	Per Cent	No.
Trait	17	56.7	13	43.3	30
Normal	283	69.5	124	30.5	407
Total	300	68.5	137	31.4	437

$X^2 = 1.6, d.f. = 1, p = .2069$

Table 37

NUMBER OF MISCARRIAGES OR STILLBIRTHS OBTAINED BY QUESTIONNAIRES FROM FEMALES IN THE LANSING SURVEY

	1	2	3	4	5+	Total
Normal	89	20	7	7	1	124
	71.8%	16.1%	5.5%	5.6%	0.8%	90.5
Trait	8	4	1	0	0	13
	61.5%	30.8%	7.7%	0	0	9.5
Totals	97	24	8	7	1	137
	70.8%	17.5%	5.8%	5.1%	0.7%	100

$X^2 = 2.54, d.f. = 4, p > .5$

difference (see Table 37).

Sixty-seven of 437 females had at least one child die during childhood (before 15 years of age); 66 mothers with normal (16.2 per cent) hemoglobin and one with sickle cell trait (3.3 per cent). Fisher's Exact Test gives a probability value of .0771. The number of early childhood deaths of children of trait women is too small for comparison (see Table 38).

In Grand Rapids a tabulation was made of females ever pregnant (14 years of age or older) after excluding the mothers of propositi. The results, as shown in Table 39, reveal that 79 per cent of the trait females have no history of pregnancy, compared to 73 per cent of the females with normal hemoglobin. The difference is not significant at the five per cent level. There is no statistical difference in the number of pregnancies among trait and normal females (including mothers of propositi) with a history of at least one pregnancy (see Table 40).

Further analysis of data obtained from those females (Table 41) with at least one pregnancy reveals that 30.2 per cent of trait females had at least one miscarriage or stillbirth, while 36.6 per cent of normal females had at least one. The difference again, is not statistically significant. Moreover, a Chi square test of independence indicates no significant difference in the number of miscarriages or stillbirths among those females with and without trait who had at least one miscarriage or stillbirth (see Table 42).

Table 38

EARLY CHILDHOOD DEATHS REPORTED BY MOTHERS WITH AND WITHOUT SICKLE CELL TRAIT IN LANSING

	None		At Least One		Total
	No.	Per Cent	No.	Per Cent	No.
Normal	341	83.8	66	16.2	407
Trait	29	96.7	1	3.3	30
Total	370	84.7	67	15.3	437

$p < .10$

Table 39

PREGNANCY HISTORY OBTAINED BY QUESTIONNAIRE FROM 73 FEMALES WITH AND WITHOUT SICKLE CELL TRAIT IN THE GRAND RAPIDS SURVEY

Age Group	Trait					Normal				
	None		At Least One		Total AS	None		At Least One		Total AA
	No.	%	No.	%		No.	%	No.	%	
14 - 17	19	95.0	1	5.0	20	30	100.0	0	0	30
18 - 25	2	33.3	4	66.7	6	2	28.6	5	71.4	7
26 - 35	1	100.0	0	0	1	0	0	2	100.0	2
36 - 45	0	0	0	0	0	1	50.0	1	50.0	2
46 - 55	0	0	0	0	0	0	0	2	100.0	2
66 +	0	0	1	0	1	0	0	2	100.0	2
Total	22	78.6	6	21.4	28	33	73.3	12	26.7	45

$X^2 = .0509$, d.f. = 1, p = .82

Table 40

NUMBER OF PREGNANCIES AMONG FEMALES WITH AND WITHOUT SICKLE CELL TRAIT IN GRAND RAPIDS

	1	2	3	4	5	6+	Total
Normal	5	9	8	10	5	34	71
	7.0%	12.6%	11.2%	14.1%	7.0%	47.9%	
Trait	4	10	10	11	7	21	63
	6.3%	15.9%	15.9%	17.5%	11.1%	33.3%	
Totals	9	19	18	21	12	55	134
	6.7%	14.2%	13.4%	15.7%	8.9%	41.0%	

$X^2 = 3.37$, d.f. = 5, $p = > .5$

Table 41

MISCARRIAGE AND STILLBIRTH HISTORY AMONG FEMALES WITH AND WITHOUT SICKLE CELL TRAIT IN GRAND RAPIDS

	None		At Least One		Total
	No.	Per Cent	No.	Per Cent	No.
Normal	45	63.4	26	36.6	71
Trait	44	69.8	19	30.2	63
Total	89	66.4	45	33.6	134

$X^2 = .37$, d.f. = 1, $p > .5$

Table 42

NUMBERS OF MISCARRIAGES OR STILLBIRTHS OBTAINED BY QUESTIONNAIRE FROM FEMALES IN GRAND RAPIDS

	1	2	3	4	5+	Total
Normal	15	4	4	2	1	26
(%)	57.7	15.4	15.4	7.7	3.8	
Trait	15	2	2	0	0	19
(%)	78.9	10.5	10.5	0	0	
Total	30	6	6	2	1	45
(%)	66.7	13.3	13.3	4.4	2.2	

$X^2 = 3.3$, d.f. = 4, $p > .5$

Table 43

EARLY CHILDHOOD DEATHS REPORTED BY MOTHERS WITH AND WITHOUT SICKLE CELL TRAIT IN GRAND RAPIDS

	None		At Least One		Total
	No.	Per Cent	No.	Per Cent	No.
Normal	63	88.7	8	11.2	71
Trait	54	85.7	9	14.3	63
Total	117	87.3	17	12.7	134

$X^2 = .07$, d.f. = 1, $p > .7$

Eight of the 71 females (11.2 per cent) with normal hemoglobin and nine of 63 (14.3 per cent) with sickle cell trait had a history of at least one childhood death among their children. Again, there is no significant difference between the two groups of mothers (see able 43).

Table 44

PREVALENCE OF USE OF ORAL CONTRACEPTIVES AMONG FEMALES WITH AND WITHOUT SICKLE CELL TRAIT IN LANSING

	Yes		No		Total
	No.	Per Cent	No.	Per Cent	No.
Normal	78	16.7	390	83.3	468
Trait	8	18.2	36	81.8	44

$X^2 = .002$, d.f. = 1, $p > .5$

K. Use of Oral Contraceptives

Table 44 shows the prevalence of the use of oral contraceptives among females with and without sickle cell trait in the Lansing population. Among those with the trait, 18.2 per cent use the pill as compared with 16.7 per cent among the controls.

Twenty-four of the 78 females with normal hemoglobin who take the pill have had problems since taking them while only one of the eight females with trait has had problems. The one trait female who indicated that she had problems,

had not seen a doctor about it. No effort was made to ascertain what the problems were unless the person had seen her doctor about the problem. Of those females (controls) who reported problems with the pill, 18 had seen their doctors. Their problems included weight gain, irregular menses, blood clots, skin rashes, nausea, tenderness in brests, vaginal discharge and kidney problems.

In Grand Rapids 15.8 per cent of normal females use the oral contraceptive as compared with 19.4 of those with sickle cell trait. The difference is not statistically significant (see Table 45).

Table 45

PREVALENCE OF USE OF ORAL CONTRACEPTIVES AMONG FEMALES WITH AND WITHOUT SICKLE CELL TRAIT (GRAND RAPIDS)

	Yes		No		Total
	No.	Per Cent	No.	Per Cent	No.
Normal	13	15.8	69	84.2	82
Trait	14	19.4	58	80.6	72

$X^2 = .14$, d.f. = 1, p .5

Only one of the 13 control females who takes the pill reported a problem, while 5 of the 14 trait females had problems resulting from the use of the pill. Only 3 of the 5 trait women who reported problems had subsequently seen their doctors.

These women indicated that their doctors said their troubles were weight gain, tenderness in breasts and irregular menses.

L. Hematological Indices

Hematological indices were done on several specimens from the Michigan State University Study. The profiles of all of the individuals included in Tables 46 and 47, were made on college students, all between the ages of 18 and 23 years of age.

Means and standard deviations of all determined values show no consistent differences between those with normal hemoglobin and those with trait. It is interesting to note that in almost all of the categories, those individuals with sickle cell trait have higher values (toward the upper limits of "normality") than those with normal hemoglobin in both sexes. When statistical tests were done none were statistically significant, thus confirming previous work demonstrating that the trait does not generally contribute to a tendency to be anemic.

Table 46

COMPARISONS OF MEANS AND STANDARD DEVIATIONS OF SEVEN HEMATOLOGICAL INDICES OF FEMALE COLLEGE STUDENTS WITH NORMAL HEMOGLOBIN AND WITH SICKLE CELL TRAIT

	AA			AS		
	No.	Mean	S.D.	No.	Mean	S.D.
Hemoglobin (g/100 ml)	17	12.7	0.9	16	13.0	0.8
Hematocrit	18	35.8	3.4	16	37.9	2.3
MCV (μ^3)	18	84.0	3.2	16	84.7	6.1
MCH ($\mu\mu$gm)	18	29.4	1.5	16	29.0	2.0
MCHC (g/100 ml)	18	34.6	1.0	16	34.1	1.3
RBC (mil/mm^3)	18	4.22	0.4	16	4.46	18.0
Total Protein (g/100 ml)	17	7.4	0.3	16	7.6	0.2

None statistically significant at .01 level.

Table 47

COMPARISONS OF MEANS AND STANDARD DEVIATIONS OF SEVEN HEMATOLOGICAL INDICES OF MALE COLLEGE STUDENTS WITH NORMAL HEMOGLOBIN AND WITH SICKLE CELL TRAIT

	AA			AS		
	No.	Mean	S.D.	No.	Mean	S.D.
Hemoglobin (g/100 ml)	18	13.8	2.5	15	15.0	1.2
Hematocrit	18	39.3	6.7	15	43.6	3.6
MCV (μ^3)	18	82.3	4.2	15	82.8	6.0
MCH ($\mu\mu$gm)	18	28.8	2.2	14	28.7	1.9
MCHC (g%)	18	34.6	0.9	14	34.3	1.5
RBC (mil/mm^3)	18	4.76	0.9	15	5.29	0.4
Total Protein (g/100 ml)	15	7.72	0.4	8	7.58	0.3

None statistically significant at .01 level.

DISCUSSION

The two populations emphasized in this report are quite different and each offered an opportunity for making reliable observations. The Lansing sample provided an opportunity for ascertaining a reliable estimate of the frequency of the hemoglobin S gene in an urban sub-population of blacks. The Grand Rapids survey provided for an opportunity to make comparisons between approximately equal proportions of individuals with sickle cell trait and normal contols. Nearly every family in this survey had at least one person with sickle cell trait and one or more persons with normal hemoglobin only. The Lansing population, though excellent for gene frequency studies, required making comparisons between large numbers of families and individuals without the hemoglobin S gene and small numbers of persons with the trait. Although the two populations could have been made comparable by the exclusion of all non-S hemoglobin families in Lansing and all probands in Grand Rapids, real trends, if any existed, could be obscured. Moreover, sample sizes would have been greatly reduced. Because of the above factors, and others, careful thought had to be given to the extent of bias and the composition of the populations when various comparisons were made.

A. Prevalence of Heomglobin Types in Lansing Survey

Few studies of frequency of the various abnormal hemoglobins, particularly hemoglobin S, are based on representative samples of defined populations. The reported

prevalence of sickle cell trait among American blacks varies from 6.5 to 14.6 per cent (Diggs, 1933; Myerson et al., 1959; Boyle and Thompson, 1968; Smoot et al., 1961; Switzer, 1950; Petrakis et al., 1970). The average figure is stated as 8.5 per cent (Wintrobe, 1967). In the recent literature, Stultz and his collaborators (1968) reported an attempted complete ascertainment of homozygotes in Erie County, New York. Estimates of heterozygotes, based on mathematical calculations suggest a rate from sickle cell disease of about eight per cent, well within the range of other studies reported in the United States. Myerson et al. (1959) reported the hemoglobin determinations on a series of 1,000 hospitalized black veterans which included comparisons with four other large groups similarly studied in different hospitals. The percentage of individuals shown to have sickle cell trait from these five studies was 8.5 per cent. The prevalence of sickle cell trait in the Lansing population is 8.2 per cent, very similar to other reported prevalences.

The reported incidence of hemoglobin C trait among American blacks ranges from 2 - 3 per cent. In the Lansing sample the incidence of hemoglobin C trait was 2.4 per cent.

Homozygous C disease is estimated to occur in about 1 in 10,000 American blacks. One was discovered in the Lansing survey. Reports on the incidence of sickle cell anemia in the U.S. range from 0.3 - 1.3 per cent. Most of the literature indicates that the homozygous disease occurs in 1 in every 500 births among American blacks (0.2 per cent).

Three (0.16 per cent) persons with sickle cell anemia were found in the Lansing sample.

Fetal hemoglobin comprises approximately 75 per cent of the pigment of cord blood at birth. By the end of the first year of life, it has fallen to its adult level of less than two per cent. Approximately one in 1,000 American blacks (Bradley et al., 1961) retains 20 per cent to 30 per cent of hemoglobin F, even into adulthood, and it appears that this trait is determined by a single Mendelian gene (Rucknagel, 1973). Nine persons (0.48 per cent) in the Lansing sample were diagnosed as heterozygotes for high persistence of fetal hemoglobin (HPFH). Four of these were in one family (a mother and three of five children).

Approximately one per cent of American blacks have beta-thalassemia trait (Goldstein et al., 1964). The most outstanding feature is that the proportion of hemoglobin A_2 is double the normal proportion of two to three per cent. Other forms of thalassemia are presently an enigma concerning both their genetics and their biochemistry. A form characterized by modest elevation of fetal hemoglobin (8-10 per cent), and normal or low levels of hemoglobin A_2 in the heterozygous state has been designated as beta delta-thalassemia (Weatherall, 1967 and Fessas, 1966). The prevalence of this latter form among American blacks has not been estimated. Eight individuals (.43 per cent) in the sample were diagnosed as thalassemia minor (beta-thalassemia heterozygotes or beta delta-thalassemia heterozygotes).

The prevalence figures of the various hemoglobin types diagnosed in the Lansing sample, are in excellent agreement with other, less randomized samples.

B. Prevalence of Hemoglobin Types in Grand Rapids

Because of the method of ascertainment in the Grand Rapids survey, the prevalence figures for the various hemoglobin types are not as would be expected in a random sample. The family studies began with 309 probands previously identified in a school-wide screening program in the city. The screening procedure was comprised of an automated solubility test, incapable of identifying non-sickling hemoglobins other than hemoglobin A.

It was expected that greater than 50 per cent of the persons diagnosed would have at least one gene for the production of sickling hemoglobin (including the probands). It was found that 51.8 per cent had no sickling hemoglobin and 48.2 per cent had at least one sickling hemoglobin. When the probands were excluded, 164 of 497 (33 per cent) were found to have at least one gene for the production of hemoglobin S. Approximately 50 per cent were expected. When an analysis was made by including only those sibships where both parents had been diagnosed and excluding one proband per family, only 39 per cent of the sibs were found to have sickle cell trait. This represents a significant difference in the proportion of trait persons expected (Chi square = 7, d.f. = 1, $p < .01$). A similar analysis in the Lansing sample revealed that 34 per cent of the sibs were carriers while 66 per cent had normal hemoglobin (Chi square = 10.24).

In every family included, the parents indicated that they were the biological parents and laboratory diagnosis for hemoglobin types among the parents and offspring failed to disprove this. It is unlikely that illegitimacy would be responsible for these differences.

An estimate was made of illegitimacy in the Lansing population where there were many matings of normal by normal parents. There was one case of illegitimacy detected in this population where the gene frequency for hemoglobin S was .043. The estimate of illegitimacy was determined to be .0605, providing evidence that it is unlikely that this would explain the small proportion of trait persons in these two populations.

These findings, along with those implied by the relatively fewer number of trait children in the age trend analysis, are provocative enough to suggest more definitive studies with respect to determining if there is a higher mortality rate in the younger age groups among persons with sickle cell trait.

C. Awareness of Sickle Cell Anemia

A surprisingly large percentage of adults in both cities indicated that they had heard of sickle cell anemia before. This may have been the result of public awareness through the various news media in both cities prior to the testing programs. In a similar survey conducted by Lane and Scott in Richmond, Virginia in 1968, only three out of ten adult blacks had ever heard of sickle cell anemia.

Another striking finding in the Richmond study was that the level of awareness of the disease was strongly related to the educational level achieved by the individuals. This was clearly confirmed in the Lansing and Grand Rapids surveys.

D. General Health

In the Lansing sample, a significantly greater proportion of persons with sickle cell trait had their general health described as fair or poor. The age group that was the most disproportionate was the 0-12 age goup. There were 621 children with normal hemoglobin in the age group of 0-12 years. Fifty-nine (9.5 per cent) had their health described as fair or poor . There were 47 trait children in this age group and eight (17 per cent) of them were described as having fair or poor general health. In most previous epidemiological studies comparing sickle cell trait with normal controls, children were not included. Also, previously reported cases did not inquire of each person's general health. Therefore, it is not possible to compare these findings with other studies.

In the Grand Rapids survey there was no significant difference in general health between trait and normal individuals.

E. Drug, Tobacco and Alcohol Usage

There was no significant difference in the prevalences of the use of drugs or tobacco in either of the two populations. However, in the Lansing sample, a significantly greater proportion of trait adults consumed alcoholic beverages regularly. As mentioned earlier, only four adults

with or without sickle cell trait in the Grand Rapids population admitted to regular consumption of alcoholic beverages. This difference in the two populations is difficult to explain. However, it is doubtful that interviewing techniques were responsible for these differneces.

These questions were asked to find out if trait persons would be more likely to show symptoms of sickling due to frequent consumption of agents that might induce in vivo sickling and/or consume drugs more frequently that would relieve pain that might be associated with in vivo sickling.

F. Symptoms of Health Problems

1. Ophthalmologic and Hearing Problems

When comparisons were made in the separate samples, there was no significant difference between the normal controls and trait persons in the use of glasses and hearing aids.

2. Infections

In the separately tabulated populations there were no differences between subjects with and without trait for infections, except in Lansing, the prevalence of sore throat, which occurred more frequently among the controls. It was expected that if differences were observed in the category of infections, they would be more prevalent among subjects with sickle cell trait.

3. Symptoms of Anemia

Among the symptoms of anemia, sense of exhaustion was the only variable significantly associated with sickle cell trait in Lansing. The magnitude of association was very

low, as with other variables associated with the trait.

4. Musculoskeletal Symptoms

Weakness in legs and pain in bones were the two variables significantly associated with the trait in the Lansing sample and swollen joints in the Grand Rapids survey. The magnitude of association in each of these is also low.

5. Genitourinary Problems

In the separate samples of thetwo cities, the prevalences of genitourinary problems were so small that statistical analysis would be meaningless. The most frequently reported and established problems among persons with sickle cell trait are hematuria, hyposthenuria and renal infarction. Also, among women with sickle cell trait, there is an increased incidence of pyeleonephritis and urinary tract infection and among men with the trait there are many reported cases of priapism. None of these hold true in the two populations in this study.

6. Cardiovascular and Gastrointestinal Problems

There were no differences in either population for any of the cardiovascular or gastrointestinal problems asked about. It was not expected that there would be any differences in the cardiovascular symptoms, except by chance. In the gastrointestinal symptomatology, if differences had been observed, the greater prevalences would have been expected to occur among trait persons.

7. Epistaxis

This condition was significantly more prevalent among trait persons in the Lansing survey and in the Grand Rapids tabulation which included the probands. However, when the probands were removed from the tabulation, the proportion of trait and normal persons was almost identical.

8. Neurologic Problems

There were no significant differences between trait and normal persons in any of the neurologic symptoms in the Lansing sample and none in this category in the Grand Rapids survey that excluded probands. However, the total surveyed Grand Rapids population showed a significantly greater proportion of trait persons with numbness in legs.

Analysis of the responses related to health symptomatology reveals in the Lansing random sample that only four of the 34 variables were significantly associated with sickle cell trait and one significantly associated with the normal controls.

In the Grand Rapids survey, excluding probands, only swollen joints was significantly associated with the trait. In addition to swollen joint problems, epistaxis and numbness in legs were significantly associated with the trait before the exclusion of the 146 probands. Since probands were all school-aged children, this finding would suggest that these symptoms might in some fashion be age related.

When a single test of association of overall health was made by categorizing respondents into "sick" and "well",

there was no statistical difference between trait and normal respondents in either of the two populations.

Further analysis of age specific relative odds ratios for sickness and general health were made for the Lansing sample because it was observed that there were relatively fewer children with sickle cell trait in this population and a greater proportion of them (trait subjects) had their health described as fair or poor.

The age specific relative odds ratios for sickness among trait persons do not show a specific age related pattern, but does show an increasing proportion of "sick" subjects among both traits and normal controls (with one exception among trait subjects).

The trend in age specific relative odds ratios for good or bad health is quite clear. The younger the trait individuals, the more likely (e.g., 0-17 nearly twice as likely) they are to view themselves (or parents view them) in bad health. This trend holds even with the increasing bad health risk, that is, the risk of bad health for traits and normals increases with age, but relative risk decreases. Hence, somewhat contrary to the age trend of poorer health, the younger trait individuals are at greater relative risk.

G. Age Trends

The observed data relating to age trends among subjects with sickle cell trait in the Lansing sample do not show a decrease in the proportion of carriers in the older age groups. If the carrier state were associated with an

increased mortality as several reports have indicated (Neel, 1951; Rucknagel and Neel, 1961; Pollitzer, 1958), one would expect a significant decrease in the proportion of carriers in the older age groups. These observed data are in agreement with the data of Petrakis et al. (1970), McCormick and Kasgarian (1965) and Heller (1968).

H. Pregnancy History

No significant differences in primary or secondary fertility were observed in either of the two populations of females of reproductive age. The mean number of pregnancies among females in the Grand Rapids survey (trait and normal controls) was 5.5.

The frequency with which sickle cell trait is encountered in pregnant black women in this country is not clear. Jenkins and Clark (1962) identified it in less than five per cent of their subjects, while Switzer and Fouche (1948) reported a frequency of more than 14 per cent. Possible criticisms of these studies, as well as the present one, are the small numbers of patients evaluated.

That the sickle cell trait group was similar to the normals with respect to miscarriages, stillbirths, secondary fertility and number of children living, is in agreement with several hospital and clinic studies reported in the literature (Adams et al., 1953; Whalley et al., 1963; Hendrickse and Watson-Williams, 1966; Abrams, 1959; Beacham and Beacham, 1960).

No differences were seen in responses of females (14 years of age or older) to questions concerning the use of oral contraceptives and problems as a result of using them.

The health-problem symptoms asked about in the interview were those that frequently occur in individuals regardless of whether they have sickle cell anemia or sickle cell trait or normal hemoglobin. Even in individuals with sickle cell anemia, these symptoms may or may not present themselves from time to time. Because of these protean symptoms, sickle cell anemia has frequently been referred to as the great "mimicker". If this type of variability of symptomatology exists among those individuals with sickle cell anemia, then the variability would be even more subtle among those individuals with sickle cell trait.

SUMMARY

A survey was undertaken to obtain a reliable estimate of the prevalence of sickle cell trait and to gather evidence for its effect on blacks in three Michigan populations. The results of the observations are listed below:

1. The prevalence of sickle cell trait in the randomly selected sample of Lansing, Michigan was 8.2 per cent. This frequency is very similar to previously reported, but less systematically sampled populations in the United States.

2. Sixty per cent of 1,097 black adults surveyed in Lansing and Grand Rapids had heard of sickle cell anemia at the time of the interview. Eighty per cent of those who had heard of the disease indicated that they knew it was inherited.

3. A comparison of general health as obtained by questionnaire from 1,755 subjects with and without sickle cell trait in the Lansing sample revealed a significantly greater proportion of trait persons who described their health as fair or poor. A similar comparison among 633 subjects in the Grand Rapids survey revealed no significant difference in response between heterozygotes and homozygous normals.

4. Responses to 34 items pertaining to health problems and symptoms revealed only four which were significantly associated with sickle cell trait in the Lansing sample (sense of exhaustion, weakness in legs, pain in bones and epistaxis)

and only three in the Grand Rapids survey (swollen joints, numbness in legs and epistaxis). No significant difference was found between trait and normal individuals in terms of the number of these symptoms more or less frequent in either group.

5. Further analysis by a single test of association of health problems and sickle cell trait revealed no significant difference between trait and control subjects.

6. In the Lansing sample there were significantly fewer trait persons in the younger age groups and a significantly greater proportion of these children had their general health described as fair or poor. These observations indicate that the younger trait individuals may be at a greater risk.

7. An age trend analysis among trait subjects in the random sample does not show a decrease in the proportion of carriers in the older age groups, providing no evidence that the carrier state is associated with an increased mortality. However, an analysis of sibships containing children with sickle cell trait revealed that significantly fewer than expected trait children were found.

8. Neither of the populations revealed a differential in primary or secondary infertility among females with sickle cell trait. Nor was there any statistical difference between trait and control females of reproductive age for miscarriages or stillbirths or number of children living.

9. The proportions of trait and normal females using oral contraceptives were similar and no statistical difference in problems resulting from the use of contraceptives was ascertained.

10. A comparison of means and standard deviations of seven hematological indices between trait and normal subjects revealed no significant differences. These findings confirm previous reports demonstrating that the trait does not generally contribute to a tendency to be anemic.

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APPENDIX A

LETTER OF INTRODUCTION

APPENDIX B

HEALTH SURVEY AND QUESTIONNAIRE

MICHIGAN STATE UNIVERSITY EAST LANSING • MICHIGAN 48823

CENTER FOR URBAN AFFAIRS • OWEN GRADUATE CENTER

July 28, 1971

Dear Lansing Resident:

Do you know that if you are black, the chances are about 1 in 10 that you carry a gene for sickle cell anemia (SCA)?

Do you know that if you carry a gene for this inherited disorder that the chances are 1 in 2 that you may pass this gene on to your children?

SO WHAT?!?

Carriers of the gene for sickle cell anemia often have no idea that they have this gene which can have harmful effects on the individual. Frequently the effects of this gene are so similar to other sicknesses that they are often overlooked by doctors.

Because of the high prevalence of this gene among blacks, we, the black members of the genetics group of the department of zoology, feel that all blacks should know if they have this gene. Therefore, we, in collaboration with the Model Cities health program and the Ingham County Health Department, will be coming into your neighborhood to offer a quick, easy test. You owe it to yourself and to your children to obtain this free, important information.

Beginning August 2, 1971, our team will be in your neighborhood days and evenings for the test. At this time we would like to ask you a few questions about your family's health and give the test to as many family members as possible, especially all parents and adults in your household.

Approximately one week following the testing you will be notified of the results (positive or negative). If your test is positive, we will provide you with free additional information, genetic counseling and inform your doctor if you desire. Also, we can refer you to a doctor for help in medical management in case of complications.

Respectfully,

Frankie J. Brown,
Graduate Student

Astrid K. Mack,
Graduate Student

Ajovi Scott-Emuakpor, PHD.
Ass't. Prof.

Department of Zoology

GENERAL OBJECTIVES

1. To obtain a reliable estimate of the frequency of the sickle cell gene in the Black population. Previous United States studies exploring this question have largely employed non-systematic sampling procedures, institutionalized populations, and the like.

2. To investigate the overall effect of the gene for sickle cell anemia on the health of the Black population. It has been claimed that there is a higher incidence of certain clinical symptoms and more diffuse patterns of social adjustment among persons with one gene for sickle cell anemia than in persons without this gene.

3. To make the public aware of Sickle Cell Anemia, its mode of inheritance, and its manifestations as a major health problem of the Black community so as to encourage more funding, research and better management of the disease.

4. To identify carriers and those with the disease so that persons with health problems related to this disease may be able to take advantage of existing treatments for the disease.

5. To establish referral services so that individuals with the disease may be sent to centers for effective treatment to be employed.

6. To provide genetic counseling, based on information from this study.

PURPOSE AND INSTRUCTIONS FOR THE HEALTH SURVEY

General Introduction

1. Sample every dwelling unit - addresses and apartment numbers will be provided.

2. If addressee designated is not at home, note this and make arrangements to return later, leave cards with number to call.

3. Sample household in DU - i.e., the entire group of persons who live in one dwelling unit. It may be several persons living together or one person living alone. It may include more than one family. For our purposes, we are interested in obtaining health data and blood samples from as many individuals as possible. We are especially interested in getting blood samples from all biological parents of the children in each dwelling unit and all other adults.

4. One health questionnaire should be completed for all members of one nuclear family - i.e. father, mother, and children. In cases where several families occupy one dwelling unit (household) or where there is an extended family situation a separate questionnaire should be completed for each nuclear family (see instructions for question #1).

5. Do not request health information on absentee members who are more or less continually away, e.g. persons away in the service, in an institution, etc. but these should be noted in remarks.

6. Health information should be obtained about all family members from whom we may potentially obtain blood samples even though some of the family may refuse to give blood at the time of the interview.

INTERVIEWER RESPONSIBILITIES AND BEHAVIOR IN THE COLLECTION OF THE INFORMATION

A. Introduction

1. Every question in the questionnaire is here because of a need to obtain information to help us determine the effects of the gene for SCA on the health of its possessors.

2. There should be no act or mannerism or any statement or other indication of judgement by you as to "good or bad" in terms of social acceptance of any topic in the course of the interview.

3. Even if you feel that a given question might be personnally offensive, not all respondents would agree. Experience has shown that most people are willing to give the information sought if an adequate explanation is given about the purpose and the needs.

4. Analysis and use of these data are designed to obtain accurate frequency estimates and effects of the SCA gene on the health of the Black community, to help us recommend better management procedures for this disease. The information sought is respectfully requested of the household as a gift of time and information. This gift should be given and received in dignity. It must not be demanded nor obtained by coercion. A refusal is the perogative of the respondent; it is no personal affront, but the expression of a fundamental human right.

B. Your Responsibility in Contact With the Public

In collecting information, the first responsibility is to maintain a high standard of accuracy in the data which you record on the questionnaires. To honor this responsibility and as a representative of the Sickle Cell Anemia Testing Program, you are expected to conduct each interview in a straight-forward business-like way and to conduct each interview in such a manner as to reflect credit to the profession of which you are a part. Some of your respondents may seek advice from you regarding health matters; for example, you might be asked for your views on fats in the diet, the relation of smoking to lung cancer, or the like. You should avoid giving advice on any subject whatsoever. Refer them to the clinic or a doctor. You should also avoid conversation which is not directed at the details you desire. You should refrain from any discussion of politics, religion, sex, income or other topics which may cause unrelated conversation or create an unprofessional atmosphere.

Having found the specified sample dwelling unit, you should identify yourself, and briefly state the purpose of the visit. If not invited in immediately, you should add, "May I come in?" If the respondent appears to be reluctant, you should further explain the purpose and add, "May I come in and talk with you about it?" If there is still no response, request an appointment at a later time. Lengthy discussion should be avoided. The interview should NOT be conducted at the door; for the sake of consistency, the results should be obtained in a setting which will allow careful consideration and recording.

The introduction should serve to:

1. Let the respondent know who you are and why you are there.
2. Set the scene and arrange for you to conduct the health appraisal interview.
3. Point out all information about individuals and families will be held strictly confidential and will be seen only by scientists and health and medical professionals. The information about individuals will not be revealed to any other agency, local, state or federal, although summary information for groups of blocks or larger areas will be usable by all.

You should be prepared to discuss and explain the purpose and philosophy of the project.

You will find that most respondents will accept a brief explanation in the introduction. However, there will be a few who will want more information, or who may actually refuse to be interviewed for a variety of reasons. Their attitudes and intentions are their own and are to be honored at all times.

Our experience has been that very few respondents actually refuse to cooperate. However, if you have difficulty in obtaining an interview, explain the purpose and importance of the project and stress the

confidential treatment accorded all information furnished by the respondent. This should be done also at any point during the interview if the respondent should hesitate to answer certain questions.

If the respondent states that she has no time right now for an interview, find out when you can come back. However, always assume (without asking) that the respondent has the time right now unless she tells you otherwise.

C. Selection of Respondent

The wife or mother is the preferred respondent. If she is not at home at the initial visit, arrange to return when you can talk to her. Another adult may be interviewed if the spouse so desires. People present may respond for themselves, but usually a parent's interpretation of an illness should be accepted if conflicting statements are given by child and mother.

When there is no obvious "mother" and if the opportunity presents itself choose as a respondent the adult in the family who seems most likely to know the family's health.

D. Confidentiality

Collection of valid information on any topic, and particularly on matters related to health or ill health, requires the establishment and constant maintenance of confidnece on the part of the respondent. A prime requisite for establishing proper rapport is a clear understanding of how the information will be used and, more importantly, that it will not be misused.

In most instances, the legitimacy of your mission will not be questioned. When it is, considerable effort on your part may be required. The information will be used only as a part of a scientific and statistical picture, and will not be used in any way which would be harmful to anyone. You can reinforce this by describing the care that is taken: This project uses the same kinds of protection controls as the U.S. Census; while in your possession, any completed questionnaires are kept in special folders and your car is locked when not in use; no unauthorized person is ever permitted to see the forms and, at all points of handling, strict security is maintained. Names and addresses will not be used except for the necessary purpose of making sure that the recorded information is for the person to whom it refers and for sending test results. The responses obtained are summarized and shown only in the form of statistical summaries, in groupings such as age, sex, or neighborhood, so that published details cannot be traced back to families nor to individuals.

E. Interviewing Techniques

Your greatest asset in conducting an interview efficiently is to combine a friendly attitude with a business-like manner. If a respondent's conversation wanders away from the interview, try to cut it off tactfully - preferably by asking the next question on the questionnaire. Over-friendliness and concern on your part about the respondent's personal troubles may actually lead to your obtaining less information.

Start each section by asking the questions as worded on the record. Listen to the respondent until she finishes her statement. (Failure to do so can result in your putting down incorrect or incomplete entries). The two most common types of errors made in this regard are:

1. Failure to listen to the last half of the sentence because you are busy recording the first half.
2. Interrupting the respondent before she has finished, especially if the respondent hesitates. A respondent often hesitates when trying to recollect some fact, and you should allow sufficient time for this to be done. Also, people will sometimes answer "I don't know" at first, when actually they are merely considering a question. When you think that this may be the situation, wait for the respondent to finish the statement before repeating the question or asking an additional question.

Sometimes a person will give you an answer which does not furnish the kind of information you need or one which is not complete. You should always ask additional questions in such cases, being careful to encourage the respondent to explain without your suggesting what the response "should be". In all sections of the questionnaire, you should ask as many questions as necessary to satisfy yourself that you have obtained complete and accurate information insofar as the respondent is able to give it to you. NEVER frame a question in the negative (eg. "You don't have any heart trouble, do you?").

Every effort should be made to encourage the respondent to give specific and complete answers to the questions. Sometimes the respondent doesn't have the information needed to answer a question. In such cases, you should enter "DK" for "don't know" or enter a check in the space for the answer. Ask additional questions as required in order to get a recordable answer, but you should not probe beyond the intent of the question.

Record any pertinent remarks which the respondent may volunteer. Do this at any point in the questionnaire, even though the information may have to do with some question other than the one you are dealing with. Later, you can make the needed cross-referencing.

There may be some items of information which the respondent doesn't know, for example, height of child. In such cases, you should enter "DK" for "don't know". Do not leave any items blank where entries

are required. If the respondent refuses to give the required information for a particular item and still is unwilling to give it after you have explained how the information is protected for confidentiality, you should enter "Ref." for refused in the "DK" column.

F. Making Contact with the Household

1. Having selected the dwelling unit for health appraisal work and blood sampling, inquiry as to persons, relationships and location of the people will verify the place as the true dwelling unit and will raise questions which will help determine whether more than one set of health records is indicated.
2. Absent households - Since a household respondent is required, you need to find out who she is and when she is likely to be at home. Housekeepers, babysitters, neighbors and even small children will be helpful. Some night visits will be required and Saturday is usually a good day to catch working people at home.
3. The respondent is at home but says she is too busy - If she says so, she is. But she may be just putting you off: If you think that is the case, ask if you could take a few minutes to tell her about it. This should result in completing the interview at the time. If not, set a definite appointment for a return visit.
4. Procedure for handling call backs - Always try to complete the interview at your first visit to the dwelling unit. However, there will be cases where no one is at home during the day and an evening or Saturday call will be required. These are often working people and they must be equally represented in the results. Your work schedule should be arranged so that the necessary evening calls can be made.

AN ENTHUSIASTIC AND EARNEST ATTITUDE IS PERHAPS THE MOST IMPORTANT - AND YET UNSPOKEN - ASPECT OF YOUR ABILITY TO OBTAIN RELIABLE AND COMPLETE INFORMATION.

Sample Group_____

Address and Description of Location
(Include apt. number)

_____ Family Sample Nos._____

_____ _____

_____ _____

Telephone No._____

Scheduled Appointment_____

Best Time to Visit_____

Signature_____

Not Completed (Check One)

_____Household refusal

_____Extended Absence

_____Other (Specify)

Record of Calls to Complete Interview:_____

Date: ____/____/____

Date: ____/____/____

Time Interview Began_____

Time Interview Completed_____
Mo. Day Yr.

Interviewer_____

No. Bloods to be Drawn_____

Date of Drawing_____

Time of Drawing_____

Sample Block #_____

1.	What is the name of the head of this family? (Continue with other household members. At the end ask:) "Is there anyone else, anyone temporarily away, any baby not mentioned?" (Circle respondent number)	1.	2.
2.	How is --- related to the head of this family? (Are all children of this marriage? - if appropriate). (Specify)		
3.	Sex (Circle)	M F	M F
4.	Before being contacted by this group, had you ever heard of sickle cell anemia? (Ask adults only). (Circle)	Yes No DK	Yes No DK
5.	Before being contacted by this group, did you know that sickle cell anemia is an inherited kind of anemia and is passed from parent to offspring? (Circle)	Yes No DK	Yes No DK
6.	Would you say that (---'s) general health is excellent, good, fair, or poor? (Circle)	1. Excellent 2. Good 3. Fair 4. Poor 5. DK	1. Excellent 2. Good 3. Fair 4. Poor 5. DK
7.	When was --- born? (Date)		
8.	In what state was --- born? (Specify) (State or Country)		
9.	What is the highest grade (or years) of school --- last attended (or is now attending)? (Number)		

REMARKS:

M F	M F	M F	M F	M F
Yes No DK	Yes No DK	Yes No DK	Yes No DK	Yes No DK
Yes No DK	Yes No DK	Yes No DK	Yes No DK	Yes No DK
1. Excellent 2. Good 3. Fair 4. Poor 5. DK	1. Excellent 2. Good 3. Fair 4. Poor 5. DK	1. Excellent 2. Good 3. Fair 4. Poor 5. DK	1. Excellent 2. Good 3. Fair 4. Poor 5. DK	1. Excellent 2. Good 3. Fair 4. Poor 5. DK

10. What is ---'s height? (specify)	Ft. In. DK	Ft. In. DK
11. What is ---'s weight? (specify)	Lbs. DK	Lbs. DK
12. What is ---'s current work status? (Probe as needed to enter code for each person aged 14 or older). Working at a job or business - Full time .....01 Part time .....02 Incidental.....03 Not working.....04 DK as to work status.....09 (Enter appropriate code #)	code	code
IF CODED 02, 03, OR 04 UNDER WORK STATUS a. Is --- not working full time because of illness or some disability? (circle)	Yes No DK	Yes No DK
IF YES b. What is the illness or disability? (specify)		
c. How long has --- been limited in his ability to wrok because of this? (specify)		

REMARKS:

Ft. In. DK	Ft. In. DK	Ft. In DK	Ft. In. DK	Ft. In.
Lbs. DK	Lbs. DK	Lbs. DK	Lbs. DK	Lbs.
Code	Code	Code	Code	Code

13. Does anyone, on most days or every day: Yes No DK Yes No DK

a. Wear glasses or contact lenses?

b. Use a hearing aid?

c. Smoke cigarettes?

d. Use patent medicines or "pain killers"?

(specify what and reason)

e. Use any drug prescribed by doctor?

(specify what and reason)

f. Drink any alcoholic beverages?

g. Take "relaxing" pills?

14. How many times in the past year has --- had a cold?

(specify)

(If at least once, ask: Did --- see a doctor for it (them)? How many times?

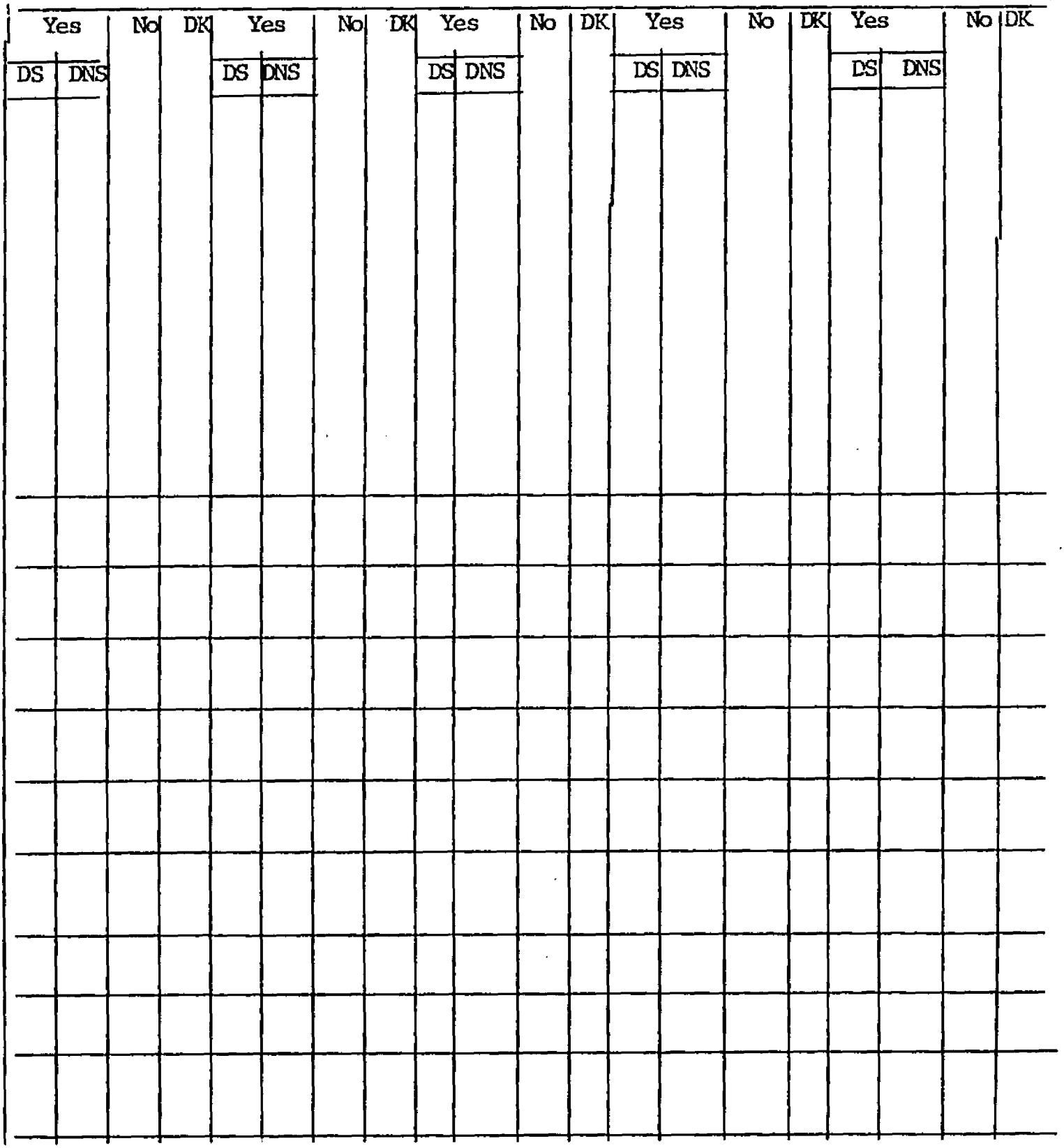
(specify)

REMARKS:

Yes	No	DK	Yes	No	DK	Yes	No	DK	Yes	No	DK	Yes	No	DK
DS	DNS	DK	DS	DNS	DK	DS	DNS	DK	DS	DNS	DK	DS	DNS	DK

15. In the past year has --- had trouble with any of the following conditions or diseases? (If yes) Did --- see a doctor about it? (check) (If yes) Was --- rushed to see a doctor or to the hospital for this? (Double check) (If yes) Was --- required to be in a hospital overnight or longer? (X) (How many days?) (If yes) Did the illness cause --- to be away from his usual activities? (XX) (How many days?)	Yes		No	DK	Yes		No	DK
	DS	DNS			DS	DNS		
a. Flu?								
b. Jaundice?								
c. High blood pressure?								
d. Low blood pressure?								
e. Blood in stool?								
f. Blood in urine?								
g. Blood in sputum?								
h. Nosebleeds?								
i. Faintness?								

REMARKS:


Yes
No
DK
Yes
No
DK
Yes
No
DK
Yes
No
DK
Yes
No
DK
DS
DNS
DS
DNS
DS
DNS
DS
DNS
DS
DNS

15. cont'd.	Yes		No	DK	Yes		No	DK
	DS	DNS			DS	DNS		
j. Shortness of breath?								
k. Trouble breathing?								
l. Tire easily (easy fatigue)?								
m. Sense of exhaustion?								
n. Pain in chest?								
o. Dizziness?								
p. Confusion and disorientation?								
q. Convulsions?								
r. Sore throat?								
s. Swelling joints?								
t. Painful joints?								
u. Muscle pain?								
v. Weakness in legs?								
w. Numbness in legs?								

REMARKS:

Yes		No	DK	Yes		No	DK	Yes		No	DK	Yes		No	DK	Yes		No	DK
DS	DNS			DS	DNS			DS	DNS			DS	DNS			DS	DNS		

15. cont'd.	Yes		No	DK	Yes		No	DK
	DS	DNS			DS	DNS		
x. Pain in bones:								
y. Kidney or bladder trouble?								
z. Liver trouble								
aa. Increased urine flow?								
bb. Pain in stomach or abdomen?								
cc. Excessive formation of tissue? (unusual growth - tumor)								
dd. Ulcers (sores)? -- Leg, foot or arm								
ee. Earaches?								
ff. Diarrhea or loose bowels?								
gg. Vaginal discharge? (females only)								
hh. Persistent erection penis without sexual excitement (priapism)? (males only)								

REMARKS:

Yes		No	DK	Yes		No	DK	Yes		No	DK	Yes		No	DK	Yes		No	DK
DS	DNS			DS	DNS			DS	DNS			DS	DNS			DS	DNS		

16.	In the past year has --- been seen by a doctor because of any other illness? (If yes) What was it? (If yes) Was it an emergency? (double check) (If yes) Was --- required to be in a hospital overnight or longer? (X) How many days? (If yes) Did the illness cause --- to be away from is usual activities? (XX) (How many days?)	Yes	No	DK	Yes	No	DK
a.	What?						
b.	What?						
c.	What?						
d.	What?						
17.	How many pregnancies has each female had? (Number or DK)						
a.	Has there been any trouble connected with any pregnancy? (Circle) (Specify)	Yes	No	DK	Yes	No	DK
b.	Have there been any miscarriages or stillbirths? (Number or DK)	Misc.		Still.	Misc.		Still.

REMARKS:

Yes	No	DK	Yes	No	DK	Yes	No	DK	Yes	No	DK	Yes	No	DK
Yes	No	DK	Yes	No	DK	Yes	No	DK	Yes	No	DK	Yes	No	DK
Misc.	Still.		Misc.	Still.		Misc.	Still.		Misc.	Still.		Misc.	Still.	

17. cont'd. c. Any early childhood deaths or other deceased family members? (Circle) (If yes) Age at death: ____ ____ ____ Cause of death: _____	Yes No DK	Yes No DK
d. How many children are now living? (Number or DK)		
e. Is anyone taking birth control pills? (females only) (Circle)	Yes No DK	Yes No DK
f. Have there been any problems noticed since --- has been taking the contraceptives? (Circle)	Yes No DK	Yes No DK
(If yes) Was a doctor seen? (Circle) (If yes) What did the doctor say the trouble was?	Yes No DK	Yes No DK

REMARKS:

Yes No DK	Yes No DK	Yes No DK	Yes No DK	Yes No DK
Yes No DK	Yes No DK	Yes No DK	Yes No DK	Yes No DK
Yes No DK	Yes No DK	Yes No DK	Yes No DK	Yes No DK
Yes No DK	Yes No DK	Yes No DK	Yes No DK	Yes No DK
Yes No DK	Yes No DK	Yes No DK	Yes No DK	Yes No DK

18. FAMILY INCOME. Now I'd like to show you a table which shows the broad levels of income and ask you to tell me the number next to the amount which comes closest to the combined total income which all members of your household received during the past 12 months. We would like it to be as close as you can estimate, but we don't want it any closer than the broad levels shown. (Include the combined incomes, before tax or other deductions, of all members of the family. Where the income is from other than salaries or wages, gross profit before deductions determines the level).

LEVEL OF FAMILY INCOME DURING PAST 12 MONTHS

A.	$2,499 or below	D.	$7,500 - above
B.	$2,500 - $4,499	E.	DK
C.	$5,000 - $7,499		

(Circle appropriate code letter)

19. Do you know of anyone in your family who has sickle - cell anemia? (Circle) Yes No DK

(If yes) specify

REMARKS:

3.	4.	150 5.	6.	7.

APPENDIX C

QUESTIONNAIRES USED IN MICHIGAN STATE UNIVERSITY SURVEY

Please fill out the following questionnaire completely.
Information is confidential and for use in this project only.

Name_____
Last First Middle

Address_____

Student No._____ Date of Birth_____

Birthplace_____ Age_____

PART II

1. Before being contacted by this group, had you ever heard of Sickle Cell Anemia (SCA)? yes no (circle one)

2. Did you know that SCA is an inherited abnormality and is transmitted from parent to offspring? yes no

3. Do you know of anyone in your family who has SCA? yes no

4. How many sisters and brothers do you have?

LIVING	DEAD **
No. _____	No. ____

**Cause of death_____

**Age at death_____

5. Is your general health: Good_____, Fair_____, Poor_____.

PART III: Check at the left all of the following which apply now or in the past:

Yes	Check at left	Yes	Check at left
____	Easy fatigue	____	High blood pressure
____	Sense of exhaustion	____	Low blood pressure
____	Pneumonia	____	Swelling or painful joints
____	Pain in chest	____	Dizziness
____	Shortness of breath	____	Kidney disease
____	Poor appetite	____	Sugar or albumin in urine
____	Jaundice	____	Stomach, liver, or intestinal trouble