Age Trends in the Prevalence of the Sickle Cell Trait

D. T. JANERICH, DDS, MPH, J. H. KELLY, MD, F. D. ZIEGLER, PhD, S. SELVIN, PhD, I. H. PORTER, MD, J. B. ROBINSON, MD, and R. C. HERDMAN, MD

INFORMATION on the age-specific prevalence of the sickle cell trait has played an important part in the development of the presently held theory that explains the prevalence of sickle cell trait and anemia in terms of malarial resistance. The agreement between predicted and observed patterns in the age-specific prevalence of the trait has been used to supplement clinical data suggesting that the sickle cell trait helps protect a person from malaria (*1*). African studies (2,3) have shown an increase in prevalence of the trait with age. It was assumed that this pattern of increasing prevalence with age was evidence that carriers of the trait survived longer than their unaffected counterparts, thus raising the ratio of trait to nontrait persons in the older population.

Early studies in the United States, where malaria has not been a significant health threat, suggested that the prevalence of the sickle cell trait declined with age (*4–7*). This result was interpreted as conforming to the theoretical expectation and as suggesting that carriers had poorer survival rates than noncarriers in nonmalarial areas. These studies were based on data from hospital and clinic patients. In 1961 Rucknagel and Neel (*8*) noted that ". . . the outstanding gap in our knowledge of the population genetics of hemoglobin S is the question of age-incidence trends under nontropical conditions."

In 1965, McCormick and Kashgarian (*9*), using autopsy material to examine the relationship of the patient's age at death with the sickle cell trait, found no evidence that the trait was associated with increased age-specific mortality. The age-specific prevalence of sickle cell trait reported in a 1968 study based on a random sample of black adults in South Carolina also produced no evidence of selective mortality associated with the trait (*10*). The question, therefore, regarding age-specific trends under nontropical conditions seems as relevant today as in 1961.

Lack of an answer to this question poses imme-

All the authors except Dr. Kelly and Dr. Selvin are with the New York State Department of Health, Albany. Dr. Janerich is director of the Division of Epidemiology and Population Genetics, Birth Defects Institute, and Dr. Porter is that institute's director. Dr. Ziegler is senior research scientist, Division of Laboratories and Research. Dr. Robinson is director of the Sickle Cell Program. Dr. Herdman is deputy commissioner for research and development.

Dr. Kelly, formerly a clinical pathologist in the department, is now director of the Bender Hygienic Laboratory in Albany, and Dr. Selvin is assistant professor, School of Public Health, University of California, Berkeley.

Tearsheet requests to Dwight T. Janerich, DDS, Director, Epidemiology and Population Genetics, Birth Defects Institute, State Department of Health, Albany, N.Y. 12208.

diate and practical problems for persons who have the trait because many life insurance companies increase premium costs for carriers. Although this practice is not universal, approximately half of the 45 insurance companies we recently surveyed had increased their premiums for carriers of the sickle cell trait, presumably because the trait was believed to be associated with reduced life expectancy.

Our report summarizes selected data from sickle cell screening programs with voluntary participants in New York State (exclusive of New York City). The data were generated as part of the comprehensive sickle cell program established by the New York State Department of Health. The project includes a statewide educational program, central laboratory facilities, and regional genetic counseling programs. The availability of this relatively large set of data from a U.S. population allowed us the opportunity to reexamine the question of age-specific trends for sickle cell trait.

Methods

The tests reported here were performed by the New York State Department of Health Laboratories in Albany. Specimens were submitted to the Albany laboratory in mailing kits specifically developed for the sickle cell program. The data included are from the initial phase of the program, which ended June 30, 1972.

To make the data as representative of the general population as possible, we excluded subsets in which the data were affected by an obvious selection bias. Examples of these excluded sets are data from family followup screening where other family members were tested after a person with an initial positive test result had been identified in that family, data from program areas in which any pretesting had been done, and data from tests performed during any type of hospital admission.

Specimens were collected in heparinized capillary tubes and mailed to the Albany laboratory for processing. Preliminary screening was done by lysing the red cells in a high-molarity phosphate buffer in the presence of dithionite, a technique which is a modification of the Itano solubility test (*11–13*). Under these conditions, hemoglobin S forms insoluble crystals that produce a turbid solution. Samples that showed a positive turbidity were subjected to electrophoresis on cellulose acetate (Tris-glycine buffer, pH 9.3) to determine the type of sickling hemoglobin present. Whole blood samples were either lysed by freezing and thawing in distilled water or treated with a commercial lysing agent. Samples demonstrating both hemoglobin S and A were considered heterozygous; those with hemoglobin S alone were designated homozygous; the remainder were designated as normal.

Results

Among the 19,838 blacks in our study, 1,371 (6.9 percent) had the sickle cell trait. This value is within the range of 6–14 percent suggested by Motulsky (*14*) and very close to the most likely value for U.S. blacks of 8 percent positive for the trait. Infants under 1 year old were excluded from the analysis to reduce the chance of introducing the presence of fetal hemoglobin as a confounding variable. In addition, we excluded the small number of persons who were homozygous for hemoglobin S.

The age-specific and sex-specific prevalence of the trait based on our data is shown in the table below. Prevalence tended to increase with age

Prevalence of sickle cell trait among blacks, by age and sex

Age (years)	Total			Male			Female		
	Number tested	Positive		Number tested	Positive		Number tested	Positive	
		Number	Percent		Number	Percent		Number	Percent
1–9.....	6,947	479	6.90	3,358	229	6.82	3,589	250	6.97
10–19.....	9,189	604	6.57	4,167	293	7.03	5,022	311	6.19
20–29.....	1,805	139	7.70	720	56	7.78	1,085	83	7.65
30 and over.....	1,897	149	7.86	598	52	8.70	1,299	97	7.47
Total.....	19,838	1,371	6.91	8,843	630	7.12	10,995	741	6.74

in both sexes and was slightly higher among males. The pattern of the age-specific increase was not identical in males and females, and in neither case was it linear. However, the percentage with the sickle cell trait in the under 20 age group (6.7 percent) was significantly smaller than in the over 20 age group (7.8 percent). (The chi-square value was 5.60, $P<.05$.) The reasons for the increasing prevalence with age and the higher prevalence among males are not clear. Before interpretation of this trend is attempted, it would be prudent to await confirmation of these observations in a more precise population sample.

We have eliminated all data subsets that were generated under circumstances in which we recognized that a real or potential selection bias operated. Although we made every possible effort to rule out the possibility of any self-selection that might result from the patient's awareness of his status vis-a-vis the sickle cell trait, we cannot completely rule out this possibility. For this bias to operate, the person would either (*a*) have to have symptoms associated with the trait or (*b*) be otherwise aware of his status. We cannot exclude the second possibility, but hematocrit data were available to explore one aspect of the first possibility.

Hematocrit readings were determined for selected specimens on the basis of available time of the technicians, with emphasis on determining hematocrit values for specimens that were positive for the trait. The mean hematocrit values for persons with normal hemoglobin and those with the trait were as follows:

Sex	*Trait*		*Normal*	
	Value	*Number tested*	*Value*	*Number tested*
Male	40.55	503	40.33	3,868
Female	39.29	616	39.41	5,010

As expected, females had slightly lower hematocrit values than males. Nevertheless, the mean value for persons with the trait and those with normal hemoglobin was the same within each sex group. Therefore if carriers of the sickle cell trait are symptomatic and aware of their condition, the symptoms do not appear to be due to circumstances related to a low hematocrit.

Discussion and Recommendations

Sickle cell anemia and sickle cell trait have become increasingly significant public health problems, but epidemiologic data on the trait are scarce. For example, our knowledge of the relationship between age and the presence of the sickle cell trait is based on a theoretical expectation, and that expectation is reinforced by minimal data. This theoretical expectation rests on the tenet that the sickle cell trait protects, or did protect, against malaria. Studies which have provided data from nonmalarial areas such as the United States have produced ambivalent results. Some of the data show the prevalence declining with age, and this decline has been attributed to increased mortality associated with the trait. But since these studies are based on small numbers of hospital patients, the data may not be sufficient to warrant that conclusion. The results of two reported studies (*9,10*) agree with our findings, in that they produce no evidence of a decrease in prevalence of the trait with increasing age.

Discrimination is being practiced against carriers of the sickle cell trait, presumably on the grounds of theorized health considerations. Bowman has pointed out a number of these areas (*15*). In addition, we have noted that some insurance companies increase the cost of life insurance for carriers of the trait. Therefore, the issue needs to be resolved for both scientific and humanistic reasons.

Of six previous studies (*4–7,9,10*), only one was based on a sample of the black population. Although the results of this one study agree with our findings, the study group was small and included only the older age groups (*10*). Our data set is fairly large and does not have the potential health bias of some of the earlier studies based on hospital patients (*4–7*); however, it has other potential biases. Retrospectively, we have tried to minimize the effect of the potential selection bias in these data, but such an approach can never produce totally adequate results. Our ultimate conclusion is that the critical issue of age trends under nontropical conditions is not yet closed, but rather is in urgent need of further and definitive study. Both biological and demographic explanations for the observed age trends should be considered in future studies. Among the demographic issues that need to be explored are the effects of long-term and short-term migration patterns on the prevalence of sickle cell trait.

Several areas in need of specific study can be identified. First, a population sample should be

selected in which the relationship between the prevalence of sickle cell trait and a number of relevant demographic variables can be investigated. Second, prospective followup studies are necessary. In these studies attempts should be made to identify morbidity and mortality differentials between matched groups of blacks that differ only by the presence or absence of the sickle cell trait. Third, the factors that may be responsible for the amount of hemoglobin S found in heterozygotes have been discussed in two studies (*16, 17*). Variations in the phenotypic expression of the gene for hemoglobin S may be affected not only by familial aggregation, as was shown in these two studies, but also by other mechanisms that are age related. These are just a few suggestions for some of the many epidemiologic studies which are needed if we are to understand the health implications of the carrier state of hemoglobin S.

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Data from the statewide sickle cell voluntary screening program in New York State were used to assess age-specific trends in the prevalence of sickle cell trait. In selecting the data, subsets that were affected by an obvious selection bias were excluded.

Among the 19,838 blacks in the study, 1,371 (6.9 percent) carried the sickle cell trait. Prevalence of the trait increased with age in both sexes and was slightly higher among males. The percentage with the trait in the under 20 age group (6.7 percent) was significantly smaller than in the over 20 age group (7.8 percent). In addition, the data showed no difference in the average hematocrit values between carriers and noncarriers.

The data in this study do not support previous studies that showed a declining prevalence of the trait with age and attributed this decline to increased mortality associated with the trait.