(2)

AD-A199 932

DOCUMENTATION PAGE

Form Approved
OMB No 0704 0188
Exp Date Jun 30 1986

1a REPORT SECURITY CLASSIFICATION
UNCLASSIFIED

1b RESTRICTIVE MARKINGS

2a SECURITY CLASSIFICATION AUTHORITY

3 DISTRIBUTION / AVAILABILITY OF REPORT

2b DECLASSIFICATION / DOWNGRADING SCHEDULE
UNCLASSIFIED

4 PERFORMING ORGANIZATION REPORT NUMBER(S)

5 MONITORING ORGANIZATION REPORT NUMBER(S)

6a NAME OF PERFORMING ORGANIZATION	6b OFFICE SYMBOL (If applicable)	7a NAME OF MONITORING ORGANIZATION
DEPT OF HEMATOLOGY		Walter Reed Army Inst. of Research

6c ADDRESS (City, State, and ZIP Code)	7b ADDRESS (City, State, and ZIP Code)
Washington, DC 20307-5100	Washington, DC 20307-5100

8a NAME OF FUNDING / SPONSORING ORGANIZATION	8b OFFICE SYMBOL (If applicable)	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
Ft Detrick, Frederick, MD		

8c ADDRESS (City, State, and ZIP Code)	10 SOURCE OF FUNDING NUMBERS			
	PROGRAM ELEMENT NO.	PROJECT NO	TASK NO	WORK UNIT ACCESSION NO
US Army Medical Res & Dev Command Ft Detrick, Frederick, MD 21701-5012				

11 TITLE (Include Security Classification)
SICKLE-CELL TRAIT AS A RISK FACTOR FOR SUDDEN DEATH IN PHYSICAL TRANING

12 PERSONAL AUTHOR(S)
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13a TYPE OF REPORT	13b TIME COVERED	14 DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
Manuscript	FROM _____ TO _____		

16 SUPPLEMENTARY NOTATION

17 COSATI CODES			18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

DISTRIBUTION STATEMENT A
Approved for public release;
Distribution Unlimited

20 DISTRIBUTION / AVAILABILITY OF ABSTRACT	21 ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	

22a NAME OF RESPONSIBLE INDIVIDUAL	22b TELEPHONE (Include Area Code)	22c OFFICE SYMBOL
JOHN A. KARK		

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted
All other editions are obsolete

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

SICKLE-CELL TRAIT AS A RISK FACTOR FOR SUDDEN DEATH IN PHYSICAL TRAINING

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Abstract Case reports of sudden death during exertion have not established an association between the sickle-cell trait (hemoglobin AS) and exercise-related death. To test this association, all deaths occurring among 2 million enlisted recruits during basic training in the U.S. Armed Forces in 1977 to 1981 were classified from autopsy and clinical records as non-sudden deaths or as sudden deaths explained or unexplained by preexisting disease.

On the basis of known numbers of entering recruits (according to race, age, and sex) and published prevalence rates for hemoglobin AS (8 percent for black and 0.08 percent for nonblack recruits), death rates (per 100,000) were 32.2 for sudden unexplained deaths, 2.7 for sudden explained deaths, and 0 for non-sudden deaths among black recruits with hemoglobin AS, as compared with 1.2, 1.2, and 0.7 among black recruits without hemoglobin S and 0.7, 0.5, and 1.1 among nonblack recruits without hemoglobin S. Among black recruits the relative risk of sudden unexplained death (hemoglobin AS vs. non-hemoglobin S) was 27.6 (95 percent confidence interval, 9 to 100; $P<0.001$), whereas among all recruits this risk was 39.8 (95 percent confidence interval, 17 to 90; $P<0.001$). The relative risk of sudden unexplained death among all recruits increased with age ($P<0.04$), from 13 (ages 17 to 18) to 95 (ages 26 to 30).

We conclude that recruits in basic training with the sickle-cell trait have a substantially increased, age-dependent risk of exercise-related sudden death unexplained by any known preexisting cause. (N Engl J Med 1987; 317:781-7.)

THE sickle-cell trait has been regarded as a risk factor for sudden death during exertion, because of reports of single cases and small clusters of cases in which the hemoglobin AS phenotype was associated with sudden fatal or severe illness during exertion, especially in military basic training.[1-12] Most of these patients had exertional rhabdomyolysis, heat stroke, or heat stress with acute renal failure,[2-12] although a few died before diagnostic evaluation was possible.[1,3,5,9] However, more deaths related to heat exposure during exertion or to rhabdomyolysis have been reported in members of the military or athletes who did not have hemoglobin S.[2,13-20] Since there is no means of distinguishing histologically between inconsequential postmortem sickling and serious antemortem vascular obstruction by sickled erythrocytes, the only way to determine whether hemoglobin AS is truly associated with death in such cases would be to establish that the sickle-cell trait posed an increased risk of death during comparable exposures.[7,9,12] The increased risk of mortality associated with hemoglobin AS was discussed in two reports describing spatial and temporal clusters of cases with this association.[3,6] However, studying unusual single case clusters can lead to biased estimates of disease risk. Three series of cases of sudden unexplained death among military men with the sickle-cell trait, collected from the Autopsy Registry of the Armed Forces Institute of Pathology (AFIP) (Washington, D.C.), have been cited by Diggs.[1,9] These data, which were not reported in peer-reviewed journals, provide no population base for calculation of death rates.

We investigated the risk of sudden death in comparable populations with and without hemoglobin AS who experienced similar physical stress, by examining all deaths occurring during basic training of enlisted recruits in the U.S. Armed Forces from 1977 to 1981. The number of recruits according to race, age, and sex was known, and the frequency of hemoglobin AS was estimated with use of well-established prevalence rates among American recruits. All natural deaths during basic training were investigated by means of a critical review of clinical data, eyewitness accounts, and autopsy, which included performance of hemoglobin electrophoresis if the recruit was black. Deaths were classified on the basis of sudden or non-sudden onset and the presence or absence of a likely preexisting cause for death. This report presents estimates of

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Presented in abstract form at meetings of the Aeromedical Association, May 1984 (Aviation Space Environ Med 1984; 55:459), and the American Society of Hematology, December 1986 (Blood 1986; 68:63a).

The opinions expressed herein are the private views of the writers and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Reprinted from the *New England Journal of Medicine*
317:781-787 (September 24), 1987

natural death rates among subjects with and without the sickle-cell trait, examines the effect of age on the mortality risk, and notes the association of hemoglobin AS with deaths of sudden onset during exertion that were unexplained by a predisposing cause.

Methods

Study Population

The study population consisted of all enlisted recruits 17 to 34 years old who entered basic training in the period from January 1, 1977, through December 31, 1981. Data on the recruits were obtained from the Defense Manpower Data Center (Monterey, Calif.) and Accessions Operations, Department of Defense (Washington, D.C.). Annual rates of entry of black and nonblack recruits were subdivided according to sex and age. The totals of these recruits were known with at least 1 percent accuracy for the Regular Armed Forces components and with 5 percent accuracy for the active Reserve Armed Forces components (20 percent of the total). Published studies of American military recruits have reported that the prevalence of hemoglobin AS was 8 percent among 20,000 black recruits[21,22] and 0.08 percent among 19,000 nonblack recruits.[24] Similar prevalence rates have been reported for American civilians.[24-27] These rates were used to calculate the numbers of black and nonblack recruits in the study population who had hemoglobin AS. Basic military training lasted 8 to 11 weeks (with rare exceptions), depending on the branch of service.

Identification of Deaths and Records

The records of all deaths during the period 1977–1981 among active-duty or retired enlisted personnel 17 to 34 years old were obtained from autopsy files, morgue logs, patient administration files, and patient administration logs of the 17 hospitals serving the 15 basic-training centers for recruits. Personnel who had been transferred to civilian facilities for medical care or autopsy, which rarely happened, were identified in the logs of the military hospitals and their records were obtained. If hospital records were missing, copies were obtained from the Autopsy Registry of the AFIP and the National Personnel Records Center (St. Louis).

The military service records were used to determine which deaths had occurred among recruits during basic training. Deaths of retired enlisted personnel were examined to determine whether retirement occurred during hospitalization due to recruit training. The accuracy of case identification was confirmed by reviewing records in data bases maintained by the Defense Manpower Data Center (Monterey, Calif.), the National Personnel Records Center, the Naval Medical Data Services (Bethesda, Md.), and the Patient Administration Systems and Biostatistics Activity (Fort Sam Houston, Tex.).

Military hospitals routinely conduct a comprehensive study of natural deaths of recruits, which are always unexpected deaths. These investigations use the following records, sought for each subject in this study: (1) the death certificate, (2) the complete autopsy protocol with toxicology reports, (3) the AFIP autopsy consultation, (4) the clinical records (including the military-entry medical examination, outpatient clinic records of recruits in basic training, and ambulance and hospital records of the fatal illness), (5) the service record, and (6) the report of the investigation into the circumstances of the death, which includes a critical search for undisclosed previous medical history and eyewitness accounts of the events surrounding the fatal illness.

Sixty-three of 80 deaths in the recruit population were considered to be natural. The autopsy protocol was reviewed in classifying all deaths except that of one subject dying with meningitis, in whom autopsy was not performed. One black recruit who died of acute complications of sickle cell disease was excluded from the study. Hospital and clinical records were reviewed for 60 of the 63 deaths. The four deaths for which autopsy or hospital records were missing all occurred among nonblack recruits without hemoglobin S. The AFIP autopsy consultation was reviewed for the 51 cases that were submitted to the AFIP Autopsy Registry. Eyewitness accounts were known to the autopsy prosector for all cases of sudden death, except for one unwitnessed death during sleep, and were available to the study investigators for 35 of 42 sudden deaths.

Classification of the Manner and Cause of Death

The investigators critically reviewed each case in order to select natural deaths and to exclude deaths due to accident, suicide, or homicide. In contrast to the situation in most sudden deaths among civilians,[28-30] immediate cardiopulmonary resuscitation, rapid transport by ambulance, and institution of life support on an intensive care unit were routinely provided to recruits collapsing at military training sites. Sudden natural death was therefore defined as death due to an illness producing an irreversible critical condition within one hour of onset. This definition included cases in which survival was extended by the continuous use of life-support system. Sudden deaths were further divided into those thought to be explained or unexplained by a known preexisting cause. Important attributed causes for such explained deaths in young adults are silent structural heart disease, epilepsy, intracranial bleeding, asthma, medications, and drug abuse.[28-31] The present collection of cases was similar except for the absence of deaths attributed to epilepsy, medications, or drug abuse. Sudden unexplained deaths included those due to exertional heat stress, heat stroke, or rhabdomyolysis, as well as those in which the mechanism was completely unknown, which are generally classified as cardiac deaths.[31] The remaining deaths with slower onset were classified as non-sudden natural deaths. Causes of these deaths in the study population included pneumonia, meningitis, viral infections, structural heart disease, and systemic diseases missed during the physical examination at entry, which are similar to causes reported previously for young American adults.[28-31]

Diagnosis of the Sickle-Cell Trait

Testing for hemoglobin AS was performed and the results were reported during the acute illness or post mortem in all 26 black recruits with natural deaths, but only 3 of 36 nonblack recruits with natural deaths. The histologic findings were reviewed for sickled erythrocytes in all cases submitted with tissues or slides to the AFIP. The results of routine screening of black recruits for hemoglobin S at entry into the Navy and Air Force were recorded in the medical records when positive. All subjects with the sickle-cell trait were identified both by the finding of sickling morphology post mortem and, more important, by hemoglobin electrophoresis on cellulose acetate at an alkaline pH consistent with the hemoglobin AS genotype — i.e., less than 50 percent hemoglobin S, more than 50 percent hemoglobin A, and normal levels of hemoglobin A_2 and hemoglobin F. In addition, we required that pathological examination of the spleen not show evidence of chronic hemolytic anemia or prior infarction due to sickling.[12,32,33]

Statistical Analysis

In computing death rates and relative risks, the actual numbers of recruits were used. Death rates (per 100,000 recruit entries) were computed for the categories of death (non-sudden, sudden explained, and sudden unexplained) among subgroups defined by race (black vs. nonblack) and by the presence or absence of the sickle-cell trait (hemoglobin AS vs. non-hemoglobin S). In order to test the possible association between hemoglobin AS and risk of mortality, the relative risk for each category of death (sudden death [explained and unexplained], non-sudden death, and natural death) was calculated as the death rate for a hemoglobin AS group defined by race (black, nonblack, and all races) divided by the death rate for the corresponding non-hemoglobin S racial group.[15] To examine the risk associated with race alone, relative risks were also calculated for each category of death, by dividing the death rate for the black group without hemoglobin S by the death rate for the nonblack group without hemoglobin S. Assuming that the number of deaths followed Poisson distributions (the small-rate assumption), significance tests for the difference in death rates and 95 percent confidence intervals for relative risks were obtained with the exact conditional method.[16] For observed relative risks of zero, an upper 97.5 percent confidence interval was calculated. All stated P values are two-sided. The attributable risk (or risk difference) of

death as related to hemoglobin AS was calculated as the death rate for black recruits with hemoglobin AS minus the death rate for black recruits without hemoglobin S.[35]

The effect of age on the relative risk of death in relation to hemoglobin AS was examined by stratifying death rates according to age, using five groups with approximately equal numbers of cases with hemoglobin AS. The age distribution of black and nonblack recruits (obtained from the Defense Manpower Data Center) showed little difference between these racial groups (5 percent more nonblacks in the youngest group, aged 17 to 18, and less than a 2 percent difference in all older age groups). Age-specific death rates were calculated under the assumption that recruits with hemoglobin AS had the same age distribution as those without hemoglobin S. This assumption is supported by reports of a similar prevalence of hemoglobin AS among American black populations of different ages[21-27] and by reports of a nearly constant prevalence of hemoglobin AS with aging.[7,12,37,38] Trends in relative risk with age were examined with the maximum-likelihood method for testing a common relative risk against a trend.[39]

Results

The distribution of the 62 natural deaths of recruits during military basic training (1977 to 1981) is shown in Table 1 according to hemoglobin phenotype (hemoglobin AS vs. non-hemoglobin S), race (black vs. other), and category of death. Thirteen recruits with hemoglobin AS died during basic training. All were black, and all had sudden deaths related to exercise. Twelve deaths were classified as unexplained, and one as explained. Forty of the 42 sudden deaths (both explained and unexplained) among the entire recruit population were closely associated with exercise, presenting as collapse during or closely following exercise. The other two deaths occurred in nonblack recruits without hemoglobin S; one died from allergic epiglottitis and the other was found dead in bed. Thirty-five sudden deaths related to exertion occurred during scheduled military training, three during strenuous activity in the first few days at the training camp before the start of formal physical training, and the remaining two during recreational athletics. The proportion of women was similar in the total recruit population (12 percent), the group with sudden deaths (12 percent), and the group with sudden deaths who had hemoglobin AS (15 percent). Sudden unexplained

Table 1. Distribution of Deaths during Basic Training (1977–1981), According to Hemoglobin Phenotype, Race, and Category of Death.

Category of Death	With Hemoglobin AS		Without Hemoglobin S		Total
	Black	Nonblack	Black	Nonblack	
	number of deaths				
Sudden death*					
Unexplained	12	0	5	11	28
Explained	1	0	5	8	14
Non-sudden death	0	0	3	17	20
Total of sudden deaths	13	0	10	19	42
Total of all deaths	13	0	13	36	62
No. of recruits (×10⁻³)†	*37.3*	*1.3*	*429*	*1617*	*2084*

*Explained or unexplained by preexisting disease or exogenous agents.

†In Tables 1 through 3, the actual numbers of recruits have been rounded off to the nearest hundred or thousand for clarity.

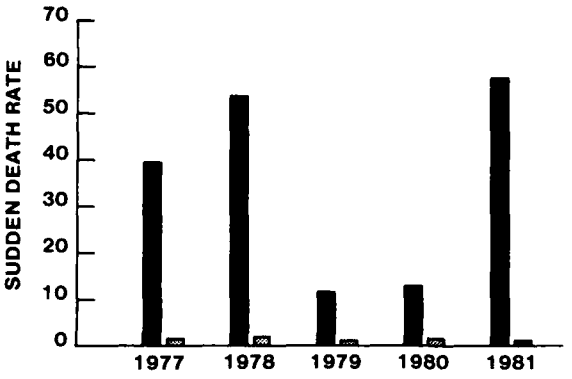

Figure 1. Annual Incidence of Sudden Death among Enlisted Recruits during Military Basic Training.

Values are the numbers of deaths per 100,000 recruits in subjects with hemoglobin AS (solid bars) and those without hemoglobin S (hatched bars).

deaths could be divided into those with no known mechanism (sudden unexplained cardiac deaths) and those due to heat stroke, heat stress, or exertional rhabdomyolysis (or any combination of these three syndromes). Within the category of sudden unexplained deaths, the unexplained cardiac deaths accounted for 5 of 12 deaths among black recruits with hemoglobin AS, 4 of 5 deaths among black recruits without hemoglobin S, and 6 of 11 deaths among nonblack recruits without hemoglobin S. Annual rates for sudden death per 100,000 recruits did not exhibit any consistent trend during the five-year period studied (Fig. 1).

Table 2 summarizes the death rates for subjects with and without hemoglobin AS and compares the relative risk related to hemoglobin AS among black recruits and among recruits of all races. Among black recruits, the relative risk of sudden unexplained death was 27.6 (95 percent confidence interval, 9 to 100), with no significant increased risk of sudden explained death or non-sudden death. The increased relative risk of sudden death or natural death was due to the large contribution of sudden unexplained deaths (in 12 of 13 recruits with hemoglobin AS). There were no deaths in the small group of nonblack recruits with hemoglobin AS. The corresponding relative risks among the nonblack groups were all zero, and the 95 percent confidence intervals were broad, extending from 0 to at least 300 (data not shown). Among recruits of all races (Table 2), the relative risk of sudden unexplained death was 39.8 (95 percent confidence interval, 17 to 90). Again, the risk of sudden death or natural death was significant, but the risk of sudden explained death or non-sudden death was not. The higher relative risks found among all recruits were due to higher rates of sudden death among black recruits without hemoglobin S than among nonblacks without hemoglobin S (data from Table 1). Death rates per 100,000 among recruits without hemoglobin S were 1.2 sudden unexplained deaths, 1.2 sudden explained deaths, and 0.7 non-sudden deaths among blacks, as compared with 0.7, 0.5, and 1.1 among

Table 2. Risk of Death among Recruits with and without Hemoglobin AS.*

Category of Death	Death Rate†		Relative Risk	95% CI	P Value
	Hb AS	Non-Hb S			
Black recruits					
Sudden death					
Unexplained	32.2	1.2	27.6	9–100	<0.001
Explained	2.7	1.2	2.3	0.05–21	NS
Non-sudden death	0	0.7	0	0–28	NS
All sudden deaths	34.9	2.3	15.0	6–38	<0.001
All deaths	34.9	3.0	11.5	5–27	<0.001
All recruits					
Sudden death					
Unexplained	31.1	0.8	39.8	17–90	<0.001
Explained	2.6	0.6	4.1	0.2–27	NS
Non-sudden death	0	1.0	0	0–9	NS
All sudden deaths	33.7	1.4	23.8	11–47	<0.001
All deaths	33.7	2.4	14.1	7–26	<0.001

*Hb denotes hemoglobin, CI confidence interval, and NS not significant.
†Number of deaths per 100,000 recruits.

nonblacks. The relative risk of death among blacks as compared with nonblacks was therefore examined among subjects without hemoglobin S. The relative risks of sudden unexplained death, sudden explained death, and sudden death were 1.7, 2.4, and 2.0, respectively. None of these relative risks were statistically significant (95 percent confidence intervals, 0.5 to 5.3, 0.6 to 8.2, and 0.8 to 4.5). The relative risk of non-sudden death was 0.7 (P not significant; 95 percent confidence interval, 0.1 to 2.3).

To examine the sensitivity of the relative risks shown in Table 2 to the estimated prevalence of hemoglobin AS, similar calculations were made that assumed an improbably high prevalence of hemoglobin AS among both the black and nonblack recruits. If 12 percent of black recruits had hemoglobin AS, the relative risks of sudden unexplained death, sudden death, and natural death would have been 18, 9.5, and 7.3, respectively. These risk ratios would still be significant ($P<0.001$), with corresponding 95 percent confidence intervals of 6 to 64, 4 to 24, and 3 to 17. If 0.16 percent of nonblack recruits had hemoglobin AS, the relative risk of death in subjects with hemoglobin AS among the entire recruit population would decrease by only 5 percent in each of the categories of death shown in Table 2. Furthermore, the absence of identified deaths among such a nonblack population with hemoglobin AS, consisting of 2600 recruits, would not have suggested a statistically significant difference in risk when compared with the deaths in the black group with hemoglobin AS, which averaged one sudden unexplained death per 3200 recruits.

None of the subjects with hemoglobin AS had significant elevations of hemoglobin A_2 or hemoglobin F, and none had evidence of chronic hemolysis or sickle cell disease on examination of the spleen. The fraction of hemoglobin S varied between 30 and 44 percent in the 12 recruits with sudden unexplained death. The median was 39 percent, and the extremes were low values of 30, 35, 35, and 36 percent and high values of 41.5, 42, 42, and 44 percent.

Table 3 summarizes the relation of age-specific rates and relative risks for sudden unexplained death to increasing age among those with and without hemoglobin AS. Table 3 demonstrates an increasing trend in the rate of sudden unexplained death among recruits with hemoglobin AS, but no trend in the death rate with age for recruits without hemoglobin S. The trend in relative risk with age was significant ($P<0.04$).[39] Age-specific rates for sudden explained deaths and non-sudden deaths could be examined for trends only among the recruits without hemoglobin S; these death rates showed no significant trend with age.

Discussion

We have identified the sickle-cell trait as an important risk factor for sudden death unexplained by prior disease, by estimating the rates of natural death in a cohort of 2.1 million recruits who entered the U.S. Armed Forces for basic training during the period 1977–1981. The risk of exertion-induced sudden unexplained death was 28 to 40 times higher among those with *hemoglobin* AS, as estimated among black recruits or among recruits of all races, respectively. The risk of sudden unexplained death attributable to hemoglobin AS among black recruits was 31 deaths per 100,000. Hemoglobin AS was not significantly associated with sudden explained or non-sudden deaths. The risk of sudden death (both explained and unexplained) among the subjects without hemoglobin S was approximately twice as high in black as in nonblack recruits. Although the increase in the risk among black recruits was not statistically significant, it is consistent with findings of much larger national mortality surveys conducted during the same period, which have suggested that blacks in the same age range as that of the recruits had higher rates of natural death than whites.[10] The number of nonblack re-

Table 3. Age-Specific Death Rates and Relative Risk of Sudden Unexplained Death.*

Age Group	Percentage of Recruits†		Sudden Unexplained Deaths		Death Rate‡		Relative Risk
	Hb AS	Non-Hb S	Hb AS	Non-Hb S	Hb AS	Non-Hb S	
17–18	43.4	47.4	2	9	12.0	0.9	12.9
19–20	31.9	30.4	2	4	16.3	0.6	25.2
21–22	12.2	11.0	2	0	42.6	0.0	—
23–25	7.9	7.0	4	2	131	1.3	94.2
26–30	3.8	3.4	2	1	136	1.4	95.1
31–34	0.9	0.8	0	0	0	0	—
Total			*12*	*16*	*31.1*	*0.8*	*39.8*

*Hb denotes hemoglobin. P<0.04 for test for trend with age.
†The total number of recruits with hemoglobin AS was 38,600, the total number without hemoglobin S was 2,046,000.
‡Per 100,000 recruits.

cruits with hemoglobin AS was too small to provide a reliable estimate of risk associated with hemoglobin AS in this group.

Attempts were made in this study to eliminate potential sources of bias by ensuring that identification of cases of natural death was complete and that such cases involved only recruits in basic training, that classifications of the type of death and hemoglobin phenotype were accurate, that demographic data on the recruits (numbers according to race, sex, and age) were accurate, and that conclusions were not dependent on unreasonably low estimates of the prevalence of hemoglobin AS. Selection bias was avoided by attempting to identify all cases of deaths of recruits with use of the record systems maintained separately by military hospitals, personnel branches, and Department of Defense organizations. The study search reviewed a larger set of cases than the actual number of deaths so that rare cases would not be overlooked because of misdiagnosis at autopsy, delayed entry, high rank, transfer out of the local hospital, or retirement during the terminal illness. To ensure that cases involved the deaths of recruits in basic training, military status was not inferred from medical records but was established by military personnel records. The diagnosis of the sickle-cell trait and its distinction from sickle-cell disease were based on reliable and sensitive laboratory and histologic criteria. In contrast to many retrospective studies in which reliance on the death certificate alone has resulted in erroneous diagnosis,[11] the present study determined the manner and cause of death from full autopsy protocols, including biochemical studies, clinical data, and contemporaneous critical review by the AFIP staff. Accurate recognition and description of illness of sudden onset, without selection bias, would be expected because recruits are constantly under observation and eyewitness accounts of such events are consistently reported. Moreover, subclassification of natural deaths was not essential to demonstrate the risk associated with the sickle-cell trait, since the relative risk of natural death had a high level of significance. Precise figures for the populations at risk were obtained from contemporaneous Department of Defense records of recruits entering the services. The prevalence of hemoglobin AS was not measured in this study, but consistent values have been observed in similar populations, including military recruits (see Methods). The relative risks of death in persons with hemoglobin AS remained statistically significant even when a much greater prevalence than has been reported among recruits was assumed.

All of the 12 cases of sudden unexplained death in subjects with hemoglobin AS occurred during exertion. These cases could be divided into deaths presenting with acute cardiac arrest of undefined mechanism[4,5,41] and deaths related to exertional heat stroke, heat stress, or rhabdomyolysis. The data were insufficient to test whether hemoglobin AS was more closely associated with any specific subset of sudden unexplained deaths. It has been suggested that higher fractions of hemoglobin S would be an important risk factor for complications related to sickling, since relatively many affected persons have hemoglobin S fractions above 42 percent and relatively few have fractions below 36 percent.[12,43] However, differences from the expected distribution of hemoglobin S fractions among cases with complications related to the sickle-cell trait appear to have been subtle.[7,9,12,31,42,43] The proportion of deaths in our study with very low or very high fractions of hemoglobin S was not different from expected values in healthy persons with the sickle-cell trait.[12,43,44] Although the metabolic changes occurring in severe cases of heat stroke or rhabdomyolysis would be expected to provoke polymerization of hemoglobin S, which in theory could increase mortality by causing tissue infarction,[6,7,9,12] there is no evidence permitting one to determine whether the association between sudden unexplained death and the sickle-cell trait is a direct causal relation or an indirect one, such as (for example) the consequences of some unrecognized genetic variant linked to hemoglobin S.

There was a significant trend with age in the relative risk of sudden unexplained death in subjects with hemoglobin AS, because the risk-ratio numerator (the rate of sudden unexplained death among recruits with hemoglobin AS) increased with age while the risk-ratio denominator (the rate of sudden unexplained death among recruits without hemoglobin S) did not change substantially with age (Table 3). This observation is potentially important since it implies that the pathogenesis of sudden death associated with hemoglobin AS differs from that of sudden death not associated with hemoglobin S. This trend in relative risk was consistent with data on age groups varying in number and range, subsets defined according to race or military status (regular or reserve forces), and categories of death (sudden unexplained deaths or all sudden deaths). The principal limitation of this analysis was the low degree of precision of death rates in the older age groups, which were relatively small, so that the trend in relative risk would be sensitive to the movement of a few deaths between the higher and lower age groups. However, the age distribution of the eight additional published cases of sudden unexplained death in persons with hemoglobin AS among recruits in U.S. military basic training seems consistent with our data.[3-6,8,10, 1] Although only approximately 23 percent of all recruits were older than 20, 67 percent (8 of 12) of our subjects with hemoglobin AS who had sudden unexplained deaths and 63 percent (5 of 8) of the subjects of these published cases were above this age.

It is tempting to explain the age dependence of the risk in persons with hemoglobin AS as a consequence of partial hyposthenuria (attributed to silent renal papillary necrosis), because this concentrating defect progresses with age and is observed in about 8% percent of men in the age range of recruits.[45,46] However

it remains to be shown that the extra fluid loss due to the defect would be clinically important. Other potentially important factors that could increase the risk of complications of sickling, such as viral infection of the upper respiratory tract with transient hypoxia,[6] elevated hematocrit, and transient causes of dehydration, would not appear to explain the increasing risk with age.

An important question is whether the excess risk of sudden death observed during basic training of recruits with hemoglobin AS would be present in other populations with hemoglobin AS, such as young men engaged in athletics, heavy labor, or advanced military training. Previous studies of the effect of the sickle-cell trait on health have not examined sufficiently large populations to detect a process responsible for a death rate of about 1 per 3000.[21,24-26,37,38,49,50] The largest studies examined only approximately 4000 enlisted men in the Navy[30] and 5000 hospitalized veterans.[20] In our search among recruits for cases of sudden unexplained death in persons with hemoglobin AS, we were struck by the relatively small number of cases among members of the military past basic training, but we have not yet determined the size of the population base searched. Civilian activities are seldom as stressful as basic military training with respect to the rapid conditioning of poorly developed muscle groups, the severity of exposure to conditions causing heat stress and dehydration during exertion, and the frequency and duration of exertion.

In 1982, responding to the initial collection of data for this study, the Army Medical Corps reminded the commands overseeing recruit training about the potential risk associated with the sickle-cell trait and stressed the importance of regulations designed to reduce the incidence of casualties due to exertion; these regulations enforce gradual acclimatization, gradual conditioning for each type of activity, maintenance of hydration, and adjustment of activities according to the climatic conditions at the training site, as measured by a wet-bulb thermometer. Comparing mortality rates for the years subsequent to 1981 with the rates found in this study might be useful in assessing whether the excess risk of deaths during training associated with hemoglobin AS could be reduced by a rigorous application of such regulations.

We are indebted to James J. Canik, Maj., Robert R. McMeekin, Col., M.C., Bruce Chase, Col., M.C., and to the pathologists responsible for services to military recruits for their assistance in conducting the study; to Richard Hodder, M.D., John F. Brundage, Maj., M.C., for epidemiologic advice; to Douglas B. Tang, Ph.D., and Craig R. Morrisette for statistical analysis; to Samuel K. Martin, Maj., M.C., Victor W. Macdonald, Ph.D., and Cecil U. Hicks, Jr., for preparation of reports from data bases and for critical comments; and to Daniel B. Kimball, Jr., Col., M.C., for encouragement.

References

1. Diggs LW, Jones RS. Clinicopathologic conference. Am J Clin Pathol 1952; 22:1194-200.
2. Schrier RW, Henderson HS, Tisher CC, Tannen RL. Nephropathy associated with heat stress and exercise. Ann Intern Med 1967; 67:356-76.
3. Jones SR, Binder RA, Donowho EM Jr. Sudden death in sickle-cell trait. N Engl J Med 1970; 282:323-5.
4. Zimmerman J, Mummert K, Granatir R, Ciofli R. Sickle crisis precipitated by exercise rhabdomyolysis in a patient with sickle cell trait: case report. Milit Med 1974; 139:313-5.
5. Death of an athlete with sickle cell trait. Med World News 1974; 15(Oct. 25):44.
6. Koppes GM, Daly JJ, Coltman CA Jr, Butkus DE. Exertion-induced rhabdomyolysis with acute renal failure and disseminated intravascular coagulation in sickle cell trait. Am J Med 1977; 63:313-7.
7. Sears DA. The morbidity of sickle cell trait: a review of the literature. Am J Med 1978; 64:1021-36.
8. Helzlsouer KJ, Hayden FG, Rogol AD. Severe metabolic complications in a cross-country runner with sickle cell trait. JAMA 1983; 249:777-9.
9. Diggs LW. The sickle cell trait in relation to the training and assignment of duties in the Armed Forces. III. Hyposthenuria, hematuria, sudden death, rhabdomyolysis, and acute tubular necrosis. Aviat Space Environ Med 1984; 55:358-64.
10. Hynd RF, Bharadwaja K, Mitas JA, Lord JT. Rhabdomyolysis, acute renal failure, and disseminated intravascular coagulation in a man with sickle cell trait. South Med J 1985; 78:890-1.
11. Sateriale M, Hart P. Unexpected death in a Black military recruit with sickle cell trait: case report. Milit Med 1985; 150:602-5.
12. Serjeant GR. The sickle cell trait. New York: Oxford University Press, 1985:329-37.
13. Malamud N, Haymaker W, Custer RP. Heat stroke: a clinico-pathological study of 125 fatal cases. Milit Surg 1946; 99:397-449.
14. Smith RF. Exertional rhabdomyolysis in naval officer candidates. Arch Intern Med 1968; 121:313-9.
15. Schrier RW, Hano J, Keller HI, et al. Renal, metabolic, and circulatory responses to heat and exercise: studies in military recruits during summer training, with implications for acute renal failure. Ann Intern Med 1970; 73:213-23.
16. Grossman RA, Hamilton RW, Morse BM, Penn AS, Goldberg M. Nontraumatic rhabdomyolysis and acute renal failure. N Engl J Med 1974; 291:807-11.
17. Demos MA, Gitin EL. Acute exertional rhabdomyolysis. Arch Intern Med 1974; 133:233-9.
18. Demos MA, Gitin EL, Kagen LJ. Exercise myoglobinemia and acute exertional rhabdomyolysis. Arch Intern Med 1974; 134:669-73.
19. Clowes GHA Jr, O'Donnell TF Jr. Heat stroke. N Engl J Med 1974; 291:564-7.
20. Butkus DE. Sickle cell trait (SCT): an opposing view. Milit Med 1984; 149:164-5.
21. Binder RA, Jones SR. Prevalence and awareness of sickle cell hemoglobin in a military population, determination by a rapid screening method. JAMA 1970; 214:909-11.
22. Uddin DE, Dickson LG, Brodine CE. Screening of military recruits for hemoglobin variants. JAMA 1974; 227:1405-7.
23. McGrew CJ Jr. Sickle cell trait in the white population. JAMA 1973; 224:1762-3.
24. Murphy JR. Sickle cell hemoglobin (Hb AS) in black football players. JAMA 1973; 225:981-2.
25. Diggs LW, Flowers E. High school athletes with the sickle cell trait (Hb A S). J Natl Med Assoc 1976; 68:492-3, 497.
26. Heller P, Best WR, Nelson RB, Becktel J. Clinical implications of sickle-cell trait and glucose-6-phosphate dehydrogenase deficiency in hospitalized black male patients. N Engl J Med 1979; 300:1001-5.
27. Winter WP. Hemoglobin variants in human populations. Vol. I. Boca Raton, Fla.: CRC Press, 1986; 49-69.
28. Kuller L, Lilienfeld A, Fisher R. Sudden and unexpected deaths in young adults: an epidemiologic study. JAMA 1966; 198:248-52.
29. Thompson PD, Funk EJ, Carleton RA, Sturner WQ. Incidence of death during jogging in Rhode Island from 1975 through 1980. JAMA 1982; 247:2535-8.
30. Neuspiel DR, Kuller LH. Sudden and unexpected natural death in childhood and adolescence. JAMA 1985; 254:1321-5.
31. Phillips M, Robinowitz M, Higgins JR, Boran KJ, Reed T, Virmani R. Sudden cardiac death in Air Force recruits: a 20-year review. JAMA 1986; 256:2696-9.
32. Diggs LW. Siderofibrosis of the spleen in sickle cell anemia. JAMA 1935; 104:538-41.
33. *Idem*. Anatomic lesions in sickle cell disease. In: Abramson H, Bertles JF, Wethers DL, eds. Sickle cell disease: diagnosis, management, education, and research. St. Louis: C.V. Mosby, 1973:189-229.
34. *Idem*. The sickle cell trait in relation to the training and assignment of duties in the Armed Forces. II. Aseptic splenic necrosis. Aviat Space Environ Med 1984; 55:271-6.
35. Schlesselman JJ. Case-control studies: design, conduct, analysis. New York: Oxford University Press, 1982:32-3, 40-1.

36. Ederer F, Mantel N. Confidence limits on the ratio of two Poisson variables. Am J Epidemiol 1974; 100:165-7.
37. Janerich DT, Kelly JH, Ziegler FD, et al. Age trends in the prevalence of the sickle cell trait. Health Serv Rep 1973; 88:804-7.
38. Stark AD, Janerich DT, Jereb SK. The incidence and causes of death in a follow-up study of individuals with haemoglobin AS and AA. Int J Epidemiol 1980; 9:325-8.
39. Breslow NE. Elementary methods of cohort analysis. Int J Epidemiol 1984; 13:112-5.
40. National Center for Health Statistics. Health, United States, 1984. Washington, D.C.: Government Printing Office, 1984:51-69. (DHHS publication no. (PHS) 85-1232.)
41. Kircher T, Nelson J, Burdo H. The autopsy as a measure of accuracy of the death certificate. N Engl J Med 1985; 313:1263-9.
42. Kennedy AP, Walsh DA, Nicholson R, Adams JG III, Steinberg MH. Influence of HbS levels upon the hematological and clinical characteristics of sickle cell trait. Am J Hematol 1986; 22:51-4.
43. Steinburg MH, Embury SH. α-Thalassemia in blacks: genetic and clinical aspects and interactions with the sickle hemoglobin gene. Blood 1986; 68:985-90.
44. Huisman THJ. Trimodality in the percentages of β chain variants in heterozygotes: the effect of the number of active Hb_A structural loci. Hemoglobin 1977; 1:349-82.
45. Keitel HG, Thompson D, Itano HA. Hyposthenuria in sickle cell anemia: a reversible renal defect. J Clin Invest 1956; 35:998-1007.
46. Zarafonetis CJD, McMaster JD, Molthan L, Steiger WA. Apparent renal defect in sicklemic individuals. Am J Med Sci 1956; 232:76-82.
47. Statius van Eps LW, Pinedo-Veels C, de Vries GH, de Koning J. Nature of concentrating defect in sickle-cell nephropathy: microradioangiographic studies. Lancet 1970; 1:450-2.
48. de Jong PE, Statius van Eps LW. Sickle cell nephropathy. In: van der Hem GK, ed. Nephrology. Princeton: Excerpta Medica, 1982:346-63.
49. Ashcroft MT, Miall WE, Milner PF. A comparison between the characteristics of Jamaican adults with normal hemoglobin and those with sickle cell trait. Am J Epidemiol 1969; 90:236-43.
50. Hoiberg A, Ernst J, Uddin DE. Sickle cell trait and glucose-6-phosphate dehydrogenase deficiency: effects on health and military performance in black Navy enlistees. Arch Intern Med 1981; 141:1485-8.

THE NEW ENGLAND JOURNAL OF MEDICINE is published weekly in the English language by the Massachusetts Medical Society (Waltham, MA, USA). Editorial offices: 10 Shattuck Street, Boston, MA 02115, USA. **SUBSCRIPTIONS:** Subscription offices: 1440 Main Street, Waltham, MA 02254, USA; Saxon Way, Melbourn, Royston, Hearts SG8 6NJ, UK. Subscription prices: U.S.A., $66 per year (interns, residents $39 per year; students $33 per year). Outside U.S.A. (US funds on a US bank: $83 per year (interns, residents $60 per year; students $50 per year); pounds sterling drawn on a U.K. bank: £57 per year (interns, residents £41 per year; students £34 per year). Rates are subject to change without notice. Sample copies available upon request. *International copies are delivered by airlift, at no additional* charge, to all countries except Canada and the U.K. Payments and correspondence for all subscriptions delivered to Japan should be sent directly to: Nankodo Co., Ltd., 42-6, Hongo 3-chome, Bunkyo-ku, Tokyo 113, Japan.