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Sickle Cell Trait

Introduction

Sickle cell trait usually is not regarded as a disease state because it has complications that are either uncommon or mild. Nevertheless, under unusual circumstances serious morbidity or mortality can result from complications related to polymerization of deoxy-hemoglobin S. Such problems include increased urinary tract infection in women, gross hematuria, complications of hyphema, splenic infarction with altitude hypoxia or exercise, and life-threatening complications of exercise, exertional heat illness (exertional rhabdomyolysis, heat stroke, or renal failure) or idiopathic sudden death (1-4). Pathologic processes that cause hypoxia, acidosis, dehydration, hyperosmolality, hypothermia, or elevated erythrocyte 2,3-DPG can transform silent sickle cell trait into a syndrome resembling sickle cell disease with vaso-occlusion due to rigid erythrocytes. Compound heterozygous sickle cell disease can be mistaken as uncomplicated sickle cell trait, particularly when an unusual globin variant is involved.

In addition some disease associations have been noted with sickle cell trait which might not result from polymerization of hemoglobin S but from linkage to a different gene mutation. The association of hemoglobin S with cases of renal medullary carcinoma, early end stage renal failure in autosomal dominant polycystic kidney disease, and surrogate end points for pulmonary embolism are not necessarily the result of hemoglobin S polymerization. Complications from sickle cell trait are important because about three million people in the United States have this genotype, about 40 to 50 times the number with sickle cell disease.

People with uncomplicated sickle cell trait have a normal blood examination as assessed by conventional clinical methods, including normal red cell morphology, indices, reticulocyte counts, and red blood cell survival by chromium labeling. Conventional methods of detecting hemolysis are negative, such as measurements of serum haptoglobin, bilirubin, and LDH. Erythrocyte density distribution is normal, adherence to endothelium is not increased, altered membrane lipids and proteins are not detectable, cytoplasmic inside-out vesicles with high calcium content are absent, and permanently distorted erythrocytes are not observed.

When blood is drawn with anaerobic technique into a syringe with dilute buffered glutaraldehyde one obtains an accurate picture of circulating erythrocytes in vivo (the Sherman test). No sickled

cells are observed at rest, but exercise to exhaustion at sea level regularly induces mild levels of reversible sickling in peripheral venous blood (less than 1%). Exposure to altitude hypoxia will progressively increase the extent of sickling observed with sickle cell trait from 2% at 4,050 ft. to 8.5% at 13,123 ft. Hypobaric chamber exposures used for military aviation training, involving hypoxic exposures simulating 10,000 to 25,000 ft from ninety to six minutes, did not cause hemolysis in subjects with uncomplicated sickle cell trait (3).

Determination that a clinical syndrome is due to sickle cell trait rather than a subtle form of sickle cell disease is difficult. Reversible sickling and unsickling of erythrocytes (reflecting the rapid formation and dissolution of deoxy-hemoglobin S polymers) takes place in seconds. Hence, the presence or absence of intravascular sickled erythrocytes in tissue specimens depends upon the degree of oxygenation of the sample just before fixation and only has clinical relevance if fixation occurred at oxygen tensions identical to those extant during generation of primary lesions. Agonal hypoxemia causes artifactual intravascular sickling. Conversely, blood samples smeared in room air and then fixed will show artifactual unsickling. One cannot determine the role of hemoglobin S in clinical events from the presence or absence of intravascular sickling in blood samples, biopsy specimens, or autopsy specimens unless these were rapidly fixed at physiologic oxygen tension.

While fatal intravascular sickling with extensive microvascular obstruction could theoretical result from sickle cell trait, such an event cannot be demonstrated by histologic examination at autopsy. If a clinical event is not specific for hemoglobin S, one may need to show that the complication occurs significantly more often in people with sickle cell trait relative to a control group. Such an association does not prove cause. Stronger evidence that polymerization of hemoglobin S causes a problem is demonstration of relative protection by alpha thalassemia.

The common African polymorphism causing alpha thalassemia is the product of a prior mismatched cross over event which creates chromosome 16 expressing only one of the two alpha globins and a chromosome 16 carrying three alpha globin exons. Loss of one or two alpha globin genes decreases the fraction of hemoglobin S and produces obvious microcytosis. Anemia is absent or mild.

Examination of maximal urinary concentrating ability in people with sickle cell trait relative to alpha globin gene number demonstrated that one or two alpha globin gene deletions were associated with better preserved renal function (5). In other words the less hemoglobin S that was present, the less renal function that was lost. This implied a significant role of polymerized hemoglobin S in the pathogenesis of renal isosthenuria (see below). In some instances the anatomic lesions due to sickle cell trait are so distinct that a relationship to polymerization of Hb S can be reasonably inferred. Such complications of sickle cell trait include glaucoma or recurrence after treatment for hyphema and splenic infarction in the absence of primary trauma, infection, inflammation or tumor in the spleen.

People with sickle cell trait often experience subclinical tissue infarction from microvascular obstruction by rigid erythrocytes. Most people with sickle cell trait develop microscopic infarction of the renal medulla because the extreme hypoxemia, hypertonicity, acidosis, and hyperthermia of arterial blood passing through the long vasa recta of the renal medulla promote

polymerization of deoxy-hemoglobin S (6). Flow through these vessels requires more than ten seconds, providing an unusually long exposure time for polymerization of hemoglobin S. Cumulative focal lesions result in loss of maximal urine concentrating ability which is progressive with age and develops in most adults with sickle cell trait (3, 6). The functional defect limits urine concentration to approximately the osmolality of serum, causing isosthenuria rather than hyposthenuria. In people with sickle cell trait urine osmolality can usually reach values higher than plasma during overnight dehydration (400 to 800 mOsmol). Although one may speculate that this lesion might predispose to development of mild exertional heat illness (EHI) during exercise in hot weather, clinically significant problems related to this deficit have not been demonstrated. Necrosis of the renal papillae can result in hematuria, which is usually microscopic. Gross hematuria is occasionally provoked by heavy exercise or occurs spontaneously.

Life-threatening complications of exercise

An important potential complication of sickle cell trait is unexpected exercise-related death (ERD). The validity of this association aroused heated controversy (4). The possibility that previously healthy young people with sickle cell trait might suffer increased mortality from exercise was first suggested by observations of enlisted recruits in US Armed Forces basic training. A military trainee with Hb AS suffered exercise related hypernatremia during physical training in the field. He only survived a critical illness that included acute renal failure because of dialysis (8). During a single summer, there were four exercise-related deaths among recruits at Fort Bliss, all of whom were black and had sickle cell trait, while no recruits with normal hemoglobin died. Only 1.5% of these recruits had sickle cell trait. The authors suggested a significant risk association with sickle cell trait (8).

Twelve cases of natural exercise-related death (ERD) among apparently healthy young men with Hb AS were reported by 1981. These deaths were predominantly due to exertional rhabdomyolysis, although some were sudden idiopathic deaths with cardiopulmonary arrest, associated in two cases with hyperkalemia. Identical presentations were observed in recruits without Hb S. There is no direct proof that sickle cell trait contributed to ERD through microvascular obstruction by rigid erythrocytes. There is little evidence that these deaths involve the typical acute complications of sickle cell disease, such as acute focal infarction of the spleen, kidneys, lungs, bone, retina, or brain, sudden extensive sequestration of blood in the spleen or liver, or overwhelming infection with encapsulated bacteria.

In 1981 we embarked on studies of exercise-related death among US military enlisted recruits in basic training which took advantage of the potential for accurate epidemiologic analysis. Large exercising populations of apparently healthy young adult recruits were enumerated with an accuracy greater than 96% in a database describing each individual. Because of medical, legal, and military command concerns, each recruit death has been investigated in detail, with a full autopsy and toxicology, clinical records, and eyewitness accounts. We added assessment of these materials by experts in forensic pathology, cardiovascular pathology, and internal medicine. Selection bias was eliminated by obtaining all cases of exercise-related death in the study

population. In contrast, the frequently cited surveys of civilian athlete deaths usually required selection of those cases identified as sudden deaths, often were selected from poorly defined or poorly measured athlete populations, and athlete cases frequently lack a complete autopsy, toxicology, or full eyewitness accounts (14).

We performed complete cohort study of ERD among the 2.1 million people who entered US Armed Forces basic enlisted military training during the five years, 1977-1981 (9). The population was dived into black and non-black groups to estimate the fraction with Hb AS from published surveys. Prevalence of Hb AS was 8% among 20,600 black recruits (10) and 0.046% among 57,600 non-black recruits (11). There were 37,300 black recruits with Hb AS, 1,300 non-black recruits with Hb AS, 429,000 black recruits without Hb AS, and 1,620,000 non-black recruits without Hb S. Forty-one exercise-related deaths occurred. Hb AS was only found among natural deaths. Risk ratios were examined among the black recruits, ignoring the small number of non-blacks with Hb AS.

The relative risk of ERD explained by preexisting disease (largely silent heart disease) was 2.3 for Hb AS , but this was not statistically significant. The relative risk of ERD unexplained by preexisting disease was 28 for Hb AS. This was highly significant with p less than one per thousand. The relative risk ratio has since been corrected to 30 (3). If one eliminates restrictions by race and cause of ERD, the risk of exercise-related death for sickle cell trait was 28-fold. The excess ERDs with sickle cell trait seemed to result from the immediate stress of exercise. About 50% of cases resulted from exertional heat illness and the remaining cases were idiopathic sudden deaths (ISD). Clinical features and distribution of cases between EHI and ISD did not differ by the presence or absence of hemoglobin S, except that rhabdomyolysis was the predominant form of EHI among cases with sickle cell trait (3).

We examined the effect of age on risk of ERD unexplained by preexisting disease. There was an eight-fold increase in mortality going from age 17-18 to age 28-29 among recruits with Hb AS but no such trend for recruits without sickle cell trait (3, 9). This difference in effect of age suggests that there may be a difference in pathogenesis of death depending on the presence or absence of hemoglobin S. This effect might be due to renal papillary necrosis from Hb AS, a lesion increasing linearly in severity with age and present in at least 80% of recruits (figure 1 in 3, 6). The resulting deficit in renal concentrating ability might predispose that person toward more severe EHI since obligatory loss of free water might increase the hyperosmolar state important in the pathogenesis of EHI.

We were surprised by the high excess mortality associated with sickle cell trait. It is often said that the absolute risk of mortality with sickle cell trait we reported was low (12, 13). This excess mortality was one per three thousand recruits with sickle cell trait or one death per 60 to 90,000 person-hours of exercise equivalent to middle distance running. This mortality rate for 18 year old recruits is about 4 to 7 times higher than the mortality observed from artherosclerosis among middle aged runners: one death per 400,000 hours of running (14). Other population surveys of sickle cell trait have shown only mild effects of trait on hospitalization rates and none on mortality rates (3). Whereas our survey observed 5,000 person-years of exposure (38,600 people with Hb AS for a median of 8 weeks exposure) (9), other surveys of young adults with sickle cell trait examined exposures two to four logs smaller.

Heller et al. examined hospital admissions over three years for 4,900 veterans with Hb AS with a median age of 49 years and no time for follow-up (15). This older population would not be expected to engage in conditioning exercise and therefore would not be subject to a comparable risk of exercise related-death. An important study of Navy enlisted members with sickle cell trait examined 599 recruits with sickle cell trait during a four year tour of duty, about 2,400 person-years of exposure (16). Exercise-related mortality rates with Hb AS are at least ten-fold lower for military members than recruits, making this study too small to identify mortality related to sickle cell trait (4).

We subsequently determined ERD rates in US Armed Forces basic training for 98,800 black recruits with Hb AS and 1.14 million black recruits without Hb S. We found that Hb AS was associated with a 21-fold higher relative risk of ERD unexplained by preexisting disease (17, table 6). This implies an excess mortality with sickle cell trait of one per 5,500 recruits exposed to eight weeks of training. The reduction in risk is explained by intervention to reduce mortality for a subset of these (see below).

All but one of the large autopsy series of exercise-related deaths among athletes have shown that exertional heat illness accounted for less than 1% of cases and that idiopathic sudden death accounted for between 5 and 12% of such deaths (3, 17). However, our survey of 41 recruit ERDs, demonstrated that non-sudden exertional heat illness deaths and idiopathic sudden death each accounted for about one-third of ERD (3, 17). Only five percent of sudden deaths, whether explained by preexisting cardiac disease or idiopathic, were appropriately screened by determination of body temperature near death and by serum and urine chemistry studies to exclude exertional heat illness. It seemed possible that EHI contributed to a much larger fraction of recruit deaths than was found in most of the autopsy studies of ERD of civilian athletes.

We have reviewed 55 cases of unexpected ERD with sickle cell trait (3). At least two-thirds occur under conditions of high risk for EHI. Most deaths were non-sudden. Those few cases of sudden ERD which were properly examined demonstrate hyperthermia or chemical abnormalities diagnostic of acute EHI. In our recruit cohort study of 94 consecutive recruit ERDs at least two-thirds of ISD (with or without hemoglobin S) resulted from middle distance running during the hot season but early in the morning when the immediate heat stress was considered safe (3). Unrecognized exertional EHI might have contributed to these deaths.

Current military standards were designed in the 1950's for recruits whose physical conditioning was predominantly marching at 6 METS (METS are units of oxygen consumption for a given weight over a minute. Moderate walking is 3 METS, cycling is 6 METS). Since the 1970's recruit conditioning has been predominantly middle distance running at 12-14 METS, implying a need for altered activity at lower heat index levels. Substantial risk of EHI might also result from prior-day heat exposure, which is not considered a risk factor for heat illness by current military or sports medicine standards. We examined these issues in a ten year cohort study of Marine recruits (18). We related rates of EHI from 1,454 consecutive cases of non-fatal exertional heat illness to hourly values for the wet bulb black globe temperature index (WBGT), the heat index best related to physiologic response to exercise in heat.

This study demonstrated that prior-day exposures and heat stress at WBGT values between 70 and 84ûF were important determinants of rates of EHI among recruits (18). A preliminary analysis of 94 consecutive recruit ERD cases was performed, using WBGT values for the 24 hours prior to presentation of EHI to identify conditions in which the risk of EHI was increased at least 15-fold. This study suggests an association between high-risk of exertional heat illness from environmental exposure and ERD with sickle cell trait (all ISD cases), a substantial association for ISD without hemoglobin S (54% of cases), and sudden explained cardiac death without hemoglobin S (42% of cases versus 11% of recruit deaths unrelated to EHI) (19). We have been able to describe in detail eight cases in which sudden death occurred with acute exertional heat stroke or rhabdomyolysis. In a small cohort study at one training center, we demonstrated a strong relation between severe exertional heat illness and life-threatening or fatal cardiovascular complications for recruits without hemoglobin S (3).

The ultimate test of the hypothesis that unrecognized EHI contributes to ISD (especially among people with sickle cell trait) would be to conduct effective prevention of EHI during exercise and observe an appropriate reduction in mortality. In February 1982 we proposed stricter rules for drill instructors in order to correct the major deficiencies in preventative measures for EHI which we noted at most recruit training centers during 1981. These rules provided prevention based on 30 to 60 minute measures of the WBGT at the actual exercise site and direct observation that each recruit was drinking the amount of water recommended to prevent EHI. This intervention was applied to all trainees and did not require prior identification or different management of individuals with sickle cell trait. We tested the effect of this intervention on ERD rates prospectively during the next ten years of training (1982-1991). Participating centers adhered to this intervention while training 2.3 million recruits and non-participating centers did not adopt these unproven recommendations while training 1.2 million recruits. Preliminary analysis of this trial has been presented (20).

Based on the ERD rates observed in 1977-1981 (3, 9), we predicted 15 deaths with sickle cell trait at participating centers. No deaths were observed in the training of 40,000 recruits with sickle cell trait. There was a trend toward better survival among recruits without hemoglobin S (19 deaths predicted but only 11 observed). Among non-participating centers there was no significant difference between predicted and observed deaths (14 each) regardless of hemoglobin type. These data support the view that preventable unrecognized exertional heat illness is the predominant factor causing exercise-related deaths with sickle cell trait and may be a substantial factor contributing to such deaths in recruits without hemoglobin S. This approach appeared able to prevent excess mortality with sickle cell trait in recruit basic training. This study has not undergone peer review nor have the full details of the trial been published.

The question remains of whether or not excess ERD rates with sickle cell trait are caused by polymerization of hemoglobin S. We have attempted to determine whether alpha-thalassemia is protective for ERD with sickle cell trait. We sought well-defined cases of fatal or life-threatening complications of exercise in healthy young adults with sickle trait and a report of quantitative hemoglobin electrophoresis. Preliminary analysis of 33 cases showed that the frequency of alpha-thalassemia in these cases was more than ten-fold below the expected value for unselected African-Americans (3, 21). Current analysis of 44 cases substantiates this. We conclude that a low fraction of hemoglobin S must be protective for ERD with sickle cell trait. Polymerization of

hemoglobin S must be a necessary part of pathogenesis of excess fatalities with sickle cell trait. The possibility remains that additional mutations genetically linked to the beta globin gene are critical and define a susceptible subset of people with sickle cell trait.

Important risk factors for EHI which have been associated with ERD of young adults with sickle cell trait include inadequate hydration, environmental heat stress with a WBGT of at least 75ûF during the preceding 24 hours (18), heat retaining clothing, sustained heroic effort above customary activity, incomplete acclimation to heat, obesity with poor exercise fitness (22), inadequate sleep, and delay in recognition and treatment of EHI. The majority of cases were among recruits in basic training, and very few cases among permanent military members. About one-third of published cases resulted from civilian athletic or physical training programs. We are unaware of cases resulting from heavy work. The largest group of American athletes reported with sickle cell trait and fatal EHI was football players during preseason training. It is plausible that this situation combines risk factors from high environmental heat stress, poor acclimation, poor conditioning, heat retaining clothing, and a higher frequency of sustained metabolic exercise.

An important question is why ERD rates are more than ten-fold lower among military members than in entry training. While it is possible that highly susceptible individuals are removed by discharge or death in entry training, circumstances may be more dangerous during entry training. In support of this view, many of the fatalities during military service have come from demanding conditioning programs in specialized training schools for military members. The increased risk with age noted for recruits does not seem to apply to military members, with only two military and one published civilian case aged more than 30 years. We believe that risk of unexpected ERD is largely confined to periods of intense conditioning for a new form of exercise or a sustained event at a level of performance for which the individual is unprepared. There are many reports indicating no increased morbidity or mortality for competitive professional athletes with sickle cell trait (3). Professional athletes remain fit during the off-season and seldom have to go through conditioning at an intensity comparable to military basic training. Further, water for hydration is readily available during athletic events.

Our recommendations for safe exercise by individuals with sickle cell trait are based upon the premise that the predominant cause of excess morbidity and mortality is preventable exertional heat illness. At least half of these cases were proven to suffer from acute exertional heat illness, with rhabdomyolysis the predominant component. The other half of cases died suddenly without a clear etiology, but with evidence for increased risk of unrecognized EHI when such evidence was sought. The controlled study supporting this view has not undergone peer review and publication.

Effective prevention of EHI during demanding physical conditioning requires following measures similar to those used by recruits and distance runners (3, 18-20). Performance levels should be built up gradually, avoiding severe muscle pain. Training should cease and restart gradually when substantial myalgia occurs. Adequate hydration with increased water intake rising with environmental heat stress is essential. In the evening of any hot day with a WBGT value above 75ûF, the athlete should be sure to ingest adequate amounts of salt and potassium to replace sweat losses and water to replace fluid deficits. We recommend checking the color of the

first AM urine in a clear plastic cup as an easy method to identify people who are dehydrated from prior day heat exposure if measurement of urine specific gravity is not readily available. Those with darker urine can drink an additional pint or quart of water before starting exercise. Athletes in a demanding training program can keep a log of daily weights from the same scale on waking and on going to sleep.

Over-hydration is possible with consequent hyponatremia, seizures, and death. Oral hydration should not exceed one quart per hour or 12 quarts per day without monitoring of blood chemistries. Patients with muscle cramps require additional salt, which can be taken orally as two teaspoons of salt in a quart of water or intravenously as half-normal or normal saline. During sustained exercise, such as marching, middle to long distance running, basketball, and soccer, athletes should drink water at intervals of approximately 15-20 minutes.

Sodium and potassium replacement with meals avoids aggravating the common trend toward hypernatremia during exercise in heat. One should be careful to avoid sustained full intensity efforts lasting more than two minutes that require at least six METS, with special attention to exercise at full competitive intensity or that requires over ten METS for more than two minutes. Levels of activity should be adjusted for the WBGT level at the exercise site measured every 30-60 minutes. At the same time the fraction of time spent at rest and the minimal level of hourly hydration should increase with rising WBGT.

The level of heat stress is affected by the extent to which clothing permits heat loss and blocks radiant sunlight. High metabolic activity should be conducted in loose, light clothing during hot weather, with appropriate protection from radiant sunlight, such as head cover, during lesser activity. Rapid treatment in the field and during transport to a hospital is the best was to minimize the severity of exertional heat illness. Demanding physical conditioning is safer when conducted with an experienced trainer or medical personnel.

The athlete with sickle cell trait should understand the non-specific early warning symptoms and signs of EHI and obtain medical advice immediately. Common sense measures to optimize hydration and cooling should be started as soon as EHI is suspected. People with sickle cell trait should also be aware of the presenting symptoms and signs of hematuria and splenic infarction, both of which can occasionally occur as a consequence of heavy exercise. Individuals with sickle cell trait are potentially at greater risk with higher metabolic activity, longer periods of sustained effort, and exposure to high altitude.

Splenic infarction from sickle cell trait is more common with exercise at high altitude but has occurred with altitude exposure at rest or with exercise at sea level (3). Since there is no means to acclimate to this risk we advise against high altitude exposure and sustained exercise at an altitude greater than 7,000 feet, but there is contrary evidence in the literature. Many individuals with sickle cell trait have participated at professional and international levels of sport, including reports from the Olympic competition in Mexico City and high altitude long distance running in the Cameroon. Theoretically consistent maintenance of conditioning and consistent adjustments to minimize EHI permit continued safe levels of participation.

A relatively common clinical problem is what advice to give a person with sickle cell trait who has experienced exertional heat illness. I recommend permanent avoidance of physical activity at a comparable level after a single occurrence of severe EHI (heat stroke, or rhabdomyolysis with renal failure, or isolated renal failure). The level of risk following serious EHI has never been adequately measured, but expert opinions for patients with normal hemoglobin is that an increased risk of EHI is very likely for at least three to six months and may exist for years.

A more difficult problem is how to advise someone with Hb AS who develops asymptomatic elevations of serum muscle enzymes or myoglobinuria with a particular activity. Often this problem will resolve if the activity is conducted with attention to maintaining a low risk of EHI. However, several case reports described fatal rhabdomyolysis from middle distance running following such warning events. After a single warning event, one can cautiously condition the patient to a lower maximal activity, ensure that circumstances are optimal to avoid EHI and retest serum muscle enzyme levels 24 hours post-exercise. If inappropriate elevation of muscle enzymes persists, we advise that the person permanently limit their maximal physical activity to a level which does not raise the serum muscle enzymes. The physician should consider the possibility of an inherited metabolic disorder contributing to unexpected elevation of serum muscle enzymes.

Splenic infarction due to sickle cell trait

The spleen is unusually susceptible to vaso-occlusion related to hemoglobin S polymerization and red cell deformation. When persons with hemoglobin S are exposed acutely to high altitude hypoxia, the spleen is the organ most consistently injured by micro-vascular obstruction. Splenic infarction usually presents as severe abdominal pain localizing within a few hours to the left upper quadrant, accompanied by nausea and vomiting. Splinting of the left hemithorax, left pleural effusion, and atelectasis of the left lung often follow. A tender enlarged spleen often becomes palpable. Fever, leukocytosis, and an acute elevation of serum LDH level occur during the first 72 hours, out of proportion to serum CK, AST, or ALT levels. Splenic infarcts are best imaged by CT scan, which usually shows a few large regions of hemorrhage of variable size. Often small hemorrhages collect outside the splenic capsule.

While this appearance can be mimicked by a number of other processes, such a pattern of necrosis with acute onset is unlikely when the precipitating disorder is not obvious (for example, myeloid metaplasia). One exception is traumatic hemorrhage, which can progress over months or years, causing slow enlargement of the spleen and even erosion of adjacent ribs. Splenic infarction is readily differentiated from the early lesions of DIC, which are tiny foci of hemorrhagic necrosis diffusely scattered throughout the spleen. Prolonged DIC may produce large areas of hemorrhage, mimicking infarction from sickle erythrocytes. Liver-spleen scan with sulfur colloid usually demonstrates decreased perfusion of large regions of the spleen but are not as sensitive as the CT scan. Splenic infarction with sickle cell trait is usually self-limited, resolving in 10 to 21 days, and rarely requiring surgical intervention.

Non-traumatic splenic infarction following altitude hypoxia is most likely to occur in people with sickle cell disease and an enlarged and functional spleen prior to exposure. Such patients usually have hemoglobin SC or hemoglobin S/ß$^{+}$ -thalassemia genotypes rather than hemoglobin SS (3). Those with hemoglobin SS genotype have an atrophic, fibrotic spleen and are relatively protected from splenic infarction. These patients do, however, develop pain crisis in other locations. Splenic infarction with sickle cell disease occurs after shorter and milder exposures and is often more severe than with sickle cell trait. Presentation with severe anemia or progression of splenectomy are much more likely with sickle cell disease. People with sickle cell trait account for more cases of splenic infarction by dint of their larger number. The per capita incidence of splenic infarction is lower than with sickle cell disease. Sickle cell trait does not produce gradual chronic fibrosis or gradual splenomegaly. Rupture of the spleen requiring emergency splenectomy has been described twice in people with sickle cell trait (26, 27). Two patients with sickle cell trait and spherocytosis required splenectomy because of severe sequestration crisis (28).

When reviewing cases of splenic infarction attributed to sickle cell trait, it is important to confirm that the patient did not have a form of sickle cell disease. Strict criteria to identify sickle cell trait as a cause of this syndrome are: a positive phosphate precipitation test or slide test for sickling (establishing the presence of hemoglobin S), a hemoglobin electrophoresis pattern consistent with sickle cell trait (e.g. more hemoglobin A than hemoglobin S and normal levels of trace hemoglobins), and a normal erythrocyte morphology, hemoglobin concentration, hematocrit, erythrocyte indices, and reticulocyte count when not acutely ill. Published case reports frequently lack comprehensive data, especially descriptions of erythrocyte morphology, splenic pathology and demonstration of recovery from acute anemia and an explanation of abnormal red cell indices, morphology, or acute elevations of reticulocyte counts. In adults with sickle cell disease there may be congestion and hemorrhage around terminal arterioles, fibrosis and thickening of terminal arteriolar walls, discreet infarcts, and scattered siderofibrotic and calcified nodules, the characteristic chronic lesion left at the end of hemorrhage or infarction. While these changes will follow symptomatic infarction with sickle cell trait, if there is no gross scarring and fibrosis and no siderofibrotic bodies in the spleen of an adult known to have hemoglobin S, one can reasonably conclude that the patient did not have sickle cell disease.

We summarized the published case reports of splenic infarction with sickle cell trait available to April 1994 (3, Table 8). Since then six published cases fulfill criteria for adequately documented cases of splenic infarction due to sickle cell trait and one did not. Two cases were added from my practice, for a total of forty-seven documented cases. Eleven of these cases exhibited acute recticulocytosis attributed to splenic hemorrhage and sequestration. Seven patients had abnormal erythrocyte morphology implying an additional red cell abnormality. Two cases exhibited an elevated hemoglobin concentration. Recovery from anemia was unconfirmed in the absence of follow-up studies for 13 patients.

Fifteen cases resulted from exposure to hypoxia at rest in aircraft and one additional case involved exposure in aircraft followed by exercise on the ground. Only one case involved a crew member, who might have been physically active during flight. No published cases have involved pilots. Twelve of the 25 cases with splenic infarction on the ground were related to exercise. Four case reports did not clearly exclude exercise at altitude. Two patients had hypoxemia from

disease rather than ambient oxygen tension. Splenic infarction was reported in at least ten patients with sickle cell trait who were exposed to no substantial altitude hypoxia, denied any exercise near the onset of symptoms, and were not known to have any defect in blood oxygenation. Two patients had acute hypoxemia in the hospital attributed to the effects of respiratory splinting, but without values after recovery to exclude chronic hypoxemia. Splenic infarction occurred previously with hypoxic exposure in ten cases.

The first adequately documented association of sickle cell trait with splenic infarction involved the large population of black servicemen flying in unpressurized aircraft during the Korean War. Subsequently many cases of splenic infarction were reported from Lake Tahoe and other resorts in the Rocky Mountains. These cases were often of Mediterranean or mixed ancestry. The possibility that white individuals with sickle cell trait are at greater risk of splenic infarction was suggested because of their predominance among cases occurring on the ground (3, 29). Among 32 patients with sickle cell trait whose splenic infarction occurred while on the ground, at least 24 had white ancestry (75%). Since roughly four percent of Americans with sickle cell trait are non-black, one would expect only one non-black patient. This difference was significant with p less than 0.01. Among 15 patients with splenic infarcts in aircraft, two were white. Perhaps even more striking, only four out of the 47 reported cases of splenic infarction with sickle cell trait were female. It is unclear whether the high association of risk with male gender or with non-black ancestry is due to undefined additional factors or is partially explained by the unusual populations from which cases are reported. High normal levels of MCV may be a risk factor for splenic infarction, possibly as a marker for red cell membrane defects which are thought by some to increase risk of splenic sequestration and splenic hemorrhage (3). It is surprising that splenic infarction has not been detected among cases of non-sudden death from exertional heat illness during heavy exercise, as reported for twenty of our patients (3). These observations support the view of Lemeul W. Diggs that sickling might not initiate the serious complications of exercise but may increase the severity when serious episodes occur (30).

The effect of α -thalassemia on frequency of complications related to sickle cell trait was discussed above. We performed an estimate of the frequency of alpha-thalassemia among cases of splenic infarction with sickle cell trait, using a hemoglobin S fraction less than 35% as a marker among the 33 patients with quantitative hemoglobin electrophoresis known to us. Three patients had hemoglobin fractions less than 35% versus the ten expected. This demonstrates approximately a three-fold protective effect of alpha-thalassemia trait, and implies that pathogenesis of splenic infarction involves polymerization of hemoglobin S.

Hematuria

The frequency of hematuria with sickle cell trait from renal papillary necrosis has been accurately measured in a single large study of elderly patients in Veterans Hospitals (15). Patients with sickle cell trait had a 4% admission rate for hematuria , a significantly higher rate than the 2% admission rate for patients with normal hemoglobin. The absolute rate of substantial hematuria requiring admission was probably higher than would be the case for a population not selected by hospitalization. It is reasonable to conclude that sickle cell trait results in an

approximate doubling of the incidence of hematuria from an unknown absolute incidence of 2% or less of hospitalizations. This implies that hematuria in people with sickle cell trait is often unrelated to sickling or papillary necrosis.

Patients with hematuria should be evaluated by an urologist, who will perform imaging studies and obtain tissue as needed to exclude structural lesions such as neoplasms and stones and correct any related problems with flow of urine from the calyces to the urethra. Hematuria from a coagulopathy should be considered. A few patients have been described whose hematuria was associated with otherwise asymptomatic von Willebrand's disease. A small number of case reports suggest that patients with sickle cell trait and hematuria who have von Willebrand's disease may have responded to infusion of DDAVP or cryoprecipitate. Efficacy has not been demonstrated by controlled studies. Since such therapy is low risk and has been effective for a few patients, one could consider screening for von Willebrand Factor deficiency. In the absence of controlled data for prevalence and effectiveness of therapy, most physicians only search for von Willenbrand factor deficiency if the prior history or the family history suggests a bleeding disorder.

Gross hematuria producing anemia and requiring blood transfusions has an unpredictable course. The problem can persist for weeks to months with many recurrent episodes. Occasionally bleeding becomes so profuse that anemia is life-threatening. Episodes of severe bleeding are more common in men than in women. Most are unilateral with the left kidney involved more frequently than the right, while 10% are bilateral. Spontaneous resolution without any treatment occurs frequently, making the evaluation of any form of treatment difficult in the absence of controls. Patients with serious hematuria usually have involvement of multiple papillae in both kidneys, with a high risk of eventual bleeding on the opposite side. Nephrectomy should be avoided if at all possible.

Evaluation of hematuria routinely includes an IVP, ultrasound, and CT scan. The IVP will often show lesions at the tip of multiple calcynes in both kidneys. The most sensitive tests are a retrograde IVP and urteroscopy, which are reserved for patients with problems requiring intervention to reduce bleeding.

When patients with sickle cell trait present with substantial bleeding the standard practice in the past was to place patients at bed rest under sedation in hospital, and give intra-venous hydration, reduce tonicity by infusion of water, alkalinize the urine by giving sodium bicarbonate, and administer diuretics to sustain a high urine output. These measures have been justified by theoretical considerations rather than substantial controlled observations (6, 31).

A subsequent controlled trial of aggressive reduction in serum tonicity was conducted for patients with sickle cell disease, using hypotonic fluids and infusions of DDAVP. A clear effect reducing in vivo hemolysis required a dangerous level of hyponatremia. This observation dampened enthusiasm for aggressive methods to reduce serum tonicity in sickle cell trait. With no controlled trials this treatment has now fallen out of use. Physicians at our institution seldom put patients on complete bed rest when not hospitalized but ask people with persistent hematuria to avoid exercise while continuing to perform sedentary work. Alkalinization of urine has been considered useful, but controlled studies have not been done. Patients are often given 800 to

1,000 meq per day, in the hope that less polymer will form with a lower urine pH. The lower urine pH is thought to encourage the passage of pieces of renal tissue which may slough from the papillae during gross bleeding.

With more experience treating sickle cell disease all of these measures have been pursued less completely. Most physicians place patients on restricted activity, continuing sedentary office work without exercise, and omit sedation. Water infusion is not used. Patients are hydrated with half normal saline to sustain a high urine output and keep serum osmolality in the low normal range. Sodium bicarbonate 650 to 1200mg per day is sometimes used based on anecdotal experience. This might assist in excretion of pieces of necrotic renal papillae which may slough into the calyces during hematuria. Some physicians give modest doses of furosemide supported by adequate intravenous hydration to sustain a high urine output.

If these measures do not work in a few days, it is now customary to use antifibrinolytic agent, usually epsilon aminocaproic acid (EACA) (32). These agents inhibit urokinase, the major fibrinolytic enzyme in the urinary tract. They are concentrated in the urine, so the doses required to reduce hematuria may be 75-fold less than those required to inhibit serum fibrinolysis. They are used at doses far below those producing a systemic coagulopathy. The main side effect is an increased risk of clot formation in the urinary collecting system. Two leading investigators in this field stated the following: "until 1964 nephrectomy was needed in 50% of those patients with severe persistent hemorrhage. In that year Immergut and Stevenson showed the favorable effect of EACA in the control of hematuria associated with hemoglobinopathies." (6). They reported four consecutive cases of hematuria with sickle cell trait or disease, who responded to EACA (33). Since the use of EACA, nephrectomy for intractable hematuria has become quite rare.

An important controlled study of EACA was conducted a decade later (34). The duration of hematuria was examined for patients with hemoglobin S. Nineteen episodes treated with EACA stopped bleeding at a mean of 2.2 ± 0.3 days versus 11 episodes untreated with EACA which lasted 4.5 ± 1.9 days. The treated patients were selected for a more severe prior history (bleeding for 22.5 ± 6 days prior to EACA versus controls bleeding for $10.3 \pm 1,7$ days prior to observation). This treatment utilized 6 to 8 grams EACA per day in four to six divided doses. The authors imply that therapy should continue at least three days beyond clearing of gross hematuria but they do not state the duration used. There was a trend toward shorter hematuria with an additional loading dose of five grams of EACA at the start of therapy but the difference in time to recovery was not statistically significant. This study reported a high incidence of ureteral obstruction by clots accompanied by flank pain (15/38 episodes with an IVP) which resolved without specific therapy over 2 to 37 days. Surprisingly, urteral obstruction by clot was not more frequent with than without EACA. Five patients received EACA while clot was present, three with pre-treatment clots and two with clots starting during EACA. These patients cleared their ureteral clots despite completing the planned course of EACA. In this small study preexisting or new clots in the ureters were not considered an indication to avoid using EACA at the low doses stated.

Formal controlled studies to establish the best dose range and duration of EACA for hematuria associated with hemoglobin S are incomplete (34). An uncontrolled study reported the use of

loading doses of EACA, 5 grams rapidly and then 10 grams over 12 hours, repeated once if hematuria continued (quoted in 34). After cessation of hematuria they kept the patients in hospital and gave a tapering dose for three days , starting with EACA at 15 grams orally per day and continuing with the lowest dose for another three days as an outpatient. This was successful for 8/11 patients with sickle cell trait and hematuria.

A number of clinicians performed controlled studies of EACA for prostatectomy during the 1960's and 1970's. The now outmoded technique for prostatectomy in use at that time resulted in substantial prolonged hematuria which was managed with EACA. These studies are most valuable for documenting tolerated doses of EACA and risk of complications. Probably EACA was being used at higher doses and longer durations than can be justified by studies of hematuria with sickle cell trait. Controlled studies demonstrated no increase in thromboembolism with administration of 6 grams of EACA in one day or 18 grams in 18 hours.

The largest published experience using EACA to treat hematuria was a report from Scandinavia, in which 526 patients with various forms of hematuria were treated (35). These authors felt that EACA in doses of 3 grams 3 to 4 times per day did not result in thromboembolism. The most relevant group in this study was a collection of patients with essential hematuria who were treated with 3 grams of EACA three times per day for a period of six weeks after cessation of hematuria. Contrary to claims made by McInnes (31), there are no reports of treatment of hematuria with sickle cell trait in this text. There were no controlled observations to justify the long duration of treatment after cessation of hematuria. The largest single group of patients they studied were patients with hematuria post-prostatectomy (250 patients), many of whom received larger doses of EACA. Interpretation of this post-prostatectomy experience with EACA is difficult because they used heparin at 650 units/hour to decrease risk of thromboembolsim. Several authors have quoted a remark that as little as 2 grams of EACA per day might be adequate to treat post-surgical bleeding disorders (6, 31). Review of the context in which this remark was made shows that it cannot be regarded as more than unsubstantiated opinion.

The best dose and duration for use of EACA in treatment of hematuria related to sickle cell trait has not been adequately investigated. The best documented effective dose schedule is 3 grams three times to four times per day for a period of one week, expecting to stop hematuria in two to three days for most patients. Whether given orally or intravenously seems to make little difference. The optimal treatment duration after macroscopic hematuria has stopped remains unknown with a range of clinical experience from three days to six weeks. Our recommendation is to continue with 9 to 12 grams of EACA daily for one to two weeks after cessation of hematuria using the longer period for patients who seem at high risk for recurrence.

Occasionally bleeding is so brisk or so persistent that it is necessary to perform invasive surgery to visualize bleeding sites to identify the pathology at those sites and to stop the bleeding by local measures in order to save the patient and the kidney. Often the surgeon will find multiple damaged calyces in both kidneys. Bleeding is unilateral for 90% of cases, with the left kidney the dominant site. Removal of necrotic or sloughed tissue may be necessary. Bleeding can be stopped by applying local pressure, by cauterizing small vessels which are bleeding, or by using chemicals thought to promote coagulation of injured surfaces.

It is important to avoid nephrectomy because the patient then acquires a high risk of losing both kidneys. At our hospital approximately 20 individuals with sickle cell trait are admitted for hematuria per year and approximately 5-8 patients have undergone surgery to stop bleeding with consideration of nephrectomy over the past ten years. All of these responded to local measures and avoided nephrectomy. In part because these cases are rare no controlled demonstration of efficacy has been conducted. In the future it may be possible to use new recombinent coagulant proteins under development which promote clotting to stop bleeding by systemic or by local treatments.

Urinary tract infection

Studies in Jamaica, England and America established that the rates of urinary tract infection are higher for women with sickle cell trait in comparison to racially matched controls (1, 2, 4, 6). This is best established for asymptomatic bacteruria of pregnancy, in which the rate is approximately doubled with sickle cell trait (36). Rates of pyelonephritis may be modestly increased during pregnancy. No increase in urinary tract infection was noted among men in the large Veteran's Hospital study (15).

Autosomal dominant polycystic kidney disease

Studies of families with autosomal dominant polycystic kidney disease indicate that the incidence of end stage renal failure from this disorder is identical for whites and blacks, but that age of onset of end stage renal failure is lower for black people with sickle cell trait (38 years versus 48 years, $p < 0.003$). Half of 12 black patients on dialysis for this disorder had sickle cell trait, as opposed to 7.5% of 80 black patients on renal dialysis for other conditions. Sickle cell trait is an important risk factor for early onset of renal failure in patients with autosomal dominant polycystic kidney disease (37).

Renal Medullary Carcinoma

Over a period of 22 years the Genitourinary Pathology Department of the Armed Forces Institute of Pathology collected 34 cases of a unique neoplasm, which they named renal medullary carcinoma (38). This is a highly aggressive carcinoma with unique radiologic signs and anatomic and microscopic histology. Thirty-three of the thirty-four cases they described had hemoglobin S (32 with Hb AS and one with Hb SC) and all the known victims were young people aged 11 to 39. When race was known all were black. Males predominated by 3 to 1 to age 24, after which the case number was similar by gender.

The dominant tumor mass, from 4 to 12 cm diameter, was in the renal medulla. Satellite lesions in the renal cortex and pelvic soft tissues and invasions of veins and lymphatics were usually present. "The lesions exhibited a reticular, yolk sac-like, or adenoid cystic appearance, often with

poorly differentiated areas in a highly desmoplastic stroma admixed with neutrophils and usually marginated by lymphocytes". In all cases metastases outside the kidney were noted at the time of nephrectomy. The mean survival after surgery was 15 weeks.

Radiologic studies demonstrated tumors arising from the central kidney, growing in an infiltrative pattern and invading the renal sinus. A few cases demonstrated caliectasis without pelviectasis and one case showed tumor necrosis into the collecting system. Contrast enhancement and echotexture were heterogeneous. A single angiogram showed hypovascularity.

Six additional patients were found in military records (39). All were young black adults, aged 24 to 36 years. Average survival from diagnosis was 3 months. Cytogenic abnormalities included monosomy 11 in 4/4 patients and abnormalities of chromosome three. Since 1995 at least seven other case reports have been published. Survival has been poor with minimal response to a wide variety of chemotherapy agents and some immunotherapies.

This very rare carcinoma has unusual biologic features since it is largely restricted to patients of African ancestry who are between 11 and 39 years of age. The relative rates of presentation with sickle cell trait versus sickle cell disease are approximately the same as the prevalence of these two genotypes (40 to one). In contrast to this the prevalence of renal cell carcinoma, a much more common tumor in this age group, is nearly 17 times higher than predicted in people with sickle cell disease but not higher with sickle cell trait (40). Early diagnosis of renal medullary carcinoma at a time which would improve survival has not yet been possible.

Other medical complications associated with sickle cell trait

In their large study of hospitalized veterans at a median age of 49 years, Heller et al. found a statistically significant association between surrogate markers for pulmonary embolism and sickle cell trait (15). The diagnosis of pulmonary embolism was made for 2.2% of those with sickle cell trait versus 1.5% (95% CI of 1.1 to 1.9). Since pulmonary angiograms were only rarely performed, diagnosis depended upon surrogate markers with a low specificity. Dr. Heller was therefore reluctant to regard these statistically significant results as clinically meaningful and feels that the observation of increased incidence of pulmonary embolism in this population is not adequately substantiated.

Among patients with sickle cell trait diagnosed with pulmonary embolism the frequency of thrombophlebitis was significantly higher but the frequency of hemoptysis was significantly lower. This study demonstrated a two-fold increase in essential hematuria (see above). This large study did not find an association between sickle cell trait and risk of vascular complications of diabetes, pyelonephritis, in-hospital mortality from acute myocardial infarction, or mortality or hospital stay post-surgical hospitalization. The combination of erythrocyte glucoe-6-dehydrogenase deficiency with sickle cell disease had no effect on mortality or length of stay, including the subset of patients with pneumonia. There was no significant decline in the fraction of elderly patients with sickle cell trait in comparison to younger patients, confirming no increased mortality with sickle cell trait.

Isolated case reports of unusual adverse events raise the possibility that surgery involving hypoxia or reduced perfusion could result in vaso-occlusion and serious complications for people with sickle cell trait. Some have recommended exchange transfusion to reduce the fraction of cells containing hemoglobin S prior to the tourniquet surgery (4) or for intra-thoracic surgery, especially open-heart surgery on cardio-pulmonary bypass (41). However, the best published controlled study appeared to show no additional risk for people with sickle cell trait who were not transfused, including some intra-thoracic cases (42). A subsequent controlled study of open heart surgery in Africa was interpreted as showing no adverse effects related to sickling for eleven patients with sickle cell trait and two with doubly heterozygous sickle cell disease (43). However, two patients with sickle cell trait died from complications of surgery. The authors attributed these deaths to unavoidable risk from severe cardiac lesions rather than any effect from sickling. Authorities differ in their recommendations for high risk surgery on patients with sickle cell trait, several favoring no exchange transfusion (2, 44) and others advocating exchange transfusion for both cardiac by-pass surgery and tourniquet surgery (42), or limiting this to tourniquet surgery (41).

A number of studies have shown association of sickle cell trait with prematurity and lower birth weight of babies (1, 2, 4). However, data supporting these trends indicate small effects not seen in all studies. These effects seem to have little real public health implication for the long term outcome for mothers or babies.

People with sickle cell trait are more susceptible to complications following treatment of hyphema. Slow flow of relatively hypoxic fluid in the chamber of the eye out of the filtration apparatus is a location in which both polymerization of hemoglobin S and obstruction of flow by rigid erythrocytes is likely (1, 2, 4). This can result in glaucoma and secondary hemorrhage. In a study from Tennessee of 99 eyes from 97 children with hyphema, secondary hemorrhage only occurred in 14 eyes of 13 children with sickle cell trait. The frequency with sickle cell trait was 64%, significantly higher than among 57 eyes without sickle cell trait (0%).

Complications attributed by some to sickle cell trait include proliferative retinopathy, worsening of diabetic retinopathy, stroke, myocardial infarction, leg ulcers, avascular necrosis and arthritis of joints, and increased frequency of the bends from diving. There is no convincing evidence that sickle cell trait increases the incidence of these problems. Some case reports may represent situations in which other variants of beta (4) or alpha globin produced undiagnosed sickle cell disease (4, 45). Others may be the consequence of phenotypes with increased 2,3-DPG or with arterial desaturation which has increased the rate of polymerization of hemoglobin S sufficiently to convert a patient with sickle cell trait into phenotypic sickle cell disease (4, 42, 46).

A study of 355 hospitalized black men with sickle cell trait was conducted to examine stratification of risk by hemoglobin S fraction for pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, and idiopathic hematuria. Hemoglobin S did not influence the frequency of these syndromes, providing evidence that sickling is not associated with these forms of vascular disease. However, the absence of a significant difference for hematuria, which was influenced by hemoglobin S concentration in a larger study, suggests that this study was not sufficiently sensitive.

Hemoglobin S Antilles

In 1986, Jean Rosa and colleagues in Paris evaluated a patient who had symptoms consistent with sickle cell disease, including recurrent episodes of pain crisis. The patient's hemoglobin evaluation by electrophoresis and HPLC showed evidence only of sickle trait. Structural analysis of the patient's hemoglobin S gene revealed two mutations. The expected mutation of glutamic acid to valine at position ß-6 was accompanied by a second substution at position ß-23 of valine to isoleucine (47). Since the mutation at ß-23 produced no chance in the charge of the hemoglobin, it separated identically to hemoglobin S by standard techniques. Only analysis at the level of a research laboratory can detect the second abnormality in the hemoglobin molecule. The mutant hemoglobin was named hemoglobin S Antilles, since the patient came to Paris from the French Antilles. Hemoglobin S Antilles is much less soluble than hemoglobin S. The consequence is that people heterozygous for hemoglobin A and hemoglobin S Antilles have symptoms and complications similar to those of patients with homozygous sickle cell disease.

A summary of the risks associated with sickle cell trait is as follows.

1. Splenic infarction at high altitude, with exercise, or with hypoxemia
2. Isothenuria with loss of maximal renal concentrating ability
3. Hematuria secondary to renal papillary necrosis
4. Fatal exertional heat illness with exercise
5. Sudden idiopathic death with exercise
6. Glaucoma or recurrent hyphema following a first episode of hyphema
7. Bacteruria in women
8. Bacteruria or pyelonephritis associated with pregnancy
9. Renal medullary carcinoma in young people (ages 11 to 39 years)
10. Early onset of end stage renal disease from autosomal dominant polycystic kidney disease

Increased risk of pulmonary embolism among older hospitalized patients and adverse outcomes from intrathoracic or open heart surgery remain unresolved areas of controversy. The level of evidence available is suggestive but not convincing for a substantial association with sickle cell trait.

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