not similar to SCT alone (22). Moreover, subjects with SCT may also be different with regard to all their remaining genes. New technologies in genomics and proteomics are revolutionizing the study of adaptation to environmental stress, particularly the adaptation to hypoxia and exercise (23). Of interest are the recent studies about the gene expression profiles of white blood cells (for the heat shock proteins) and skeletal muscle tissue in response to exercise and training stimuli, both showing many interindividual differences (5, 30). Together, these studies could explain some of the observations—exertional heat illness, training level of recruits—reported by Scoville et al. (20). Knowledge on human globin genes and their polymorphism shows that a mutation happens in a population and spreads because of its selective advantage (6). The HbS mutation occurred in regions of malaria endemicity and appeared to be, per se, asymptomatic and as a benign condition during physical activity. However, the fitness of this single mutation could depend on the genetic background of subjects when the mutation arose (6).

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COUNTERPOINT: SICKLE CELL TRAIT SHOULD NOT BE CONSIDERED ASYMPTOMATIC AND AS A BENIGN CONDITION DURING PHYSICAL ACTIVITY

Sickle cell trait (SCT; or AS hemoglobinopathy) is the heterozygous form of sickle cell anemia and is present in over 2.5 million African Americans. Its prevalence can reach 20–40% in some areas of sub-Saharan Africa and 10% in the French West Indies (12). SCT is usually considered a benign disorder compared with sickle cell anemia.
(SS hemoglobinopathy; Ref. 27) and the longevity of SCT carriers seems to be unaffected (2).

However, Kark and Ward (16) underlined that serious morbidity or mortality can result from complications related to polymerization of deoxy-HbS in SCT. Bergeron et al. (4) demonstrated that only 45 min of brisk walking at 33°C significantly increased erythrocyte sickling in SCT carriers when hydration was not sufficient to offset a body weight deficit that may contribute to the exertional heat illness sometimes reported in SCT (15, 16). Several cases of splenic infarction with altitude hypoxia or exercise, exertional heat illness (exertional rhabdomyolysis, heat stroke, or renal failure), or idiopathic sudden death have been described in SCT carriers (10, 14, 16, 17, 25). Wirthwein et al. (30) recently described three cases of young black individuals with no significant medical history who died following physical exertion. In all three cases, postmortem hemoglobin (Hb) electrophoresis demonstrated the presence of HbS. Kark et al. (15) demonstrated a substantially higher risk of exercise-related death unexplained by prior disease in Army, Air Force, Navy, and Marine Corps recruits with SCT from 1977 through 1981. Metabolic or environmental changes such as hypoxia, acidosis, dehydration, hyperosmolality, or hyperthermia may transform silent SCT into a syndrome resembling sickle cell disease with vaso-occlusive crisis due to an accumulation of low deformable red blood cells (RBCs) in the microcirculation (16). Although the causal relationship between SCT and these medical complications have not been directly demonstrated, these reports have introduced doubts about the medical status of SCT carriers and led Ajayi (1) to recently propose that SCT has been misclassified as benign and asymptomatic and should be reclassified as a disease state.

Several studies have reported biological and clinical differences between SCT carriers and subjects with normal Hb that suggest that SCT carriers should be considered as symptomatic. Westerman et al. (29) demonstrated elevated d-dimers, thrombin-antithrombin complexes, and prothrombin fragments 1 and 2 in SCT carriers at rest, indicating that they may be prone to a hypercoagulable state in resting conditions. In addition, several reports have observed impaired RBC deformability at rest in this population using either a filtration method, optical tweezers, or a viscometer (5, 6, 23). The low RBC deformability observed in SCT carriers could be due to membrane disorganization related to abnormal interaction of HbS with the cell membrane and to dehydration promoted by higher activity of the RBC K⁺-Cl⁻ cotransporter and monocarboxylate transporter (MCT-1; Refs. 6, 19, 24). Impaired RBC deformability may adversely affect capillary recruitment and the physiological mechanisms that ensure adequate delivery of oxygen to tissue (22). Low deformable RBCs cannot pass through the narrowest capillaries leading to plasma skimming (plasma flow without RBCs) and tissue ischemia (18). Therefore, SCT carriers are often marked by high blood viscosity in comparison with subjects with normal Hb (6, 7) that can cause blood flow structuring disorders in both the microand macrocirculation (3) and promote tissue hypoxia (9). These hemorheological alterations are also thought to explain why SCT carriers may be prone to asthma (21) and cardiac events (8, 20).

Connes et al. (8) recently demonstrated that SCT carriers with high blood viscosity presented impaired nocturnal autonomic nervous system activity compared with subjects with normal Hb. A loss or imbalance of autonomic nervous system activity is a powerful and independent predictor of adverse prognosis in patients with heart disease, as well as in the general population (28). Therefore, SCT carriers might be more predisposed to cardiovascular complications than subjects with normal Hb (8), although older studies using more classical methods suggested normal cardiac function in this population at rest and during exercise (11, 13).

The fatal events observed in SCT carriers often occur in response to exercise (10, 14–16). Senturk et al. (26) recently suggested that the often observed hemorheological alterations induced by exercise in healthy subjects could have deleterious effects on tissue perfusion, especially during the immediate recovery, because the hemodynamic enhancements of shear rates are rapidly reversed after the cessation of exercise. Thus the prolonged hemorheological changes that persist during recovery increase the risk of exercise-related morbidity and mortality (26). The picture of blood rheological changes induced by exercise was recently investigated in SCT carriers in air-conditioned conditions and showed higher blood viscosity and lower RBC deformability in this population compared with subjects with normal Hb, both at rest and during a short supramaximal exercise and the subsequent recovery (7). This may constitute a risk factor for microcirculatory disorders and cardiovascular complications in this group, especially during the recovery when blood flow returns to baseline value. Although the SCT carriers were marked by hemorheological alterations, exercise did not magnify the difference with the control group that already existed at rest because the pattern of hemorheological changes induced by exercise was exactly the same in the SCT carriers and control subjects. Therefore, the risk for health complications in SCT carriers in response to exercise is not really due to the hemorheological changes induced by exercise but rather to the pre-exercise hemorheological alterations that are amplified during exercise and the immediate recovery.

These experimental data demonstrate that SCT carriers are marked by biological and clinical differences in comparison with subjects with normal Hb. Therefore, we do not agree with the assumption that SCT is asymptomatic. Moreover, the assumption that SCT is a benign condition should be reconsidered because the biological and clinical characteristics of SCT carriers could predispose them to harmful events, particularly during and after a strenuous exercise performed in high temperature without sufficient hydration (16).

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REBUTTAL FROM PROF. LE GALLAIS

Biological differences with subjects with normal hemoglobin (Hb) and data on morbidity and mortality led Connes and colleagues to suggest that sickle cell trait (SCT) should be considered as asymptomatic and not as a benign condition during physical activity.

Several reports have pointed out the occurrence of splenic infarction, heat illness, rhabdomyolysis, coagulopathy, and finally sudden death in subjects with SCT. Unfortunately, these reports are anecdotal and the causal effect of HbS has never been demonstrated (4). An epidemiological study has reported a substantially higher risk of exercise-related sudden death unexplained by prior disease in recruits with SCT during the 1977–1981 period (5). However, this result has been contradicted by a recent study, unbiased, and during a longer period, 1977–2001 (9). Lastly, high blood viscosity, impaired red blood cell deformability, increased coagulation activity, high plasma levels of adhesion molecules (7), and decrease in heart rate variability have been reported in subjects with SCT. Together, these risk factors may have resulted in well-documented cardiovascular deaths in subjects with SCT participating in these studies. This was not the case, nor was it in the above epidemiological studies, nor in trained athletes throughout the United States during 10 years (6). One would thus suggest that the risk factors hypothesized in SCT may have been compensated by some advantages, such as an increase in plasma HDL cholesterol levels (8) and/or unidentified markers that may have protected subjects with SCT from cardiac events.

Sudden deaths during exercise remain rare in SCT. It thus appears unjustified to consider all subjects with SCT at risk for exercise-induced sudden death and SCT as a disease state. Since 1950, all data on SCT have failed to ascertain a causal relationship between HbS and sudden death. This means that the single HbS mutation may be asymptomatic and benign and that sudden deaths in SCT may be due not to HbS mutation but to another Hb-dependent or -independent associated mutation or coexistent disease, possibly diabetes (1). This hypothesis now can be tested using new technologies in genomics and proteomics (10). DNA chips may be used to analyze polymorphisms and mutations that may underlie SCT and SCT individual variations (2). The polymorphism of cardiovascular enzymes (3) and the gene expression in skeletal muscle and white blood cells may provide new insights into the mechanisms of possible rhabdomyolysis, heat shock, and sudden

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