There is a long-standing controversy in the literature as to whether sickle-cell trait (SCT) should be viewed as a benign carrier state or as an intermediate disease phenotype. Because SCT is routinely detected by neonatal screening for sickle-cell disease, it becomes imperative that consensus on this issue be achieved in order to provide the best medical advice to affected individuals. The issue of selective screening in the post-neonatal period was thrust into the limelight recently by the National Collegiate Athletic Association’s recommendation that its member colleges and universities test student-athletes to confirm their carrier status if not already known. The stated goal of this recommendation was to prevent exercise-related sudden death in athletes with SCT. We review some of the reported complications of SCT for which new information has emerged, focusing particularly on venous thromboembolism and renal manifestations.

Introduction
Sickle-cell trait (SCT) is the term used to describe the presence in an estimated 300 million individuals worldwide of a heterozygous glutamic acid-to-valine substitution in the β-globin gene on chromosome 11 (HbAS). In the United States, 6% to 9% of the African-American population and 0.01% to 0.05% of the remaining population (primarily those of Arab, Indian, Hispanic, and Mediterranean descent) are carriers of the β+ mutation.1 In aggregate, this equates to approximately 3 million people. It has been appreciated for almost half a century that the high prevalence of HbAS and other hemoglobinopathy carrier states reflects the selection pressure afforded by protection of affected subjects against falciparum malaria.2 Protection appears to be quite specific for this organism, and it seems to mitigate the development of severe complications rather than mild, symptomless parasitemia.3 The molecular, cellular, and immunologic basis for the protective effect of SCT continues to be debated, but given the estimated 1 million annual deaths from malaria—primarily in sub-Saharan Africa—it remains a high-priority research area.

Early publications linked SCT to a wide variety of medical conditions,2 but many of these studies were small case series or uncontrolled observational studies. Appropriate concerns were raised about unwarranted stigmatization of sickle carriers, particularly considering that neonatal screening programs for sickle-cell disease (SCD) were being implemented at the time.4 A more recent review5 revisited the current understanding of the complications of SCT, listing them as: i) “definite”: renal medullary carcinoma, hematuria, renal papillary necrosis, hyposthenuria, splenic infarction, exertional rhabdomyolysis, exercise-related sudden death, and protection against severe falciparum malaria; ii) “probable”: complicated hyphema, venous thromboembolism (VTE), fetal loss/deemise, and low birth weight; iii) “possible”: acute chest syndrome, asymptomatic bacteriuria in pregnancy, and proliferative retinopathy; and iv) “unlikely”: stroke, choledolithiasis, priapism, leg ulcers, and avascular necrosis of the femoral head. However, it should be noted that the assignment of complications into these categories was not based on a systematic review of the literature, and thus the importance of some of the conditions may have been overrated while others might have been underrated. This review focuses on a few selected complications for which new information has emerged and discusses practical clinical implications.

Screening for SCT: When and Why
The neonatal screening programs that are now established in all 50 states and the District of Columbia have proven their effectiveness in the identification of SCD and the administration of life-saving antibiotic prophylaxis in early childhood.6 However, universal screening also “incidentally” identifies subjects with SCT. The success rate in notifying and providing genetic counseling to individuals with SCT has been noted to vary considerably by state.7 In addition, the changing demographics of the United States related to immigration from parts of the world with a high prevalence of SCT have also contributed to the recognition that only a minority of affected subjects are aware of their carrier status. Currently, subjects with SCT in the United States may also be identified when they enlist in the military (where screening has been employed for many years), when pregnant (although screening of pregnant women is non-uniform), and occasionally when donating a kidney for transplantation.8 In addition, for some years, college athletes have been screened for SCT in some but not other educational institutions. In June 2009, the National Collegiate Athletic Association (NCAA) recommended that all of its members and universities test student-athletes to confirm their carrier status if not already known. In 2007, a similar recommendation was issued by the College of American Pathologists, although it did not attract the same degree of attention. This controversial decision was precipitated by a lawsuit filed against the NCAA by the family of a student-athlete who died in 2006 from exertional rhabdomyolysis during football practice.

Exercise-Related Complications in SCT
During exercise, SCT appears to be a risk factor for sudden death and/or rhabdomyolysis, particularly when the exercise is intense, occurs in suboptimally conditioned individuals, is performed at high altitude, and especially when the subject is dehydrated or hyperthermic. This association has been recognized for several decades, but the best available epidemiologic evidence comes from the military. Kark et al. demonstrated an approximately 30-fold increased risk of sudden death in black Army recruits with SCT, with an absolute risk of sudden unexplained death of 32.2 per 100,000 in SCT, compared
with those without the β+ gene, who had an absolute risk of 1.2 per 100,000.11 More seasoned servicemen did not appear to be at the same high risk. The subsequent modification of drills and improved attention to hydration status in recruits during boot camp appeared to reduce the rate of SCT-related sudden death, although more recently, it has been on the rise again.12 The pathophysiology underlying these complications in SCT is not known, but is probably related (at least in part) to the hemorheological changes that can occur as a result of sickling of SCT erythrocytes within intensely exercising muscle.13 Recently, it has also been demonstrated that the skeletal muscle capillary structure in subjects with SCT may differ significantly from controls matched for fitness level.14 Specifically, muscle biopsies from SCT volunteers manifested a higher proportion of larger (>10 μm) microvessels, with an overall reduction of capillary density and degree of vascular tortuosity. Whether these changes contribute to maldistribution of muscle perfusion that contributes to exercise-related acidosis and rhabdomyolysis is unknown.

**VTE**

Although it has long been recognized that patients with SCD manifest laboratory evidence of constitutive hyperactivation of coagulation and platelets,15 and although a resultant tendency to develop VTE might be expected, the epidemiologic evidence to support this hypothesis has been sparse until recently. Two studies have now reported an increased risk of VTE in women with SCD during pregnancy and the postpartum period.16,17 Stein et al. analyzed National Hospital Discharge Survey data to demonstrate a higher prevalence of pulmonary embolism (but not deep vein thrombosis) in African-American patients with SCD compared with those without SCD.18 With regard to SCT, a similar analysis of more than 65,000 African-American males admitted to 13 Veterans Administration hospitals demonstrated that 7.8% were carriers of the β+ globin mutation, with no age-dependent decrease in the frequency of SCT.1 These data, in keeping with others available in the literature, suggest that SCT has little or no impact on overall life expectancy. Furthermore, in this study, no difference in the frequency of any diagnosis was observed between those patients with or without SCT, with the exception of “essential hematuria” (discussed below) and pulmonary embolism. Among patients with the HbAA genotype, 1.5% received a diagnosis of pulmonary embolism, compared with 2.2% of those with HbAS (p < 0.001).1

We utilized a case-control study of VTE in African Americans (the Genetic Attributes and Thrombosis Epidemiology or GATE study19), based in Atlanta, to determine whether SCT might be a risk factor for VTE. The GATE study included more than 500 hospitalized black patients with a recently diagnosed first or recurrent episode of VTE between March 1998 and September 2005, and an equivalent number of controls recruited from local medical clinics. The prevalence of SCT (6.2%) in the control group was similar to other African-American populations in the southeastern United States. The risk of VTE was increased approximately 2-fold among subjects with HbAS compared with those with HbAA (odds ratio [OR] = 1.8; 95% confidence interval [CI] 1.2–2.9). More strikingly, the OR for pulmonary embolism was 3.9 (95% CI 2.2–6.9).20 These results suggest a potentially novel mechanism for thrombophilia in African Americans, in whom the risk of VTE is 30% to 40% higher than that in Caucasian Americans. In fact, given the 6% to 9% prevalence of HbAS in the African-American community, our data suggest that the proportion of VTE attributable to HbAS in this population is approximately 7% compared with an attributable risk of about 3% for the prothrombin G20210A mutation in the white population.20 In a follow-up study, we evaluated the effect of oral and other hormonal contraceptive use on VTE risk in African-American women, and whether the association was modified by SCT. As with other case-control studies that have primarily included subjects of European descent, hormonal contraception was associated with about a 3-fold increased risk of VTE in African-American women.21 Furthermore, although the numbers were relatively small, we observed some evidence of synergy between SCT and hormonal contraception use, a finding that requires confirmation in other larger studies.

Because certain plasma “pre-thrombotic” biomarkers such as D-dimer have been shown to have predictive value in the assessment of future risk of primary VTE,22 it might be reasonably asked whether baseline levels of D-dimer are elevated in healthy SCT subjects compared with controls matched for race, age, and gender. In fact, such an association has been previously reported,23 and is confirmed by our own data obtained in healthy ambulatory African-American subjects with SCT (C. Amin, unpublished data). Currently, however, the mechanism(s) underlying the increased risk of VTE in SCT remains unknown.

Until further confirmation of the association between SCT and VTE is forthcoming, widespread screening of any racial/ethnic group with VTE cannot be recommended. It is also premature to conclude that women with SCT should be denied access to hormonal contraceptive therapy in any situation. VTE in subjects with known SCT should be managed according to accepted evidence-based recommendations, which have shown that with only a few exceptions, the most important determinant of the duration of anticoagulation therapy is whether the thrombosis occurred in a predictably high-risk situation (such as after surgery or trauma) or if it was unprovoked.

**Renal Complications**

Renal abnormalities are among the most widely acknowledged complications of SCT. Hematuria was first reported in SCT more than 50 years ago.24 It is thought to be the most common manifestation of SCT, although its true incidence remains uncertain.7,25,26 Based upon data from a large series of African-American patients admitted to Veterans Administration hospitals, hematuria accounted for 4% of hospitalizations among those with SCT, approximately twice the rate among those patients with a normal hemoglobin phenotype.1 The renal medulla represents an acidic environment characterized by low oxygen tension and high interstitial osmolarity. As blood traverses the slow-moving circuit of the medullary vasa recta, the hyperosmolar milieu may enhance dehydration of erythrocytes, allowing sickling and probable vaso-occlusion and medullary microinfarctions.25,26 Bleeding, which is typically painless, presents as microscopic or gross bleeding and may be associated with renal papillary necrosis. Involvement of the left kidney is more common due to its slightly larger size and higher venous pressure that results from compression of the left renal vein by the aorta and superior mesenteric vein.25,26 Conservative management of bleeding with bed rest and aggressive hydration is usually sufficient. In refractory cases, medical intervention with desmopressin or ε-aminocaproic acid, or even invasive intervention with ureteroscopy or angiography, has been advocated.26

The same vascular abnormalities that cause hematuria from ischemia and microinfarction also lead to the impairment of urinary concentration and even isoosmeneria. Microradiographs of the SCT kidney performed more than 30 years ago demonstrated reduction
and disruption of the vasa recta, the intricate vascular system of the kidney responsible for generating an osmolar gradient.\textsuperscript{27} Although not as severe as those seen in SCD, these vascular changes likely lead to the observed impairment of urinary concentration in patients with SCT.\textsuperscript{27} This loss of urinary concentration with dehydration may be a contributing factor in the development of rhabdomyolysis and sudden death related to exercise in SCT.\textsuperscript{7,12,13,28} The degree of impairment of urinary concentration is also variable among subjects with SCT, and may be related to the percentage of hemoglobin S, which in turn is determined by the co-occurrence of an α-globin gene deletion(s).\textsuperscript{29,30} Thus, among individuals with SCT, maximal achievable concentration of urine following administration of intranasal desmopressin acetate ranges between 530 and 845 mOsm, and is inversely correlated with the number of α-globin gene deletions.\textsuperscript{31} In the presence of two α-globin gene deletions (HbS concentration ~29%), urine concentration is only moderately reduced, while in those with no α-globin gene deletions (HbS concentration ~42%), the ability to concentrate urine is maximally impaired.\textsuperscript{31}

A rare but serious complication of SCT is renal medullary carcinoma. The original description of this neoplasm was reported in a series of 34 patients, 33 of whom had SCT.\textsuperscript{32} It still remains the case that nearly all instances reported in the literature occur in patients with SCT.\textsuperscript{33} This aggressive malignancy occurs twice as commonly in males, with mean age at presentation of 21 years. Chronic ischemia has also been implicated in the pathogenesis of renal medullary carcinoma, where it has been proposed that constant regeneration of the distal collecting duct epithelium gives rise to malignant transformation.\textsuperscript{26}

Given the architectural and functional renal aberrations, it is biologically plausible that SCT could be a risk factor for chronic kidney disease. In particular, SCT may augment the risk associated with a primary condition such as hypertension or diabetes, which are commonly implicated in chronic kidney disease in the African-American community. Among a cohort of African-American patients with end-stage renal disease (ESRD) due to autosomal dominant polycystic kidney, SCT was found in 6 of 12 (50%), compared with only 7.5% of African-Americans with ESRD due to other causes.\textsuperscript{34} This study did not evaluate the background prevalence of SCT among African Americans in the population from which patients were drawn. The investigators did find that those patients with autosomal dominant polycystic kidney and concomitant SCT developed ESRD nearly 10 years earlier than those without SCT, suggesting that SCT might enhance the progression of renal disease.\textsuperscript{34} Microalbuminuria, an early marker of renal injury, has also been demonstrated to be more common among patients with SCT, particularly among diabetic men.\textsuperscript{35,36} However, another study in diabetics failed to demonstrate this association.\textsuperscript{37} More importantly, there have been no studies addressing whether interventions typically employed for proteinuria, such as pharmacological blockade of the renin-angiotensin-aldosterone system, are beneficial in SCT.

We evaluated the prevalence of SCT among 188 African-American ESRD patients receiving care at four dialysis units. In this cohort, nearly 15% of patients were found to have SCT. In comparison, prevalence of SCT the local African-American population was only 7%, as determined by the results of the North Carolina state newborn screening program.\textsuperscript{38} This observation provides some support for the contention that SCT may indeed influence the progression of renal disease. However, given the observational nature of the study in a relatively confined population, it is possible that familial clustering could play a role in the heightened prevalence noted. Additionally, SCT patients were noted to have been on dialysis for a longer duration, raising the possibility that SCT could confer some survival advantage that would also manifest as a higher proportion among ESRD patients.\textsuperscript{38,39} In contrast to our findings, another study explored the influence of SCT in 376 African-American diabetics using routine HgbA1C assays to identify patients expressing HbS.\textsuperscript{40} African-American non-HbAS patients and HbAS patients had similar estimated glomerular filtration rates and prevalence of microalbuminuria. Using multivariate modeling, the investigators noted no difference in the combined outcome of peripheral vascular disease, retinopathy, and kidney failure.\textsuperscript{40} The absolute incidence of kidney failure in this population was not reported, although it was presumably low given the mean estimated glomerular filtration rate reported. Additionally, the cohort of African-American patients studied included a high proportion with SCT (~29%), which may indicate some unique characteristic of this cohort. The conflicting data from these two recent studies highlight the need for larger, prospective studies to determine the possible contribution of SCT to ESRD.

Finally, SCT may also affect the clinical course of ESRD. Anemia is almost universal among ESRD patients, and is routinely treated with erythropoiesis-stimulating agents (ESAs). African-American ESRD patients require higher doses of ESAs to achieve similar target hemoglobins as Caucasian patients.\textsuperscript{41} We recently examined whether the presence of variant hemoglobins influences the required dose of ESAs in the setting of ESRD. Among 155 African-American ESRD patients receiving hemodialysis at the University of North Carolina, the 24 with SCT and 10 with other hemoglobin variants (principally HbAC) were three times as likely to be ESA resistant.\textsuperscript{42} With both a possible high prevalence and the potential to modify ESA therapy, knowledge of SCT status may become important in the management of ESRD patients. However, these observations require confirmation (and consensus regarding the underlying pathogenic mechanism) before they are adopted into clinical practice.

**Conclusions**

Overall, the evidence suggests that SCT may be neither a completely benign carrier state nor a true disease entity, but rather a risk factor for certain adverse outcomes that result from the interplay between genetic and environmental influences. VTE and renal disease are among the manifestations under reevaluation. At present, the findings from case-control studies remain suggestive of an association with these outcomes but must be regarded as being far from definitive. Until such time as these observations have been confirmed, expanding screening efforts must be considered to be of little benefit. Nonetheless, with ongoing newborn screening identifying individuals with SCT, furthering research to better characterize the consequences of SCT is of paramount importance to providing better counseling on any associated health risks.\textsuperscript{28,39}

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