 Articles in PresS. J Appl Physiol (April 19, 2007). doi:10.1152/japplphysiol.00338.2007

Point-Counterpoint: Sickle cell trait should/should not be considered asymptomatic and as a benign condition during physical activity

Point: Sickle cell trait should be considered asymptomatic and as a benign condition during physical activity

Daniel Le Gallais,[1] Jean Lonsdorfer,[2] Pascal Bogui,[3] and Slaheddine Fattoum[4]

[1]*Dynamics of Cardio-Vascular Incoherences, EA 2992, Montpellier 1 University, CS 83021 – 30907 Nîmes, France*

[2]*La Robertsau Hospital, 67091, Strasbourg Cedex, France*

[3]*Department of Physiology, Cocody Hospital, Abidjan, Ivory Coast*

[4]*Molecular Biological and Biochemical Laboratory, Children Hospital, 1007, Tunis, Tunisia*

SICKLE CELL TRAIT (SCT) is found in approximately 8% of African Americans, and may reach up to 40% of West Africans. However, most of them are unaware of their status. This observation suggests that SCT may be asymptomatic and remains a benign condition for daily life activities (5). Indeed, numerous studies have reported that subjects with SCT had normal growth and development, normal morbidity (10) and mortality (21), and finally, normal life expectancy (12). Moreover, in worldwide countries of malarial endemicity, subjects with SCT have been found to be more healthy and apt to heavy physical labor than subjects without the trait. Our hypothesis that SCT can also be considered asymptomatic and as a benign condition during physical activity is based on. five kinds of data.

1 - Epidemiological studies on large popular sporting events. Of 1506 black males participating in the first Abidjan semi-marathon, SCT was detected in 123, i.e. 8.7%, a percentage similar to that observed in the general Ivory Coast population (15). Similarly, of 266 Cameroonian runners engaged in the International Mount Cameroun Ascent Race, SCT was found in 33 (12.4%), a prevalence similar to that of the ethnically corrected general population (25). These results suggest that, unlike patients with symptoms or subjects with

deleterious condition, there is no selective exclusion of individuals with SCT from participation to sports and physical activities.

2 - Epidemiological studies on specific sports practitioners. Murphy et al. (16) reported the presence of 39 (6.7%) subjects with SCT among the black football players in the National Football League. Similarly, 15 black high school athletes with SCT (10.5%) were observed by Diggs et al. (7). In physical education and sports colleges in Ivory Coast and Cameroon, the prevalence of SCT was reported to be 13.7% and 18,6%, respectively, i.e. percentages similar to those observed in the general population of these countries (12% and 17.3%, respectively) (13, 24). Theses studies suggest that SCT does not discourage its carriers from practicing high-level competitive activities, and from engaging themselves in sportive professions. Moreover, there are subjects with SCT among champions and record holders. Among 129 national Ivory Coast champions or record holders in races during the 1956-1989 period, we found 13 athletes with SCT (10.1%) (14). Among 122 national Ivory Coast track and field throw and jump champions during the 1956-1995 period, 34 were found to wear SCT (27.8%) (3). These percentages were similar, and significantly higher than that of subjects with SCT in the general population of Ivory Coast. Athletes with SCT participated to the 1968 Mexico Olympic Games, as reported by Pearson (17). These data indicate that athletes with SCT are quite able to perform at the highest level, which imply long-lasting and strenuous training.

3 - Physical aptitude of subjects with SCT. Aerobic (maximal oxygen uptake and ventilatory threshold) (18, 27) and anaerobic (maximal anaerobic power) (2) metabolisms have been found similar in subjects with SCT, and in controls with normal hemoglobin. However, blood lactate concentrations [La] during incremental exercise remain a controversial issue. Freund et al. (9) reported significantly higher [La] in SCT subjects than in controls. Unfortunately, these subjects exhibited significantly lower hemoglobin level than controls. In contrast, Gozal et al. (11), and Bilé et al. (3), found significant lower [La] in physical education students and sedentary subjects with SCT, respectively. Thiriet et al. (26) reported significantly lower [La] during consecutive anaerobic exercises in physical education SCT students than in controls. Recently, Sara et al. (19) took into account the different bias of the above mentioned studies, and measured [La] in the blood compartments of physical education students with SCT during incremental exercise and immediate recovery. They found no significant difference in whole blood, plasma or red blood cell [La] between SCT carriers and control subjects with normal hemoglobin. Neither the red blood cell / plasma [La] ratio nor the plasma-to-red blood cell

lactate gradient differed between groups. Lactate distribution in the blood compartments did not differ between the two groups. These findings suggest that lactate production and/or clearance is quite similar during exercise in subjects with or without SCT. High [La] during exercise are associated with acidosis, which may, in turn, trigger sickle cell crisis. The observation of similar physical aptitude, and similar or lower [La] in trained and untrained subjects with SCT during incremental (i.e. mainly aerobic) and anaerobic exercises is a key point to support our hypothesis that SCT should be considered asymptomatic and as a benign condition during physical activity.

4 - Studies on exercise tolerance in subjects with SCT. The cardiac responses to exercise of children (1), and of males and females with SCT (8) were similar to those of control subjects. Cardiopulmonary and gas exchange responses to acute strenuous exercise at low altitude (1,270 meters) (27), and at moderate inspiratory hypoxia corresponding to simulated altitude of 2,300 meters (28) were found comparable in healthy, black male basic recruits with SCT, and in control subjects.

5 - Follow-up of subjects with SCT engaged in official sports activities and military duty. During two seasons, the football and basket-ball squads of Melrose High School, which included students with SCT, participated in training programs and in competition, without apparent disability which could be ascribed to the SCT (7). Similarly, a prospective and carefully controlled study on the effect of army basic training at an altitude of 1,270 meters on SCT subjects failed to report any medical problem that could be directly attributed to SCT (29). Finally, an extensive epidemiological study on the nontraumatic deaths during U.S. armed forces basic training, 1977-2001, revealed that 26 deaths occurred in recruits with SCT. Interestingly, these 26 SCT deaths were all exercise-related, and due to congenital mitral valve disease, exertional heat illness, and idiopathic sudden death (20). One would thus suggest that none of the recruits with SCT died from a sickle cell crisis, i.e., due to SCT, and that the occurrence of idiopathic sudden death is inconsistent with the presence of symptoms.

Overall, SCT has to be reconsidered as a single-hemoglobin gene mutation. This means that subjects with SCT are similar for this gene, but that they may be different for all other hemoglobin genes. SCT associated with alpha-thalassemia is 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 spread because of its selective advantage (6). The HbS mutation occurred in regions of malarious 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).

Acknowledgments. The authors are grateful to Professor Michel Dauzat for his contribution to the manuscript preparation**.**

REFERENCES

1. **Alpert BS, Flood NL, Strong WB, Blair JR, Walpert JB, Levy AL.** Responses to exercise in children with sickle cell trait. *Am j Dis Child* 136:1002-1004, 1982.
2. **Bilé A, Le Gallais D, Mercier B, Martinez B, Ahmaidi S, Préfaut C.** Anaerobic exercise components during the force-velocity test in sickle cell trait. *Int J Sports Med* 17:254-258, 1996.
3. **Bilé A, Le Gallais D, Mercier J, Bogui P, Préfaut C.** Sickle cell trait in Ivory Coast athletic throw and jump champions, 1956-1995. *Int J Sports Med* 19:215-219, 1998.
4. **Browne RJ.** Sickle cell trait and sudden death. *Sports Med* 18:373-374, 1994.
5. **Büttner P, Mosig S, Lechtermann A, Funke H, Mooren FC.** Exercise affects the gene expression profiles of human white blood cells. *J Appl Physiol* 102:26-36, 2007.
6. **Charmot-Bensimon D.** Human globin genes: what can we learn from their polymorphism ? *Bull Soc Pathol Exot* 92:242-248, 1999.
7. **Diggs LW, Flowers E.** High school athletes with the sickle cell trait (Hb A/S). *J Nat Med Assoc* 68:492-493, 1976.

8. **Francis CK, Bleakley DW.** The risk of sudden death in sickle cell trait: noninvasive assessment of cardiac responses to exercise. *Catheter Cardiovasc Diag* 6:73-80, 1980.
9. **Freund H, Lonsdorfer J, Oyono-Enguéllé S, Lonsdorfer A, Dah C, Bogui P.** Lactate exchange and removal abilities in sickle cell trait carriers during and after incremental exercise. *Int J Sports Med* 16:428-434, 1995.
10. **Gima AS, Bemis EL.** Absence of major illnesses in sickle cell trait: results from a controlled study. *J Nat Med Assoc* 67:216-219, 1975.
11. **Gozal D, Thiriet P, Mbala E, Wouassi D, Gelas H, Geyssant A, Lacour JR.** Effect of different modalities of exercise and recovery on exercise performance in subjects with sickle cell trait. *Med Sci Sports Exerc* 24:1325-1331, 1992.
12. **Kramer MS, Pearson HA.** Growth and development in children with sickle cell trait. A prospective study of matched pairs. *N Engl J Med* 299:686-689, 1978.
13. **Le Gallais D, Lonsdorfer J, Fabritius H, Bogui P, Sangaré A, Cabannes R.** Prevalence of the sickle cell trait among students in a physical education college in Côte d'Ivoire. *Nouv Rev Fr Hematol* 31:409-412, 1989.
14. **Le Gallais D, Préfaut C, Dulat C, Macabies J, Lonsdorfer J.** Sickle cell trait in Ivory Coast athletic champions. *Int J Sports Med,* 12 :509-510, 1991.
15. **Le Gallais D, Préfaut C, Mercier J, Bilé A, Bogui P, Lonsdorfer J.** Sickle cell trait as a limiting factor for high-level performance in a semi-marathon. *Int J Sports Med* 15:399-402, 1994.
16. **Murphy JR.** Sickle cell hemoglobin (Hb AS) in black football players. *Jama* 225: 981-982, 1973.
17. **Pearson HA.** Sickle cell trait and competitive athletics: is there a risk ? *Pediatrics* 83:613-614, 1989.
18. **Robinson JR, Stone WJ, Asendorf AC.** Exercise capacity of black sickle cell trait males. *Med Sci Sports* 8:244-245, 1976.
19. **Sara F, Hardy-Dessources MD, Marlin L, Connes P, Hue O.** Lactate distribution in the blood compartments of sickle cell trait carriers during incremental exercise and recovery. *Int J sports Med* 27:436-443, 2006.
20. **Scoville SL, Gardner JW, Magill AJ, Potter RN, Kark JA.** Nontraumatic deaths during U.S. armed forces basic training, 1977-2001. *Am J Prev Med* 26:205-212, 2004.
21. **Stark AD, Janerich DT, Jereb SK.** The injcidence and causes of death in a follow-up study of individuals with haemoglobin AS and AA. *Intern J Epidemiol* 9:325-328, 1980.

22. Steingberg MH, Embury SH. Alpha-thalassemia in Blacks: genetic and clinical aspects and interactions with the sickle hemoglobin gene. *Blood* 68:985-990, 1986.

23. Storey KB. Gene hunting in hypoxia and exercise. *Adv Exp Med Biol* 588:293-309, 2006.

24. Thiriet P, Lobe MM, Gweha I, Gozal D. Prevalence of the sickle cell trait in an athletic West African population. *Med Sci Sports Exerc* 23:389-390, 1991.

25. Thiriet P, Wouassi D, Bitanga E, Lacour JR, Gozal D. Hyperoxia during recovery from consecutive anaerobic exercises in the sickle cell trait. *Eur J Appl Physiol* 71:253-258, 1995.

26. Thiriet P, Le Hesran JY, Wouassi D, Bitanga E, Gozal D, Louis FJ. Sickle cell trait performance in a prolonged race at high altitude. *Med Sci Sports Exerc* 26:914-918, 1994.

27. Weisman IM, Zeballos RJ, Johnson BD. Cardiopulmonary and gas exchange responses to acute strenuous exercise at 1,270 meters in sickle cell trait. *Am J Med* 84:377-383, 1988a.

28. Weisman IM, Zeballos RJ, Johnson BD. Effect of moderate inspiratory hypoxia on exercise performance in sickle cell trait. *Am J Med* 84:1033-1040, 1988b.

29. Weisman IM, Zeballos RJ, Martin TW, Johnson BD. Effect of army basic training in sickle cell trait. *Arch Intern Med* 148:1140-1144, 1988c.

30. Wittwer M, Billeter R, Hoppeler H, Flück M. Regulatory gene expression in skeletal muscle of highly endurance-trained humans. *Acta Physiol Scand* 180:217-227, 2004.

Counterpoint: Sickle cell trait should not be considered asymptomatic and as a benign condition during physical activity

Philippe Connes[1], Marie-Dominique Hardy-Dessources[2] and Olivier Hue[1]

[1]Laboratoire ACTES (EA 3596), Département de Physiologie, Université des Antilles et de la Guyane, Guadeloupe, pconnes@yahoo.fr – [2]UMR-Inserm U763/Université des Antilles et de la Guyane, Pointe-à-Pitre, Guadeloupe, F-97159 France.

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) (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 has 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) (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 micro- and 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), even though 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-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).

References

1. **Ajayi AA**. Should the sickle cell trait be reclassified as a disease state? *Eur J Intern Med* 16: 463, 2005.

2. **Ashcroft MT and Desai P**. Mortality and morbidity in Jamaican adults with sickle cell trait and with normal haemoglobin followed up for twelve years. *Lancet* ii: 784-786, 1976.

3. **Baskurt OK and Meiselman HJ**. Blood rheology and hemodynamics. *Semin Thromb Hemost* 29: 435-450, 2003.

4. **Bergeron MF, Cannon JG, Hall EL and Kutlar A**. Erythrocyte sickling during exercise and thermal stress. *Clin J Sport Med* 14: 354-356, 2004.

5. **Brandao MM, Fontes A, Barjas-Castro ML, Barbosa LC, Costa FF, Cesar CL and Saad ST**. Optical tweezers for measuring red blood cell elasticity: application to the study of drug response in sickle cell disease. *Eur J Haematol* 70: 207-211, 2003.

6. **Connes P, Sara F, Hardy-Dessources MD, Etienne-Julan M and Hue O**. Does Higher Red Blood Cell (RBC) Lactate Transporter Activity Explain Impaired RBC Deformability in Sickle Cell Trait? *Jpn J Physiol* 55: 385-387, 2005.

7. **Connes P, Sara F, Hardy-Dessources MD, Marlin L, Etienne F, Larifla L, Saint-Martin C and Hue O**. Effects of short supramaximal exercise on hemorheology in sickle cell trait carriers. *Eur J Appl Physiol* 97: 143-150, 2006.

8. **Connes P, Martin C, Barthelemy JC, Monchanin G, Atchou G, Forsuh A, Massarelli R, Wouassi D, Thiriet P and Pichot V**. Nocturnal autonomic nervous system activity impairment in sickle cell trait carriers. *Clin Physiol Funct Imaging* 26: 87-91, 2006.

9. **Connes P, Yalcin O, Baskurt O, Brun JF and Hardeman M**. In health and in a normoxic environment, VO2 max is/is not limited primarily by cardiac output and locomotor muscle blood flow. *J Appl Physiol* 100: 2099, 2006.

10. **Dincer HE and Raza T**. Compartment syndrome and fatal rhabdomyolysis in sickle cell trait. *Wmj* 104: 67-71, 2005.

11. **Estrade G, Poitrineau O, Bernasconi F, Garnier D and Donatien Y**. [Left ventricule function and sickle-cell anemia. Echocardiographic study]. *Arch Mal Coeur Vaiss* 82: 1975-1981, 1989.

12. **Fabritius H, Millan J and Le Corroller Y**. [Systematic screening of hemoglobinopathies in blood donors in Guadeloupe (French West Indies)]. *Rev Fr Transfus Immunohematol* 21: 937-950, 1978.

13. **Francis CK and Bleakley DW**. The risk of sudden death in sickle cell trait: noninvasive assessmanet of cardiac response to exercise. *Cathet Cardiovasc Diagn* 6: 73-80, 1980.

14. **Jones SR, Binder RA and Donowho EM, Jr.** Sudden death in sickle-cell trait. *N Engl J Med* 282: 323-325, 1970.

15. **Kark JA, Posey DM, Schumacher HR and Ruehle CJ**. Sickle-cell trait as a risk factor for sudden death in physical training. *N Engl J Med* 317: 781-787, 1987.

16. **Kark JA and Ward FT**. Exercise and hemoglobin S. *Semin Hematol* 31: 181-225, 1994.

17. **Kerle KK and Nishimura KD**. Exertional collapse and sudden death associated with sickle cell trait. *Am Fam Physician* 54: 237-240, 1996.

18. **Mchedlishvili G**. Disturbed blood flow structuring as critical factor of hemorheological disorders in microcirculation. *Clin Hemorheol Microcirc* 19: 315-325, 1998.

19. **Olivieri O, Vitoux D, Galacteros F, Bachir D, Blouquit Y, Beuzard Y and Brugnara C**. Hemoglobin variants and activity of the (K+Cl-) cotransport system in human erythrocytes. *Blood* 79: 793-797, 1992.

20. **Ould Amar AK, Pi Gibert A, Darmon O, Besse P, Cenac A and Cesaire R**. [AS heterozygote hemoglobinopathy and coronary risk]. *Arch Mal Coeur Vaiss* 92: 1727-1732, 1999.

21. **Palma-Carlos AG, Palma-Carlos ML and Costa AC**. Minor hemoglobinopathies: a risk factor for asthma. *Allerg Immunol (Paris)* 37: 177-182, 2005.

22. **Parthasarathi K and Lipowsky HH**. Capillary recruitment in response to tissue hypoxia and its dependence on red blood cell deformability. *Am J Physiol* 277: H2145-2157, 1999.

23. **Reid HL and Obi GO**. A study of erythrocyte deformability in sickle cell disease. *Trop Geogr Med* 34: 43-46, 1982.

24. **Sara F, Connes P, Hue O, Montout-Hedreville M, Etienne-Julan M and Hardy-Dessources MD**. Faster Lactate Transport across Red Blood Cell Membrane in Sickle Cell Trait Carriers. *J Appl Physiol* 100: 437-442, 2006.

25. **Sears DA**. The morbidity of sickle cell trait: a review of the literature. *Am J Med* 64: 1021-1036, 1978.

26. **Senturk UK, Yalcin O, Gunduz F, Kuru O, Meiselman HJ and Baskurt OK**. Effect of antioxidant vitamin treatment on the time course of hematological and hemorheological alterations after an exhausting exercise episode in human subjects. *J Appl Physiol* 98: 1272-1279, 2005.

27. **Steinberg MH**. Sickle Cell Trait. In: *Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management.*, edited by Steinberg MH, Forget BG, Higgs DR and Nagel RL. Cambridge: Cambridge University Press, 2001, p. 811-830.

28. **Task Force**. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 93: 1043-1065, 1996.

29. **Westerman MP, Green D, Gilman-Sachs A, Beaman K, Freels S, Boggio L, Allen S, Schlegel R and Williamson P**. Coagulation changes in individuals with sickle cell trait. *Am J Hematol* 69: 89-94, 2002.

30. **Wirthwein DP, Spotswood SD, Barnard JJ and Prahlow JA**. Death due to microvascular occlusion in sickle-cell trait following physical exertion. *J Forensic Sci* 46: 399-401, 2001.

Rebuttal

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 symptomatic, 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 it was in the above epidemiological studies, nor in that of 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 which 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 other 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 analyse polymorphisms and mutations which may underlie SCT, and SCT

individual variations (2). The polymorphism of cardiovascular enzymes (3), the gene expression in skeletal muscle and white blood cells may provide new insights into the mechanisms of possible rhabdomyolysis, heat shock, and sudden death reported in SCT during exercise, and thus, add to the debate.

1. Ajayi AA, Kolawole BA. Sickle cell trait and gender influence type 2 diabetic complications in African patients. *Eur J Intern Med,* 15:312-315, 2004.
2. Fehrenbach E, Ziegler D, Niess AM, Moeller E, Russwurm S, Northoff H. Microarray technology-the future analyses tool in exercise physiology ? *Exerc Immunol Rev* 9:58-69, 2003.
3. Folland J, Leach B, little T, hawker K, Myerson S, Montgomery H, Jones D. Angiotensin-converting enzymes genotype affects the response of human skeletal muscle to functional overload. *Exp Physiol* 85:575-579, 2000.
4. Jones SR, Binder RA, Donowho EM. Sudden death in sickle-cell trait. *N Engl J Med* 282:323-325, 1970.
5. Kark JA, Posey DM, Schumacher HR, Ruehle CJ. Sickle-cell trait as a risk factor for sudden death in physical training. *N Engl J Med* 317:781-787, 1987.
6. Maron BJ, shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. *JAMA* 276:199-204, 1996.
7. Monchanin G, Serpero LD, Connes P, Tripette J, Wouassi D, Bezin L, Francina A, Ngongang J, de la Pena M, Massarelli R, Gozal D, Thiriet P, Martin C. Effects of progressive and maximal exercise on plasma levels of adhesion molecules in athletes with SCT with or without alpha-thalassemia. *J Appl Physiol* 102: 169-173, 2007.
8. Rahimi Z, Merat A, Haghshenass M, Madani H, Rezaei M, Nagel RL. Plasma lipids in Iranians with sickle cell disease: hypocholesterolemia in sickle cell anemia and increase of HDL-cholesterol in sickle cell trait. *Clin Chim Acta* 365:217-220, 2006.
9. Scoville SL, Gardner JW, Magill AJ, Potter RN, Kark JA. Nontraumatic deaths during U.S. armed forcers basic training, 1977-2001. *Am J Prev Med* 26:205-212, 2004.
10. Storey KB. Gene hunting in hypoxia and exercise. *Adv Exp Med Biol* 588:293-309, 2006.

Rebuttal

Connes

The Point by Le Gallais et al. (8) does not provide clear evidence that sickle cell trait (SCT) should be considered asymptomatic and as a benign condition during physical activity.

The authors tried to convince us that SCT is not a limiting factor to practice sports activities at high level. However, as already demonstrated by the same authors more than one decade ago (6, 7), it is not right for endurance performance. These authors demonstrated that although the percentage of participation of SCT carriers in the first Abidjan semi-marathon was similar to the percentage of SCT in the general Ivory Coast population, none SCT carrier (without alpha-thalassemia) was internationally ranked (7). Moreover, when arguing that SCT carriers

are not prone to exercise tolerance, Le Gallais et al. (8) do not refer to recent data showing lower aerobic capacity in that population (2).

Le Gallais et al. (8) also based their argumentation on experimental data collected on lactate metabolism during exercise showing normal lactic response in SCT carriers. Red blood cells (RBCs) from SCT carriers are able to uptake lactate more rapidly than RBCs from non carriers (9). Although this adaptation could constitute an advantage during exercise, higher RBCs lactate transport activity could be responsible for lower RBCs deformability and therefore increased risk for blood microcirculation impairment (1).

At least, using the data published by Scoville et al. (10), Le Gallais et al. (8) tried to demonstrate that SCT carriers are not prone to substantially higher risk of exercise-related sudden death. However, Scoville et al. (10) found 35% of idiopathic sudden death (ISD) associated with SCT: it is not negligible. Eckart et al. (3) reinforced the analysis conducted by Scoville et al. (10) and reported 26 deaths in U.S. army recruits with SCT between 1977 and 2001 for a total of 126 nontraumatic sudden deaths related to exercise (3). Of 126 deaths, 44 were classified as ISD and 27% (i.e. 12 subjects) of ISD was associated with SCT. However, of 44 ISD, 24 occurred in African American recruits. Therefore, 50% of the ISD related to exercise that occurred in black recruits were associated with SCT. That comforts previous studies showing high prevalence of SCT in black military basic trainees with exertional sudden death (4, 5).

In conclusion, it is clear that SCT should not be considered asymptomatic and as a benign condition during physical activity.

References

1. Connes P, Sara F, Hardy-Dessources MD, Etienne-Julan M and Hue O. Does Higher Red Blood Cell (RBC) Lactate Transporter Activity Explain Impaired RBC Deformability in Sickle Cell Trait? *Jpn J Physiol* 55: 385-387, 2005.

2. Connes P, Monchanin G, Perrey S, Wouassi D, Atchou G, Forsuh A, Debaud J, Djoda B, Owona FX, Francina A, Banga PE, Massarelli R, Thiriet P and Martin C. Oxygen Uptake Kinetics During Heavy Submaximal Exercise: Effect of Sickle Cell Trait With or Without Alpha-Thalassemia. *Int J Sports Med* 27: 517-525, 2006.

3. Eckart RE, Scoville SL, Campbell CL, Shry EA, Stajduhar KC, Potter RN, Pearse LA and Virmani R. Sudden death in young adults: a 25-year review of autopsies in military recruits. *Ann Intern Med* 141: 829-834, 2004.

4. Kark JA, Posey DM, Schumacher HR and Ruehle CJ. Sickle-cell trait as a risk factor for sudden death in physical training. *N Engl J Med* 317: 781-787, 1987.

5. Kark JA and Ward FT. Exercise and hemoglobin S. *Semin Hematol* 31: 181-225, 1994.

6. Le Gallais D, Prefaut C, Dulat C, Macabies J and Lonsdorfer J. Sickle cell trait in Ivory Coast athletic champions, 1956-1989. *Int J Sports Med* 12: 509-510, 1991.

7. Le Gallais D, Prefaut C, Mercier J, Bile A, Bogui P and Lonsdorfer J. Sickle cell trait as a limiting factor for high-level performance in a semi-marathon. *Int J Sports Med* 15: 399-402, 1994.

8. Le Gallais D, Lonsdorfer J, Bogui P and Fattoum S. Point: Sickle cell trait should be considered asymptomatic and as a benign condition during physical activity. *J Appl Physiol*, 2006, this issue.

9. Sara F, Connes P, Hue O, Montout-Hedreville M, Etienne-Julan M and Hardy-Dessources MD. Faster Lactate Transport across Red Blood Cell Membrane in Sickle Cell Trait Carriers. *J Appl Physiol* 100: 437-442, 2006.

10. Scoville SL, Gardner JW, Magill AJ, Potter RN and Kark JA. Nontraumatic deaths during U.S. armed forces basic training, 1977-2001. *Am J Prev Med* 26: 205-212, 2004.