EDITORIAL

“Asymptomatic” Sickle Cell Trait

Of approximately 19,000,000 American Negroes, about 1,520,000 or 8 per cent possess the heterozygous genetic abnormality of AS hemoglobin. Only 2.5\textsuperscript{1} to 3.8 per cent\textsuperscript{2} of those whose erythrocytes contain S hemoglobin have sickle cell anemia (homozygous S hemoglobin); this invariably produces severe hemolytic and thrombotic disease. In addition, the large segment of the population possessing the sickle cell trait has a certain disease-producing potential, which in most instances can probably be prevented if certain types of stress are avoided.

Until recently, the sickle cell trait was considered to be completely asymptomatic. However, critical analysis of the morphologic defect of erythrocytes induced by the presence of reduced S hemoglobin indicates that certain clinical abnormalities may develop, particularly when unique anatomic or functional conditions exist. This is supported by repeated observations of in vitro sickling of AS erythrocytes and by the recent demonstration that the degree and ease of in vitro sickling and of blood viscosity are influenced by the total quantity of S hemoglobin in the erythrocytes and by alterations of pH in the presence of heterozygous S hemoglobinopathies.\textsuperscript{3} These and other experimental observations can be correlated with a number of clinical manifestations of disease which occasionally occur in patients with AS hemoglobinopathy.

Spontaneous hematuria has been observed in patients with sickle cell trait.\textsuperscript{4} Of equal significance, it has been demonstrated that certain individuals with this trait are incapable of concentrating urine normally.\textsuperscript{5} It is suggested that these aberrations of renal function are dependent upon the unique nature of the renal circulation which results in a “plasma skimming” effect, which in turn produces hemoconcentration within certain peripheral renal arterioles.\textsuperscript{6} Hemoconcentration encourages the development of increased viscosity of the blood, localized tissue hypoxia, and may eventually evoke in vivo sickling. On the other hand, the infrequency of occurrence of hematuria among patients with sickle cell trait requires consideration. It is possible that one of the normal functions of the kidney may protect most affected individuals from hematuria and other overt renal abnormalities. This function is concerned with the excretion of acids and the production and excretion of ammonia by the kidneys, resulting in tissue alkalosis within the kidney substance. Such a shift in pH may indeed prevent significant in vivo sickling and hematuria in the great majority of individuals with AS hemoglobinopathy.

The spleen also possesses a unique type of circulation. In the sinusoids of this structure circulatory stasis is normally encountered. This probably accounts for the development of regularly recurring splenic infarctions in patients with homozygous S hemoglobinopathy (sickle cell anemia) with the result that necropsy examination of adult patients with this disease almost invariably reveals the spleen to be a small mass of fibrous tissue.\textsuperscript{7} This circulatory peculiarity of the spleen, producing localized tissue hypoxia within the splenic sinusoids, may also be responsible for the development of splenic
infarction in patients with sickle cell trait during flight. The ease with which infarction occurs is directly related to the amount of S hemoglobin present. Flight at lower altitudes than those necessary to produce splenic infarction in the presence of sickle cell trait will evoke this phenomenon in patients with hemoglobin S thalassemia disease and hemoglobin SC disease.

In the latter two instances S hemoglobin is 50 per cent to 100 per cent more abundant than in patients with sickle cell trait.

It has been possible to produce a similar effect experimentally in sickle cell trait volunteers exposed to hypoxia simulating flight. The duration of hypoxia was usually 75 to 90 minutes. At or above a simulated altitude of 7,000 feet, splenic hypersequestration of erythrocytes labelled with radioactive sodium chromate was observed. This effect was usually evident within an hour after exposure to hypoxia was begun, and it persisted for 3 to 5 days. Coincident reduction of apparent erythrocyte survival time occurred. Complete reversal of both splenic hypersequestration of erythrocytes and shortening of apparent erythrocyte survival time occurred within three to five days following exposure to hypoxia. The double trauma of chromium-labelling and hypoxia on AS erythrocytes appears to produce selective splenic hypersequestration of these erythrocytes. Such an effect is reversible if the duration of hypoxia is brief and if the severity of hypoxia is moderate. It follows that more intense hypoxia of longer duration may produce an irreversible state which may be clinically expressed as splenic infarction.

Recently, in our clinic, we observed an elderly patient with sickle cell trait who also had arteriosclerotic heart disease and severe congestive failure. During the episode of cardiac decompensation, the patient developed clinical manifestations of hemolytic disease, and splenic hypersequestration of erythrocytes labelled with Cr was demonstrated. This observation suggests the possibility of splenic infarction and/or the production of an hemolytic state in patients with sickle cell trait in whom hypoxia may be due to causes other than flight at high altitudes.

There have been reports of cerebrovascular manifestations occurring in patients with sickle cell trait who presented no other obvious cause for thrombotic disease. It is tempting to suggest that this complication too may result from tissue hypoxia provoking in vivo sickling and thrombosis, but conclusive proof is lacking. At least one example of pulmonary infarction developing spontaneously in a patient with sickle cell trait has been described.

These clinical experiences and experimental data clearly indicate that the presence of the sickle cell trait imposes a very real threat. Exposure to hypoxia of either exogenous origin such as flight or of endogenous origin such as cardiac decompensation may produce a variety of clinical abnormalities. These are often dramatically acute in onset and may be of sufficient severity to threaten the life of the patient. Prompt recognition of the development of such an event usually permits the institution of a successful therapeutic regimen.

Since such a large segment of the population is involved, awareness of the problem should be encouraged among members of the medical profession,
the air transportation industry, the medical services of the Armed Forces and among Negroes themselves. The simplicity of performance of hemoglobin electrophoresis makes it practical to recommend that all Negroes entering military service be screened for this hemoglobinopathy. Further, the demonstration of sickle cell trait should be the basis for exclusion of affected personnel from flight status. Similar principles may be applied in civilian practice.

Finally, these observations point to the need for investigation of possible prophylactic measures which may be developed for the protection of almost 1 per cent of our population.

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