ANTI-SICKLING EFFECT OF DIETARY THIOCYANATE IN PROPHYLACTIC CONTROL OF SICKLE CELL ANEMIA

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As a clinical entity, sickle cell anemia (SCA) is known to be relatively rarer in Africans than in the African-American population of the United States. Paradoxically, sickle cell trait (SCT), the non-anemic, heterozygous condition, is about three times more common among indigenous Africans than in African-Americans. The ratio of SCA to SCT is 1:50 for African-Americans, and less than 1:1,000 for tropical Africans. This etiological disparity is attributed to an anti-sickling agent, thiocyanate, (SCN-) found abundantly in staple African foods, such as the African yam (Dioscorea sp) and cassava (Manihot utilissima). Staple American foods have negligible SCN-concentrations. Nonstaple foods in the American diet, such as carrots, cabbage, and radishes, have SCN-levels far below the African yam and cassava. This finding explains the high incidence of SCA among African-Americans and its rarity in Africans.

The author concludes that SCA is a congenital deficiency anemia, ameliorable by prophylactic diets of foods with high SCN-contents. Thus, "thiocyanate deficiency anemia" is nutritionally a more correct clinical status for those born with the homozygous sickle hemoglobin genome. Just as any iron undernourished person can suffer from iron deficiency anemia, sickle hemoglobin homozygotes suffer from "thiocyanate deficiency anemia" when they subsist on SCN-deficient foods. This article reviews the role of dietary SCN- in SCA control.

The rarity of sickle cell anemia (SCA) in Africans was in the past attributed to an unknown environmental protective factor. Song has noted that the active form of SCA is quite rare, while the harmless heterozygous sickle cell trait (SCT) occurs more frequently in Africans than in African-Americans in the United States. He pointed out that "the genetic theory of Neel and Pauling does not seem to explain fully the relationship between sickle cell trait and sickle cell anemia." Song then proposed that a protective factor is present in regions of Africa with negligible SCA etiology. The protective factor against SCA is now known to be thiocyanate (SCN-), which is found in the African yam (Dioscorea sp) and cassava (Manihot utilissima).

Lower levels of SCN- are found in nonstaples in the American diet, in carrots, cabbage, and radishes. Houston has estimated that a daily African meal contains about 40 times more SCN-than that of the African-American. The relative SCN-deficiency of American staple foods allows for the full and predictable incidence of SCA. Jamaicans experience the same nutritional prophylaxis against SCA as do Africans because of cassava diets in Jamaica. Serjant et al have reported that SCA is remarkably mild in Jamaica, and that the homozygous sickle hemoglobin phenotype is compatible with survival into and beyond middle age.
age. They pointed out that the benign clinical course of SCA in Jamaica must be because of the presence of an unknown indigenous protective factor, as patients with mild SCA suffer severe crises when they immigrate to the United States and are relieved on return to Jamaica.

Cassava (or manioc), popularly known as the "bread of the tropics," is among the cyanogenetic plants with the highest SCN- levels. In Africa, a popular cassava staple product, "gari," contains about 60 mg of thiocyanate for each 100 grams of cassava. In Jamaica, and other West Indian islands, "farine" is a well-known cassava-derived food. Hence, cassava, common to tropical countries, provides the major amount of SCN- needed for prophylactic control of SCA.

The yam (Dioscorea sp) is another tropical staple food with high SCN-. Yam flour is reported to have 50 to 60 mg/100 g. Both cassava and yam provide the African with effective dosages of SCN- to prevent clinical manifestations of SCA. It has been estimated that a daily African meal contains about 1 g of SCN-, which is about twice the dosage used to effectively resolve cases of sickle cell crises.

It is noteworthy that for a period of about 25 years, 1925 to 1950, fewer than 100 cases of SCA were documented in the whole of Africa. This included all ages of the population. After 1950, and to the present day, SCA is still relatively rare. Long-lived, almost asymptomatic adult cases have been reported in West Africa by Konotey-Ahulu and Ringelmann in East Africa, in Rhodesia, and in the southern part of Africa. Generally, the pathophysiology of childhood SCA in Africa is more benign than in the United States, and African adults on high SCN- foods rarely express any clinical anemia.

SPECIFIC REGIONAL DIETARY THIOCYANATE AND SICKLE CELL ANEMIA INCIDENCE

An inverse relationship between the incidence of SCA and SCN- yield of foods has been observed by Houston. In Rhodesia, clinical expression of SCA is mild and infrequent, and the onset in Rhodesian children is at about the age of 6, while SCA manifestations begin at about the age of 5 in African-American children. The Baamba people of Uganda with the highest SCT frequency in Africa (39 to 45 percent) showed no clinical expression of SCA and a virtual absence of Hb SS electrophoretic bands in all ages. Yet, a 4 percent Hb SS incidence for the Baamba was expected in accordance with gene dynamic calculations of the Hardy-Weinberg law. "Surprisingly none [Hb SS] were found," in the words of Lehmnn and Raper. The survival rate of Luo people with Hb SS of Western Kenya to adulthood is higher than in the United States. In West Africa, the protection accorded by SCN- foods against SCA is well documented. A passage in one Medical College Admission Test review manual states that many West Africans are protected from "both sickle cell anemia and malaria, not by medicine, but by yams . . . . Yams contain thiocyanate, a compound which prevents red blood cells from contracting into their crescent-like shape . . . ." Cassava and yams are staple foods in the above regions.

The survival rate of individuals with Hb SS to adulthood and old age varies in Africa depending on the variation of SCN- content of foods. For instance, in the regions where cassava, yam, and high-protein foods are given to children as a part of the weaning meal, SCA is rare. But, there are some regions where the traditional weaning meal is mainly a corn product, a semi-solid meal called "pap" or "akamu," which is devoid of SCN-. Hence, children in such regions may suffer from SCA, as they lack the protective factor. The survival rate is reported to be lowest in the lower Congo River, in Zaire, where kwashiorkor, a protein-deficiency disease, is also common among children. This fact is in keeping with the report that SCN- formation requires sulfur-containing amino acids, such as cysteine and methionine, contained in protein foods. Thus, high SCN- meals must be coupled with adequate protein intake to achieve the prophylactic, anti-sickling effect against SCA.

METABOLIC SIGNIFICANCE OF THIOCYANATE

Thiocyanate is a naturally occurring compound in body fluids—blood, urine, saliva, sweat, and tears. In plants, the parent compounds are nontoxic, sugary compounds called cyanogenetic glycosides, termed nitrilosides (or vitamin B17) by Krebs. Nitrilosides are initially hydrolyzed to
hydrogen cyanide (HCN) by β-glucosidase, an enzyme produced by intestinal bacteria as well as body tissues. The released HCN, in the presence of a sulfur donor (cysteine or methionine), is converted to nontoxic SCN- by rhondanese, an enzyme found in various organs and tissues of the body, with the highest concentration in the liver. Released HCN is used also by the liver for the production of vitamin B₁₂, cyanocobalamin, from provitamin B₁₂, hydrocobalamin.¹⁵ The liver is thus the organ most responsible for the formation of SCN- and vitamin B₁₂ from the HCN metabolic pool. High levels of preformed SCN-, as found in some plants (cassava and yam), arise from similar enzymatic hydrolysis of nitrilosides.

**ANTI-SICKLING EFFECT OF THIOCYANATE**

In 1932, Torrance and Schnabel¹⁶ used potassium thiocyanate (KSCN) to successfully resolve two cases of sickle-cell crisis. It was observed that KSCN promptly and effectively eliminated pain and discomfort in the patient. The KSCN dosage administered was less than half the effective dosage of cyanate, a well-known anti-sickling agent. Thus, KSCN is more than twice as potent as cyanate.² It is regretful that SCN- therapy for SCA was neglected subsequently, requiring a rediscovery after almost half a century!

Oxidation of the SCN- ion to cyanate is catalyzed in the erythrocytes by hemoglobin, which acts as a peroxidase.¹⁷ In this reaction, the intermediate product, HCN, is spontaneously converted to cyanate. Some investigators¹⁸,¹⁹ have shown that cyanate inhibits sickling of erythrocytes irreversibly in vitro and extends the life span of erythrocytes to almost normal in vivo.²⁰ In preliminary clinical trials with cyanate at the Rockefeller University, Gillette et al observed a decrease in hemolytic anemia in patients with the Hb SS phenotype as shown by the significant increase of hemoglobin and hematocrit in patients on an oral cyanate regimen. A daily cyanate dosage of 1,200 mg or 20 mg/kg of body weight was uniformly tolerated by the 12 patients studied. No significant toxicity was observed.²¹

Cyanate, the end product of SCN- oxidation in erythrocytes, binds to amino terminal valine residues of hemoglobin.¹⁸ Such a binding reaction, called carboxymylation, occurs at the site of error on the sickle hemoglobin molecule and thus corrects it. This error is known to be the substitution of nonpolar valine for polar glutamic acid on the sixth position of the beta chain of hemoglobin. Carboxymylation increases oxygen affinity of Hb S, thus increasing the proportion of oxygenated conformers of Hb S that cannot sickle. The electrophoretic mobility of Hb S treated with cyanate shows two bands: one band with the mobility of Hb A, and one with the mobility of Hb S²² instead of just one band for Hb S found in untreated Hb SS phenotypes. Carboxymylation causes a structural modification of the amino terminal of Hb S resulting in a protein variant with the functional characteristics of the normal hemoglobin A.²³

**DISCUSSION**

Neel’s formulation of the genetic basis for SCA states that SCT results from a heterozygous (Hb AS) inheritance, while SCA arises from a homozygous (Hb SS) condition.²⁴ The paucity of SCA in the face of high SCT frequency in Africans has led many investigators to refute Neel’s theory¹,²⁵ and to propose other theories to account for the observed clinical rarity of SCA. Edington et al²⁶ have also rejected the notion of early loss of Hb SS gene (by universal mortality of SCA infants) on the grounds that such a loss would have decreased SCT frequency in Africans, and that “it would have been such a ‘slaughter of innocents’ that it could not have escaped our attention.”²⁷ Lehmann²⁸ thought that a beneficial type of sickle cell gene (a term suggested by Raper²⁹) might exist in Africans, repressing the clinical syndromes of SCA. Working in Uganda for several years, Lehmann found only two cases of SCA. He stated that, “Even when electrophoresis became available, homozygotes seemed to escape us.”³⁰ Consequently, Lehmann traveled to the United States (Harlem Clinic in New York) “to look at sickle cell anemia patients for myself.” He commented that, “I had not seen patients like that in Uganda. Perhaps there was something wrong with the homozygous sickle cell anemia theory.”³¹

Neel’s theory of SCA inheritance is based on accepted contemporary mendelian genetic principles. Various investigators and laboratory scientists in Africa failed to detect significant numbers of people with the Hb SS phenotype because high SCN- in staple African meals converts Hb SS to a
Hb AS electrophoretic pattern. Hence, SCT frequency is raised, while SCA incidence is lowered by nutritional SCN-. As Hb AS is nonpathologic, clinicians could not diagnose the anemia either. In the United States, the expected incidence of SCA was observed as a result of dietary SCN- deficiency. Jamaicans subsisting on cassava have a similar nutritional protection to Africans, giving rise to Jamaican SCA of extremely mild clinical course.1

It is concluded that high SCN- diets give rise to low incidence of SCA in Africans, while SCN- deficient American meals cause an increased number of cases of SCA in the African-American population. The nutritional prophylaxis for SCA is achieved effectively by diets high in SCN- and protein foods. Such a nutritional regimen provides the tropical African with the protective factor against SCA, leading to the clinically observed relative paucity and better prognosis of SCA in Africa.

Dietary prophylaxis will certainly help solve the problem of SCA in the United States and in the world. African yams and cassava (gari), which are readily available in the United States, can provide the effective SCN- prophylactic dosages for SCA control. It is logical for cassava and yams, which are the staples for more than 300 million people of the tropics and subtropics, and have protected Africans against SCA for centuries, to be utilized for SCA protection for the African-American whose ancestral origin is also the African continent.

Literature Cited