ABNORMAL HEMOGLOBINS AND THALASSEMIAS IN COSTA RICA, OTHER COUNTRIES OF CENTRAL AMERICA, AND PANAMA[1]

German F. Sáenz,[2] Marciaq Altafulla,[3] Guillermo Sancho,[4] and Miriam Salgado[5]

INTRODUCTION

The hematologic heritage of the people of Costa Rica—and of Central America in general—is derived from the genetic traits of the native Amerindians and of the African, Asian, and European immigrants who settled there. In turn, these genetic traits tend to reflect the varied ecologic conditions of these peoples' historic backgrounds. Among other things, some of the genetic markers involved are characterized by a balanced polymorphism—this being especially true of the genes for hemoglobins S and C, both clearly of African extraction, that are considered deleterious to proliferation of malarial parasites, especially *Plasmodium falciparum.*

The influence of Asian immigrations in this picture has not been properly established. But it is well known that Black and Caucasian populations emigrated to Central America from various parts of Africa, the Antilles, and Europe; that native Amerindians made contributions to the present populations that vary greatly from country to country; that there have been differences, which persist, in the degree of racial mixing in the different countries; and that the selective pressure exerted by malaria has also been highly variable in the different regions. All of these factors are responsible for the different frequencies of abnormal hemoglobins and thalassemias found today in Central America and throughout tropical America *(1).*[6]

[2] Professor, Center for Research on Abnormal Hemoglobins and Related Disorders (Centro de Investigación en Hemoglobinas Anormales y Trastornos Afines—CIHATA), University of Costa Rica, San Juan de Dios Hospital, San José, Costa Rica.
[3] Physician, Hematology Service, Central Hospital, Social Security, Panama City, Panama.
[4] Physician, Rosales Hospital, San Salvador, El Salvador.
[5] Instructor, School of Microbiology, National Autonomous University of Honduras, Tegucigalpa, Honduras.

[6] An exhaustive search of the existing Central American literature on abnormal hemoglobins and thalassemias was made in the course of preparing this review. Among the disappointments encountered, our failure to find any published Nicaraguan literature on this topic appears especially unfortunate.

ABNORMAL HEMOGLOBINS

The treatment and control of malnutrition and various infectious diseases illustrate the advances achieved in medicine over the last two decades. As medicine has increased its knowledge of these illnesses, other inborn conditions capable of producing disease in human beings (especially children) have taken on greater importance. Among these we should note what are termed innate errors of metabolism, previously considered untreatable medical or research curiosities.

In times past, individuals afflicted with these hereditary ailments were obviously subject to infections and malnutrition; and it is logical to think that being more susceptible, they probably tended to die in their first years of life, and even when recognized did not constitute a large or significant group within the population. At present—thanks to better clinical control, improved knowledge, and more accessible laboratory techniques—a steadily growing proportion of the medical problems related to innate metabolic errors are being recognized; a certain amount of genetic counseling is being provided for affected families; and some treatment methods are being used.

Among the hemoglobinopathies, the problems of abnormal hemoglobins S and C and related disorders (such as G6PD deficiency) are of special interest to the countries of the Americas in general because of their prevalence and damaging effects. In 1971 an account by Arends (2) sought to report the prevalence of abnormal hemoglobins and related disorders in the countries of Latin America. Since then there has been growing interest in learning about the hemoglobinopathies in our countries—about both their epidemiologic aspects and their genetic, clinical, and anthropologic contexts.

Hemoglobins S and C

These hemoglobins are found in Central America among Black and mixed populations of clearly African extraction. No hemoglobin (Hb) polymorphism has been found in the small purely indigenous groups studied in Costa Rica (3, 4) and Panama (5).

In Costa Rica, a significant difference has been noted between the frequency of the Hb C marker among Black subjects in the Atlantic Coast province of Limón (2.40%) and subjects of mixed racial origins in the northern Pacific region of the province of Guanacaste (0.29%) (6, 7). The frequency of the Hb S marker is nearly the same in both regions (8.2% and 8.8%, respectively).

Superficially, at least, population movements suggest an explanation for this difference (8). Specifically, the Blacks living in the northern Pacific region of Costa Rica appear to have come from parts of Africa where the prevalence of Hb C is relatively low; in contrast, the Jamaican immigrants who became agricultural workers along Costa Rica's Atlantic Coast may have come originally from parts of West Africa such as Ghana where the prevalence of Hb C is relatively high.

Prevalences of Hb S and Hb C problems in other parts of Central America show great variability—both from one country to the next and within the populations of individual countries. Table 1 summarizes the results of surveys carried out in a wide range of Central

TABLE 1. Frequencies of heterozygous Hb S and Hb C markers (AS and AC) found by various investigators in a wide range of Central American populations.

Country and area	Race or type of study population	No. of study subjects	AS (%)	AC (%)	Reference No. of data source
Panama:					
Bocas del Toro	Blacks	356	10.4	5	9
Upper coast	Blacks	106	21.0	0	9
Upper coast	Blacks	268	15.0	2.2	9
Colón	Panamanians (general)	3,000	30.0	nt[a]	10
Chipre	Students	1,500	17.0	nt	10
Panama City	Hospital patients	896	6.0	nt	5
Panama City	Hospital patients	850	18.60	0.80	11
Colón	Hospital patients	428	21.02	nt	11
Chiriquí	Panamanians (general)	200	4.5	nt	12
El Salvador:					
San Salvador	Hospital patients	2,100	1.65	nc[b]	13
Honduras:					
Corozal	Caribbean Blacks	293	10.6	0.0	14
Santa Rosa	Caribbean Blacks	342	6.1	1.8	14
Limón	Caribbean Blacks	327	16.8	2.4	14
Tocamacho	Caribbean Blacks	209	8.6	0.0	14
Trujillo	Caribbean Blacks and mulattoes	500	8.2	nt	15
Guatemala:					
Livingston	Caribbean Blacks	82	18.3	—	16
Livingston	Blacks	68	17.6	—	16
Costa Rica:					
Santa Cruz, Guanacaste	Mestizos	227	7.5	nc	17
Liberia, Guanacaste	Mestizos	539	4.82	nc	18
Whole country	Adults	947	1.05	0.100	19
Whole country	General population	1,053	2.0	0.2	20
Limón	Blacks	621	8.2	2.4	6
Santa Cruz, Guanacaste	Mestizos	1,702	8.87	0.29	7
San José	University students	1,500	1.06	0.20	21
Nicoya, Guanacaste	Hospital patients (postpartum mothers)	231	3.90	0.87	22
Nicoya, Guanacaste	Hospital patients (newborns)	538	3.72	0.37	22
Whole country	Schoolchildren	12,000	0.80	0.10	23
Cartago	Caucasians (newborns)	671	0.30	nc	24
Limón	Blacks (newborns)	280	6.10	3.60	25
Santa Cruz, Guanacaste	Preschoolers	1,000	10.60	0.20	26

[a] nt = not tested.
[b] nc = no cases found.

American populations to detect Hb S and Hb C. Some of the apparent variations in these frequencies could arise from different laboratory techniques employed by different research groups, and also from the fact that many investigators employed relatively imprecise tests of sickling induced with 2% sodium metabisulfite (27) to demonstrate the presence of Hb S. In addition, use of phenotypically subjective criteria for racial classification could have caused substantial variation in the results listed in Table 1—including results of the survey of 12,000 Costa Rican schoolchildren (23), more detailed data from which are shown in Table 2.

Aside from exceptional conditions of hypoxia, the heterozygous hemoglobin S condition ($\beta^A\beta^S$) is benign and by itself causes no significant public health problem (28). But it appears to have no positive adaptive value when the selective pressure of malaria is absent. And since sickle cell disease caused by the homozygous condition ($\beta^S\beta^S$) and by β^S in combination with other genes for abnormal hemoglobin makes this gene a social liability, over the generations in places where malaria is absent its prevalence can be expected to decline (29). Of course, this decline is so slow as to be all but irrelevant for most health purposes.

Therefore, it is important to know the prevalences of this and other genes for abnormal hemoglobins in affected populations, so that health authorities can be alerted to watch for associated illness, so that physicians can have an indication of the relative significance of sickle-cell and related diseases among the hemolytic anemias of a given population, and so that appropriate countermeasures can be taken (1).

In this context it is worth noting the program for education and genetic counseling on sickle-cell disease that is now under way in Panama. Under this program, a commission of Social Security officials and community members seek to improve the approach to this public health problem.

The problem is serious in Panama because the prevalence of the Hb S gene is very high. As a result, the disease places major demands on health resources and imposes a heavy economic burden on the patients' families and the national economy—quite aside from the physical and psychological toll it takes on the patients themselves and the signifi-

TABLE 2. Frequencies of Hb S and Hb C markers among 12,000 Costa Rican schoolchildren classified as belonging to different racial groups.

Hb genotype	Racial classification of subjects		
	Caucasian[a] (%)	Mestizo[b] (%)	Black[c] (%)
AS	0.84	4.43	10.90
SS	0.00	0.04	0.29
AC	0.14	0.40	3.72
SC	0.00	0.04	0.29

[a] N = 6,911
[b] N = 4,740
[c] N = 349

cant social consequences for the patients and their relatives (11). The dimensions of the problem among populations of mainly African extraction are indicated by the relatively high percentages of patients with the homozygous genotype among groups of hospital patients studied in the provinces of Panamá and Colón (12). These percentages are shown in Table 3.

In Costa Rica, the first case of homozygous hemoglobin C disease (involving the Hb CC genotype) ever detected in the country was found in a boy 12 years of age in 1985 (30). The boy, who was Black, had marked splenomegaly, an infectious process, and an important anemic picture—possibly because he was experiencing a hemolytic crisis mediated by infection.

Sickling Syndromes

Sound information is lacking on the natural history and clinical picture of sickle-cell disease in the Central American countries. However, studies of hospitalized patients have been performed in Cuba (1) and Jamaica (31), and a cohort study begun in 1973 in Jamaica is seeking to define the clinical and hematologic behavior from birth of children with sickle-cell disease. Generally speaking, most of these studies have not focused on the benign forms of sickle-cell anemia, since these can only be identified through systematic studies covering a large part of the population.

Overall, the limited clinical experience to date in Costa Rica suggests that sickle-cell anemia shows the same broad variation in degrees of clinical severity that is found in other countries. Thus, we observe patients who are severely affected and others with benign manifestations.

In 1961, Elizondo (32) showed the Central American Medical Conference of that year a case of priapism caused by sickle-cell disease in a Mestizo subject with a Panamanian father and a Costa Rican mother. In 1965, Elizondo and Solano (33) reported a heterozygous hemoglobin S and hemoglobin C (SC) case in a subject of mixed racial origins from Guanacaste who exhibited a long-standing untreated chorioretinitis, neurologic alterations, and splenomegaly.

Zomer, in an unpublished report (34), has reviewed the files of 20 patients with sickle-cell disease at the San Juan de Dios Hospital in San José, Costa Rica, from 1967 to 1974. The ages of "adult" subjects at their first admission to this hospital ranged from 13 to 45 years, the average being 21 years. All of these patients came from parts of the country known to have an Hb S problem. In all, the 29 study patients had been hospitalized 114 times, for a total

TABLE 3. Frequencies of heterozygous Hb AS subjects and subjects with sickle cell disease (Hb SS) reported by studies of hospital patients in two provinces of Panama in 1981 (12).

Province	No. of subjects	Hb AS (%)	Hb SS (%)
Panamá[a]	850	18.6	6.0
Colón	428	21.0	8.9

[a] Also cited: 1.3% Hb SC and 0.80% Hb AC (12).

of 2,419 days, the average stay being 21 days. This latter figure contrasts with the overall average length of stay at this hospital, which was 11.5 days during the study period. The reasons for hospitalization of these patients and the main complications observed are shown in Table 4.

Since 1978 we have been trying to correctly identify the hemoglobin genotypes of patients with the sickling syndrome. At times these genotypes have not been identified correctly for lack of adequate analytic and genetic criteria. However, it is known that electrophoretic testing based on the positions of the Hb A, Hb F, and Hb S bands can serve to distinguish between various sickling syndromes including SS disease ($\beta^S\beta^S$); Hb S—β^0 thalassemia ($\beta^S\beta^{\text{thal }0}$); Hb S—$\delta\beta^0$ thalassemia ($\beta^S(\delta\beta)^{\text{thal }0}$); SS combined with alpha thalassemia (for example: $\alpha-/\alpha-$; $\beta^S\beta^S$); Hb S combined with the hereditary persistence of (pancellular) fetal hemoglobin found in Black populations (β^S, HPFH); SS combined with hereditary persistence of (heterocellular) fetal hemoglobin ($\beta^S\beta^S$,

HPFH); and Hb S combined with abnormal beta chain hemoglobins such as Hb Korle Bu ($\beta^S\beta^{\text{Korle Bu}}$).[7] This last doubly heterozygous condition has been found in a Black Costa Rican patient, now quite old, who for many years was diagnosed as having "atypical sickle-cell disease."

A careful analytical examination that includes electrophoresis of hemoglobin under both alkaline and acidic conditions, a quantitative solubility test, measurement of A_2 and F hemoglobins,[8] staining of Hb F in a blood smear, and examination of the patient's family history will generally permit determination of the patient's true genotype. Routine hematologic and clinical studies in such cases make it possible to advise the clinic of the existence of a disorder related to classic sickle-cell disease. This diagnostic

---

[7] The Greek letters alpha (α), beta (β), gamma (γ), and delta (δ) refer to different kinds of polypeptide chains in hemoglobin molecules. The principal type of hemoglobin found in the normal adult—known as hemoglobin A or Hb A—consists of two α and two β polypeptide chains, each chain being folded around a pocket containing a heme molecule. Thalassemias, caused by partially functional or nonfunctional genes for production of the alpha or beta chains, are termed α or β thalassemias. Since each person possesses two separate genes for production of the α chain, the normal α globin genotype can be designated as $\alpha\alpha/\alpha\alpha$. Varying degrees of thalassemia are associated with partially or completely nonfunctional genotypes designated as $\alpha-/\alpha\alpha$, $\alpha-/\alpha-$, $\alpha\alpha/--$, or $--/--$. Alternatively, the genotypes or phenotypes of subjects with thalassemia can be written using $+$ and $\circ$ superscripts, with α^+ and β^+ designating partial function and α° and β° indicating nonfunction.

In this system of annotation, β^A indicates normal production of the β chain found in hemoglobin A, β^S indicates presence of the sickle cell gene, and $(\delta\beta)^\circ$ indicates nonfunction of the genes responsible for producing both the β and δ chains. To designate genes involved with thalassemia, the letters "thal" (e.g., $\beta^{\text{thal }0}$) may be used (35).

[8] A_2 hemoglobin, normally a minor constituent of adult hemoglobin, contains two delta (δ) polypeptide chains instead of two beta chains; Hb F (fetal hemoglobin) contains two gamma (γ) chains instead of the β chains.

TABLE 4. Reasons cited for 114 hospitalizations and for various complications observed in 29 sickle cell anemia patients over 13 years of age who were admitted to the San Juan de Dios hospital in San José, Costa Rica, in the 1967–1974 period (32).

Reason cited	No. of patients
Painful crises	48
Leg ulcer	24
Jaundice	9
Anemia	9
Bone alterations	8
Lung problems	5
Urinary infection	4
Septic arthritis	3
Obstetric problems	3
Gluteus abscess	2
Enterocolitis	2

process is relatively easy when the hemoglobin level exceeds 9.0 g/dl, when microcytosis is evident, when splenomegaly persists in an adult, and when moderate clinical symptoms are present. The level of reticulocytes and the percentage of irreversibly sickled cells are also important factors.

On studying cases of sickle-cell disease in 14 individuals with mixed racial backgrounds (36), we found the hematologic values indicated in Table 5. The family study carried out in connection with this work led to detection of four people with the homozygous SS genotype combined with alpha thalassemia whose cases met the criteria cited for this double condition (37). These four subjects yielded the average hematologic values shown in Table 6. In addition, 38 relatives of the homozygous SS patients were found to possess the heterozygous Hb S gene. These 38 subjects were classi-

TABLE 6. Hematologic values found for four subjects with the homozygous sickle-cell genotype and alpha thalassemia in Costa Rica.

Item	Average value
Hb (g/dl)	9.55
Hematocrit (ml/dl)	29.1
Mean corpuscular hemoglobin concentration (MCHC, g/dl)	30.4
Reticulocytes (%)	8.0
Irreversibly sickled cells (ISC, %)	11.0
Hb A_2 (%)	3.1
HB F (%)	14.6

fied according to whether Hb S accounted for more or less than 34% of their total hemoglobin, as shown in Table 7. (The table only includes 36 subjects because two with iron deficiency were dropped from the "less than 34%" group.)

In general, it is known that a significant subgroup of the Black population with the homozygous sickle cell trait ($\beta^S\beta^S$) also has α^{thal} (38, 39). Many of these cases are confused with $\beta^S\beta^{thal \, o}$. This coexistence of $\beta^S\beta^S$ and α^{thal} (especially $\alpha^{thal \, o}$) gives rise to a hematologic picture characterized by microcytosis, hypochromia, high levels of Hb F, and higher figures for total Hb than is observed in classic sickle-cell disease. A slight relative increase of Hb A_2 (39) has also been described in these cases.

The clinical symptomatology of these $\alpha^{thal} \, \beta^S\beta^S$ syndromes, especially those with $\alpha^{thal \, o}$, is less severe than that of classic sickle-cell disease (40), possibly because the mean corpuscular hemoglobin concentration is reduced—a circumstance that (along with the increased Hb F) reduces the tendency to sickle. It is important to point out that splenomegaly, which is found in some 50% of the classic sickle-cell disease cases, may be found in the SS cases with α^{thal}; but it

TABLE 5. Hematologic values found for 14 subjects with sickle-cell disease in Costa Rica.

Item	Average value, ±1 standard deviation
Hb (g/dl)	7.9 ± 1.4
Hematocrit (ml/dl)	25.5 ± 3.5
Mean corpuscular hemoglobin concentration (MCHS, g/dl)	31.4 ± 1.3
Reticulocytes (%)	10.2 ± 4.2
Irreversibly sickled cells (ISC, %)	12.4 ± 6.6
Hb F (%)	10.6 ± 5.0
Hb A_2 (%)	3.5 ± 0.33
Serum iron (μg/dl)	75.0 ± 31.1
Total iron-binding capacity (μg/dl)	328.2 ± 69.8
Folates (nanograms/ml)	14.7 ± 9.4
Vitamin B_{12} (picograms/ml)	670 ± 254.6

TABLE 7. Concentrations of Hb S, Hb F, and Hb A$_2$ as a percentage of total hemoglobin (plus or minus one standard deviation) in 36 subjects heterozygous for Hb S. The subjects were divided into two groups for analytical purposes, those with over 34% Hb S and those with less than that percentage (30, 33).

Hb S (%)	Possible genotype	No.	Hb S (%)	Hb F (%)	Hb A$_2$ (%)
>34%	AS without $\alpha^{thal\,+}$	28	37.2 ± 1.6	1.1 ± 0.9	3.3 ± 0.3
<34%	AS with $\alpha^{thal\,+}$	8	32.9 ± 1.0	1.1 ± 0.9	3.3 ± 0.5

tends to be more conspicuous with $\alpha^{thal\,o}$ than with $\alpha^{thal\,+}$ (41).

In this regard, eight of the 36 Hb S (AS) cases listed in Table 7 also appeared to have $\alpha^{thal\,+}$, a logical finding since a large percentage of the people where the study subjects resided (in the province of Puntarenas) are of African extraction, and since the $\alpha^{thal\,+}$ gene is very prevalent among Blacks (42).

While environmental factors such as temperature and altitude may diminish the clinical picture of sickle-cell disease, socioeconomic factors are of primary importance, since improvement of the clinical picture and life expectancy of sickle-cell disease patients depends on general improvement of living standards (1).

It should also be noted that we have observed Costa Rican disease cases caused by the $\beta^S\beta^{thal}$ combination (both $\beta^{thal\,+}$ and $\beta^{thal\,o}$). These cases have had variable clinical pictures that were sometimes indistinguishable from SS disease and sometimes slight or moderate, independent of whether they involved $\beta^{thal\,+}$ or $\beta^{thal\,o}$. Thus the prognosis for such a case cannot be arrived at merely on the basis of these hemoglobin patterns.[9] We have also confirmed the usual and mild clinical picture of the disease caused by the combined presence of

hemoglobins S and C, together with the serious ocular complication involving proliferative retinitis and vitreous hemorrhage (43).

Uncommon Abnormal Hemoglobins

Several abnormal hemoglobins have been detected in Central America. These abnormalities involve the alpha, beta, and delta chains as well as combinations of portions of those chains such as that found in Hb Lepore. Table 8 lists the electrophoretic mutants reported as of 1984. The list is modest, partly for lack of systematic studies in the Central American countries except for surveys conducted in Costa Rica (23). (To support efforts that are needed in this regard, the Costa Rican multidisciplinary group studying hemoglobinopathies, with PAHO support, has published an analytical protocol applicable to developing countries for identifying Hb variants, thalassemia syndromes, and glucose-6-phosphate dehydrogenase (G6PD) deficiency—50.)

To help assess the presence of uncommon hemoglobins identified thus far in our countries, it should be mentioned that no Hb polymorphisms have yet been detected among the indigenous peoples of Central America, and most of the variants present in nonindigenous

---

[9] There are a good many molecular variations within the general thalassemia α^+, α^o, β^+, and β^o categories; many of these molecular variations are not yet well understood.

TABLE 8. Uncommon hemoglobin variants reported in Central America as of 1984.

Country and Hb variant	Cases or families involved	Racial group	Reference No. of data source
Costa Rica:			
Korle Bu	1 family	Black	44
J Cubujuquí	1 case	Caucasian	45
E	1 family	Spanish-Indian	46
Suresnes	2 families	Mestizo	47
New York	2 cases	Asiatic-Mestizo	48
G Philadelphia	1 case	Black	49
A′$_2$	32 cases (in 17,000 subjects)	General population	50
El Salvador:			
N Baltimore	1 case		51
Panama:			
Q Iran	1 case		52
Korle Bu	1 case		52
G Philadelphia	1 case		52
Lepore	1 case		52
Babinga	1 case		52

ethnic groups (such as Hb Korle Bu and Hb G Philadelphia) have come from Africa *(44, 49, 53)*. Some of these markers are specific to particular regions of Africa; hence, their presence in Central America tends to define the regions of origin of the Black populations among which they appear. For example, Hb Korle Bu, associated with populations in Ghana and the Ivory Coast, has been found in both Costa Rica and Panama *(44, 53)*.

Hb Cubujuquí, an abnormal hemoglobin produced by substitution of serine for arginine at position 141 (helix HC 3) on the α polypeptide chain, has been found in one instance in Costa Rica. The clinically silent condition, which was identified in a Caucasian Costa Rican schoolboy, resulted from a spontaneous point mutation *(45)*. Point mutations of this sort should give rise to slight polycythemia whenever the argi-

nine at position 141 of the α chain is compromised in stabilizing the desoxy form of the hemoglobin molecule.

Hemoglobin E has been found in Costa Rica in three members of a Caucasian-Mongoloid Salvadoran family *(46)*. Hb E is very frequent in Burma and Thailand, as well as in certain Mongoloid populations of India and Malaya; and it has been suggested that much of El Salvador's present population has resulted from the interbreeding of an indigenous (Mongoloid) race with Blacks and Caucasians, giving rise to Mongoloid (~80%) and Caucasian-Black (~20%) mixtures *(54)*. It has also been suggested that Hb E may have reached tropical America directly from Asia, or else via Africa (assuming that people from Malaysia traveled to the East Coast of Africa and then to the Americas—*1*).

Hb Suresnes, produced by substitution of histidine for arginine at position 141 (helix HC 3) of the α polypeptide chain, has also been found in a Costa Rican patient. This was the second Hb Suresnes case identified internation-

ally *(47)*, the first having been described in France in a male Caucasian child *(55)*. The Costa Rican involved was a healthy woman 23 years old with Hispanic-Indigenous ancestors and a racially mixed appearance. In the original report on Hb Suresnes, it was noted that the indicated substitution of histidine for arginine would mildly upset the oxy-deoxy balance of the hemoglobin molecule, producing slight erythrocytosis.

Hb New York—produced by substitution of glutamic acid for valine at position 113 (helix G15) on the β chain—was first described in a Chinese-North American family *(56)*. This hemoglobin has been reported in Costa Rica *(48)* in three members of two related families of Asian-Mestizo appearance. This apparent ancestry could explain Hb New York's presence, since subsequent publications report it being found among Chinese subjects in Taiwan *(57)*.

Hemoglobin B_2, also known as hemoglobin A'_2, results from a mutation affecting the delta chain (causing substitutions of arginine for glycine at position 16, helix A13). A study carried out in Costa Rica *(23)* has confirmed the existence of small amounts of Hb B_2 in some subjects. Specifically, its prevalence among Black study subjects was found to be considerable (2.58%); its prevalence was lower (0.29%) among Mestizos, and still lower among Caucasians (0.07%).

In Panama, the Babinga delta chain variant (produced by substitution of aspartic acid for glycine at position 136, helix H14) has been found, as have hemoglobins Q Iran and Lepore *(52)*. Panama has experienced tremendous Spanish-Black-Amerindian racial mixing and significant Arab, Jewish, and Asian immigration—including arrival of a large number of Hindu immigrants from India.

THALASSEMIAS

The indigenous peoples of Central America do not appear to have genes for thalassemia. That is, the few reports citing such genes indicate that they have resulted from relatively recent racial mixing, in the manner of the Hb S genes found among these Amerindians *(58)*. It can thus be inferred that the genes for thalassemia in these countries have been introduced by immigrants from places where these hereditary defects are relatively common.

In this vein, it is plausible to think that the epidemiology of the thalassemias, like that of the abnormal hemoglobins, has undergone significant changes in Central America because of racial mixing, a process that in the past was sometimes limited or controlled by racial segregation. At present, given the modern trend toward ethnic dilution and lowering of social barriers, the situation could continue to change significantly.

It is not generally possible to pinpoint the regions of origin of the thalassemias, partly because genes for thalassemia were widely distributed among various ancestral populations. In general, although there are marked variations in their frequency, both alpha and beta thalassemias are found in African and Mediterranean countries *(59, 60)*. In Spain, for example, β^{thal} is present in 1.1% to 3.43% of the population *(61, 62)*, although α^{thal} in that country is much less common *(63)*.

In most cases it is not possible to establish the racial origin of a specific thalassemia gene, partly because the clinical picture produced by each type of

thalassemia tends to be similar in different racial groups. Thus, even though beta thalassemia is usually moderate among Blacks, it sometimes shows the severe sorts of clinical pictures more commonly observed in Europeans.

At the molecular level, a great heterogeneity has been observed in both alpha and beta thalassemias, different genetic lesions having been demonstrated in different racial groups (64). In this vein, gene mapping has shown individual and demographic variations of each thalassemia variant studied in Black, Oriental, and Caucasian individuals. Since tropical America has a largely mixed population, it is expected that such genetic analyses will yield worthwhile anthropologic information and shed considerable light on the heterogeneity of existing thalassemia phenotypes and genotypes.

Alpha Thalassemias

Costa Rica is the only Central American country where the presence of α^{thal} has been reported (Table 9). Identification of this marker has always been accomplished on the basis of hematologic criteria and family studies. In general, it seems clear that the prevalence of α^{thal} in Costa Rica has arisen from a racial/ethnic mixing of the population that has mediated the Caucasian (European) influence as well as the Black (African) and Asian (especially mainland Chinese) influences.

The different forms of alpha thalassemia generally result from the interaction of two basic alleles ($\alpha\alpha$), both of which produce the alpha polypeptide chain. $\alpha^{thal\,+}$, involving partial nonfunction, is associated with the ($-\alpha$) haploid genotype; while $\alpha^{thal\,o}$, involving complete nonfunction, is associated with the ($--$) haploid genotype. Studies of Asian newborns suggest that the α^+ and α^o genes occur frequently among the Chinese, Malaysian, and Thai peoples (69). Different molecular lesions producing α^+ and α^o phenotypes have also been detected in Mediterranean peoples, though with a lesser frequency (70).

The α^o gene is not generally found in the Black race, a circumstance that may explain the absence of hemoglobin H disease among Blacks (71). (The presence of this disease in the Costa Rican and Panamanian populations is due to those populations' European and Asian ancestries—65–67).

Thai experience has demonstrated that the presence of Bart's hemoglobin among newborns provides the most practical basis for diagnosing α^{thal}

TABLE 9. Cases of alpha thalassemia diagnosed in Costa Rica.

Race of study subjects	No. of subjects	% with defect and the defect reported	Reference No. of data source
Mestizo	538[a]	1.12% (α^+ and α^o)	22
Mestizo	400	0.25% (α^o; $\beta^A\beta^S$)	65
Chinese-Spanish	1	Hb H disease ($\alpha-/--$)	66
Caucasian	671[a]	2.48% (α^+ and α^o)	24
Mestizo-Chinese	2	Hb H disease ($\alpha-/--$)	67
Chinese-European	1	Hb H disease ($\alpha\alpha/--$)	68
Black	270[a]	25% α^+, 3.5% α^o	25

[a] Umbilical cord samples.

in Oriental populations *(69)*. (Blacks who are heterozygous for $\alpha^{thal\,+}$ do not always show increased levels of Bart's hemoglobin—*1*).

In Costa Rica, as Table 9 indicates, three population surveys of alpha thalassemia have been conducted. The one involving 671 Caucasian subjects (newborns) evaluated the concentration of Bart's hemoglobin semiquantitatively using starch-gel electrophoresis. This study found the frequency of the silent α^+ phenotype to be 2.08%, and that of the $\alpha^{thal\,o}$ gene (severe thalassemia) to be 0.40% *(24)*. Another survey, of umbilical cord blood samples from 270 Black newborns, yielded Bart's hemoglobin values indicating that 25% of the newborns had the α^+ character while 3.5% had α^o *(25)*.

Beta Thalassemia

Aside from data obtained in Costa Rica, there is no precise information on either the presence or the frequency of the β^{thal} marker in Central America. This is partly because no analytical methodology has been devised to permit detection of the β^{thal} marker. The available Costa Rican data on the marker's presence, summarized in Table 10, were obtained by means of a simple and practical analytical approach that has been described elsewhere *(83)*.

Another important point here is that data on the prevalence of β^{thal} in Central America tend not to be representative of the ethnic groups comprising the population, either because only a few samples were analyzed or because sound criteria for adequately determining the racial composition of the study populations were lacking.

TABLE 10. Cases of beta thalassemia and hereditary persistence of fetal hemoglobin (HPFH) diagnosed in Costa Rica. (β^+ indicates the beta thalassemia gene with some β-chain production; β^o indicates the beta thalassemia gene with no β-chain production.)

Study subjects' classification or racial group	No. of cases	Phenotypes	Reference No. of data source
Mestizo	2	$\beta^S\beta^+$	72
Hospital patients	11	β^{thal}	73
Caucasian	9	$(\delta\beta)^{thal\,o}$	74
University students	2/1,500	HPFH (pancellular, Greek type)	74
Mestizo	5/1,702	HPFH (pancellular, Black type)	75
Caucasian	1	Cooley's anemia ($\beta^+\beta^+$)	76
Mestizo	2	$(\beta^S\beta^o)$	77
Black	1	$(\beta^{thal}$, increased Hb A$_2$ and Hb F)	78
Mestizo	2	$(\beta^S\beta^o)$	79
Schoolchildren	31/12,000	β^{thal}	50
Mulatto (Nicaragua)	1	Cooley's anemia ($\beta^+\beta^+$)	80
Italian (Costa Rica)	2/64	β^{thal}	81
Caucasian	1	Mild Cooley's anemia— thalassemia intermedia, $\beta^o(\delta\beta)^o$	82

Regarding actual cases of beta thalassemia, isolated cases have been reported in El Salvador and Panama. Also, the previously mentioned study of 12,000 Costa Rican schoolchildren showed 0.26% to have the disorder—a finding illustrating the relative importance of this gene in a fundamentally Caucasian population.

Since the eradication of malaria in Costa Rica, it has not been possible to corroborate the controversial finding of high hemoglobin A_2 values in connection with that pathology *(84)*.

The doubly heterozygous condition $\beta^S\beta^{thal}$—i.e., $\beta^S\beta^{thal\,+}$, $\beta^S\beta^{thal\,o}$, or $\beta^S(\delta\,\beta)^{thal\,o}$—has also been reported in Costa Rica *(72, 77, 79)*. However, it is not possible to identify the heterozygous β^+ and β^o states with routine or conventional hematologic methods unless one uses an appropriate genetic approach. The most solid evidence for specific primary action by β^+ and β^o genes is therefore obtained from hematologic and biochemical studies of doubly heterozygous states that involve another structural variant (such as β^S) of the beta chain. For this reason, the distinction between β^+ and β^o should only be made on the basis of an appropriate framework of genetic information—as was done, for example, in an article relating detection of the β^o gene in conjunction with hemoglobin S to the observed concentrations of hemoglobins F and S *(79)*.

In addition, homozygous beta thalassemia (known as thalassemia major or Cooley's anemia) has been reported in Costa Rica *(76, 80)*. The first reported case was diagnosed in a Caucasian Costa Rican subject and the second was found in a Black girl from Nicaragua. (This latter diagnosis provided the basis for our conclusion that this pathology existed in Nicaragua.) Subsequently, a case of mild Cooley's anemia (thalassemia inter-

media) with one delta chain gene involved—$\beta^{thal\,o}(\delta\beta)^{thal\,o}$—was diagnosed in a Caucasian girl *(82)*.

It is well known that the ethnic distribution of thalassemia major varies from country to country, although in general the disorder is found most often in Caucasians, among whom it produces a clinical picture similar to that observed in Mediterranean populations *(1)*. It is generally accepted that this disease is less severe among Blacks, a conclusion supporting the theoretical existence of a Black β^{++} gene distinct from the Mediterranean β^+ gene *(64)*.

Finally, within this context, it should be noted that both Black and Greek varieties of hereditary persistence of fetal hemoglobin (HPFH) have been reported in Costa Rica *(21, 75)*.

GLUCOSE-6-PHOSPHATE-DEHYDROGENASE POLYMORPHISM IN COSTA RICA

The role of glucose-6-phosphate-dehydrogenase (G6PD) deficiency in hemolysis, especially among Blacks, has been under study in Costa Rica for over 15 years *(6)*. This hemolytic phenomenon has also been detected in El Salvador and Honduras *(15, 51, 54)*. Regarding Costa Ricans, the frequency detected in males by giving the methemaglobin reduction test to 621 subjects was 12.6% *(85)*; a lower frequency (4.3%) was found in a mixed (primarily Black) population in Guanacaste *(86)*. The previously mentioned nationwide survey of 12,000 Costa Rican schoolchil-

dren showed 2.3% of the boys (irrespective of race) to be affected *(23)*.

In 1974 a new G6PD variant called Gd San José was reported in a male Costa Rican Caucasian subject *(87)*. In 1982 another new mutant with strong clinical expression, designated Gd Puerto Limón, was identified *(13)*; and this was followed by identification of another pathogenic variant, Gd E Santamaría, in 1983 *(88)*. At present, electrophoretic studies permit phenotypic characterization of all the G6PD variants studied in our laboratories, and also permit us to determine their degree of activity.

Summary

The prevalences of abnormal hemoglobins and thalassemias depend largely upon the hereditary racial composition and geographic origins of the affected populations. For this reason, the highly varied immigration and racial patterns found in Central America and Panama make it logical to expect prevalences that vary greatly from one country to another and even from one population to another within a given country. Unfortunately, literature on the problem is scanty, and so the review presented here draws heavily upon fairly extensive information available from Costa Rican studies, supplemented wherever possible with data from Panama and other parts of Central America.

The sickle cell gene for hemoglobin S (Hb S) has not been found among purely indigenous groups studied in Costa Rica and Panama. However, noteworthy prevalences of Hb S have been reported among Blacks and other population groups in Costa Rica, El Salvador, Guatemala, Honduras, and Panama, with apparent levels of the heterozygous Hb S marker reaching as high as 30% of one survey population in the latter country. In addition, the presence of the hemoglobin C marker has been reported in Costa Rica, Honduras, and Panama; and various sickling syndromes—including heterozygous Hb S C, Hb S combined with Hb Korle Bu, homozygous Hb S with alpha thalassemia, heterozygous Hb S with alpha (α^+) thalassemia, and Hb S with beta thalassemia (both β^+ and β^0)—have been found in Costa Rica.

Regarding uncommon abnormal hemoglobins, the hemoglobins A'_2, E, G Philadelphia, Korle Bu, J Cubujuquí, New York, and Suresnes have been found in Costa Rica; the hemoglobin N Baltimore has been found in El Salvador; and the hemoglobins Babinga, G Philadelphia, Korle Bu, Lepore, and Q Iran have been found in Panama.

Costa Rica is the only Central American country where precise information is available on the presence of α^{thal} and β^{thal} markers. The α^{thal} studies involved have detected α^{thal} marker prevalences ranging from 1.12% to 25% of the various study populations, as well as isolated cases of hemoglobin H disease. The β^{thal} studies have detected various kinds of beta thalassemia genotypes—including Cooley's anemia ($\beta^+\beta^+$), mild Cooley's anemia ($\beta^0(\delta\beta)^0$), $(\delta\beta)^0$, $\beta^S\beta^+$, $\beta^S\beta^0$, and beta thalassemia associated with increased concentrations of hemoglobins A_2 and F.

In addition, pancellular hereditary persistence of fetal hemoglobin (both Black and Greek varieties) has been reported in Costa Rica, and considerable work has been done on glucose-6-phosphate dehydrogenase (G6PD) deficiency in that country. Three G6PD

variants (Gd E Santamaría, Gd Puerto Limón, and Gd San José) have been found initially in Costa Rica, and Costa Rican studies designed to detect associated hemolysis have found frequencies ranging from 2.3% to 12.6% in various study populations. Such hemolysis has also been detected in El Salvador and Honduras.

REFERENCES

1 Colombo, B., and G. Martínez. Hemoglobinopathies: II. Tropical America. *Clin Haematol (London)* 10:730, 1981.

2 Arends, T. Hemoglobinopathies and Enzyme Deficiencies in Latin American Populations. In: *The Ongoing Evolution of Latin American Populations*, C. C. Thomas, Springfield, 1971, pp. 509–559.

3 Cordero, R., and B. Monge. Análisis sanguíneo y parasitoscópico en indígenas en Costa Rica. *Revista Médica de Costa Rica* 4:43, 1972.

4 Sáenz, G. F. Unpublished data, 1976.

5 Calero, C. Drepanocitemia y anemia drepanocítica en el Istmo de Panamá, con especial referencia a sus manifestaciones clínicas e incidencia por raza. *Archivos del Hospital Santo Tomás (Panama City)* 1:27, 1946.

6 Sáenz, G. F., G. Arroyo, J. Jiménez, A. Gutiérrez, M. Barrenechea, E. Brilla, and E. Valenciano. Investigación de hemoglobinas anormales en población de raza negra costarricense. *Rev Biol Trop* 19:251, 1971.

7 Sáenz, G. F., M. A. Alvarado, F. Atmetlla, G. Arroyo, R. Jiménez, and E. Valenciano. Investigación de hemoglobinas anormales en población costarricense del Guanacaste. *Acta Médica Costarricense* 16:147, 1973.

8 Meléndez, C., and Q. Duncan. *El Negro en Costa Rica.* Editorial Costa Rica, San José, 1976.

9 Ferrell, R. E., A. Núñez, T. Bertin, D. R. Labarthe, and W. J. Schull. The blacks of Panama: Their genetic diversity as assessed by 15 inherited biochemical systems. *Am J Phys Anthropol* 48:269, 1978.

10 Espino, H., and A. Santamaría. Personal communication, 1980.

11 Altafulla, M. La enfermedad por células falciformes en Panamá. *Revista Médica de Panamá* 6:620, 1981.

12 Altafulla, M. Origen e incidencia del gene falciforme en la República de Panamá. *Revista Médica de Panamá* 6:233, 1981.

13 Elizondo, J., G. F. Sáenz, C. A. Páez, and M. Ramón. G6PD-Puerto Limón: A new deficient variant of glucose-6-phosphate dehydrogenase associated with congenital nonspherocytic hemolytic anemia. *Hum Genet* 62:110, 1982.

14 Rucknagel, D. L. Personal communication, 1976.

15 Stefan, R. Estudio epidemiológico-clínico de la drepanocitosis en la población garífuna de Honduras. Thesis. National Autonomous University of Honduras, Tegucigalpa, 1982.

16 Tejada, C., N. L. S. González, and N. Sánchez. El factor Diego y el gen de células falciformes entre los Caribes de raza negra en Livingston, Guatemala. *Rev Col Méd* 16:83, 1965.

17 Solano, L., M. Cabezas, and L. Elizondo. Estudio sobre drepanocitosis y hemoglobina "S" en Santa Cruz de Guanacaste. *Acta Médica Costarricense* 9:59, 1966.

18 Solano, L., and F. Mainieri. Estudio sobre drepanocitosis y hemoglobina S en Liberia, Guanacaste. *Acta Médica Costarricense* 10:175, 1967.

19 Rivera, A., and G. F. Sáenz. Datos numéricos y estadísticos mínimos sobre la incidencia de hemoglobinas anormales en Costa Rica. *Revista Médica del Hospital Nacional de Niños (Costa Rica)* 2:95, 1968.

20 Elizondo, J., and M. Zomer. Hemoglobinas anormales en la población asegurada constarricense. *Acta Médica Costarricense* 13:249, 1970.

21 Sáenz, G. F., G. Arroyo, M. Alvarado, A. G. Montero, J. Jiménez, and E. Valenciano. Hemoglobinas anormales en una población estudiantil universitaria. *Rev Biol Trop (Costa Rica)* 21:117, 1974.

22 Sáenz, G. F., M. Alvarado, E. Alfaro, M. Barrenechea, J. Jiménez, and G. Montero. Diagnóstico neonatal de hemoglobinopatías. *Sangre* 22:339, 1977.

23 Sáenz, G. F., J. Elizondo, G. Arroyo, E. Valenciano, L. F. Rojas, J. Jiménez, A. G. Montero, and J. E. Sánchez. Hemoglobinopatías en 12.000 escolares. *Acta Médica Costarricense* 23:89, 1980.

24 Sáenz, G. F., E. Blanco, J. Jiménez, A. G. Montero, E. Valenciano, G. Arroyo, and J. E. Sánchez. Diagnóstico neonatal de alfa-talasemia en población caucásica. *Revista Costarricense de Ciencias Médicas* 2:97, 1980.

25 Sáenz, G. F., M. Chaves, M. Barrenechea, S. Grant, J. Jiménez, and G. A. Montero. Hemoglobinas anormales, alfa talasemia y deficiencia de la G6PD eritrocítica en recién nacidos de raza negra. *Sangre* 29:861, 1984.

26 Sáenz, G., M. Chaves, J. Briceño, E. Quintana, G. Arroyo, E. Valenciano, and A. Montero. Polimorfismo de la hemoglobina y de la G6PD eritrocítica en población pre-escolar de Santa Cruz, Guanacaste. *Revista Costarricense de Ciencias Médicas* 6:126, 1985.

27 Schneider, R. G., et al. Sickling test: Pitfalls in performance and interpretation. *JAMA* 202:419, 1967.

28 World Health Organization. *WHO Weekly Epidemiological Record.* Geneva, vol. 55, 4 July 1980.

29 Livingstone, F. B. Aspects of the population dynamics of the abnormal hemoglobins and G6PD deficiency genes. *Am J Hum Genet* 16:435, 1964.

30 Sáenz, R. I., G. F. Sáenz, and M. Chaves. Enfermedad homocigótica por Hb C: Reporte del primer caso costarricense. *Revista Médica del Hospital Nacional de Niños (Costa Rica)* 19:25, 1984.

31 Serjeant, G. R. *The Clinical Features of Sickle Cell Disease.* North Holland Publishing, Amsterdam, 1974.

32 Elizondo, J. Anemia de células falciformes. Reporte de un caso de priapismo por drepanocitosis. Estudio de una familia costarricense. Presentation to the IX Central American Medical Congress (Costa Rica, 1961), pp. 162–171.

33 Elizondo, J., and L. Solano. Hemoglobinopatía SC. *Acta Médica Costarricense* 8:15, 1965.

34 Zomer, M. Anemia drepanocítica: Experiencia en el Hospital San Juan de Dios (1967–1974). Unpublished paper, 1975.

35 Serjeant, G. R. *Sickle Cell Disease.* Oxford University Press; Oxford, New York, and Tokyo; 1985.

36 Sáenz, G. F., M. Cháves, E. Castro, M. Ramón, M. Barboza, J. Jiménez, P. Montero, G. Arroyo, and E. Valenciano. Síndromes drepanocíticos en población de la provincia de Puntarenas. *Revista Costarricense de Ciencias Médicas (Costa Rica)* (in press).

37 Serjeant, G. R., K. P. Mason, and B. E. Serjeant. Negro α-thalassaemia: Genetic studies in homozygous sickle cell disease. *J Med Genet* 17:281, 1980.

38 Embury, S. H., A. M. Dozy, J. Miller, and J. R. Davis. Concurrent sickle cell anemia and α-thalassemia. *N Engl J Med* 306:270, 1982.

39 Sewell, A., D. Millard, and G. Serjeant. The interaction of alpha thalassemia with SS disease. In: G. J. Brewer (ed.). *The Red Cell.* Alan R. Liss, New York, 1978, pp. 93–102.

40 Honig, G. R., M. Koshy, G. Mason, and L. N. Vida. Sickle cell syndrome: II. The sickle cell anemia and α-thalassemia syndrome. *J Pediatr* 92:556, 1978.

41 Milner, P. F. Thalassemias, Hemoglobinopathies and Sickle Cell Disease. In: V. F. Fairbanks (ed.). *Hematology (vol. 2).* John Wiley and Sons, 1983.

42 Higgs, D. R., L. Pressley, J. B. Clegg, D. U. Weatherall, and G. R. Serjeant. Alpha-thalassemia in black populations. *Johns Hopkins Med J* 146:300, 1980.

43 Sáenz, G. F., V. Ramírez, and M. Chaves. Enfermedad por hemoglobina SC y patología ocular: A propósito de un caso. *Acta Médica Costarricense* 3:249, 1982.

44 Elizondo, J., G. F. Sáenz, M. A. Alvarado, and M. Ramón. Hallazgo de la hemoglobina Korle-Bu (alfa$_2$beta$_2$ 75 asp-asn) en Costa Rica. *Sangre* 1:54, 1976.

45 Sáenz, G. F., M. Alvarado, J. Elizondo, G. Arroyo, and F. Atmetlla. Chemical characterization of a new haemoglobin variant, Haemoglobin J Cubujuquí (alpha$_2$ 141 (HC3) Arg-Ser beta$_2$). *Biochim Biophys Acta* 494:48, 1977.

46 Sáenz, G. F., J. Elizondo, B. Colombo, M. Alvarado, G. Arroyo, and F. Atmetlla. Hallazgo de la hemoglobina E (Beta[26 glu-lis]) en Costa Rica. *Sangre* 5:652, 1977.

47 Sáenz, G. F., M. Alvarado, G. Arroyo, E. Alfaro, G. Montero, and J. Jiménez. Hemoglobin Suresnes in a Costa Rican woman of Spanish-Indian ancestry. *Hemoglobin* 4:383, 1978.

48 Sáenz, G. F., J. Elizondo, G. Arroyo, J. Jiménez, and A. G. Montero. Finding of the hemoglobin New York in Costa Rica. *Hemoglobin* 1:101, 1980.

49 Sáenz, G. F., J. Elizondo, G. Arroyo, E. Valenciano, J. Jiménez, A. G. Montero, E. Sánchez, and S. Grant. Hallazgo de la hemoglobina G Philadelphia (alfa 68 (E 17) Asn-Lis) en Costa Rica: Consideraciones bioquímico-genéticas. *Sangre* 2:224, 1981.

50 Sáenz, G. F., J. Elizondo, G. Arroyo, J. Jiménez, A. G. Montero, and E. Valenciano. Diagnóstico de hemoglobinopatías y de trastornos afines: Enfoque poblacional del problema. *Bol Of Sanit Panam* 2:127, 1981.

51 Bloch, M., and H. Rivera. Hemoglobinas anormales y déficit de G6PD en El Salvador. *Sangre* 14:121, 1969.

52 Castillo, Z., and M. Altafulla. Hemoglobinopatías en Panamá. *Revista Médica de Panamá*, 1983.

53 Altafulla, M. Personal communication, 1983.

54 Bloch, M., G. Sancho, R. A. Cea, H. Rivera, A. N. Zelaya, and E. Montes. La deficiencia de glucosa-6-fosfato dehidrogenasa en El Salvador. *Revista del Instituto de Investigaciones Médicas (El Salvador)* 1:397, 1972.

55 Poyart, C., R. Krishnamoorthy, E. Bursuax, G. Gacon, and D. Labie. Structural and functional studies of haemoglobin Suresnes or α_2 141 (HC3) Apg-His β_2, a new high-oxygen affinity mutant. *FEBS Lett* 69:103, 1976.

56 Ranney, H. M., A. S. Jacobs, and R. L. Nagel. Haemoglobin New York. *Nature* 213:876, 1967.

57 Blackwell, R. Q., C. S. Liu, and C. L. Wang. Hemoglobin New York in Taiwan. *Am J Phys Anthropol* 34:329, 1971.

58 Livingstone, F. B. *Abnormal Hemoglobins in Human Populations.* Aldine Publishers, Chicago, 1967.

59 Silvestroni, E., and I. Bianco. Diffusione e frequenze della microcitemia e delle anemie microcitiche nell'Italia Continentale e in Sicilia, Atti II problema sociale della microcitemia e del morbo di Cooley'. *Instituto Italiano di Medicina Sociale (Rome)* 1:51, 1962.

60 Stamatoyannopoulos, G., and P. Fessas. Thalassaemia, glucose-6-phosphate dehydrogenase deficiency, sickling and malaria endemicity in Greece: A study of five areas. *Br Med J* 1:875, 1964.

61 Cotrina de Luna, J. L., F. S. Suárez, P. Llorente Gutiérrez, F. Villanueva, J. Rico, and A. Peña. Hemoglobinopatías en la Provincia de Granada. *Rev Clin Esp (Madrid)* 157:373, 1980.

62 Pellicer, A., and A. Casado. Frequencies of thalassaemia and G6PD deficiency in five provinces in Spain. *Am J Hum Genet* 22:298, 1970.

63 Rozman, C., J. Capdevila, S. Woessner, and I. Martí. Hemoglobinopatía H en una familia española. *Rev Clin Esp (Madrid)* 103:373, 1966.

64 Weatherall, D. J., and J. B. Clegg. *The Thalassaemia Syndromes.* Blackwell Scientific Publishers, Oxford, 1980.

65 Sáenz, G. F., J. Elizondo, G. Arroyo, J. Jiménez, and A. G. Montero. Síndromes drepanocíticos en Costa Rica: VI. Síndrome de heterocigosis doble S/alfa-talasemia. *Sangre* 24:205, 1979.

66 Sáenz, G. F., J. Jiménez, and L. Mora. Enfermedad por hemoglobina H en Costa Rica. *Sangre* 3:333, 1979.

67 Sáenz, G. F., J. Briceño, A. G. Montero, J. Jiménez, and M. Chaves. Enfermedad por hemoglobina H: Estudio de una nueva familia. *Acta Médica Costarricense* 24:151, 1981.

68 Sáenz, G. F., M. Castillo, and L. Salazar. Talasemia intermedia: A propósito de un caso de alfa talasemia tipo enfermedad por Hb H. *Acta Médica Costarricense* 27:179, 1984.

69 Wasi, P., S. Na-Nakorn, and S. Pootrakul. The Alpha Thalassaemias. In: D. J. Weatherall (ed.). *Clinics in Haematology (vol. 2).* 1974, p. 382.

70 Kan, Y. W., A. M. Dozy, G. Stamatoyanno-poulos, M. G. Hadijminas, Z. Zachariades, M. Furbetta, and A. Cao. Molecular basis of hemoglobin H disease in the Mediterranean population. *Blood* 54:1434, 1979.

71 Dozy, A. M., Y. W. Kan, and S. H. Embury. Alpha globin gene organization in blacks precludes the severe form of alpha thalassaemia. *Nature* 280:605, 1979.

72 Zomer, M., and A. Rivera. Primer caso de hemoglobinopatía S—talasemia en Costa Rica. *Acta Médica Costarricense* 10:71, 1967.

73 Zomer, M., J. Elizondo, and E. Quesada. Análisis de 11 casos de beta talasemia en Costa Rica. *Acta Médica Costarricense* 2:129, 1973.

74 Sáenz, G. F., M. A. Alvarado, and G. Arroyo. F(delta-beta) talasemia en Costa Rica. *Acta Médica Costarricense* 1:63, 1974.

75 Sáenz, G. F., M. A. Alvarado, G. Arroyo, and G. Montero. Persistencia hereditaria de hemoglobina fetal (PHHbF) en Costa Rica. *Revista Médica del Hospital Nacional de Niños (Costa Rica)* 2:135, 1975.

76 Sáenz, G. F., B. Monge, G. Arroyo, and M. A. Alvarado. Enfermedades de Cooley (Beta⁺ Talasemia mayor) en Costa Rica. *Sangre* 1:117, 1976.

77 Sáenz, G. F., G. Sánchez, and B. Monge. Síndromes drepanocíticos en Costa Rica: IV. Hemoglobina S/beta-delta talasemia (S/F-talasemia). *Acta Médica Costarricense* 4:3, 1976.

78 Sáenz, G. F., J. Elizondo, G. Arroyo, G. Montero, and J. Jiménez. Talasemia A₂F en raza negra costarricense: A propósito de un caso. *Acta Médica Constarricense* 4:373, 1977.

79 Sáenz, G. F., J. Elizondo, and C. A. Páez. Hallazgo del gene β⁰-talasémico (supresor) en Costa Rica: V. Síndrome de heterocigosis doble S/beta⁰-tal. *Sangre* 2:196, 1978.

80 Sáenz, G. F., M. Navarette, L. Mora, J. Jiménez, A. G. Montero, and G. Arroyo. Beta talasemia mayor (enfermedad de Cooley): Consideraciones sobre biología molecular y estudio de una nueva familia. *Acta Médica Costarricense* 2:143, 1981.

81 Sáenz, G. F., M. Chaves, G. Arroyo, E. Valenciano, J. Jiménez, A. G. Montero, J. E. Sánchez, C. Vega, and P. Contreras. Escrutinio de hemoglobinopatías y G6PD en una población italiana radicada en Costa Rica. *Revista Costarricense de Ciencias Médicas* 2:185, 1982.

82 Sáenz, G. F., J. M. Carrillo, L. Mora, M. Chaves, L. G. Rojas, R. Jiménez, J. Jiménez, and A. G. Montero. Beta talasemia intermedia de genotipo δβ⁰/(β)⁰: Reporte de un caso. *Sangre* 29:467, 1984.

83 Sáenz, G. F. Diagnóstico convencional de los síndromes talasémicos. *Sangre* 25:63, 1980.

84 Arends, T. High concentration of Hb A₂ in malaria patients. *Nature* 215:1517, 1962.

85 Sáenz, G. F., E. Brilla, G. Arroyo, B. Valenciano, and J. Jiménez. Deficiencia de la dehidrogenasa de la glucosa-6-fosfato (G6PD) eritrocítica en Costa Rica: I. Generalidades sobre el defecto y hallazgos en población de raza negra. *Revista Médica del Hospital Nacional de Niños (Costa Rica)* 2:129, 1971.

86 Sáenz, G. F., et al. Deficiencia de G6PD eritrocítica en población guanacasteca. Unpublished data, 1983.

87 Castro, G. A. M., and L. M. Snyder. G6PD San José: A new variant characterized by NADPH inhibition studies. *Humangenetik (Berlin)* 21:361, 1974.

88 Sáenz, G. F., M. Chaves, A. Barrantes, J. Elizondo, A. G. Montero, and A. Yoshida. A glucose-6-phosphate dehydrogenase variant, Gd (-) Santamaría found in Costa Rica. *Acta Haematol (Basel)* 72:37, 1984.