PREVALENCE AND GEOGRAPHIC DISTRIBUTION OF ABNORMAL HEMOGLOBINS IN THE STATE OF SÃO PAULO, BRAZIL[1]

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A large-scale survey of abnormal hemoglobins in Brazil's São Paulo State was performed to assess the importance of this problem. The results, reported here, provide strong justification for programs capable of effectively identifying the pathologies involved and making carriers of the responsible traits aware of the need to take preventive measures.

Introduction

The State of São Paulo, located in the southeastern region of Brazil, covers an area of 247,320 km^2 and is inhabited by approximately 25 million persons distributed among 930 cities and towns. During the period 1827-1932 its population, which for almost 300 years had consisted basically of Portuguese colonists, African slaves, and mestizos, was supplemented by approximately 2.6 million immigrants; of these, Italians constituted some 36%; Portuguese 15%; Spaniards 14%; Japanese 4%; Germans, Arabs, Austrians, Russians, and Poles 20%; and immigrants of other nationalities 11% *(1)*. These groups, which came to be distributed unevenly within the state's various economic-demographic subregions (Figure 1), began an active process of miscegenation with the other basic elements of the state's population. In addition, significant numbers of migrants came to São Paulo from other parts of Brazil, the number of such people totaling about 850,000 between 1908 and 1945; of these, some 70% came to settle in various regions of the state *(2)*. In this manner a multitude of diverse genetic features—among them hereditary diseases, and among those a number of disorders involving abnormal hemoglobins—came to be assimilated into the new population being created.

Studies made in various regions of Brazil have shown a broad polymorphic diversity of abnormal hemoglobins, of which types S and C (of known African origin) and types producing thalassemias (in particular those of Mediterranean origin) have been found with the greatest frequency *(3-7)*. In addition, other abnormal hemoglobin variants considered rare—such as hemoglobins D Punjab, M Boston, J Rovigo, and Koln—have been identified sporadically among the state's inhabitants *(8-11)*.

In view of the ethnic diversity behind the state's present population and the considerable prevalence of abnormal hemoglobins described in Brazilian populations, we decided to undertake a broad-based study of the prevalence and distribution of abnormal hemoglobins in various cities within São Paulo State for the purpose of confirming the public health importance of this hereditary pathology, to verify the areas where such abnormal hemoglobins are found, and to determine the prevalence of these hemoglobins among caucasoid and negroid inhabitants of different ages.

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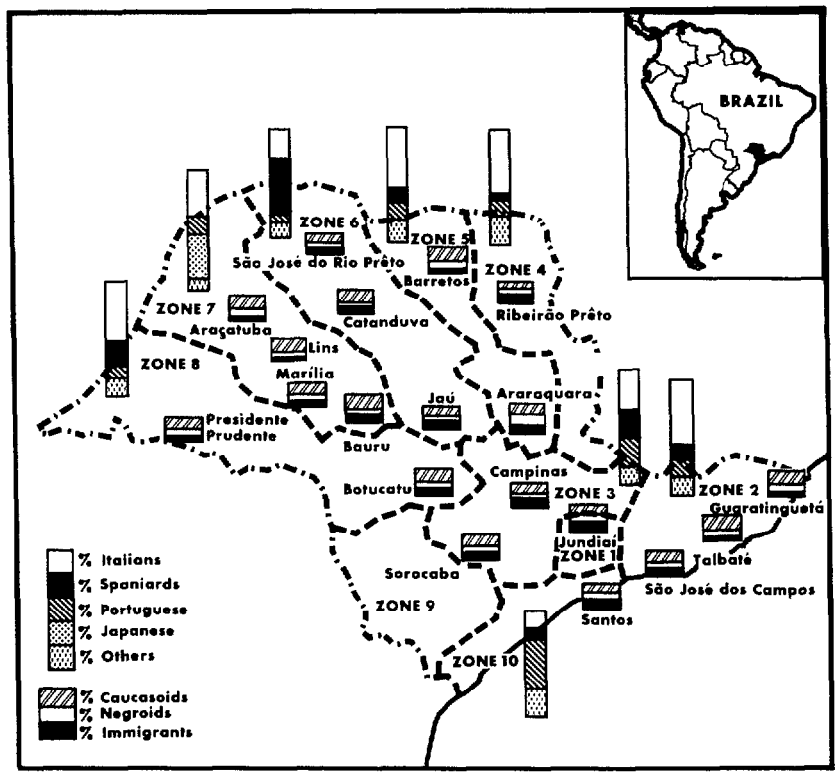
Figure 1. The ethnic makeup of the state population in São Paulo's economic-demographic zones as of 1920 (*1*) and the composition of the 19 study city populations (in terms of Brazilian caucasoids, Brazilian negroids, and foreigners) in 1940 (*2*).



Materials and Methods

Blood samples were obtained from 17,439 males and females between one month and 85 years of age at 19 cities in the State of São Paulo. These cities were considered "poles of medical attraction" drawing people seeking medical care from surrounding areas. The samples, collected in 5% EDTA[5] from April 1978 to May 1980, were obtained at health centers and health posts of the selected cities from blood donors and patients receiving services such as general examinations, medical consultations, and vaccinations. The individuals providing samples were classified as caucasoids or negroids (negroes, dark mulattoes, or light mulattoes), primarily on the basis of skin color and the presence or absence of negroid features. In all, 14,957 of those providing specimens were classified as caucasoids and 2,482 were classified as negroids.

All the samples were initially studied by electrophoresis on agar-amide plates with a capacity for 80-100 test samples in Tris-edta-borate buffer solution at pH 8.6 and were stained with benzidine *(12)*. Those specimens found to show abnormalities by this procedure were subjected to electrophoresis on cellulose acetate in Tris-edta-borate buffer solution at pH 8.6 *(13)* and in agar-phosphate at pH 6.2 *(14)*. Specimens containing hemoglobins S

[5]Ethylene-diamine tetra-acetic acid.

and C in the usual combinations (AS, AC, SS, SC, and CC) could then be identified without further testing.

To study variants involving abnormal hemoglobins other than S and C, specific techniques were employed for the separation of polypeptide chains by means of electrophoresis on cellulose acetate using Tris-edta-borate buffer combined with 6 M urea and 0.05 M 2-mercaptoethanol at pH 6.0 and pH 8.9 *(13)*. When needed, molecular stability tests *(15)*, quantitative and qualitative determinations for metahemoglobin *(16)*, and tests for quantification of hemoglobin A2 *(17)* and fetal hemoglobin *(18)* were performed.

Alpha and beta thalassemias were diagnosed in accordance with the principles established by WHO *(19)*.

Rare variants were characterized structurally by peptide mapping *(20)* and were confirmed by Prof. H. Lehmann of Cambridge, England. These variants included hemoglobins D Punjab, G Philadelphia, J Oxford, J Rovigo, M Boston, and Constant Spring.

Results

Analysis of the 17,439 samples showed 452 (2.59%) of the study subjects to have abnormal hemoglobins. These consisted of defined molecular variants (2.28%), types causing thalassemias (0.26%), induced alterations (0.04%), and hereditary persistence of fetal hemoglobin (0.01%). A more detailed breakdown of these results is provided in Table 1. Overall, the 398 molecular variants detected included the following 12 genotypes: AS, SS, SC, AC, CC, AJ Oxford (or α 15 Gly → Asp), AD Punjab (or β 121 Glu → Gln), AM Boston (or α 58 His → Tyr), AI (or α 16 Lys → Glu), AG Philadelphia (or α 68 Asn → Lys), AJ Rovigo (or α 43 Ala → Asp), and A B2 (or δ 16 Gly → Arg). The 45 cases of thalassemia detected included alpha, beta, and interactive thalassemias of the seven genotypes listed in Table 1. Seven cases of metahemoglobinemia, involving deficiencies of erythrocytic enzymes or oxyhemoglobin toxicity due to oxidizing drugs, were consid-

Table 1. Abnormal hemoglobins detected in 17,439 individuals examined.[a]

Hemoglobin variants	Genotype	Abnormalities detected	
		No.	% of total
S	AS, SS, SC	295	74.12
C	AC, CC	75	18.85
J Oxford	AJ	16	4.02
D Punjab	AD	5	1.26
M Boston	AM	2	0.50
I	AI	2	0.50
G Philadelphia	AG	1	0.25
J Rovigo	AJ	1	0.25
B2	A B2	1	0.25
Subtotal		398	100
Thalassemias:			
Heterozygous beta	A A2 increased	22	48.89
Homozygous beta	A F increased	6	13.33
Interactive	β^0/S, β^+/S, α/S	11	24.45
Alpha	AH, A Constant Spring	6	13.33
Subtotal		45	100

[a]Seven cases of metahemoglobinemia, induced by drugs or enzymatic deficiencies, and two cases of hereditary persistence of fetal hemoglobin are not included in this table.

ered induced alterations. In addition, two cases of hereditary persistent fetal hemoglobin were detected.

Table 2 shows the prevalences of abnormal hemoglobins found among caucasoids and negroids by city. Overall, these prevalences were found to be higher among negroids than among caucasoids in 17 cities, being similar for the two groups only in Campinas and Catanduva. Among caucasoids the highest prevalence found for any city was 3.2% (in Jundiaí), while among negroids the prevalence exceeded 5% in 13 cities and surpassed 10% in six (Botucatu, Jundiaí, Santos, São José dos Campos, São José do Rio Prêto, and Sorocaba). The means and standard deviations of the overall prevalences were 7.79 ± 4.32% and 1.75 ± .67% for negroids and caucasoids, respectively, the mean for negroids thus being almost 4.5 times higher than that for caucasoids. This difference is statistically significant ($t_{36} = 6.014$; $p < 0.001$). The coefficients of variance were 38% for caucasoids and 55% for negroids.

Table 3 shows the observed distribution of specific molecular variants and thalassemias in the 19 cities studied. The overall observed prevalences of abnormal hemoglobin in those cities ranged from 1.06% (in Bauru) to 5.00% (in Jundiaí). The Table 3 data also show that hemoglobin variants AS and AC were the types most commonly detected in the bulk of the study cities—accounting for at least 80% of the detected cases in 12 cities and for 60 to 71% in six others. Only in Campinas, where five of the 10 abnormal hemoglobins detected were of the J variety, did hemoglobins S and C account for less than half the cases.[6]

[6] In general, the prevalence of hemoglobin J variants in Brazil appears quite low, having been on the order of 0.077% in surveys we have conducted in other parts of Brazil. It is also interesting to note that a large majority of J variant carriers are of Spanish or Portuguese extraction (especially the latter), although the trait has also been found in people of Italian and English descent. The five subjects with hemoglobin J in Campinas, as well as the four in Presidente Prudente (see Table 3), found in people from different families, accounted for 52.9% of the total hemoglobin J cases detected in São Paulo State. The heterogeneous distribution demonstrated by this finding could be related to the particular ethnic groups that settled each of these cities.

Table 2. Observed prevalences of abnormal hemoglobins among the 17,439 study subjects, by racial classification and city.

City where blood sample was taken	Caucasoids		Negroids	
	No. tested	% with abnormal hemoglobin	No. tested	% with abnormal hemoglobin
Araçatuba	623	1.44	159	7.55
Araraquara	1,026	2.34	162	6.17
Barretos	413	1.94	52	3.85
Bauru	871	0.57	169	3.55
Botucatu	965	0.93	213	12.68
Campinas	639	1.41	57	1.75
Catanduva	560	1.61	76	1.31
Guaratinguetá	751	1.73	144	5.55
Jaú	1,175	1.45	85	5.88
Jundiaí	405	3.21	95	12.63
Lins	661	1.66	346	4.33
Marília	812	1.60	303	8.91
Presidente Prudente	810	2.84	78	7.69
Ribeirão Prêto	632	1.74	82	9.76
Santos	780	1.41	176	13.07
São José dos Campos	858	2.45	39	15.38
São José do Rio Prêto	1,402	1.93	157	10.19
Sorocaba	806	1.12	64	14.06
Taubaté	768	1.95	25	4.00
Total	14,957	1.72	2,482	7.86

Table 3. Observed prevalence of genotypes relating to abnormal hemoglobins in the blood samples obtained from 19 study cities, by city.

City where blood sample was taken	No of samples tested	Abnormal hemoglobins detected		Molecular variants, by genotype												Thalassemias, by genotype				
		No	% of samples tested	AS	AC	AD	AJ	AM	AI	AB2	AG	SS	SC	CC	PHF[a]	βho[b]	βhc[c]	β°/S	β⁺/S	α
Araçatuba	782	21	2.68	9	8		1	1					2							
Araraquara	1,188	34	2.86	21	7				1						1	1	3			
Barretos	465	10	2.15	9	1															
Bauru	1,040	11	1.06	3	4	1		2				1								
Botucatu	1,178	36	3.06	21	1	2			1			5				1	1	2		2
Campinas	696	10	1.44	2	1		5	1									1			
Catanduva	636	10	1.57	6	2											1				1
Guaratinguetá	895	21	2.35	10	5	1	1										4			
Jaú	1,260	22	1.75	17	2							1					2			
Jundiaí	500	25	5.00	19	3							1		1			1			
Lins	1,007	26	2.58	15	8							1				1	1			
Marília	1,115	40	3.59	25	7			3				4						1		
Presidente Prudente	888	29	3.27	16	3		4										2		3	1
Ribeirão Prêto	714	19	2.66	14	2					1	1									1
Santos	956	34	3.56	25	5		1					3								
São José dos Campos	897	27	3.01	20	2		2										3			
São José do Rio Prêto	1,559	43	2.76	22	8		2					1			1	2	2	4		1
Sorocaba	870	18	2.07	14	2	1	1													
Taubaté	793	16	2.02	7	3			2				1					2	1		
Total	17,439	452	2.59	275	74	5	17	9	2	1	1	18	2	1	2	6	22	8	3	6

[a]Persistence of fetal hemoglobin.
[b]Homozygous beta thalassemia.
[c]Heterozygous beta thalassemia.

Figure 2 provides a graphic illustration of the distribution of hemoglobins S and C, thalassemias, and other abnormal hemoglobins in the caucasoids and negroids tested in each of the 19 study cities. Figure 3 provides a graphic presentation of the distribution of the thalassemias detected.

The appearances of various test results indicating normal or abnormal hemoglobins are shown in photos 1-3.

The prevalences of abnormal hemoglobin genotypes, broken down by racial grouping and specific age groups, are shown in Tables 4 and 5. As can be seen, the overall prevalence of abnormal hemoglobins was lower among caucasoids than among negroids in all the age groups studied. It should also be mentioned that the abnormal AS and AC genotypes were found among all the caucasoid and negroid age groups, and were the only abnormal hemoglobin genotypes found among subjects less than one year old. In addition, it appears noteworthy that the SS and homozygous beta thalassemia genotypes were detected only in relatively young subjects (caucasoids in the 1-20 year age range and negroids in the 1-30 year age range). In contrast, low prevalences of heterozygous beta thalassemia were detected in negroids over 50 years of age and in members of all caucasoid age groups except infants less than one year old.

The overall prevalences of abnormal hemoglobins, by age group, among caucasoids and negroids were compared by the X^2_5 method *(21)*. The result ($X^2_5 = 20.06$; $p<0.01$) indicates the statistical disparity of the data for the two groups, with abnormal hemoglobin prevalences being significantly higher, by age group, among the negroids than among the caucasoids.

Discussion

The limited number of researchers concerned with abnormal hemoglobins in Brazil—together with the technical problems involved in the detection, identification, and characterization of these proteins—probably accounts for the fact that only eight genotypes for hemoglobin variants and four for thalassemias had previously been identified among 18,500 individuals examined over a period of nearly 20 years *(20)*.

By comparison, the results of the study reported here demonstrated that, using the aforementioned technical procedures, it was possible to conduct a population survey of abnormal hemoglobins, one involving the analysis of blood samples from 17,439 individuals distributed over a large geographic area, within a two-year period. This survey detected 12 genotypes for hemoglobins with defined molecular variations and seven thalassemia genotypes. It also led to the identification of three rare hemoglobins—J Oxford, G Philadelphia, and Constant Spring—for the first time in the Brazilian population.

The observed 2.59% prevalence of abnormal hemoglobins in the State of São Paulo differs little from prevalences observed in other regions of Brazil—such as the cities of Natal (*4*), Curitiba (*5*), and Pôrto Alegre (*6*) and the state of Amazonas (*7*). Within the State of São Paulo, however, it was possible to separate the 19 study cities into three groups on the basis of different abnormal hemoglobin prevalences in the negroid portion of the study population—the three groups being cities where the prevalence was less than 5% (Barretos, Bauru, Campinas, Catanduva, Lins, and Taubaté), cities where it was between 5 and 10% (Araçatuba, Araraguara, Guaratinguetá, Jaú, Marília, Presidente Prudente, and Ribeirão Prêto), and cities where it was over 10% (Botucatu, Jundiaí, Santos, São José dos Campos, São José do Rio Prêto, and Sorocaba). This heterogeneous distribution, shown in Figure 2, attests to the significance that this hereditary pathologic problem has for public health in the State of São Paulo. More specifically, hemoglobins S and C accounted for more than 60% of the abnormal hemoglobins found in 18 of the 19 study cities (see Table 3); in all, the recessive sickle-cell trait (AS), the homozygous (SS) and heterozygous (SC) genotypes for sickle-cell disease, the genotypes for C-type

Figure 2. Prevalences of abnormal hemoglobins in each of the 19 city populations studied, by racial classification of the study subjects. The largest circles indicate overall abnormal hemoglobin prevalences in excess of 10% (over one positive subject per 10 subjects tested), while the smallest indicate overall prevalences below 1% (less than one positive subject per 100 subjects tested). The shadings of the circles indicate the share of the abnormal hemoglobins accounted for by hemoglobin S, hemoglobin C, beta thalassemia, and other abnormal hemoglobins (numerical breakdowns of these data are presented in Tables 2 and 3).

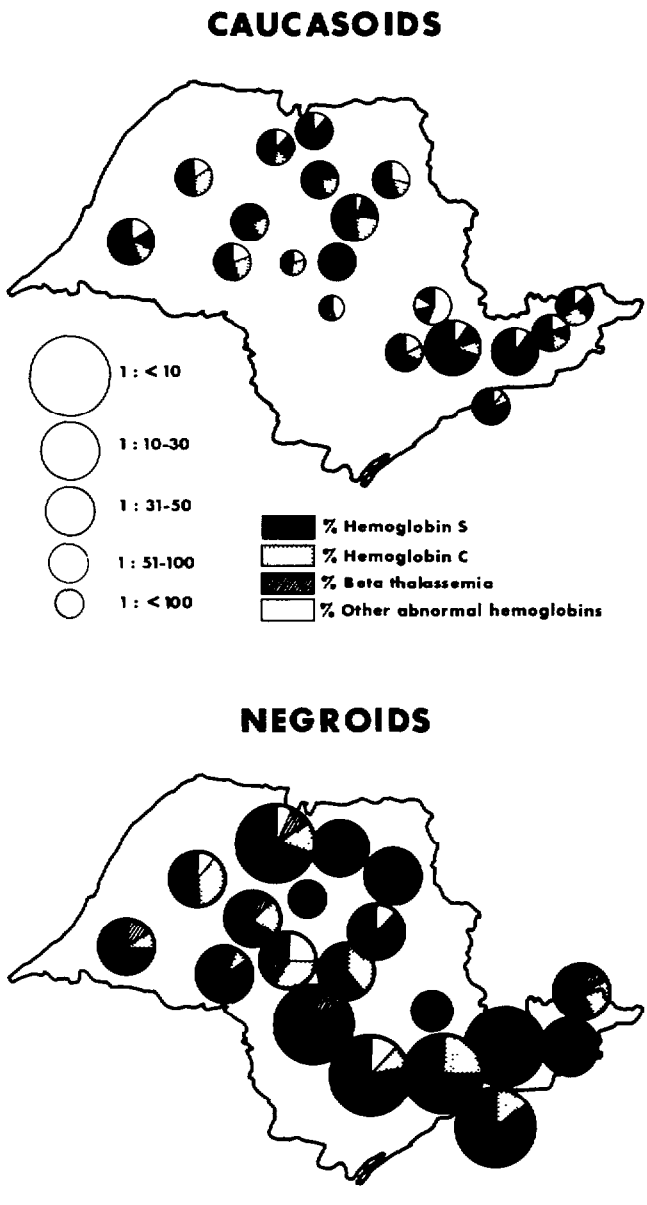


Figure 3. Prevalences of beta thalassemias in each of the 19 city populations studied. Where a given economic-demographic region contained more than one study city, the data from all the study cities in that region were combined to yield the indicated prevalence for that region.

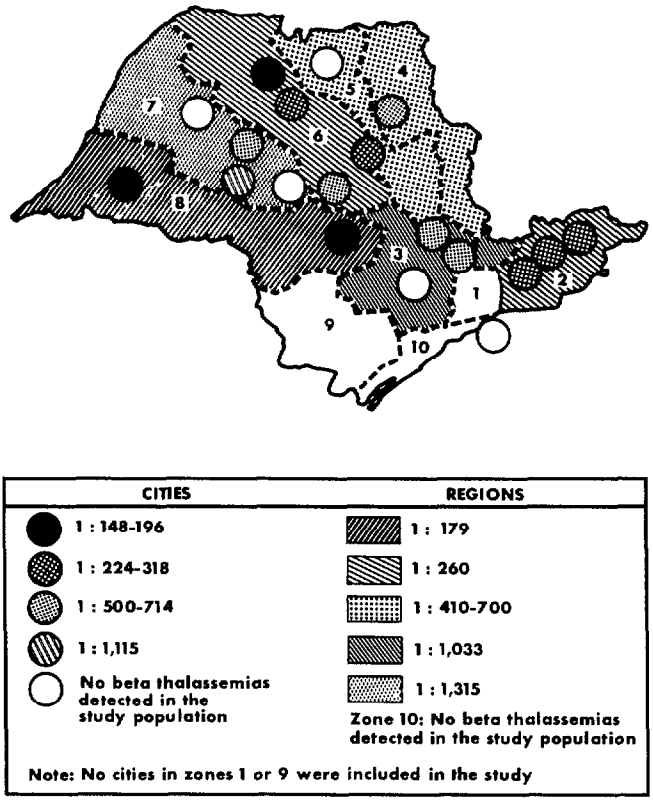


Table 4. Prevalences of genotypes for abnormal hemoglobins detected among caucasoids in the study population, by age group.

Age group of subjects	No. of samples tested	Abnormal genotypes detected (%)							Total (%)
		AS	AC	SS	βho[a]	βhe[b]	βS[c]	Others	
<1 year	793	0.88	0.38	–	–	–	–	–	1.26
1-10 years	2,281	0.83	0.39	0.04	0.04	0.04	0.08	0.29	1.71
11-20 "	1,880	1.28	0.26	–	0.16	0.16	0.11	0.15	2.12
21-30 "	2,697	1.26	0.44	–	–	0.22	–	0.49	2.41
31-40 "	1,837	1.31	0.22	–	–	0.11	0.11	0.15	1.90
41-50 "	1,568	0.45	0.25	–	–	0.19	–	0.21	1.10
> 50 "	3,271	0.55	0.18	–	–	0.12	–	0.16	1.01
Total[d]	14,327	0.92	0.30	0.007	0.02	0.14	0.04	0.26	1.68

[a]Homozygous beta thalassemia.
[b]Heterozygous beta thalassemia.
[c]Interactive beta thalassemia (β°/S and β^{+}/S).
[d]Data on 630 subjects have not been included because their ages were unknown.

Table 5. Prevalences of genotypes for abnormal hemoglobins detected among negroids in the study population, by age group.

Age group of subjects	No. of samples tested	Abnormal genotypes detected (%)							Total (%)
		AS	AC	SS	βho[a]	βhe[b]	βS[c]	Others	
<1 year	107	0.93	0.93	–	–	–	–	1.88	3.74
1-10 years	467	5.78	1.28	1.71	0.42	–	0.21	0.23	9.63
11-20 "	356	5.89	1.12	1.12	–	–	0.28	0.58	8.99
21-30 "	485	3.50	1.03	1.03	–	0.21	–	0.62	6.39
31-40 "	305	5.90	1.64	–	–	–	0.65	0.33	8.52
41-50 "	272	2.94	2.57	–	–	–	–	–	5.51
> 50 "	391	5.63	0.25	–	–	0.25	0.25	–	6.38
Total[d]	2,383	4.78	1.22	0.71	0.08	0.08	0.21	0.38	7.46

[a]Homozygous beta thalassemia.
[b]Heterozygous beta thalassemia.
[c]Interactive beta thalassemia (β °/S and β⁺/S).
[d]Data on 99 subjects have not been included because their ages were unknown.

Photo 1. Electrophoresis of several abnormal hemoglobins on cellulose acetate at pH 8.6. These results demonstrate (1) heterozygous beta-thalassemia with increased Hb A2, (2) and (3) the hemoglobin variant J Oxford, and (4) the interactive (β⁺/S) form of beta thalassemia.

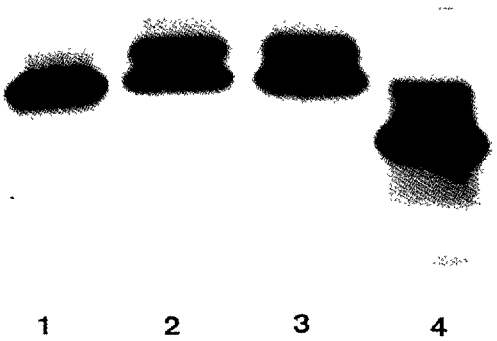
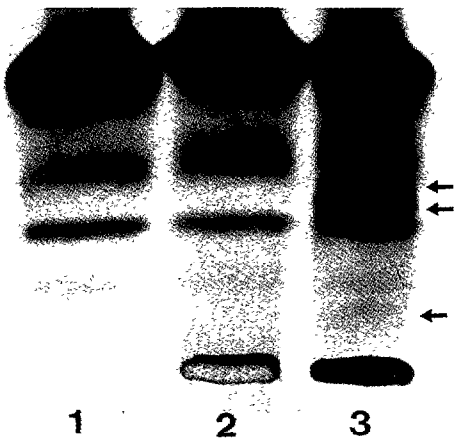


Photo 2. Electrophoresis of normal hemoglobins (1 and 2) and Constant Spring hemoglobin (3) on cellulose acetate at pH 8.6.

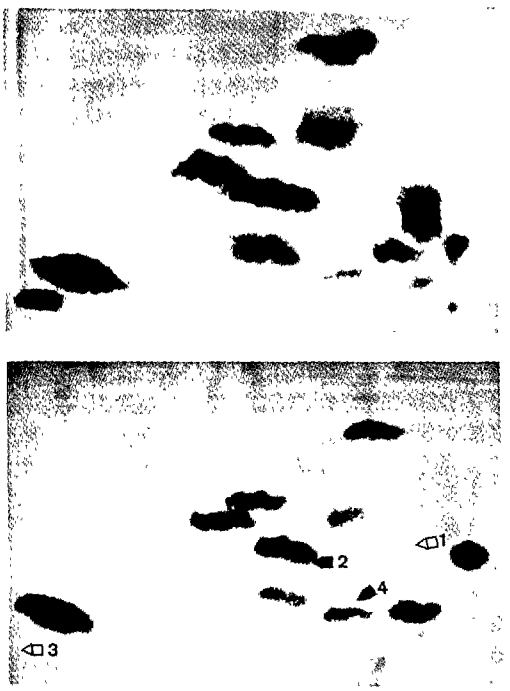


hemoglobinopathies (AC and CC), hemoglobins responsible for thalassemic syndromes, and M metahemoglobins represented 92.25% of the abnormalities detected.

Regarding the homozygous sickle-cell disease genotype SS, which seems responsible for the highest morbidity and mortality index of the abnormal hemoglobins *(23)*, we found an incidence of one such abnormality per 968 individuals studied in the total population and one per 145 negroids. Indeed, within the negroid sector of the São Paulo State population the prevalence of the disease appears considerably higher than in North American populations, where studies similar to ours have shown an average on the order of one case per 330 people *(24-26)*.

Among the thalassemic syndromes, heterozygous thalassemia predominated, followed by the interactive forms—the presence of

Photos 3A and 3B. Peptide mapping of the alpha chain of Hb A (above) and Hb G Philadelphia (below). The numbers on the bottom picture show (1) where one constituent of normal hemoglobin (α Tp IX) is missing, (2) where abnormal α Tp IX (with a mutant amino acid) appears, (3) where another constituent of normal hemoglobin (the peptide α Tp VII-VIII) is missing, and (4) where abnormal α Tp IX associated with normal α Tp VIII appears.



these latter demonstrating the process of racial mixing that has involved genes of African and Mediterranean origin. The geographic distribution of these thalassemic syndromes by city and economic-demographic region (see Figure 3) shows an interesting dispersion of this hereditary pathology that may be closely related to the ethnic groups that settled each city and the various surrounding regions (see Figure 1).

The distribution of abnormal hemoglobin genotypes by age group, a distribution unknown in any part of Brazil before the present survey, showed that the homozygous sickle cell and beta thalassemia genotypes were found only among relatively young people—possibly reflecting the fact that these genotypes are harmful and can produce early death in those who bear them. On the other hand, even though people with the interactive forms of beta thalassemia (beta°/S and beta +/S) exhibited clinical and hematologic manifestations similar to those with homozygous beta thalassemia *(19)*, these interactive types were found among nearly all the age groups studied.

Overall, the findings of this study demonstrate the public health importance of abnormal hemoglobins, specifically for the people of São Paulo State; and they strengthen the assertion that propagation of the homozygous and interactive disease states, as well as perpetuation of the genetic traits involved, justifies the implementation of effective programs for identifying these pathologies and for making carriers of the responsible traits aware of the need to take preventive measures.

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SUMMARY

A study of abnormal hemoglobins among the inhabitants of Brazil's São Paulo State was conducted using blood samples collected from 17,439 subjects attending health facilities in 19 cities during 1978-1980. For purposes of analysis, the subjects were grouped by age and racial features, 14,957 being classified as "caucasoids" and 2,482 as "negroids," the latter category including negroes, dark mulattoes, and light mulattoes.

Electrophoretic techniques were used to detect abnormal hemoglobins, determine the presence of hemoglobin types S and C, and isolate the polypeptide chains of other abnormal hemoglobins. Molecular stability tests, quantitative and qualitative tests for metahemoglobin, and tests for quantification of hemoglobin A2 and fetal hemoglobin were performed as needed. Rare variants were characterized structurally by peptide mapping. Alpha and beta thalassemias were diagnosed in accordance with principles established by the World Health Organization.

These procedures detected abnormal hemoglobins in 452 (2.59%) of the study subjects. These included 398 specific molecular variants (370 of them being type S or type C variants), 45 thalassemias, seven metahemoglobin variants, and two fetal hemoglobin variants. Overall, the prevalence of abnormal hemoglobins was found to be higher among negroids than among caucasoids in 17 of the 19 study cities; and while the prevalence among caucasoids was no higher than 3.2% in any city, among negroids it exceeded 5% in 13 cities and surpassed 10% in six. The tests, which detected 12 "molecular variant" genotypes and seven thalassemia genotypes, also revealed the presence of several rare hemoglobins, including three (J Oxford, G Philadelphia, and Constant Spring) not previously found in the Brazilian population.

While the overall prevalence of abnormal hemoglobins among the São Paulo subjects (2.59%) did not differ greatly from prevalences previously found in other parts of Brazil, the prevalences appeared far greater in some of the study cities than in others.

Regarding the thalassemias, while heterozygous thalassemia predominated, a considerable number of interactive forms were observed—these having resulted from the process of racial mixing involving genes of African and Mediterranean origin.

Overall, the results of this survey demonstrate the public health importance of this problem in São Paulo and provide strong justification for establishing programs that will effectively identify the pathologies involved and will make carriers of the responsible traits aware of the need to take preventive measures.

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INTERNATIONAL DIARRHEAL DISEASE CENTER TO OPEN IN BUFFALO, NEW YORK, USA

A new International Center of Infant Nutrition and Gastrointestinal Disease is to open at the Buffalo Children's Hospital in upper New York State in August 1984. The first of its kind, the center will train physicians from around the world in the treatment of acute and chronic infant diarrhea. It is also expected to perform research and to provide instruction for people seeking to establish associated centers in other countries.

Funded by a US$3 million grant from the U.S. Agency for International Development, the center will offer two training programs, one lasting six months and the other lasting two years. Initially, the facility is to train 23 physicians from countries outside the United States.

Much of the center's attention will be focused on chronic diarrhea resulting from persistent injury to the mucous lining of the small intestine. Specifically, it will seek to develop an infrastructure of pediatricians and health professionals in developing countries who will involve themselves in promoting the care of infants with chronic diarrhea.

Besides its regular training program, the center will offer annual workshops and is planning to host an international symposium on infant nutrition and gastrointestinal disease in August 1985. That symposium, designed to accommodate roughly 700 participants, is expected to provide a forum for presentations by some 70 world experts in the field. Further information about these events, and also about the new center's regular training programs, may be obtained by writing to the International Center of Infant Nutrition and Gastrointestinal Disease, care of Dr. Emanuel Lebenthal, Buffalo Children's Hospital, Buffalo, New York, U.S.A.

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