DUPLICATION OF STRUCTURAL GENES FOR HEMOGLOBIN α AND β CHAINS IN MAN *

D. L. Rucknagel † and W. P. Winter

Department of Human Genetics
University of Michigan Medical School
Ann Arbor, Michigan 48104

The prevalence of multiple loci governing α-chain synthesis in many other animal species has been adequately documented by earlier papers in this volume. Until rather recently the world of the human geneticist has been relatively simple, there being only one structural locus for each of the six types of polpeptide chains identified in man—the α, β, γ, δ, ε, and ζ chains. The work of Huisman and Schroeder and their colleagues [1] assures us that there are at least two and perhaps four loci for the γ chains of fetal hemoglobin; one or more of these have glycine at residue 136 and one or more have alanine. They further propose the existence of major and minor loci for each of these types.[2]

The possibility of two Hb_α loci was first raised by Lehmann and Carrell [3] who drew attention to the fact that heterozygotes for many α-chain variants possess approximately 20% of the abnormal component, whereas heterozygotes for mutants of the β-chain structural locus possess 30 to 40% of the variant. The proportions of abnormal components present in published α- and β-chain mutants are shown in TABLE 1. With some notable exceptions the proportion of abnormal α-chain variants vary between 15 and 35%. A few variants fall below this range; for instance, Hb Ann Arbor, comprising 2 to 4%,[4] Hb Torino,[5] comprising 6 to 10%, and Hb Bibba,[6] comprising 11% of the total hemoglobin, are unstable and are probably denatured within the red cell. At the other extreme Hb G Philadelphia [7] and Hb G Chinese [8] comprise as much as 40 to 50% of the total hemoglobin. The majority of the β-chain variants vary between 25 and 40% of the total hemoglobin. Again, variants such as Hb Genova,[9] comprising 25%, Hb Zurich,[10] comprising 20–36% Hb Sabine,[11] comprising 8% and Hb Köln,[12] comprising 10–15% of the total hemoglobin, are unstable. However, in no less than sixteen α-chain variants, the proportion of abnormal hemoglobin is 50% or more of the total hemoglobin.

Published data must be interpreted cautiously, however, because, aside from the variation imposed by instability, a wide variety of techniques were employed in the various studies. Moreover, since there is probably only a single Hb_β locus, in all likelihood the wide range of values among β-chain variants also reflects additional intrinsic differences in gene expression from one variant to the next. Taking all of these factors into account, however, the differences in the expression between α-chain and β-chain variants seems valid.

One possible explanation for at least part of the variability is that α-chain mutants are more sensitive to amino acid substitution. That possibility has not been excluded. Nevertheless, in a number of mutants the qualitative abnormali-

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† Visiting Professor, Departments of Pediatrics and Medicine, Center for Sickle Cell Disease, Howard University College of Medicine.

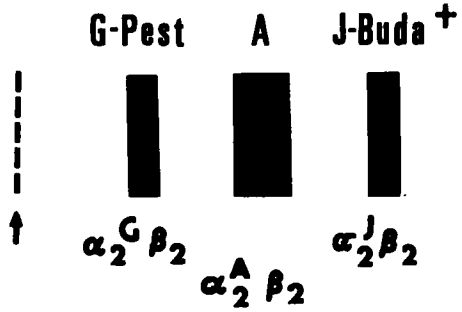

FIGURE 1. Diagram of electrophoretic pattern at pH 8.6 of Hb J α Buda α 61 Lys → Asn and Hb G α Pest α 74 Asp → Asn. Each mutant comprises approximately 25% of the total hemoglobin.

ties and genetic data allow inferences regarding multiple loci as the explanation.

Hb J Buda and G Pest

The first is a Hungarian Caucasian family in which three brothers possess, in addition to Hb A, two abnormal hemoglobins with variant α-chains, (FIGURE 1) Hb J Buda and Hb G Pest.[13, 14] These are distinct and independent mutants, the former having an asparagine molecule substituted for lysine at residue 61 and the latter an asparagine for aspartic acid at position 74. These men transmitted one or the other gene to six of their offspring. These observations indicate that these persons have two Hb_α loci, each locus having one mutant allele and one α^A allele from which the Hb A is derived (FIGURE 2). Each variant comprises approximately 20% of the total hemoglobin, suggesting that the two loci contribute equally to the α-chain pool. In addition, one son of each of the brothers reportedly had only Hb A, suggesting that the two Hb_α loci are not closely linked. Subsequent genotyping has cast doubt upon the paternity of these offspring, however, leaving the linkage of the two loci in doubt.[13, 14] In addition, the amino acid composition of all of the tryptic peptides of the three types of α chains present in these three brothers are identical, indicating that there are no amino acid differences between the chains normally produced by the two loci.

Hb J Tongariki

A second seemingly contradictary family is from a Kilenge village in New Britain. In it numerous individuals are heterozygous for Hb J Tongariki, α 115 Ala → Asp, a rapidly migrating component comprising 45 to 50% of the total

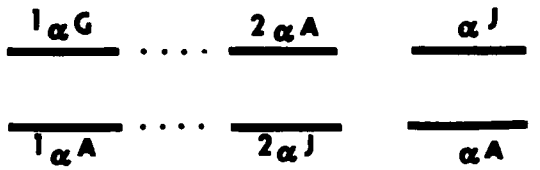

FIGURE 2. Diagramatic representation of the relationship of the two loci in a heterozygote for Hb J α Buda and Hb G α Pest (left) and in a heterozygote for Nb J α Tongariki (right).

TABLE 1

THE PROPORTION OF ABNORMAL HEMOGLOBIN IN HETEROZYGOTES FOR STRUCTURAL MUTANTS *

Substitution	Name	Ethnic Origin	Proportion	References
		α Chain Mutants		
5 Ala to Asp	J Toronto	English Cauc	20	
12 Ala to Asp	J Paris	Spanish Cauc	26	
15 Gly to Asp	J Oxford	English Cauc	20	
16 Lys to Glu	I	U.S. Negro	20–30	
		U.S. Cauc	21–24	
		English Cauc	15	37
22 Gly to Asp	J Medellin	Colombian Negro	20	
23 Glu to Lys	Chad	Chad Negro	16	
23 Glu to Val	G Audhali	S. Arabian Cauc	25	
27 Glu to Gly	Ft. Worth	U.S. Negro	5	38
30 Glu to Gln	G Honolulu	U.S. Chinese	50	
43 Phe to Val	Torino	Italian Cauc	8	
47 Asp to Gly	L Ferrara	Italian Cauc	30	
	Kokura	Japanese	16	
47 Asp to His	Hasharon	Ashk. Jewish	14–19	
51 Gly to Arg	Russ	U.S. Cauc	11–12	
54 Gln to Arg	Shimonoseki	Japanese	16–20	
54 Gln to Glue	Mexico	Mexican Indian	20	
57 Gly to Asp	Norfolk	English Cauc	27	
		Italian Cauc	37	
		Japanese	25	
57 Gly to Arg		Iranian Cauc	18	39
58 His to Tyr	M Boston	European Cauc	22–42	
		Japanese		
61 Lys to Asn	J Buda	Hungarian Cauc	21	14
64 Asp to His	Q India	Indian	19.6	40
68 Asp to His	Ube-2	Japanese	25	
68 Asn to Lys	G Philadelphia	U.S. African		
		West Indies Negro	33–45	
74 Asp to His	Mahidol, Q	Chinese, Thai	30–33	41, 42
74 Asp to Asn	G Pest	Hungarian Cauc	23	14
75 Asp to His	Q	Iranian Cauc	25	42
80 Leu to Arg	Ann Arbor	U.S. Cauc	2–4	4
84 Ser to Arg	Etobicoke	Irish	15	
85 Asp to Asn	G Norfolk	English Cauc	20	
85 Asp to Val	Inkster	U.S. Cauc	21.3–22.9	58
87 His-Tyr	M Iwate,	Japanese, Euro-		
	M Kankakee	pean Cauc	30	
90 Lys to Asn	J Broussais	French	20	
	Tagawa I	Japanese	18	
90 Lys to Thr	J Rajappen	India	26–28	43
92 Arg to Gln	J Cape Town	Hottentot-Euro-		
		pean	30–40	44
92 Arg to Leu	Chesapeake	German-Irish	23–30	45
102 Ser to Arg	Manitoba	Canadian En-		
		glish	5	46
114 Pro to Arg	Chiapos	Mexican Indian	25	
115 Ala to Asp	J Tongarkiki	Melanesian		15
136 Leu to Pro	Bibba	U.S. Cauc	11	

TABLE 1 (Continued)

Substitution	Name	Ethnic Origin	Proportion	References
		β Chain Mutants		
6 Glu to Val	S	African, Middle East, Indian Aborigines, Greeks, Sicilian	25–45	
6 Glu to Lys	C	W. African	30–40	
6 or 7 Glu deletion	Leiden	Dutch Cauc	30	
7 Glu to Lys	Siriraj	Thai	40	
9 Ser to Lys	Porto Alegre	Brazilian Portuguese	20	
14 Leu to Arg	Sogn	Norwegian	30–32	
16 Gly to Arg	D Bushman	Kalahari Bushman	37	
16 Gly to Asp	J Baltimore	U.S. Negro, English, Dutch Cauc	40–53	
20 Val to Met	Olympia	U.S. Cauc	40	
22 Glu to Ala	G Coushatta	American Indians	50	
22 Glu to Lys	E Saskatoon	Scottish Cauc	40	
22 Glu to Gln	D Iran	Iranian Cauc	40	
23 Val deletion	Freiburg	German Cauc	27–32	
24 Gly to Arg	Riverdale-Bronx	German Jewish	30	
25 Gly to Arg	G Taiwan-Ami	Taiwan Aborigines		
26 Glu to Lys	E	S.E. Asian	22–40	
28 Leu to Pro	Genova	Italian Cauc	25	
30 Arg to Ser	Tacoma	U.S. Cauc	43	
35 Tyr to Phe	Philly	Italian Cauc	30–35	
37 Try to Ser	Hirose	Japanese	30	
42 Phe to Leu	Bucuresti	Roumanian Cauc	45	
42 Phe to Ser	Hammersmith	English Cauc	30	
43 Glu to Ala	G Galveston	U.S. Negro	40–50	
46 Gly to Glu	K Ibadan	Yoruka (Nigeria)	50	
52 Asp to Asn	Osu-Christiansborg	Ghana Negro	36	
56 Gly to Asp	J Bangkok	Thai	50–60	
58 Pro to Arg	Dhofar	So. Arabian	15	
58 Pro to Arg	Jukuhashi	Japanese	40–56	
61 Lys to Asn	Hikari	Japanese	54	
61 Lys to Glu	N Seattle	U.S. Negro	50	
63 His to Arg	Zurich	Swiss Cauc	20–36	
63 His to Tyr	M Saskatoon	European Cauc, Japanese	30–40	
74 Gly to Asp	Sheperds Bush	S. Afr. English	24	
74–75 Gly-Leu deletion	St. Antoine	French	25	
76 Ala to Glu	Seattle	U.S. Cauc	40	
77 His-asp	J Iran	Iranian Cauc	50	
79 Asp to Asn	G Accra	Ghangian, Jamaican Negro	50	
87 Thr deletion	Tours	French	25	
90 Glu to Lys	Agenagi	Japanese	40–44	
91 Leu to Pro	Sabine	English-Scottish-German	8	
92 His to Tyr	M Hyde Park	U.S. Negro	40	

TABLE 1 (Continued)

Substitution	Name	Ethnic Origin	Proportion	References
92 His to Tyr	M Aikita	Japanese	30	
92 His to Glu	Istanbul	Turkish Cauc	12–15	
15 Lys to Glu	N-Baltimore	U.S. Negro	50	
97 His to Gln	Malmö	U.S. Swedish	48	
98 Val to Met	Köln	English-Scottish-German	10–15	
99 Asp to His	Yakima	Swedish	37–38	
99 Asp to Tyr	Ypsilanti	U.S. Negro	37	
102 Asn to Thr	Kansas	U.S. Cauc	51	
106 Leu to Pro	Casper	U.S. Cauc	30–40	
120 Lys to Glue	Hijiyama	Japanese	58	
121 Glu to Gln	D Punjah	Indian, Iranian European, Thai	30–40	
121 Glu to Lys	O Arab	Sudanese, Egyptian, Bulgarian, U.S. Negro	35	
126 Val to Glu	Hofu	Japanese	50	
136 Gly to Asp	Hope	U.S. Negro	40–45	
143 His to Asp	Hiroshima	Japanese	51	
145 Tyr to His	Ranier	U.S. Cauc	30	
91–98 Deletions	Gun Hill	German-English	50	
145–156 Addition	Tak	Thai	40	

* Modified from De Jong.[36] See this source for additional references.

hemoglobin.[15] In that family there were two individuals who were apparent homozygotes, having no Hb A or Hb A_2, suggesting that these individuals possess only one Hb_α locus (FIGURE 2). Unfortunately, both of the parents of these individuals were not available for study. An obvious alternate hypothesis is that these individuals also carry an α-thalassemia gene responsible for the complete suppression of synthesis of α^A chains. This in itself would be remarkable, if, in fact, there are two Hb_α loci present, both of which were influenced by a pair of α-thalassemia alleles. Nevertheless, there were no hematologic manifestations suggestive of thalassemia, and the high frequency of heterozygotes among individuals marrying into this family increased the odds that these two individuals were indeed homozygotes. Subsequently three additional homozygotes were observed among 717 inhabitants of KarKar, an island off the northern coast of New Guinea.[16] Again the parents of the apparent homozygotes were not studied. In the meantime, one of us (DLR) has restudied the New Britain family with Dr. Jan Saave, and this study should put the question to rest.[17] In that family one of the homozygotes was married to a heterozygote but blood had not been obtained from their only child.[15] Now we have obtained blood from their two children and both are homozygotes. In addition, a trait by trait mating also produced a homozygote. Thus, at least some Melanesians have only one Hb_α locus.

Structural data for Hb Hopkins-2 are purported[18] to show a mixture of two abnormal α chains in both of which aspartic acid is substituted for the normally occurring histidine at residue 112. But one chain also contains two

additional substitutions at positions 114 and 118. The authors believe that there are normally two Hb_α loci encoding chains that differ at the latter two residues. They propose that the substitutions at position 112 arose as a point mutation in one locus and then became transmitted to the other by unequal crossing over. These conclusions are based upon leucine aminopeptidase digestions of peptides isolated from tryptic digests by Dowex column chromtography followed by purification by paper electrophoresis. The latter technique cannot be relied upon to purify the peptides sufficiently to allow the interpretations rendered. Furthermore, Brimhall and colleagues[14] examined the amino acid composition of every tryptic peptide of the α chains of the Hb A, the Hb J Buda, and the Hb G Pest of one of their doubly heterozygous individuals and found no evidence for other differences in amino acid composition of the α chains of the two loci. Therefore, these findings on Hb Hopkins-2 must be held in abeyance until confirmation by more reliable methods.

A Hypothesis For Variable Numbers of α Loci

Additional evidence bearing upon the number of Hb_α loci has come to our attention through the family of a child who is heterozygous for $Hb_\alpha{}^{\text{G-Philadelphia}}$, $Hb_\beta{}^{S}$ and $Hb_\beta{}^{C}$.[19] In this family seven individuals were heterozygous for both $Hb_\alpha{}^{G}$ and $Hb_\beta{}^{S}$ and five were heterozygous for the $Hb_\alpha{}^{G}$ allele only. Among the latter, two had approximately 40% of Hb G whereas three had values of 28.5, 30.2, and 30.9% as measured by elution[20] from cellulose acetate electrophoresis strips (TABLE 2). This method is quite reproducible and more accurate than densitometry.[21] We perceive these values as beyond the range of variation encountered within most families with Hb S or Hb C trait, suggesting that the proportion of Hb G is bimodally distributed.

Having made this observation, we then scrutinized other data on Hb G in our possession. Rising and colleagues[22] have described a family in which both $Hb_\beta{}^{S}$ and $Hb_\alpha{}^{\text{G-Philadelphia}}$ are segregating and in which two individuals are heterozygous only for $Hb_\alpha{}^{G}$. We also quantified the proportion of Hb G in those persons' blood employing the technique used above (they employed densitometric analysis of cellulose acetate electrophoretic strips in their report). We obtained 27.0 and 29.0% Hb G on these two specimens (TABLE 2). We have also examined four specimens obtained from presumably unrelated persons in a survey of 25,000 Negroes enrolled in the Job Corps of the United States Government,[23] for which we were a reference laboratory. These four values were 39.2; 40.0; 28.9; and 27.8% of Hb G (TABLE 2). Thus, among eleven specimens, four clustered around 40% Hb G and seven around 30%. Since these data were examined retrospectively, a proper analysis of variance that took into account replicability of the technique could not be employed.

We propose that the apparent bimodality in the proportion of Hb G is due to variability in the number of Hb_α loci among Negroes, such that individuals with 40% of Hb G have only one Hb_α locus, whereas those with 30% of Hb G possess an additional Hb_α gene derived from a second locus (FIGURE 3). Values clustering around 15 to 20% of an abnormal α-chain variant (Hb X, FIGURE 3), thus far not observed with Hb Gα Philadelphia, would suggest that these persons possess two Hb_α loci; that is, one mutant and three normal genes. We shall assume in the ensuing discussion that the two loci are closely linked, although this need not be so. The occurrence of low proportions of Hb G

TABLE 2

HEMATOLOGIC VALUES AND PROPORTION OF ELECTROPHORETIC COMPONENTS IN Hb Gα PHILADELPHIA

References	Age	Sex	Hb Conc.	Hct	MCH Mg/ cell	MCV μ^3	% Hb G	% G/C	% G+G/ C	Morpho-logic Abnor-mality *
Hb Gα-Philadelphia Trait										
1. Rucknagel & Rising [19]	21	F	12	37.5	23.1	74	40.5			N
	9	F	11.9	37.8	21.4	69	39.1			H, M
	56	M	15.3	47.8	29.4	94	30.2			H, A
	16	M	15.7	49.6	26.5	85	28.5			A
	31	M	16.0	49.3	25.9	82	30.9			A
2. Rising, *et al.*[22]	25	M	14.7	41.4	26.9	76	27.0			
	21	F	12.7	38.1	25.9	78	29.0			
3. Fielding, *et al.*[23]		F					39.2			
		M					40.0			
							28.9			
		F					27.8			
4. Lie Injo, *et al.*[27]	14	F	12.6	39.	22.	68	26.9			
5. Raper, *et al.*[28]		F					45.			
Hb Gα Philadelphia/Hb C traits										
Fielding, *et al.*[23]		F					22.9	11.5	34.4	
Atwater, *et al.*[27]	28	F	12.4	38.	27.	84	24.	16.	40.	T
Raper, *et al.*[28]		M	17.8				23.	11.	34.	N
McCurdy, *et al.*[30]	47	M		38.		72	14	24.	38.	
Weatherall, *et al.*[31]	1	M	13.3	39.			24.4	8.1	32.5	H, M, T
			12.3	37.			23.5	8.2	31.7	A, T
			15.0	46.			23.2	9.6	32.8	A, T

* N=normal; H=hypochromic; M=microcytic; A=anisocytosis; T=target cells.

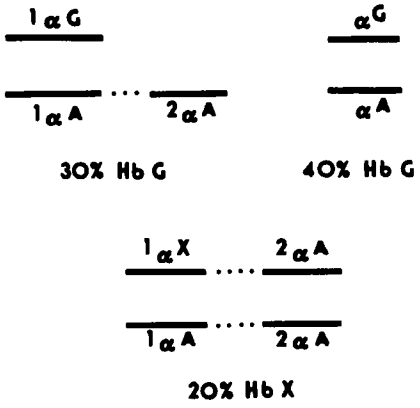

FIGURE 3. The various chromosomal arrangements of α-chain structural loci responsible for the bimodality in the proportion of Hb G α Philadelphia and for the diminished proportion of abnormal hemoglobin in various α-chain mutants (Hb X).

Philadelphia would suggest that crossing over had occurred between a chromosome bearing a single Hb_α gene and one bearing two Hb_α loci.

Other possible explanations cannot be completely excluded, given the paucity of data. The most obvious one is that the persons with the greater amount of Hb G are also heterozygous for an α-thalassemia gene. French and Lehmann,[24] concerned that the high proportions imputed to Hb Gα Philadelphia and Hb Gα Honolulu are incompatible with the two loci hypothesis, further proposed that this is due to linkage in the coupling phase of the Hb G and α-thalassemia genes. To support this contention they described a mother and three children with Hb G trait who had red cells resistant to hypotonic saline. Martinez and colleagues[25] observed a slightly decreased osmotic fragility also in an individual heterozygous for this same mutant. The two siblings with 40% Hb G in the "index family" described above[19] were microcytic, suggesting that either α thalassemia or iron deficiency is also present; inasmuch as they were young females and from poor families they are more likely to be iron deficient. Furthermore, other isolated individuals in that family having other genotypes had inconsistent hematologic abnormalities, suggesting sporadic nutritional deficiencies. We think these abnormalities are not indicative of a closely linked α-thalassemia gene because heterozygotes for Hb I and α-thalassemia[25] or β-chain structural variants and β thalassemia have 70% or more of the abnormal hemoglobin. In addition, we have not observed consistent hematologic evidence for such a phenomenon accompanying the $Hb_\alpha{}^G$ allele among the twelve relatives of the "index family" who had the $Hb_\alpha{}^G$ gene in combination with heterozygosity for $Hb_\beta{}^S$; at most slight anisocytosis was a frequent accompaniment of the gene. Finally, osmotic fragility changes noted by French and Lehmann[24] could also be effects of the Hb G per se, rather than thalassemia, analogous to the target cells regularly observed in heterozygotes for $Hb_\beta{}^C$ or $Hb_\beta{}^E$.

Further data bearing upon this hypothesis have been garnered from the literature (TABLE 2). Since different amino acid substitutions may affect synthesis differently (as demonstrated by the variability among Hb_β mutants), only the data for Hb G Philadelphia, the most common of the Hb_α mutants, are presented. Older data, probably from Hb G Philadelphia but in which the identity of the mutant had not been established by peptide mapping have been excluded. The data should also be scrutinized with the realization that different methods of quantification are employed in the various reports. Lie-Injo and colleagues[27] described one heterozygote with 26.9% Hb G, whereas Raper and colleagues[28] described another with 45%. Six individuals who are heterozygous for $Hb_\alpha{}^{G\text{-Philadelphia}}$ and $Hb_\beta{}^C$ have been described.[28–31] Among the four components visible upon electrophoresis, the sum of the Hb G and the G/C hybrid reflects the amount of α-chain content. The values obtained for these two components vary between 31.7 and 40% (TABLE 2). One such person in the Job Corps study possessed 34.5% of the two components. These data should not be pooled with those for the simple Hb G trait, but only the within-group variation considered for evidence of bimodality.

Numerous individuals heterozygous for $Hb_\alpha{}^{G\text{-Philadelphia}}$ and $Hb_\beta{}^C$ have been reported. In this genotype the Hb S and Hb G molecules migrate identically or nearly so. The proportion of Hb G/S hybrid is not informative since in the model described above—and assuming β^S chains comprise 35% of the total β-chain content—the proportion of G/S expected in the two- and three-

gene models are 14.0 and 10.5%, respectively, too small a difference to provide an adequate test of the model.

Population Implications

Hb Gα Philadelphia is widely distributed in American Negroes at a trait frequency [23] of approximately one in 5,000, indicating that the gene is of African origin. From TABLE 1 it is apparent from the fact that none of the Hb_α mutants in Caucasians possess over 30% of the variant molecule that most Caucasians have two Hb_α loci. Assuming the above hypothesis regarding heterogeneity of Hb_α loci in American Negroes to be correct, the proportion of unrelated persons having high and low proportions of Hb G provide an estimate of the frequency of the second locus in this race. Family data present a more complicated situation in that, when siblings with the Hb G trait fall in the same mode, one cannot be certain of the genotype of the non-Hb G parent until a large number of offspring with the trait have proven to have uniform proportions of Hb G, whereas when siblings fall in the different classes the parent not having $Hb_\alpha{}^G$ is thereby shown to have three $Hb_\alpha{}^A$ genes. In the collection of data described in this report we have identified eight chromosomes homologous to $Hb_\alpha{}^G$ to be counted. In a single sibship of the "index family" [19] two sisters have 40% and a brother 30% of Hb G, so we have counted the chromosomes of the non-Hb G parent as one single and one double locus chromosome. In another sibship of this family a single heterozygote had 30% of Hb G so we count the chromosome not containing Hb G of that person as a two-locus chromosome. In the family of Rising and colleagues [22] the two persons with approximately 30% Hb G trait are siblings so we had discarded one of them in order to not count the same parental chromosome twice. The four Job Corpsmen with $Hb_\alpha{}^G$ trait are presumably unrelated, so their non-Hb G chromosomes are counted. Thus, among eight chromosomes, five presumably bear two Hb_α loci (yielding 30% Hb G) and three were chromosomes having only one Hb_α locus (yielding 40% Hb G). Although this is a very small body of data on which to base an estimate, nevertheless, assuming that 25% of the genes in the American Negro gene pool are of Caucasian origin,[32] we can estimate that the frequency of the chromosome bearing only one Hb_α locus among African Negroes is $3/8 \times 4/3 = 0.5$. The finding of Brimhall and colleagues [14] that the α-chains produced by the two Hb_α loci have identical amino acid compositions suggests that the duplication of the two loci in Caucasians, most likely by the process of unequal crossing over, was too recent an event for mutational differences to have arisen and become fixed.

The nature of the selective pressure responsible for the difference in the frequency of the two chromosomes in the two races is unclear. If the racial frequencies were reversed and Negroes had a higher frequency of the second locus, one would be tempted to assume that the same selection pressures resulting in the high frequencies of $Hb_\beta{}^S$ and $Hb_\beta{}^C$ are responsible for the two Hb_α loci. The prevalence of multiple Hb_α loci among a large number of different species of animals compels one to look for a more general mechanism, however. Boyer (this volume) has suggested a population genetic mechanism. It seems to us that a physiologic mechanism of selection pressure may be related to the switching from embryonic to fetal to adult hemoglobin that is prevalent also among many species. Presumably differing needs of the fetus and adult favor differing non-α loci. Thus differing Hb_α loci may also be required. In most

animals the primary structure of the various α chains differ so that the argument can be couched in qualitative terms. In man, the primary structure of the two α chains appears identical,[14] so it is necessary to argue in more quantitative terms; namely, that either the adult or fetus finds it advantageous to possess more than one copy of the Hb_α locus.

Duplication of β-Chain Loci

At first glance, the fact that homozygotes for the gene for sickle cell anemia, Hb C, or Hb E have no Hb A indicates the existence of only one structural locus for β polypeptide chains. In 1963 Nance [33] proposed that some persons may have a chromosomes in which the $Hb_\beta{}^S$ and $Hb_\beta{}^A$ genes are closely linked. This proposal was made in part to explain the apparent bimodality in the proportion of Hb S among heterozygotes. The most likely explanation for that bimodality is the coexistence of a gene for α thalassemia, which is present in approximately 2% of the American Negro population.[34] Nance further proposed that such a tandem duplication would result in a deficiency of apparent homozygotes among trait by trait matings if unbiased population data were scrutinized. Family data ascertained through the presence of clinically affected homozygotes would be expected to be biased toward the single Hb_β chromosome. It is unlikely that the existence of a tandem duplication can be proven by such family data, however, since even family data ascertained through symptomatic homozygotes show a deficiency of this genotype, perhaps due to loss of homozygotes *in utero*.[35] The data at the present time, therefore strongly favor only a single Hb_β locus.

Duplication of the Hb_α and Hb_γ loci in man is supported by a growing body of data. This mechanism must be seriously contemplated when formulating models for genetic variability in man.

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