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Genetic studies on the Ticuna, an enigmatic tribe of Central Amazonas

BY JAMES V. NEEL,* HENRY GERSHOWITZ,* HARVEY W. MOHRENWEISER,* BERNARD AMOS,† DONNA D. KOSTYU,† FRANCISCO M. SALZANO,‡ MOACYR A. MESTRINER,§ DALE LAWRENCE,‖ AGUINALDO L. SIMÕES,§ PETER E. SMOUSE,* WILLIAM J. OLIVER,* RICHARD S. SPIELMAN¶ AND JAMES V. NEEL, Jr**

INTRODUCTION

The Ticuna are an Amerindian tribe speaking an 'isolated' language who, at the time of first contacts in the seventeenth century, occupied the triangular area between the Putumayo-Içа River and the Solimões River (Upper Amazon), between longitudes 71° 15′ and 68° 40′ W, as shown in Fig. 1. They were apparently denied access to the Solimões by the Arawak-speaking Omagua and, for most if not all of its course, to the Putumayo-Içа by the Arawak-speaking Mariaté, Yumána and Pasé. With the passage of time these latter tribes were decimated–assimilated through contacts with neo-Brazilians, but the free movement of the Ticuna to the river banks was again limited, this time by the local dealers in rubber, who, establishing trading stations at the mouths of the many small tributaries to these rivers, controlled movement from the interior. Unwittingly, first these Arawaks, and then the rubber traders, provided the Ticuna a remarkable degree of protection against intermixture for a tribe so close to great waterways, so that even today, as we shall show, the genetic heritage is still approximately 98 % Amerindian.

During the past 50 years, with the collapse of the rubber trade and the suppression of some of its practices, the Ticuna have progressively moved to occupy both banks of the Solimões and adjacent regions, between longitudes 70° 30′ and 66° 30′ W. There has also been some migration to the banks of the Lower Içа. The situation in the area that they formerly occupied, between these two rivers, is somewhat unclear. Fig. 2 presents their present approximate distribution. Subsequent to their appearance on the banks of the Solimões, under the stimulus of several religious leaders, there has been a great deal of movement up and down the river. Population numbers have increased dramatically in the past half-century. Today the Brazilian Ticuna are thought to number approximately 11,000 persons; we have no satisfactory figure for those in Colombia and Peru. Accounts of their history and demographic trends will be found in Nimuendaju (1952), Cardoso de Oliveira (1977) and Salzano, Callegari Jacques & Neel (1980).

In recent years our group has been engaged in multidisciplinary studies of various 'minimally acculturated' Indian tribes of Central and South America. One aspect of these studies has been an effort to develop a genetic topology for those Amerindian tribes where admixture was less

* University of Michigan Medical School, Ann Arbor, Michigan USA 48109.
† Duke University School of Medicine, Durham, North Carolina USA 27710.
‡ Instituto de Biociências, Universidade Federal do Rio Grande do Sul, Porto Alegre, R.G.S., Brasil.
§ Faculdade de Medicina, Universidade de São Paulo, 14100 Ribeirão Preto, SP, Brasil.
‖ Bureau of Laboratories, Center for Disease Control, U.S. Department of Health and Human Services, Atlanta, Georgia USA 30333.
¶ University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania USA 19174.
** University of Washington School of Medicine, Seattle, Washington USA 98195.

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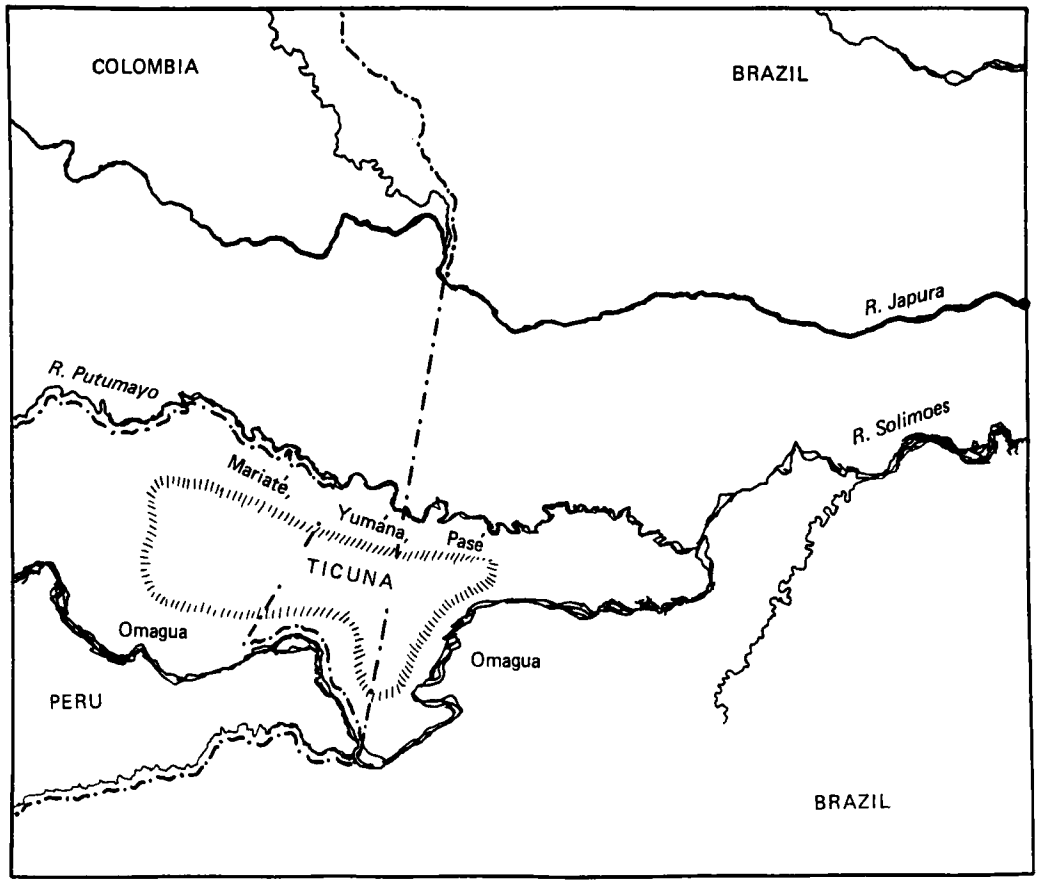

Fig. 1. The approximate distribution of the Ticuna at the time of earliest contacts.

than 5%, with the long-range objective of contributing to the understanding of the evolution of man in South America. As these studies have progressed, the Ticuna emerged as a tribe of particular interest, since, although by now scarcely 'minimally acculturated', they were reputed to be one of the very few large, relatively pure tribes of Central Amazonas. The principal hypothesis of the peopling of eastern South America involves ascent of the Amazon River and/or a sweep south around the northeastern extremity of the Andes. The area occupied by the Ticuna represents an important location under either theory. The key reason for this study was thus to define the genetic characteristics of a strategically located tribe, not only with respect to the genetic polymorphisms of widespread distribution but also the 'private' variants, which, when encountered as 'private polymorphisms', are so useful in establishing tribal relationships.

This paper will report the results of extensive genetic typings on some 1760 blood samples collected from the Ticuna during the summer of 1976, in the course of fieldwork along the Rio Solimões, fieldwork which was greatly facilitated by the use of the Research Vessel *Alpha Helix*, then maintained by the National Science Foundation. The locations of the eight villages sampled are shown in Fig. 2. We present here a preliminary treatment of the genetic relationships of this tribe; a more detailed treatment will come later. Major attention will be directed towards two quite unusual and unanticipated features of the group: specifically, a remarkable degree of intra-tribal homogeneity, and, in proportion to tribal size, a relative paucity of

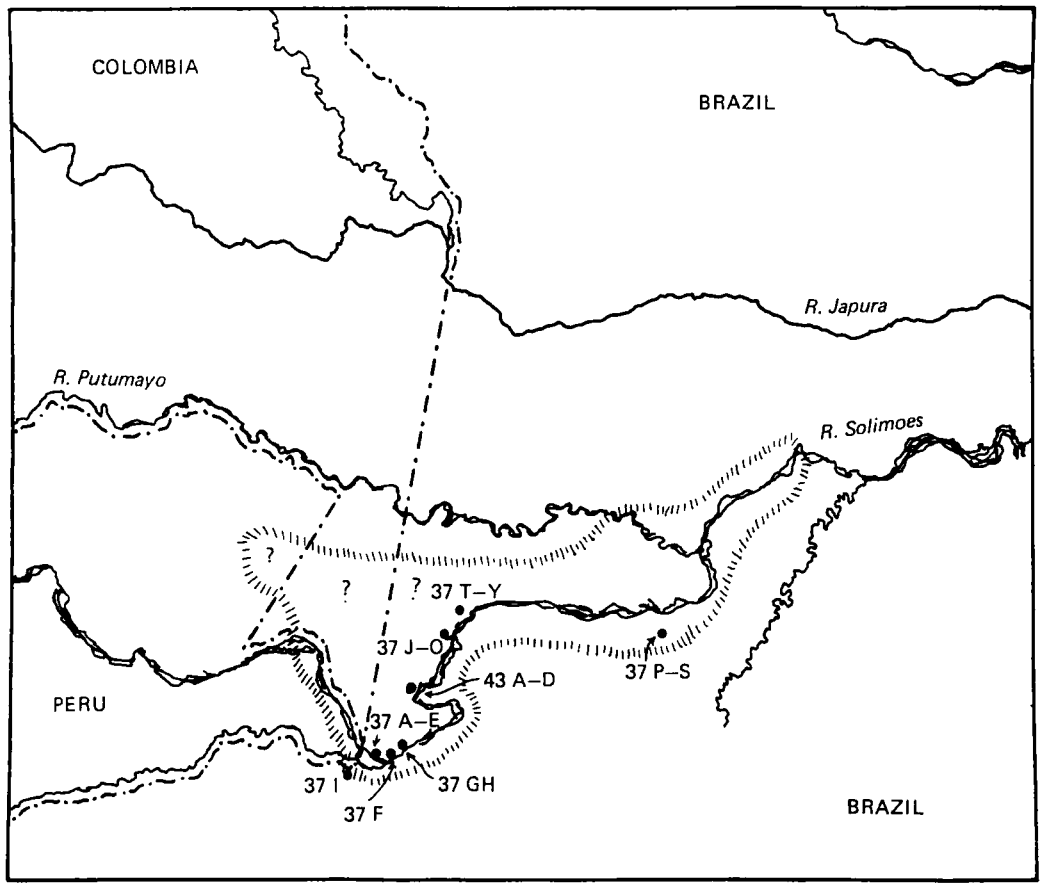

Fig. 2. The approximate distribution of the Ticuna in 1976, with locations of the villages in which blood samples were obtained.

'unique' tribal genetic variants of the type so regularly encountered in studies of the other Amerindian populations (rev. in Neel, 1978). Possible explanations will be developed for both these findings. The single 'unique' tribal variant encountered is present in polymorphic proportions, contributing further to the already recognized possibility that, when the 'standard' polymorphisms are excluded from consideration, Amerindians exhibit more residual genetic variation than Caucasoids or Japanese (cf. Neel, 1978).

PROCEDURES

Venous blood samples were collected in 13 ml Becton Dickinson vacutainers containing 2·25 ml of ACD solution. They were chilled immediately upon collection and air-lifted back to the Ann Arbor lab as soon as possible, usually arriving within 3–5 days after collection. In Ann Arbor cells and plasma were separated and stored at either − 72 °C or in liquid nitrogen until the determinations were performed. In each village, samples were obtained from as many persons as possible, regardless of relationship.

Blood groups. Single typings were performed on red cells that had been preserved in glycerol-sorbitol freezing solution in liquid N_2 for 18–33 months. The following systems were investigated: ABO, Rh, MNSs, P, Kell (K), Duffy (Fy), Kidd (Jk), Diego (Di), Lutheran (Lu), and

Table 1. *Phenotype frequencies with reference to 15 polymorphic genetic systems studied in the Ticuna*

The local designations of the villages sampled are as follows: 37A–E, Mariaçu; 37F, Maraja; 37GH, Feijoal, 37I, Bom Jardin; 37J–O, Vendaval; 37P–S, Nova Italia; 37T–Y, Campo Alegre; 43A–D, Belem.

		Village								
System	Phenotype	37A–E	37F	37GH	37I	37J–O	37P–S	37T–Y	43A–D	Total
MNS	MS	3	3	3	0	0	5	1	0	15
	MSs	75	14	19	11	19	36	39	39	252
	Ms	214	60	74	44	242	77	263	168	1142
	MNS	0	1	0	0	0	0	1	1	3
	MNSs	18	4	5	5	3	7	8	22	72
	MNs	55	6	22	17	32	22	52	29	235
	NS	2	0	0	0	0	0	1	1	4
	NSs	2	1	0	0	0	0	0	3	6
	Ns	2	0	3	1	4	2	4	2	18
	Total	371	89	126	78	300	149	369	265	1747
Rh	R_1R_1	140	41	48	41	152	52	142	126	742
	R_1R_0	2	0	1	0	6	2	6	6	23
	R_1R_2	164	36	44	28	113	76	157	104	722
	R_zR_1	7	2	18	3	2	1	12	12	57
	R_zR_2	8	1	1	1	0	0	8	4	23
	R_2R_2	48	9	12	6	25	18	37	19	174
	R_2R_0	2	0	1	0	2	0	8	0	13
	R_1^ur or R_1^ur'	0	0	1*	0	0	0	0	0	1*
	Total	371	89	126	79	300	149	370	271	1755
Fy	a+b−	162	34	57	28	102	68	156	123	730
	a+b+	161	49	60	34	145	71	167	108	795
	a−b+	48	6	9	16	53	10	46	38	226
	Total	371	89	126	78	300	149	369	269	1751
Jk	a+b−	68	11	42	26	26	19	49	63	304
	a+b+	176	35	61	36	134	77	181	115	815
	a−b+	126	43	23	16	140	53	139	88	628
	Total	370	89	126	78	300	149	369	266	1747
P	P+	290	70	94	64	222	119	232	187	1278
	P−	81	19	32	14	78	30	138	84	476
	Total	371	89	126	78	300	149	370	271	1754
Di	a+	101	33	49	11	59	52	119	86	510
	a−	269	56	77	67	241	97	250	180	1237
	Total	370	89	126	78	300	149	369	266	1747
Le	a−b+	238	64	85	58	156	94	176	182	1053
	a−b−	133	25	41	20	144	55	194	88	700
	Total	371	89	126	78	300	149	370	270	1753
Lu	a+	3	0	1	0	1	0	0	1	6
	a−	367	89	125	77	299	149	368	264	1738
	Total	370	89	126	77	300	149	368	265	1744
Hp	1	156	35	62	34	107	73	163	135	765
	1–2	163	44	54	34	159	65	167	121	807
	2	55	11	11	11	34	11	44	16	193
	Total	374	90	127	79	300	149	374	272	1765

Table 1 (*cont'd*)

System	Phenotype	Village 37A–E	37F	37GH	37I	37J–O	37P–S	37T–Y	43A-D	Total
Gc	1	245	56	78	66	238	100	288	161	1232
	1–2	123	34	46	13	57	47	75	97	492
	2	6	0	3	0	5	2	11	14	41
	Total	374	90	127	79	300	149	374	272	1765
Tf	C	361	88	124	76	294	143	373	263	1722
	C+D Chi	13	2	3	3	6	6	1	9	43
	Total	374	90	127	79	300	149	374	272	1765
ACP 1	A	1	0	0	0	2	0	0	1	4
	AB	31	5	27	19	23	35	18	38	196
	B	281	66	92	59	188	83	249	188	1206
	A+V	5	0	1	0	1	3	3	3	16
	B+V	49	17	7	1	76	27	94	37	308
	V	6	2	0	0	10	1	9	5	33
	Total	373	90	127	79	300	149	373	272	1763
GALT	1	335	78	121	75	282	138	341	246	1616
	1+D	37	8	6	3	17	10	30	25	136
	D	1	4	0	1	1	1	0	1	9
	Total	373	90	127	79	300	149	371	272	1761
GLO	1	12	3	4	8	5	5	11	6	54
	1–2	117	37	42	23	84	31	92	58	484
	2	243	50	81	48	211	113	270	208	1224
	Total	372	90	127	79	300	149	373	272	1762
PGM 1	1	215	61	66	50	263	98	284	180	1217
	1–2	144	26	50	24	36	45	84	82	491
	2	15	3	11	5	1	6	6	10	57
	Total	374	90	127	79	300	149	374	272	1765

* Not included in gene frequency.

Lewis (Le). The procedures employed in this Department have been described previously (Gershowitz *et al.* 1972).

Plasma proteins. Albumin (ALB), transferrin (Tf), haptoglobin (Hp), and group specific component (Gc) types were determined by starch gel electrophoresis according to previously referenced techniques (Tanis *et al.* 1973; Neel, Ferrell & Conard, 1976; Neel *et al.* 1977*a*). However, ceruloplasmin (CRPL) typings employed acrylamide electrophoresis, following the technique of Maurer & Allen (1972).

Erythrocyte proteins. The following erythrocyte proteins were examined for variants by starch gel electrophoresis: hemoglobin A (Hb A_1), hemoglobin A_2 (Hb A_2), acid phosphatase-1 (ACP 1), adenosine deaminase (ADA), adenylate kinase-1 (AK 1), carbonic anhydrase-I (CA 1), carbonic anhydrase-II (CA 2), galactose-1-phosphate uridyl transferase (GALT), glyoxalase I (GLO), isocitrate dehydrogenase (ICD), lactate dehydrogenase (LDH), malic dehydrogenase (MDH), nucleoside phosphorylase (NP), peptidase A, B, C and D (PEPA, PEPB, PEPC, PEPD), 6-phosphogluconate dehydrogenase (6PGD), phosphoglucomutase I and II (PGM 1 and PGM 2), phosphohexoseisomerase (PHI), triosephosphate isomerase (TPI), and inorganic

pyrophosphatase (PPASE). The techniques employed here have for the most part been enumerated in the references of the preceding section. However, data on four enzymes are being reported from this laboratory for the first time. The enzymes and the references to the basic techniques are as follows: PEPC and PEPD (Harris & Hopkinson, 1976), PPASE (Fisher *et al.* 1974), and GLO (Parr, Bagster & Welch, 1977). Data on the erythrocyte esterases are reported by Mestriner, Simões & Salzano (1980). These latter investigators also report the results of screening for CA 1 and 2 as do we, but different methodologies were employed.

HLA typings. Histocompatibility studies were performed in Ann Arbor on lymphocytes isolated by ficoll-hypaque sedimentation of whole blood samples which on average had been collected 3–4 days earlier and kept chilled in the interim. Ninety-six antisera were used to define the following HLA antigens: A1, 2, 3, 9, (w23, w24), 10, 11, 28, w19 (29–33); B5 (w51, w52, B5.y), w53, 7, 8, 12, 13, w15, 16 (w38, w39), 17, 18, w21 w22, 27 and w35. Typing was performed by a three-stage complement-dependent cytotoxicity assay as previously described (Amos *et al.* 1970). Gene frequencies were calculated using the formula $p = 1 - \sqrt{(1-P)}$, where p, P are respectively the dominant gene and phenotype frequencies.

THE DATA

Phenotype and allele frequencies for the 15 genetic systems in which variation was encountered (other than HLA) are given in Tables 1 and 2. No electrophoretic variation was encountered in the following systems (numbers in parentheses indicate number of tests): ALB (761); CRPL (758); Hb A, (1765); Hb A_2 (1765); LDH (1765); MDH (1765); NP (1764); PEPA (1765); PEPB (1765); PEPC (1763); PEPD (1763); 6PGD (1764); PGM 2 (1765); PHI (1765); TPI (1765); and PPASE (1760). Two persons of ADA type 1–2 were encountered among a total of 1763 examinations, and one AK 1 type 1–2 among 1762 examinations. We attribute these three variants to admixture (see below). The Rh typings yielded a single $R_1^u r$ individual. The R_1^u allele is not encountered in Amerindians in whom there is no evidence for mixture with non-Indians, and we also attribute this finding to admixture. The variation in the number of persons reported for the different test systems is due to the fact that for a variety of technical and administrative reasons, not all specimens could be, or were, tested for all systems.

The most noteworthy finding was the presence in polymorphic proportions of a variant of ACP 1 of a previously unreported type. The variant is illustrated in Fig. 3, along with the suitable controls, and two pedigrees are shown in Fig. 4. It presents as two slowly migrating components relative to the normal B type isozymes. The relative staining intensity between the two bands in homozygous individuals is similar to that observed for B-type individuals, as is the total staining activity when 4-methyl umbelliferyl phosphate is the substrate. The variant has been observed alone or with the A and B forms of ACP 1, in heterozygous individuals. It has been designated ACP_1 TIC-1 and the allele, $ACP_1^{TIC\text{-}1}$. The allele has a frequency of 0·111. A more complete characterization of the biochemical aspects of this variant will be presented elsewhere, (Yoshihara & Mohrenweiser, 1980).

Peptidase A is well known for variation in the intensity of its staining activity in erythrocyte preparations. Lewis (1973) has shown that in Caucasians the extreme of this variation, characterized by virtual absence of activity, is due to the presence of an allele ($PEPA^s$) associated with an unstable protein. In this study we encountered 12 individuals for whom no PEPA

Table 2. *Allele frequencies with reference to the* 15 *polymorphic genetic systems studied in the Ticuna*

System	Allele	Village								Total
		37A–E	37F	37GH	37I	37J–O	37P–S	37T–Y	43A–D	
MNS	*MS*	0·118	0·122	0·119	0·086	0·034	0·178	0·061	0·081	0·089
	Ms	0·767	0·805	0·750	0·760	0·894	0·711	0·843	0·798	0·807
	NS	0·023	0·030	0	0·017	0·002	0	0·011	0·047	0·019
	Ns	0·091	0·043	0·131	0·137	0·069	0·111	0·085	0·074	0·086
Rh	R^z	0·020	0·017	0·077	0·025	0·003	0·003	0·027	0·030	0·023
	R^1	0·610	0·674	0·635	0·715	0·708	0·614	0·620	0·690	0·651
	R^2	0·364	0·309	0·279	0·260	0·275	0·376	0·333	0·269	0·315
	R^o	0·006	0	0·009	0	0·013	0·007	0·020	0·011	0·011
Duffy	Fy^a	0·654	0·657	0·690	0·577	0·582	0·695	0·649	0·658	0·644
Kidd	Jk^a	0·422	0·320	0·575	0·564	0·310	0·386	0·378	0·453	0·407
P	P^1	0·533	0·538	0·496	0·576	0·490	0·551	0·389	0·443	0·479
Diego	Di^a	0·147	0·207	0·218	0·073	0·104	0·197	0·177	0·177	0·159
Lewis	*Le*	0·401	0·470	0·430	0·494	0·307	0·392	0·276	0·429	0·368
Lutheran	Lu^a	0·004	0	0·004	0	0·002	0	0	0·002	0·002
Hp	Hp^1	0·635	0·633	0·701	0·646	0·622	0·708	0·659	0·719	0·662
Gc	Gc^1	0·821	0·811	0·795	0·918	0·888	0·829	0·870	0·770	0·838
Tf	Tf^o	0·983	0·989	0·988	0·981	0·990	0·980	0·999	0·983	0·988
ACP 1	ACP_1^A	0·051	0·028	0·110	0·120	0·047	0·128	0·028	0·079	0·062
	ACP_1^B	0·860	0·855	0·858	0·874	0·792	0·765	0·818	0·829	0·827
	ACP_1^{TIC1}	0·089	0·117	0·032	0·006	0·161	0·107	0·154	0·092	0·111
GALT	$GALT^1$	0·948	0·911	0·976	0·968	0·968	0·960	0·960	0·950	0·956
GLO	GLO^1	0·190	0·239	0·197	0·247	0·157	0·138	0·153	0·129	0·168
PGM 1	PGM_1^1	0·767	0·822	0·717	0·785	0·937	0·809	0·872	0·813	0·829

activity appeared during the usual period of observation. If they are homozygotes for this allele, the gene frequency in the Ticuna is 0·082.

The results of the HLA typings are shown in Tables 3 and 4. Three HLA-A antigens, A2, A9 and Aw19, and four HLA-B antigens, B5, Bw15, B16 and Bw35, were predominant. HLA-A9 has now been subdivided into Aw23 and Aw24. Most of the HLA-A9 positive Ticuna individuals carried the Aw24 variant rather than the Aw23, since they failed to react with serum Rodbro (anti-Aw23). However, cells from several individuals not reacting with Rodbro or with an anti-Aw24 serum BiM, did react with another Aw24 serum New and with anti-A9 sera Kisch, BSt and DMi. This would suggest the existence of a new A9 variant.

Variant patterns of reactivity were also seen for B16. B16 has now been subdivided into Bw38 and Bw39 and most Ticuna appeared to carry the Bw39 variant. However, cells from 13 individuals failed to react with the Bw38 serum (OVE) or with two Bw39 sera (RC and Hib). These individuals were reactive with other Bw39 sera, and this may represent a new B16 variant separate from Bw38 and Bw39.

A large number of individuals reacted with sera defining the Aw19 group of antigens (A29, Aw30, Aw31, Aw32, Aw33). Clear distinction between these specificities was difficult since many sera detected more than one antigen of this group. As a result, these cells have been labelled Aw19, with the understanding that they may be A29, Aw30, Aw31, Aw32 or Aw33.

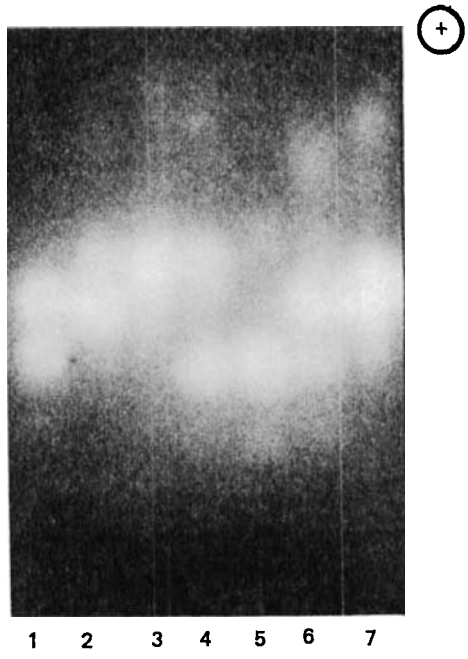

Fig. 3. A comparison of the ACP_1 TIC 1 variant with ACP_1 types A, B, and AB, in a starch-gel electrophoretic system employing histidine-citrate buffer and stained with 4 methyl umbelliferyl phosphate as substrate. The wells were as follows: 1, TIC 1/B; 2, A/B; 3, A; 4, TIC 1/A; 5, TIC 1; 6, TIC 1/B; 7, B.

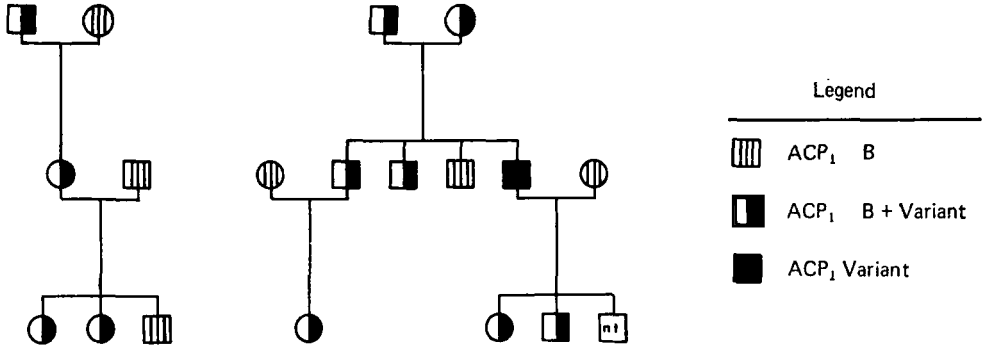

Fig. 4. Two illustrative pedigrees of the Ticuna ACP_1 variant.

The B5 specificity has recently been found to include at least three variants, Bw51, Bw52 and B5.y (Payne *et al.* 1978). Ticuna individuals were found that typed as Bw51 or Bw52. In addition, four individuals typed as B5, but failed to react with the Bw51 sera (PA101.12 and JD) or with the Bw52 serum (PD202), and therefore may carry a new variant which has provisionally been designated B5.x.

DISCUSSION

The admixture of the tribe with non-Indians has been estimated from the frequency of the A and B alleles of the ABO system and the $Gm^{f;b}$ and $Gm^{a;b}$ alleles of the Gm system. For the former (as in our previous calculations) the combined frequency of A and B in Negroes and Caucasians was assumed to be 0·35. For the latter, $Gm^{f;b}$ is assumed to have a frequency of 0·70

Table 3. *HLA phenotype and gene frequencies in the Ticuna population*

	No. positive	Phenotype frequency	Estimated gene frequency*	Observed gene frequency†
		HLA–A		
A9‡	101	78·3	0·534	0·482
Aw19§	55	42·6	0·242	0·268
A2	45	34·9	0·193	0·232
A3	1	0·8	0·004	—
A1	1	0·8	0·004	—
A28	1	0·8	0·004	0·018
Blank			0·019	—
		HLA–B		
Bw35	37	28·9	0·157	0·161
B5	22	17·0	0·088	0·125
Bw51	3	2·3	0·012	—
Bw52	15	11·6	0·060	0·089
B5.x	4	3·1	0·016	0·036
Bw53	1	0·8	0·004	—
B7	1	0·8	0·004	—
B40	1	0·8	0·004	—
Bw39 (B16)‖	55	42·6	0·242	0·250
Bw15	33	25·6	0·137	0·178
Blank			0·364	0·286

* Calculated from phenotype frequency, $p = 1 - \sqrt{(1 - P)}$, $N = 129$ unrelated individuals.
† Determined from 56 haplotypes by direct count.
‡ Probably Aw24, but may include Aw23 and undefined variant A9 antigens.
§ Aw19 includes A29, Aw30, Aw31, Aw32 and Aw33.
‖ May include undefined variant B16 antigens.

in Caucasians (and to be absent in Negroes), and $Gm^{a;b}$ a frequency of at least 0·95 in Negroes (and absent in Caucasians). In making this calculation, we have excluded from all our data those persons encountered in Ticuna villages (and their offspring), 50 in number, who stated they were Brazilians rather than Indians.

The Gm data on the Ticuna have been presented in Gershowitz & Neel (1978). For the ABO alleles, the findings were: type A_1, 11; type A_2, 9; type B, 19; type O, 1716. From the Gm data, we calculate the non-Indian admixture to be 1·1 %; from the ABO data, 3·2 %. We will accordingly adopt a figure of 2·2 %. (Because of the 'familial cluster effect' with our sampling design, we do not feel it appropriate to use some of the less common genetic polymorphisms for the calculation of admixture.) Given this amount of admixture, it seemed reasonable to attribute the R_1^u allele and the ADA and AK 1 variants mentioned earlier to the non-Indian contribution to the Ticuna gene pool.

With respect to the 15 polymorphic systems which we have tabled, most of the allele frequencies are well within the range encountered in Amerindians. The only noteworthy findings are the exceptionally high frequency of L^{Ms} and, as noted above, the presence of a previously undescribed variant of ACP 1 in polymorphic proportions. The $Tf^{D\,Chi}$ polymorphism, an inconstant feature of Amerindian tribes, is present in a low frequency, but the PGD^C allele of 6PGD, another inconstant polymorphism of Amerindian tribes, is absent. Thus far there is little information concerning the GLO polymorphisms in Amerindians, but the Ticuna GLO^1 allele

Table 4. *Haplotype frequencies as obtained from pedigree material for a subset of 56 identifiable haplotypes, with an analysis of linkage disequilibrium*

Haplotype	Observed haplotype frequency ($\times 10^{-3}$)	Expected haplotype frequency ($\times 10^{-3}$)†	Δ ($\times 10^{3}$)	Significance
A2-Bw52	54	20	34	—
A2-Bw15	54	41	13	—
A2-Bw35	71	37	34	—
A2-B5.x	18	8	10	—
A9-Bw15	107	86	21	—
A9-Bw35	89	77	12	—
A9-Blank	214	138	76	*$P<0.05$
Aw19-B16	143	67	76	***$P<0.01$
Aw19-B5.x	18	10	8	—
A28-Bw52	18	3	15	—
A2-B16	36	58	−22	—
A2-Blank	0	66	−66	**$P<0.025$
A9-Bw52	0	42	−42	
A9-B5.x	0	17	−17	
A9-B16	71	121	−50	—
Aw19-Bw15	18	48	−30	—
Aw19-Bw35	0	43	−43	—
Aw19-Bw52	18	24	−6	—
Aw19-Blank	71	77	−6	—
A28-B5.x	0	1	−1	—
A28-Bw15	0	3	−3	—
A28-B16	0	5	−5	—
A28-Bw35	0	3	−3	—
A28-Blank	0	5	−5	—

* Significant linkage disequilibrium.
† Estimated on the assumption of equilibrium in allele associations.

frequency is similar to that of the sample of 295 Colombian Amerindians of undesignated tribe (0·30) reported by Ghosh (1977).

In past discussions of the relationships of Amerindian tribes, we have on several occasions presented an intertribal 6-locus genetic distance matrix based on allele frequencies for the MNSs, Rh, Kidd, Duffy, Diego, and haptoglobin alleles as well as the distance of each tribe from the multivariate mean of all tribes (e.g. Ward *et al.* 1975; Neel *et al.* 1977*b*). For the purposes of this paper, we have updated the calculation, so that it now includes 23 tribes. Distances have been calculated by the 'chord approximation' technique of Cavalli-Sforza & Edwards (1967). Fig. 5 presents the distribution of tribal distances from the multivariate mean. Note the intermediate position of the Ticuna. The average tribal distance from the all-tribes multivariate mean is 0·356; the value for the Ticuna is 0·339. Relative closeness to the multivariate mean may imply either a primary resemblance to the 'founding' Amerindian stock or, as we have pointed out in the instance of the Macushi and Wapishana (tribes 10 and 16), could also result from recent tribal admixtures that recreate an 'average' picture (Neel *et al.* 1977*b*). The fact that the language of the Ticuna is not clearly related to any of the languages of the surrounding tribes (Loukotka, 1968) suggests considerable isolation (here or elsewhere), which we presume to be synonymous with relatively little admixture with other tribes. Pending a more comprehensive treatment of Amerindian tribal relationships, we conclude rather cautiously that despite the

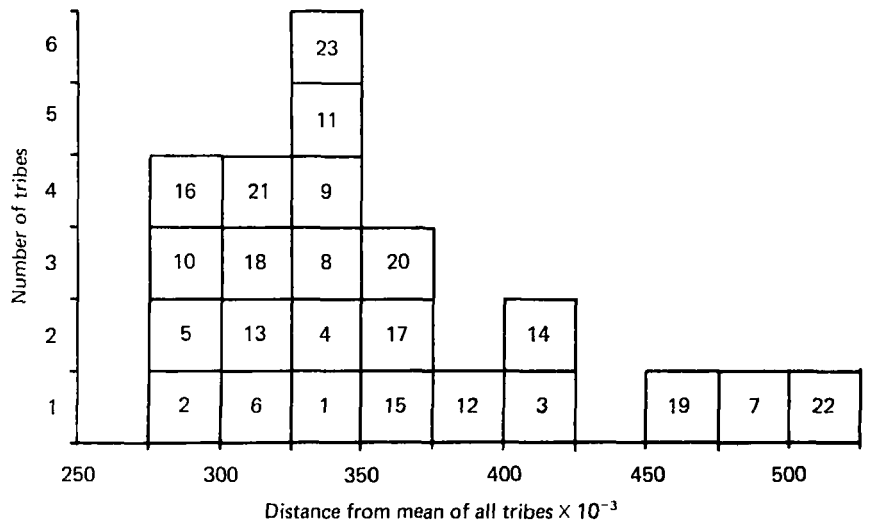

Fig. 5. Distance from an all-tribes multivariate mean of 23 different Amerindian tribes of Central and South America. Detailed explanation in text. The tribal designations are as follows: (1) Aymara; (2) Cakchiquel; (3) Cashinaua; (4) Cayapa; (5) Cayapo; (6) Cuna; (7) Guaymi; (8) Jivaro; (9) Makiritare; (10) Macushi; (11) Pemon; (12) Piaroa; (13) Quechua; (14) Shipibo; (15) Trio; (16) Wapishana; (17) Wajana; (18) Xavante; (19) Yanomama; (20) Yupa; (21) Kraho; (22) Ayoreo; and (23) Ticuna.

Ticuna's geographic location with respect to a probable route of Amerindian dispersion, as mentioned in the Introduction, they do not exhibit a noteworthy resemblance to a composite 'average' Amerindian tribe.

The data concerning HLA antigens in Central and South American Indians are still relatively limited, but the tribes tested thus far all show certain features in common, notably a high frequency of HLA – A2, A9 (Aw24), Aw19 (Aw31), and B5, B16, Bw35, B40 and sometimes Bw15. The Ticuna show these trends to an extreme degree. Aw19, A2 and A9 account for 96% of the A locus polymorphism, and B5, Bw35 and B16 account for 63% of the HLA-B antigens. Interestingly, the Ticuna failed to show evidence of A28 (which was found in the Guatemalan Ixils with an allele frequency of 0·28 (Corley *et al.* 1973)) and the B40 allele (frequency 0·18 in Chilean Indians (van der Does *et al.* 1973)) was detected in only a single person. The Ticuna did have Bw15, which was absent from two North American tribes (Pima (Spees *et al.* 1973) and Papago (Perkins *et al.* 1973)) and one Central American tribe (Ixil (Corley *et al.* 1973)). Some antigens commonly found in Caucasians and Blacks (A1, A3, A10, A11, B7, B8, B12, B13, B14, B17, B18, Bw22 and B27) (Dausset & Colambani, 1973) were absent or found only in a single individual, reflecting the low admixture with non-Indian populations. Amerindians are, in general, similar to Mongoloid populations, A2, A9, B5, B40, Bw15 and B16 being common in both groups. However, most Mongoloids, except Eskimos, also exhibited A11 and Bw22, which have not been found in Amerindian populations (Dausset & Colombani, 1973).

In past publications we have emphasized the amount of genetic microdifferentiation encountered in the villages of a *relatively* undisturbed Amerindian tribe, when microdifferentiation is measured by the same type of 6-locus distance employed earlier (Neel & Ward, 1970). Care must be exercised in intertribal comparisons, for at least two reasons. Firstly, 'relatively undisturbed' is a relative term indeed, there of course being no Amerindian tribes the disposition

Table 5. *Mean pairwise genetic distance between Amerindian villages for three tribes (further explanation in text)*

Tribe	Number of villages	Mean pairwise distance	Smallest distance	Largest distance
Makiritare	12	0·425 ± 0·121	0·164	0·763
Yanomama	52	0·403 ± 0·115	0·135	0·785
Ticuna	8	0·187 ± 0·047	0·099	0·295

of whose members is uninfluenced by contacts with non-Indians. Secondly, within a tribe one can often define related clusters of villages; for a proper comparison the sampling of any tribe should be over a wide area (across clusters). Given this structure, average distance will tend to be a function of number of villages sampled. The two least-disturbed tribes we have studied are the Yanomama and Makiritare. Table 5 reveals that the intervillage genetic distances in these two tribes, computed on the same basis as tribal distance, is roughly twice that encountered in the Ticuna, with a correspondingly larger standard deviation. While the average distance would be expected to increase somewhat in the Ticuna with the sampling of additional villages, it will nevertheless remain substantially below that of either of the other two tribes. Mean intervillage distance undoubtedly is determined by many factors, but we suggest that one principal reason for the relatively small mean distance for the Ticuna is the recent tribal turmoil described earlier. This decrease in the Ticuna of the internal intervillage genetic heterogeneity so characteristic of relatively undisturbed Amerindian tribes probably occurred in two phases, the first accompanying the migrations from the interior to the river bank, with consolidation of villages, the second as individuals moved up and down the Solimões in consequence of the religious developments mentioned in Salzano *et al.* (1980). If this thesis is correct, the Ticuna illustrate how quickly an important feature of tribal population structure, genetic microdifferentiation, may be lost, even by actions initiated within the tribe.

In contrast to the 'average' position occupied by the Ticuna with respect to the allele frequencies for these six polymorphisms, they are most unusual with respect to another type of genetic variation: only one 'private' variant, of ACP 1, was encountered in the relatively extensive electrophoretic survey of 45617 proteins (98294 locus products) in this tribe. The extent to which this tribe differs from the 12 other tribes in which we have undertaken similar surveys to date may be approached objectively as follows: Rothman & Adams (1978) have demonstrated that $\hat{K}$, the average number of rare alleles per polypeptide in the adult generation of any given tribe, can be estimated from k, the observed number per polypeptide; n, the sample size; and N, the number of the tribe in the adult generation, by

$$\hat{K} = \frac{k}{1 - \Sigma \tilde{g}(i) \left(\frac{2N-i}{2n}\right) \Big/ \left(\frac{2N}{2n}\right)},$$

where $\tilde{g}(i)$ represents the estimated proportion of alleles that occur exactly i times in the population. Fig. 6 depicts the relationship between $\hat{K}$ and $2N$ in the 12 tribes previously studied in this respect, plus the Ticuna (data in Neel & Rothman, 1978). This calculation, based on 29 polypeptides, excludes the established polymorphisms of wide distribution, permitting the assumption that the variants in question predominantly reflect simple mutation pressure. The

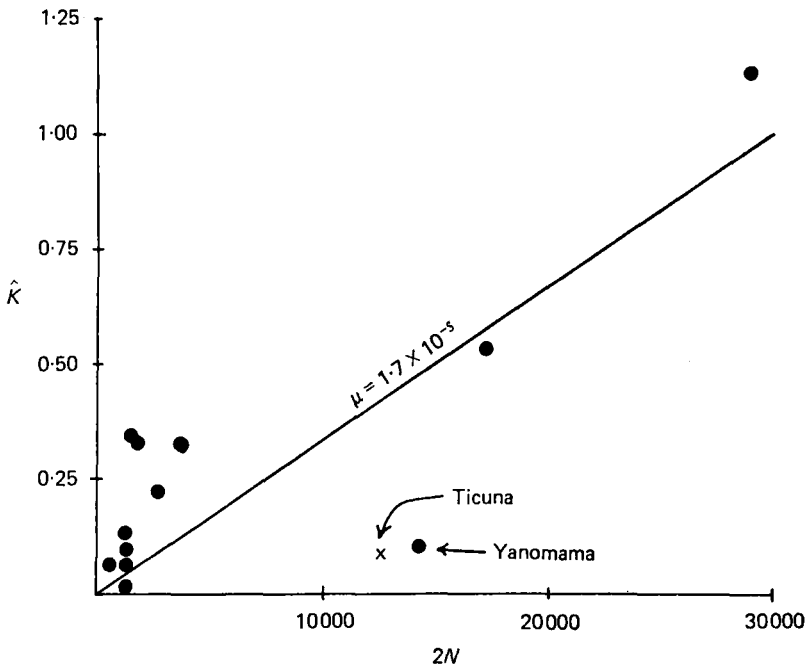

Fig. 6. The observed relationship between $\hat{K}$ and $2N$ in 13 Amerindian tribes, together with the predicted relationship at $\mu = 1{\cdot}7 \times 10^{-5}$ per locus per generation. Further explanation in text.

position of the Ticuna in this data set is indicated by (x). For this calculation, we have estimated that the Ticuna (including Colombian and Peruvian Ticuna; see Schwaner & Dixon, 1974) currently number 13000 persons. From this the 'equilibrium N' was estimated at 6240 from our observation that, in a little disturbed tribe such as the Yanomama, roughly 48% of the tribe fall into the age interval 15–40 years (Neel & Weiss, 1975). $\hat{K}$, from the data of this paper, can thus be estimated at 0·095. We see that the Ticuna exhibit a relative paucity of variants in relation to $2N$.

On the assumption of stable population size (i.e. stable N) and neutrality of the allele in question, one can compute the mutation rate (μ) necessary to maintain $\hat{K}$ if one can estimate, in addition to N, average mutant survival in generations ($\bar{t}_0$) or its equivalent, the pattern of allele transmission from one generation to the next (cf. Kimura & Ohta, 1969; Nei, 1977; Neel & Rothman, 1978). In our treatment (Neel & Rothman, 1978) we calculated μ from the relationship

$$\hat{\mu} = \frac{\hat{K}}{2N}[g(1) - \Sigma g(i) P_{i1}],$$

where P_{i1} is the conditional probability of transmitting 1 copy of a mutant from any given number, i; from a simulation of one of the tribes studied (the Yanomama) (cf. Li, Neel & Rothman, 1978), P_{i1} was estimated to be 0·2096. This calculation requires assigning to each tribe a value for N characteristic of the tribal history, a value which at best can only be approximated. It also requires assuming that the value for P_i derived from the Yanomama, the least acculturated tribe we have studied, was characteristic of the other tribes prior to their (greater) acculturation. The error of an individual estimate of μ is thus large but cannot be computed with any accuracy. Finally, as noted, one assumes neutrality of all the alleles in question, but

while this is almost surely incorrect, such is the importance of the stochastic process in these tribes that small departures from neutrality do not greatly influence the probability of allele loss (or survival) (Kimura, 1968; Ohta, 1973). The average value of the 12 estimates of μ derived from the 12 Amerindian tribes for whom the necessary data were available was $1{\cdot}7 \times 10^{-5}$ per locus per generation. The nominal standard deviation of this estimate is $1{\cdot}26 \times 10^{-5}$, but in view of the uncertainties referred to earlier and also departures from the precise conditions of the model, the true standard deviation is probably even larger, and it would be misleading to compute a standard error for the estimate of μ.

Fig. 6 also depicts the relationship which should obtain between $2N$ and $\hat{K}$ on the assumption that $1{\cdot}7 \times 10^{-5}$ is the true value of μ. (It should be emphasized that the regression of K on $2N$ was not derived from fitting a regression to the data points shown in the figure, but from deriving an average mutation rate for the 12 tribes for whom data are available and then depicting the $\hat{K}$ values predicted by the value of $2N$). Given the size of the Ticuna, the relationship between $2N$ and $\hat{K}$ at $\mu = 1{\cdot}7 \times 10^{-5}$ would call for the demonstration of 3 or 4 additional electrophoretic variants beyond the one observed. Despite the statistical uncertainties just mentioned, the relative paucity of variants in the Ticuna is probably a real phenomenon.

A plausible explanation of this finding may be found in the recent demographic history of this tribe. Salzano *et al.* (1980) review the evidence that the *Brazilian* Ticuna *since* 1942 have increased from 2000 to 11 000 persons. Some of this increase is undoubtedly due to immigration of Colombian and Peruvian Ticuna, but the data on the vital statistics of the Ticuna also suggest a rapidly expanding population. We can identify no reliable estimate of the number of Brazilian Ticuna at the time of early contacts or in the intervening period. Given, however, the usual deleterious impact on Amerindian tribal size of even minimal contacts with European culture, we may surmise that their numbers were even lower in the eighteenth and nineteenth centuries. Estimating the total tribal size in earlier times is especially complicated by lack of information on the Colombian and Peruvian Ticuna. However, it does seem clear that a cardinal reason for the paucity of different variants is the fact that, until recently, effective population size (N_e) was very much less than at present. We note that if $2N$ were historically roughly 4000, the Ticuna would not appear so aberrant. This would require that the Ticuna have approximately doubled their numbers in each of the last two generations; current data on completed family size are consistent with such an increase (Salzano *et al.* 1980). If this argument is correct, the Ticuna would not be an appropriate tribe on which to base an estimate of mutation rate, and we will refrain from doing so.

It is noteworthy that among the other tribes treated in Fig. 6, it is the Yanomama who exhibit the greatest departure from the theoretical regression. They too appear to have undergone a significant population expansion recently (Neel & Weiss, 1975), to the extent that the propriety of our previous utilization of the results from this group in a calculation of mutation rates by an indirect method may be questioned. However, the data set also includes tribes whose numbers may have been reduced in recent years (or who have absorbed remnant tribes) and in the earlier treatment we have taken the position that, in a calculation as rough as this, these contrariwise perturbations in the assumptions balance out.

The single private variant encountered in the Ticuna (ACP 1 TIC 1) presents several noteworthy features. The allele frequency of 0·111 is, among Amerindians, thus far exceeded by only one other private polymorphism, also involving acid phosphatase, the $ACP_1^{GUA\text{-}1}$ allele of the

Guaymi, with a frequency of 0·148 (Tanis *et al.* 1977). Village allele frequencies of $ACP_1^{TIC\text{-}1}$ vary from 0·006 to 0·161 which, by inspection of Table 2, is no greater variability than encountered in other genetic systems. Unlike the private polymorphism of albumin encountered in the Yanomama (ALB YAN 2), where the allele exhibited a clear geographic cline, there is no apparent spatial pattern for $ACP_1^{TIC\text{-}1}$, nor would one be expected in view of the recent intense intratribal migration. To our knowledge, no remnants of other tribes in the immediate vicinity of the Ticuna have been sampled for the presence of this allele. The nearest tribes for which there are data are the Baniwa to the north and the Central Pano and Kanamari to the south; the variant is lacking in all 3 tribes (Mohrenweiser *et al.* 1979). For the present, then, there is no evidence that the allele has spread beyond the Ticuna.

It has been of some interest to attempt to estimate the age of the mutants comprising the various private polymorphisms encountered to date in Amerindian tribes, as one approach to the antiquity of tribal diversification (cf. Thompson, 1976). However, estimation requires the assumption of an approximation to steady-state population dynamics, clearly incorrect, or rather precise knowledge of the tribal growth pattern, lacking in this case. Accordingly, we do not consider it appropriate to attempt to estimate the age of the $ACP_1^{TIC\text{-}1}$ allele encountered in the Ticuna. We do note, however, that the apparent restriction (until now) of this allele to this one tribe is further evidence for the hypothesis (see Neel, 1980) that, in the peopling of South America, the forerunners of the present tribes in general established their identity relatively early, with very limited intertribal exchange subsequently (until the disruptions occasioned by the second discovery of the New World).

Neel (1978) has discussed at some length the problems that arise in attempting to compare the average frequencies of 'rare' or 'private' variants (no one of which by *arbitrary* definition is present in more than 2 % of the population tested) in tribal and detribalized civilized populations. The present findings illustrate the difficulty very well. For 23 polypeptides, the average frequency of such variants was 1·6 per 1000 determinations in Caucasians (Harris, Hopkinson & Robson, 1974) and 1·5 in Japanese (Neel *et al.* 1978). The corresponding frequency in Amerindians was 2·2 (Neel, 1978) but the private polymorphism of albumin present in the Yanomama was arbitrarily excluded from the Amerindian calculation because in the totality of the data on albumin (9611 determinations), this variant occurred in more individuals (491) than the arbitrary 2 % cut-off for a 'rare' variant. In the present study, among a total of 49147 polypeptides surveyed electrophoretically, we found, excluding from consideration the established polymorphisms, 357 individuals with a variant, all of ACP 1, for a variant frequency of 7·1 per 1000. If, however, we consider only the ACP 1 determinations reported to date, combining the determinations of this paper with those previously summarized (total of 10934), then this new variant, like the Yanomama albumin, is a polymorphism and must be arbitrarily excluded from the calculation of 'rare' variant frequency. If this variant is restricted to a single tribe, as so many of the 'private' polymorphisms appear to be, then with the accumulation of further tribal data the impact of this polymorphism will be diluted to where it falls below a 2 % frequency in the total data, and so it will be scored as a rare variant. It would also have been scored as a rare variant in the total material were the Ticuna sample not so large!

If, following the above argument, the Yanomama albumin variant and the Ticuna acid phosphatase variant are included in the Amerindian averages, then the frequency of variants other than the well-known polymorphisms (data summarized in Neel, 1978, plus this paper) for

all the appropriate studies to date on Amerindians becomes 7·1 per 1000, some three times that of Japanese and Caucasians. It seems unlikely that technical factors can provide the entire explanation of these differences. (We have deliberately in the Amerindian studies continued throughout to use starch gel as the supporting medium for electrophoresis, except for CRPL, to have comparability with the older data on Japanese and Caucasians.) The numerical distribution of these variants in populations is consistent with the thesis that they are maintained by mutation pressure (Thompson & Neel, 1978; Neel & Thompson, 1978), although the analysis does not exclude small selective pressures. The implication is of higher mutation rates (or lower selection against mutations at these loci!) in Amerindians (see Neel, 1973), although the inability to define the sizes of the tribal populations in which the bulk of the Caucasian and Japanese variants arose renders the actual calculation of mutation rates by an indirect approach impossible for the latter.

SUMMARY

The Ticuna are an Amerindian tribe of Central Amazonas, a key location in theories of the peopling of eastern South America. The results of typing some 1760 members of the tribe with respect to 37 different genetic systems are reported, as are the results of HLA typings on a subsample of 129 persons. Salient findings include the following. (1) Except for a high frequency of the L^{Ms} allele and an unusual combination of HLA allele frequencies, there are no notable findings with respect to the commonly studied polymorphic systems. A multivariate treatment of six of the most commonly studied genetic polymorphisms accords the Ticuna an 'average' position among Amerindian tribes. (2) There is much less intervillage heterogeneity than usually encountered in Amerindian tribes; this is attributed to recent high rates of intervillage migration due to religious developments. (3) A thus-far unique polymorphism of ACP_1 was identified, the responsible allele having a frequency of 0·111. (4) In proportion to the size of the tribe, there was a relative paucity of 'private' genetic variants, the ACP_1 allele being the only one. This discrepancy is attributed to a relatively recent numerical expansion of the tribe; effective population size over the past several thousand years is thought to have been well below what present numbers would suggest. (5) The thesis is again advanced that 'private variants' (alleles not occurring as polymorphisms of wide distribution) are more common in Amerindian than in Caucasian or Japanese populations.

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