ABO BLOOD GROUPS AND SEX RATIOS
IN SOUTH AMERICA

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ABSTRACT: Two characteristics of South American Indian populations conventionally have been attributed to independent causes. The first characteristic, homogeneity for blood type O, is conventionally attributed to forces other than natural selection. The second characteristic, excess male children, has been suggested to result from female infanticide.

We propose a unified explanation incorporating a known force of natural selection at the ABO locus. Our simulations show that natural selective pressures from ABO maternofetal incompatibility can lead to O homogeneity. Evidence reviewed here shows an association of O homogeneity with excess male births. On the basis of our model of South American microevolution, we speculate about the evolutionary origins and destination of the ABO polymorphism. We hypothesize that molecular mimicry may have fostered the polymorphism. The implication of our analysis for today's human populations is that, where ABO maternofetal incompatibility is the main mechanism of natural selection, it may eventually result in O homogeneity.

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INTRODUCTION

The native populations of South America differ from most populations outside the western hemisphere in their blood type frequencies, nearly 100 percent type O (Mourant et al. 1976; see Table 1), and in their uncommonly high proportions of male births (see Table 2 and accompanying note). We will show that the co-occurrence of these two apparently unrelated phenomena may not be fortuitous, that high proportions of male births can be expected to result from O homogeneity, and that O homogeneity of South American Indians may be explained in part by the mechanism of ABO maternofetal incompatibility. Also, we speculate that the O allele may have evolved last among the major ABO alleles, and that other populations may be evolving toward O homogeneity.

Other authors have tended to examine the ABO blood system in a worldwide scope (see Brues 1954 and 1963, Boyd 1963, Chung and Morton, 1961, Ford 1945, Otten 1967, Race and Sanger 1968, Vogel 1968). The view represented here focuses on one continent to examine a set of geographically contiguous populations. The populations of South America share some historical commonalities, especially with regard to infectious disease, in relation to the peopling of the New World and the effects of the Conquest, and with regard to gene flow, providing a means for diffusion of adaptive genotypes.

Few scholars have preoccupied themselves with the reasons for the high proportions of male infants among South American Indians. Of those who have noted the fact, most have accepted the explanation that it resulted from the cultural practice of female infanticide. However, closer examination does not support female infanticide as a universal characteristic of South American societies. In at least one population, the infanticide explanation requires implausibly high rates of both infanticide and fertility (Beckerman 1976 but see also Rutenberg and Beckerman 1981). In several others, there is no positive indication whatsoever of sexually selective infanticide (Cooper 1946, Harner 1973, Schaden 1962). In the following, we examine natural selective and genetic factors as alternatives to female infanticide in explaining the skewed sex proportions found in South American Indian populations.

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TABLE 1.   FREQUENCY OF THE O ALLELE IN 129 LOWLAND SOUTH AMERICAN POPULATIONS

O Frequency (1.00 = 100%)	N (Groups)
1.00	84
0.99	15
0.98	15
0.97	11
0.96	3
0.90	1

From Millard and Berlin 1983, Table 4; compiled from Post et al. 1968.
Most New World Indian populations are 0-homogeneous, the major exceptions being
some North American populations, including Athabaskan speakers and Eskimos (Kirk
1979, Laughlin 1951, Laughlin et al. 1979, Spuhler 1979, Szathmary 1979). Because
some highland South American Indian groups show strong evidence of admixture with
people of European descent, and because the present work is based on indigenous
gene frequencies as they had evolved before the Conquest, this table focuses on
lowland populations.

TABLE 2.   SEX RATIOS IN 33 LOWLAND AND HIGHLAND SOUTH AMERICAN GROUPS

Sex Ratio (Males/100 Females)	Male Proportion (Males/Total)	N (Groups)	
		Lowland	Highland
104	0.511	1	5
105–106	0.512–0.516	0	1
107–110	0.517–0.525	0	1
111–119	0.526–0.544	3	2
120–149	0.545–0.599	6	7
150	0.600	5	2

The human sex ratio is generally accepted as 104 to 106 males/100 females.
Because no compendium of sex proportions of lowland groups has been published,
Table 2 presents only those data readily available. For lowland groups, sex
proportions were calculated at birth whenever possible or as close to birth as
possible -- for ages 0 to 6, 0 to 9, or 0 to 14 depending on the data provided
by the references: Beckerman 1976; Berlin and Markell 1977; Brown et al. 1974;
Johnston et al. 1969; Neel 1971; Neel and Chagnon 1968; Salzano et al. 1970;
Weinstein et al. 1967.   Highland data, which were calculated at birth, were
compiled from a survey by Bolton (1980).

SEX PROPORTIONS

There is evidence that the O allele is genetically associated with high proportions of male births. Allan (1959, 1972, 1973) and others have shown that among babies with type O mothers, male proportions are significantly higher among type O than among non-O infants (Table 3). These findings may be related in several ways to natural selection operating through ABO incompatibility (Millard and Berlin 1983).

Natural Selection and Reproductive Roles. Comparisons of fathers and mothers (Table 4) show that, in fathers, the O allele is adaptively advantageous. Offspring who receive an O allele from their fathers are not subject to ABO incompatibility, while offspring of type O mothers can be A- or B-bearing and thus subject to incompatibility selection (Table 4, row 5). Additionally, among males, OO is the only genotype incapable of producing incompatible offspring. Thus, type O fathers have a higher fitness than type A, B, and AB fathers, who can produce incompatible offspring (Table 4, column 5). Hence, in a polymorphic population, type O men would have a higher fitness, in the sense of reproductive advantage, than type O women and than men of other blood types. If natural selection could act on blood type in association with sex proportion, then among type O individuals, there would be a relative excess of males.

Other Hypothesized Causes of Skewed Sex Proportions. Crow and Kimura (1970) made a theoretical prediction that sex proportions could change as a coincidental by-product of certain genes that also confer a selective advantage on individuals. Type O fetuses have a selective advantage because they are not subject to ABO maternofetal incompatibility, while those of other blood types are. A by-product of the advantageous OO genotype thus could be a sex proportion at birth different from that of other genotypes. Hence, the findings summarized by Allan and showing excess males among type O offspring may offer an empirical example of Crow and Kimura's theoretical prediction.

Additionally, if ABO incompatibility selection is one of the stresses eliminating more male than female fetuses (see Golovachev 1978), then in a homogeneous O population, lack of incompatibility selection would result in a sex proportion at birth that is closer to that at conception, estimated as at least 54.54 percent males (a sex ratio of over 120), according to McMillen (1979) following methods proposed by Cavalli-Sforza and Bodmer (1971). This factor alone could explain high sex proportions in South American Indians.

Natural Selection on Skewed Sex Proportions. If they were genetically determined, skewed sex proportions could have two possible natural selective results. First, natural selection could act to equalize sex proportions. The rate of transition would depend directly on the variance in the sex proportion in families (Bodmer and Edwards 1960). In theory, assuming genetic determination of human sex proportions, the transition in sex proportion from 52.00 to 50.74 percent has been estimated to require about 100 generations or about 2500 years (Cavalli-Sforza and Bodmer 1971).

The second possible natural selective result involves no evolutionary change from a skewed sex proportion at birth. Unequal secondary (newborn) sex proportions would not be subject to equalizing pressures of natural selection as long as the tertiary (reproductive-onset) sex proportions of the entire population remained equal (Fisher 1930, Pianka 1974). In some South American groups, despite excess male births, tertiary sex proportions are equal, in which case natural selection cannot be expected to change primary and secondary sex proportions. While there is generally little information regarding causes of mortality by sex and age in these populations, the available data suggest a cultural component is present, tending to eliminate more young males than females. Warfare could be such a factor, although its current prevalence in South American indigenous cultures is unclear. Warfare directly reduces the proportion of adult males since they are both the warriors and

TABLE 3. SEX PROPORTIONS OF BABIES NEWBORN TO WOMEN WITH TYPE O BLOOD

| Blood Types | | N | Sex Ratios | Male Proportion |
Mothers	Babies	(Babies)	(Males/100 Females)	(Males/Total)
O	O	14,754	111	0.5251
O	non-O	6,786	103	0.5078

Compiled from Allan 1973, 1959.
In Allan's (1973) compilations, among babies of O mothers, the sex ratio of type O babies differs significantly from that of non-type O babies; by the chi-square test, $\chi^2 = 5.56$; $p < 0.03$ with 1 degree of freedom. Among babies of the same blood type as their mothers, type O and type A babies differ significantly in sex ratio; by the chi-square test, $\chi^2 = 13.9$; $p < 0.001$ with 1 degree of freedom. Considering the most recent study alone, the chi-square test shows a significant difference in sex ratio between O babies of O mothers (227 males; 168 females), and A babies of A mothers (326 males; 349 females): $\chi^2 = 8.4$; $p < 0.01$ with 1 degree of freedom.

TABLE 4. GENOTYPE FREQUENCY AND FITNESS COEFFICIENTS UNDER ABO MATERNOFETAL INCOMPATIBILITY SELECTION

| Genotypes | Genotype frequencies in the absence of natural selection | Proportionate coefficients: genotype frequencies weighted by fitnesses[a] | | |
		Offspring	Maternal	Paternal
AA	p^2	p^2	$p^2(1-s_1q)$	$p^2[1-s_1(1-p)^2]$
AO	$2pr$	$pr[2-s_1(1-p)]$	$2pr(1-s_1q)$	$pr[2-s_1(1-p)^2]$
BB	q^2	q^2	$q^2(1-s_1p)$	$q^2[1-s_1(1-q)^2]$
BO	$2qr$	$qr[2-s_1(1-q)]$	$2qr(1-s_1p)$	$qr[2-s_1(1-q)^2]$
OO	r^2	r^2	$r^2(1-s_1p-s_1q)$	r^2
AB	$2pq$	$pq[2-s_1(1+r)]$	$2pq$	$pq[2-s_1(1-2pq+r^2)]$

From Millard and Berlin 1983, Table 1.
[a]Within each column, the coefficients can be compared. To compare across columns, calculate relative frequencies by dividing each genotype proportion by the column total.
The frequencies of the A, B and O alleles are represented by p, q and r respectively; s_1 is the percentage of incompatible fetuses lost because of ABO maternofetal incompatibility. In the last three columns, each genotype contributing to incompatibility incorporates the factor s_1, representing decreased fitness from maternofetal incompatibility.

the primary intended victims. While some women also are killed, they are more often captured and taken as wives (Steward 1963, Grupo D.A.M. 1979).[1] Mechanisms such as homicide and the capture of women could equalize tertiary sex proportions, allowing the proportion of male births to remain high with no selective consequences.

Thus high proportions of male births in indigenous South American populations can be explained with two possible causes--a heritable association with blood group O, or the tendency of the primary sex proportion to persist through birth, because there is no ABO incompatibility selection. There are two possible natural selective effects on the preponderance of male births--slow equalization of sex proportions which should occur with excess male tertiary proportions, or maintenance of skewed proportions at birth, which should occur if tertiary proportions are equal.

Two of our hypothesized explanations for high male proportions in South America depend on their genetic association with type O blood. Thus our hypotheses lead us to examine reasons for the universality of the O allele in these populations. O fixation has usually been explained by invoking stochastic mechanisms, genetic drift, and the founder effect during the peopling of the Americas.[2] An alternative hypothesis, and one that we propose here, is that in the ancestral populations of South American Indians, the ABO polymorphism was unstable, and that a major factor in its transitory nature was ABO maternofetal incompatibility selection.

ABO INCOMPATIBILITY

ABO maternofetal incompatibility involves the systematic force of natural selection. Over the course of this century, a number of researchers have carried out studies of the phenomenon (see Allen 1964, Chung and Morton 1961, Cohen 1970, Cohen and Sayre 1968, Crawford et al. 1953, Dienst 1905, Halbrecht 1944, Hirszfeld 1928, Krieg and Kasper 1968, Lauritsen et al. 1975, Levine 1943, Levene and Rosenfield 1961, Matsunaga 1962, Ottenberg 1923, Peritz 1967 and 1971, Polayes 1945, Takano and Miller 1972, Vos and Tovell 1967, Waterhouse and Hogben 1947, Wiener et al. 1960, Wren and Vos 1961, Zuelzer and Kaplan 1954). Further work is nonetheless required to arrive at a complete understanding.

Incompatibility can affect a fetus whenever the father has contributed an A or B antigen that is absent in the mother. It is similar to Rh incompatibility in that incompatible offspring can suffer from hemolytic disease (see de Gruchy 1978, Grundbacher 1980, Mollison 1972). However, under ABO incompatibility, hemolytic disease affects only 0.09 percent of newborns, whereas incompatible embryos suffer high rates of loss, often early enough in pregnancy to be undetectable (Chakravartti and Chakravartti 1977, see also Satyanarayana et al. 1978). Levene and Rosenfield's 1961 review of the literature concludes that early fetal loss due to ABO incompatibility generally is 25 percent, varying among studies from 14 to 32 percent (see also Mourant et al. 1978 for a more recent summary).

Studies from 1960 onward show different estimates of early fetal loss. Many researchers note that the biochemical mechanism resulting in early loss of ABO-incompatible fetuses remains unclear. Also some studies cited below show no evidence of fetal loss from ABO maternofetal incompatibility. Such findings have been discussed by Reed (1975), who states that failure to find evidence of selection in rates of live births per woman, when there is independent clinical evidence for its existence, probably is the result of insufficient sample size. He calculates that, in measures such as the number of pregnancies or number of spontaneous abortions per couple, undetected selection differentials of the order of 10 percent may occur, even in large samples (on the "order of 10^4"). The variation among studies in loss rates may be related also to genetic systems modifying maternofetal incompatibility effects and to environmental conditions of pregnancy discussed below.

Factors Modifying ABO Maternofetal Incompatibility: Hypothesized Relationships Needing Further Investigation. Although our analysis focuses on the ABO locus, it is important to note that other loci may interact with it.   Variation in the rate of fetal loss due to ABO maternofetal incompatibility is probably, at least in some cases, related to the presence of genetic systems modifying the severity of incompatibility.   The ABH secretor locus, in concert with the Lewis locus, apparently affects ABO hemolytic disease rates; fetal secretion of A or B antigen seems to promote maternal production of antibodies, which may intensify the severity of incompatibility (Ceppellini 1959, Crawford et al. 1953, Mourant et al. 1978; Levene and Rosenfield 1961; Watkins 1966, Wiener et al. 1960, Zuelzer and Kaplan 1954).

Furthermore, one study shows that incompatibility may result in apparent couple sterility, hypothesized to result from the disabling of incompatible sperm by vaginal secretions determined by the secretor locus (Behrman et al. 1960; but see also Chakravartti and Chakravartti 1978).[3] The secretor locus thus may contribute to the observed sterility rates in polymorphic populations. Indigenous South American populations are virtually universally secretors, a characteristic which may have exacerbated incompatibility selection in the past and which may shape gene flow today.

The haptoglobin locus has been hypothesized to affect the severity of ABO-related erythroblastosis fetalis (Ananthakrishnan et al. 1973, Kirk et al. 1970, Kirk 1971).   The product of the Hp^1 allele removes dissolved hemoglobin from the blood and conserves the contained iron more efficiently than that of Hp^2 (see Mourant et al. 1978 for a summary).

Decreased hemolytic disease of the newborn is observed when the offspring is doubly incompatible with the mother in both the ABO and Rh systems (Levine 1943, Vos 1965).   However, for most populations, double incompatibility is so rare that its evolutionary effect on the ABO locus is slight (Mourant et al. 1978, Bottini et al. 1972).

There is evidence from one series of observations (Bottini et al. 1972; see also Mourant et al. 1978) that placental alkaline phosphatase affects susceptibility to hemolytic disease. Pl^f_1 homozygous fetuses seem to have protection against hemolytic disease if they are type B but not if they are type A.

Studies of different Japanese groups indicate that environmental components may affect the severity of incompatibility selection, which may be stronger under harsh environmental conditions.   Women who worked as miners well into pregnancy showed considerable fetal loss from ABO incompatibility (Matsunaga and Itoh 1958) while other women not engaged in physical labor showed slight (Haga 1959) or immeasurable (Hiraizumi et al. 1973, Matsunaga et al. 1962) incompatibility effects. In summary, a number of loci and environmental factors are hypothesized to modify the outcome of ABO maternofetal incompatibility, resulting in different rates of fetal loss in different populations (see also Golovachev and Bokarius 1980, Grundbacher 1980, Hiraizumi et al. 1973, Monnet and Cabadi 1975).

Simulations of Evolution at the ABO Locus. To examine the implications of our hypothesis that the ABO polymorphism is transient and that ABO incompatibility is a major factor in its transitory nature, we designed a computer simulation. The simulation uses simplified conditions of natural selection: ABO maternofetal incompatibility selection and other sources of selection against the antigen-bearing genotypes.[4] Our simulations model the evolution of gene frequencies of South American Indians under forces of natural selection alone (see Brues 1963 for a simulation incorporating worldwide ABO incompatibility selection, heterozygote advantage and genetic drift).

In our simulations, the six possible genotypes of individuals and their frequencies were generated by the expression $(p + q + r)^2 = 1$, where p, q, and r represent the frequencies of the A, B, and O alleles respectively. That expression was squared, $[(p + q + r)^2]^2 = 1$ to yield 36 distinct mating types. For each possible parental mating, relative frequencies of offspring genotypes were generated in

accord with Mendelian segregation ratios. Next, each pair of offspring and maternal genotypes was examined for ABO incompatibility. Incompatible offspring genotypes were assigned a fitness of $(1-s_1)$ where s_1 is the rate of fetal loss of incompatible offspring. A-bearing genotypes were assigned a fitness of $(1-s_2)$ and B-bearing genotypes a fitness of $(1-s_3)$ with s_2 and s_3 being the forces of natural selection discussed below.

Figure 1 shows four of our simulations. The O allele is shown as the last major allele to evolve at the locus for reasons discussed below. These simulations demonstrate that the pressures of ABO incompatibility selection can cause the O allele to reach fixation, as long as other conditions are met. Regardless of the starting point of the locus, once the O allele has reached the frequencies of any current population, it proceeds to reach fixation under the sole natural selective force of ABO maternofetal incompatibility.

Figures 1a and b show O fixation when A and B frequencies are equal and under the force of ABO maternofetal incompatibility alone. Figures 1c and d show O fixation when A and B frequencies are unequal, as is true in all polymorphic populations today. The latter simulations required selection against the A and B alleles to increase O from low frequencies.

The simulations shown in Figure 1 also incorporate two different forces of incompatibility selection. Figures 1a and c result when the rate of fetal loss from ABO incompatibility is 25 percent $(s_1 = 0.25)$. This rate is Levene and Rosenfield's (1961) estimate of the most likely rate of loss of ABO incompatible fetuses. Figures 1b and d show slower rates of O fixation resulting from Levene and Rosenfield's minimal rate of loss of ABO incompatible fetuses, 14 percent $(s_1 = 0.14)$.

In Figure 1a, the period required for O to increase in frequency from 0.01 to 0.99 is about 1520 generations, or about 38,000 years. In figure 1c, O fixation occurs in about 130 generations, or about 3250 years. Figures 1b and d show less rapid estimates for the rate of O fixation. Figure 1b shows that O fixation requires 2751 generations, over 60 millenia; Figure 1d shows that O fixation starting from a frequency of $r = 0.03$ requires about 200 generations, or about 5000 years.

The simulations reveal two problems of relying on incompatibility selection as the sole natural selective force at the ABO locus. Under ABO maternofetal incompatibility selection alone, the O allele does not always increase in frequency. Simulations not shown in Figure 1 reveal that under the force of ABO incompatibility selection alone, the allele with the highest frequency reaches fixation. Thus, incompatibility selection alone cannot explain the evolution of the polymorphism because incompatibility tends to prevent the introduction of major alleles.

On the other hand, once a polymorphism is present, incompatibility selection tends to drive the locus toward fixation. O homogeneity is the end-point for simulations beginning at all current populations' gene frequencies.

This phenomenon brings us to the second problem of relying on incompatibility as the sole selective force. O fixation tends to occur rapidly, suggesting a relatively short duration of the polymorphism. The polymorphism can be expected to have had a longer existence because it is found in many parts of the world today. Below, we make a case for a more complex model relying on ABO incompatibility as a fundamental but not the unique evolutionary pressure.

FITNESS

ABO maternofetal incompatibility creates unusual variation within each genotypic class. Fitness varies according to reproductive role, fetal, maternal, or paternal. Table 4 compares coefficients related to reproductive role, gene frequency and fitness. Table 5 shows the results of calculations using specific gene frequencies and assuming that 25 percent of ABO incompatible fetuses are lost. The initial gene frequencies that were chosen best display characteristics of incompatibility selection though they do not illustrate frequencies of any living population. These results show the gene-frequency dependent nature of evolution when ABO incompatibility selection is the only force acting on the locus.
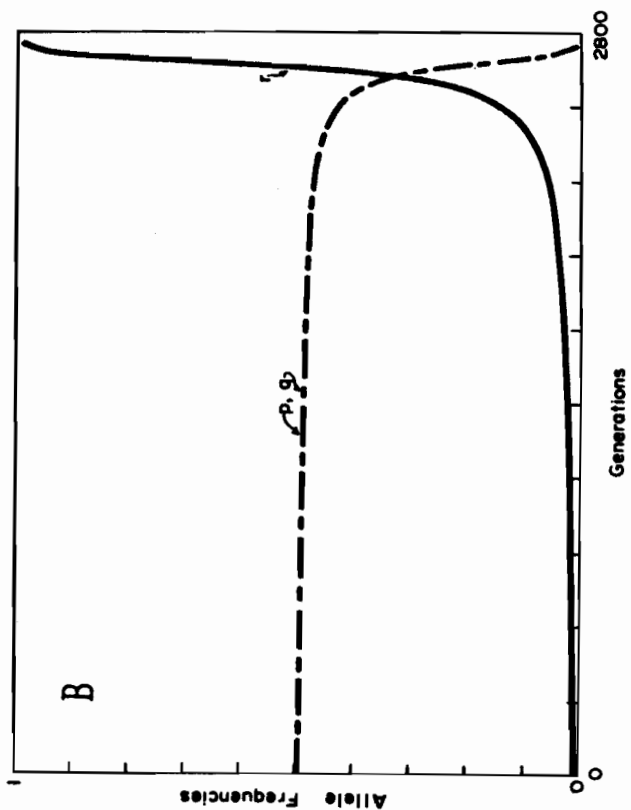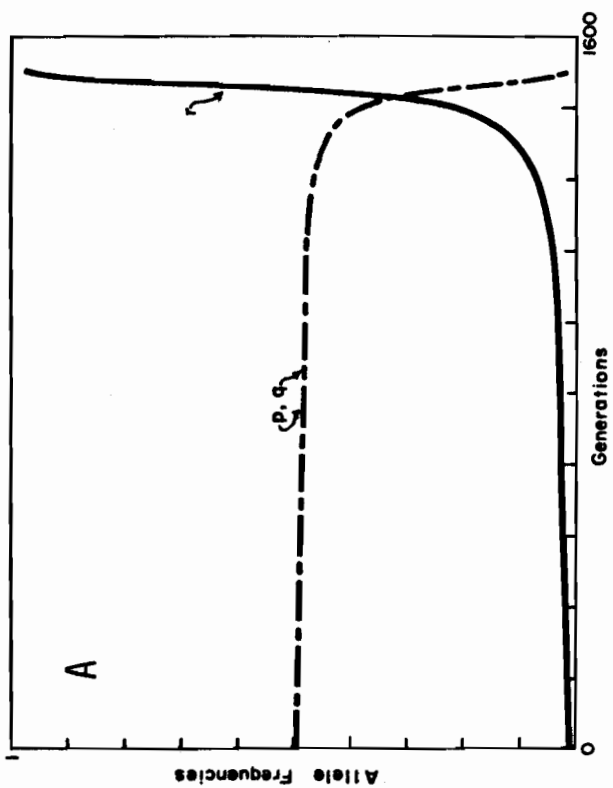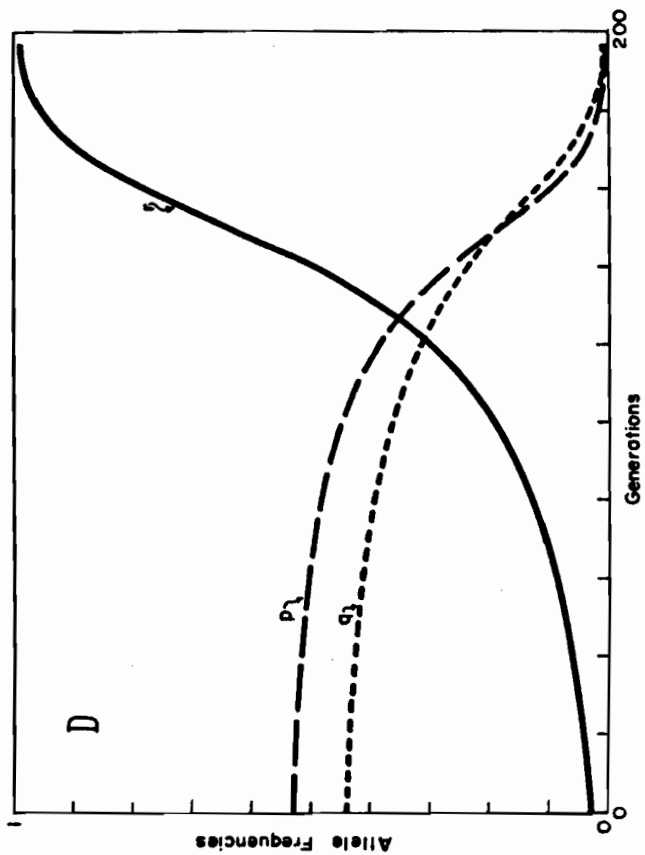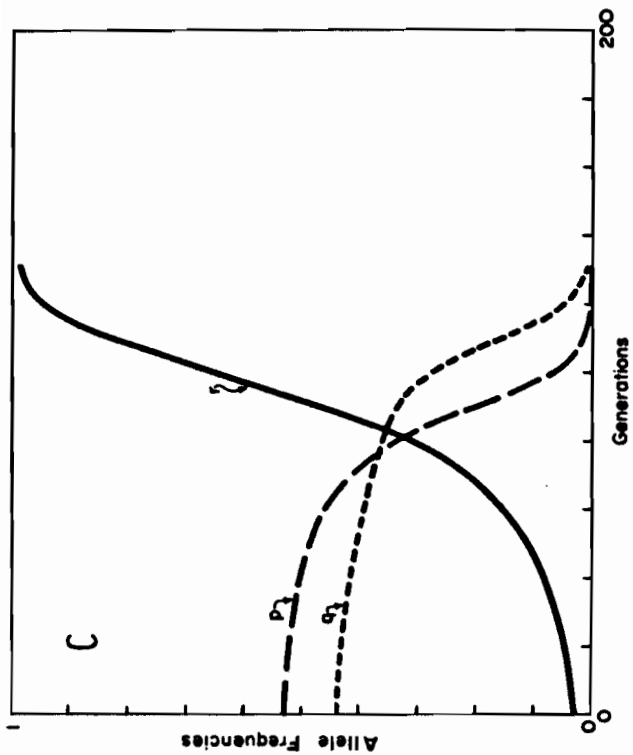
FIGURE 1

FIGURE LEGEND. Simulations of the evolutionary consequences of ABO maternofetal incompatibility, showing the O allele evolving last and eventually reaching fixation, as discussed in the text. The simulations began with the following parameters: (A) p=q=0.4949, r=0.01, s_1=0.25; (B) p=q=0.4949, r=0.0101, s_1=0.14; (C) p=0.53, q=0.44, r=0.03, s_1=0.25, s_2=0.06, s_3=0.0310; (D) p=0.53, q=0.44, r=0.03, s_1=0.14, s_2=0.04, s_3=0.0225.

TABLE 5. EFFECTS OF ABO MATERNOFETAL INCOMPATIBILITY

Initial Gene Frequencies			Genotypes	Genotype frequencies in the absence of natural selection	Relative genotype frequencies weighted by fitnesses (s_1 = 0.25)		
p	q	r			offspring	maternal	paternal
0.3333	0.3333	0.3333	AA	0.1111	0.1200	0.1100	0.1067
			AO	0.2222	0.2200	0.2200	0.2267
			BB	0.1111	0.1200	0.1100	0.1067
			BO	0.2222	0.2200	0.2200	0.2267
			OO	0.1111	0.1200	0.1000	0.1200
			AB	0.2222	0.2000	0.2400	0.2133
0.50	0.40	0.10	AA	0.2500	0.2680	0.2412	0.2513
			AO	0.1000	0.1005	0.0965	0.1039
			BB	0.1600	0.1715	0.1501	0.1561
			BO	0.0800	0.0793	0.0750	0.0819
			OO	0.0100	0.0107	0.0083	0.0107
			AB	0.4000	0.3698	0.4288	0.3961

From Millard and Berlin 1983, Table 2.

The upper half of Table 5 illustrates the importance of reproductive role to fitness. The results show the selective forces illustrated in Figure 1a at the intersection of the p, q and r trajectories. The three ABO alleles were set equal in frequency to examine differences among reproductive roles. In the offspring column in both Tables 4 and 5, the disadvantages to heterozygotes are clear. Only heterozygous offspring are selected against. This brings to mind the characterization of heterozygote disadvantage as a classic sign of an unbalanced polymorphism (see Haldane 1942, Li 1953, Wiener 1942).

The maternal reproductive role confers a different set of fitnesses on the ABO genotypes. AB has the highest reproductive fitness; women with this genotype bear both antigens and thus are ABO-compatible with all offspring. Women with OO genotypes have the lowest reproductive success, but these women boost the frequencies of O the most by screening preferential survival of homozygous O fetuses. In the paternal role these genotype fitnesses are reversed--OO fathers have the highest reproductive fitness because they cannot contribute antigen-forming alleles to their offspring, who thus will be compatible with any maternal genotype. AB fathers, on the other hand, always confer antigen-forming alleles on their offspring, who thus have increased probability of maternofetal incompatibility.

The variation of fitness by reproductive role helps to explain why O fixation does not occur more rapidly, even in simulations using high rates of fetal loss. First, only a portion of heterozygotes is conceived by incompatible mothers; the other heterozygotes are not subject to ABO incompatibility. Second, among adults, genotypes can differ from their pre-natal fitnesses according to the sex of the bearer. Pressures of natural selection which favor an allele at one stage but select against it at another tend to maintain a polymorphism (Mettler and Gregg 1969).

ADMIXTURE

Reproductive-role and gene-frequency-dependence imply that once the O allele has reached fixation, the other alleles can be reintroduced only by considerable admixture with A- or B-bearing groups. While virtual secretor homogeneity in indigenous South American populations may exacerbate incompatibility selection against introduced A and B alleles, cultural factors also impede their reintroduction. Since most Europeans who reached isolated regions of South America were males, males would have provided the path of introduction of the A and B alleles to South American Indian populations. Matings of A- or B-bearing males with O females would have produced A- or B-bearing fetuses subject to incompatibility selection. Meanwhile, European males could have contributed the O allele to the gene pool along with introduced variants at other loci. Thus, the absence of the A and B alleles would not, as sometimes assumed, constitute proof of genetic isolation in South American populations. Mating of O Indian males with A- or B-bearing European females largely would have been prevented by cultural barriers. Furthermore, the few offspring of such matings would have belonged to Indian gene pools only rarely, when their mothers had become members of Indian societies. Thus, the low A and B frequencies could reflect much higher rates of admixture than formerly expected.

EVOLUTIONARY IMPLICATIONS

Although the ABO locus has been studied longest of all the blood systems, its evolutionary past remains enigmatic. A well-known problem in its evolutionary reconstruction is the effect of ABO maternofetal incompatibility. In selecting against heterozygotes (i.e. heterozygous fetuses), ABO maternofetal incompatibility selects against the introduction of new alleles and thus tends to maintain homogeneity at the locus. Thus, if ABO maternofetal incompatibility is accepted as a significant mechanism of natural selection at the locus, another evolutionary

pressure is necessary to explain the early transition of the locus from an invariant system to a polymorphism. Such an explanation is required regardless of which allele was ancestral.

A proposed evolutionary pressure capable of promoting polymorphism is molecular mimicry (Damian 1962, 1964). Damian (1964) suggests that this evolutionary process originally may have contributed to the evolution of the ABO polymorphism. In molecular mimicry, some members of an infective species fortuitously possess molecular structures that are similar to an antigen present in the host. Because a host would not be expected to form antibodies against its own antigens, it would not distinguish a mimic as a foreign antigen. Thus, infection by the mimic would be successful, and any fortuitous mutations resulting in molecular mimicry would tend to proliferate under natural selection. In response, immunological protection could be expected to evolve in the host, depending on the processes of mutation and natural selection, and resulting in the spread of new antigens.

This hypothesized evolutionary process might be expected to have occurred in relation to antigens specified by the ABO locus. ABO-specified antigens are present in most tissues and secretions of the human body (see Race and Sanger 1975 for a recent summary on this topic), providing a broad spectrum of opportunities to molecular mimics colonizing a human host. Organisms bearing A-like and B-like antigens are known to be ubiquitous in the environment. Of these organisms, some can infect humans, and there is evidence implicating a few of them in infectious diseases well known in human populations (see Chakravartti et al. 1966, Otten 1967, Tyrell et al. 1968, Vogel 1968, Vogel et al. 1960; some of these studies also implicate mimicry of the H antigen by currently virulent organisms, which would be expected under our hypothesis, but see also Azevedo et al. 1964).[5] Thus, molecular mimicry, if it has occurred at all, may well have occurred in the case of the antigens specified by the ABO locus. This evolutionary process may help to explain the antigenic diversity of the ABO locus, including alleles A_1 and A_2, that are the common variants of A, and several rare variants of the A and B alleles that may represent less successful biochemical modifications than O.

The identification of the ancestral allele is known to be a difficult, perhaps impossible, task. Some researchers have inferred from biochemical evidence that the O allele evolved first, followed by the A and B alleles. In the biochemical pathways specifying red blood cell antigens, the A and B alleles cause the addition of a polysaccharide chain to a precursor that is essentially a type O structure. Although the hypothesis that ontogeny reflects phylogeny is logical in this case, it is not conclusive; the biochemical evolution of the antigens need not have followed the pathway of their synthesis in living populations. As further criticism of the hypothesis that O evolved first, we are uncomfortable with the interpretation that South American Indians, as they became O-homogeneous, were on an evolutionary trajectory opposite from other human populations, where according to the O-first hypothesis, the O allele was decreasing.

We suggest that, as molecular mimics arose, the host evolved, under the pressures of mutation and natural selection, an antigenic molecular structure that permitted an immune response to molecular mimics of both the A and B antigens. This newly evolved molecular structure, we suggest, was blood group O. In support of this hypothesis, it is notable that O can result from a variety of changes in the biochemical pathway involved in the synthesis of the A and B antigens. Theoretically, then, the A or B antigen is capable of mutating to O more rapidly than the reverse. A higher rate of mutation would aid the introduction of a new allele in the presence of incompatibility selection.

Mutual evolutionary responses over generations of hosts and infectious organisms can be viewed as altering the forces of natural selection.[6] The succession of selective pressures against genotypes bearing the antigen-conferring alleles could have forced the ABO locus through a series of unstable equilibria (Wright 1929 and 1977), allowing the increase of the O allele from very low frequencies.

SUMMARY

Our hypotheses to explain male proportions at birth in indigenous South American populations are related to high frequencies of the O allele.   We hypothesize two sufficient and non-conflicting explanations: that the high male proportions may be the consequence of diminished fetal wastage in the absence of incompatibility selection, and that they may be a genetic characteristic associated with blood group O. If adult sex proportions were unequal, natural selection would tend to bring the population to equilibrium over thousands of years. However, adult sex proportions presently appear to be at equilibrium, in which case natural selection cannot come into play to reduce male proportions at birth.

Furthermore, we argue that the fixation of O in the New World involves the selective advantage of the allele under ABO incompatibility. Once the O allele has reached fixation, the other alleles can be introduced only with considerable admixture with A- or B-bearing groups.   Socially determined characteristics of mating types in South America would have kept frequencies of the A and B alleles low even in the face of admixture.

The rest of our analysis is more tentative because further research on large samples from different populations with different environmental stresses during pregnancy is necessary to substantiate our hypotheses. The mechanism causing early loss of ABO-incompatible fetuses needs to be elucidated.   The effects of other loci need to be examined further. Above all, a biogeographical approach should be taken in recognition of variability among populations in the apparent forces of selection at the ABO locus.

Our model of ABO evolution in South America leads us to hypothesize that the phenomenon of molecular mimicry may have had a major evolutionary impact on the ABO locus.   The pervasiveness of ABO-specified antigens in human tissues and the common synthesis of similar molecular structures in other living forms suggest that molecular mimicry could be expected to occur in disease organisms and would prove adaptive for infestation of humans.   The evolutionary importance of molecular mimicry is that it could have provided a means of selection against the most common allele, thus it could have fostered the evolution of polymorphism. Further, we tentatively advance the hypothesis that O was the last of the ABO alleles to evolve.

Regardless of early evolution at the locus, our simulations show that from all current gene frequencies, O would reach fixation, if incompatibility constituted the only selective force.   Thus, we speculate that, in human populations, the ABO polymorphism may be transient. Assuming that ABO maternofetal incompatibility selection is and remains a major selective force, universality of blood group O is the logical end point of evolution at the ABO locus.
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[1] In the 1979 report by the Grupo D.A.M., homicide accounted for 16 percent of male deaths and 2.6 percent of female deaths in one Amazonian group.

[2] We also note that the bottleneck effect, resulting from the drastic population losses brought about by the European Conquest, could have played a major role in elimination of the A and B alleles (see Crosby 1972, Hohenthal 1951, and Ribeiro 1971 for detailed discussion of indigenous population losses at the time of contact).

[3] In 102 couples with persistent and otherwise inexplicable sterility, 87.3% were found to be ABO incompatible, in contrast to only 38.6% who were ABO incompatible in

a group of 171 fertile couples (Behrman et al. 1960; see also Levene and Rosenfield 1961 and Mourant et al. 1978). It should be noted, however, that other infertility studies yield different results (see Grubb and Sjostedt 1954-5, Bennett and Walker 1955-6), and further research is necessary to clarify these relationships.

[4]For simplicity, our simulations do not distinguish among the two major subgroups and eleven rare subgroups of A, nor among the one major and seven rare subgroups of B, nor among the major form of O and its three rare variants (Bryan 1976); however, we suggest that they may offer a rewarding direction for future research.

[5]The same mechanisms we propose could explain the ABO-like polymorphisms found in other species. However, it seems to us that the ABO locus has been subject to such rapid evolution that non-human primate distributions are not relevant to recent ABO evolutionary history in humans.

[6]Small isolated populations cannot maintain certain infectious diseases. It is even questionable whether organisms which were highly virulent could have been maintained in early human populations long enough for molecular mimicry to occur.

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