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The Evolution of Human Populations: A Molecular Perspective

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Human evolution exhibits repeated speciations and conspicuous morphological change: from *Australopithecus* to *Homo habilis, H. erectus,* and *H. sapiens;* and from their hominoid ancestor to orangutans, gorillas, chimpanzees, and humans. Theories of founder-event speciation propose that speciation often occurs as a consequence of population bottlenecks, down to one or very few individual pairs. Proponents of punctuated equilibrium claim in addition that founder-event speciation results in rapid morphological change. The major histocompatibility complex (MHC) consists of several very polymorphic gene loci. The genealogy of 19 human alleles of the *DQB1* locus coalesces more than 30 million years ago, before the divergence of apes and Old World monkeys. Many human alleles are more closely related to pongid and cercopithecoid alleles than to other human alleles. Using the theory of gene coalescence, we estimate that these polymorphisms require human populations of the order of $N = 100{,}000$ individuals for the last several million years. This conclusion is confirmed by computer simulations showing the rate of decay of the polymorphisms over time. Computer simulations indicate, in addition, that in human evolution no bottlenecks have occurred with fewer than several thousand individuals. We evaluate studies of mtDNA, Y-chromosome, and microsatellite autosomal polymorphisms and conclude that they are consistent with the MHC result that no narrow population bottlenecks have occurred in human evolution. The available molecular information favors a recent African origin of modern humans, who spread out of Africa approximately 100,000 to 200,000 years ago.

The process of speciation involves the evolution of reproductive isolation among descendants of individuals that previously shared in a common gene pool. The founder-event model of speciation claims that speciation is often triggered by population bottlenecks (Carson, 1968, 1986; Mayr, 1963). The theory of punctuated equilibrium makes the additional claim that bursts of morphological change occur in association with speciation, whereas stasis prevails over the long time intervals between speciation events (Gould, 1982a,b; Stanley, 1979, 1982). According to this theory, extreme population bottlenecks would facilitate speciation as well as rapid morphological change.

The human evolutionary line of descent for the last four million years (Myr) goes back from *Homo sapiens* to *H. erectus, H. habilis, Australopithecus afarensis,* and *A. onamensis.* Humans and chimpanzees shared a last common ancestor about six Myr ago; their last common ancestor with the gorillas lived somewhat earlier; and the last common ancestor of humans, African apes, and orangutans lived some 15 Myr ago. The succession of hominid species from *Australopithecus* to *H. sapiens* occurred in association with some species splitting, as illustrated by such extinct lineages as *Australopithecus africanus, A. robustus,* and *A. boisei.* Earlier species-splitting events include at least the successive divergence of the orangutan, gorilla, and chimpanzee lineages; and earlier still, the divergence of the hylobatids. Additional speciation events are illustrated by the splitting of the chimpanzee and bonobo (or pygmy chimpanzee), as well as by the various species of gibbons and siamangs.

The question arises whether the notable morphological changes that have occurred in hominoid evolution may have been triggered by population bottlenecks, perhaps even extreme bottlenecks down to only one or a few pairs of individuals, as postulated by theories of founder-event speciation. The population genetics theory of gene coalescence makes it possible to investigate the size of ancestral populations by examining the gene polymorphisms found in modern populations. The techniques of molecular biology make it feasible to identify these polymorphisms at the DNA level.

The HLA Complex

The human leucocyte antigene (HLA) complex consists of about 100 genes located in chromosome 6, within a DNA segment of four million bp in length. The HLA genes specify molecules with a critical role in tissue compatibility and the defense against foreign substances. These genes are arranged in two distinct groups, class I and class II, separated by several score genes that have functions mostly unrelated to the immune response (Fig. 1).

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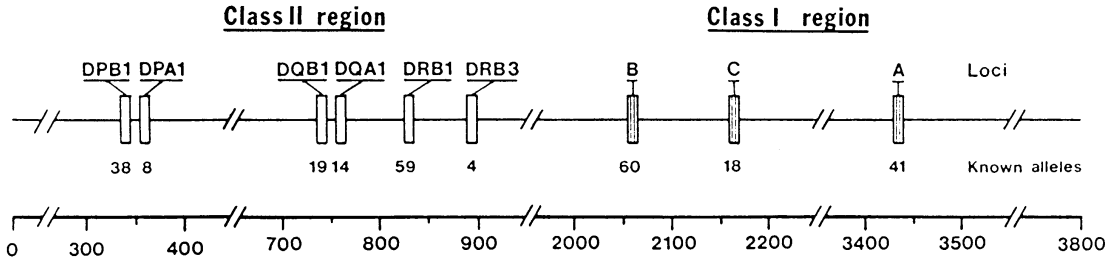

FIG. 1. Location of some polymorphic genes within the HLA complex in human chromosome 6. There are two sets of genes, class I and class II, separated by a region with unrelated genes. The number of alleles known at a locus is written below the box that indicates the location of the gene. The scale below is in kilobases.

The HLA complex is homologous to the major histocompatibility complex (MHC) of mammals and other vertebrates (Kaufman *et al.*, 1995; McDevitt, 1995; Schwaiger and Epplen, 1995). MHC molecules present on the surfaces of certain cells bind fragments of proteins (antigens) and present them to thymus-derived lymphocytes (T cells) expressing T-cell receptors on their surfaces. The clone of T lymphocytes that bear receptors matching a particular combination of protein fragment and MHC molecule is stimulated, by the contact with the antigen-presenting cells, to proliferate and to initiate the specific arm of the immune response, including the secretion of specific antibodies. The MHC molecules thus protect against pathogens and parasites in general.

The recognition of protein fragments is mediated by a specialized groove on the surface of the MHC molecule, the so-called peptide-binding region (PBR) composed of some 50 amino acid residues (Bjorkman *et al.*, 1987a,b; Brown *et al.*, 1993). The composition of the amino acids in the PBR varies from one MHC molecule to another, and it is primarily this variation that is responsible for the tremendous polymorphism characteristic of the MHC molecules and their encoding genes. In people, as well as in some mammalian species (e.g., the house mouse), scores of alleles may exist at any one of several MHC loci, and some of the allelic pairs may differ by more than 100 nucleotide substitutions (Bontrop, 1994; Bontrop *et al.*, 1995; Klein and Figueroa, 1986; Marsh and Bodmer, 1991, 1993; McDevitt, 1995; O'hUigin *et al.*, 1993; WHO, 1992).

The MHC polymorphisms are ancient, with allele lineages tracing back for millions of years, in primates (Bergström and Gyllenstein, 1995; Fan *et al.*, 1989; Gyllenstein and Erlich, 1989; Gyllenstein *et al.*, 1990; Lawlor *et al.*, 1988; Mayer *et al.*, 1988) as well as in rodents (Arden and Klein, 1982; Figueroa *et al.*, 1988; McConnell *et al.*, 1988). For example, 58 human alleles analyzed at the *DRB1* locus coalesce more than 30 Myr ago, much before the divergence of humans and the great apes (Ayala *et al.*, 1994). In the present paper we investigate another class II locus, the *DQB1* locus, at which many alleles are known in humans as well as in other primates.

Age of the DQB1 Human Polymorphism

Exon 2 of the *DQB1* gene consists of 270 nucleotides that specify β-chain amino acids involved in peptide binding. This exon is extremely polymorphic in humans and other hominoids. We have analyzed 64 alleles, of which 19 are human, 31 from nonhuman apes, and 14 from Old World monkeys (Table 1). We have calculated the pairwise genetic distance between the 64 alleles using Kimura's (1983) two-parameter distance. Table 2 is the matrix of genetic distances for the 19 HLA alleles. Figure 2 is a phylogenetic tree of the 64 alleles, constructed by the neighbor-joining method (Saitou and Nei, 1987).

It is apparent in Fig. 2 that some human allelic lineages are very old. The clade of 31 alleles on the upper part of the figure includes pongid and hominid alleles, but none from cercopithecoids. We may notice that the human *Hs*0302* allele is more closely related to the orangutan *Or*1701* than to *Hs*0606* (which in turn is more closely related to *Or*0603* than to the other two alleles). If we assume that the divergence of the orangutan and human lineages occurred 15 Myr ago, it fol-

TABLE 1

Species and Number of DQB1 Alleles

Code	Species	Number of alleles
	Hominoidea	
Hs	*Homo sapiens* (human)	19
Pp	*Pan paniscus* (bonono)	5
Pt	*Pan troglodytes* (chimpanzee)	10
Gg	*Gorilla gorilla* (gorilla)	10
Or	*Pongo pygmaeus* (orangutan)	4
Hl	*Hylobates lar* (gibbon)	2
	Cercopithecoidea	
Ma	*Macaca arctoides*	2
Mf	*Macaca fascicularis*	5
Mm	*Macaca mulatta* (rhesus macaque)	5
Ph	*Papio hamadryas* (hamadryas baboon)	2

Note. References for the sequences are: Marsh and Bodmer (1993); O'hUigin *et al.* (1993); and WHO Nomenclature Committee (1992).

TABLE 2

Genetic Distance between Pairs of 19 *DQB1* (Exon 2) Human Alleles, Calculated According to Kimura's (1983) Two-Parameter Model for All Sites Sequenced in the 19 Alleles

	0301	0302	0304	0401	0402	0501	0502	0504	0601	0602	0603	0604	0605	0606	3031	3032	5031	5032
0201	0.141	0.117	0.133	0.149	0.141	0.149	0.141	0.117	0.117	0.133	0.141	0.133	0.133	0.133	0.125	0.125	0.141	0.149
0301		0.035	0.007	0.094	0.086	0.086	0.079	0.094	0.064	0.056	0.071	0.071	0.064	0.064	0.035	0.028	0.071	0.079
0302			0.028	0.086	0.078	0.086	0.078	0.094	0.071	0.049	0.064	0.057	0.049	0.049	0.014	0.007	0.063	0.071
0304				0.101	0.094	0.086	0.078	0.094	0.071	0.063	0.078	0.071	0.064	0.064	0.042	0.035	0.078	0.086
0401					0.007	0.094	0.086	0.071	0.071	0.093	0.109	0.109	0.101	0.101	0.071	0.078	0.064	0.071
0402						0.086	0.079	0.064	0.063	0.086	0.101	0.101	0.094	0.094	0.063	0.071	0.056	0.064
0501							0.028	0.057	0.078	0.056	0.056	0.042	0.049	0.049	0.094	0.086	0.028	0.021
0502								0.028	0.071	0.064	0.064	0.056	0.064	0.064	0.086	0.078	0.021	0.028
0504									0.056	0.078	0.094	0.086	0.078	0.078	0.101	0.094	0.049	0.057
0601										0.064	0.079	0.079	0.071	0.071	0.071	0.063	0.049	0.056
0602											0.014	0.028	0.021	0.021	0.049	0.042	0.056	0.049
0603												0.014	0.021	0.021	0.064	0.056	0.056	0.049
0604													0.007	0.007	0.064	0.056	0.056	0.049
0605														0.000	0.056	0.049	0.064	0.056
0606															0.056	0.049	0.064	0.056
3031																0.007	0.063	0.071
3032																	0.056	0.063
5031																		0.007

lows that the divergence of *Hs∗0302* and *Hs∗0606* is still older. But the human *DQB1* polymorphism is much older than 15 Myr. Toward the lower part of the genealogy in Fig. 2, we see that *Hs∗0601* is more closely related to several macaque and baboon alleles (*Ma∗0602*, *Mf∗0602*, and *∗0601*, *Mm∗0601*, and *Ph∗0601*) than to the previously mentioned *Hs∗0302* and *Hs∗0606*. This implies that the *DQB1* human polymorphism is at least 35 Myr old, if we take this as the age of the divergence between the apes and the Old World monkeys.

The age of the *DQB1* human polymorphism may be estimated by calibrating first the rate of evolution of the *DQB1* (exon 2) clock. This has been done in Fig. 3 in two different ways, the "minimum" and the "minimum-minimum" methods (Satta *et al.*, 1991, 1993). The figure plots the genetic distance between pairs of alleles from different species (ordinate) against the time of divergence between the species (abscissa). In the minimum method, the rate of evolution is estimated to be the regression on time of the minimum distance observed for each pair of species that diverged at a certain time. Thus, three values (among all those plotted) are used for 15 Myr, namely the minimum distance observed between humans and orangutans, chimps and orangs, and gorillas and orangs. In the minimum-minimum method, only the lowest of these three values is used; and similarly for the other points along the abscissa.

The minimum allelic distance between two species is assumed to involve alleles that diverged about the time when the species lineages diverged, rather than earlier as would be the case for more differentiated alleles. Thus, the time of divergence between two such alleles is the same as, or only slightly greater than, the time of the species divergence. The minimum-minimum method attempts to approximate the time of divergence even more closely by using only the minimum value of all pairwise comparisons between species that diverged at a certain time. The minimum-minimum method may, however, correct excessively, because alleles that have evolved slower than the average will be the ones included in the correlation. In any case, the rates of divergence estimated by the two methods are fairly similar, 0.207 and 0.192% per million years, or approximately a substitution rate of 1×10^{-9} per site per year. We shall use the faster of the two rates, obtained by the minimum method.

Figure 4 is a genealogy of the HLA alleles obtained by the UPGMA method, which assumes constant rates of evolution and thus aligns all 19 alleles at the zero-distance point that corresponds to the present. The genealogy suggests that 8 allele lineages were already in existence 15 Myr ago, at the time of the divergence of the orangutan from the lineage of African apes and humans; and that 12 allele lineages were in existence 6 Myr ago, at the time of divergence of humans, chimps, and gorillas. If we ignore allele *0201*, the allelic lineages coalesce around 35 Myr ago. Allele *0201* appears to be the most divergent of the HLA alleles in both Figs. 2 and 4, but its remote coalescence in Fig. 4 may be in part a distortion due to the imposed condition that all lineages evolve at the same rate. The average genetic distance between allele *0201* and all others is 0.134, larger than that observed between any two other alleles, which is 0.109 between allele *0401* and either *0603* or

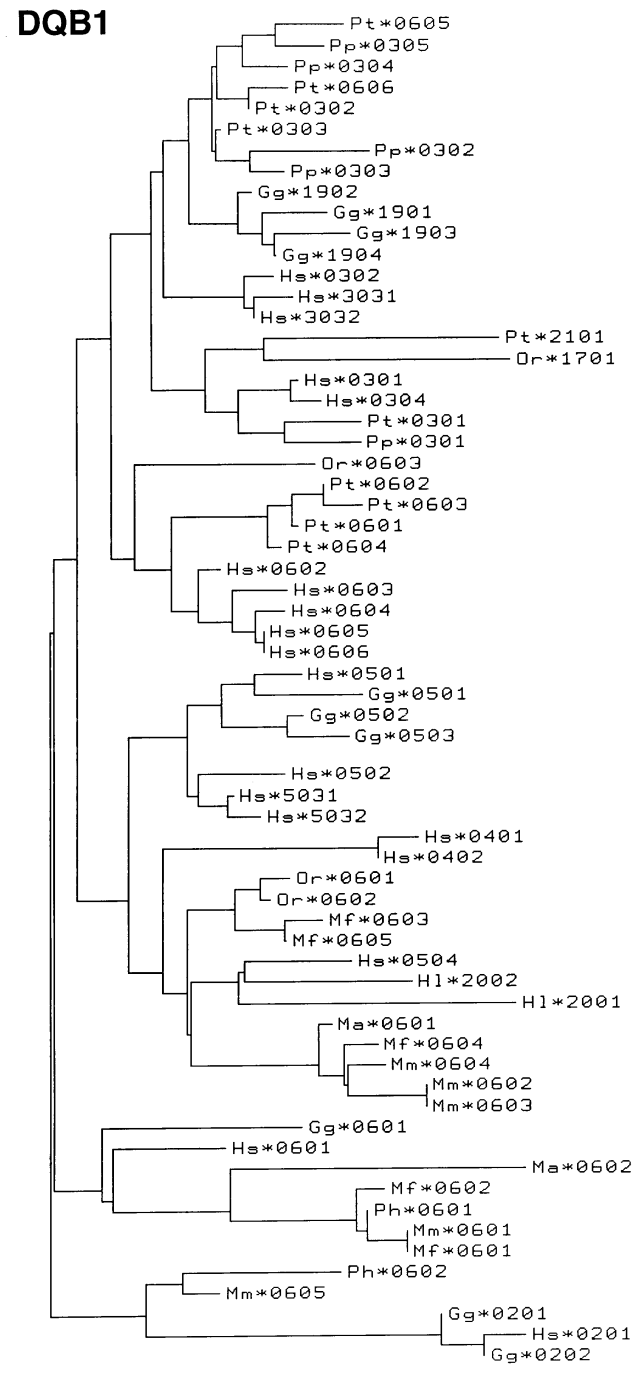

FIG. 2. Evolutionary tree (genealogy) of 64 DQB1 alleles (exon 2) of 10 primate species listed in Table 1. The tree is obtained by the neighbor-joining method (Saitou and Nei, 1987) based on pairwise genetic distances estimated by Kimura's (1983) two-parameter model for those sites sequenced in all 64 alleles.

0604. Using the evolutionary rate of 1×10^{-9} substitutions per site per year, the lineage of allele *0201* diverged from the other alleles 67 Myr ago. The *DQB1* polymorphism is thought to be older than the *DRB1* polymorphism and, indeed, one of the oldest among the class II loci (Bergström and Gyllenstein, 1995).

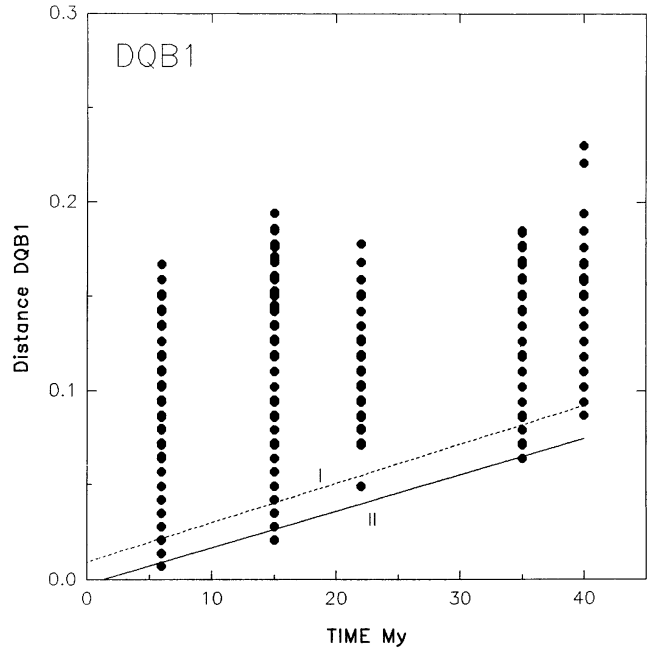

FIG. 3. Rate of evolution of *DQB1* (exon 2) obtained by the regression of minimum genetic distance on time. The times of divergence and species compared are: 6 Myr, *Homo-Pan, Homo-Gorilla, Pan-Gorilla;* 15 Myr, *Pongo* versus each of *Homo, Pan,* and *Gorilla;* 22 Myr, *Hylobates* versus each of *Homo, Pan, Gorilla,* and *Pongo;* 35 Myr, *Macaca* versus each of *Pan, Gorilla,* and *Hylobates;* 40 Myr, *Cebus* versus each of *Homo, Pan, Gorilla, Pongo,* and *Hylobates.* When the minimum values are used for each species-pair comparison, the regression equation is $D = 0.009 + 0.00207$ Myr, with a fit of $r = 0.89$ (I in the figure); when only the minimum-minimum value observed at each time point is used, the regression equation (II in the figure) is $D = -0.002 + 0.00192$ Myr, with $r = 0.98$.

Coalescence Theory and the Size of Human Populations

The persistence of 12 *DQB1* allelic lineages over the last 6 Myr of hominid evolution implies of necessity that no fewer than six individuals could have existed at any one time throughout that time. In fact, the minimum number of individuals must have been much larger, since the probability that all six individuals in a population are heterozygous, each for two different alleles, is effectively nil. To assess the numbers of individuals required in human ancestral populations in order to account for the size of the *DQB1* polymorphism, we will use the theory of gene coalescence which relates the effective number (N) of individuals in a population to the coalescence time (T), and thus permits estimating one parameter in terms of the other (T calculated from N, or vice versa).

The coalescence theory examines the genealogical relationships between genes (Griffiths, 1980; Hudson, 1990). According to this theory, all alleles present in an extant pool must have descended from a single allele (to which they coalesce). For neutral alleles in a random

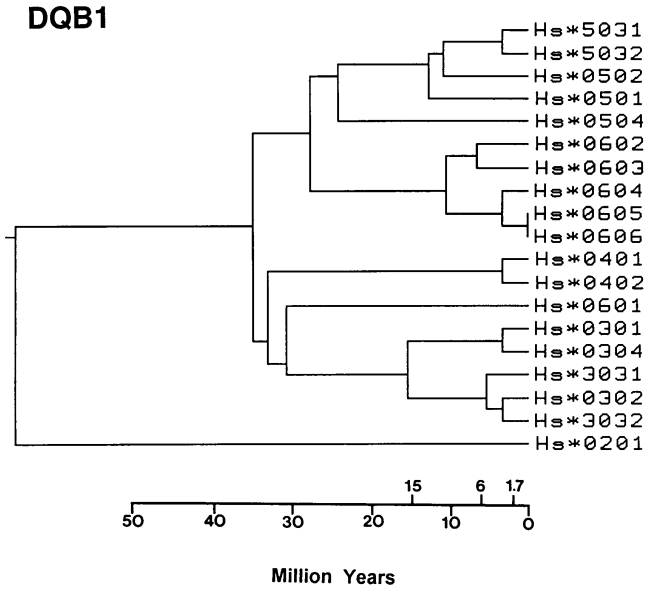

FIG. 4. Genealogy of 19 *DQB1* human alleles obtained with a standard unweighted pair-group method of averages (UPGMA) algorithm based on the genetic distances given in Table 2. The rate of nucleotide divergence, given by I in Fig. 3, is 2.07×10^{-9} per site per year. On top of the time scale are marked the approximate times of divergence of the orangutan lineage (15 Myr), the human-chimp-gorilla split (6 Myr), and the emergence of *H. erectus* (1.7 Myr).

mating population at equilibrium, the mean coalescence time is given by $4N[1 - (1/i)]$ generations, where i is the number of sampled genes. For any two genes ($i = 2$), the mean coalescence time reduces to $2N$ generations; for a large number of genes, the mean coalescence time is, approximately,

$$T = 4N, \tag{1}$$

where T is the number of generations to coalescence.

If we assume a long-term generation time of 15 years in the human lineage, an estimate of 35 Myr to coalescence corresponds approximately to 2.3 million generations and $N = 575{,}000$ individuals. Two observations are apposite at this point. First is that N as an estimate of mean population size has the properties of a harmonic mean. Thus, a mean value of $N = 575{,}000$ is compatible with much larger population sizes for many generations, but is not compatible with much smaller population sizes for very many generations. The second observation is that the estimate in equation (1) has a very large variance. Thus, a coalescence determined to have occurred 35 Myr ago is compatible with mean population sizes of, say, $N = 250{,}000$ or $N = 1{,}000{,}000$ individuals.

Equation (1) applies to selectively neutral alleles (Kingman, 1982a,b; Tajima, 1983; Takahata and Nei, 1985; Tavaré, 1984). But the coalescence theory has been extended to allelic genealogies under balancing selection (Takahata, 1990, 1993; Takahata and Nei, 1990). In this situation, the theory has the same mathematical structure as in neutral gene genealogy except for a scaling factor, $f(s)$, so that the time to coalescence in generations for a large number of genes is, approximately,

$$T(s) = 4Nf(s). \tag{2}$$

If u is the selected mutation rate per gene per generation and s is the selection coefficient, then, approximately,

$$f(s) = \frac{\sqrt{2Ns}}{2Nu} \cdot \left[\ln \frac{Ns}{8\pi(Nu)^2}\right]^{-3/2} \tag{3}$$

Given i sampled genes, the coalescence theory permits one to estimate the number of distinct genes, j, that existed at a certain time, with time measured in $2Nf(s)$ generations. Generally, the population size necessary for a given polymorphism is substantially smaller for balanced selected alleles than for neutral alleles.

Various sources of evidence suggest that HLA polymorphisms are subject to balancing selection. One reason to suspect balancing selection is, of course, the long-term persistence of the allelic lineages. The presence of balancing selection is manifested by the analysis of the DNA sequences of HLA alleles. In codons specifying amino acids of the PBR, variation at the first and second positions is significantly higher than at the third position, and this observation is taken as evidence that positive selection acts on the first two positions (Hedrick, 1994; Hughes and Nei, 1988, 1992; Kaufman *et al.*, 1995; Klein and O'hUigin, 1994; Potts and Slev, 1995). Moreover, Hill *et al.* (1991, 1992a,b; see Miller, 1994) have shown that MHC polymorphism may increase resistance to *Plasmodium falciparum*, the parasite responsible for malignant malaria.

Estimates of the magnitude of the selection coefficient, s, that maintains the MHC polymorphisms vary from locus to locus, but range from 0.0007 to 0.019 (Ayala *et al.*, 1994). It seems unlikely that the selection coefficient would be in any case much larger than 0.01–0.03, but even larger selection coefficients do not allow for the long-term persistence of polymorphisms except in the presence of large populations (Ayala *et al.*, 1994).

If the heterozygotes' advantage over the homozygotes is $s = 0.01$ and the selected mutation rate per site per gene per generation is $u = 2.0 \times 10^{-6}$, a mean effective size of approximately $N = 131{,}000$ individuals is required for a polymorphism that survives for 3 million generations (which amounts to 36–45 Myr if we as-

TABLE 3

Effective Population Size, *N*, as a Function of Various Parameter Values

T^a	u^b	s	N
3.0×10^6		0	750,000
	4.5×10^{-6}	0.01	211,793
		0.02	178,691
		0.03	157,795
	2.0×10^{-6}	0.01	131,196
		0.02	98,992
		0.03	82,505
2.5×10^6		0	625,000
	4.5×10^{-6}	0.01	169,720
		0.02	141,111
		0.03	123,668
	2.0×10^{-6}	0.01	101,920
		0.02	76,118
		0.03	63,105

Note. T, time in generations; s, selective advantage of the heterozygotes; u, selected mutation rate per locus per generation.

[a]If the long-term generation time is 12–15 years, $T = 3.0 \times 10^6$ corresponds to 36–45 Myr.

[b]By way of example $u = 2.0 \times 10^{-6}$ if the mutation rate per nucleotide site per year is $m = 10^{-9}$, half the sites yield selected alleles ($n = 135$), and the generation time is $g = 15$ years; or if $m = 5 \times 10^{-9}$, $n = 40$, $g = 10$.

sume a long-term generation of 12–15 years) (Table 3). For $s = 0.02$ and 0.03, $N = 99{,}000$ and 82,500 approximately. Persistence of the polymorphism for 2.5 million generations (30–37 Myr) requires, approximately, $N =$ 102,000, 76,000, and 63,000 individuals, respectively, for $s = 0.01$, 0.02, and 0.03 (Table 3). The conclusion seems fairly robust, as to the order of magnitude, that the mean effective size of human ancestral populations has been 100,000 individuals throughout hominoid evolution. A similar conclusion has been derived from the analysis of the human *DRB1* polymorphism (Ayala, 1995; Ayala *et al.*, 1994; Takahata *et al.*, 1992).

Computer Simulation Experiments

We can test the conclusions obtained in the previous section by means of experiments simulated in a computer. The coalescence theory starts with current polymorphisms and makes inferences as to the number of generations required for gene coalescence. In the computer simulations the time direction is reversed. The process starts with a certain number of alleles, initially all in identical frequencies, and their fate is ascertained as the generations proceed. Each individual, formed by random sampling two genes, reproduces with a probability that is s higher for heterozygotes than for homozygotes. The pool of genes collected from the reproducing individuals is sampled again, and the process repeated generation after generation. The number of alleles persisting in the population is scored at 100-generation intervals.

Figure 5a examines the fate of 20 alleles in a population of $N = 1000$ individuals over 100,000 generations, approximately the time elapsed from the emergence of *H. erectus* to the present. If there is no selection ($s = 0.00$), the population reaches fixation in a few thousand generations as expected (the expected value is $4N$ generations, 4000 in this case). When the heterozygotes have a selective advantage of $s = 0.01$ or 0.02, as it has been estimated in human populations, the number of alleles persisting after 100,000 generations is only two or three, respectively. Even unrealistically large overdominance values of 10 and 20% are insufficient to maintain 20 alleles in populations with $N = 1000$ individuals.

Figure 5b presents a similar simulation for a population with $N = 10{,}000$ individuals. In the neutral case, fixation occurs at approximately the expected value of 40,000 generations. Nine alleles persist after 100,000 generations when the overdominance advantage is 0.01; 12 alleles persist with overdominance of 0.02. There is no migration, and mutation is ignored in this as well as in the previous simulation.

If we assume a mutation rate to selected alleles of 5×10^{-7} per gene per generation, a new overdominant mutation is expected to appear every one thousand generations in a population of one thousand individuals, which is much too slow to counteract the process of random elimination. In a population of 10,000 individuals, however, a new overdominant mutation would appear every 100 generations. Even though a new overdominant mutation has a high probability of being lost by chance in the first or following generations, the process would increase somewhat the number of alleles maintained by a population of 10,000 individuals.

Population Bottlenecks

The computer-simulation experiments are consistent with the conclusion drawn using coalescence theory, namely that the long-term persistence of the *DQB1* allelic lineages requires a mean effective population size of the order of 100,000 individuals over the last 35 Myr of hominoid history. When population sizes oscillate, small numbers have a disproportionately large effect on the value of N, since the effective population size is the harmonic mean of the population size over time. But the question remains whether an occasional population bottleneck may have occurred, and how small could the bottleneck be. It has been suggested that a very narrow population bottleneck occurred at the transition from archaic to modern *H. sapiens,* some 100,000 to 200,000 years ago (Cann *et al.*, 1987; Goldstein *et al.*, 1995; Stoneking *et al.*, 1990; Vigilant *et al.*, 1991; see also Dorit *et al.*, 1995).

The consequences of a bottleneck depend not only on the size, N_b, of the bottleneck, but also on the number, t_b, of bottleneck generations. A useful measure for evaluating the effects of a bottleneck is the ratio N_b/t_b,

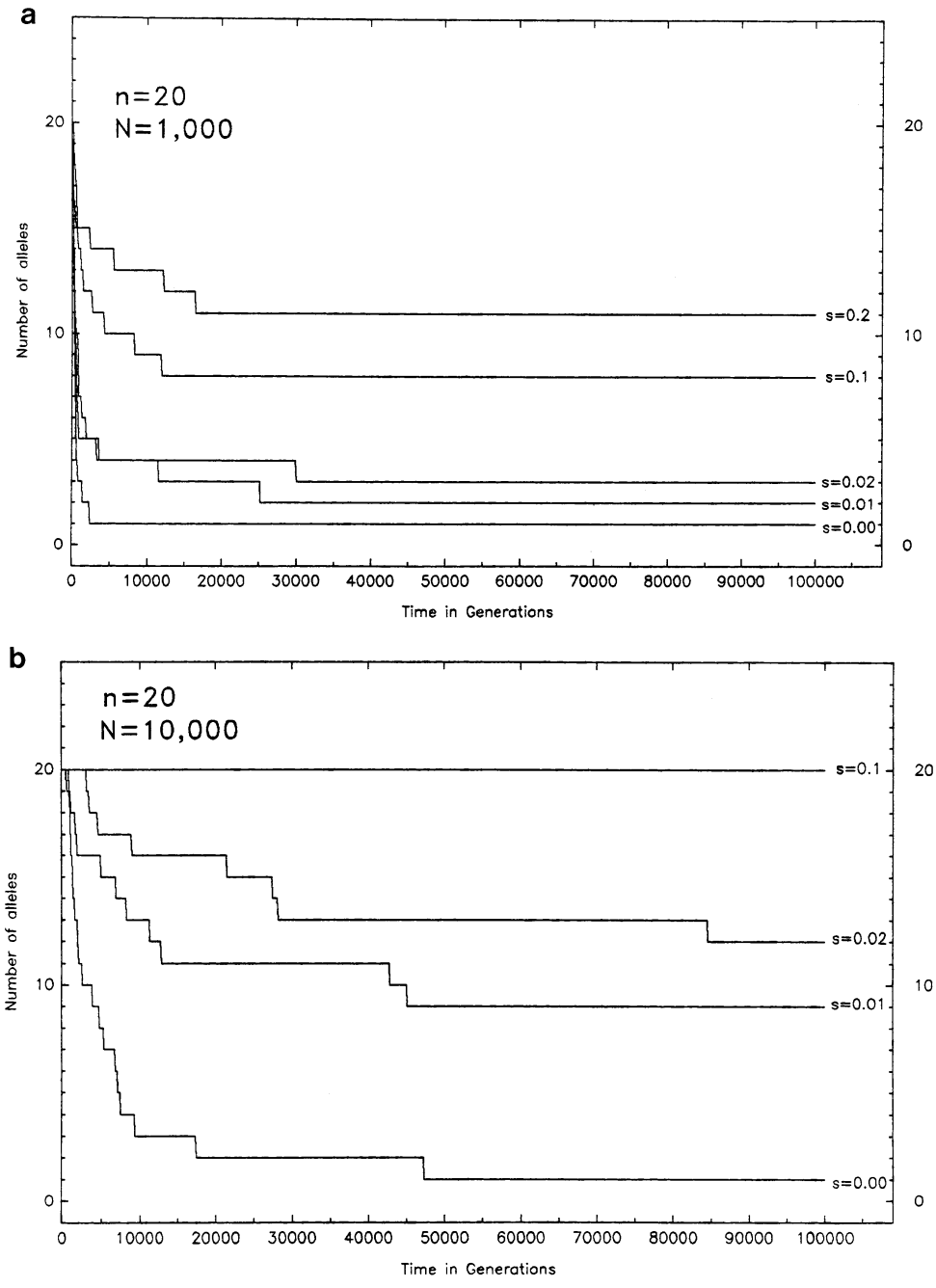

FIG. 5. Computer simulation of the loss of alleles over 100,000 generations in a population consisting of (a) 1000 or (b) 10,000 individuals. Initially 20 alleles are present, each at 0.05 frequency. Mating is random and there is no mutation or migration. Heterozygotes reproduce with a probability s higher than homozygotes. Without selection, all alleles but one are soon eliminated. With selection advantages of 0.01 and 0.02, such as operate in real populations, all but two or three alleles are soon eliminated in the population with $N = 1{,}000$, but as many as 10–12 are still present after 100,000 generations, when $N = 10{,}000$.

which if smaller than 10 will have drastic effects in reducing genetic variation (Takahata, 1993). Thus a bottleneck of 100 individuals would substantially reduce genetic variation if it would last 10 or more generations. Balancing selection facilitates the persistence of polymorphisms through a bottleneck. But because alleles behave as neutral whenever $Ns < 1$, if the selection is weak, such as $s = 0.01$, N has to be correspondingly large, at least 100, for selection to play a role. The persistence of HLA polymorphisms over millions of years requires that the size of human ancestral populations be at least $Ns = 10$ at all times. If $s = 0.01$, the minimum population size possible at any time would be $N_b = 1000$ (Ayala *et al.*, 1994; Takahata, 1990). The

minimum number must have been in fact much larger, because human population bottlenecks cannot last just a few generations, since many generations are required for a human population to grow from 1000 to its long-term mean, which we have estimated to be around 100,000 individuals. The rate of growth of human populations throughout the Pleistocene has been estimated to be about 0.02% per generation (Spuhler, 1993).

We have used computer simulations to explore the minimum bottleneck size that would allow the persistence of a certain number of alleles through the bottleneck, allowing for some alleles to be lost through the bottleneck. The results given in Figs. 6 and 7 and Table 4 are based on 200 separate computer runs. If there is no selection and we ignore the time required for a population to grow back to its long-term population size, the smallest bottleneck that would allow the persistence of 20 allelic lineages, out of 30 present before the bottleneck, with a probability of 95%, is 140–180 individuals (Fig. 6a). When we take into account the time required for the population to recover to its average size, the minimum population size at the bottleneck becomes substantially larger. For example, if we assume a rate of population increase of $R = 1\%$ per generation (which is 50 times greater than the average growth rate of human populations throughout the Pleistocene; Spuhler, 1993, p. 279), a minimum effective population size of 1080–1150 individuals is required to pass 20 of the preexisting 30 alleles, if the population grows to $N = 10{,}000$; and 1180–1280 individuals if the population has to grow to $N = 100{,}000$ (Table 4).

Overdominant selection reduces only slightly the minimum number of individuals required at the bottleneck. As illustrated in Fig. 6b, when $s = 0.02$, the bottleneck size for passing 20 of 30 alleles is 130–170 individuals if we ignore the required growth back to long-term numbers, but 980–1030 and 1010–1070 when we take into account population growth to 10,000 and 100,000 individuals, respectively.

If we take only into account the *DQB1* genes, it is plausible that a small population bottleneck of about 1000 individuals might have occurred in recent human evolution. But we cannot ignore that other multiple-allele polymorphisms occur in present human populations, including those shown in Fig. 1 for HLA loci. Thus, for example, 59 human alleles are known at the *DRB1* gene locus. The minimum bottleneck required to pass 60 alleles of 70, when we take into account population growth back to long-term numbers of 100,000, is about 4500 individuals if there is no selection, and about 4350 individuals with $s = 0.01$ (Figs. 7a and 7b). Growth to just 10,000 individuals requires bottlenecks only slightly smaller. Table 4 summarizes the data obtained for a variety of assumptions.

It seems fair to conclude that ancestral human populations are unlikely to have been reduced to fewer than several thousand individuals at any time in their evolutionary history.

Adam, Eve, and Other Ancestors

The evolution of the hominids, from *Australopithecus* to the emergence of *H. erectus*, occurred in Africa. The hominid lineage diverged from the chimpanzee lineage about 6 Myr B.P., and the first known hominid, *Ardipithecus ramidus*, lived more than four Myr B.P. (White *et al.*, 1994, 1995; WoldeGabriel *et al.*, 1994). *H. erectus* emerged from *H. habilis* in Africa somewhat before 1.7 Myr B.P., and shortly afterward spread to other continents. Fossil remains of *H. erectus* are known from Africa, Indonesia (Java), China, the Middle East, and Europe (Clark, 1992, 1994; Clark and Lindly, 1989; Jones *et al.*, 1992). *H. erectus* fossils from Java have been dated 1.81 ± 0.04 and 1.66 ± 0.04 Myr B.P. (Swisher *et al.*, 1994).

Some anthropologists argue that the transition from *H. erectus* to archaic *H. sapiens* and later to anatomically modern humans occurred consonantly in various parts of the Old World. Proponents of this "multiregional model" emphasize fossil regional continuity in the transition from *H. erectus* to archaic and then modern *H. sapiens*, but postulate that genetic exchange occurred from time to time between populations, so that the species evolved as a single gene pool, even though geographic differentiation occurred and persisted, just as geographically differentiated populations exist in other animal species (Bräuer, 1992; Clark, 1992; Clark and Lindly, 1989; Jones *et al.*, 1992; Waddle, 1994; Wolpoff *et al.*, 1988).

Other scientists argue instead that modern humans first arose in Africa somewhat prior to 100,000 years B.P. and from there spread throughout the world, replacing elsewhere the preexisting populations of *H. erectus* or archaic *H. sapiens* (Goldstein *et al.*, 1995; Horai *et al.*, 1995; Rogers and Jorde, 1995; Ruvolo *et al.*, 1993; Stringer, 1990, 1992; Stringer and Andrews, 1988). Some proponents of this African replacement model argue further that the transition of archaic to modern *H. sapiens* was associated with a very narrow bottleneck, consisting of only two or very few individuals who are the ancestors of all modern mankind. This proposal is buttressed by an interpretation of mitochondrial DNA analysis showing that the diverse mitochondrial DNA sequences found in modern humans coalesce to one ancestral sequence, the "mitochondrial Eve" or "mother of us all," that existed in Africa about 200,000 years ago (Cann *et al.*, 1987; Stoneking *et al.*, 1990; Vigilant *et al.*, 1991). This conclusion has been challenged on grounds concerning (i) whether the coalescence is to Africa, (ii) the time of the coalescence, and (iii) the inference of a population bottleneck (e.g., Templeton, 1992). The actual date of coalescence depends on assumptions about evolutionary rates. Based on a time of divergence between humans and chimpan-

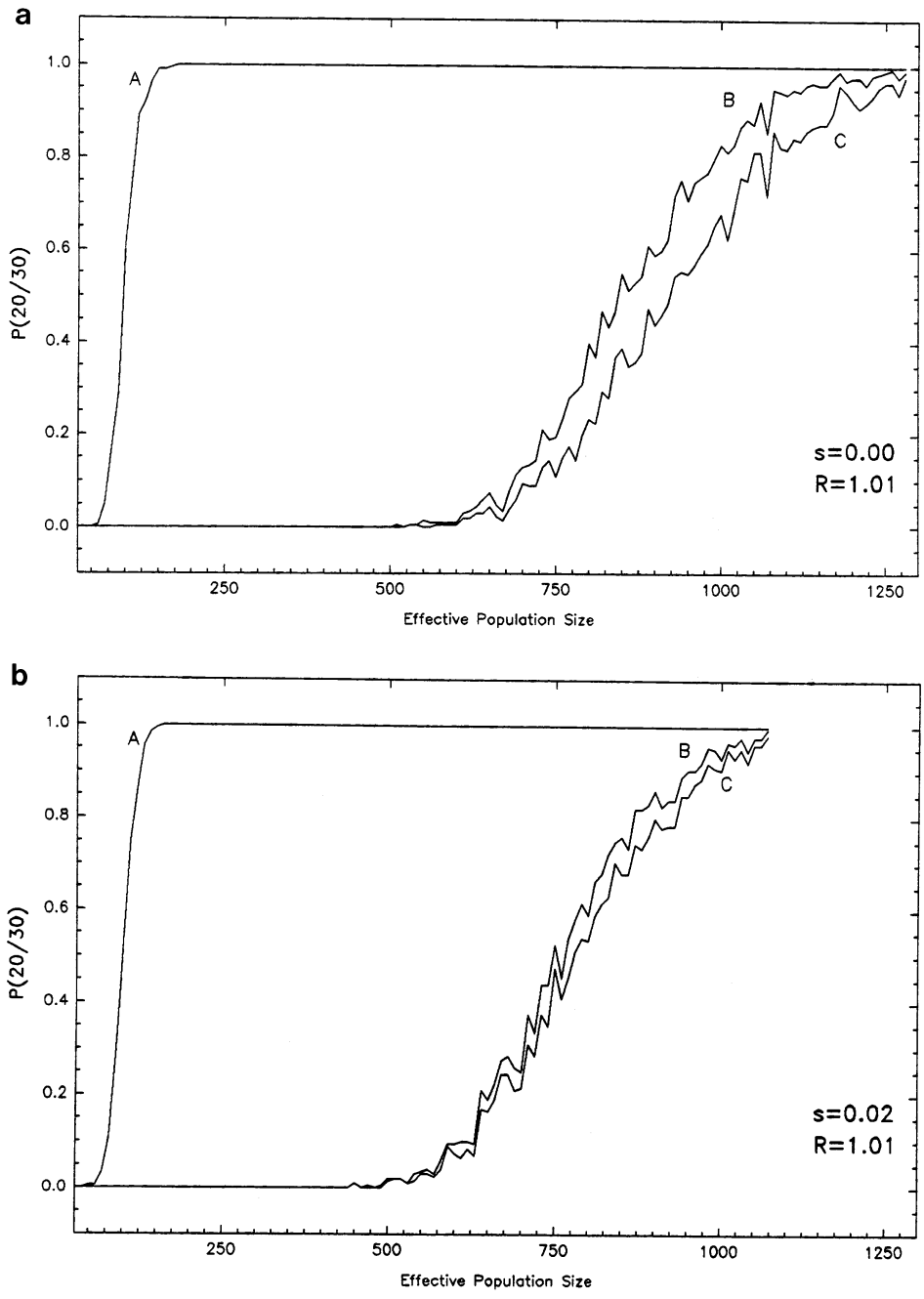

FIG. 6. Probability that 20 of 30 alleles, initially in identical frequencies, will persist after a bottleneck lasting 10 generations, as a function of population size at the bottleneck, when either (a) alleles are neutral or (b) $s = 0.02$. The graphs represent averages of 200 computer simulations. A ignores population growth after the bottleneck; B takes into account growth until the population reaches $N =$ 10,000 individuals; C population growth occurs until $N = 100{,}000$ individuals. The exponential rate of growth is $R = 1.01$ per generation, with discrete generations. The 95% value ranges are given in Table 4.

zees of 6 Myr, the time to coalescence for mitochondrial DNA polymorphism has been recently estimated at 298,000 years B.P., with a 95% confidence interval of 129,000–536,000 years (Ruvolo *et al.*, 1993).

The inference that a narrow bottleneck occurred at the time of the coalescence is based on a confusion between gene genealogies and individual genealogies. Gene genealogies gradually coalesce toward a unique DNA ancestral sequence, whereas individual genealogies increase by a factor of two per generation: an individual has two parents in the previous generation, four ancestors in the generation before that, and so on. (The theoretical number of ancestors for any one individual becomes enormous after some tens of generations, but

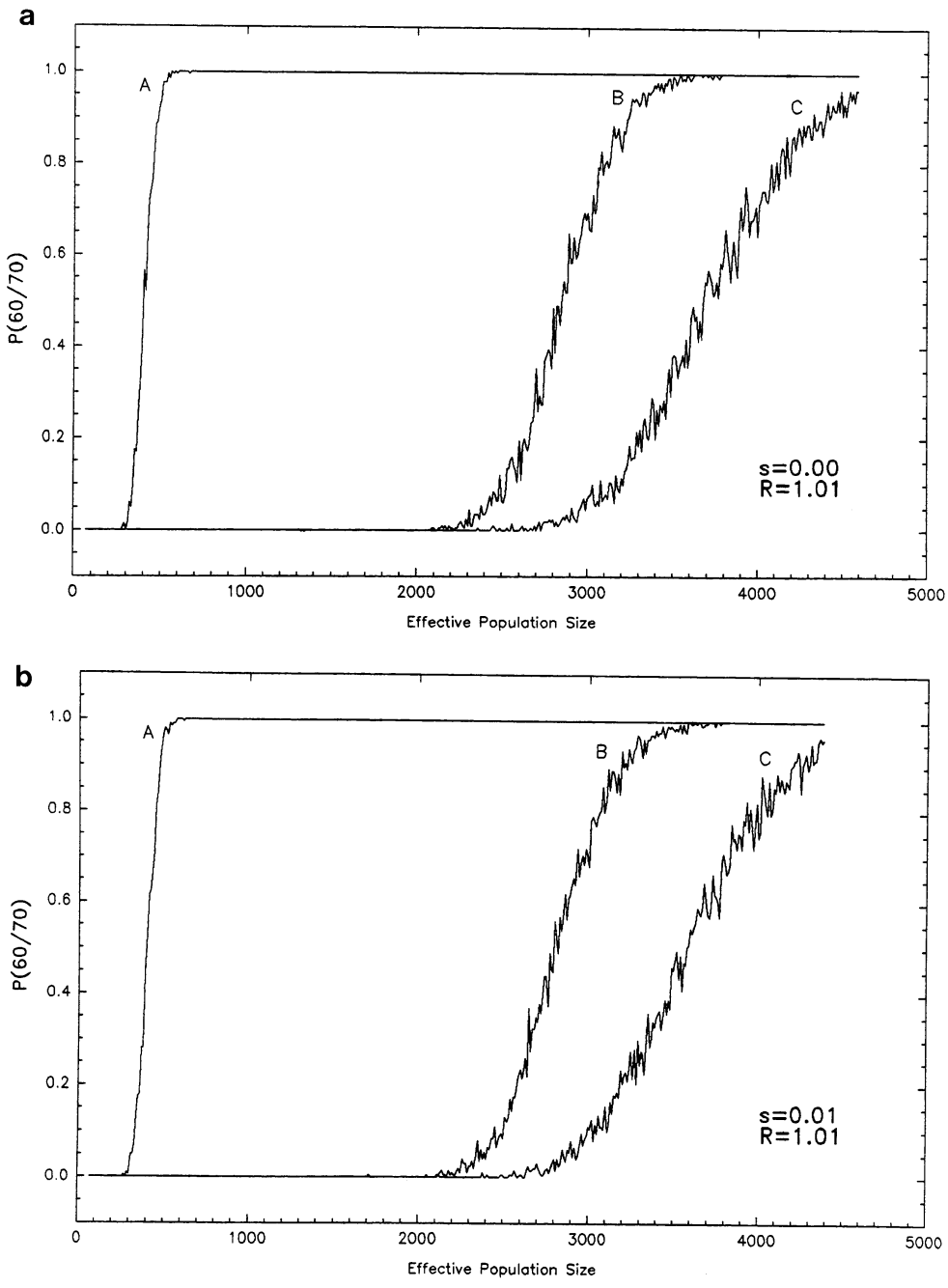

FIG. 7. Probability that 60 of 70 alleles, initially in equal frequencies, will persist after a bottleneck lasting 10 generations, as function of population size at the bottleneck, for $s = 0$ (a) and $s = 0.01$ (b). A, B, and C as in legend to Fig. 6. Based on 200 computer simulations. See Table 4 for 95% value ranges for these and other simulations.

"inbreeding" occurs: after some generations, ancestors appear more than once in the genealogy.)

As we pointed out above, assuming an effective population of N individuals, mean coalescence is $4N$ generations for neutral nuclear polymorphisms. Mitochondrial DNA is haploid and maternally inherited; hence, the mean coalescence is $2N_f$, where N_f is the number of mothers. If we assume 20 years for a human generation throughout the Pleistocene, 298,000 years to coalescence implies an effective mean population size of 7450 mothers or an effective population size of 14,900 humans. The 95% confidence time estimate of 129,000–536,000 years yields 6,450–26,800 generations corresponding to a mean effective population size of 6,450–26,800 individuals.

There is one more factor to take into account in the

TABLE 4

Minimum Population Size at a Bottleneck That Lasts 10 Generations

			Alleles through bottleneck		
s	*R*	*N*	20/30	40/50	60/70
0	—	—	140–180	310–350	510–550
0.01	—	—	130–170	300–340	500–540
0.02	—	—	130–170	—	—
0.10	—	—	—	300–340	490–530
0	1.01	10,000	1080–1150	2280–2330	3320–3370
0.01	1.01	10,000	1050–1100	2190–2280	3280–3350
0.02	1.01	10,000	990–1030	—	—
0.10	1.01	10,000	—	1840–1890	2950–3010
0	1.01	100,000	1180–1280	2770–2850	4490–4590
0.01	1.01	100,000	1150–1190	2640–2750	4310–4380
0.02	1.01	100,000	1010–1070	—	—
0.10	1.01	100,000	—	1920–1990	3410–3510
0	1.10	10,000	240–280	—	860–910
0.01	1.10	10,000	230–270	—	840–880
0.02	1.10	10,000	220–260	—	—
0.10	1.10	10,000	—	—	810–860

Note. The three columns on the right give the minimum number of individuals required for passing 10 (of 20 at the start of the bottleneck), 40 (of 50), and 60 (of 70) alleles, with a 95% probability. In some cases it is assumed that the population grows at a rate R per generation before reaching the equilibrium size N. The selective advantage of heterozygotes is s. Each value is based on 200 computer simulations.

calculations just made. We have used *mean* estimates to coalescence time, but these estimates have large variances. When the sample of genes is large, the standard deviation of the mean for nuclear genes is larger than $2N$ (Nei, 1987, eq. 13.74); for mitochondrial DNA it is larger than $N/2$. The 95% confidence interval for the number of generations to coalescence will correspondingly extend at the upper end to more than $2N$ (53,600) generations for mitochondrial DNA.

Thus the mitochondrial DNA sequence data are consistent with a mean effective population size between somewhat less than 10,000 and more than 50,000 individuals throughout the Pleistocene. This population size is, in turn, consistent with the estimate based on the *HLA–DQB1* polymorphism of a long-term mean population size on the order of 100,000 individuals for human ancestors over the last 30–40 Myr. The mitochondrial DNA data are also consistent with the result that no bottleneck smaller than several thousand individuals could have happened in hominid history.

Dorit *et al.* (1995) have provided evidence favoring a recent replacement of human populations. They have sequenced a 729-bp intron located between the third and fourth exons of the Y-chromosome *ZFY* gene, thought to be involved in the maturation of testes or sperm. No sequence variation was observed in a sample of 38 men of diverse geographic origins, representing all the world continents. Comparison with the homologous region of the great apes yields a rate of substitution of 1.35×10^{-9} per site per year. Assuming that substitutions in the intron are neutral, coalescence theory yields 270,000 years as the expected date for the last common ancestor of modern humans, with 95% confidence limits from 0 to 800,000 years (Dorit *et al.*, 1995).

The Y chromosome is haploid and paternally inherited. The expected mean coalescence is $2N_m$, where N_m is the number of males. If the human generation is 20 years, the expected coalescence yields an effective population size of 6750 fathers, or 13,500 humans, with a 95% confidence upper limit of $N = 40{,}000$ individuals. If we take into account the standard deviation of the mean coalescence, the 95% upper limit for N would increase to 80,000 individuals.

The Y-chromosome results do not provide information about the geographic origin of the ancestral *ZFY* intron. It would be possible, for example, that the intron might derive from an Australasian ancestor, even if the mtDNA would have been inherited from an African woman. Nor is there any reason to assume that the ancestral *ZFY* intron and mtDNA would have lived in the same generation; rather, they might be separated by tens of thousands of years. It would, of course, be more parsimonious to assume a single ancestral population for both the coalescent *ZFY* intron and the mtDNA, but parsimony has little if any value in this context.

Evidence favoring African ancestry derives, however, from the analysis of 30 microsatellite autosomal polymorphisms (Goldstein *et al.*, 1995). The phylogeny derived from average genetic distances separates ancestral African from derived non-African populations. Using a directly measured average mutation rate for

microsatellite loci, the deepest split in the phylogeny is dated about 156,000 years ago, which thus estimates the time when modern humans spread from Africa throughout the world.

The method of Goldstein *et al.* (1995) compares multi-locus genetic distances between populations, but it does not determine the coalescence of individual genes. Therefore, no estimates of population size can be inferred on that basis alone. A significant advantage of the method is precisely that the conclusions are valid for human populations, rather than just for individual genes. However, there seems to be no reason to exclude the possibility that different genes may have different populational origins. The average distances would then reflect the relative genomic contribution of various ancestral populations. The results would thus be compatible with a model, such as proposed by Clark and others (Clark, 1992, 1994; Clark and Lindly, 1989), in which a modern African replacement was concomitant with some regional continuity. An argument in favor of this conclusion might be constructed from the troublesome observation that the average distances between African and non-African populations obtained by Goldstein *et al.* (1995) range from 0.21 for the *FES* locus to 58.77 for the *D13S122* locus.

We conclude that the present weight of the molecular evidence favors a recent African origin for modern humans and consequently that ethnic human differentiation has largely, and perhaps exclusively, originated within the last 50,000 to 200,000 years. A more definite conclusion will require the investigation of additional, preferably autosomal, gene polymorphisms. There is, however, no evidence supporting the claim that extreme bottlenecks of just a few individuals, such as postulated by some speciation models (Mayr, 1963; Carson, 1968, 1986), have occurred in association with hominid speciation events, or with major morphological changes, at any time over that last several million years.

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