Deleterious mutations and the evolution of sexual reproduction

Alexey S. Kondrashov

Research Computer Center, Pushchino, Moscow Region 142292, USSR

The origin and maintenance of sexual reproduction continues to be an important problem in evolutionary biology. If the deleterious mutation rate per genome per generation is greater than 1, then the greater efficiency of selection against these mutations in sexual populations may be responsible for the evolution of sex and related phenomena. In modern human populations detrimental mutations with small individual effects are probably accumulating faster than they are being eliminated by selection.

SEXUAL reproduction—the alternation of meiosis and syngamy with attendant segregation and recombination—is one of nature’s wonders (Fig. 1). Individuals who generally compete for existence cooperate in the key process of reproduction. With obligate asexual reproduction, as in many prokaryotes1 and in some eukaryotes, such as the dandelion Taraxacum officinale, which probably lost sex only recently, every individual has only one parent and all the genes in the genome are permanently linked together. Sexual reproduction which is predominant among eukaryotes, disrupts this linkage even when sporadic, and the gene sensu Johanssen (the unit of function) becomes equivalent to the gene sensu Mendel (the unit of heredity). It also leads to important characteristics of individuals and populations, such as frequency of genetic recombination and mode of mate choice, which are absent in asexual populations.

Although the investigation of genetic segregation and recombination, both direct results of sex, was initiated by Mendel, the evolution of these processes was neglected until the 1930s, probably because biologists were satisfied with a general explanation proposed by Weismann more than a century ago2 (see also ref. 3). By the early 1970s, it was appreciated, however, that asexual reproduction has an intrinsic twofold advantage over anisogamous sexual reproduction (the most common in higher organisms). In an asexual population of stable size, each individual produces an average of one progeny, whereas in a sexual population with a 1:1 sex ratio each female produces an average of one male and one female progeny. Hence, if a mutation appears causing females to produce two asexual female offspring, its frequency will double in each generation3–5. Furthermore, the increased complexity associated with the sexual mode of reproduction imposes additional inherent costs6,10. So what maintains sex, despite the large advantage of asexual reproduction? This has led to an explosive growth in the number of theories trying to resolve the ‘problem’ of sex6,10,11. It has been tempting to look for non-evolutionary explanations: for example, sexual reproduction could have some physiological advantage; or sex, having originated for some purpose in the past, exists now only as a vestige; or sexual reproduction, although inherently disadvantageous, is maintained as a by-product of another useful process, such as meiotic DNA repair12 or biased gene conversion13.

Several observations contradict these explanations. As a physiological means of self-propagation, asexual reproduction is quite efficient in many species from various taxa5,6,10. Sometimes individuals from the same population can reproduce both sexually and asexually (facultative sex), which could readily lead to the rapid fixation of obligate asexual reproduction. Sex must therefore be maintained by some strong factor that continues to operate. This factor must not only provide an advantage for the whole sexual population, but also operate in terms of individual intrapopulation selection5. Some processes for which sex or recombination have been claimed to be an unavoidable concomitant can function well without them, as exemplified by meiosis in Drosophila melanogaster males, which is not normally accompanied by crossing over5,10,11. With many other authors5,6,10,11, I argue that sexual reproduction must enjoy some evolutionary advantage. This means that the advantage is not caused by the process itself but by the changes it causes in progeny genotypes (as a result of recombination), which should drive the evolution of sex.

Survey of hypotheses

In 1887 Weismann proposed that sex is advantageous because it is ‘a source of individual variability furnishing material for the operation of natural selection’2. Some data suggest that sexual reproduction can actually cause enhanced fitness of at least a portion of the progeny4,15, but the mechanism of this is obscure. Any evolutionary explanation for the maintenance of sexual reproduction can probably fit into Weismann’s framework, because sex does not immediately change allele frequencies and consequently cannot directly improve the population.

Fig. 1 Life cycle with a, asexual and b, sexual reproduction. With asexual reproduction each new organism originates from mitotic cell division, which does not change the genotype. With sexual reproduction the life cycle consists of two parts. Diplophase begins with syngamy, that is, fusion of two haploid gametes, so that each cell in this phase contains two sets of genes. Haplophase begins with meiotic cell division, which involves a halving of the amount of DNA as well as genetic recombination from independent segregation of nonhomologous chromosomes and crossing over between homologous chromosomes. In some taxa, for example some plants and fungi, multicellular organisms can be produced by mitosis from either phase to give either haploid or diploid individuals. In other taxa, however, syngamy immediately follows meiosis, as in animals, or meiosis immediately follows syngamy, as in some algae, so only one phase is represented by a multicellular organism.
finite populations or to deterministic factors that would also operate in very large populations. So, four types of hypotheses about the evolution of sex have been proposed: stochastic and deterministic for both environmental and mutational.

My purpose is to consider mutational hypotheses, so I will not review the numerous and varied environmental hypotheses in detail. The advantage of sex has been attributed to increasing differences between either sibs or parents and offspring, which are advantageous under some circumstances, or to increasing the ability of the population to track various kinds of environmental fluctuations. The occurrence of favourable mutations implies environmental changes, so hypotheses that propose that the advantage of sex is a result of increasing the efficiency of directional selection, starting from single advantageous alleles or their low initial frequencies, should be classified as environmental (see refs 10 and 11 and the other chapters from the same book for reviews).

Some environmental hypotheses do not contradict our knowledge of population biology, even though conditions providing the more-than-twofold advantage of sex necessary to offset its twofold disadvantage are restrictive. But each environmental hypothesis relies on specific assumptions about environment and can hardly explain sex in all the species in which it occurs. The assumption that all sexual populations undergo fast evolutionary changes or live in environments sharply fluctuating in space and/or in time is unreasonable. Many living fossils which have changed very little in hundreds of millions of years, as well as the inhabitants of very stable and uniform deep-sea ecosystems, are obligate sexual reproducers. Some experimental data also do not support these hypotheses.

Mutation hypotheses are free from this drawback because mutability is an inherent feature of the gene and most non-neutral mutations are deleterious. Two such hypotheses have been proposed. The first of these is a stochastic hypothesis known as Muller’s ratchet (see also refs 5, 10 and 23–25). In a finite asexual population under the pressure of deleterious mutations, Muller noted that a random loss of all mutation-free individuals is irreversible, whereas with sexual reproduction these genotypes would be re-established by recombination. This mechanism, however, provides a large advantage of sex only in small populations, because with a large population the random loss of the best genotype becomes improbable. Moreover, this hypothesis can explain only the disadvantage of obligate asexual reproduction, but not the evolution into a sexual population.

Until recently, in studies of the evolution of sex and recombination it has always been presumed that, in a very large or infinite population, selection against mutations works independently of the reproduction mode. Because this is not really the case, the deterministic mutation hypothesis, with which I will now be concerned, was developed.

The ciliate protozoan *Paramaecium* can reproduce both asexually and sexually. Here two pairs are conjugating, the sexual process during which there is an exchange of genetic material between individuals. Photo: John Walsh.

The question remains as to precisely what kind of selection is facilitated by sex. There are two ways of classifying the hypotheses proposed for the evolution of sex: first, what changes (environmental or genomic) lead to selection which sex is supposed to facilitate, and second, by what mechanism (deterministic or stochastic) are the genetic consequences of sex supposed to facilitate selection. In all populations the prevalent genotypes match the environmental demands to some degree. The better the match, the better the adaptation. Sex, if it is to be advantageous, must maintain a better genotype-environment match than that under asexual reproduction. If this match is perfect in an asexual population, sex would be harmful, because it destroys perfect gene combinations and gives rise to segregation and recombination loads. The match can be impaired by either environmental changes or errors in genome copying. Hence, two types of hypotheses, environmental (ecological) and mutational (genetical), are possible.

Introduction of sexual reproduction will not necessarily improve this imperfect match in an asexual population. What sex does is to reduce correlations between the population distributions of alleles at different loci—in other words it destroys linkage disequilibria. Naturally, this randomization of population genetic structure will be advantageous only when it increases the frequency of genotypes with many useful alleles. If some alleles are advantageous in one genetic background and deleterious in another, recombination will be harmful because it destroys coadapted gene combinations. In other words, under conditions where sex would have an advantage, in an asexual population favourable alleles should be distributed more uniformly than at random, leading to lack of both ‘very good’ and ‘very bad’ genotypes compared with linkage equilibrium. In this case sex may be favourable both at population and individual levels, as ‘very good’ genotypes that are sexual in origin reproduce more readily, leading to the spread of sex.

Existing hypotheses attribute the suggested lack of favourable genotypes in asexual populations either to stochastic events in

![Fig. 2](image-url) Various types of selection against mutations: a, exponential selection (no fitness interactions between mutations); b and c, positive interaction, that is, each additional mutation leads to a larger decrease in relative fitness; d, negative interaction.
Deterministic mutation hypothesis

Kimura and Maruyama have shown that in a sexual population the mutation load depends on the mode of selection and may be much smaller than in an asexual population, where the proportion of individuals that do not reproduce as a result of selection against mutations (\(L_u\), mutation load) is always \((1 - e^{-u})\) under mutation-selection equilibrium, where \(u\) is the deleterious mutation rate per genome per generation. They did not apply this idea to the evolution of sex, however, probably because at that time mutation rates were thought to be small, even per genome (see below).

The condition for \(L_u < L_{sex}\) is a positive epistasis under which each additional deleterious mutation leads to a larger decrease of relative fitness; in the extreme case it gives rise to truncation selection under which individuals carrying more than some specific number of mutations do not reproduce at all. Under truncation selection or something similar, \(L_{sex}\) could be small even with large \(u\), and the advantage of sex \((1 - L_{sex})/(1 - L_u)\) can be more than twofold if \(u > 1\), as \(L_{sex} > 0.5\) with such \(u\). With asexual reproduction deleterious mutations are eliminated separately according to Muller's principle, 'one mutation, one genetic death'. On the other hand, sex with truncation or similar selection obviates this principle because the genotypes that are eliminated can contain many mutations, which may give a sexual population an enormous advantage. This is the deterministic mutation hypothesis of the evolution of sex.

The underlying mechanism is very simple. We will designate the number of deleterious mutations in the genome as genome contamination, assuming for simplicity that all mutations confer the same deleterious effect. Mode of selection is a function relating fitness of the individual to its genome contamination (Fig. 2). Selection with positive epistasis decreases the variance of the population distribution of genome contamination, \(p\). In a sexual population recombination restores the variance and maintains a roughly independent distribution of alleles at different loci. This means that \(p\) is close to normal (as the limit of the Poisson), with the variance \(\sigma^2\) equal to the mean \(\sigma\). On the other hand, in an equilibrium asexual population \(p\) has a much smaller variance; in other words, an asexual population is deficient in very good and very bad genotypes. So, sex enhances the efficiency of truncation selection by maintaining a larger variance (Fig. 3).

At equilibrium the decrease of \(c\) resulting from selection is equal to its increase resulting from mutation, \(u\), and the mutation load depends mainly on \(c = u/\sigma\). I have called this quantity the genome degradation rate as it takes into account both mutation rate and the deleterious effect of the mutations. Under truncation-like selection, even with large \(c\), the fitness of many individuals may be about as high as that of mutation-free ones. In this case, with small \(c\) the mutation load is close to zero. As \(c\) increases, the mutation load also increases, approaching 1 when \(c > 2\). This is because only a small proportion of individuals have contaminations deviating by more than \(2\sigma\) from the average, and selection decreasing \(c\) by \(2\sigma\) must eliminate a large majority of the population (Fig. 3).

The situation seems paradoxical: when \(c\), and consequently \(\sigma\), increases (because \(\sigma \approx \sqrt{c}\)), the mutation load necessary to counterbalance a given mutation rate decreases. With sufficiently large \(c\), a sexual population can be at equilibrium for any given \(u\) with an arbitrarily small \(L\). Even with large \(u\), some progenies in sexual populations (in contrast to the asexual ones) receive less contaminated genomes than the genome of either parent, and under a given \(u\) the proportion of such progeny increases with the increase of \(c\), which leads to more effective selection, provided the shape of the selection curve does not depend on \(c\).

This comparison of sexual versus obligate asexual reproduction is relatively simple, as we have to consider only the overall population characteristics. When some form of sexual reproduction is established, however, evolution of features of sexual reproduction such as recombination frequency, mate choice and inbreeding avoidance becomes possible. The large hereditizable variance of crossing-over and inbreeding rates show that these characters could readily be selected. To address such evolution, as well as the problem of the origin of sex theoretically, one needs to study intrapopulational processes, considering selection at a modifier locus influencing some feature of reproduction.

These problems have given rise to much controversy. Reduction of recombination frequency leads to decrease of recombination load and of mate choice if no advantage when the population reaches the selection optimum, as fitness heritability is zero in this case, and close inbreeding may be advantageous as it reduces the cost of meiosis. Besides, crossing over may decrease the fitness of an individual in which it occurs. Hence, although it has been possible to demonstrate potential advantages of these processes, the problem remains. Nevertheless, crossing over exists in all sexual species, although sometimes only in one sex; mate choice is also quite frequent, and there are various mechanisms for avoiding inbreeding. In some cases an increase in progeny fitness resulting from mate choice has been demonstrated.

Theoretical investigations show that the deterministic mutation hypothesis can be applied to these problems. Crossing over, mate choice and inbreeding avoidance (outcrossing) and genetic transformation might be advantageous if the mutation load is at the mutation-selection equilibrium with positive epistasis.

Evolution of obligate versus facultative sexual reproduction needs a similar approach. In this case selection favouring obligate sex is much weaker and appears under more restrictive conditions than in the comparison of obligate sexual versus asexual reproduction: the gene pools of the sexual and asexual subpopulations are not completely separated, so the advantage of sex cannot accumulate in successive generations. The deterministic mutation hypothesis can, however, explain the existence of various forms of facultative sexual reproduction, cyclical included.

In the evolution of most of these phenomena, \(v\) is decisive. With \(v < 0.5\), selection against mutation does not influence the
evolution of features of reproduction within a sexual population. With $v > 0.5$, a modifier allele increasing mate choice or crossing-over rate enjoys a considerable advantage. I have probably underestimated this advantage for crossing over in the multichromosome genome. Note that selection does not favour the increase of the crossing-over frequency beyond 1-2 per chromosome, which is in good accord with the fact that the chromosomes of most species studied have genetic maps of relatively constant length, no longer than 200–300 centimorgans, although the amount of the DNA per chromosome varies by several orders of magnitude.

Avoiding inbreeding completely may be advantageous only when deleterious mutations are recessive to some degree. The whole picture may be rather complex: under the same conditions, for example, both obligate outcrossing and a high rate of self-fertilization may be stable. The increase of the outcrossing rate and the chiasmatas number per chromosome in species that live longer can easily be attributed to the possible increase of $u$ and $v$ in these species.

Obligate sex becomes established instead of facultative sex if $v > 1.25$, when the twofold cost of sexual reproduction is considered. A similar approach could be applied to the evolution of gender, or mate types, as mating between two gametes produced by the same haploid individual is genetically equivalent to apomixis. Probably the more stringent conditions necessary for the evolution of obligate sexual reproduction and obligate outcrossing, compared with those leading to the evolution of crossing over, are responsible for the observation that facultative asexual reproduction and inbreeding are very common, but there are no known sexual species without crossing over. Because with $v > 2$ the mutation load becomes intolerable, we can conclude that $0.5 < v < 2.0$ in all sexual populations provided, of course, that selection against mutations really is a leading factor in the evolution of reproduction, both at the inter- and intrapopulation level. The next three sections consider the evolution of mutability and data on $u$ and $v$, respectively, which are of primary importance to the hypothesis.

The evolution of mutability

If we assume that most non-neutral mutations are deleterious, selection will favour the unlimited decrease of mutation rate. Quantitative considerations show that in sexual populations this selection is stronger than in sexual ones, because in the absence of recombination a modifier allele that increases mutation rate will always stay with a contaminated background. The strength of selection for reduction of mutation rate in a sexual population depends mainly on $v$, being small when $v < 0.5$ and growing rapidly as $v$ increases.

What prevents zero mutability being established? If we do not consider rare favourable mutations, the only factor remaining is the physiological cost of high fidelity in the handling of DNA, which would lead to decrease in the fitness of individuals producing less contaminated progeny. If such a cost really exists and is high enough, a large mutation rate is to be expected. The two main sources of mutations are mistakes in DNA repair and in replication. It has become evident that the maintenance of the integrity of DNA molecules in the cell is very complicated. Long DNA molecules are very unstable even in the absence of such ‘unnatural’ agents as radiation and chemical mutagens. According to Vilenchik, in a mammalian cell under physiological conditions... each hour approximately 2,500 purine and 120 pyrimidine bases are detached, about 2,000 one-strand breaks occur, many cytosines are deaminated and at least 100 guanines are methylated. Other authors suggest similar figures, and other kinds of DNA damage are also possible. To prevent mutation, all this damage must be correctly repaired at some cost.

The fidelity of DNA replication also requires many complicated mechanisms because a simple conformational correspondence between bases forming Watson-Crick pairs cannot provide good selectivity. In Escherichia coli, DNA-polimerase detaches a large proportion even of correctly attached nucleotides in the process of proof reading, one of the mechanisms for increasing fidelity. This and other mechanisms, including those acting immediately after replication, involve costs in both excessive energy requirements and time delay. With fixed accuracies of the separate stages (limited by chemical factors), the attempt to achieve the zero error frequency through higher activity of controlling processes leads to the infinite growth of the cost. So, the correct question is not ‘why mutations occur’ but ‘what mechanisms reduce the rate and at what cost’.

A population of D. melanogaster exposed to mutagenic conditions (radiation) for many generations has a decreased rate of spontaneous mutation without radiation. This indicates that the natural mutation rate exceeds the lowest possible value and it could be decreased further under intensified selection for its reduction. I suggest that the high cost of fidelity precludes this decrease in nature. So, although there are no quantitative data for the cost of fidelity in terms of individual fitness, the idea that it precludes the genome degradation rate becoming less than about 0.5 seems reasonable.

Data on mutation rates

Classic methods that took into account only mutations with drastic phenotype and/or fitness effects suggested that mutations are very rare events. Traditional figures for mutability per loci are about $10^{-8}$–$10^{-7}$. The overall numbers of functional units (loci) are about $10^4$ in the Drosophila genome and perhaps $10^5$ in Homo. Hence, this implies low (< 1) mutation rates even for the whole genome of mammals. Mutations with only small effects are, however, much more frequent, as only a minority of possible genotype alterations leads to a qualitative change of function. To study such mutations one must observe changes at the molecular level, namely in protein or (preferably) DNA sequences. The necessary methodology of protein electrophoresis and DNA hybridization or (later) sequencing became available in the late 1960s. Alternatively, it is possible to count mutations by their effects on fitness if the method allows the detection of small changes. Two approaches to mutation rate measuring are possible, the direct comparison of parental and progeny genotypes and the indirect estimation from data on population parameters (variability) at a fixed time. The direct approach yields two sets of data:

- **Short-term mutation accumulation.** Observations may last one generation (parent-offspring genotype comparison) or several. As in this case the mutation rate per locus is low, an analysis of large samples is necessary. Protein electrophoresis is appropriate, but suitable methods at the DNA level are still absent. Fitness monitoring is also applicable, as it counts mutations in the whole genome.

- **Long-term measurements.** Although ancestors’ genotypes are unavailable, one can compare genotypes of different progenies of a common ancestor. In this case mutations are frequent enough to allow the use of DNA analysis methods.

In both cases it is necessary to exclude selection in the course of accumulation of mutations. As most non-neutral mutations are deleterious, selection usually leads to underestimation of mutation rates. If some DNA region is really neutral (silent, excessive, junk and so forth), it accumulates mutations at the rate of their appearance in over both short and long time scales. As most methods yield data per locus or per nucleotide, it is necessary to recall that minimal haploid genome sizes are about $3 	imes 10^6$ for algae and fungi, $10^6$ for lower invertebrates and higher plants, $3 	imes 10^8$ for echinoderms and lower vertebrates and $3 	imes 10^9$ for mammals.

Here I present a brief review of recent results. The most extensive data on human parent-offspring genotype comparisons have been obtained for the Japanese population. Three mutations altering the electrophoretic mobility of some...
blood enzymes were observed in about 500,000 locus tests. Some substitutions lead to enzyme inactivation, but many substitutions are synonymous, that is, do not cause any protein change. As electrophoresis reveals that about half of all substitutions do not cause protein inactivation, the overall substitution rate is about $2 \times 10^{-8}$ per locus or $2 \times 10^{-8}$ per nucleotide, or about 100 per diploid genome per generation. Analogous data for *D. melanogaster* revealed a similar frequency of noninactivating substitutions per nucleotide, which implies about 2 substitutions per diploid genome. In this case mutations to inactive alleles were also counted and their rate was even higher. Some other data also indicate that insertions and deletions, which normally inactivate protein when they occur in the coding region, are at least as frequent as substitutions.

Measurement of mutation rate through viability-change monitoring during several generations in *D. melanogaster* showed about one mutation lowering larval competitive ability occurred in the diploid genome in each generation, on the average. Probably the overall mutation rate is much higher because (1) neutral and nearly neutral mutations were neglected; (2) deleterious mutations influencing other fitness components (for example, those active only at the imago stage and responsible for fertility, mating success and/or longevity) were not counted; and (3) competitive ability under simplified experimental conditions, where factors of selection such as starvation and cold were excluded, probably revealed mutations only in a subset of genes active at the larva stage. Data on quantitative traits other than fitness also demonstrate measurable mutation rates but it is impossible to express them in terms of genome mutation rate.

Data on long-term mutation accumulation have become abundant in recent years. Comparison of pseudogene sequences reveals mutation rates (and probably mutation rates) of about $1 \times 10^{-7}$ or even $1 \times 10^{-6}$ per nucleotide per generation in mammals. Data on DNA hybridization also show similar evolution rates. Probably the average genomic rate of evolution is lower than mutation rate (because of selection) and the rate of change of the most rapidly evolving fraction is more relevant. Evolution rate of DNA in some invertebrates is higher than that of mammals. This should be compared with the indirect mutation rate, estimated by various methods, which yield human population values of about $1 \times 10^{-8}$ per nucleotide for the noninactivating substitution rate.

These approaches give remarkably similar results and suggest that classical figures for genomic mutation rates are underestimated by several orders of magnitude. The most abundant data for mammals indicate mutation rates at about 100 per diploid genome per generation. Scarc data on invertebrates suggest about 10 mutations per genome. Unfortunately there are no comparable data for plants and fungi where patterns of reproduction are highly varied. We suggest that the deleterious mutation rate per genome is about 1 in these taxa, which allows maximal diversity of the reproduction modes.

As we are interested in the rate of deleterious mutations, the problem of what part of the genome is functional becomes the most important. Some authors, starting from high genome mutation-rate data, claim that most of the genome is functionless because a high deleterious mutation rate would otherwise lead to an excessive mutation load. As shown above, if we assume truncation selection this conclusion is not valid, so the problem remains. Unfortunately, here we have only indirect evidence.

In protein-coding regions insertions and deletions are practically always deleterious, as are about 9/10 of nonsynonymous and a smaller proportion of synonymous nucleotide substitutions. But although about half of the unique DNA (which makes up the majority of small genomes) is transcribed in some tissues, only 2-5% of it codes for proteins. Recent data reveal many functional regions in noncoding DNA, such as promoters, enhancers and other transcription regulators, and signals for splicing, replication and recombination. Both direct sequence comparison and molecular hybridization indicate that many sequences evolve more slowly than pseudogenes, which implies some selection. Other evidence also suggests that a large proportion of the genome is functioning but the data are insufficient for quantitative conclusions. For all these reasons, I believe it is unlikely that mutations at 99% of the genome are neutral, which would be necessary to make the rate of deleterious mutations in mammals acceptable from the traditional point of view. As Neel et al. wrote, "The amount of selfish DNA is steadily shrinking. The question of how our species accommodates such mutation rates is central to evolutionary thought."

As we have seen, truncation selection with large average genome contamination can solve this problem. With $u > 1$, reproduction must be sexual and selection must be truncation-like or the mutation load will be too large. Thus, if the values of $u$ are 1 are justified, they strongly support the validity of the deterministic mutation concept of evolution of sexual versus obligate asexual reproduction.

**Selection against mutations**

The problem of the evolutionary processes in sexual populations remains, however, because here $u$ and not $u$, is decisive, and $v$ can easily be small even when $u$ is large, providing that $c > u$ (see above). It is very difficult to measure $v$ directly as existing methods do not permit evaluation of the genome contamination of an individual. A reasonable approach is to measure the intensity of selection against mutations. My estimate of $0.5 < u < 2.0$ implies strong selection, as the mutation load even with $v = 0.5$ is at least $\sim 50\%$. Fitness variance should also be large in this case, as well as average selection against new mutation, which is about $1/u$ (ref. 33), although average selection against mutation existing at equilibrium may be lower as the population is enriched by mutations with slight effects.

Unfortunately, there are no data on natural populations to confirm or reject the reality of this intensity of selection, because measuring of selection in nature is very difficult. In some cases strong selection has been reported but it is difficult to separate selection against mutations from other forms of selection. In all species, each female produces an average of about 10 progeny during her reproductive life, so selection with the required intensity is possible. Data on controlled populations are hardly relevant, as experimental conditions are quite different from natural ones and it may take a long time for a new equilibrium to be established. Studying correlations between the fitnesses of relatives is a reasonable approach but the problem of measuring both fitness and the degree of relatedness in nature remains. In a human population not exercising any birth control, a high correlation has been reported between the fertility of relatives, which is consistent with strong selection.

The shape of the selection curve is also very important, because most previous results depend on the assumption that selection is similar to truncation. This type of selection is reasonable from a theoretical point of view, for example, if only the winners in pair competitions reproduce. Some data also indicate this type of selection in *Drosophila* and RNA viruses but more data are necessary.

**Applications to human genetics**

The idea is well established that all normal human beings carry a number of slightly deleterious mutations and some purifying selection is unavoidable to keep a population in equilibrium. The hypothesis presented here, if correct, leads to some new quantitative conclusions about mutation-selection balance. We have suggested that $u > 1$ and $v$ is about 1. Suppose that at some moment selection against mutations with slight effects disappears. If such conditions remain stable for a long time, the average genome contamination will be doubled after $u$-gener-