Proc. Natl. Acad. Sci. USA
Vol. 79, pp. 142–145, January 1982
Genetics

Rates of change in quantitative traits from fixation of new mutations

(population genetics/evolution/animal breeding/finite population size)

WILLIAM G. HILL

Institute of Animal Genetics, West Mains Road, Edinburgh EH9 3JN, Scotland

Communicated by Alan Robertson, September 1, 1981

ABSTRACT **Expressions are derived for the response to directional selection for a quantitative trait that comes from fixation of new mutations in a finite population. For additive genes with a distribution of mutant gene effects symmetric about zero, the response from fixing mutations occurring in a single generation is $2Ni\sigma_M^2/\sigma$, in which N is the effective population size, i is the selection intensity, σ is the phenotypic standard deviation, and σ_M^2 is the increment in variance in the generation immediately after occurrence of the mutations. This response is $2N$ times that immediately after occurrence of the mutations. With continuous mutation each generation, the asymptotic rate of response is also $2Ni\sigma_M^2/\sigma$ and the asymptotic variance is independent of i. For completely dominant mutations with symmetric effects, the rates are $Ni\sigma_M^2/\sigma$; and for recessive mutations the rates are proportional to $(Ni)^{1/2}$. If the distribution of mutant gene effects, a, is not symmetric about zero, responses depend on the mean square of effects of mutations with positive effect, rather than on the variance of their effects. Rates of change in fitness and of traits correlated with fitness are also analyzed. It is argued that new mutations have contributed substantially to long-term responses in many laboratory selection experiments.**

Theory for predicting rates of response and limits to selection of quantitative traits deals with the utilization of existing variation in the population rather than with the possible role of new mutations that occur while selection is proceeding (1, 2). In artificial selection programs the time scale is usually considered too short for mutations to influence the rates or limits substantially, but this view has been questioned (3). There have been continued responses over periods of 50 or more generations in some selection experiments (4–6); genes of visible phenotype and large effect have been detected in several selection lines but not in the base population (3) and, if recessive, have been detected later than would be expected if initially segregating (7); the "bobbed" phenotype, with reduced copy number at the rRNA tandon, has been found in selected *Drosophila* populations (8); and long-term selection from highly inbred populations has, in some cases, led to responses in *Drosophila* bristle number (9).

On an evolutionary time scale new variation from mutation is obviously utilized by natural selection, but there is little theory to indicate the rates of change possible and how they might be related to observations. Most theoretical studies of evolutionary rates have focused on gene or base substitution rates and the role of neutral mutations (10) rather than on the consequent changes in fitness or mean performance of other traits. The role of mutations in maintaining quantitative variation with stabilizing, but not directional, selection has been analyzed, however (11, 12).

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U. S. C. §1734 solely to indicate this fact.

An attempt is made here to develop a theory for predicting selection responses from directional selection due to fixing new mutations in finite populations, which extends Robertson's (2) theory of selection limits from existing variation. The analysis is in terms of simple point mutations, but other sources of new variability are also covered by this analysis—e.g., insertion elements and duplication or deletion of a single copy of a gene; but changes in number of multiple-repeat copies of a gene require extensions of Ohta's theories (13).

ANALYSIS

Let us assume that a population has constant size and breeding structure, in which T individuals are scored each generation and N is the effective population size. Mutations affecting some quantitative trait under selection are assumed to be unlinked and to show no epistasis for the trait.

Consider some locus currently fixed for allele A, which can mutate to allele A'. The relative genotypic values for the trait and consequent fitnesses, expressed in two equivalent ways, are as follows:

Genotype		AA	AA'	$A'A'$
Genotypic value		0	ha	a
Fitness		1	$1 + hs$	$1 + s$
		1	$1 + hia/\sigma$	$1 + ia/\sigma$.

The selective value is $s = ia/\sigma$, in which i is the selection intensity (standardized selection differential) and σ is the phenotypic standard deviation of the trait under directional selection (1). This linear relationship between s and a depends on ia/σ not being too large, say less than 0.5. Heterozygote superiority or inferiority (i.e. $h > 1$ or $h < 0$) is ignored.

The mutation rate per chromosome from A to A' is μ, and the total number of mutants per chromosome set is $\lambda = \Sigma_L \mu$, in which L denotes summation over all possible mutants at all loci. The frequency of A' is q; its initial frequency, if it appears, is $1/2T$.

The mutation rates at any locus are assumed to be sufficiently small that simultaneous segregation of more than two alleles at a locus can be ignored. For selectively neutral genes, which require $4N$ generations for fixation, this implies $4N\mu < 1$, but advantageous genes are fixed more rapidly and larger mutation rates can be incorporated.

The initial increase in variance in the population from one mutation to A' is $2a^2h^2q(1 - q) \doteq a^2h^2/T$, so the expected initial increase in variance is $2T\mu \times a^2h^2/T = 2\mu h^2a^2$. From all loci, the increase in variance per generation (σ_M^2) is expected to be

$$\sigma_M^2 = 2\sum_L \mu a^2 h^2$$

$$= 2\lambda \int_{-\infty}^{\infty}\int_0^1 a^2h^2 f(a,h)dh\,da = 2\lambda E(a^2h^2), \quad [1]$$

in which $f(a,h)$ is the joint density function of effect and dominance of mutant genes—i.e., the relative frequency of mutants of specified effect and degree of dominance—and is assumed to remain constant over time. Many mutations may be neutral with respect to the trait—e.g., third-base substitutions. The density $f(a,h)$ may thus have a spike at $a \approx 0$; alternatively, such mutations can be ignored, and λ can be defined as the expected number of those having any effect on the trait. As noted previously (12, 14), σ_M^2 does not depend on the population size. The expected response to selection in the generation immediately after the mutation is $i\sigma_M^2/\sigma$ because all variance is initially additive. Subsequent responses depend on the effects and on changes in gene frequency and the total selection advance from these mutants on their probability of fixation.

The probability that a mutant gene with initial frequency $1/2T$ is ultimately fixed in the population is, from Kimura's formula (15),

$$u(s,h) = \frac{\int_0^{1/2T} e^{-2Nsx(2h\,-\,2hx\,+\,x)}dx}{\int_0^1 e^{-2Nsx(2h\,-\,2hx\,+\,x)}dx}. \quad [2]$$

If this gene is fixed there is an increment in mean performance of the metric trait of a units, so the expected advance from a single mutant is $au(s,h) = au(ia/\sigma,h)$, providing sufficient time is allowed for its fixation. The total selection advance R, from new mutations at all loci in any generation that are ultimately fixed, is

$$R = 2T\sum_L \mu au(ia/\sigma,h)$$

$$= 2T\lambda \int_{-\infty}^{\infty}\int_0^1 au(ia/\sigma,h)f(a,h)dh\,da\,. \quad [3]$$

Assuming mutations appear at the same rate continuously, Eq. 3 is also the asymptotic rate of response per generation. Although Eqs. 2 and 3 can be integrated numerically for any set of assumptions, insight into the formulas can be obtained only by considering special cases. Most attention will be given to additive genes.

Additive Genes ($h = \frac{1}{2}$). If all genes are additive Eq. 1 reduces to $\sigma_M^2 = \frac{1}{2}\lambda E(a^2)$ and Eq. 2 to

$$u(s, \tfrac{1}{2}) = (1 - e^{-Ns/T})/(1 - e^{-2Ns}) \quad [4]$$

(ref. 15). The fixation probability in Eq. 4 can be approximated as follows:

$$\begin{aligned} Ns > 1 \quad &: u \doteq Ns/T \\ |Ns| \le 1 \quad &: u \doteq 1/2T + Ns/2T \\ Ns < -1 \,&: u \doteq 0. \end{aligned} \quad [5]$$

The approximation for large Ns is given by Kimura (15) and requires that $Ns/T < \frac{1}{2}$; that for small Ns derives from Robertson's (2) expression, $u(q) = q + Nsq(1 - q)$. Eqs. 4 and 5 are compared in Fig. 1 with $Tu(s,\frac{1}{2})$ plotted against Ns, assuming N to be very large; only for $|Ns|$ near 1 is much error involved. Also in Fig. 1 values of $Tu(s,\frac{1}{2})$ are shown computed for a smaller value of N, using a Wright–Fisher haploid model (ref. 16, p. 16) with $2N = 50$. Eqs. 4 and 5 based on a diffusion model give a good fit until s values become large.

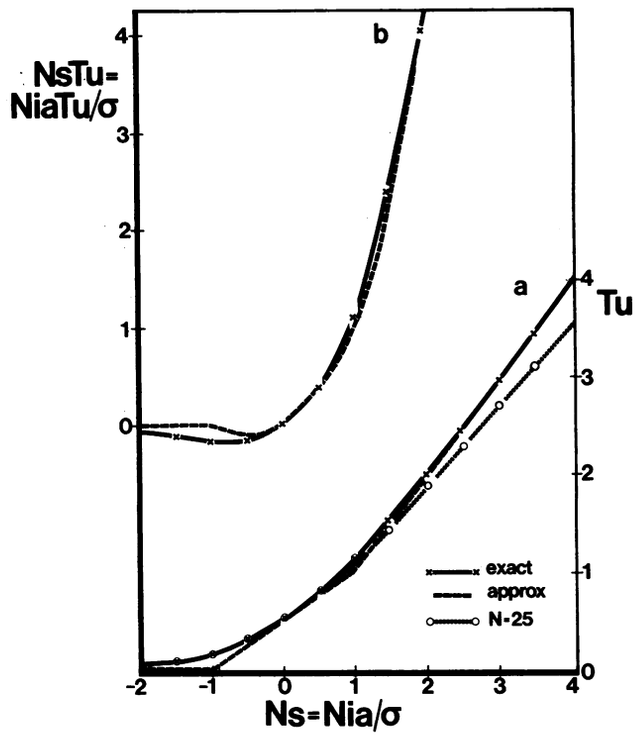

FIG. 1. Curves a, relationship between fixation probability, expressed as Tu, and gene effect or selective value, expressed as $Ns = Nia/\sigma$ for additive mutations computed by using the exact formula 4 and approximation 5 for large N values, and by matrix iteration for $N = 25$, assuming an initial frequency of $1/2N$. For large N and Ns, $Tu = Ns$. Curves b, relationship between expected response, expressed as $NsTu = NiaTu/\sigma$ and gene effect, expressed as $Ns = Nia/\sigma$, using formulas 4 and 5 with 6. For large N and Ns, $NsTu = (Ns)^2$.

The expected selection advance, $r = au(ia/\sigma, \frac{1}{2}) = au(s, \frac{1}{2})$, for a gene with effect a, using the approximation of Eq. 5, is as follows:

$$\begin{aligned} Nia/\sigma > 1 \quad &: r \doteq (Ni/T\sigma)a^2 \\ |Nia| \le 1 \quad &: r \doteq \tfrac{1}{2}(Ni/T\sigma)a^2 + a/2T \\ Nia\sigma < -1 \,&: r \doteq 0. \end{aligned} \quad [6]$$

The relationship between the expected advance and the gene effect is also shown in Fig. 1, in which $(NTi/\sigma)r$ is plotted against $Nia/\sigma = Ns$, with fixation probabilities computed by using Eqs. 4 and 5. The approximation is again seen to be generally satisfactory. Fig. 1 illustrates the quadratic relationship between the gene effect and its contribution to selection advance because for mutant genes with $a > 0$ both the fixation probability and the response, if fixed, are proportional to a.

Integrating over loci in Eq. 3 by using the approximations of Eq. 5, and writing the density function for additive genes, $f(a,\frac{1}{2})$, as $f(a)$,

$$R = (2N\lambda i/\sigma)\left\{\int_{\sigma/Ni}^{\infty} a^2 f(a)da + \tfrac{1}{2}\int_{-\sigma/Ni}^{\sigma/Ni} a^2 f(a)da\right\} + \lambda\int_{-\sigma/Ni}^{\sigma/Ni} af(a)da. \quad [7]$$

Several special cases lead to simpler results.

(i) *Mutant effects distributed symmetrically about zero.* If $E(a) = 0$ and $\mathrm{Var}(a) = \sigma_a^2$, from Eq. 1, $\sigma_M^2 = \frac{1}{2}\lambda\sigma_a^2$ and Eq.

7 simplifies to

$$R = N\lambda i\sigma_a^2/\sigma = 2Ni\sigma_M^2/\sigma. \quad [8]$$

This value of R is $2N$ times the response in the first generation after the mutations appear. Robertson (2) showed that the ratio of the limit to the initial response was $2N$ for additive genes already segregating in the population, providing they had small values of Ns—i.e., $|a| \leq \sigma/Ni$, approximately. Eq. 8, however, applies for any value of Ns because, as shown by Eq. 5, for all $|a| \leq \sigma/Ni$, the coefficient of a in the fixation probability is $Ni/2T\sigma$, and this is the average of the values, $Ni/T\sigma$ and 0, for $a > \sigma/Ni$ and $a < -\sigma/Ni$, respectively.

Eq. 8 also shows that the additive genetic variance in the population with continued mutation reaches $2N\sigma_M^2$, because the response equals $(i/\sigma) \times$ the additive variance. This value of $2N\sigma_M^2$ would also be that achieved if no selection were practiced and a balance were reached between new variance deriving from mutation and that lost by drift (14). The somewhat surprising result is that, for this model of a symmetric distribution of effects of additive genes, the equilibrium variance in the population depends only on the effective population size and not on the selection intensity. The model here is quite different from that of Lande (12), who considers stabilizing selection in a population of infinite size.

(ii) *Divergent selection.* In some experiments selection is practiced in opposite directions in two lines. If these are maintained with the same size and selection intensity, the asymptotic rate of divergence (D) between high and low lines is, from Eq. 7,

$$D = (2N\lambda i/\sigma)\int_{-\infty}^{\infty} a^2 f(a)da = (4Ni/\sigma)\sigma_M^2 \quad [9]$$

for any distribution, $f(a)$, in which σ_M^2 is given by Eq. 1 with $h = \frac{1}{2}$. The rate of divergence reaches $2N$ times the initial rate, regardless of the mean effect of mutant alleles.

(iii) $Ni\sigma_a/\sigma$ (*i.e.*, Ns) *large.* In this case the terms involving small selective values, $s \leq |\sigma/Ni|$, can be ignored in Eq. 7, which reduces to

$$R = (2N\lambda i/\sigma)\int_0^{\infty} a^2 f(a)da = (2N\lambda i/\sigma)E^+(a^2)$$

$$= \{4Ni\sigma_M^2/\sigma\}\{E^+(a^2)/\sigma_a^2\}, \quad [10]$$

in which $E^+(a^2)$ denotes the mean square of effects of mutants having positive effect. For example, if effects are normally distributed with mean μ_a, $E^+(a^2) = p(\sigma_a^2 + \mu_a^2) - z\sigma_a\mu_a$, in which $p = \Pr(a > 0)$ and z is the ordinate of the standardized normal corresponding to p. For:

μ_a/σ_a	$= -1.00$	-0.75	-0.5	-0.25	0.00	0.25
$E^+(a^2)/\sigma_a^2 =$	0.075	0.128	0.210	0.329	0.500	$0.733.$

This shows how substantially the rate depends on the mean effect of the mutants. Other distributions could be considered: Kimura (17), for example, assumed that mutants were all unfavorable for fitness with selective disadvantage $(-s)$ having a gamma distribution, such that fitness or a similarly distributed metric trait would gradually decline; incorporation of some mutants with selective advantage would require specification of four parameters in all.

(iv) $i\sigma_a/\sigma$ *large.* Eq. 5 no longer holds adequately, as seen in Fig. 1, if sN/T exceeds 0.5 or so. A better approximation to the fixation probability is, by expansion of Eq. 4, $\mu = (Ns/T)(1 - \frac{1}{2}Ns/T)$ and Eq. 10 can be extended to give

$$R = (2N\lambda i/\sigma)\{E^+(a^2) - \tfrac{1}{2}(Ni/T\sigma)E^+(a^3)\}. \quad [11]$$

Assuming, for example, normally distributed effects with zero mean,

$$R = (N\lambda i/\sigma)\sigma_a^2\{1 - (2/\pi)^{1/2}(Ni\sigma_a/T\sigma)\}$$

$$= (2Ni\sigma_M^2/\sigma)\{1 - 0.8(Ni\sigma_a/T\sigma)\}.$$

If $N = T/5$ and $i = 1.4$, then $0.8Ni\sigma_a/T\sigma = 0.22\sigma_a/\sigma$, requiring mutant genes to have standard deviation of effect nearly as large as the phenotypic standard deviation for the third moment correction in Eq. 11 to be important. For more leptokurtic symmetric distributions, for example with many mutants having negligible effect, the correction is relatively larger.

Nonadditive Genes ($h \neq \frac{1}{2}$). For small values of Ns, Eq. 2 reduces to

$$u(s,h) \doteq 1/2T + (Ns/3T)(1 + h) \quad [12]$$

(refs. 2, 18), the approximate bounds on Ns for validity of Eq. 12 depending on h. For large Ns the fixation probability depends greatly on whether the mutant shows an effect in the heterozygote:

$$\begin{aligned} h > 0,\ Nsh > 2\ (\text{approx}) &: u(s,h) \doteq 2Nsh/T \\ Nsh < -2\ (\text{approx}) &: u(s,h) \doteq 0 \\ h = 0,\ Ns > 1\ (\text{approx}) &: u(s,0) \doteq (2Ns/\pi)^{1/2}/T \\ Ns < -1\ (\text{approx}) &: u(s,0) \doteq 0\,. \end{aligned} \quad [13]$$

Complete dominance (h = 1). Summarizing parts of Eqs. 12 and 13:

$$\begin{aligned} Ns > \tfrac{3}{8} &: u(s,1) \doteq 2Ns/T \\ -\tfrac{3}{4} \leq Ns \leq \tfrac{3}{8} &: u(s,1) \doteq 1/2T + 2Ns/3T \\ Ns < -\tfrac{3}{4} &: u(s,1) \doteq 0. \end{aligned} \quad [14]$$

Therefore, if $Ni\sigma_a/\sigma$ is sufficiently large that most variance due to genes of positive effect is contributed by dominant genes having $Ns > 3/8$, from Eq. 3,

$$R = (4N\lambda i/\sigma)E^+(a^2). \quad [15]$$

For a symmetric distribution around zero of mutant effects, from Eq. 1, $\sigma_M^2 = 2\lambda\sigma_a^2$ and from Eq. 15, $R = 2N\lambda i\sigma_a^2/\sigma = Ni\sigma_M^2/\sigma$; this asymptotic rate is half that applying for additive genes. If $Ni\sigma_a/\sigma$ is small and gene effects are symmetrically distributed, from Eq. 14, $R = \frac{2}{3}Ni\sigma_M^2/\sigma$. The limiting additive genetic variance for complete dominance is therefore close to $N\sigma_M^2$ for any selection intensity.

Complete recessivity (h = 0). If $Ni\sigma_a/\sigma$ is small and gene effects are symmetrically distributed, from Eq. 12, $R = \frac{2}{3}3N\lambda i\sigma_a^2/\sigma$. If $Ni\sigma_a/\sigma$ is large, from Eq. 13,

$$R = 2(2Ni/\pi\sigma)^{1/2}\lambda E^+(a^{3/2})\,. \quad [16]$$

These responses cannot be related to the initial variance, because $\sigma_M^2 = 0$ in the absence of homozygotes. Although recessive mutations have a very low fixation probability, when they are fixed the response is very large relative to the variance and response in the first few generations immediately after the mutation. The limiting additive genetic variance is proportional to $(N/i)^{1/2}$ (from Eq. 16).

The response from recessive mutants (unless $Ni\sigma_a/\sigma$ is small) is proportional to $(N/i)^{1/2}$, rather than proportional to Ni for additive or dominant genes. With the possibility of reverse mutations the degree of dominance must vary from one mutant to another; but the contribution of recessives can mostly be dis-

counted because they are rarely fixed, so, assuming a range of dominance deviations (h) around the additive value of $h = \frac{1}{2}$, the asymptotic response seems unlikely to differ far from the values for additive genes of $R = 2Ni\sigma_M^2/\sigma$, if effects are symmetrically distributed or, more generally, $R = \{4Ni\sigma_M^2/\sigma\}\{E^+(a^2)/\sigma_a^2\}$.

DISCUSSION

Some data are available for evaluating the formulas derived. Analyses of bristle number in *Drosophila melanogaster* have shown that most genetic variation is additive (19) and that natural or induced mutants do not change the mean (14), so it seems reasonable to assume a symmetric distribution around zero of additive effects for such traits. Summarized from several analyses, the amount of new mutational variance for abdominal and sternopleural bristle number has been estimated as $\sigma_M^2 = 10^{-3}\sigma_E^2$, in which σ_E^2 is the environmental variance (12). In an isogeneic line, the phenotypic variance (σ^2) equals σ_E^2, and for abdominal bristle number, $\sigma_E = 2$, approximately. Thus $\sigma_M^2 = 4 \times 10^{-3}$ and with 20% selection, typical of *Drosophila* experiments, $i = 1.4$, giving an initial response of $\sigma_M^2/\sigma_E = 0.0028$ bristle per generation. The rate of response ultimately achieved in an isogeneic line with recurrent mutation is $2N$ times as large for a symmetric distribution of effects (from Eq. 8)—i.e., about 0.06 bristle per generation for $N = 10$ and 0.6 for $N = 100$, or $\frac{1}{40}$ and $\frac{1}{4}$ standard deviations, respectively. Yoo (6) observed an almost linear response of 0.3 bristle per generation from generations 50 to 80 of selection in a population with $\sigma_E = 2$, 20% selection, and 50 pairs of parents. Assuming $N = 70$, the predicted rate is 0.4 bristle per generation from mutations occurring after the experiment started.

Theory and observations on rates and patterns of response to selection in laboratory experiments derived from isogeneic lines or continued for many generations will be discussed in more detail in another paper, but an important point needs to be made here. Until mutations accumulate and reach frequencies at which their additive variance is appreciable, the rates of response in initially isogeneic lines, whether or not extra variation is induced by mutation, are expected to be small. Depending on the variance of gene effects, and thus on the magnitude of selective values, it may take 20 or so generations for responses to become noticeable and many more for rates of response due to mutations to approach values such as $2Ni\sigma_M^2/\sigma$ given here. Similarly, mutations are unlikely to contribute significantly to response in early generations of selection from segregating populations. Nevertheless, the magnitude of the figures calculated here suggests that, in populations maintained in large size, new variants eventually contribute a substantial response. The selection limits frequently observed in selection experiments (1) may thus be due to opposing natural selection or other influences, rather than to lack of useful variation unless, of course, the number of useful mutations is so restricted that all have appeared.

The formulas derived here can be extended in a straightforward way to natural rather than artificial selection, providing interactions among loci in fitness can be ignored. Fitness itself can be regarded as the quantitative trait, and in formulas for responses both the effect a and the selective value ia/σ are replaced by s. Thus rates of change in fitness are computed rather than rates of gene substitution as by Kimura (17). For example, Eq. 7 becomes

$$R_S = 2N\lambda\left\{\int_{-1/N}^{\infty} s^2 f_S(s)ds + \tfrac{1}{2}\int_{-1/N}^{1/N} s^2 f_S(s)ds\right\} + \lambda\int_{-1/N}^{1/N} s f_S(s)ds, \quad [17]$$

in which $f_S(s)$ is the density function of fitness, and if the contribution from the "effectively neutral" genes (10) with $|Ns| \leq 1$ can be ignored, Eq. 10 becomes $R_S = 2N\lambda E_S^+(s^2)$. The distribution of effects of mutants on viability and the relationship of effects to degree of dominance can be obtained from the study of Mukai *et al.* (20). The distribution is clearly not symmetric about zero, and a gamma distribution of deleterious effects (17) may be more reasonable; if, however, the distribution were symmetric, the initial rate would be $\frac{1}{2}\lambda\sigma_s^2$, corresponding to Fisher's fundamental theorem, and the asymptotic rate would be $2N$ times as large. Similarly, the correlated changes in another quantitative trait due to natural selection would be $N\lambda\mathrm{Cov}(s,a)$, in which $\mathrm{Cov}(s,a)$ is the covariance of effects and fitness, and the change in a quantitative trait from a combination of artificial and natural selection would be $N\lambda\{i\sigma_a^2/\sigma + \mathrm{Cov}(s,a)\}$.

A feature of the formulas, whatever the distribution of effects or fitness, is the proportionality of response to population size, simply because the number of mutations per generation is proportional to population size and their fixation probability is almost independent of it unless the mutations are selectively neutral. The formulas become less relevant as population size gets very large, because more than two alleles per locus segregate, the initial mutant frequencies are so low that the asymptotic rate of response takes very long to achieve and the assumption of a constant distribution of mutant effects becomes less reasonable if much progress is made. Nevertheless, in situations in which selection objectives remain constant, faster rates in breeding programs and of evolution in nature are possible in larger populations; that, as Kimura (17) remarked, this is "contrary to actual observations" on evolution indicates the changing or nondirectional mode of selective forces in nature.

Further theoretical analysis will be required to remove many of the simplifying assumptions, notably of no linkage, epistasis, or multicopy genes.

I thank Dick Frankham, Trudy Mackay, and Alan Robertson for useful comments and Maureen Edwards for computational assistance.

1. Falconer, D. S. (1981) *Introduction to Quantitative Genetics* (Longman, London), 2nd Ed.
2. Robertson, A. (1960) *Proc. R. Soc. London Ser. B.* **153**, 234–249.
3. Frankham, R. (1980) in *Selection Experiments in Laboratory and Domestic Animals*, ed. Robertson, A. (Commonw. Agric. Bur., London), pp. 56–68.
4. Dudley, J. W. (1977) in *Proceedings of the International Conference on Quantitative Genetics*, ed. Pollack, E., Kempthorne, O. & Bailey, T. B. (Iowa State Univ. Press, Ames, IA), pp. 459–473.
5. Enfield, F. D. (1980) in *Selection Experiments in Laboratory and Domestic Animals*, ed. Robertson, A. (Commonw. Agric. Bur., London), pp. 69–86.
6. Yoo, B. H. (1980) *Genet. Res.* **35**, 1–17.
7. Robertson, A. (1978) *Genet. Res.* **31**, 255–264.
8. Frankham, R., Briscoe, D. A. & Nurthen, R. K. (1978) *Nature (London)* **272**, 80–81.
9. Mather, K. & Wigan, L. G. (1942) *Proc. R. Soc. London Ser B.* **131**, 50–64.
10. Kimura, M. (1968) *Nature (London)* **217**, 624–626.
11. Latter, B. D. H. (1970) *Genetics* **66**, 165–186.
12. Lande, R. (1976) *Genet. Res.* **26**, 221–235.
13. Ohta, T. (1980) *Evolution and Variation of Multigene Families* (Springer, Berlin).
14. Clayton, G. A. & Robertson, A. (1964) *Genet. Res.* **5**, 401–422.
15. Kimura, M. (1957) *Ann. Math. Stat.* **28**, 882–901.
16. Ewens, W. J. (1979) *Mathematical Population Genetics* (Springer, Berlin).
17. Kimura, M. (1979) *Proc. Natl. Acad. Sci. USA* **76**, 3440–3444.
18. Silvela, L. (1980) *Genetics* **95**, 769–782.
19. Clayton, G. A., Morris, J. A. & Robertson, A. (1957) *J. Genet.* **55**, 131–151.
20. Mukai, T., Chigusa, S. I., Mettler, L. E. & Crow, J. F. (1972) *Genetics* **72**, 335–355.