Deleterious Mutations, Apparent Stabilizing Selection and the Maintenance of Quantitative Variation

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ABSTRACT

Apparent stabilizing selection on a quantitative trait that is not causally connected to fitness can result from the pleiotropic effects of unconditionally deleterious mutations, because as N. Barton noted, ". . . individuals with extreme values of the trait will tend to carry more deleterious alleles . . . ." We use a simple model to investigate the dependence of this apparent selection on the genomic deleterious mutation rate, U; the equilibrium distribution of K, the number of deleterious mutations per genome; and the parameters describing directional selection against deleterious mutations. Unlike previous analyses, we allow for epistatic selection against deleterious alleles. For various selection functions and realistic parameter values, the distribution of K, the distribution of breeding values for a pleiotropically affected trait, and the apparent stabilizing selection function are all nearly Gaussian. The additive genetic variance for the quantitative trait is $\bar{k}Qa^2$, where $\bar{k}$ is the average number of deleterious mutations per genome, Q is the proportion of deleterious mutations that affect the trait, and a^2 is the variance of pleiotropic effects for individual mutations that do affect the trait. In contrast, when the trait is measured in units of its additive standard deviation, the apparent fitness function is essentially independent of Q and a^2; and β, the intensity of selection, measured as the ratio of additive genetic variance to the "variance" of the fitness curve, is very close to $s = U/\bar{k}$, the selection coefficient against individual deleterious mutations at equilibrium. Therefore, this model predicts appreciable apparent stabilizing selection if s exceeds about 0.03, which is consistent with various data. However, the model also predicts that β must equal V_m/V_G, the ratio of new additive variance for the trait introduced each generation by mutation to the standing additive variance. Most, although not all, estimates of this ratio imply apparent stabilizing selection weaker than generally observed. A qualitative argument suggests that even when direct selection is responsible for most of the selection observed on a character, it may be essentially irrelevant to the maintenance of variation for the character by mutation-selection balance. Simple experiments can indicate the fraction of observed stabilizing selection attributable to the pleiotropic effects of deleterious mutations.

TWO alternative theories of mutation-selection balance have coexisted peacefully for the last 60 years. The first is the classical theory of equilibrium between mutation to unconditionally deleterious alleles and directional selection against them. HALDANE (1927) considered completely recessive mutations; WRIGHT (1929), EFROIMSON (1932) and HALDANE (1937) treated one locus with some degree of dominance. The multilocus case was studied first by KIMURA and MARUYAMA (1966) (see also CROW 1970), and its behavior and implications were elaborated by KONDRASHOV (1982, 1984, 1988) and CHARLESWORTH (1990). These models assume that fitness decreases with the number of deleterious alleles carried, and they do not relate fitness directly to selection on specific phenotypes. For realistic parameter values, only one mutation-selection equilibrium is possible, with the "wild-type" alleles in high frequency at all loci [multiple equilibria appear only when deleterious alleles are completely recessive (ALLENDORF 1979)].

The second theory, concerned with maintaining genetic variance for quantitative traits, was introduced by FISHER (1930, Ch. 5) and WRIGHT (1935) and developed by LATTER (1960) and LANDE (1975, 1980). Inspired by LANDE's (1975) observation that its parameters may be estimated from quantitative genetic experiments, this theory has enjoyed much more attention in recent years [reviewed by BULMER (1989) and BARTON and TURELLI (1989)]. In these analyses, genotypic fitnesses are determined by stabilizing selection acting *directly* on one or more polygenic traits (*i.e.*, intermediate phenotypes have the highest fitness), and new mutations are generally assumed to increase or decrease the genotypic value of each affected trait with equal probability. If the effects of new mutations at each locus tend to be large relative to the standard deviation of effects of segregating

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alleles (*i.e.*, if the "rare alleles" condition of BARTON and TURELLI (1987) holds), the direct-selection theory also predicts that most new mutations are deleterious in their average fitness effects. Thus, both theories presumably treat the fitness-decreasing mutations studied in standard Drosophila mutation-accumulation experiments (CROW and SIMMONS 1983).

However, at the individual level under direct stabilizing selection, new mutations may increase or decrease the fitness of their immediate carriers depending on whether they move the phenotype toward or away from the phenotypic optimum. As the effects of individual mutations, in units of the standard deviation of phenotypes in the population, decrease, the probability that a mutation will be beneficial to its immediate carrier approaches 50%. Moreover, the same mutation can move the phenotype either towards or away from the optimum and thus be either beneficial or deleterious, depending on the genotype at other loci. The effect of each mutation on the phenotype and fitness can also be easily reversed by frequent backward mutations or by "compensatory" mutations at other loci (MAYNARD SMITH 1989, p. 243; WAGNER and GABRIEL 1990). Multiple stable equilibria are possible, because even when only one allele can have high frequency at each locus, the identity of this allele will vary with initial conditions, because no allele has an inherent advantage (LANDE 1975; BARTON 1989). These features are inconsistent with the classical view (LEWONTIN 1974) that: 1) the vast majority of non-neutral mutations are unconditionally deleterious to their carriers, 2) reverse mutations are relatively rare, 3) there is only one stable mutation-selection equilibrium and 4) the most common allele generally confers the highest fitness, irrespective of genetic background.

The theory based on direct stabilizing selection assumes a known relationship between genotypic fitnesses and selection on specific phenotypes. A fundamental problem with these models is that under realistic genetic assumptions, the equilibrium genetic variance for one trait cannot be predicted accurately unless we know how selection acts on *all* traits connected to it via pleiotropy (see TURELLI 1985, 1988; BARTON 1990; SLATKIN and FRANK 1990). To circumvent this problem, a hybrid model, which we will call the HK model, was proposed by HILL and KEIGHTLEY (1988) and elaborated by KEIGHTLEY and HILL (1990) and BARTON (1990). This model summarizes all of the pleiotropic fitness effects of an allele affecting a specific trait in terms of a net deleterious effect on fitness. The phenotypic origin of this selection is not specified, but the model captures the conventional wisdom that essentially all mutations are pleiotropic and deleterious.

An important feature of the HK model is that it produces apparent stabilizing selection even when the trait considered is irrelevant to fitness. The mechanism is simple. If unconditionally deleterious alleles can either increase or decrease the value of a specific trait, individuals carrying more deleterious alleles will tend to have more extreme phenotypes. Therefore, "Since individuals with extreme values of the trait will tend to carry more deleterious alleles, we expect a negative correlation between fitness and deviation from the mean" (BARTON 1990). The attraction of this model is that it explains both the appearance of stabilizing selection and the maintenance of quantitative variation as consequences of the pleiotropic effects of mutations which are, in accord with the classical view, unconditionally deleterious.

Although HILL and KEIGHTLEY (1988) introduced this deleterious-allele model, the idea that stabilizing selection may be an epiphenomenon caused by pleiotropy and some other form of "real" selection was analyzed much earlier by ROBERTSON (1956; 1967a,b; 1973) (see also BARTON and TURELLI 1989). Following LERNER (1954), ROBERTSON (1956) noted that apparent stabilizing selection will result if alleles held polymorphic by overdominance make additive contributions to the trait. Under this model, more deviant individuals tend to be more homozygous and hence less fit. Such pleiotropic explanations of stabilizing selection in quantitative traits are indirectly supported by various data summarized by KEIGHTLEY and HILL (1990) and BARTON (1990) and discussed below. Recently, S. GAVRILETS and G. DE JONG (unpublished results) have developed a general framework for analyzing polygenic models with pleiotropy (see also GIMELFARB 1992). Although there are some cases in which the causal connection between trait and fitness is clearly documented [*e.g.*, bill size in Darwin's finches (PRICE *et al.* 1984; GIBBS and GRANT 1987) and wing patterns in mimetic heliconious butterflies (MALLET and BARTON 1989)], we generally do not understand the mechanisms underlying the stabilizing selection that is routinely observed for quantitative traits (ENDLER 1986). Similarly, the causes of heritable quantitative variation, which tends to decrease under stabilizing selection, remain uncertain (*cf.* LANDE 1988; TURELLI 1988; HOULE 1989; BARTON and TURELLI 1989). Given the ubiquity of deleterious mutations, it is important to determine how much variation and stabilizing selection they may explain.

KEIGHTLEY and HILL (1990) studied by Monte Carlo simulations an HK model in which the dual effects of new mutations on an unselected quantitative trait and fitness *per se* are described by a continuous bivariate distribution. They assumed additive contributions of alleles to both the trait and to fitness and assumed that all mutations are deleterious. Whenever the correlation between fitness effects and the mag-

nitude of contributions to the trait is less than one, their model allows for mutations with arbitrarily large effect on the trait but arbitrarily small effect on fitness. In this case, the model predicts that as population size increases, the additive variance of the quantitative trait increases without bound due to the accumulation of essentially neutral alleles of large phenotypic effect. In contrast, the level of apparent stabilizing selection asymptotes as population size increases. Unfortunately, the complexity of their model seems to preclude simple analytical predictions.

BARTON (1990) studied a simpler HK model as well as an overdominance model of the sort analyzed by ROBERTSON (1956). Barton's mutation-selection model assumes that all mutations have equal deleterious fitness effects that combine multiplicatively to determine the fitness of an individual. In this case, rare mutant alleles are expected to be in linkage equilibrium implying that the total number of mutations affecting a trait per diploid genome has a Poisson distribution. Its mean is $\bar{k}_T = U_T/s$, where U_T is the total deleterious mutation rate per diploid genome across all loci affecting a trait, and s is the selection coefficient against individual heterozygous deleterious alleles (*cf.* KIMURA and MARUYAMA 1966). Although all alleles are assumed to be equally deleterious, their effects on the trait follow a symmetrical distribution with variance α^2 and fourth central moment $3\kappa\alpha^4$. The equilibrium genetic variance of the trait is $\bar{k}_T\alpha^2$, and the apparent fitness function is approximately Gaussian. The intensity of apparent stabilizing selection can be measured as $\beta = V_G/V_s$, where V_G denotes the genetic variance of a trait and V_s denotes the "variance" of the fitness curve. In the simplest case, with all deleterious alleles having pleiotropic effects of equal magnitude (*i.e.*, $\kappa = 1/3$ in BARTON's notation), $V_G/V_s \cong 2U_T/(1 + 2\bar{k}_T)$ (Equation 1b).

Both KEIGHTLEY and HILL (1990) and BARTON (1990) assume particularly simple forms of selection against deleterious mutations (additive and multiplicative, respectively) and linkage equilibrium among segregating deleterious alleles. Their general conclusion is that for realistic parameter values, this mechanism is likely to produce only weak apparent stabilizing selection. BARTON (1990) came to the conclusion that, because the total mutation rate is limited by "load arguments" (CROW 1970), deleterious mutations alone cannot account for the quantitative variation and stabilizing selection observed in nature. If, however, selection against deleterious mutations involves synergistic epistasis, the genomic deleterious mutation rate U is not, in principle, limited by load arguments, and intense selection against mutations is possible (KONDRASHOV 1988). Thus, generalizing the HK model to include synergistic epistasis may permit much stronger apparent stabilizing selection.

Here we explore this possibility and study a general epistatic model of directional selection against deleterious mutations. Interestingly, the intensity of apparent stabilizing selection is essentially independent of the details of the selection scheme and can still be expressed in terms of estimable quantities as found by BARTON (1990).

MODEL

The analysis has two parts. First, the equilibrium between unconditionally deleterious mutations and directional selection against them must be found, then quantitative variation and apparent stabilizing selection can be investigated. To deal with the first problem, we use a standard approach (KIMURA and MARUYAMA 1966; KONDRASHOV 1982). A sexual population is considered, and selection operates in either the haploid or diploid phase. In the first case, "individuals" are haploid and U is the deleterious mutation rate per haploid genome; in the second, they are diploid and U is the deleterious mutation rate per diploid genome. These two cases are described by the same equations, because mutant alleles are assumed to be rare.

We will analyze the distribution of K, the total number of deleterious mutations per genome (haploid or diploid), just before selection. Two alternative life cycles can be described by similar equations: 1) selection followed by reproduction (which consists of: syngamy then meiosis, if selection acts in haploids; or meiosis then syngamy with diploid selection) and mutation, or 2) selection followed by mutation and reproduction. If we assume a Poisson mutation process, both life cycles result in identical distributions before selection. All the mutations are assumed to be equally deleterious and very rare at each locus so that no two uniting gametes carry the same deleterious allele. Therefore, assuming free recombination, a genome is completely characterized by K, the number of deleterious alleles it contains. We assume that selection acts only on K, with a non-increasing fitness function $s(k)$. BARTON (1990) considered multiplicative selection against different mutations, which results in the fitness function $s(k) = (1 - s)^k$ or, in a continuous approximation, $s(k) = e^{-sk}$, where s is the selection coefficient against each mutant allele. In contrast, we will consider selection with synergistic epistasis, so that additional deleterious alleles cause larger decreases in relative fitness. In this case, one cannot assign a constant selection coefficient to individual mutant alleles, as it depends on the population state. Our numerical examples will employ truncation selection, with $s(k) = 0$ for $k > T$, and "exponential quadratic" selection, with $s(k) = \exp\{-[\alpha k + (\beta k^2/2)]\}$ (see CHARLESWORTH 1990).

Under these assumptions, equations describing the effects of selection, mutation and reproduction on $g(k)$, the population distribution of K, are straightforward and can be found in KONDRASHOV (1982). They can be solved numerically to find the equilibrium distribution before selection, denoted $\hat{g}(k)$, which depends on U and $s(k)$. We denote the mean and standard deviation of $\hat{g}(k)$ by $\bar{k}$ and σ_K. Numerical analyses show that even when selection causes large departures of $g(k)$ from Gaussian, the equilibrium distribution after reproduction, $\hat{g}(k)$, is very close to Gaussian.

Under free recombination, σ_K^2 must lie between $\bar{k}/2$ and $\bar{k}$. To see this, note that the number of deleterious mutations can be treated as an additive quantitative trait (CHARLESWORTH 1990). At linkage equilibrium, different mutations are distributed independently in an equilibrium population, so that $\hat{g}(k)$ would be Poisson and $\sigma_K^2 = \bar{k}$. Hence from BULMER (1971), we have the following recursion for the variance before and after reproduction:

$$\sigma_{K,a}^2 = \frac{\bar{k}_b + \sigma_{K,b}^2}{2}, \tag{1}$$

where $\bar{k}_b$ and $\sigma_{K,b}^2$ denote the mean and variance of K before reproduction and $\sigma_{K,a}^2$ denotes its variance after reproduction. In contrast to exponential selection, which does not change the variance in K, synergistic epistasis (defined as $d^2[\ln(s(k))]/dk^2 < 0$) decreases the variance (E. E. SHNOL, personal communication). However, even if selection completely eliminates the genetic variance each generation, recombination would restore it to half of its linkage equilibrium value, $\bar{k} = \bar{k}_b$.

Once $\hat{g}(k)$ is found, we can consider the pleiotropic effects of these deleterious mutations on a specific quantitative trait, denoted Z. We seek the resulting distribution of phenotypes and the intensity of apparent stabilizing selection. Our model of pleiotropy is essentially BARTON's (1990). We assume that each new deleterious mutation has an independent and identically distributed additive effect, denoted X, on Z. To reflect the fact that not all mutations affect all traits, we assume that $P(X = 0) = 1 - Q$, so that Q denotes the probability that each mutation affects Z. Thus, $\bar{k}_T$, the mean number of mutations affecting the trait per genome, is $Q\bar{k}$; and U_T, the mutation rate to alleles affecting the trait, is QU. We assume that when $|X| > 0$, it has a symmetrical distribution with variance a^2. This symmetry implies that apparent selection is purely stabilizing in the sense that the mean phenotype has the highest average fitness and there is no apparent directional selection on Z.

Let us denote the conditional distribution of phenotypes among individuals with given genotype (*i.e.*, a given number of mutations, or $K = k$) by $p(z \mid K = k)$. Because selection acts only on K, the phenotypic contributions of individual mutations, denoted X_i, are indistinguishable to selection. Initially we will ignore environmental variance, so that for individuals of each genotype, the distribution of Z is determined by

$$(Z \mid K = k) = \sum_{i=1}^{k} X_i, \tag{2}$$

where the X_i are independent and identically distributed random variables with mean 0 and variance Qa^2. The distribution of phenotypes at mutation-selection equilibrium is

$$p(z) = \sum_{k=0}^{\infty} p(z \mid K = k)\hat{g}(k). \tag{3}$$

We also need $g(k \mid Z = z)$, the conditional distribution of K among individuals with phenotype z. By definition,

$$g(k \mid Z = z) = \frac{\hat{g}(k)p(z \mid K = k)}{p(z)}. \tag{4}$$

Finally, the apparent fitness function $W(z)$ can be calculated as

$$W(z) = \sum_{k=0}^{\infty} s(k)g(k \mid Z = z). \tag{5}$$

This direct method is used in our numerical analyses, but we will use an alternative approach to analytically approximate apparent selection. Because our interest centers on relative fitness, we consider $w(z) = W(z)/\bar{W}$, where $\bar{W} = \sum p(z)W(z) = \sum \hat{g}(k)s(k)$.

Apparent stabilizing selection can be quantified in several ways. Relative fitness depend on both $W(z)$ and $p(z)$; and in our model, both are symmetrical about 0 and are nearly Gaussian for realistic parameter values (see *Numerical Results*). Denoting the (additive genetic) variance of Z by σ_Z^2 and assuming that $W(z) = \exp[-z^2/(2V_s)]$, we will call $\beta = \sigma_Z^2/V_s$ the intensity of stabilizing selection. Note that as phenotypic selection gets weaker, V_s increases and β approaches zero. β can be related to four alternative measures of selection intensity:

1) mutation (genetic) load (CROW 1970),

$$L = \frac{W(0) - \bar{W}}{W(0)}; \tag{6a}$$

2) variance of relative fitness (FISHER 1930),

$$D = \sum p_Z(z)[w(z) - 1]^2; \tag{6b}$$

3) the difference between the relative fitnesses of the optimal phenotype (*i.e.*, $Z = 0$) and that of phenotypes one standard deviation away,

$$S = w(0) - w(\sigma_Z); \quad \text{and} \tag{6c}$$

4) minus the regression of relative fitness on the

squared deviation from the population mean, measured in units of phenotypic standard deviations (LANDE and ARNOLD 1983; BARTON 1990; KEIGHTLEY and HILL 1990),

$$B = \frac{\sigma_z^2 \mathrm{Cov}(w(Z), Z^2)}{\mathrm{Var}(Z^2)}. \quad (6d)$$

For Gaussian selection and phenotypic distributions as described above, these measures become

$$L = 1 - \frac{1}{\sqrt{1+\beta}}, \quad (7a)$$

$$D = (1+\beta)\left(1 - \frac{2}{\sqrt{1+\beta}} + \frac{1}{\sqrt{1+2\beta}}\right), \quad (7b)$$

$$S = [1 - \exp(-\beta/2)]\sqrt{1+\beta}, \quad (7c)$$

and

$$B = \frac{\beta}{2(1+\beta)}. \quad (7d)$$

When selection is weak, *i.e.*, $\beta \ll 1$, these simplify to

$$L \cong S \cong B \cong \beta/2 \quad \text{and} \quad D \cong 3\beta^2/4. \quad (8)$$

Given U and $s(k)$, all these distributions and indices can be found numerically (a MACFORTRAN program is available on request). However, simple analytical approximations can be obtained that provide greater insight.

ANALYTICAL RESULTS

Once $\hat{g}(k)$ is known, the phenotypic mean and variance can be found from (2). Letting E and Var denote mean and variance, we have

$$E(Z) = E[E(Z \mid K)] = 0 \quad \text{and} \quad (9a)$$

$$\mathrm{Var}(Z) = E[\mathrm{Var}(Z \mid K)] + \mathrm{Var}[E(Z \mid K)] \quad (9b)$$

$$= E[K\ \mathrm{Var}(X_i)] = \bar{k}Qa^2 \equiv \bar{k}_T a^2.$$

These results depend only on the assumption that for each k, the X_i have mean zero and are independent, which follows from our assumption that selection acts only on K.

We can approximate the mean of the conditional distributions $g(k \mid Z = z)$ as follows. From (3) and (4) we see that

$$E(K \mid Z = z) = \sum kg(k \mid Z = z) = \frac{\sum kp(z \mid K = k)\hat{g}(k)}{\sum p(z \mid K = k)\hat{g}(k)}, \quad (10)$$

which we can rewrite as

$$E(K \mid Z = z) = \frac{E[Kp(z \mid K)]}{E[p(z \mid K)]}, \quad (11)$$

where E denotes expectation with respect to the probability density $\hat{g}(k)$. We will assume that for realistic values of K, the conditional distribution of Z given K described by (2) can be approximated by a Gaussian distribution with mean 0 and variance KQa^2. With this approximation, (11) becomes

$$E(K \mid Z = z) \cong \frac{E\{\sqrt{K}\exp[-z^2/(2KQa^2)]\}}{E\{\exp[-z^2/(2KQa^2)]/\sqrt{K}\}}. \quad (12)$$

If we express trait values in units of phenotypic standard deviations, $\sigma_Z = \sqrt{kQa^2}$,

$$E(K \mid Z = y\sigma_Z) \cong \frac{E\{\sqrt{K}\exp[-\bar{k}y^2/(2K)]\}}{E\{\exp[-\bar{k}y^2/(2K)]/\sqrt{K}\}}. \quad (13)$$

We can approximate each of the expectations in (13) via the "delta method" (for any nonlinear function f, $E[f(X)] \cong f[E(X)] + f''[E(X)]\mathrm{Var}(X)/2$, whenever the higher-order terms in the expansion of f about $E(X)$ are small relative to the first three terms). Recall that σ_K^2 is proportional to $\bar{k}$. Hence if we drop terms proportional to $1/\bar{k}$ after approximating (13), we obtain

$$E(K \mid Z = y\sigma_Z) \cong \bar{k}\left[1 - \frac{\sigma_K^2}{2\bar{k}^2}(1 - y^2)\right]. \quad (14)$$

This formula, which plays a central role in determining apparent selection, has two important consequences. First, it is independent of the pleiotropy parameters Q and a^2, which are likely to be very difficult to estimate. Second, for the common phenotypes in the population, *i.e.*, $-2\sigma_Z \leq Z \leq 2\sigma_Z$, the relative differences in the mean genotypes for different phenotypes, *i.e.*, $[E(K \mid Z = y\sigma_Z) - \bar{k}]/\sigma_K$, are proportional to $\sigma_K/\bar{k}$, which will be proportional to $1/\sqrt{\bar{k}}$ and hence relatively small for reasonable values of $\bar{k}$ (e.g., $\bar{k} \geq 20$).

This same approach can be used to approximate the conditional variance of K given Z. The qualitative result is that the relative differences in the conditional variances, *i.e.*, $[\mathrm{Var}(K \mid Z = y\sigma_Z) - \sigma_K^2]/\sigma_K^2$, are proportional to $\sigma_K^2/\bar{k}^2$ and hence small. Thus, we expect

$$\mathrm{Var}(K \mid Z = y\sigma_Z) \cong \mathrm{Var}(K) = \sigma_K^2 \quad (15)$$

for common phenotypes.

We can use this information on the conditional distribution of K given Z to estimate the intensity of apparent stabilizing selection. This is simplest under assumption (15), so that the relative phenotypic fitness function $w(z)$ is determined completely by $E(K \mid Z = z)$. According to (14), the conditional distributions of genotypes given Z differ only slightly in mean. Hence, we can approximate the fitness consequences of these small differences by a simple linear approximation (*cf.* BULMER 1971; KIMURA and CROW 1978; FALCONER 1989, Ch. 11; HASTINGS 1990). The relative fitness of a group of individuals having genotype distribution

shifted upward by a small amount α from that of the whole population, $\hat{g}(k)$, is

$$w(\alpha) = \sum s(k)\hat{g}(k - \alpha)/\bar{W}. \quad (16)$$

To calculate the intensity of apparent selection, we are interested in the rate of change of relative fitness with α for small values of α. This can be approximated by evaluating the derivative of (16) with respect to α at $\alpha = 0$. Based on our numerical work, we will assume that $\hat{g}(k)$ is approximately Gaussian. Using this approximation, we find that for small α,

$$\frac{dw}{d\alpha} \cong \frac{\Delta_K}{\sigma_K^2}, \quad (17)$$

where Δ_K is the selection differential on the number of deleterious alleles, *i.e.* the difference in the mean of K after *vs.* before selection (see Equation 16a of KIMURA and CROW 1978). At mutation-selection equilibrium, $\Delta_K = -U$, so that

$$\frac{dw}{d\alpha} \cong -\frac{U}{\sigma_K^2}. \quad (18)$$

This can now be combined with (14) to describe the intensity of apparent selection. According to (14) we can express α as $\alpha(y)$, *i.e.*, $\alpha(y) = E(K \mid Z = y\sigma_Z) - \bar{k}$, the shift in the mean of K for different phenotypes, as compared with the whole population. Letting $w(y)$ denote the relative fitness of individuals that deviate from the population mean by $y\sigma_Z$,

$$\frac{dw(y)}{dy} = \frac{dw}{d\alpha}\frac{d\alpha(y)}{dy} = -\frac{U}{\sigma_K^2}\frac{y\sigma_K^2}{\bar{k}}, \quad (19)$$

where the second term follows from (14). In particular, for $Z = -\sigma_Z$ (*i.e.*, $y = -1$),

$$\frac{dw(-1)}{dy} = \frac{U}{\bar{k}}. \quad (20)$$

At mutation-selection equilibrium, the ratio $U/\bar{k} = -\Delta_K/\bar{k}$ equals s, the selection coefficient against individual deleterious mutations. This is true because under the assumption that the deleterious alleles are rare, homozygotes can be ignored and selection decreases the frequency of each deleterious allele by approximately s, the per-locus selection coefficient, times its current frequency. Thus, the decrease in the mean number of deleterious alleles per genome is $s\bar{k}$, and this must equal U at equilibrium.

Using (20), we can approximate β, the intensity of apparent stabilizing selection. If we scale the phenotype in units of phenotypic standard deviations, *i.e.*, set $Y = Z/\sigma_Z$, the Gaussian selection function $W(z) = \exp[-z^2/(2V_s)]$ is equivalent to $W(y) = \exp[-y^2\beta/2]$ where $\beta = \sigma_Z^2/V_s$ as in (7). Relative fitness is given by

$$w(y) = \sqrt{1 + \beta}\,\exp\left(-\frac{y^2\beta}{2}\right). \quad (21)$$

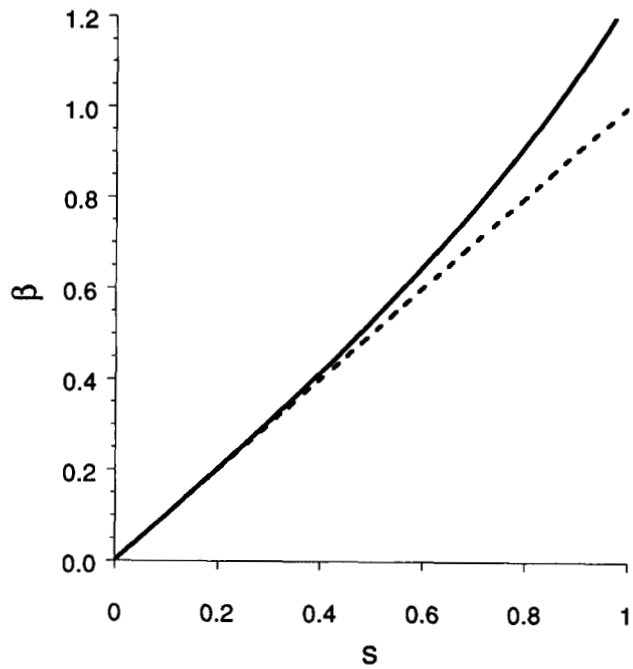

FIGURE 1.—The dependence of β on s: the dotted line $\beta = s$ is compared with the numerical solution of the equation obtained from (20) and (22).

The derivative of this relative fitness curve at $y = -1$ is

$$\frac{dw(-1)}{dy} = \beta\sqrt{1 + \beta}\,\exp\left(-\frac{\beta}{2}\right) \cong \beta - \frac{\beta^3}{4} + \frac{\beta^4}{6} + O(\beta^5), \quad (22)$$

which we can equate to s, according to (20), to determine β in terms of $s = U/\bar{k}$. The resulting equation can be solved numerically; but it is clear from Figure 1 that for any biologically reasonable s, *e.g.*, $s \leq 0.5$,

$$\beta \cong s \equiv \frac{U}{\bar{k}}, \quad (23)$$

which generalizes BARTON's (1990) result (1b) for $\bar{k} \gg 1$ to our more general selection model. In general, $w(y)$ is not Gaussian; nevertheless, our Gaussian approximation provides accurate predictions of apparent selection intensity, as shown by the numerical results below.

Environmental variance: To simplify our presentation, we have ignored environmental contributions to the quantitative trait. However, under the standard simplifying assumption that all genotypes experience identically distributed environmental perturbations with mean 0 and variance V_E, our results need only a slight reinterpretation. The "phenotypic variance," σ_Z^2, discussed above is actually the additive genetic variance for Z, which we will denote by V_G since all genetic variance is additive in our model. Similarly, the parameter V_s actually describes apparent selection

on breeding values for Z rather than phenotypes. Assuming that phenotypic selection has variance ω^2, *i.e.*, $W(P) = \exp[-P^2/(2\omega^2)]$, $V_s = \omega^2 + V_E$ (LANDE 1975). Our parameter $\beta = \sigma_Z^2/V_s \equiv V_G/V_s$ remains a sensible measure of apparent stabilizing selection. It can be easily related to heritability and the intensity of stabilizing selection on phenotypes (see KEIGHTLEY and HILL 1990) and to the index V_s/V_E discussed by TURELLI (1984).

NUMERICAL RESULTS

Our approximations are based on the assumption that the equilibrium distribution of the number of deleterious mutations per genome, $\hat{g}(k)$, is approximately Gaussian after reproduction. We have found that under truncation selection with different U and truncation points, the deviation of $\hat{g}(k)$ from Gaussian depends mainly on $\bar{k}$. With $\bar{k}$ about 20, skewness and kurtosis of $\hat{g}(k)$, measured by $\gamma_3(K) = E[(K - \bar{k})^3]/\sigma_K^3$ and $\gamma_4(K) = E[(K - \bar{k})^4]/\sigma_K^4 - 3$, are about -0.01 and 0.30; and they tend to 0 as $\bar{k}$ increases (data not presented). Genetically this means that reproduction with free recombination effectively destroys most of the higher-order disequilibria created by epistatic selection (TURELLI and BARTON 1990). Pairwise disequilibria, however, persist; because with synergistic epistasis $\sigma_K^2 < \bar{k}$ (KONDRASHOV 1984).

We are mainly interested in the distribution of Z and the apparent fitness function. To determine the accuracy of our analytical approximations, we iterated numerically the equations described in KONDRASHOV (1982) to obtain $\hat{g}(k)$. We used a simplified model of pleiotropy in which deleterious alleles have no effect on Z with probability $1 - Q$, contribute $+1$ with probability $Q/2$, or -1 with probability $Q/2$. In the notation of the previous section, this corresponds to $a^2 = 1$. For simplicity, we also assumed $V_E = 0$. Figure 2 presents results for a population with $U = 4$ under truncation selection with $T = 50$. In this case, $\bar{k} = 49.508$, $\sigma_K = 5.777$, $\gamma_3(K) = 0.015$, $\gamma_4(\mathrm{K}) = -0.020$, and mutation load $L = 0.431$. Data for the trait are calculated with $Q = 0.2$.

Like $\hat{g}(k)$, the distribution of phenotypes, $p(z)$, is very close to Gaussian with mean 0 and variance $\bar{k}Q$. (Note that even if K has a Gaussian distribution and each $(Z \mid K = k)$ is Gaussian, the population is composed of a mixture of Gaussians with different variances and so will not be Gaussian.) Figure 2a presents the phenotypic distribution ($\sigma_Z = 3.147$, $\gamma_3(\mathrm{Z}) = 0$, and $\gamma_4(Z) = 0.081$) and a Gaussian distribution with the same mean and variance. Our analytical prediction of $W(z)$ is based on approximation (14) for $E(K \mid Z = z)$ and the assumption that $\mathrm{Var}(K \mid Z = z) \cong \sigma_K^2$ for all common phenotypes. Figure 2b compares predicted and observed values of $E(K \mid Z = z)$, and Figure 2c presents computed genotypic variances for different phenotypes. We can see that the analytical approximation for $E(K \mid Z = z)$ is quite good; and for most phenotypes, the conditional variance differs from σ_K^2 by only $\pm 5\%$.

We next consider apparent stabilizing selection. With truncation and similar selection regimes, the apparent stabilizing selection function is platykurtic (*i.e.*, $\gamma_4 < 0$; under our assumptions, it is always symmetrical, so that $\gamma_3 = 0$). Figure 2d presents the numerically determined apparent fitness function and the approximating Gaussian predicted from Equations 21 and 23. It is convenient to normalize the selection function, so that it can be treated as a probability density and characterized by its moments. The computed selection function has $\sigma = 9.564$ and $\gamma_4 = -0.333$, while the Gaussian approximation has $\sigma = 11.062$. Despite this discrepancy, Figure 2d shows that in the range where the phenotypic distribution is concentrated, the agreement between predicted and observed apparent fitnesses is nearly perfect. This suggests that the "variance" of the apparent fitness function is not a very useful measure. Although it works well when all of the functions are precisely Gaussian, it seems too sensitive to what happens outside the range $\pm 3\sigma_Z$.

To illustrate this point, consider Figure 3, which presents data on calculated and estimated selection over a wide range of phenotypes, together with the phenotypic distribution. This figure assumes $U = 2$ and exponential-quadratic selection against mutations with $\alpha = 0.0$ and $\beta = 0.0012$ [*i.e.*, $s(k) = \exp(-0.0006\mathrm{k}^2)$]. At equilibrium, $\bar{k} = 42.945$, $\sigma_K = 6.427$, $\gamma_3(\mathrm{K}) = 0.144$, $\gamma_4(\mathrm{K}) = 0.019$, and $L = 0.660$. As before, we considered $Q = 0.2$. The small deviation of $\hat{g}(k)$ from Gaussian is caused largely by the discreteness of K; note that the skewness and kurtosis are near what we expect from a Poisson with the same mean, *i.e.*, $\gamma_3 = 0.153$ and $\gamma_4 = 0.023$. The phenotypic distribution has $\sigma_Z = 2.931$ and $\gamma_4(Z) = 0.114$. The predicted "standard deviation" of Gaussian selection, $\sigma = 13.577$, is smaller that the numerically computed value $\sigma = 19.156$ with $\gamma_4 = -0.004$. However, for phenotypes actually present in the population, the fitness curve is very close to the Gaussian with the analytically predicted σ. Figures 2 and 3 show that the departure from the Gaussian fitness curve is mostly outside the range of common phenotypes, *i.e.*, beyond $\pm 3\sigma_Z$. Our analytical approximation for β predicts the other indices of selection intensity much better than the value obtained from the numerically computed variance of the fitness curve (see Figure 5 below). Curiously, the main cause of the deviation of the apparent fitness curve from Gaussian seems to be the sixth moment. Letting $\gamma_6(X) = E[(X - E(X))^6]/\sigma_X^6 - 15$, $\gamma_6(X) = 0$ for a Gaussian, while our empirical distribution of apparent fitnesses gives $\gamma_6 = -1.76$, even though γ_4 is only -0.004.

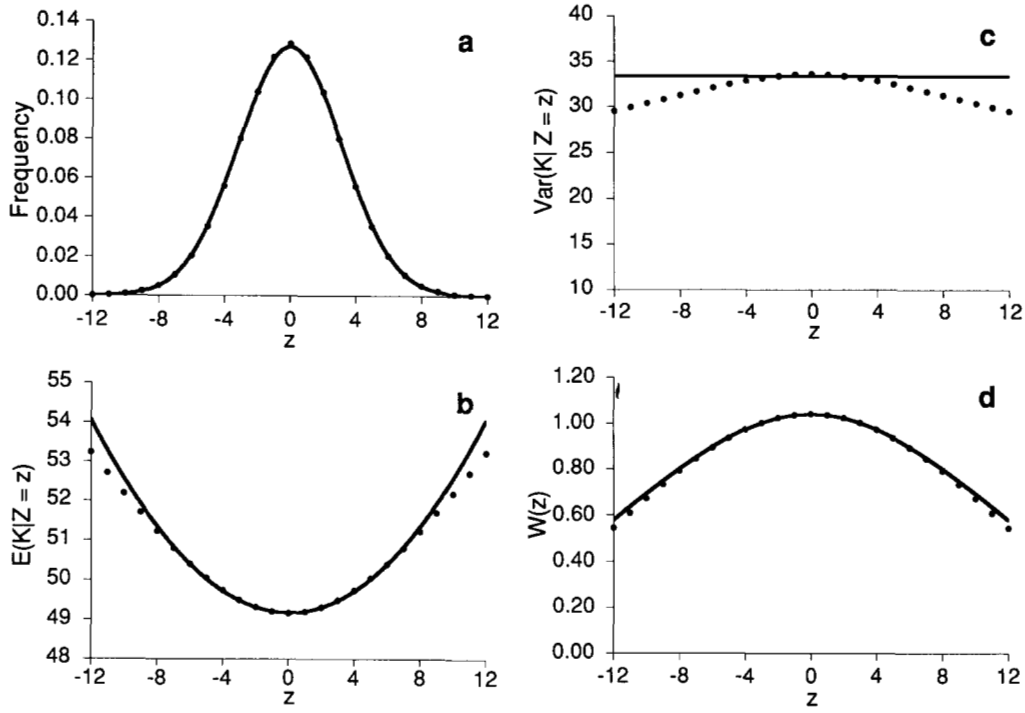

FIGURE 2.—Phenotypic distribution (a), $p(z)$; the conditional mean number of mutations for different phenotypes (b), $E(K \mid Z = z)$; the conditional variances (c), $\mathrm{Var}(K \mid Z = z)$; and apparent stabilizing selection function (d), $W(z)$, calculated numerically for truncation selection with $U = 4$, $T = 50$, $V_E = 0$, $Q = 0.2$ and $a^2 = 1$. Numerical results are dots, and analytical approximations are presented as lines (see text for additional details).

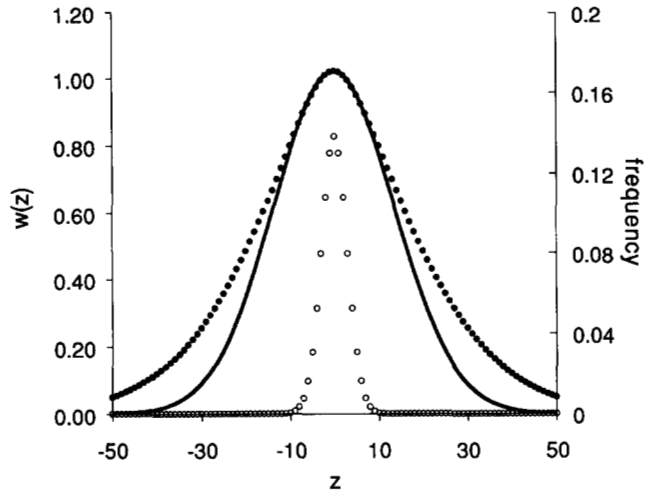

FIGURE 3.—Phenotypic distribution (open circles) and the analytically predicted (line) and numerically computed (dots) apparent fitness curves under exponential-quadratic selection (see text for details).

Our analytical approximations predict that the intensity of apparent stabilizing selection, as measured by β, does not depend on Q. Figure 4 presents phenotypic distributions and apparent fitness functions using the same model as in Figure 2 for various Q. Although the variance of the phenotypic distribution (Figure 4a) and the variance of the fitness function (Figure 4b) are proportional to Q, the fitness functions are practically identical when measured in units of phenotypic standard deviations (Figure 4c). With $Q = 1$ and strict truncation, the fitness curve is jagged (data not presented). When T is even, even phenotypes have enhanced fitness, with odd T, odd phenotypes have enhanced fitness. This artificial effect rapidly disappears with deviation from strict truncation, $V_E > 0$, and/or $Q < 1$.

Let us now consider the intensity of apparent selection. Figure 5 shows the dependence of β, the apparent genetic load (L), the fitness variance (D), and the difference between the relative fitness of the "optimal" phenotype versus those one standard deviation away (S) on $s = U/\bar{k}$. Two series of mutation-selection equilibria are considered: $U = 2$ and $U = 6$. For each, we assumed truncation selection with $T = 10, 20, \ldots, 100$. Analytical predictions for β were obtained from the numerically determined $s = U/\bar{k}$ using (20) and (22), and these values of β were substituted into (7) to obtain predictions for L, D and S. Although the predicted β deviates substantially in relative magnitude from the ratio of the empirically computed variances, the agreement between our analytical predictions and the observed values of the other indices of selection intensity is excellent for $s \leq 0.1$. As noted above, this reflects the deviation of the apparent stabilizing selection function from Gaussian. Overall, the numerical results strongly support our analytical approximations.

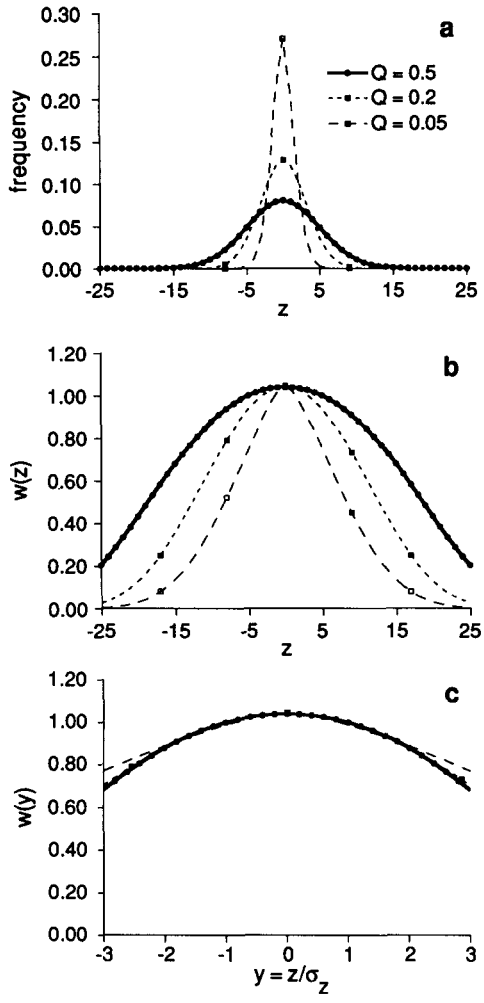

FIGURE 4.—Phenotypic distributions (a) and apparent selection curves, (b) before normalizing to the phenotypic standard deviations and (c) after normalizing, using the same selection model as in Figure 2 but with $Q = 0.05$, 0.2, and 0.5.

DISCUSSION

Our analysis suggests that pleiotropic effects of unconditionally deleterious mutations may account for substantial quantitative genetic variation and produce significant apparent stabilizing selection. The genetic variance maintained for a trait is $\bar{k}Qa^2$, where $\bar{k}$ is the average number of deleterious mutations per genome and Qa^2 is the variance of pleiotropic effects on the trait averaged over all deleterious mutations. The intensity of apparent selection, measured as β, the ratio of the genetic variance to the variance of the apparent fitness function, is close to s, the selection coefficient against individual deleterious alleles. Although we assumed that all deleterious mutations are equivalent, in the sense that fitness depends only on the total number of deleterious alleles carried, we allowed arbitrary directional selection against them. We have emphasized synergistic epistasis, which produces repulsion disequilibria among the deleterious alleles (*i.e.*, a more even distribution of deleterious alleles across genomes than expected under independence). BARTON's (1990) results, obtained assuming multiplicative selection and complete linkage equilibrium, are identical if the number of deleterious alleles affecting the trait is large, *i.e.*, $\bar{k}_T = Q\bar{k} \gg 1$. Our analysis implicitly assumes $\bar{k}_T \gg 1$ in approximation (14) and by assuming that the sum (2) is approximately Gaussian. We will compare the HK model's predictions with various data and discuss how our generalization of BARTON's results might modify their interpretation.

Variance in quantitative traits: The result $V_G \equiv \sigma_Z^2 = \bar{k}Qa^2 = \bar{k}_T a^2$ requires only the conditional independence of allelic effects on the trait within individuals carrying a fixed number of deleterious alleles. This follows from our assumption that these allelic effects do not influence fitness. This would be violated if an allele's effects on fitness and the trait were correlated, as assumed by KEIGHTLEY and HILL (1990), or if selection acts directly on the trait.

It is unclear how much variation $V_G = \bar{k}Qa^2$ predicts, since $\bar{k}$, Q and a^2 are difficult to estimate. In particular, we do not know Qa^2, the variance of phenotypic effects averaged over all deleterious mutations. This quantity translates the mean number of deleterious mutations into "phenotypic units." To our knowledge, the only relevant data appear in MACKAY, LYMAN and JACKSON (1992), who examined the effects of *P* element inserts on viability and abdominal and sternopleural bristle number in *Drosophila melanogaster*. They estimated heterozygous effects of $Qa^2 = 0.003V_E$ per insert, which could account for significant variation if $\bar{k}$ is on the order of 100. However, we do not know if *P* element insertions are "typical" deleterious mutations.

Although our analysis assumes that the number of genes affecting a particular trait, *i.e.*, $\bar{k}Q = \bar{k}_T$, is much larger than one, it is not clear what $\bar{k}_T$ is consistent with experimental data. Although very small values, *e.g.*, much less than one, would be inconsistent with high levels of additive variance, values of $\bar{k}_T$ near 1 would be difficult to reject. Even though each individual might carry only one allele affecting the trait, this allele would occur at different loci in different individuals. Thus, selection could produce long-term changes in the mean phenotype and environmental variance could produce a continuous phenotypic distribution. With, say, $\bar{k} = 100$ (as suggested by CROW 1979) and $Q = 0.1$, each genome carries on average 10 mutations affecting the trait. With $a^2/V_E \cong 0.1$, which may be reasonable (*e.g.*, FALCONER 1989, Table 12.2), this model could account for heritabilities near 0.5.

Obviously, pleiotropy can produce variance for many traits simultaneously. For fixed $\bar{k}$ and Q, one can imagine 100 traits with heritability 0.5 and only

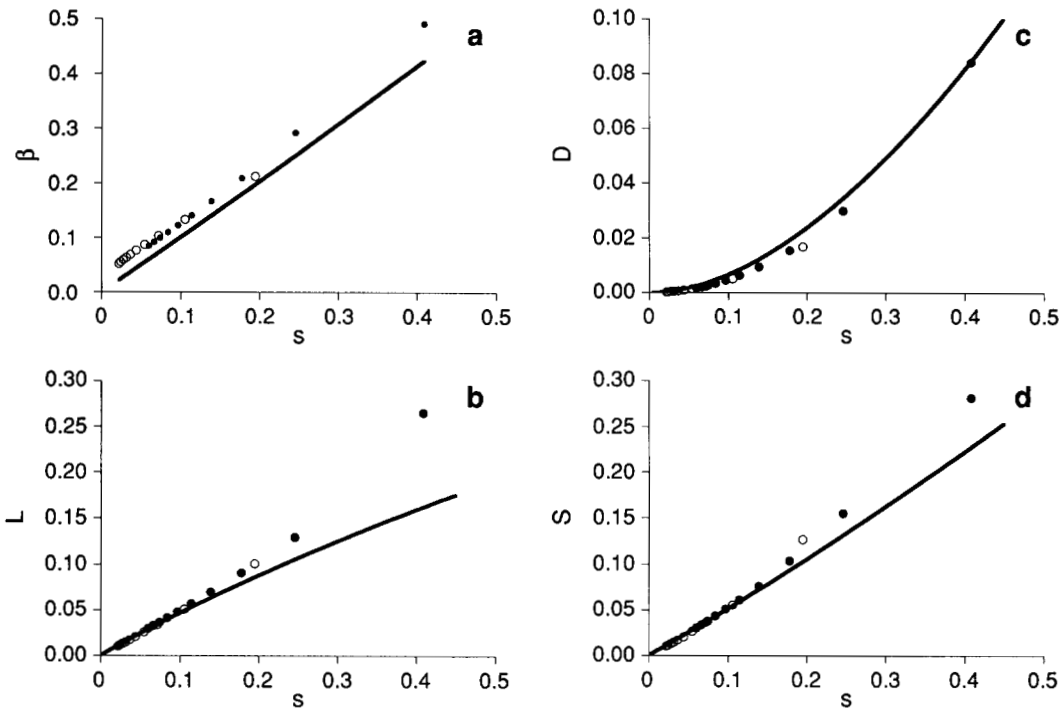

FIGURE 5.—Different characterizations of apparent selection intensity plotted against $s = U/\bar{k}$: β (a); L, apparent load (b); D, variance in relative fitness (c); and S, the difference between the apparent fitness of the optimal phenotype and phenotypes one standard deviation away (d). Analytical predictions are solid lines, numerical values are open circles for $U = 2$ and dots for $U = 6$ (see text for additional details).

small pairwise genetic correlations. In this model, correlations arise from overlap in the deleterious mutations that affect two traits and correlations in their bivariate pleiotropic effects. Although shared developmental pathways will ensure correlations between some traits (WAGNER 1989), selection against deleterious mutations might account for selection on a large number of essentially independent traits affected by different sets of loci.

Apparent stabilizing selection and actual genetic load: Our model implies that at mutation-selection equilibrium, the intensity of apparent stabilizing selection, as measured by β, is approximately s, the selection coefficient against individual deleterious alleles. Consequently, apparent stabilizing selection can be reasonably intense (*e.g.*, $\beta > 0.03$) if $s = 0.03 - 0.1$ for deleterious mutations. Under our assumptions, s can be represented as both $U/\bar{k}$ and $U_T/\bar{k}_T$. Other characterizations of selection intensity depend only on β if the fitness curve and phenotype distributions are Gaussian (see Equations 7 and 8). Although our model does not produce precisely Gaussian fitnesses or phenotypes in general, our Gaussian-derived approximations for apparent load, variance in relative fitness, and differences between the apparent fitness of the mean phenotype versus phenotypes one standard deviation away are quite accurate (Figure 5). Because even individuals with the "optimal" phenotype usually carry deleterious alleles, the apparent load computed from (6a) is always smaller than the actual one.

An alternative representation of β is instructive. Note that

$$\beta \cong s \equiv \frac{U}{\bar{k}} = v\sqrt{\frac{c}{\bar{k}}}, \tag{24}$$

where $v = U/\sigma_K$ is the "genome degradation rate" (KONDRASHOV 1984), and $c = \sigma_K^2/\bar{k}$, which is between 0.5 and 1, quantifies the linkage disequilibrium produced by selection. At equilibrium, $v = -\Delta_K/\sigma_K$ (*cf.* Equation 17), which equals the "intensity of selection" under truncation selection and determines the fraction of the population that survives (FALCONER 1989, Ch. 11). For fixed v, the intensity of apparent stabilizing selection decreases as $\sigma_K/\bar{k}$, which is proportional to $1/\sqrt{\bar{k}}$. This is because the apparent selection results from phenotypic variance increasing with K. As $\sigma_K/\bar{k} \to 0$ when $\bar{k} \to \infty$, this effect disappears. On the other hand, for fixed $\bar{k}$, the strength of apparent selection increases approximately linearly with v. The increase is actually slightly slower than linear, because c, which depends mainly on v (KONDRASHOV 1984), decreases as v increases. However, this departure from linearity is small, because c is between 0.5 ($v \to \infty$) and 1 ($v \to 0$) under synergistic epistasis.

It is noteworthy that in this idealized model, the strength of apparent stabilizing selection does not depend on either Q or a^2, because the parameter combination Qa^2 simply determines the scale of measurement for the trait (*cf.* Equations 12 and 13). Therefore, we have only two parameters, $\bar{k}$ and either U or

v, and the theory produces clear predictions concerning the effects of each.

There is a negative trade-off between V_G and β in this model, because $V_G\beta \cong (\bar{k}Qa^2)(U/\bar{k}) = UQa^2 = U_T a^2$. Under multiplicative selection, the mutation load is $1 - \exp(-U)$, which constrains U to be smaller than 1 or 2 (CROW 1970). This fact, among others, led BARTON (1990) to conclude that "mutation-selection balance is an unlikely cause of quantitative variation" (p. 779). However, this constraint is essentially eliminated by synergistic epistasis. Under truncation or similar selection regimes (CROW and KIMURA 1979), mutation load depends not on U but on the genome degradation rate $v = U/\sigma_K$. By calculating the fraction of the population that must be "culled" to produce selection intensity v, one sees that the mutation load becomes intolerable only for $v > 2$ (corresponding to less than 5% survival under truncation selection, ignoring nongenetic sources of mortality). For $v \leq 2$, the load remains reasonable even for arbitrarily large U (KONDRASHOV 1984, 1988). Because $\sigma_K \geq \sqrt{\bar{k}/2}$ even under strong synergistic epistasis (Equation 1), $v = U/\sigma_K \leq 2$ whenever $\bar{k} \geq U^2/2$. Consequently, for fixed U, load constraints imply only that $V_G \geq QU^2a^2/2$ and $s \leq 2/U$. These are not significant restrictions when $U < 20$–30. For instance, with $U = 5$, $\bar{k} = 100$, and $Q = 0.1$, our model implies $V_G = 10a^2$ and $\beta \cong 0.05$, so that both quantitative variance and apparent stabilizing selection can be substantial. The question is, however, whether the data on deleterious mutations and quantitative variance are compatible with this model.

Data on mutation-selection equilibrium for deleterious alleles: Despite its enormous theoretical significance, data relevant to mutation-selection balance for deleterious alleles are scarce. MUKAI *et al.* (1972) suggest $U \cong 1.0$; but this is probably an underestimate, particularly because: a) some slightly deleterious mutations may have been neglected, b) these data concern only one component of fitness, viability, and c) larval viability was measured under simple laboratory conditions, which may mask many mutations affecting viability in nature (see SIMMONS and CROW 1977; CROW 1979; CROW and SIMMONS 1983). Recently, D. HOULE, B. CHARLESWORTH and collaborators (personal communication) obtained higher estimates for U by considering all fitness components. For mammals, data on mutation rates per nucleotide and molecular evolution imply about 100 new mutations per diploid genome per generation; but the deleterious rate U is an unknown fraction of this, equal to the fraction of genome constrained by selection (see KONDRASHOV 1988). For Drosophila, molecular evolutionary rates of about 10^{-8}–10^{-7} per nucleotide per year have been reported (CACCONE, AMATO and POWELL 1988; ROWAN and HUNT 1991). With diploid genome size about 3×10^8 bp and several generations per year, this suggests $U = 0.1$–2.0, if we assume arbitrarily that about a third of all DNA can produce deleterious effects. However, data on rates of molecular evolution may significantly underestimate mutation rates because of purifying selection which apparently influences the majority of Drosophila scnDNA (CACCONE, AMATO and POWELL 1988) and can operate outside transcribed regions (COHN and MOORE 1988; LI and SADLER 1991). CHARLESWORTH, CHARLESWORTH and MORGAN (1990) estimate $U \cong 1$ from inbreeding depression in highly selfed plants. Overall, the scanty data for multicellular eukaryotes are consistent with any value of U between 0.1 and 100.

The mean equilibrium number of slightly deleterious mutations per genome and the average selection coefficient against them are not known with any confidence for any species. The best estimates for Drosophila are $\bar{k} \cong 50$ and $s \cong 0.02$ (the estimate of s is the harmonic mean and the estimate of $\bar{k}$ assumes $U \cong 1$; CROW 1979), but they both are likely to be underestimated. MACKAY, LYMAN and JACKSON (1992) found deleterious heterozygous fitness effects of 0.055 per P element in a homozygous genetic background. As they noted, their inserts could produce significant apparent stabilizing selection.

Transposable elements may account for a substantial proportion of the deleterious mutations we discuss. They comprise about 10% of the *D. melanogaster* genome, with on the order of 10^3–10^4 individual elements per genome (BINGHAM and ZACHAR 1989). They are apparently deleterious, and their copy number seems to be controlled by some form of mutation-selection balance (CHARLESWORTH and LANGLEY 1989). In *D. melanogaster*, the total genomic mutation rate caused by transposable elements may exceed 1 (W. R. ENGELS, personal communication), and many of these mutations are deleterious. Moreover, they contribute to observed quantitative variation (MACKAY AND LANGLEY 1990).

Nevertheless, these transpositions probably make only a small contribution to apparent stabilizing selection. The genomic mutation rate caused by transpositions equals the per-element transposition rate times the copy number. Thus, according to (23), the intensity of apparent stabilizing selection they produce should equal the per-element transposition rate. For different transposable elements, the estimates of "normal" transposition rate vary from about 10^{-5} (CHARLESWORTH and LANGLEY 1989) to about 0.03 per element per generation (PRESTON and ENGELS 1984). However, the latter figure is for the unusually mobile P elements; and current data suggest that the average for all elements is unlikely to exceed 10^{-3} (CHARLESWORTH and LANGLEY 1989; HARADA, YUKUHIRO and

MUKAI 1990). Thus they would produce only very weak apparent selection.

Data on quantitative traits: Although the scanty data on deleterious mutations may be consistent with explaining quantitative variation and apparent stabilizing selection, much stronger constraints emerge from considering parameters associated with quantitative genetic variation. In our notation, V_m, the amount of new genetic variance for trait Z introduced per zygote by mutation each generation (CLAYTON and ROBERTSON 1955), is UQa^2 (*cf.* Equation 9b). On the other hand, $V_G = \bar{k}Qa^2$. Hence, our analysis, like BARTON's (1990), implies that

$$\frac{V_m}{V_G} = \frac{U}{\bar{k}} = s \cong \beta, \tag{25}$$

i.e., the intensity of apparent selection is approximately equal to the ratio of the variance introduced by mutation each generation to the equilibrium genetic variance. This ratio can be estimated either directly from experiments concerned with the buildup or maintenance of variation, or indirectly from the rate of long-term selection response (HILL 1982; MATHER 1983; LYNCH 1988). Some studies estimate V_m/V_E rather than V_m/V_G, but these should not differ from β under our model by more than a factor of 5 given that heritabilities for the traits examined are typically between 0.2 and 0.6.

Although data on V_m/V_G are not abundant, the consensus estimate for *D. melanogaster* bristle numbers is about 10^{-3} (LANDE 1975; HILL 1982; MATHER 1983; MACKAY *et al.* 1992), an order of magnitude too low to explain appreciable apparent stabilizing selection. Similar values were obtained for Daphnia (LYNCH 1985), although the loss of many lines might have led to underestimation. In some other cases, however, values of V_m/V_E as high as 0.01–0.05 have been reported (see LYNCH 1988; KEIGHTLEY and HILL 1992). Hybrid dysgenesis can produce much higher values (MACKAY, LYMAN and JACKSON 1992), but this situation is not typical.

Thus, the highest estimates of V_m/V_G are consistent with fairly strong apparent stabilizing selection; but the lowest estimates, and in fact most estimates, (corresponding to $\beta = 0.001$ or even 0.0001) imply negligible selection. This may well reflect a real difference between the factors causing quantitative variation *vs.* stabilizing selection in nature, but more data on different organisms and traits are necessary. In some cases, very strong stabilizing selection has been reported (see ENDLER 1986), corresponding to $\beta = 0.1$ or more under our model. Although this is not precluded by load considerations, it is difficult to reconcile with most estimates of V_m/V_G. If additional studies find small values of V_m/V_G, the mechanism considered here must be abandoned as the explanation for significant stabilizing selection, unless our simplified analysis overlooks something that dramatically modifies (23) and (25) (*cf.* BARTON 1990). It is possible, however, that V_m has been substantially underestimated if mutations are deleterious and selection is not completely excluded during their accumulation (MACKAY *et al.* 1992).

Because β does not depend on Q under our model, data on $U_T = UQ$, the total mutation rate to alleles contributing variation to the trait considered, are relevant only to explaining V_G. Estimates from Drosophila, maize and mice imply $U_T = 0.01$–0.1 (*see* TURELLI 1984, 1988). With $U = 3$, this means that $Q = 0.03$–0.003, so that $\bar{k}a^2/V_E$ must exceed 100 to maintain substantial heritable variance. However, these parameters would produce an s too small to account for significant apparent stabilizing selection. Although U_T may well have been underestimated if mutations with small contributions were not counted, even estimates as low as 0.01 are difficult to reconcile with traditional estimates of per-locus mutation rates and numbers of loci underlying quantitative variation (*cf.* LANDE 1988; TURELLI 1984, 1988).

Direct *vs.* pleiotropic mutation-selection balance models: Direct-selection models assume that the alleles producing trait variation experience selection only from stabilizing selection acting directly on the trait. To compare them to our pleiotropy model, we will use the "rare alleles" (house of cards) approximation (TURELLI 1988), where, as in our HK model, all alleles contributing significant variation are rare at each locus.

The main result from one-trait, direct-selection models is $V_G \cong 2U_T V_s$. Here V_s is a parameter describing direct stabilizing selection, and the question addressed is "How much variance can be maintained?" In contrast, with the HK model, both V_G and V_s depend on selection extrinsic to the trait, and a central question is "What is their ratio β, *i.e.*, what is the intensity of apparent selection?" Under direct stabilizing selection, the intensity of stabilizing selection, in units of V_G, is $\beta = V_G/V_s = 2U_T$. In contrast, our HK model gives $\beta = s = U_T/\bar{k}_T$. Given that $\bar{k}_T$ must exceed 1 in biologically reasonable situations, we can conclude that for fixed U_T, direct selection models will generally entail more intense stabilizing selection (*i.e.*, larger β) than the apparent selection produced by our pleiotropic model. However, the variance prediction of the HK model seems far more robust. Pleiotropy tends to reduce equilibrium genetic variance under direct-selection models by an amount that is difficult to predict (TURELLI 1985; WAGNER 1989; SLATKIN and FRANK 1990), whereas it is an inherent feature of the HK model. Under this model, U_T is the mutation rate to all alleles that affect the trait; so it is reasonable to assume that the relevant loci are very numerous

(even $Q = 0.01$ implies many hundreds or thousands of loci).

For rare alleles, direct and pleiotropic models make identical predictions concerning the connection between newly introduced additive variance, the equilibrium genetic variance, and the intensity of selection against new mutations at individual loci. Under direct selection, we have $V_m = U_T a^2$, so that

$$\frac{V_m}{V_G} = \frac{a^2}{2V_s}. \tag{26}$$

This ratio is approximately s, the selection coefficient against a rare allele. Thus, direct selection reproduces the first equality in (25); but this ratio is no longer equal to β, the intensity of stabilizing selection. This relation also holds under direct-selection models with rare alleles that incorporate selection on pleiotropic effects (*e.g.*, the five-allele model of TURELLI 1985). It presumably reflects the general fact that at mutation-selection equilibrium for rare alleles, the rate of introduction of variance must equal its rate of elimination by selection, irrespective of the nature of selection.

Obviously the direct and pleiotropic models are not mutually exclusive. Many traits are clearly associated with adaptation, whether or not we understand the causal mechanism [*e.g.*, body size and temperature adaptation in Drosophila (ANDERSON 1973; COYNE and BEECHAM 1987)]. Nevertheless, although stabilizing selection is commonly observed, statistical analyses of selection cannot determine the actual targets of selection (ROBERTSON 1967b; LANDE and ARNOLD 1983; MITCHELL-OLDS and SHAW 1987). Because deleterious mutations are so common, it seems inescapable that the HILL-KEIGHTLEY mechanism produces some of the stabilizing selection observed. The question is how much.

Can the HK model explain both quantitative variation and selection? As with the deterministic mutation-selection-balance hypothesis for the evolution of sexual reproduction (KONDRASHOV 1988), the highest estimates of mutation rates and selection against deleterious alleles imply that the mechanism can work, while the lowest ones are inconsistent with it. One of our key simplifying assumptions is that all deleterious mutations have equal effects. The numerical results of KEIGHTLEY and HILL (1990), who relaxed this assumption, suggest that decreasing the correlation between the deleterious effects of mutations and their effects on a trait increases the variance maintained but decreases the intensity of apparent stabilizing selection. Variability of pleiotropic effects perfectly correlated with fitness effects probably does not influence our conclusions, but this requires further analysis. A complete treatment should consider both direct and indirect selection on the quantitative trait.

Equation 26 shows that the connection imposed by the HK model between the input of additive variance from mutation and the intensity of observed stabilizing selection disappears when direct selection is considered. If one considers both direct and pleiotropic selection, the causes of genetic variation and stabilizing selection can be decoupled. BULMER (1973) and GILLESPIE (1984) analyzed models in which genetic variance is maintained by overdominant selection acting directly on the individual loci producing variation for a quantitative trait under stabilizing selection; but they did not partition the net stabilizing selection into direct and apparent components.

A simple qualitative argument suffices when mutation, rather than overdominant selection, is the primary factor maintaining variation. If we assume that selection is a stronger force than mutation, the rare allele frequencies responsible for additive variance will be of the form μ/s, where μ is the mutation rate to the allele and s is the selection coefficient against heterozygotes. Assuming that selection is weak on individual loci, we can approximately partition s as $s = s_d + s_p$, where s_d arises from direct selection on the trait and s_p denotes selection attributable to pleiotropic effects (*cf.* GILLESPIE 1984). The direct component, s_d, is given approximately by the right hand side of (26). Using a fairly large value for a^2/V_E, *e.g.*, 0.1, and a moderate value for V_s/V_E, *e.g.*, 20, implies $s_d \cong 0.0025$. This is an order of magnitude lower than the average value for s_p, 0.02, estimated for deleterious mutations in *D. melanogaster* (CROW and SIMMONS 1983). Thus, even when most of the selection observed *for a trait* is caused by direct selection, that direct selection may be essentially irrelevant to the dynamics of the alleles responsible for variation in the trait. This is less likely if variation is maintained by some form of balancing selection acting on individual loci, because such selection is likely to correspond to s_d on the order of 10^{-3} or less (GILLESPIE 1991). In contrast to the one-trait analyses of LANDE (1975) and TURELLI (1984), we see that even if mutation is the primary factor maintaining variation for a specific trait, the level of variation may not be predictable in terms of observations on that trait *alone* once pleiotropy is taken into account (*cf.* TURELLI 1985, 1988).

Our analysis assumes that the pleiotropic effects of deleterious alleles are symmetrically distributed. Recent data on transposable elements suggest that distributions of effects may generally be asymmetrical (MACKAY and LANGLEY 1990; MACKAY, LYMAN and JACKSON 1992), yet may have mean effects near zero (MACKAY, LYMAN and JACKSON 1992). Generalizing our model to include asymmetrical pleiotropic effects will produce both directional and stabilizing apparent selection. This might contribute to some discrepancies observed between trait means and apparent pheno-

typic optima [*e.g.*, for human birth weight, CAVALLI-SFORZA and BODMER (1971), Figure 9.7].

Response to artificial selection is often accompanied by a reduction in population fitness (FRANKHAM, YOO and SHELDON 1988). Similarly, genetic changes in natural populations caused by strong selection under new conditions can also lead to decreased fitness under old conditions, *e.g.*, industrial melanism in *Biston betularia* and metal tolerance in plants (COOK, LEFÈBVRE and MCNEILLY 1972). Therefore, these selection responses may depend on mutations that were originally deleterious, as postulated by the HK model.

The data of MACKAY and LANGLEY (1990), which give a molecular description of alleles underlying quantitative variation, provide additional empirical support for the HK model. They found that the presence of transposable elements in the *achaete-scute* region of *D. melanogaster* was associated with differences in bristle number. Thus, transposable elements contribute to additive variance. However, the intra- and interspecific distributions of these elements suggest that they are deleterious and do not contribute to between-species differences (CHARLESWORTH and LANGLEY 1989). These characteristics of "polygenes" are consistent with the HK model.

Experimental investigation of the HK model: The parameters U_T and V_m must be measured more precisely to decide whether unconditionally deleterious mutation pressure plays a dominant role in maintaining additive variance. The pleiotropic models require more data on deleterious mutations and selection against them. Although simple tests can, in principle, discriminate between direct and pleiotropic models of stabilizing selection, the results to date are ambiguous. ROBERTSON (1967a) suggested a test of the pleiotropic model based on heterozygosity. LINNEY, BARNES and KEARSEY (1971) analyzed viability differences among homozygous and outbred lines to show that heterozygote advantage does not produce the apparent selection on bristle number in Drosophila larvae. In contrast, ROBERTSON (1967b) describes data that support pleiotropy rather than direct selection (also see BARTON's (1990) account of SPIERS' unpublished data). K. FOWLER (personal communication) compared the mating success of males with different sternopleural bristle numbers from an outbred population and from an F_1 between two isogenic lines. In both cases, intermediate individuals were most fit. Differential mating success among the F_1, all with the same genotype, implicates direct selection rather than pleiotropy. In contrast to the examples cited by KEIGHTLEY and HILL (1990) and BARTON (1990) suggesting deleterious pleiotropic effects of alleles responsible for artificial selection response, the data of FRANKHAM, YOO and SHELDON (1988) seem not to support this. They found that by culling the least fit lines from their selected populations, they could significantly improve the fitness without diminishing selection response.

J. F. CROW (personal communication) has suggested a simple test for the HK model. The fitness of F_1 individuals between opposite extreme phenotypes should be measured and compared to the fitnesses of individuals with the same phenotypes in the initial population. Assuming approximately additive allelic effects, both the pleiotropic and direct-selection models predict phenotypically intermediate progeny. However, under direct selection (or overdominance-mediated apparent selection), the F_1 should have high fitness equal to (or greater than) that of intermediate individuals in the initial population due to their "optimal" phenotype (or heterozygous genotype). In contrast, under the HK model, the F_1 fitness should be as low as that of their "deviant" parents, because they will on average carry the same number of deleterious alleles.

Of course, this experiment, as well as the whole of our analysis, is based on an assumption that mutations are at least partially dominant. If, on the contrary, extreme phenotypes and low fitnesses are caused only by homozygous mutations, a cross between two extreme phenotypes will produce intermediate phenotypes with normal fitnesses, as with direct selection. However, with recessive pleiotropic mutations, the variance of the trait would increase drastically after inbreeding, which can be used to test this possibility (J. F. CROW, personal communication).

Anther possible experiment is to impose strong artificial stabilizing selection on one or more quantitative traits simultaneously. Under the HK model, this would decrease the number of deleterious alleles, so that after several generations we might expect to see an increase in fitness for all phenotypes. In particular, the average phenotype should have a higher fitness than any phenotype in the starting population. Clearly, such a result would be inconsistent with direct-selection models, in which fitness is directly determined by the phenotype. Additional experiments along these lines are needed to determine the causes of quantitative genetic variation and stabilizing selection.

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