Comparing Mutational Variabilities

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ABSTRACT

We have reviewed the available data on V_M, the amount of genetic variation in phenotypic traits produced each generation by mutation. We use these data to make several qualitative tests of the mutation-selection balance hypothesis for the maintenance of genetic variance (MSB). To compare V_M values, we use three dimensionless quantities: mutational heritability, V_M/V_E; the mutational coefficient of variation, CV_M; and the ratio of the standing genetic variance to V_M, V_G/V_M. Since genetic coefficients of variation for life history traits are larger than those for morphological traits, we predict that under MSB, life history traits should also have larger CV_M. This is confirmed; life history traits have a median CV_M value more than six times higher than that for morphological traits. V_G/V_M approximates the persistence time of mutations under MSB in an infinite population. In order for MSB to hold, V_G/V_M must be small, substantially less than 1000, and life history traits should have smaller values than morphological traits. V_G/V_M averages about 50 generations for life history traits and 100 generations for morphological traits. These observations are all consistent with the predictions of a mutation-selection balance model.

MUTATION, as the source of all genetic variation, is ultimately responsible for both variation and adaptation. A long-standing, fundamental debate in evolutionary genetics concerns the strength of the relationship between mutation and variation. The two most plausible mechanisms for the maintenance of variation are mutation-selection balance and various models of balancing selection (BARTON 1990). With mutation-selection balance, a steady input of mutation is necessary to maintain genetic variance, so we expect a positive correlation between mutation and variation. With balancing selection, mutation need only produce alleles leading to such polymorphisms infrequently, so mutation and variation may be only weakly related.

An equally long-standing question concerns the relationship between mutation and adaptation. On the one hand, a popular model of adaptation assumes that the standing variance in a population is the principal source of the response to selection (*e.g.*, LANDE 1979). Under this assumption, it is the amount of variation that limits the rate of adaptation. This justifies the widespread use of quantitative genetics in evolutionary biology. The extreme alternative view is that the alleles that potentially give rise to adaptations do not normally segregate in populations. In that case, the mutational processes that give rise to advantageous genotypes would limit the rate of evolution, regardless of the mechanism that maintains standing variation. Under pleiotropic mutation-selection balance models, much of the variation segregating may be unconditionally deleterious (KONDRASHOV and TURELLI 1992), and therefore not available to promote adaptation. Under balancing selection, the same processes that maintain variation may retard the use of that variation in promoting adaptation. An understanding of mutation is therefore required to answer both the question of what maintains genetic variance and the question of what determines the rate of response to selection.

For quantitative traits the parameter V_M, the increase in genetic variance due to a single generation of mutation, is important in models of both response to selection and maintenance of genetic variation (LYNCH 1988; BARTON and TURELLI 1989). Even if all the variation is unconstrained by conflicting selection pressures, further response will be limited by V_M if directional selection is strong and prolonged for more than about N_e generations, where N_e is the effective population size (HILL 1982). V_M thus may be of particular importance as human-mediated changes in the environment challenge a wide variety of species, particularly those with the smallest populations (LYNCH and LANDE 1992). In addition, V_M determines the rate of divergence in neutral models of phenotypic evolution (LANDE 1976b; CHAKRABORTY and NEI 1982; LYNCH and HILL 1986; LYNCH 1994).

To compare the variability of different traits, previous reviews of V_M have standardized estimates with the environmental variance of the trait, V_E (LANDE 1976a; HILL 1982; LYNCH 1988). V_M/V_E is the rate of increase in

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heritability in an initially homozygous population, and therefore is called the mutational heritability. LYNCH's (1988) review confirmed previous generalizations that the average V_M/V_E value is about 1×10^{-3}. LYNCH also identified considerable variation about this figure, although much of this may be due to sampling error. Mutational heritability is widely used in models of quantitative traits under stabilizing selection to eliminate V_E as a free parameter.

An alternative class of measures of mutational variability are those where V_M values are standardized by the trait mean, such as the mutational coefficient of variation, $CV_M = 100 \times \sqrt{V_M}/\bar{X}$, where $\bar{X}$ is the trait mean. These measures are valuable because an intuitively reasonable way of standardizing the potential response to selection is relative to the trait mean (HALDANE 1949). A rate of response to selection of 10% per generation would always be regarded as high, and a rate of 0.01% low. Genetic coefficients of variation, including CV_M, are correlated with the potential proportional response to selection (BURTON 1952; JOHNSON *et al.* 1955; CHARLESWORTH 1984; HOULE 1992). In addition, when fitness components are modeled, it is convenient to think in terms of mean standardized values, as standardized variances are readily converted to variance in relative fitness (CROW 1958) or to selection coefficients.

Both the mutational heritability and coefficient of variation are thus useful in specific models of quantitative traits. However, previous reviews have depended exclusively on V_M/V_E as a basis for summarizing and comparing V_M values. This can obscure important information. For example, comparisons reveal that life history traits have lower standing heritabilities than morphological traits (MOUSSEAU and ROFF 1987; ROFF and MOUSSEAU 1987). This can be due either to smaller additive genetic variances or larger residual variances, where residual variance (V_R) is the difference between phenotypic and additive genetic variance. Until recently, the differences in heritability between life history and morphological traits were usually assumed to be due to lower additive genetic variance in life history traits. However, comparisons of variation standardized by the mean show the opposite (HOULE 1992). The additive genetic coefficients of variation (CV_A) of life history traits are, on average, about three times as large as those for morphological traits, while the residual coefficients of variation are an order of magnitude larger. The low heritability of life history traits occurs in spite of larger genetic variances, rather than because of low genetic variance. Considering only ratios of these variances has therefore concealed variation in each quantity. If this pattern holds for mutational variation, the similarity of traits in mutational heritabilities may be misleading.

There are three nonexclusive hypotheses that can explain the higher CV_As of life history traits (HOULE 1992). First, a larger proportion of the genome could affect the average life history trait than the average morphological trait. Every locus in the genome must potentially affect fitness, and life history traits that summarize major components of fitness must therefore also be affected by large numbers of loci (HOULE 1991). Second, loci with effects on life history traits may be particularly likely to have balanced polymorphisms, for example, because of genotype-environment interactions or antagonistic pleiotropy (ROSE 1982; GILLESPIE and TURELLI 1989). Third, selection directly on trait variance could favor modifiers that reduce the variance in morphological traits or increase the variance in life history traits. Variance in traits under stabilizing selection is selected against; if the fitness function is locally concave upward (both first and second derivatives positive), an increase in variance is favored, for a given mean (LANDE 1980). This argument is plausible because fitness is by definition under linear directional selection so variance of fitness itself is a neutral trait; morphological traits will usually be subject to stabilizing selection and be selected for decreased variance. However, all of the life history traits with genetic data are at best fitness components rather than measures of fitness itself. The conditions under which variance in a fitness component will be neutral or favored are complex, once potential tradeoffs are taken into account (D. HOULE and L. ROWE, unpublished data).

Under the first hypothesis, that life history traits are a larger mutational target, we predict that V_M should also be higher for these traits. This would be true whichever process maintains genetic variance. However, we cannot explain high CV_A for life history traits by mutation-selection balance unless this expectation is met. Under mutation-selection balance, genetic variance will be negatively correlated with the average selection coefficient against mutant alleles, and positively correlated with V_M. The higher CV_As of life history traits (HOULE 1992) run counter to the expected negative correlation of variation with the strength of selection, since life history traits are often under strong directional selection. Given this, if the mutation-selection balance hypothesis is true, we predict that life history traits must have high values of CV_M to compensate. Mutation data thus provide a partial test of both mutation-selection balance and the target size explanation for the high genetic variance in life history traits. The tests are partial in that low CV_M values would reject these hypotheses, while high CV_M values would not reject the alternative hypotheses.

A useful alternative measure of the importance of mutational variance is the ratio V_G/V_M, the inverse of which was originally used to summarize V_M values by CLAYTON and ROBERTSON (1955). In a large population, genetic variance is increased by V_M every generation and decreased by a proportion s, where s is the

selection coefficient against the average mutant genotype. In diploids, s represents the average selection against a mutant heterozygote, as deleterious alleles will be eliminated chiefly through their heterozygous effects. This leads to the simple expression for the equilibrium, or standing genetic variance, $V_G = V_M/s$ (BARTON 1990; CROW 1993). In this case, each mutant allele will affect an average of V_G/V_M individuals before being eliminated from the population (LI and NEI 1972). It is also the mean persistence time in an infinite population of a cohort of mutant alleles arising in the same generation (CROW 1979). For convenience, we will follow CROW (1979, 1993) in calling V_G/V_M the persistence time. V_G/V_M may also be related to the strength of direct or induced stabilizing selection on quantitative traits (KONDRASHOV and TURELLI 1992).

Under mutation-selection balance we expect that persistence times for life history traits will be shorter than for morphological traits, because we predict a higher correlation between mutant effects on life history traits and fitness than their effects on morphological traits and fitness. There is clear empirical evidence that the genetic correlations due to unselected mutations among major fitness components are large and positive (HOULE *et al.* 1994), so the average mutant allele must be quite deleterious. Mutations affecting morphological traits, on the other hand, may not affect fitness components outside of selection on the morphology itself, and so may be less deleterious on average. There is direct evidence that this is the case for bristle mutations in Drosophila (MACKAY *et al.* 1992a). Under balancing selection, we have no prediction as to what the relative persistence times for different types of traits should be. The proportion of new mutations that lead to balanced polymorphisms must be quite small and could easily differ between trait classes.

Since the average mutation is deleterious to fitness, regardless of which other traits it affects, the smaller the ratio V_G/V_M, the more likely that mutation-selection balance can explain standing variance. The mean value of V_G/V_M therefore provides a qualitative test of the mutation-selection balance model. Common practice has been to accept the typical V_E/V_M value of 1000 (LYNCH 1988) as a good approximation of V_G/V_M (*e.g.*, BARTON 1990; KONDRASHOV and TURELLI 1992), but this is clearly unjustified in general, as shown by the variation in heritabilities and coefficients of variation (MOUSSEAU and ROFF 1987; ROFF and MOUSSEAU 1987; LYNCH 1988; HOULE 1992). If V_G/V_M is as large as 1000, this causes serious, if not absolutely fatal, difficulties for the mutation-selection balance hypothesis (BARTON 1990). Clearly a compilation of V_G/V_M estimates is desirable.

In this paper, we compare mutational variabilities using mutational heritability, the mutational coefficient of variation, and the ratio of genetic to mutational variance. We also perform the tests of mutation-selection balance outlined above.

THE V_M DATA SET

We have reviewed the literature on mutational variances (V_M) published through April 1995. A summary of these estimates is given in Table 1. A detailed explanation of Table 1 is given in the section Comparing Coefficients of Variation, below. KEIGHTLEY *et al.* (1993) have recently reviewed and reanalyzed the extensive literature on bristle traits in *Drosophila melanogaster*, and we have adopted their estimates in preference to the original analyses (see below). Estimates from studies published before 1986 were compiled by LYNCH (1988), and those studies are included here, with some exceptions. Three studies in mice of discontinuous variation were excluded (CARPENTER *et al.* 1957; DEOL *et al.* 1957; YONG 1972), as was a single study in corn that reported only significant changes among generations (SPRAGUE *et al.* 1960). These approaches are expected to lead to particularly biased estimates of V_M.

KEIGHTLEY *et al.* (1993) demonstrated that there is substantial bias in many estimates of V_M for bristle traits in *D. melanogaster*. It is important to consider this source of bias in some detail, to help judge the quality of the remaining estimates. Two ideal experiments for estimating V_M may be envisioned (LYNCH 1994). First, V_M may be estimated from the response to selection of a population that is in mutation-drift equilibrium. Second, V_M may be estimated from the rate of increase in variance by mutation and drift among replicates of a population in mutation-drift equilibrium. In both ideal cases, the observed parameters (response to selection or among-replicate variance) are simple functions of the effective population size (N_e) before and during the experiments, and of V_M. Natural selection on mutations affecting the traits of interest constitute the chief obstacle to performing such experiments. Natural selection will prevent the base population from reaching mutation-drift equilibrium and will bias the divergence from both designs, for example, by eliminating deleterious mutations.

The simplest tool available to combat the effects of natural selection is a reduction in the effective population size. The efficacy of natural selection is proportional to $N_e s$ where s is the difference in relative fitness between selected genotypes. Reduction of N_e has the additional benefit of reducing the time necessary to achieve mutation-drift equilibrium, which is substantially reached in $6N_e$ generations for neutral variants (MALECOT 1969). This reasoning makes it clear that the ideal experiment would use the smallest possible base population. In an accumulation experiment one should also minimize N_e during the accumulation phase. When using artificial selection to estimate V_M, the goals of minimizing natural selection and maximiz-

TABLE 1

Summary of mutation parameter estimates

Species	Trait	Dm class	V_M/V_E ($\times 10^{-3}$)	CV_M	N	Reference
Daphnia pulex (water flea)	Adult size	1 M	3.26	0.245	3	LYNCH (1985)
	Age 1st reprod.	1 L	1.34	0.386	1	
	Clutch size	1 L	1.40	2.976	3	
	Fitness	1 L	0.83	1.090	1	
	Offspring size	1 G	0.98	0.126	3	
Drosophila melanogaster (fruit fly)	Adh activity	1 N	0.62	0.570	2	MUKAI *et al.* (1984)
	Abdominal bristles	1 M	0.80	0.205	1	CLAYTON and ROBERTSON (1955)[a]
			2.20	0.214	1	CLAYTON and ROBERTSON (1964)[a,b]
			2.30	0.216	1	HOLLINGDALE and BARKER (1971)[a]
			0.60	0.099	1	KITAGAWA (1967)[a]
			2.40	0.319	2	LÓPEZ and LÓPEZ-FANJUL (1993a)[a]
			13.45	0.582	2	LÓPEZ and LÓPEZ-FANJUL (1993b)[a]
			3.33	0.647	1	MACKAY *et al.* (1992b)[a]
			7.80	1.157	1	MACKAY *et al.* (1994)[a]
			1.70	0.252	1	MATHER and WIGAN (1942)[a]
			0.38	0.129	1	PAXMAN (1957)
	Ethanol resistance	1 N	0.89	0.154	2	WEBER and DIGGINS (1990)
	Fecundity	1 L	3.44	1.891	2	HOULE *et al.* (1994)
	Fitness	1 L	[c]	4.147	1	
	Longevity	1 L	1.36	1.347	2	
	Male mating	1 L	0.63	2.886	2	
	Productivity	1 L	1.02	2.236	1	
	Sternopleural bristles	1 M	6.90	0.549	1	MACKAY *et al.* (1992)[a]
			8.10	0.669	1	MACKAY *et al.* (1994)[a]
			3.10	0.408	1	MATHER and WIGAN (1942)[a]
			1.84	0.360	1	PAXMAN (1957)
			1.80	0.361	2	SANTIAGO *et al.* (1992)[a]
	Viability	1 L	0.54	4.537	1	CARDELLINO and MUKAI (1975)
			0.22	1.140	1	MUKAI (1964)
			0.13	2.004	3	MUKAI *et al.* (1972)
			0.30	0.873	1	OHNISHI (1977)
	Wing dimensions	1 M	2.02	0.136	4	SANTIAGO *et al.* (1992)
Hordeum vulgare (barley)	Biomass yield	3 G	0.26	0.425	6	COX *et al.* (1987)
	Grain yield	3 L	0.24	0.559	6	
Mus musculus	6-week weight	3 G	4.23	0.208	3	KEIGHTLEY and HILL (1992); CABALLERO *et al.* (1995)
			0.94	0.131	2	CABALLERO *et al.* (1995)
	Limb lengths[d]	1 M	23.34	0.256	4	BAILEY (1959)
	Mandible lengths	1 M	29.22	0.242	13	FESTING (1973)
	Skull lengths[d]	1 M	4.50	0.166	8	BAILEY (1959)
Oryza sativa (rice)	Grain yield	3 L	2.95	0.621	1	SAKAI and SUZUKI (1964)
	Heading date	1 N	3.77	1.174	1	OKA *et al.* (1958)
	No. of panicles	1 G	2.46	1.302	1	SAKAI and SUZUKI (1964)
	No. tillers	1 L	2.89	1.377	1	
	Panicle length	1 G	2.08	0.499	1	
	Plant height	1 M	1.51	0.186	1	OKA *et al.* (1958)
	Plant height	1 M	5.57	0.718	1	SAKAI and SUZUKI (1964)
	Plant weight	3 G	1.79	0.493	1	
Tribolium castaneum (flour beetle)	Pupal weight	3 M	0.83	0.077	4	ENFIELD and BRASKERUD (1989)
		3 M	9.64	0.279	6	GOODWILL and ENFIELD (1971)

TABLE 1

Continued

Species	Trait	Dm class	V_M/V_E ($\times 10^{-3}$)	CV_M	N	Reference
Zea mays (maize)	Ear diameter[e]	1 G	5.16	0.715	2	RUSSELL *et al.* (1963)
	Ear length	1 G	3.10	1.028	1	
	Grain yield	3 L	4.99	0.882	1	
	Leaf width[f]	1 M	14.20	1.296	1	
	Plant height	1 M	8.23	1.266	1	
	Silking date	1 N	6.59	3.493	1	
	Tassel branches	1 L	19.24	3.950	1	
	Weight of 100 grains	3 G	4.54	2.224	1	

These estimates constitute data grouping 2. Dm, dimensionality of the trait; M, adult morphological trait; G, trait is a body dimension during growth; L, life history trait; N, number of grouping 1 estimates included in these estimates.

[a] V_M/V_E from KEIGHTLEY *et al.* (1993).

[b] Mean from DURRANT and MATHER (1955).

[c] No estimate of V_E for fitness.

[d] Means from LEAMY (1974), or from direct measurement of mouse skeletons in the Royal Ontario Museum.

[e] Ear diameter includes number of kernel rows, which is highly correlated with ear diameter (HALLAUER and MIRANDA 1988). The mean for ear diameter is from SPRAGUE *et al.* (1960). The mean for kernel row number is from VELDBOOM and LEE (1994).

[f] Mean from SPRAGUE *et al.* (1960).

ing the response to the artificial selection are necessarily in conflict, and the optimal population size, intensity of selection and length of experiment vary with the distribution of mutant effects.

The distributions of mutational effects on the trait and fitness are generally unknown. Two potential exceptions are abdominal and sternopleural bristle numbers in Drosophila. MACKAY *et al.* (1992a) estimated the joint effects of *P*-element insertions on bristle numbers and egg-to-adult viability. KEIGHTLEY *et al.* (1993) used these distributions in their reanalysis of bristle studies, taking account of the bias introduced by natural selection through pleiotropic effects on viability. The degree of bias estimated by KEIGHTLEY *et al.* and the effective population sizes of the base and experimental populations used in these studies are shown in Table 2. In this table and Table 3, N_e was calculated assuming $N_e = 0.7N$, unless family sizes were equalized by the investigator, in which case $N_e = 2N - 1$. On average, there was roughly a threefold increase in V_M when pleiotropic viability effects were taken into account. However, the bias is clearly much larger when N_e is large, particularly N_e in the base population. The least biased studies are those that accumulated variance during full sib mating from a full-sib mating base.

The quantitative results of KEIGHTLEY *et al.*'s reanalysis are themselves subject to two contradictory biases (KEIGHTLEY *et al.* 1993). First there is some evidence that the pleiotropic fitness costs of *P*-element insertions are larger than those of other spontaneous mutants (MACKAY *et al.* 1992a; KEIGHTLEY 1994). Second, the effect of a mutation on viability is usually less than its effect on fitness (SVED 1971, 1975; MACKAY 1986). Nevertheless, the qualitative conclusion that estimates of V_M are biased downward is inescapable.

Table 3 provides the design of and effective population sizes in studies of traits other than Drosophila bristles. In most cases, these studies have used designs with smaller N_es than the bristle studies. The study of OKA *et al.* (1958) stands out in having utilized a population size of 500 during accumulation. This study is also unusual in that the accumulation phase was only five generations, which minimizes the bias due to selection. If the average heterozygous effect of a mutation on fitness is 5% or less (as in *D. melanogaster*), selection can only eliminate a small additional proportion of mutations, relative to the neutral expectation, in such a short time. The large base population size in ENFIELD and BRASKERUD's (1989) study (maintained for only 1.5 N_e generations) suggests that the bias in this study is particularly large; this is borne out by the large discrepancy with the results of GOODWILL and ENFIELD (1971). Consequently, this study is not considered further.

In addition to their favorable population sizes, some of the studies in Table 3 have also minimized natural selection in other ways. For example, KEIGHTLEY and HILL (1992) practiced within-family selection in their mouse lines, which eliminates natural selection due to mate choice, fecundity and fertility. Similarly, in studies that involve cloned (LYNCH 1985) or selfed lines (OKA *et al.* 1958; RUSSELL *et al.* 1963; SAKAI and SUZUKI 1964; COX *et al.* 1987), balancer chromosomes (Table 3), or other methods of equalizing family sizes (BAILEY 1959; FESTING 1973; SANTIAGO *et al.* 1992) selection is limited to viability and complete sterility. In many of these studies, individuals are reared in noncompetitive conditions, which will also tend to minimize natural selection (KONDRASHOV and HOULE 1994). Similar techniques to reduce selection were only utilized in three of the studies in Table 2 (MATHER and WIGAN 1942; SANTIAGO *et al.* 1992; LÓPEZ and LÓPEZ-FANJUL 1993b).

TABLE 2

Relationship between effective population size and bias in the estimation of V_M in *Drosophila melanogaster* bristle studies

Reference	Trait[a]	Selection[b]	N_e Base	N_e Expt.	Bias[c]
		Accumulation experiments			
López and López-Fanjul (1993b)	ab		2.6	2.6	1.4
López and López-Fanjul (1993b)	ab		7	7	2.1
Mackay *et al.* (1992)	ab		2.6	14	4.2
Mackay *et al.* (1992)	st		2.6	14	4.5
Santiago *et al.* (1992)	st		2.6	2.6	1.4
Santiago *et al.* (1992)	st		7	7	2.8
		Selection experiments			
Clayton and Robertson (1955)	ab	20/50	2.6	14	2.5
Clayton and Robertson (1964)	ab	20/100	60	14	5.4
Hollingdale and Barker (1971)	ab	200/400	2.6	140	3.3
Kitagawa (1967)	ab	12/60	2.6	8.4	2.2
López and López-Fanjul (1993a)	ab	50/250	0.5	35	2.1
López and López-Fanjul (1993a)	ab	10/50	0.5	7	2.7
Mackay *et al.* (1994)	st	20/80	2.6	14	2.8
Mackay *et al.* (1994)	ab	20/80	2.6	14	2.7
Mather and Wigan (1942)	st	6/60	2.6	9	2.6
Mather and Wigan (1942)	ab	6/60	2.6	9	2.4

[a] ab, abdominal (sternital) bristles; st, sternopleural bristles.
[b] Number of individuals selected/number of individuals examined each generation during selection.
[c] Factor by which V_M is underestimated by the infinitesimal model (Keightley *et al.* 1993).

This suggests that the studies in Table 3 are generally not unduly biased, while the Drosophila bristle studies are in particular need of the corrections for bias that Keightley *et al.* (1993) have applied. Consequently, we have chosen to analyze the estimates for Drosophila bristle traits corrected for viability selection along with the uncorrected estimates available for other traits. This necessitates dropping several estimates of V_M analyzed by Lynch (1988), but not reanalyzed by Keightley *et al.* (1993) (*i.e.*, Durrant and Mather 1954; Clayton and Robertson 1964). One accumulation study using balancer chromosomes not reanalyzed by Keightley *et al.* was included (Paxman 1957). Using balancer chromosomes, fixation of new mutations occurs following a single generation of viability selection in heterozygous condition, so the bias in this design is expected to be only about 1–5%, the heterozygous viability effect of a mutation (Crow and Simmons 1983; Mackay *et al.* 1992a; Keightley 1994).

If the expectation that life history traits are generally subject to stronger selection than morphological traits is correct, then results for life history traits will be more biased than those for morphological traits. Since the expectations based on mutation-selection balance suggest that V_M should be larger for life history traits, the conclusions we draw below using these data are conservative with respect to these differences in correction for bias.

For traits other than Drosophila bristles, the estimates of V_M in Table 1 were drawn directly from estimates in the papers cited or were recalculated using the methods of Lynch (1988). The only exception is egg-to-adult viability in Drosophila, which was reanalyzed as outlined in the APPENDIX to correct Lynch's (1988) estimates of V_E. These reanalyses result in estimates of the environmental variances three to 15 times less than those in Lynch. To calculate coefficients of variation, we also required trait means. In a few cases (see Table 1 notes), means were not given in the original papers, and were drawn from other studies likely to have had similar means.

Analyses were carried out on three measures of variation, V_M/V_E, CV_M, and $CV_E = 100 \times \sqrt{V_E}/\bar{X}$. The coefficients of variation were divided by the dimensionality of the trait to correct for the fact that variances of volumes are expected to be proportional to the cube of variation in linear dimensions (Lande 1977; Houle 1992).

COMPARING COEFFICIENTS OF VARIATION

To test the hypothesis that life history traits have higher mutational coefficients of variation, we classified each trait in Table 1 according to its presumed relationship to fitness. Life history traits are classified as L traits. These traits are presumably under directional selection,

TABLE 3

Effective population sizes of experiments that estimate V_M

Species	Reference	Method[a]	N_e Base	N_e Expt.
Daphnia pulex	LYNCH (1985)	C	1	1
Drosophila melanogaster	CARDELLINO and MUKAI (1975)	B	0.5	0.5
	HOULE *et al.* (1994)	B	0.5	0.5
	MUKAI (1964)	B	0.5	0.5
	MUKAI *et al.* (1972)B	B	0.5	0.5
	MUKAI *et al.* (1972)	B	0.5	2.5
	MUKAI *et al.* (1984)	B	0.5	0.5
	OHNISHI (1977)	B	0.5	0.5
	PAXMAN (1957)	B	0.5	0.5
	SANTIAGO *et al.* (1992)	I	2.6	2.6
	SANTIAGO *et al.* (1992)	I	7	7
Hordeum vulgare	COX *et al.* (1987)	I	1	1
Mus musculus	BAILEY (1959)	I	2.6	2.6
	FESTING (1973)	I	2.6	2.6
	KEIGHTLEY and HILL (1992)	S	2.6	23
	CABALLERO *et al.* (1995)	I/S[b]	2.6	23
Oryza sativa	OKA *et al.* (1958)	I	1	500
	SAKAI and SUZUKI (1964)	I	1	1
Tribolium castaneum	ENFIELD and BRASKERUD (1989)	I	100	100
	ENFIELD and BRASKERUD (1989)	S	100	96
	GOODWILL and ENFIELD (1971)	S	2.6	30
Zea mays	RUSSELL *et al.* (1963)	I	1	1

Studies in Table 2 are not included.

[a] B, accumulation using balancer chromosomes; I, accumulation by inbreeding; C, clonal propagation; S, artificial selection.

[b] Selection was carried out in a population founded from the cross of two related inbred lines.

in the sense that fitness must increase if their value could be increased while leaving all other traits equal (SCHLUTER *et al.* 1991). Note that such traits may be under stabilizing selection if the phenotypic variance is mostly generated by trade-offs between life history traits, rather than by variance in quality or condition. Morphological traits for which there is no reason to believe they are subject to directional selection are classified as M traits. These include sizes of adult body parts and meristic traits. Sizes of body parts during growth are classified as G traits. This grouping was adopted since growth rate itself is likely to be under directional selection early in life, but that selection becomes stabilizing at some point in the life cycle. This grouping is thus likely to have some traits under directional selection, and others under stabilizing selection. For ethanol resistance in *D. melanogaster* and flowering phenologies in plants the scale of measurement has no clear relationship to potential fitness functions, making coefficients of variation of questionable value. We have not attempted to classify Adh activity as a trait. These traits are designed N in Table 1 and are not considered further in this paper.

There is ambiguity concerning proper classification of some traits, such as infructescence dimensions and plant height in *Zea mays* and *Oryza sativa*. We have classified these on the basis of their genetic correlations with yield in HALLAUER and MIRANDA's (1988) review of maize quantitative genetics. Ear dimensions have modest positive correlations with yield, while plant height is essentially uncorrelated with yield. We have classified ear dimensions as G traits to reflect their somewhat ambiguous status as morphological traits apparently under directional selection. Reclassifying these and other traits has a limited impact on the results discussed below.

It is evident from Table 1 that there are many estimates for the same trait within some studies and many independent studies for other traits. In most species, data are only available for only one or two trait classes. This makes it difficult to devise a single appropriate analysis of these data. Instead, we have analyzed three different groupings of the data. In grouping 1, we calculated means for each trait within each study, which yielded a total of 73 estimates for CV_M. To calculate the estimates in grouping 2, we calculated medians of the grouping 1 estimates by species and a more general designation of trait. For example, HOULE *et al.* (1994) includes estimates of V_M for female fecundity early and late in adult life and for male and female longevity. These estimates were combined in grouping 2 into the fecundity and longevity estimates, respectively. Table 1 shows the grouping 2 estimates, except when there is more than one study that considered a trait, in which case the results of each study are summarized on a

separate line. The column labeled N in Table 1 shows the number of grouping 1 estimates combined to obtain these estimates. Grouping 3 consists of median estimates within species and trait class, which gives only 16 estimates. Grouping 3 was calculated from grouping 2 estimates, so as not to weight traits with many estimates more heavily than other traits.

A legitimate alternative starting point for the analysis of these data would be to weight each estimate by the inverse of its standard error. We have not taken this approach because it would result in estimates from *D. melanogaster* being weighted very heavily, while estimates from some other species would figure very little in the analysis. The analysis adopted will be more sensitive to real differences in the pattern of estimates among species. We feel that this is appropriate, since it is our goal to search for general patterns in the data.

Analyses were carried out on log-transformed data using the SAS procedure GLM (SAS INSTITUTE 1990). Analyses of residuals from the models reported below were normally distributed in most cases, and departures from normality were never large. We have not attempted to correct for the mean in these analyses, as was done by HOULE (1992), because the rather sparse and peculiar collection of traits, measured on all kinds of scales, makes it very likely that this would obscure real variation, rather than eliminate error variance. Instead, we have included species as a factor in our analyses, although species is confounded with the type of trait. For example, most *Mus musculus* traits are skeletal dimensions, and both *Hordeum vulgare* traits are yields.

The data for grouping 2 are graphed in Figures 1–3, and a summary of the results of the analyses of variance for all groups is presented in Table 4. Table 4 shows the results from analyses without the species by trait class interaction term, to allow us to test pairwise differences between trait classes and between species. A model including this interaction was also fit for groupings 1 and 2, but was only significant in one case, CV_E in grouping 1. Since we are *a priori* most interested in the comparison between L and M traits, the difference between these groups was tested with $P = 0.05$ as the criterion for significance. The two comparisons involving the G class were tested using the sequential Bonferoni adjustment (HOLM 1979; RICE 1989). Pairwise comparisons among species were tested using the sequential Bonferoni.

For the parameter V_M/V_E, the analyses of variance show that M traits have significantly higher V_M/V_E than G traits in all groupings, and higher than L traits in groupings 1 and 2. The pattern of differences among species is similar in all groupings, with *M. musculus* and Zea having significantly higher, and *H. vulgare* and Drosophila significantly lower V_M/V_E values. There was no evidence for class by species interactions ($P > 0.8$).

For CV_M, there is a weak indication of species by trait class interaction ($P = 0.14$, grouping 1; $P = 0.11$,

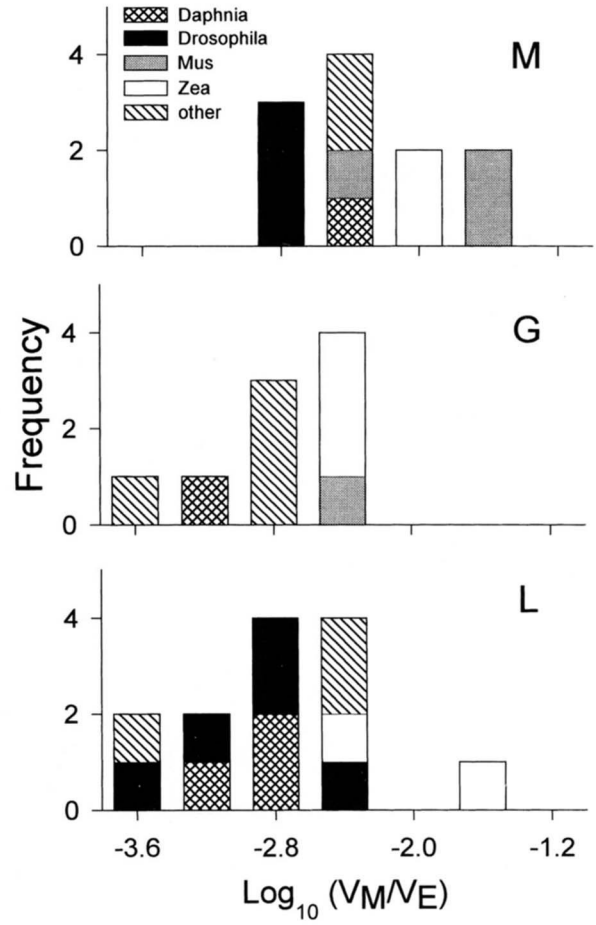

FIGURE 1.—Histogram of $\log_{10} V_M/V_E$ values by trait class and species.

grouping 2). Inspection of model parameter estimates and trait medians (shown in Figure 2) reveals that this tendency is due to differences in the magnitude of effects between species, with the effect in Drosophila being particularly strong, and not to reversals of the direction of effects. The significance and direction of differences was not changed when the interaction term is omitted. Whether or not the interaction term is included, our prediction based on the mutation-selection balance hypothesis is borne out. For all three data groupings, L traits have significantly higher values than M or G traits. The difference between L and M is significant at $P < 0.0001$ for groupings 1 and 2, and $P = 0.012$ for grouping 3. G traits have similar CV_M values to M traits. Note that the differences between morphological and life history traits are quite large; the least squares means for M, G and L traits are, respectively, 0.25, 0.70, and 1.65 on an arithmetic scale for data grouping 2. When converted to a variance scale by squaring these values, L traits have more than 40 times more mean standardized mutational variance than M traits. The significant species differences stem from Zea having higher CV_M than *Daphnia pulex* and Mus. For data grouping 3, a paired *t*-test within species also shows

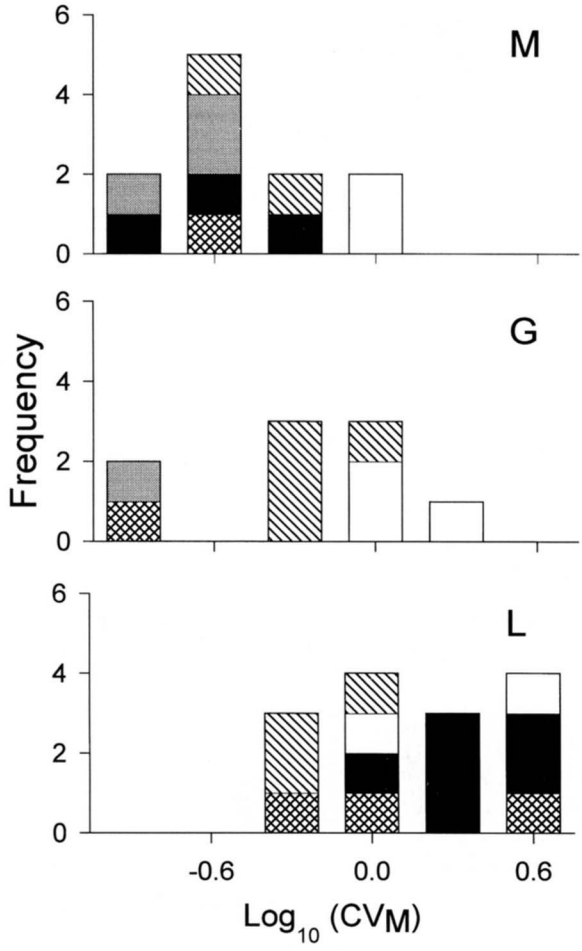

FIGURE 2.—Histogram of $\log_{10} CV_M$ values by trait class and species.

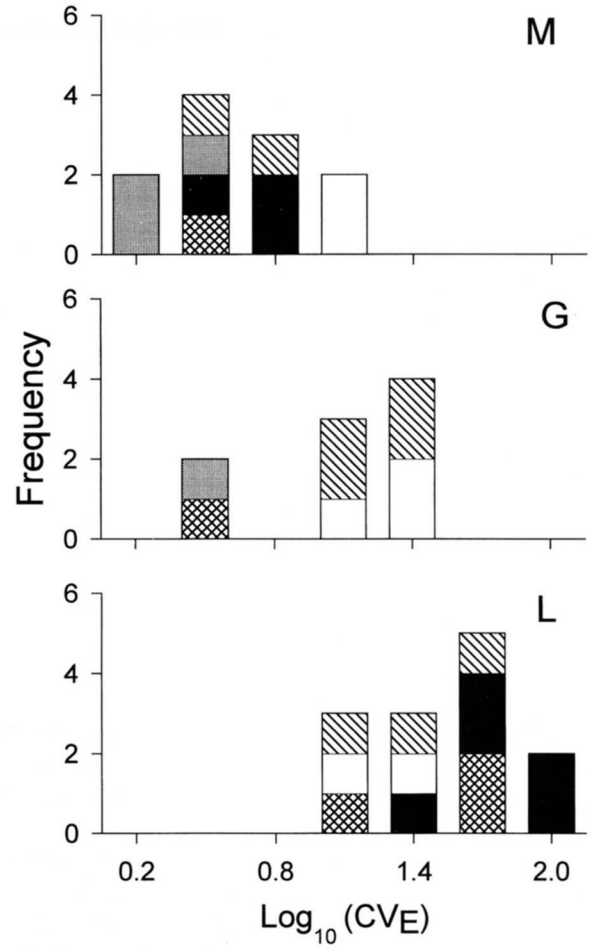

FIGURE 3.—Histogram of $\log_{10} CV_E$ values by trait class and species.

that L traits have significantly higher values than M traits ($P = 0.025$).

Analyses of CV_E show that there is less nongenetic variance in M traits than L traits, with G traits intermediate. The significant species differences involve Mus, which has low levels of environmental variation in the traits studied. The species by class interaction is highly significant for grouping 1, but as with the CV_M analysis above, this is due to there being stronger evidence for differences in Daphnia and Drosophila than in the crop plants, rather than reversals in the direction of effects. These results are comparable to those of HOULE (1992) who analyzed the mean-standardized residual variance, $V_P - V_A$.

COMPARING GENETIC AND MUTATIONAL VARIANCES

In order to compare the ratios of genetic to mutational variances with the limited data available we must make additional assumptions. There are currently no estimates of V_M and V_G from the same population, so we must assume that both the selection regime and the mutation rates are typical for the populations where data are available.

In the outbreeding species, Drosophila, Mus, or *Tribolium castaneum,* we would like to compare the additive mutational variance, when all mutants are in heterozygous condition, with the standing additive variance in an equilibrium random mating population. For these species, persistence times will be biased if mutant alleles do not act additively, since mutational effects were generally assayed in homozygous condition. There is good evidence that the assumption of additivity cannot hold exactly for both fitness components and morphological traits. For fitness components, the observation of inbreeding depression rules out additivity in favor of at least partially recessive gene action (CHARLESWORTH and CHARLESWORTH 1987). The well-established fact that most alleles with large effects on morphological traits are recessive supports this pattern. For viability in *D. melanogaster,* new mutations consist of a small proportion (<5%) of almost completely recessive lethals; the remainder have small effects that are nearly additive, with an average dominance of about 0.4 (SIMMONS and CROW 1977; CROW and SIMMONS 1983). In natural populations, selection eliminates dominant mutations more quickly, so that the average dominance at equilibrium drops to about 0.2 (CROW

TABLE 4

Summary of probability values from trait class analyses

Parameter	Group	Species	Class	Pairwise class[a]		
V_M/V_E	1	****	***	G	L	M
	2	****	***	G	L	M
	3	***	*	G	L	M
CV_M	1	***	****	M	G	L
	2	*	***	M	G	L
	3	†	*	G	M	L
CV_E	1	****	****	M	G	L
	2	*	****	M	G	L
	3	ns	*	M	G	L
V_G/V_M		****	***	L	M	G

[a] Trait classes are listed in increasing order. Solid lines connect trait classes that are not significantly different. The comparison M *vs.* L was carried out at a significance level of $P = 0.05$, while criteria for the other two comparisons were adjusted using the sequential Bonferoni correction for three comparisons. † $0.1 > P > 0.05$; * $P < 0.05$; *** $P < 0.001$; **** $P < 0.0001$.

1979; CROW and SIMMONS 1983). *P*-element insertions with relatively large effects on bristle number in *D. melanogaster* studied by MACKAY *et al.* (1992) often had effects that were partially recessive. Among these largest mutations, the degree of dominance was inversely related to their homozygous effects, as with viability mutations.

The effect of these departures from additivity is to bias the estimates of V_G/V_M downward by a factor of $1 - 4h^2$, where h is the average dominance parameter. For nonlethal mutations affecting viability, this should result in estimates that are too small by a factor of 1.5. However, since both morphological and life history traits seem to be subject to the same biases, this should not affect the comparisons between trait classes.

For Hordeum, Oryza and Daphnia, mutations were assayed in typical genotypes for the mating system: selfing for Oryza and Hordeum; clonal reproduction for long periods in Daphnia. The situation for Zea is more complicated, as the selfing rate is probably not high in a natural population. However, the mutational and standing variances are for cultivars where most selection takes place during cycles of inbreeding and hybridization.

A more general problem with the estimates of persistence is that many estimates of V_G are for populations either clearly or potentially not at equilibrium. For the three crop plants, Hordeum, Oryza and Zea, the published studies on standing variance tend to be seeking material in which the variance in desirable traits is maximized, rather than typical, biasing our estimates of standing variance upwards. On the other hand, the standing variance may have been depleted by previous artificial selection. It is not even clear that any equilibrium populations of these cultivars exist. For Daphnia, the two available studies are of wild animals brought into the laboratory and the estimates are thus potentially affected by genotype-environment interactions. For Drosophila, Tribolium and Mus, estimates of variance have been obtained from laboratory populations. In Drosophila and Tribolium, we only used variances from populations that had been in the laboratory for a hundred generations or more, so any biases are probably minor if the mutation-selection balance hypothesis is true. On the other hand, the Mus populations are relatively recently derived from crosses of inbred lines, and so the genetic variances are likely to be biased. Nevertheless we feel that these comparisons are useful, if only to spur further studies.

The available data on standing variance for traits where we have estimates of V_M are summarized in Table 5. The means for the same traits often differ from study to study, so we chose to compare the ratio of coefficients of variation, to account for possible scale effects. As with the mutational data, trait means were sometimes not available from the cited studies directly and were drawn from other sources. For Drosophila and Tribolium, variance estimates are from the more extensive compilation of HOULE (1992). We show estimates of both additive and total genetic coefficients of variation where available. In most cases where such comparisons are possible, the discrepancy between additive and total variance is not large. We calculated the persistence times, V_G/V_M, or V_A/V_M, as the ratio of the medians of the appropriate coefficients of variation squared. To minimize the potential for biases favorable to the mutation-selection balance hypothesis, analyses were carried out on the larger of the two ratios, $(CV_G/CV_M)^2$ or $(CV_A/CV_M)^2$.

The resulting ratios are graphed in Figure 4. The most striking thing about these persistence times is that the majority of them are quite small, even bearing in mind the possibility of bias due to dominance. The overall median is 83 generations, so well over half of the estimates are less than 100 generations. For L traits the median is only 48 generations, for M traits 115,

TABLE 5

Medians of standing additive and total genetic coefficients of variation for traits with mutation data

Species	Phenotype	CV_A	N^a	CV_G	N	Ref.[c]
Daphnia	Adult size	0.00	2	3.90	2	1
	Age at first reproduction	4.14	2	4.38	4	1, 2
	Clutch size	10.66	2	20.19	10	1, 2
	Offspring size	3.16	2	3.15	10	1, 2
Drosophila	Abdominal bristles	6.33	19			3, 4, 5
	Development time	2.45	2			6
	Fecundity	9.64	12			7, 8
	Longevity	10.15	7			7, 8
	Sternopleural bristles	7.32	21			3, 9
	Viability	10.40	6	10.90	6	10
	Wing dimensions	1.43	45			5, 7, 11
Hordeum	Grain yield	3.86	2			12
Mus	Limb dimensions	1.51	2			13
	Mandible dimensions	1.69	1			13
	6-week weight	2.78	4			14
	Skull dimensions	1.30	6			13
Oryza	Grain yield			2.89	4	15
	Panicle length			5.32	4	15
	Plant height			8.68	4	15
Tribolium	Pupal weight	1.95	3			16
Zea[b]	Ear diameter	8.41	53	8.88	53	17
	Ear length	9.95	36	11.48	36	17
	Grain yield	6.27	99	7.96	99	17
	Plant height	10.54	45	11.40	45	17
	Weight 100 grains	4.38	11	4.94	11	17

[a] N is the number of estimates analyzed over all references.

[b] HALLAUER and MIRANDA (1988); compiled estimates of variance components for *Zea* from the literature, but did not include data on means. Means used are the same as in Table 1.

[c] References: 1: LYNCH and DENG (1994); 2: LYNCH *et al.* (1989); 3: SEN and ROBERTSON (1964); SHERIDAN *et al.* (1968); MACKAY (1981); 4: CLAYTON *et al.* (1957); BOWMAN (1962); YOO (1980); SORENSEN and HILL (1982); 5: COYNE and BEECHAM (1987); 6: SANG and CLAYTON (1957); PROUT (1962); 7: TANTAWY and RAKHA (1964); TANTAWAY and EL-HELW (1966, 1970); 8: ROSE and CHARLESWORTH (1981); CHARLESWORTH (1984); SCHEINER *et al.* (1989); 9: LÓPEZ-FANJUL and HILL (1973); YOUSIF and SKIBINSKI (1982); GALLEGO and LÓPEZ-FANJUL (1983), 10: MUKAI (1988); 11: ROBERTSON and REEVE (1952); REEVE and ROBERTSON (1953); TANTAWY (1956); TANTAWY *et al.* (1964); TANTAWY and TAYEL (1970); COWLEY *et al.* (1986); WILKINSON (1987); 12: CHOO *et al.* (1986); 13: LEAMY (1974); 14: FALCONER (1973); MEYER and HILL (1991); 15: NEI (1960); 16: SCHEINBERG *et al.* (1967); BONDARI *et al.* (1978); HALLIBURTON and GALL (1981); 17: HALLAUER and MIRANDA (1988).

and for G traits 119 generations. On a log scale, the distribution of times is normal, so the transformed times were analysed in the SAS program GLM, as with the coefficients of variation. This analysis is summarized in the last line of Table 4. The effect of class is highly significant. Our prediction based on mutation-selection balance is borne out with L traits having significantly lower persistence times than M or G traits ($P < 0.01$ in both cases). M and G traits are not significantly different from each other. The species by trait interaction term is nearly significant ($P = 0.1$). Inclusion of this term intensifies the significance of the trait class effect slightly.

DISCUSSION

Our review reveals a pattern strikingly favorable to the mutation-selection balance hypothesis. Life history traits have much larger mutational coefficients of variation than morphological traits, which supports both mutation-selection balance and the mutational target theory for the high variance of life history traits. The persistence times are overall quite low, consistent with deleterious mutations playing an important role in the maintenance of variation. Finally, the persistence times for life history traits are significantly lower than those for morphological traits.

Patterns in mutational coefficients of variation: Standardizing mutational variance by the trait mean reveals that traits that are more closely connected with fitness have higher proportional inputs of variance. This is consistent with the hypothesis that life history traits are larger mutational targets (HOULE 1991) and that mutation-selection balance can explain the large standing genetic variance in such traits (HOULE 1992). It does not however rule out two alternative hypotheses. Balancing selection may still play an important role in the maintenance of variation, and modifiers may have

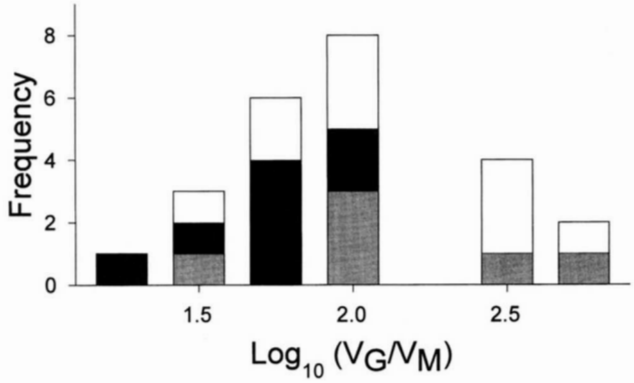

FIGURE 4.—Histogram of $\log_{10}$ *persistence times* (V_G/V_M) values by trait class. Black bars, L traits; grey bars, G traits; open bars, M traits.

evolved that reduce the variance of traits that are subject to stabilizing selection (LANDE 1980; HOULE 1992; POMIANKOWSKI and MØLLER 1995). However, our observation is clearly inconsistent with the suggestion that traits with the greatest fitness sensitivity are the most canalized (STEARNS *et al.* 1995).

The fact that measures of variation are correlated with the dimensionality of the trait (LANDE 1977; HOULE 1992) poses a problem for interpretation of differences between life history and morphological traits. For morphological traits it is clear what the appropriate dimensionality is. This is also true for life history traits that are clearly best treated as volumes, such as grain yields. Ambiguity arises for other life history traits that are potentially correlated with biomass. We favor our current interpretation of dimensionalities in Table 1 because there is no evidence that genetic correlations between size and lifetime fitness are generally positive; size is usually thought to be under stabilizing selection. If we were to reclassify all life history traits as three dimensional, this would still be insufficient to wipe out the current sixfold difference between morphological and life history traits, particularly as grain yields have already been classified as three dimensional traits (Table 1). Our favored explanation for the large mutational variance of life history traits may be seen as essentially a version of the dimensionality argument. Volumes have higher coefficients of variation because they compound variances in linear dimensions (LANDE 1977); life history traits have higher coefficients of variation because they compound variances in many different processes, over the entire life-span of the organism (PRICE and SCHLUTER 1991; HOULE 1992).

Our finding that CV_E is larger for life history traits than for morphological traits is expected based on the higher residual coefficient of variation ($CV_R = 100\sqrt{V_P - V_A}/\bar{X}$), for life history traits found by HOULE (1992) based on a much larger data set. The present comparison is superior in that most of the studies reviewed here directly estimated the environmental variance. The similarity of the results for CV_E and CV_R argue that nonadditive genetic variance is not a major contributor to the high CV_R for life history traits.

Persistence times: The ratios of standing variance to mutational variance (V_G/V_M) are surprisingly small on the average and show that life history traits again receive a larger proportion of their variation by mutation. As noted in the introduction, V_G/V_M is the average persistence time for deleterious alleles in an infinite population. In a finite population,

$$\frac{V_G}{V_M} = \frac{2N_e}{1 + 2N_e s}$$

(KEIGHTLEY and HILL 1988; BÜRGER *et al.* 1989; HOULE 1989), which approaches $2N_e$ when $2N_e s$ approaches zero, as in a small population, or under neutrality. In most cases, our estimates of standing variances are for populations where N_e is likely to be much greater than the median persistence time estimate. These values therefore suggest either that selection is important in eliminating much new mutational variance or that the populations where estimates are available have less than equilibrium levels of variation. This last possibility seems reasonable for Mus, where some populations studied had been founded as few as 40 generations earlier by crossing inbred lines (LEAMY 1974), and for the crop plants. However, this is not necessarily so, as these populations could have levels of variation higher than equilibrium, if phenotypically diverse genotypes were used to found each population.

The low median persistence time of less than 100 generations overall and less than 50 for life history traits are close to what would be expected under mutation-selection balance given what we know about the average fitness effect of unselected mutations. Estimates of the average selection coefficient against heterozygous mutants due to viability selection in *D. melanogaster* are approximately 1–5% (CROW and SIMMONS 1983; MACKAY *et al.* 1992a; KEIGHTLEY 1994), suggesting persistence times of only 20–100 generations for this trait. These experimental estimates of the average effect of mutations are subject to contradictory biases that make them somewhat uncertain. Two factors inflate these estimates. The mutation accumulation method for estimating average effects yields only a maximum value for s (CROW and SIMMONS 1983), while the *P*-element insertions studied by MACKAY *et al.* probably have larger than average fitness effects (MACKAY *et al.* 1992a; KEIGHTLEY 1994). On the other hand, the estimates are biased downward in that they measure only the deleterious effects on viability, and these are positively correlated with effects on other fitness components (YOSHIMARU and MUKAI 1985; HOULE *et al.* 1994).

In spite of these uncertainties, the estimates of V_G/V_M for three life history traits in Drosophila are all close to the expected persistence times based on the estimated average effect for viability. For viability, $V_G/V_M = 48$; for fecundity, $V_G/V_M = 26$; for longevity $V_G/V_M = 57$.

They are corroborated by an independent estimate of the persistence time for viability in *D. melanogaster* based on the ratio of the rate of decline in the mean due to mutation pressure to the mutational load, which gives persistence times of 50 generations (CROW and SIMMONS 1983). Even if the most conservative interpretations of the above data are made, doubling the largest estimates of the average deleterious effect to $s = 0.1$, which would yield persistence times of 10 generations, about 20% of the variance in fitness components in *D. melanogaster* would be explicable by mutation-selection balance. If the average selection is less than this, as various arguments suggest (KEIGHTLEY 1994), mutation-selection balance may be able to explain most of the variation in these important life history traits. While there are no comparably direct estimates of average fitness effects of mutations in other species, there is no reason to suspect that mutant effects in other species will prove different.

On the other hand, there is also evidence that the simplest mutation-selection balance model cannot explain all of the genetic variance in some cases. MUKAI's (1988) more detailed analysis of the standing variance for viability shows that *D. melanogaster* populations at low latitudes have 10 times the genetic variance of high latitude ones. Thus, while the mean genetic variance may be explicable by a simple mutation-selection balance hypothesis, the variation among populations is clearly not. MUKAI suggested that this discrepancy could be explained by increased opportunity for balancing selection due to genotype-environment interactions at low latitudes. Potential alternative explanations include more recent introduction of *D. melanogaster* to, or reduced effective population size at high latitudes. Another possibility is greater selection against deleterious alleles in a high latitude environment. The observation that relative fitnesses can change by more than an order of magnitude as the environment becomes harsher lends credence to this possibility (KONDRASHOV and HOULE 1994).

For morphological traits, this reanalysis of mutational data also strengthens the case for mutation-selection balance substantially. For example, the argument that there is insufficient mutational variance to account for observed amounts of stabilizing selection by pleiotropic effects on fitness (BARTON 1990; KONDRASHOV and TURELLI 1992) is based on using the "typical" value for V_M/V_E of 10^{-3} as an approximation for V_M/V_G, which in turn estimates the average selection coefficient against mutant alleles under mutation-selection balance. All of our estimates of V_M/V_G are greater than 10^{-3}, and more than half are greater than 10^{-2}. Part of the reason for the emphasis on the 10^{-3} figure is that it is close to V_M/V_G for the well-studied bristle traits in *D. melanogaster*. The persistence times for abdominal and sternopleural bristles are 692 and 362 generations, respectively, which are among the largest times we found, rather than typical ones. The persistence times compiled here are thus consistent with modest apparent stabilizing selection on other morphological traits.

Future studies: We are painfully aware that the data available for this review are sparse and that the quality of many available estimates is not high. For example, some estimates of V_M from LYNCH (1985) and HOULE *et al.* (1994) are not significantly different from zero or are only marginally significant. For many earlier studies, we have only an estimate of V_M, and no estimates of the statistical error. In most cases the possibility of variation in V_M among genotypes within species remains unaddressed. The exception is *D. melanogaster*, where there is strong evidence that strains possessing the *P* transposable element have substantially higher V_M for bristles traits than those without (KEIGHTLEY *et al.* 1993). Another glaring gap in the current data is the lack of estimates of V_M and V_G in the same population. There is frequently substantial variation in estimates of standing variance for the same trait in different populations (MOUSSEAU and ROFF 1987; ROFF and MOUSSEAU 1987). Much of this must be due to sampling error, but variation among populations in V_M could explain some real variation in V_G. We hope we have made clear that such estimates bear on interesting questions; part of our purpose here is to spur additional experimental work that may result in better estimates.

Mutation-selection balance and the genetics of adaptation: In supporting the mutation-selection balance model for the maintenance of variation, our results tend to cast doubt on a model of adaptation where most of the genetic variation in an equilibrium population is assumed to be available to promote adaptation under a new selective regime. This view is justified under mutation-selection balance if each aspect of the phenotype is controlled by loci with effects on just a few other traits, as in the simplest versions of mutation-selection balance (KIMURA 1965; LANDE 1976a; TURELLI 1984). Several observations argue that this cannot be generally true (BARTON 1990; KEIGHTLEY and HILL 1990). First, morphological mutants generally have pleiotropic effects on fitness that are difficult to ascribe to selection acting directly on the trait studied (*e.g.*, MACKAY *et al.* 1992a). Second, substantial apparent selection on each phenotypic trait is generally observed. In a few cases, there is direct evidence that this does not arise through selection on the trait itself (*e.g.*, NUZHDIN *et al.* 1995). More generally, if selection of this magnitude acts independently on a large number of traits this implies a larger variance in relative fitness than we observe (BARTON 1990). It would also imply a large genetic load.

The alternative to the simple, direct mutation-selection balance model is a pleiotropic one, where most loci affect many traits (ROBERTSON 1967; HILL and KEIGHTLEY 1988; BARTON 1990; KEIGHTLEY and HILL 1990). Since the average mutation is clearly deleterious, the widespread pleiotropy integral to this model

implies that these deleterious effects are probably the result of some fundamental physiological or developmental process the locus is involved in, or the combined effects of selection on many aspects of the phenotype. If either of these is the case, it will be difficult for an ecological change that affects the fitness function of only a few traits to result in selection in favor of these alternative alleles. If the average mutation only persists for 50 to 100 generations, the vast majority of mutants are so strongly selected against that their early exit from the population is assured without a large change in selective regime. Artificial selection experiments are successful because they result in such a change. The frequent observations of a large negative response following relaxation of artificial selection and of loss of fitness during selection experiments (FALCONER 1989) may show the strength of countervailing pleiotropic selection.

Undoubtedly, there are always some alleles poised on the edge between negative and positive selective value, and it is from this minority that new adaptations will tend to arise in a natural population. However, the premise of the quantitative genetic approach to the study of evolution is that the variation within populations is the same variation that is ultimately responsible for adaptation and the resulting differences among populations and species. If, instead, most of the variation within populations is deleterious junk that can only be fixed at a substantial correlated cost, then only a small proportion of the standing variance is relevant to long-term evolution. Most evolutionary change must then consist of trying to recapture the fitness of a generation ago, rather than improving on it.

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LITERATURE CITED

BAILEY, D. W., 1959 Rates of subline divergence in highly inbred strains of mice. J. Hered. **50:** 26–30.

BARTON, N., 1990 Pleiotropic models of quantitative variation. Genetics **124:** 773–782.

BARTON, N. H., and M. TURELLI, 1989 Evolutionary quantitative genetics: how little do we know? Annu. Rev. Genet. **23:** 337–370.

BONDARI, K., R. L. WILLHAM and A. E. FREEMAN, 1978 Estimates of direct and maternal genetic correlations for pupa weight and family size of *Tribolium*. J. Anim. Sci. **47:** 358–365.

BOWMAN, J. C., 1962 Recurrent selection. II. An experimental study with mice and *Drosophila*. Genet. Res. **3:** 333–351.

BÜRGER, R., G. P. WAGNER and F. STETTINGER, 1989 How much heritable variation can be maintained in finite populations by a mutation selection balance? Evolution **43:** 1748–1766.

BURTON, G. W., 1952 Quantitative inheritance in grasses. Proceedings of the Sixth International Grassland Congress **6:** 277–283.

CABALLERO, A., P. D. KEIGHTLEY and W. G. HILL, 1995 Accumulation of mutations affecting body weight in inbred mouse lines. Genet. Res. **65:** 145–149.

CARDELLINO, R. A., and T. MUKAI, 1975 Mutator factors and genetic variance components of viability in *Drosophila melanogaster*. Genetics **80:** 567–583.

CARPENTER, J. R., H. GRÜNEBERG and E. S. RUSSELL, 1957 Genetical differentiation involving morphological characters in an inbred strain of mice. II. American branches of the C57BL and C57BR strains. J. Morphol. **100:** 377–388.

CHAKRABORTY, R., and M. NEI, 1982 Genetic differentiation of quantitative characters between populations or species. I. Mutation and random genetic drift. Genet. Res. **39:** 303–314.

CHARLESWORTH, B., 1984 The evolutionary genetics of life histories, pp. 117–133 in *Evolutionary Ecology*, edited by B. SHORROCKS. Blackwell, Oxford.

CHARLESWORTH, D., and B. CHARLESWORTH, 1987 Inbreeding depression and its evolutionary consequences. Annu. Rev. Ecol. Syst. **18:** 237–268.

CHOO, T. M., A. KOTECHA, E. REINBERGS, L. S. P. SONG and S. O. FEJER, 1986 Diallel analysis of grain yield in barley using doubled-haploid lines. Plant Breeding **97:** 129–137.

CLAYTON, G. A., and A. ROBERTSON, 1955 Mutation and quantitative genetic variation. Am. Nat. **89:** 151–158.

CLAYTON, G. A., and A. ROBERTSON, 1964 The effects of X-rays on quantitative characters. Genet. Res. **5:** 410–422.

CLAYTON, G. A., J. A. MORRIS and A. ROBERTSON, 1957 An experimental check on quantitative genetic theory. I. Short-term response to selection. J. Genet. **55:** 131–151.

COWLEY, D. E., W. R. ATCHLEY and J. J. RUTLEDGE, 1986 Quantitative genetics of *Drosophila melanogaster*. I. Sexual dimorphism in genetic parameters for wing traits. Genetics **114:** 549–566.

COX, T. S., D. J. COX and K. J. FREY, 1987 Mutations for polygenic traits in barley under nutrient stress. Euphytica **36:** 823–829.

COYNE, J. A., and E. BEECHAM, 1987 Heritability of two morphological characters within and among natural populations of *Drosophila melanogaster*. Genetics **117:** 727–737.

CROW, J. F., 1958 Some possibilities for measuring selection intensities in man. Hum. Biol. **30:** 1–13.

CROW, J. F., 1979 Minor viability mutants in Drosophila. Genetics **92:** s165–s172.

CROW, J. F., 1993 Mutation, mean fitness, and genetic load. Oxford Surv. Evol. Biol. **9:** 3–42.

CROW, J. F., and M. J. SIMMONS, 1983 The mutation load in *Drosophila*, pp. 1–35 in *The Genetics and Biology of Drosophila*, Vol. 3c, edited by M. ASHBURNER, H. L. CARSON and J. N. THOMPSON, JR. Academic Press, London.

DEOL, M. S., H. GRÜNEBERG, A. G. SEARLE and G. M. TRUSLOVE, 1957 Genetical differentiation involving morphological characters in an inbred strain of mice. I. A British branch of the C57BL strain. J. Morphol. **100:** 345–375.

DURRANT, A., and K. MATHER, 1954 Heritable variation in a long inbred line of Drosophila. Genetica **27:** 97–119.

ENFIELD, F. D., and O. BRASKERUD, 1989 Mutational variance for pupa weight in *Tribolium castaneum*. Theor. Appl. Genet. **77:** 416–420.

FALCONER, D. S., 1973 Replicated selection for body weight in mice. Genet. Res. **22:** 291–321.

FALCONER, D. S., 1989 *Introduction to Quantitative Genetics*, 3rd ed. Longman Scientific and Technical, Harlow.

FESTING, M., 1973 A multivariate analysis of subline divergence in the shape of the mandible in C57BL/Gr mice. Genet. Res. **21:** 121–132.

GALLEGO, A., and C. LÓPEZ-FANJUL, 1983 The number of loci affecting a quantitative trait in *Drosophila melanogaster* revealed by artificial selection. Genet. Res. **42:** 137–149.

GILLESPIE, J. H., and M. TURELLI, 1989 Genotype-environment interactions and the maintenance of polygenic variation. Genetics **121:** 129–138.

GOODWILL, R., and F. D. ENFIELD, 1971 Heterozygosity in inbred lines of *Tribolium castaneum*. Theor. Appl. Genet. **41:** 5–12.

HALDANE, J. B. S., 1949 Suggestions as to quantitative measurement of rates of evolution. Evolution **3:** 51–56.

HALLAUER, A. R., and J. B. F. MIRANDA, 1988 *Quantitative Genetics in Maize Breeding*, 2nd ed. Iowa University Press, Ames.

HALLIBURTON, R., and G. GALL, 1981 Disruptive selection and assortative mating in *Tribolium castaneum*. Evolution **35:** 829–843.

HILL, W. G., 1982 Predictions of response to artificial selection from new mutations. Genet. Res. **40:** 255–278.

HILL, W. G., and P. D. KEIGHTLEY, 1988 Interrelations of mutation,

population size, artificial and natural selection, pp. 57–70 in *Proceedings of the Second International Conference on Quantitative Genetics*, edited by B. S. WEIR, E. J. EISEN, M. M. GOODMAN and G. NAMKOONG. Sinauer Press, Sunderland, MA.

HOLLINGDALE, B., and J. S. K. BARKER, 1971 Selection for increased abdominal bristle number in *Drosophila melanogaster* with concurrent irradiation. I. Populations derived from an inbred line. Theor. Appl. Genet. **41:** 208–215.

HOLM, S., 1979 A simple sequentially rejective multiple test procedure. Scand. J. Statist. **6:** 65–70.

HOULE, D., 1989 The maintenance of polygenic variation in finite populations. Evolution **43:** 1767–1780.

HOULE, D., 1991 Genetic covariance of fitness correlates: what genetic correlations are made of and why it matters. Evolution **45:** 630–648.

HOULE, D., 1992 Comparing evolvability and variability of quantitative traits. Genetics **130:** 195–204.

HOULE, D., K. A. HUGHES, D. K. HOFFMASTER, J. IHARA, S. ASSIMACOPOULOS *et al.*, 1994 The effects of spontaneous mutation on quantitative traits. I. Variance and covariance of life history traits. Genetics **138:** 773–785.

JOHNSON, H. W., H. F. ROBINSON and R. E. COMSTOCK, 1955 Estimates of genetic and environmental variability in soybeans. Agron. J. **47:** 314–318.

KEIGHTLEY, P. D., 1994 The distribution of effects on viability in *Drosophila melanogaster*. Genetics **138:** 1315–1322.

KEIGHTLEY, P. D., and W. G. HILL, 1988 Quantitative genetic variability maintained by mutation-stabilizing selection balance in finite populations. Genet. Res. **52:** 33–43.

KEIGHTLEY, P. D., and W. G. HILL, 1990 Variation in quantitative traits with mutation-selection balance: pleiotropic side-effects on fitness traits. Proc. R. Soc. London B Biol. Sci. **242:** 95–100.

KEIGHTLEY, P. D., and W. G. HILL, 1992 Quantitative genetic variation in body size of mice from new mutations. Genetics **131:** 693–700.

KEIGHTLEY, P. D., T. F. C. MACKAY and A. CABALLERO, 1993 Accounting for bias in estimates of the rate of polygenic mutation. Proc. R. Soc. London B Biol. Sci. **253:** 291–296.

KIMURA, M., 1965 A stochastic model concerning the maintenance of genetic variability in quantitative characters. Proc. Natl. Acad. Sci. USA **54:** 731–736.

KITAGAWA, O., 1967 The effects of X-ray irradiation on selection response in *Drosophila melanogaster*. Jpn. J. Genet. **42:** 121–137.

KONDRASHOV, A. S., and D. HOULE, 1994 Genotype-environment interactions and the estimation of the genomic mutation rate in *Drosophila melanogaster*. Proc. R. Soc. London B Biol. Sci. **258:** 221–227.

KONDRASHOV, A. S., and M. TURELLI, 1992 Deleterious mutations, apparent stabilizing selection and the maintenance of quantitative variation. Genetics **132:** 603–618.

LANDE, R., 1976a The maintenance of genetic variability by mutation in a polygenic character with linked loci. Genet. Res. **26:** 221–235.

LANDE, R., 1976b Natural selection and random genetic drift in phenotypic evolution. Evolution **30:** 314–344.

LANDE, R., 1977 On comparing coefficients of variation. Syst. Zool. **26:** 214–217.

LANDE, R., 1979 Quantitative genetic analysis of multivariate evolution applied to brain:body size allometry. Evolution **33:** 402–416.

LANDE, R., 1980 Genetic variation and phenotypic evolution during allopatric speciation. Am. Nat. **116:** 463–479.

LEAMY, L., 1974 Heritability of osteometric traits in a randombred population of mice. J. Hered. **65:** 109–120.

LI, W.-H., and M. NEI, 1972 Total number of individuals affected by a single deleterious mutation in a finite population. Am. J. Hum. Genet. **24:** 667–679.

LÓPEZ, M. A., and C. LÓPEZ-FANJUL, 1993a Spontaneous mutation for a quantitative trait in *Drosophila melanogaster*. I. Response to artificial selection. Genet. Res. **61:** 107–116.

LÓPEZ, M. A., and C. LÓPEZ-FANJUL, 1993b Spontaneous mutation for a quantitative trait in *Drosophila melanogaster*. II. Distribution of mutant effects on the trait and fitness. Genet. Res. **61:** 117–126.

LÓPEZ-FANJUL, C., and W. G. HILL, 1973 Genetic differences between populations of *Drosophila melanogaster* for a quantitative trait. I. Laboratory populations. Genet. Res. **22:** 51–68.

LYNCH, M., 1985 Spontaneous mutations for life-history characters in an obligate parthenogen. Evolution **39:** 804–818.

LYNCH, M., 1988 The rate of polygenic mutation. Genet. Res. **51:** 137–148.

LYNCH, M., 1994 Neutral models of phenotypic evolution, pp. 86–108 in *Ecological Genetics*, edited by L. A. REAL. Princeton University Press, Princeton, NJ.

LYNCH, M., and H.-W. DENG, 1994 Genetic slippage in response to sex. Am. Nat. **144:** 242–261.

LYNCH, M., and W. G. HILL, 1986 Phenotypic evolution by neutral mutation. Evolution **40:** 915–935.

LYNCH, M., and R. LANDE, 1992 Evolution and extinction in response to environmental change, pp. 234–250 in *Biotic Interactions and Global Change*, edited by P. M. KAREIVA, J. G. KINGSOLVER and R. B. HUEY. Sinauer Associates, Sunderland, MA.

LYNCH, M., K. SPITZE and T. CREASE, 1989 The distribution of life-history variation in the *Daphnia pulex* complex. Evolution **43:** 1724–1736.

MACKAY, T. F. C., 1981 Genetic variation in varying environments. Genet. Res. **37:** 79–93.

MACKAY, T. F. C., 1986 A quantitative genetic analysis of fitness and its components in *Drosophila melanogaster*. Genet. Res. **47:** 59–70.

MACKAY, T. F. C., R. F. LYMAN and M. S. JACKSON, 1992a Effects of *P* element insertions on quantitative traits in *Drosophila melanogaster*. Genetics **130:** 315–332.

MACKAY, T. F. C., R. F. LYMAN, M. S. JACKSON, C. TERZIAN and W. G. HILL, 1992b Polygenic mutation in *Drosophila melanogaster*. Estimates from divergence among inbred strains. Evolution **46:** 300–316.

MACKAY, T. F. C., J. D. FRY, R. F. LYMAN and S. V. NUZHDIN, 1994 Polygenic mutation in *Drosophila melanogaster*: estimates from response to selection of inbred strains. Genetics **136:** 937–951.

MALECOT, G., 1969 *The Mathematics of Heredity*. W. H. Freeman and Company, San Francisco.

MATHER, K., and L. G. WIGAN, 1942 The selection of invisible mutations. Proc. R. Soc. London B Biol. Sci. **131:** 50–64.

MEYER, K., and W. G. HILL, 1991 Mixed model analysis of a selection experiment for food intake in mice. Genet. Res. **57:** 71–81.

MOUSSEAU, T. A., and D. A. ROFF, 1987 Natural selection and the heritability of fitness components. Heredity **59:** 181–197.

MUKAI, T., 1964 The genetic structure of natural populations of *Drosophila melanogaster*. I. Spontaneous mutation rate of polygenes controlling viability. Genetics **50:** 1–19.

MUKAI, T., 1988 Genotype-environment interaction in relation the the maintenance of genetic variability in populations of *Drosophila melanogaster*, pp. 21–31 in *Proceedings of the Second International Conference on Quantitative Genetics*, edited by B. S. WEIR, E. J. EISEN, M. J. GOODMAN and G. NAMKOONG. Sinauer, Sunderland, MA.

MUKAI, T., S. I. CHIGUSA, L. E. METTLER and J. F. CROW, 1972 Mutation rate and dominance of genes affecting viability in *Drosophila melanogaster*. Genetics **72:** 335–355.

MUKAI, T., S. I. CHIGUSA and S. KUSAKABE, 1982 The genetic structure of natural populations of *Drosophila melanogaster*. XV. Nature of developmental homeostasis for viability. Genetics **101:** 279–300.

MUKAI, T., K. HARADA and H. YOSHIMARU, 1984 Spontaneous mutations modifying the activity of alcohol dehydrogenase (ADH) in *Drosophila melanogaster*. Genetics **106:** 73–84.

NEI, M., 1960 *Studies on the Application of Biometrical Genetics to Plant Breeding. Memoirs of the College of Agriculture, Kyoto University*, Vol. 82. Kyoto University, Kyoto, Japan.

NUZHDIN, S. V., J. D. FRY and T. F. C. MACKAY, 1995 Polygenic mutation in *Drosophila melanogaster*: the causal relationship of bristle number to fitness. Genetics **139:** 861–872.

OHNISHI, O., 1977 Spontaneous and ethyl methanesulfonate-induced mutations controlling viability in *Drosophila melanogaster*. II. Homozygous effects of polygenic mutations. Genetics **87:** 547–556.

OKA, H.-I., J. HAYASHI and I. SHIOJIRI, 1958 Induced mutation of polygenes for quantitative characters in rice. J. Hered. **49:** 11–14.

PAXMAN, G. J., 1957 A study of spontaneous mutation in *Drosophila melanogaster*. Genetica **29:** 39–57.

POMIANKOWSKI, A., and A. P. MØLLER, 1995 A resolution of the lek paradox. Proc. R. Soc. London B Biol. Sci. **260:** 21–29.

PRICE, T., and D. SCHLUTER, 1991 On the low heritability of life history traits. Evolution **45:** 853–861.

PROUT, T., 1962 The effects of stabilizing selection on the time of development in *Drosophila melanogaster*. Genet. Res. **3:** 364–382.

REEVE, E. C., and F. W. ROBERTSON, 1953 Studies in quantitative inheritance. II. Analysis of a strain of *Drosophila melanogaster* selected for long wings. J. Genet. **51:** 276–316.

RICE, W. R., 1989 Analyzing tables of statistical tests. Evolution **43:** 223–226.

ROBERTSON, A., 1967 The nature of quantitative genetic variation, pp. 265–280 in *Heritage from Mendel*, edited by R. A. BRINK. University of Wisconsin, Madison.

ROBERTSON, F. W., and E. C. R. REEVE, 1952 Studies in quantitative inheritance. I. The effects of selection for wing and thorax length in *Drosophila melanogaster*. J. Genet. **50:** 416–448.

ROFF, D. A., and T. A. MOUSSEAU, 1987 Quantitative genetics and fitness: lessons from *Drosophila*. Heredity **58:** 103–118.

ROSE, M., 1982 Antagonistic pleiotropy, dominance, and genetic variation. Heredity **48:** 63–78.

ROSE, M. R., and B. CHARLESWORTH, 1981 Genetics of life-history in *Drosophila melanogaster*. I. Sib analysis of adult females. Genetics **97:** 173–186.

RUSSELL, W. A., G. F. SPRAGUE and L. H. PENNY, 1963 Mutations affecting quantitative characters in long-time inbred lines of maize. Crop Sci. **3:** 175–178.

SAKAI, K.-I., and A. SUZUKI, 1964 Induced mutation and pleiotropy of genes responsible for quantitative characters in rice. Radiation Botany **4:** 141–151.

SANG, J. H., and G. A. CLAYTON, 1957 Selection for larval development time in *Drosophila*. J. Hered. **48:** 265–270.

SANTIAGO, E., J. ALBORNOZ, A. DOMINGUEZ, M. A. TORO, and C. LÓPEZ-FANJUL, 1992 The distribution of spontaneous mutations on quantitative traits and fitness in *Drosophila melanogaster*. Genetics **132:** 771–781.

SAS INSTITUTE, I., 1990 *SAS/STAT User's Guide*, Version 6, 4th ed. SAS Institute, Cary, NC.

SCHEINBERG, E., A. E. BELL and V. L. ANDERSON, 1967 Genetic gain in populations of *Tribolium castaneum* under uni-stage tandem selection and under restricted selection indices. Genetics **55:** 69–90.

SCHEINER, S. M., R. L. CAPLAN and R. F. LYMAN, 1989 A search for trade-offs among life-history traits in *Drosophila melanogaster*. Evol. Ecol. **3:** 51–63.

SCHLUTER, D., T. D. PRICE and L. ROWE, 1991 Conflicting selection pressures and life history trade-offs. Proc. R. Soc. London B Biol. Sci. **246:** 11–17.

SEN, B. K., and A. ROBERTSON, 1964 An experimental examination of methods for the simultaneous selection of two characters using *Drosophila melanogaster*. Genetics **50:** 199–209.

SHERIDAN, A. K., R. FRANKHAM, K. A. RATHIE and J. S. F. BARKER, 1968 Partitioning variance and estimation of genetic parameters for various bristle number characters of *Drosophila melanogaster*. Theor. Appl. Genet. **38:** 179–187.

SIMMONS, M. J., and J. F. CROW, 1977 Mutations affecting fitness in Drosophila populations. Annu. Rev. Genet. **11:** 49–78.

SORENSEN, D. A., and W. G. HILL, 1982 Effect of short term directional selection on genetic variability: experiments with *Drosophila melanogaster*. Heredity **48:** 27–33.

SPRAGUE, G. F., W. A. RUSSELL and L. H. PENNY, 1960 Mutations affecting quantitative traits in the selfed progeny of doubled monoploid maize stocks. Genetics **45:** 855–866.

STEARNS, S. C., M. KAISER and T. J. KAWECKI, 1995 The differential genetic and environmental canalization of fitness components in *Drosophila melanogaster*. J. Evol. Biol. **8:** 539–557.

SVED, J. A., 1971 An estimate of heterosis in *Drosophila melanogaster*. Genet. Res. **18:** 97–105.

SVED, J. A., 1975 Fitness of third chromosome homozygotes in *D. melanogaster*. Genet. Res. **25:** 197–200.

TANTAWY, A. O., 1956 Selection for long and short wing lengths in *Drosophila melanogaster* with different systems of mating. Genetica **28:** 231–262.

TANTAWY, A. O., and M. R. EL-HELW, 1966 Studies on natural populations of *Drosophila*. V. Correlated response to selection in *Drosophila melanogaster*. Genetics **53:** 97–110.

TANTAWY, A. O., and M. R. EL-HELW, 1970 Studies on natural populations of *Drosophila*. IX. Some fitness components and their heritabilities in natural and mutant populations of *Drosophila melanogaster*. Genetics **64:** 79–91.

TANTAWY, A. O., and F. A. RAKHA, 1964 Studies on natural populations of *Drosophila*. IV. Genetic variances and correlations between four characters in *Drosophila melanogaster* and *Drosophila simulans*. Genetics **50:** 1349–1355.

TANTAWY, A. O., and A. A. TAYEL, 1970 Studies on natural populations of *Drosophila*. X. Effects of disruptive and stabilizing selection on wing length and the correlated response in *Drosophila melanogaster*. Genetics **65:** 121–132.

TANTAWY, A. O., G. S. MALLAH and H. R. TEWFIK, 1964 Studies on natural populations of *Drosophila*. II. Heritability and response to selection for wing length in *Drosophila melanogaster* and *D. simulans* at different temperatures. Genetics **49:** 935–948.

TURELLI, M., 1984 Heritable genetic variation via mutation-selection balance: Lerch's zeta meets the abdominal bristle. Theor. Popul. Biol. **25:** 138–193.

VELDBOOM, L. R., and M. LEE, 1994 Molecular-marker-facilitated studies of morphological traits in maize. II: Determination of QTLs for grain yield and yield components. Theor. Appl. Genet. **89:** 451–458.

WEBER, K. E., and L. T. DIGGINS, 1990 Increased selection response in larger populations. II. Selection for ethanol vapor resistance in *Drosophila melanogaster* at two population sizes. Genetics **125:** 585–597.

WILKINSON, G. S., 1987 Equilibrium analysis of sexual selection in *Drosophila melanogaster*. Evolution **41:** 11–21.

YONG, H.-S., 1972 Is subline differentiation a continuing process in inbred strains of mice? Genet. Res. **19:** 53–59.

YOO, B. H., 1980 Long term selection for a quantitative character in large replicate populations of *Drosophila melanogaster* I. Response to selection. Genet. Res. **35:** 1–17.

YOSHIMARU, H., and T. MUKAI, 1985 Relationships between the polygenes affecting the rate of development and viability in *Drosophila melanogaster*. Jpn. J. Genet. **60:** 307–334.

YOUSIF, M. E., and D. O. F. SKIBINSKI, 1982 Directional-disruptive selection in *Drosophila melanogaster*. Heredity **49:** 71–79.

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APPENDIX

The approach we have taken to estimating the environmental variance for *D. melanogaster* egg-to-adult viability differs from that in LYNCH (1988). In these studies (MUKAI 1964; MUKAI *et al.* 1972; CARDELLINO and MUKAI 1975; OHNISHI 1977), a homozygous wild-type genotype (+/+) segregates with a marked heterozygous genotype (*Cy*/+), which is treated as a control. The expected Mendelian ratio in each case is 1 +/+ to 2 *Cy*/+. We will symbolize the counts of the numbers of *Cy*/+ individuals m, and the number of +/+ individuals n. Variation in the relative abundance of the two genotypes among lines is used to estimate the genetic variance following the accumulation of mutations. For analysis, the ratio of counts of the offspring of a replicate group of flies is treated as the observation. LYNCH estimated the environmental variance by multiplying the among-replicate variance by the average number of flies counted in each replicate. This extrapolates the variance to a vial in which only a single fly of any genotype emerges. This assumes that m and n are binomially distributed, which is not correct (MUKAI *et al.* 1982). The numbers of zygotes of each genotype produced are binomially distributed, but then each genotype undergoes independent binomial sampling for survival, with survival probabilities p_{Cy} and p_+. This suggests that p_{Cy}

in a replicate be treated as a standard, and so we have chosen to extrapolate to a vial in which only a single +/+ egg is laid, but which also contains the mean number of *Cy*/+ eggs. This approach gives the variance in the probability of survival of a test fly, standardized by p_{Cy}.

Two different viability indices have been used, both functions of m and n, and, implicitly of the viabilities, p_+ and p_{Cy}. MUKAI (1964) and OHNISHI (1977) used the ratio

$$\nu_0 = 100\,\frac{m}{m+n} = 100\,\frac{p_+}{2p_{Cy}^+ p_+}. \qquad \text{(A1)}$$

Using a Taylor expansion to second order, the variance of this was approximated as

$$V(\nu_0) \approx (200)^2\,\frac{\overline{p_+^2}V(p_{Cy}) + \overline{p_{Cy}^2}V(p_+)}{(2\overline{p_{Cy}} + \overline{p_+})^4} \qquad \text{(A2)}$$

where $V(p_{Cy})$ and $V(p_+)$ are the variances associated with estimates of viability of each genotype. MUKAI *et al.* (1972) and CARDELLINO and MUKAI (1975) used the viability index

$$\nu_1 = \frac{2m}{n} = \frac{p_+}{p_{Cy}}, \qquad \text{(A3)}$$

whose variance is approximately

$$V(\nu_1) \approx \frac{V(p_+)V(p_{Cy}) + \overline{p_+^2}V(p_{Cy}) + \overline{p_{Cy}^2}V(p_+)}{(\overline{p_{Cy}})^4}. \qquad \text{(A4)}$$

MUKAI *et al.* (1982) estimated that in MUKAI's experiments, the adults who survived developed from an average of 1050 eggs, 700 of which would be expected to be *Cy*/+ and 350 +/+. OHNISHI (1977) used the same number of parental flies, so we have assumed that the same was true in that experiment. These numbers were used to calculate p_+ and p_{Cy} for each experiment. Using a similar approach, MUKAI *et al.* (1982) showed that in the data of MUKAI (1964), binomial sampling variance was approximately half of the error variance among replicates, the rest being considered among-vial environmental variance. When extrapolated to replicates consisting of a single fly, the among-vial environmental variance is therefore negligible; we have ignored it in our calculations. The variances were therefore based on sampling variance alone, and calculated as

$V(p_+) = p_+(1 - p_+)$ and

$$V(p_{Cy}) = \frac{p_{Cy}(1 - p_{Cy})}{700}. \qquad \text{(A5)}$$

In addition, LYNCH (1988) calculated V_M from CARDELLINO and MUKAI (1975) using only additive variance; we have included both additive and dominance variance in our calculations.

As an example of these calculations, we take the data for generation 10 of the CH group from Table 1 of MUKAI *et al.* (1972). An average of 1946.2 flies were counted per line, from six vials, so an average of 324.4 = $m + n$ flies enclosed per vial. The relative viability of +/+ flies is reported as $v_1 = 0.9535$. From these two equations, we solve for the unknowns m and n, which in this case are 104.72 and 219.7, respectively. The Mendelian expectation is that 1050/3 = 350 +/+ eggs were laid, so the estimated survival probability p_+ equals 104.7/350 = 0.299; p_{Cy} = 219.7/700 = 0.314. The sampling variance is then calculated by plugging these values in Equation A5, and the resulting variances into Equation A4. The overall sampling variance for the CH population estimate of V_M was obtained by averaging the variances for generations 10, 20, 30 and 40.