A Pleiotropic Nonadditive Model of Variation in Quantitative Traits

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ABSTRACT

A model of mutation-selection-drift balance incorporating pleiotropic and dominance effects of new mutations on quantitative traits and fitness is investigated and used to predict the amount and nature of genetic variation maintained in segregating populations. The model is based on recent information on the joint distribution of mutant effects on bristle traits and fitness in *Drosophila melanogaster* from experiments on the accumulation of spontaneous and *P* element-induced mutations. These experiments suggest a leptokurtic distribution of effects with an intermediate correlation between effects on the trait and fitness. Mutants of large effect tend to be partially recessive while those with smaller effect are on average additive, but apparently with very variable gene action. The model is parameterized with two different sets of information derived from *P* element insertion and spontaneous mutation data, though the latter are not fully known. They differ in the number of mutations per generation which is assumed to affect the trait. Predictions of the variance maintained for bristle number assuming parameters derived from effects of *P* element insertions, in which the proportion of mutations with an effect on the trait is small, fit reasonably well with experimental observations. The equilibrium genetic variance is nearly independent of the degree of dominance of new mutations. Heritabilities of between 0.4 and 0.6 are predicted with population sizes from 10^4 to 10^6 , and most of the variance for the metric trait in segregating populations is due to a small proportion of mutations (about 1% of the total number) with neutral or nearly neutral effects on fitness and intermediate effects on the trait ($0.1-0.5\sigma_p$). Much of the genetic variance is contributed by recessive or partially recessive mutants, but only a small proportion (about 10%) of the genetic variance is dominance variance. The amount of apparent selection on the trait itself generated by the model is very small. If a model is assumed in which all mutation events have an effect on the quantitative trait, the majority of the genetic variance is contributed by deleterious mutations with tiny effects on the trait. If such a model is assumed for viability, the heritability is about 0.1, independent of the population size.

QUANTITATIVE genetic variation is a prerequisite for evolutionary change and genetic improvement of domestic plants and animals. The roles of mutation and natural selection in the maintenance of such variation is currently a major topic in genetic research. Theoretical models have been developed incorporating stabilizing selection acting directly on phenotypes (LATTER 1960; KIMURA 1965; LANDE 1975; TURELLI 1984) or selection caused by the pleiotropic-side effects of the genes on fitness (ROBERTSON 1956; HILL and KEIGHTLEY 1988; KEIGHTLEY and HILL 1990; BARTON 1990; KONDRASHOV and TURELLI 1992; GAVRILETS and DE JONG 1993). Predictions depend, however, on a long list of parameters, namely the number of loci, their distribution of effects and frequencies, dominance and epistatic relationships, pleiotropic effects, linkages and mutation rates (ROBERTSON 1967; BARTON and TURELLI 1989). Until recently, much of this information was unknown or indirect [reviewed by MACKAY (1990); see also HILL and CABALLERO (1992)]. Direct information is now available from experiments on the accumulation of spontaneous or induced mutations in selected or unselected lines,

from which data on the effects of individual mutants as well as estimates of the input of variance from new mutation can be obtained.

Directional or stabilizing selection is apparent for many quantitative traits in natural populations (ENDLER 1986), but it remains an open question as to whether this is real or spurious: pleiotropic effects of the genes on fitness can generate apparent selection, *i.e.*, selection might not be on the trait itself but on other traits genetically correlated to it. Models of stabilizing selection assume a causal connection between a quantitative trait value and fitness, this declining as a function of the squared effect on the trait (LANDE 1975; TURELLI 1984). Alternatively, pleiotropic models assume that mutants affecting the trait may have a pleiotropic effect on one or more other traits subsumed in an overall fitness effect, but there is not a fixed causal relation between the trait and fitness (KEIGHTLEY and HILL 1990; BARTON 1990; KONDRASHOV and TURELLI 1992).

To date, most theoretical models of the maintenance of quantitative genetic variation have not dealt with the possibility of nonadditive gene action. Under a neutral

model, predictions of the genetic variance maintained very little between an additive model and others including dominance (LYNCH and HILL 1986), but these may be different with selection. Dominance may also bias estimates of mutational variance (the increase in variance per generation due to new mutation; CLAYTON and ROBERTSON 1955) inferred both from the divergence between inbred lines and, particularly, from the response to selection. For example, if recessive gene action is predominant, a given input of mutational variance leads to lower responses to directional selection than for additive gene action, because recessive mutations are more likely to be lost by drift unless strong inbreeding is combined with selection (CABALLERO *et al.* 1991a; CABALLERO and HILL 1992).

Some valuable information on the pleiotropic effects and dominance relationships for new mutations affecting quantitative traits is now available from experiments on accumulation of mutations in *Drosophila melanogaster*. MACKAY *et al.* (1992) (henceforth referred to as MLJ) obtained direct information on the distribution of mutant effects on bristle number and viability from *P* element insertional mutagenesis. The distribution of mean bristle score for nearly one hundred lines containing on average 3.1 stable *P* element inserts on the third chromosome of an inbred base stock was compared to that of insert-free control lines of the same inbred base. Homozygous and heterozygous effects of inserts were inferred for the number of bristles on one abdominal sternite and for the total number of sternopleural bristles on the right and left sides, as well as for viability measured relative to that of a marker chromosome. This work provides direct information on the joint distribution of effects of mutations on a quantitative trait and a major component of fitness.

Information on rates of mutation, average effects and average coefficients of dominance of mutations affecting viability in *Drosophila* is available from the work of T. MUKAI and collaborators (*e.g.*, MUKAI 1964; MUKAI *et al.* 1972; OHNISHI 1977). These experiments involved the accumulation of mutations on protected second chromosomes, and the results suggest that the overall genomic mutation rate at viability polygenes is at least 0.3 events per generation, and that the mean effect of such mutations is a maximum of about 4%. A recent analysis of data from these experiments suggests that the distribution of mutant effects is highly leptokurtic (KEIGHTLEY 1994).

Other recent experiments give valuable information on the distribution of spontaneous mutant effects from direct analysis of mutations affecting several metric traits in *D. melanogaster* in artificially selected or inbred lines derived from an isogenic base (CABALLERO *et al.* 1991b; SANTIAGO *et al.* 1992; LOPEZ and LOPEZ-FANJUL 1993a,b). This information has a higher level of precision with respect to specific mutants than that of MLJ, but estimates of overall parameters of the distribution of effects

TABLE 1

Parameters of the distribution of mutant effects on bristle number and viability from *P* element insertional mutagenesis and spontaneous mutation

	ϵ_a	g_2	ϵ_s	ρ	λ
<i>P</i> elements	0.36	15.2–61.8	0.2	0.38	0.1
Spontaneous	0.07	?	0.01–0.02	?	1

ϵ_a (ϵ_s), root mean squared effect for bristle number (viability); g_2 , coefficient of kurtosis for bristle number; ρ , correlation between absolute effects of the mutants on bristle number and viability; λ , mutation rate per haploid genome per generation.

are difficult to obtain because mutants of small effect tend not to be detected, whereas *P* element insertional mutagenesis allows the detection of mutation events regardless of their effect on the quantitative trait. Furthermore, *P* element mutations with either a large deleterious effect on fitness or recessive gene action can be preserved, while these genes would be likely to be lost in experimental designs involving mutation accumulation under artificial selection unless the effect on the quantitative trait is very large. Conversely, although there is some evidence that *P* element mutagenesis may well mimic the properties of spontaneous mutations (see MLJ), it is plausible that *P* element insertions have more deleterious effects than the average spontaneous mutation, also introducing some bias.

In this study the effects of nonadditivity and directional natural selection through pleiotropic effects on fitness on the equilibrium genetic variance maintained in finite populations are investigated. Using the *Drosophila* data as a guide we investigate the equilibrium variance and heritability explained by mutation-selection-drift balance by means of diffusion approximations. We focus on numbers of bristles and viability for which most information has been collected. Bristle number is generally considered a nearly neutral trait with intermediate heritabilities (0.3–0.6) and little nonadditive variance, while viability is a low heritability trait (about 0.1), which shows inbreeding depression (see below for references).

CHARACTERISTICS OF MUTATIONS AFFECTING BRISTLE NUMBER IN DROSOPHILA

In what follows, observed properties of the joint distribution of effects on bristle number and on viability from *P* element-induced mutation (MLJ) and spontaneous mutation experiments are discussed and compared. Two different sets of parameters are obtained from these (Table 1), which differ because each assumes a different number of mutations per generation affecting the trait. As will be discussed later, this difference is due to the different type of mutations considered in each case.

Distribution of effects for bristles: Although the mean bristle number was not altered significantly by the

presence of heterozygous or homozygous *P* element inserts, the distribution of effects of insertions was highly skewed and leptokurtic (MLJ). The square root of the mean squared effect, $[E(a^2)]^{1/2} = \epsilon_a$, where a is the mutant effect in the homozygote, was calculated from the variance of insert line means (MLJ, Appendix by W. G. HILL) after correction for the mean. Estimates of ϵ_a were 0.31 and 0.40 for abdominal and sternopleural bristles, respectively (the average over the two traits is 0.36). The value of ϵ_a from spontaneous mutations in Table 1 will be explained later.

The kurtosis coefficients (g_2 , the fourth moment of the distribution of mutant effects divided by the square of the variance of mutant effects, minus 3) for the distribution of homozygous insert effects were 15.2 and 61.8 for abdominal and sternopleural bristles, respectively (MLJ, appendix). SANTIAGO *et al.* (1992) and LOPEZ and LOPEZ-FANJUL (1993b) analyzed the accumulation of spontaneous mutations influencing sternopleural and abdominal bristle score in unselected lines maintained by full-sib or double first cousin matings derived from an isogenic base population. Most of the accumulated genetic variance was found to be due to a few new mutations with large effects. However, estimates of parameters of the underlying distribution cannot be straightforwardly obtained, because the relevant mutation rate is unknown.

Estimates of the environmental variance for the traits (V_E , which equals the phenotypic variance in an inbred population) were about 2.6 in MLJ. Throughout this report, mutant effects will usually be expressed in phenotypic standard deviation units (σ_p).

Distribution of effects for fitness: We shall use the effects of mutants on the viability component as a measure of overall fitness. This is likely to be an underestimate of the pleiotropic effects of mutations on overall fitness as will be discussed later, but it is the only measure available at present. In MLJ, viability was measured relative to a marker chromosome, giving an average coefficient of selection (s) of -0.12 for homozygous inserts and -0.05 for heterozygous inserts. These include mutants with lethal and semilethal effects in the homozygous state. If these are not included, the average coefficient of selection for homozygous inserts is about -0.04 (KEIGHTLEY 1994). The root mean squared effect for viability, $[E(s^2)]^{1/2} = \epsilon_s = 0.2$, was obtained by similar calculations as those in the Appendix of MLJ (correcting also for the mean effect of inserts) from the data of Figure 5 in MLJ. The value of ϵ_s for spontaneous mutations shown in Table 1 will be explained later. Maximum estimates of $\bar{s}(1 - \bar{h})$ (where $\bar{s}$ and $\bar{h}$ are the average coefficients of selection and dominance, respectively) from spontaneous mutations for viability assuming equal effects for all mutants are about -0.027 [average from table in p. 14 of CROW and SIMMONS (1983)]. Thus, assuming $\bar{h} = 0.4$ (SIMMONS and CROW

1977), $\bar{s} < -0.045$. Smaller values are inferred when maximum likelihood methods are applied to MUKAI's (1964) ($\bar{s} = -0.010$) and OHNISHI's (1977) ($\bar{s} = -0.004$) data (KEIGHTLEY 1994).

The distribution of homozygous effects for viability is bimodal with a peak close to neutrality and another in the lethal region (see *e.g.*, MLJ, Figure 5). Thus, the kurtosis might not be an appropriate parameter to describe the shape of the distribution because it is only the volume of mutations near neutrality which account for the variance of the trait maintained at equilibrium, as will be seen later. The kurtosis for fitness is, however, likely to be smaller than that for bristles: many mutants may not affect bristles but are likely to affect fitness. A range of different distributions is investigated in this study.

Relationship between fitness and bristle effects: Mutants affecting bristle number frequently show pleiotropic effects on fitness. Thus, for example, 13 out of 30 mutations found in selected lines by LOPEZ and LOPEZ-FANJUL (1993b) were lethals as homozygotes with a large heterozygous effect on bristles. This relationship can be quantified as the correlation between absolute homozygous effects of the mutants on the trait and on fitness (ρ). From MLJ, estimates of this correlation with viability were 0.37 ± 0.10 for abdominal bristles and 0.39 ± 0.10 for sternopleural bristles. There are no estimates of this correlation from spontaneous mutation experiments.

Rates of mutation per generation: Rates of mutation can be estimated by relating the new input of mutational variance per generation (V_M) to ϵ_a . In this paper, V_M is defined, following LYNCH and HILL (1986) or LYNCH (1988), as the increment in variance per generation if the mutations were additive and neutral. This information allows inference of the mutation rate, and nonadditivity and non-neutrality of the mutants are taken into account thereafter in the analysis. The mutation rate per haploid genome and generation (λ) can be approximated by $\lambda = 2V_M/\epsilon_a^2$ (HILL 1982). Estimates of V_M/V_E , the mutational heritability (h_M^2), from several experiments center around 10^{-3} for both systems of bristles (LYNCH 1988). These estimates, however, are based on the assumption of an infinitesimal additive model and neutrality with respect to fitness, and tend to be biased downward. Using parameters based on information on effects of *P* element insertions, this bias depends on the experimental design used to estimate V_M , but can be as high as fivefold (KEIGHTLEY *et al.* 1993). The resulting value of h_M^2 after accounting for this bias is approximately 2.5×10^{-3} . Thus, using this value, $\epsilon_a = 0.36$ and $V_E = 2.6$, a value for $\lambda \approx 0.1$ (Table 1) can be obtained. Note that this estimate refers to the total mutation rate and not only to the mutation rate affecting bristle number, because inserts with zero effect on bristle number are also included. However, this value of λ will represent only a class of mutations (those equivalent to transposon

insertion) and not the full range of mutational events, particularly nucleotide substitutions and other point mutations.

Estimates for the genomic mutation rate for spontaneous mutations affecting viability [see SIMMONS and CROW (1977) and CROW and SIMMONS (1983) for reviews] and fitness (HOULE *et al.* 1992) are about $\lambda \approx 0.3$. These are minimum estimates and a value several times larger (say $\lambda = 1$) is likely to be more realistic (*e.g.*, MUKAI *et al.* 1972; KEIGHTLEY 1994). The discrepancy between this value and that from *P* element insertion (0.1) can be explained in two ways. The estimates of V_M used may still be biased downward and/or the estimates of ϵ_a from *P* element insertions are biased upward. The second explanation seems more likely because, as said before, *P* element insertions obviously cannot mimic the full range of mutational events.

Estimates of ϵ_a and ϵ_s from spontaneous mutation:

We can assume a genomic mutation rate of $\lambda = 1$ and the estimates of mutational variance for bristle number and viability from spontaneous mutation experiments, to obtain values of ϵ_a and ϵ_s ignoring the *P* element insertion data. Thus, if we assume $\lambda = 1$ and an increase of mutational variance per generation for bristle number of about 10^{-3} , we obtain a value of $\epsilon_a \approx 0.07$ (Table 1). Analogously, we can use an estimate of mutational variance for viability of about 0.5×10^{-4} (MUKAI 1964; MUKAI *et al.* 1972; OHNISHI 1977; C. LOPEZ-FANJUL, personal communication), to obtain a value of $\epsilon_s \approx 0.01$. Alternatively, a maximum likelihood estimate of ϵ_s from MUKAI's (1964) and OHNISHI's (1977) experiments is 0.02 (KEIGHTLEY 1994). This corresponds to a value for the mutational variance of 2×10^{-4} (using $\lambda = 1$). In summary, with $\lambda = 1$ and the observed values of mutational variation from spontaneous mutation, estimates of ϵ_a and ϵ_s are far smaller than from *P* element insertion data (Table 1). Again, a likely explanation for this difference is that ϵ_a and ϵ_s from *P* element insertions are biased upward because of the nature of the insertions.

Degree of dominance for fitness: MLJ measured the regression coefficient of heterozygous score on homozygous score for viability (LYNCH and HILL 1986), and obtained a value very close to zero and therefore suggesting nearly complete recessivity. This method, however, may result in misleading conclusions. Imagine, for example, three lines with homozygous scores of 0.1, 0.2 and 0.3, and heterozygous scores of 0.1, 0.2 and 0.1, respectively. The regression of homozygous score on heterozygous score is zero, suggesting complete recessivity while, in fact, two mutants are completely dominant and the other is partially recessive, giving on average, partial dominance. Furthermore, the relationship between gene effects and coefficients of dominance may not be linear and, as has been shown repeatedly, genes of large effect usually show degrees of dominance closer to recessivity than those of small effect (MUKAI *et al.* 1972;

FIGURE 1.—Coefficients of dominance for viability (h) plotted against mutant homozygous effects on viability for mutants with $s < -0.3$ from MLJ (a). Coefficients of dominance for bristle characters (h') plotted against mutant homozygous effects on abdominal and sternopleural bristles (σ_p units) from MLJ (b), or combined data from LOPEZ and LOPEZ-FANJUL (1993b) and SANTIAGO *et al.* (1992) (c). The four black symbols denote estimates of h far lower than zero or higher than one. The actual h values were: (a) -0.7 ; (b, upper) 1.6 ; (b, lower) -0.4 ; (c) -0.5 .

SIMMONS and CROW 1977; CROW and SIMMONS 1983; MLJ; SANTIAGO *et al.* 1992; LOPEZ and LOPEZ-FANJUL 1993b).

Figure 1a shows the coefficient of dominance for each insert line, $h = d/a + 1/2$ [first used by WRIGHT (1934)], where a is the difference between homozygotes and d is the difference between the heterozygous effect and the average effect of the two homozygotes. Only mutants with $s < -0.30$ are shown in the figure, because the estimates of h for mutants of small effect have extremely large sampling errors. Semilethals and lethals (*i.e.*, mutants with $s < -0.60$; SIMMONS and CROW 1977) are partially recessive (average 0.17 ± 0.04). Less deleterious genes ($-0.30 < s < -0.60$) are on average close to additive (0.53 ± 0.11) though, apparently, with very variable gene action. Most of this variation could, however, be due to sampling error.

Viability selection experiments [reviewed by SIMMONS and CROW (1977)] suggest that lethal mutations tend to be nearly recessive, but mildly deleterious mutations have coefficients of dominance between 0.30 and 0.50, in approximate accordance with the above observations.

Gene action for bristle number: Figure 1b shows values of the coefficient of dominance for abdominal and

sternopleural bristle score (h' , defined in a similar way as h above) in the insert lines of MLJ. Estimates for mutants with effects $a < 0.4\sigma_p$ have extremely large sampling errors and, therefore, are not included in the figure. Mutants with intermediate effects (say between 0.25 and $0.5\sigma_p$) are partially recessive (averages of 0.32 ± 0.19 and 0.34 ± 0.28 for abdominal and sternopleural bristles, respectively), but again, the individual values of h' are very variable, perhaps only due to sampling error. Inserts with an effect of more than $0.5\sigma_p$ are nearer to completely recessive (average of 0.28 ± 0.11 and 0.06 ± 0.07 , respectively), as previously observed by MLJ.

Coefficients of dominance of spontaneous mutations in selected or unselected lines are in reasonable accordance with these values. Figure 1c shows dominance coefficients for mutants affecting sternopleural and abdominal bristles from LOPEZ and LOPEZ-FANJUL (1993b) and SANTIAGO *et al.* (1992). LOPEZ and LOPEZ-FANJUL (1993b) found 8 mutants with an effect on abdominal bristles smaller than $0.5\sigma_p$ and an average $h' = 0.47 \pm 0.21$. 21 mutants had an effect greater than or equal to $0.5\sigma_p$ with $h' = 0.36 \pm 0.04$ (CABALLERO *et al.* 1991b; LOPEZ and LOPEZ-FANJUL 1993b). SANTIAGO *et al.* (1992) found 5 mutants significantly affecting sternopleural bristles, all with an effect higher than $0.5\sigma_p$ and $h' = 0.42 \pm 0.13$. These averages are larger than those from MLJ, but experiments to accumulate spontaneous mutations by selection or divergence among inbred lines are likely to give upwardly biased average coefficients of dominance, as recessive mutants tend to be lost or undetected.

In conclusion, information drawn from all sources suggests that genes with large effects (say $a > 0.5\sigma_p$) tend to be partially recessive. With respect to genes with smaller effects, little can be said from the data of MLJ, where individual measures of dominance effects had low precision. However, LOPEZ and LOPEZ-FANJUL (1993b) analyzed mutants with more precision so that statistical tests were able to discriminate between real variation and sampling variation of individual dominance effects. Thus, from the 9 mutants with the smallest effect ($a < 0.5\sigma_p$), 3 were significantly ascribed as dominant, 2 as additive, 2 as additive or recessive and 2 as recessive. Therefore, despite conclusions drawn from the analysis of metabolic traits (KACSER and BURNS 1981), it can be tentatively concluded that mutations of small effect are not necessarily additive but show highly variable degrees of dominance, though the average may be close to additivity. Finally, no mutant analyzed by SANTIAGO *et al.* (1992) and LOPEZ and LOPEZ-FANJUL (1993b) showed significant under- or overdominance.

A question of possible interest in the context of the maintenance of genetic variation is the relationship between h and h' , *i.e.*, the dominance coefficients for viability and bristles. Unfortunately, only inserts with large effects give reliable estimates of the degree of dominance, and we therefore must restrict ourselves to those

lines for which the effect on both viability and bristles is very large. The regression of h on h' using the lines with extreme effects (5 lines for abdominal and 6 for sternopleural bristles with $a > 0.5\sigma_p$ and $s < -0.6$) is 0.37 ± 0.10 (significantly different from 0 and 1). The linear relation is $h = 0.37h' + 0.07$, which would imply that genes with substantial heterozygous effect on bristle number have much smaller heterozygous effect on viability.

Further evidence on the relation between dominance coefficients among pleiotropic effects comes from studies of spontaneous mutations in inbred lines which show similar gene action for several quantitative traits (LOPEZ-FANJUL 1993). Theoretical arguments for why this should occur have been advanced (KEIGHTLEY and KACSER 1987). Finally, CABALLERO *et al.* (1991b) did not find any evidence of epistasis among detected spontaneous mutations affecting abdominal bristle number.

A MODEL FOR THE DISTRIBUTION OF EFFECTS OF NEW MUTATIONS

We have modeled a distribution of new mutations including effects on a metric trait, a , its degree of dominance, h' , an overall pleiotropic effect on fitness, s , and its degree of dominance, h , incorporating the information summarized above.

Joint effects on bristles and fitness: We assume that the mean mutant effect for bristle score is zero (in good agreement with the mean insert effects in MLJ), and that the distribution of effects on bristles is symmetrical. Possible asymmetry of the distribution of effects of mutants on the quantitative trait is not relevant here as only the square of the effects enters the calculations. Three distributions of mutant effects for the metric trait and fitness were investigated: the normal distribution, the gamma distribution with parameter one half (a squared normal), and the cube of a normal distribution. The coefficients of kurtosis for the mutant effects given by the above distributions are 0, 9 and about 50, respectively. Therefore, the last two approximately cover the range of estimates in Table 1. As the overwhelming majority of mutations are deleterious and the proportion of advantageous mutants is not known, the s values are considered to be unconditionally negative.

Several combinations of the three distributions for the trait and fitness were studied in order to construct a bivariate distribution of effects. The parameters defining the distributions are the root mean squared effect for the metric trait, ϵ_a , the analogous parameter for fitness effects, ϵ_s , and the correlation of absolute values of homozygous mutant effects on the metric trait and on fitness, ρ , which is a measure of the level of pleiotropy. The bivariate gamma distribution is the Wishart distribution, for which a more detailed description is given by KEIGHTLEY and HILL (1990). Procedures to obtain the other bivariate distributions were similar.

Dominance relationships: Figure 1 and the statistical analysis made by LOPEZ and LOPEZ-FANJUL (1993b) suggest that the distribution of coefficients of dominance is such that mutants with small effects can have any degree of dominance between completely dominant and completely recessive but as mutant effects increase, there is a tendency toward recessivity. We assumed an exponential function to define limits on the coefficient of dominance such that h' is a random value drawn from the uniform distribution such that $h' < e^{-k|a|}$ and similarly, $h < e^{ks}$, where k is the parameter which gives the slope of the function. Thus, for $a = 0$ any degree of dominance between 0 and 1 was equally probable and as $|a|$ was increased, the possible range of h' (or h) was accordingly reduced toward recessivity until for $|a| \rightarrow \infty$, $h' = 0$. For example, for $a = 1$ and $k = 1$, h' could take values between 0 and 0.37 with equal probability. A value $k = 1$ was found to fit the data reasonably well: mutants sampled from the simulated distribution with effects between 0.25 and $0.5\sigma_p$ gave an average $h' = 0.29$ and for $a > 0.5\sigma_p$, $h' = 0.14$, in good agreement with the observed values from MLJ (0.33 and 0.17, respectively, averaging both types of bristles). Similarly, values of h for simulated mutants with effects $-0.3 > s > -0.6$ and $s < -0.6$ were 0.33 and 0.22, respectively (compared to the observed 0.53 and 0.17, respectively). Nevertheless, it will be shown below that the degree of dominance for the trait does not strongly influence the total genetic variance at equilibrium.

DIFFUSION APPROXIMATION FOR THE EQUILIBRIUM VARIANCE

The contribution of a mutant with a specific effect and coefficient of dominance on the metric trait and fitness to the equilibrium genetic variance can be obtained by means of diffusion approximations under the infinite sites model of KIMURA (1969, 1983). This is based on the following assumptions. First, the number of sites for mutation is assumed to be large and the mutation rate per site small so that no more than two variants are segregating in a given DNA site at a certain time. This is reasonable as the whole genome is a target for mutation. Although more than one mutation may occur in the same locus, the model behaves as a two-allele model. This is because most mutants are assumed to be deleterious and, therefore, they are likely to be lost quickly. Thus, the model does allow for multiple alleles, but mutations at the same locus evolve independently provided they are rare (see KEIGHTLEY 1991). Secondly, mutations at different loci are assumed to segregate and act independently, *i.e.*, there is neither linkage nor epistasis. Linkage disequilibrium between two segregating sites may be common with the infinite sites model (OHTA and KIMURA 1971) but this is not likely to be an important factor as long as mutations remain at low frequencies in the majority of cases, as is expected if they are uncon-

ditionally deleterious (KEIGHTLEY and HILL 1988). Finally, coefficients of selection of mutants are assumed to be constant over time.

Let the three genotypes at a locus or DNA site be AA , Aa and aa , with frequencies $(1-x)^2$, $2x(1-x)$ and x^2 ; genotypic values for a metric trait of 0, ah' and a ; and fitness effects 1, $1+sh$ and $1+s$, respectively. The asymptotic expected value $\zeta[f(x)]$ of any function $f(x)$ when a balance between production of new mutations and extinction or fixation of others is reached for a randomly mating population with effective size N is

$$\zeta[f(x)] = \left[1 - u\left(\frac{1}{2N}\right)\right] \int_0^{1/2N} \psi(x)u(x) dx + u\left(\frac{1}{2N}\right) \int_{1/2N}^1 \psi(x)[1 - u(x)] dx, \quad (1)$$

(KIMURA 1969), where $u(z) = \int_0^z G(x) dx / \int_0^1 G(x) dx$ is the probability of fixation of a gene with initial frequency z (KIMURA 1962), and

$$\psi(x) = \frac{8N^2\lambda f(x) \int_0^1 G(z) dz}{x(1-x)G(x)},$$

with $G(x) = \exp\{2N s[x + 2h - 2xh]\}$, and λ the mutation rate per haploid genome per generation.

The asymptotic genetic variance (V_G) is obtained by substituting

$$2a^2(1-x-h'+2xh')^2x(1-x) + [a(2h'-1)x(1-x)]^2 \quad (2)$$

for $f(x)$, where the first term denotes the additive variance (V_A) and the second the dominance variance (V_D), which can be computed separately (CABALLERO and HILL 1992). Furthermore, the inbreeding depression for fitness (reduction in mean fitness due to an increase in inbreeding, F) can be obtained by substituting $f(x)$ for $x(1-x)sF(1-2h)$.

Considering the quadrivariate distribution $\Phi(a, s, h', h)$ of mutant effects and dominance outlined above, the equilibrium value of $f(x)$ ignoring overdominance can be obtained by integration of

$$\int_{-\infty}^{\infty} \int_{-\infty}^0 \int_0^1 \int_0^1 \zeta[f(x)] \Phi(a, s, h', h) da ds dh' dh.$$

In this study, however, the procedure used was to sample (simulate) mutant effects from the distribution $\Phi(a, s, h', h)$, integrate (1) numerically and average the results over mutants. Typically, 10^6 mutants were simulated and numerical integration was done by Simpson's rule.

EFFECT OF DEGREE OF DOMINANCE ON THE VARIANCE CONTRIBUTED BY SINGLE MUTANTS

Before considering the variance maintained from recurrent mutation, some useful insights can be obtained

FIGURE 2.—Genetic variance contributed by a single mutant during its lifetime (scaled by $2NV_M$) for different coefficients of dominance ($h' = h$) and different effects on fitness (Ns).

by considering the variance contributed during the lifetime of a single mutant. This can be calculated from expressions (1) and (2) above with $\lambda = 1/2N$, i.e., assuming $2N\lambda = 1$ mutant per generation.

Figure 2 shows the cumulative genetic variance (V_G) during a single mutant's lifetime for a gene with different effects on fitness (Ns), and different degrees of dominance with equal values for the trait and fitness ($h' = h$). Mutants with positive s (advantageous) are displayed for completeness though only deleterious mutants will be considered in the next section. Values are scaled by $2NV_M = a^2/2$ so that they apply to any gene effect (a). With neutrality ($Ns = 0$), a completely recessive mutant ($h' = 0$) contributes as much variance as an additive mutant ($h' = 0.5$) (see also LYNCH and HILL 1986). Partially recessive genes contribute less variance but, in general, degrees of dominance below 0.5 do not give variances very different to that for additives, as concluded by LYNCH and HILL (1986). Dominant genes, however, contribute substantially more variance and, therefore, even with neutrality it cannot be concluded that the variance is independent of the degree of dominance. For advantageous genes the effect of different coefficients of dominance is more marked and the higher the degree of dominance, the higher the variance contributed. In contrast, for deleterious genes there is very little effect of different degrees of dominance and the curves flatten (relative to the neutral case) for $Ns < -5$. The genetic variance can then be approximated by $V_G = \lambda a^2 / (-s)$ for any degree of dominance.

The partition of V_G into its components is illustrated in Figure 3 for $Ns = 0, 5$ and -5 . For neutral mutants ($Ns = 0$), the magnitude of the contribution of dominance variance is symmetrical around $h = 0.5$ (additive). However, for advantageous mutants ($Ns = 5$), dominant genes ($h > 0.5$) contribute a larger amount of dominance variance. Conversely, for deleterious mutants ($Ns = -5$), recessive genes ($h < 0.5$) contribute more dominance variance. Thus, if a large amount of variation is due to deleterious recessive mutations, the proportion

FIGURE 3.—Partition of the genetic variance (V_G) into additive (V_A) and dominance (V_D) components for different coefficients of dominance ($h' = h$) and different effects on fitness (Ns).

of dominance variance might be appreciable and nearly equal to the additive variance. Deleterious recessive mutants contribute approximately the same genetic variance as do additive genes (Figure 2) but a large part of this is dominance variance (Figure 3, lower panel) and the narrow-sense heritability is then considerably less than for additive genes. Conversely, favorable dominant genes contribute much more genetic variance than additive genes (Figure 2) but, for the same reason (Figure 3, middle panel), the heritability contributed will not be very different.

So far in this section, coefficients of dominance for fitness and for the trait have been considered to be the same. As was seen above, there is some evidence pointing to coefficients of dominance for the metric trait (h') being higher than those for fitness (h). If this were included in the model, the narrow-sense heritability would depend more on the level of dominance for deleterious mutants and, conversely, even less for advantageous mutants.

In summary, if the majority of mutations are deleterious, only those mutants with effects such that $0 \leq$

FIGURE 4.—Equilibrium genetic (V_G) (a) and additive (V_A) and dominance (V_D) variances (b), plotted against population size (N) for mutant effects with additive, recessive or variable gene action. The variance predicted under the neutral model is also shown.

— $Ns < 1$ will contribute appreciable variance (see Figure 2). In general, the degree of dominance will have a small effect on the contributed variance, though some effect on the heritability is expected, especially if the dominance for the metric trait is higher than that for fitness.

VARIANCE MAINTAINED IN EQUILIBRIUM POPULATIONS

In this section, the equilibrium genetic variance is evaluated and the characteristics of the genes segregating in an equilibrium population investigated for models involving parameters of the distribution of effects of new mutations from above.

Effect of degree of dominance on the equilibrium variance: Figure 4 shows the equilibrium genetic variance (V_G) and its components (V_A and V_D) as a function of population size with a constant flux of mutations per generation. A Wishart distribution with the parameters derived from the effects of P element insertions (Table 1) was used to simulate mutant effects.

For comparison, the uppermost continuous line in Figure 4a shows the prediction under a neutral additive model ($V_G = 2NV_M$). The other graphs in 4a and 4b represent V_G and its components predicted from the distribution of mutations modeled above, with additive gene action for all mutants ($h' = h = 0.5$, continuous line), recessive gene

action ($h' = h = 0$, dotted line) or the modeled distribution of variable gene action with parameter $k = 1$ for both bristles and fitness (coefficients of dominance are functions of mutant effects such that they take values below an exponential function with parameter $k = 1$; broken line). The total genetic variance maintained with the recessive model and with the variable dominance model are nearly the same as that with an additive model (Figure 4a). Figure 4b shows that V_A and V_D in the completely recessive model (dotted lines) are approximately equal and, therefore, about one half of V_G is dominance variance if all mutants are recessive (cf. variance maintained by deleterious recessive mutants, Figure 3, lower panel). However, for the model of variable dominance (broken lines), only about 10% of V_G is dominance variance. The additive variances for the additive model (continuous line) and the variable dominance model (broken line) are very similar.

It is clear from these results that there is very little effect of the degree of dominance on the variance maintained. The narrow-sense heritabilities for the variable dominance model and the additive model are very similar (for example, for $N = 10^4$ they are 0.40 and 0.48, respectively). Only if all mutants are completely recessive is the heritability substantially smaller (0.26 for $N = 10^4$), and this difference increases as N increases.

Using the set of parameters from spontaneous mutations in Table 1 with $\rho = 0.1$ or 0.4, the same basic conclusion of independence of the genetic variance on the degree of dominance is made.

Equilibrium heritabilities for bristle score: The narrow-sense heritability (h^2) predicted by the model for different combinations of distributions of effects for bristles and fitness as a function of population size is shown in Figures 5 and 6, for the two sets of parameters in Table 1. The three distributions investigated are a cube-normal, a gamma with parameter one half (which is the square of a normal), and a normal distribution. These are reflected about zero (one-sided for fitness effects) and give kurtosis coefficients of about 50, 9 and 0, respectively. Perhaps a better description of the distribution of effects for fitness is the volume of mutants close to neutrality, because this is the most important factor determining the variance maintained. Thus, for example, for $N = 10^4$, the proportion of mutants per generation with coefficients of selection such that $0 \leq -Ns < 1$ (effectively neutral) is about 10% for the cube-normal, about 2% for the gamma, and about 0.05% for the normal distribution. Not all combinations of the three distributions are displayed because the kurtosis for fitness is likely to be smaller than that for bristle score. The Wishart distribution, used in other sections of this paper, corresponds to the bivariate gamma distribution.

It is clear that a critical factor determining the equilibrium heritability is the shape of the distribution of mutant effects on fitness. For parameters derived from P element insertion data (Figure 5) it is observed that if

FIGURE 5.—Equilibrium heritability for bristle number plotted against population size (N), for different combinations of distribution of effects for bristle number and fitness. Parameters: $\epsilon_a = 0.36$, $\epsilon_s = 0.20$, $\rho = 0.38$.

FIGURE 6.—Equilibrium heritability for bristle number plotted against population size (N), for different combinations of distribution of effects for bristle number and fitness. Parameters: $\epsilon_a = 0.07$, $\epsilon_s = 0.01 - 0.02$, $\rho = 0.1 - 0.4$.

fitness effects have a low kurtosis (normally distributed effects) the heritability for bristles is around or below 10% (and, therefore V_A approximately below 0.3) even with population sizes as large as 10^9 . A higher kurtosis for fitness effects (9 or 50) gives higher genetic variances and heritabilities for bristle traits. In this case V_A increases without limit with increasing N . For example, for the Wishart distribution (bivariate gamma), predictions of V_A are about 1.8, 3.8 and 6.0 for $N = 10^4$, 10^5 and 10^6 , respectively, which correspond to heritabilities of about 0.4, 0.6 and 0.7, respectively. The figure also shows that

for a given distribution of fitness effects, the larger the kurtosis for bristle number, the lower the heritability, in agreement with analysis of stabilizing selection models (KEIGHTLEY and HILL 1988).

Figure 6 shows predictions with spontaneous mutation parameters. For simplicity, only two bivariate distributions of effects are considered, cube-normal for the trait and gamma for fitness or gamma for the trait and normal for fitness, with $\rho = 0.1$ or 0.4 and $\epsilon_s = 0.01$ or 0.02 . Again, a critical factor is the kurtosis of the distribution for fitness. A leptokurtic distribution for fitness effects leads to very high genetic variances and heritabilities even for small population sizes, particularly for $\rho = 0.1$. By contrast, a normal distribution for fitness effects yields intermediate V_G and h^2 and this becomes quickly independent of N .

Most experimental estimates of heritability for sternopleural and abdominal bristles are between 0.3 and 0.6 [see Figure 5 in ROFF and MOUSSEAU (1987)]. Estimates from recently captured populations are usually larger (about 0.5 to 0.6: LOPEZ-FANJUL and HILL 1973; SALGADO 1984; COYNE and BEECHAM 1987). Estimates for one abdominal sternite (that measured by MLJ) are usually smaller than those for two abdominal sternites or two sternopleural plaques (see *e.g.*, CABALLERO and LOPEZ-FANJUL 1987). Figure 5 (*P* element data) shows that these values of heritability are achieved for population sizes between 10^4 and 10^6 with leptokurtic distributions of fitness effects but never with a normal distribution. By contrast, in Figure 6 (spontaneous mutation data) these h^2 values are obtained for large population sizes ($N > 10^5$) and $\rho = 0.1$ if a normal distribution of fitness effects is assumed, and for populations sizes between 10^3 and 10^5 if a gamma distribution of fitness effects is assumed. In the next section we investigate the nature of the quantitative variation predicted for some of these bivariate distributions which generate intermediate heritabilities for bristle number.

Nature of the quantitative genetic variation: Table 2 shows a numerical example which illustrates the nature of the quantitative variation predicted with the model. The example is worked out for a Wishart distribution of mutant effects using *P* element insertion parameters from Table 1, the variable dominance model and $N = 10^4$. In this case, the total number of mutations per generation is $2N\lambda = 1975$, the asymptotic $V_G = 2.07$, $V_A = 1.85$, $V_D = 0.22$ and $h^2 = 0.40$. The table shows the number of mutants per generation (Λ) in various classes and their contributions to the variance (in percentage). The upper panel shows that although many more mutants appear with large values of $-Ns$, most of the additive and dominance variance is contributed by a few mutants in the class $0 \leq -Ns < 5$. For the interval $0 \leq -Ns < 1$, $N\sigma_s \approx 0.3$, where σ_s is the square root of the variance of selection coefficients, and for the interval $1 \leq -Ns < 5$, $N\sigma_s \approx 1$. Thus, these classes of mutant could

TABLE 2

Proportion of the additive (V_A) and dominance (V_D) variance for bristle number contributed by different types of mutant in a population of size $N = 10^4$

$-Ns$	Λ	V_A	V_D
0-1	44	54	64
1-5	60	25	26
5-10	46	6	4
10-30	107	7	4
>30	1718	8	2
a	Λ	V_A	V_D
0-0.125	1333	11	5
0.125-0.25	319	25	18
0.25-0.5	232	45	34
0.5-0.75	59	7	10
>0.75	32	12	33
h'	Λ	V_A	V_D
0.0-0.2	501	25	79
0.2-0.4	484	32	17
0.4-0.6	425	29	1
0.6-0.8	364	12	2
0.8-1.0	201	2	1

Λ , number of mutants per generation; s , coefficient of selection; a , absolute effect on bristles in σ_P units; h' , coefficient of dominance for bristles. The parameters of the model were: $\epsilon_a = 0.36$, $\epsilon_s = 0.20$, $\rho = 0.38$.

be classified as nearly neutral or weakly selected ($0 \leq -Ns < 1$) and moderately selected ($1 \leq -Ns < 5$) [see GILLESPIE (1991, p. 261) and OHTA (1992)].

The middle panel of Table 2 shows that the overwhelming majority of mutations have small or negligible effects on the trait ($a < 0.125\sigma_P$). However, most of the genetic variance is contributed by mutants with intermediate effects on the trait ($0.125 < a < 0.50\sigma_P$). This can be seen more clearly in Table 3 where a finer partition of the variation due to mutants in the nearly neutral classes ($0 \leq -Ns < 5$) for different effects on the trait is shown. The table shows that mutants where $0.125 < a < 0.50\sigma_P$ explain more than half of the total additive variance, being only 24 out of 1975 mutants per generation, *i.e.*, about 1% of the total number of mutants per generation.

The lower panel of Table 2 shows that with this model, a large fraction of V_A and practically all of V_D are contributed by recessive or partially recessive mutants. In the model, these are more frequent than more dominant mutants (Table 2), and they display a wider range of gene effects. This latter is observed in Figure 1: recessive mutants may have any gene effect on the metric trait but for increasing coefficients of dominance, the gene effects allowed are smaller. For example, completely dominant mutants are restricted to mutants of small effect.

Table 4 shows equivalent results to Table 2, but for the set of parameters from spontaneous mutation in Table 1 and with $\rho = 0.1$ assumed. Two distributions of mutant effects were investigated, a gamma distribution of effects for bristle score and normal for fitness ($G - N$) and a

TABLE 3

Proportion of the additive (V_A) and dominance (V_D) variance for bristle number contributed by different types of mutant in a population of size $N = 10^4$

$-Ns$	a	Λ	V_A	V_D
0-1	0-0.125	33	4	2
	0.125-0.25	7	13	13
	0.25-0.5	3	23	16
	0.5-1	<1	7	20
	>1	<1	7	13
1-5	0-0.125	47	2	2
	0.125-0.25	7	6	4
	0.25-0.5	6	14	14
	0.5-0.75	<1	3	6

Λ , number of mutants per generation; s , coefficient of selection; a , absolute effect on bristles in σ_P units. Parameters as in Table 2.

TABLE 4

Proportion of the additive (V_A) variance for bristle number contributed by different types of mutant in a population of size $N = 10^4$

$-Ns$	$G-N$			$cN-G$		
	$\Lambda(\%)$	V_A	V_D	$\Lambda(\%)$	V_A	V_D
0-1	1	21	35	8	51	68
1-5	2	22	26	8	21	21
5-10	2	7	15	7	7	5
10-30	8	13	13	16	11	3
30-100	26	18	6	26	7	2
>100	61	18	4	35	3	1
a	$\Lambda(\%)$	V_A	V_D	$\Lambda(\%)$	V_A	V_D
0-0.125	97	58	54	97	51	52
0.125-0.25	3	34	37	2	44	46
0.25-0.5	<1	8	9	<1	5	2
0.5-0.75	0	0	0	<1	0	0
h'	$\Lambda(\%)$	V_A	V_D	$\Lambda(\%)$	V_A	V_D
0.0-0.2	21	3	39	21	12	64
0.2-0.4	21	21	38	20	14	11
0.4-0.6	20	25	2	21	29	2
0.6-0.8	21	38	13	21	34	13
0.8-1.0	17	13	8	17	11	10

$G-N$, gamma distribution of effects for bristle number, normal for fitness, $cN-G$, cube-normal distribution of effects for bristle number, gamma for fitness; Λ , percentage of mutants per generation; s , coefficient of selection; a , absolute effect on bristles in σ_P units. The parameters of the model were: $\epsilon_a = 0.07$, $\epsilon_s = 0.02$, $\rho = 0.1$.

cube-normal distribution for bristle score and gamma for fitness ($cN - G$). The example considered is for $N = 10^4$, giving asymptotic $h^2 = 0.39$ and 0.59 , respectively. Numbers of mutants per generation (Λ) for each class are expressed in this table as a percentage of the total number. The upper panel shows that with a gamma-normal bivariate distribution, genetic variance is contributed by mutations with effects on fitness over the whole range of Ns values while for the cube-normal-gamma, most is contributed by nearly neutral mutants, similar to the results obtained with P element data (see Table 2). When a value of $\rho = 0.4$ is assumed (not shown), most of the additive variance is contributed by

very deleterious mutations ($-Ns > 30$) for both bivariate distributions. The middle panel shows that most of the variance is contributed by mutants with very small effect on the trait ($a < 0.25\sigma_p$), because the overwhelming majority of mutations are of this type (with $\rho = 0.4$ this is more accentuated), contrary to the results obtained with *P* element data (Table 2). Finally, the third panel shows that a large proportion of V_A is contributed by partially dominant mutations and most of V_D by partially recessive mutations (cf. Figure 3, lower panel).

In summary, assuming parameters derived from *P* element data, most of the variation is contributed by nearly neutral mutations with substantial effects on the trait. However, with parameters derived from spontaneous mutation data, results depend on the parameters assumed but, in general, a large part of the variance maintained is contributed by very deleterious mutations with very small effects on the trait. This latter is, to some extent, contrary to the *quasi* neutrality usually observed for the variation in bristle traits (ROBERTSON 1967) and the observation of segregating genes with substantial effect on bristles (SHRIMPSON and ROBERTSON 1988).

Robustness of the model: Table 5 shows asymptotic genetic variances and heritabilities for bristles obtained with the Wishart distribution for a population of size $N = 10^4$, $h_M^2 = 2.5 \times 10^{-3}$, and a range of values of ϵ_a , ϵ_s and ρ . The robustness of the model for the degree of dominance and the dependence on population size were illustrated in Figures 4 and 5, respectively. Thus, only $N = 10^4$ and additive effects are considered for simplicity.

The underlined h^2 in the center of the table (0.42) corresponds to the approximate parameters from *P* element insertions used in previous calculations (Table 1). The effect of a change in these parameters is shown in the table. If *P* elements have a misleadingly large effect on the metric trait, i.e., ϵ_a is much smaller than 0.4 (for example because many point mutations not affecting bristles are not included), the predicted variance and heritability are not greatly affected. In fact, any change in ϵ_a has little effect. This is because a large ϵ_a means larger gene effects but, for a given h_M^2 also a smaller number of mutants. Thus, for $\epsilon_a = 0.1, 0.4$ and 0.8 , λ is 1.3, 0.1 and 0.02, respectively, and the effects of the factors cancel each other.

Viability effects of inserts were used as a measure of effects on fitness and therefore, the former could be an underestimate of the latter. A threefold increase in ϵ_s from 0.2 to 0.6 has a less than threefold effect on the predicted variance and heritability (Table 5). Moreover, if in fact $\epsilon_s = 0.6$, the bias in the estimates of h_M^2 would be accordingly larger than estimated with $\epsilon_s = 0.2$, giving a new value of h_M^2 of about 7×10^{-3} (KEIGHTLEY *et al.* 1993). Thus, for $\epsilon_a = 0.4$, $\epsilon_s = 0.6$ and $\rho = 0.4$, the predicted V_A and h^2 with $h_M^2 = 7 \times 10^{-3}$ ($\lambda = 0.22$) are 1.97 and 0.43, respectively, very close to those obtained previously. Furthermore, a partition of the contribution

of the different types of mutants to V_A and V_D as made in Tables 2 and 3 but with these latter parameters, leads to results concerning the nature of the quantitative genetic variation similar to those discussed previously for $\epsilon_s = 0.2$ and $h_M^2 = 2.5 \times 10^{-3}$. Therefore, this suggests that the model is also very robust to underestimation of ϵ_s for the same reason as before: larger ϵ_s reduces the heritability but also increases the number of mutants predicted per generation (experimental estimates of h_M^2 would be even more biased than initially considered in this study), and both factors cancel each other. The increase in ρ seems to have the largest impact on h^2 , but again, an increase in ρ would imply a larger bias in h_M^2 , partially canceling that effect.

Equilibrium variance for viability: The variance and heritability for viability can also be computed using the same approach as above. Again, both sets of parameter values in Table 1 can be used. *P* element insertion parameters, however, give unreasonably high values of mutational variance. If we assume that ϵ_s is about 0.2 and λ is about 0.1 (from *P* element data in Table 1), the mutational variance for viability would be about 0.002 and, assuming $V_E \approx 0.1$ [average between the estimate from the control lines in MLJ, 0.07, and that from spontaneous mutation lines, 0.15 (LOPEZ-FANJUL, personal communication)], the mutational heritability would be 0.02, which is higher than experimentally observed (LYNCH 1988). This is likely to be due to the nature of *P* element insertions, producing large deleterious effects on fitness and, consequently, an inflated value of ϵ_s . Thus, it is very unlikely that *P* element insertions are general representatives of spontaneous mutations affecting viability or fitness. In what follows, results refer to the set of parameters for spontaneous mutation from Table 1.

With the three distributions of effects assumed (normal, gamma and cube-normal), the average coefficient of selection against homozygotes ($\bar{s}$) ranges from 0.008 to 0.016. Table 6 shows predictions of the asymptotic V_A and V_D . These results are independent of N because $\rho = 1$ (KEIGHTLEY and HILL 1990). It can be observed that the higher the kurtosis of the distribution (from normal to cube-normal) the smaller the variance maintained. The table also shows the range and average of estimates from 6 natural populations (MUKAI 1985), these being of the same order as the predictions. Assuming $V_E = 0.1$, the equilibrium heritability predicted with the model and the three distributions can be calculated, and is also shown in the table.

Table 7 shows a partition of the variance contributed by different classes of mutants for viability using the gamma distribution. Most of the variance is contributed by mutants with effects $s = -0.01$ to -0.1 , which in a population of size $N = 10^4$, for example, correspond to highly deleterious mutants. The lower panel of the table shows that, although mutants with all gene actions are

TABLE 5

Predicted equilibrium additive variance (V_A) and heritability (h^2) in a population of size $N = 10^4$, additive gene action, and different parameters for the Wishart distribution

$\epsilon_a (\Lambda) \dots$	0.1 (1.3)			0.4 (0.1)			0.8 (0.02)		
$\epsilon_s \dots$	0.1	0.2	0.6	0.1	0.2	0.6	0.1	0.2	0.6
$\rho = 0.2 V_A$	6.38	4.54	1.37	5.47	4.38	1.83	7.03	4.08	2.16
h^2	0.71	0.64	0.35	0.68	0.63	0.42	0.73	0.61	0.46
$\rho = 0.4 V_A$	2.74	1.70	1.18	2.48	1.86	0.74	3.19	1.93	0.82
h^2	0.52	0.40	0.31	0.49	0.42	0.22	0.55	0.43	0.24
$\rho = 0.6 V_A$	1.40	0.95	0.48	1.18	0.75	0.46	1.40	0.80	0.33
h^2	0.35	0.27	0.16	0.31	0.23	0.15	0.35	0.24	0.11

ϵ_a (ϵ_s), root mean squared effect for the metric trait (fitness); ρ , correlation between absolute effects of the mutants on the metric trait and fitness effects.

TABLE 6

Equilibrium additive (V_A) and dominance (V_D) variance and equilibrium heritability (h^2) for viability, for different distributions of mutant effects, and range of estimates from 6 natural populations from MUKAI (1985)

Distribution	V_A	V_D	h^2
Normal	0.0180	0.0007	0.15
Gamma	0.0142	0.0006	0.12
Cube-normal	0.0095	0.0005	0.09
Mukai (min)	0.0023	0.0001	
Mukai (max)	0.0202	0.0012	
Average	0.0109	0.0008	

Parameters: $\epsilon_s = 0.02$, $V_M = 2 \times 10^{-4}$, $V_E = 0.1$.

equally frequent in this model, most of the additive variance is contributed by partially dominant mutations and most of the dominance variance by recessive and partially recessive mutations. This is in agreement with the results shown in Figure 3 (lower panel). Similar conclusions to those stated above are obtained when normal or cube-normal distributions are considered (not shown).

Finally, the inbreeding depression for viability explained by the model depends on population size. The larger the population size, the smaller the inbreeding depression as genes with smaller coefficients of selection against the homozygote are segregating and these are likely to have on average additive gene action. With $N = 10^4$, 10^5 and 10^6 , and a gamma distribution, the predicted inbreeding depression is 0.9%, 0.5% and 0.2% per 1% increase in inbreeding, respectively. These are within the same order as the values experimentally observed (0.5% to 0.8%; MACKAY 1985; LOPEZ-FANJUL and VILLAVARDE 1989; GARCIA *et al.* 1994).

DISCUSSION

Diffusion approximations have been used to evaluate genetic variance maintained in finite populations with a pleiotropic model of mutation-selection-drift balance. Recent information on the joint distribution of mutant effects on bristle number and fitness in *Drosophila* from

P element insertional and spontaneous mutagenesis has been used to build a model on which to base the calculations. Particular emphasis has been given to the degree of dominance of new mutations, a feature usually not considered in most studies. One of the aims was to investigate the consequences of nonadditive gene action.

Distribution of effects and mutation rates: Overall, the distribution of effects of new mutations on bristle traits is highly leptokurtic. Mutants usually show deleterious pleiotropic effects on fitness with an intermediate correlation (at least for *P* element insertions) between effects on the trait and fitness. Genes of large effect tend to be recessive while those with smaller effect are on average additive, but gene action is apparently very variable, from completely recessive to completely dominant. Over- or underdominance seem to be, at most, very rare.

Transposable elements can contribute to quantitative variation in natural populations of *D. melanogaster* (MACKAY and LANGLEY 1990). It has been argued that *P* element insertion effects may not be very different from the effects of spontaneous mutation in this species (MLJ). However, *P* element insertions are likely to be more deleterious, on average, than other kinds of mutation. There is no evidence of the same fixation patterns of transposable elements in different lineages (*e.g.*, CHARLESWORTH and LAPID 1989), suggesting that transposable elements are invariably deleterious, though the high rate of transposition of *P* elements makes these results difficult to interpret. Some studies suggest that it is the deletions and rearrangements resulting from the mobilization of *P* elements already inserted and not the insertions *per se* that cause the drastic *P* element effects on viability and fitness observed in studies of *P* element-derived mutations (MONTGOMERY *et al.* 1987; EANES *et al.* 1988). However, the rate of lethal mutations per insert observed by MLJ was 0.04. Assuming an overall genomic mutation rate of 1, this gives a lethal mutation rate of 0.04 per haploid genome and generation, compared with the estimated rate of lethal spontaneous mutation, 0.01 (CROW and SIMMONS 1983). Moreover, the

TABLE 7

Proportion of the additive (V_A) and dominance (V_D) variance for viability contributed by mutants with different coefficients of selection (s) and coefficients of dominance (h)

$-s$	$\Lambda(\%)$	V_A	V_D
0–0.001	22	1	0
0.001–0.005	27	6	9
0.005–0.01	16	11	14
0.01–0.03	24	38	39
0.03–0.1	10	41	34
>0.1	1	3	4

h	$\Lambda(\%)$	V_A	V_D
0.0–0.2	21	7	88
0.2–0.4	20	13	7
0.4–0.6	20	21	0
0.6–0.8	21	29	2
0.8–1.0	18	30	3

Λ , percentage of mutants per generation. Parameters as in Table 6 with gamma distribution of mutant effects.

average homozygous effect of inserts on viability removing lethal and semilethal effects is about -0.04 (KEIGHTLEY 1994), while maximum likelihood estimates from spontaneous viability mutations are -0.01 and -0.004 from data of MUKAI (1964) and OHNISHI (1977), respectively (KEIGHTLEY 1994).

P element insertion data suggests a value of $\epsilon_s = 0.2$ (Table 1). Assuming λ between 0.1 and 1, this gives a value of mutational variance between 0.002 and 0.02, one to two orders of magnitude larger than usually observed. This suggests that P element insert effects cannot be considered as "typical" representatives of spontaneous viability mutations. For this reason, only the set of parameters from spontaneous mutation (Table 1) was used to investigate the variance maintained for viability.

In contrast, a comparison between P element insert effects and spontaneous mutation effects on bristle traits suggests an apparent similarity between them. We argue that, although, as stated above, P element insert effects are likely to be poor representatives of viability mutations, they might be considered good representatives of spontaneous mutation affecting bristle number. Rates of mutation were inferred from P element insertion data by relating the estimated square roots of mean squared effects for bristles (ϵ_a) to estimates of h_M^2 . An average value of 10^{-3} is widely quoted for this latter quantity (LYNCH 1988), but this is an underestimate because of the nonadditive and non-neutral nature of the mutants. A value of about 2.5×10^{-3} has been estimated including these sources of bias (KEIGHTLEY *et al.* 1993) for bristle score in M strains of *D. melanogaster*. This gives a mutation rate per haploid genome per generation of 0.1, which is smaller than estimated from the accumulation of mutations affecting viability (SIMMONS and CROW 1977; CROW and SIMMONS 1983) and fitness (HOULE *et al.* 1992). This is likely to be due to the fact that P element mutations do not represent the whole range of sponta-

neous mutations, in particular nucleotide substitutions and other point mutations. These latter, however, might have little or no effect on a trait such as bristle number and, therefore make no contribution to its variance. Hence, the essential difference between the two sets of parameters in Table 1 is that the parameters derived from P element insertions include only a small fraction (about 10%) in the class of mutations that affects the trait, while the spontaneous mutation parameter set assumes that all mutation events in the genome affect the trait. Therefore, it is justified to use the mutation rate relevant to P element insertion and their parameter estimates if we assume that these constitute the class of mutation affecting a trait such as bristle number, while many other mutations do not affect it at all. In fact, use of this set of parameters gave more reasonable results (Table 2) than for spontaneous mutation parameters (Table 4), but it should be stressed that parameters such as the kurtosis of the distribution of effects and the value of ρ are not well known for spontaneous mutation. It is likely, however, that many more mutations can affect a trait such as viability, for which the use of P element insert parameters might not be justified.

Pleiotropic effects on viability were used as an approximation for overall fitness. In principle, this would be an underestimate if correlations between fitness components are positive, or an overestimate if negative. MACKAY (1985) found positive correlations among fitness components for homozygous chromosomes and argued that positive correlations are expected among inbred lines because deleterious recessive mutations will have pleiotropic effects on many fitness components simultaneously. This agrees with recent data on the effect of spontaneous mutation on several major fitness components where positive correlations among these have been revealed in all cases (C. MARTORELL and A. GALLEGÓ, unpublished). Furthermore, SVED (1971, 1975) and MACKAY (1985) (using the technique designed by SVED and AYALA 1970), showed that viability effects in *D. melanogaster* account for about only one third of total fitness effects (see also SIMMONS and CROW 1977). In equilibrium populations, however, these correlations of effects of segregating alleles may change sign as a result of biological trade-offs (ROSE and CHARLESWORTH 1981). Since larger effects on fitness produce even larger underestimations of h_M^2 there is a corresponding increase in the estimated mutation rate. The analysis suggests (see Table 5) that the reduction in variance due to increased fitness effects is partially canceled by the effect of a larger number of mutants in increasing it. A strong caveat to the above arguments is that selection forces in the laboratory may not be the same as in the wild. Moreover, viability effects of P elements were measured relative to that of a marker chromosome, which does not necessarily give the same selection coefficients relative to the genes segregating in natural populations.

The modeled distribution assumes that all effects on fitness are unconditionally deleterious. The reason for this is that the rate of advantageous mutations is not known but the overwhelming majority of mutants will be deleterious. In any case, as KIMURA (1983) stresses, mutants with a definite selective advantage or disadvantage cannot contribute much to the heterozygosity and, therefore, to the variance, because of their rare occurrence (the former) or rapid elimination (the latter).

Effect of the degree of dominance on the variance maintained: The equilibrium variance of the metric trait is practically independent of the model of dominance assumed, and the same can be said about the equilibrium narrow-sense heritability, unless there is complete recessivity. A model with variable dominance in which values of h' and h are a function of the mutant effects fits the experimental observations very well. A comparison between the degrees of dominance for the trait (h') and fitness (h) of mutants with extreme effect ($a > 0.5\sigma_p$, $s < -0.60$) suggests a relationship $h' \approx 0.4h$. However, the contribution of mutants with such large effects to the genetic variance in equilibrium populations is very small (see Table 2). Moreover, a model in which this relationship was used gave similar results to those with the variable dominance model.

Nature of quantitative variation: Assuming Pelement insertion data, the model of variable dominance predicts the observed heritabilities for bristle number with population sizes of about 10^4 – 10^6 when fitness effects have a slightly leptokurtic distribution of effects. These effective population sizes could be reasonable for natural *D. melanogaster* populations. For example, MUKAI and YAMAGUCHI (1974) estimated effective population size for a *D. melanogaster* population to be between 14,000 and 115,000 based on the allelism rate of lethal-carrying chromosomes and their frequency. KREITMAN (1983) estimated $N_e = 3.3 \times 10^6$ from the DNA polymorphism observed in 11 Adh sequenced genes from 5 natural populations.

With *P* element parameters, partitioning of the contribution to the genetic variance from different categories of mutations (Table 2) shows that most of the variance is contributed by a small number of nearly neutral mutants with intermediate effects (between 0.125 and $0.5\sigma_p$) and with recessive to additive gene action. The average effect of genes controlling bristle number inferred from selection experiments is about $0.2\sigma_p$ [see Table 12.2 in FALCONER (1989)]. The identification of regions containing genes with substantial effect on bristles (SPICKETT and THODAY 1966; SHRIMPTON and ROBERTSON 1988) is also in agreement with the predictions though these latter experiments detect only heterozygous effects.

In the variable dominance model, additive mutants contribute more additive variance than recessives for a given gene effect, but recessive mutants are more abundant and can have larger effects than additive mutants. Thus, the overall contribution of both types of mutants

is similar (see Table 2, lower panel). Despite this, the dominance variance predicted by the model is only about 10% of the total genetic variance and about 5% of the phenotypic variance. This is in agreement with studies on bristle number. CLAYTON *et al.* (1957) found a variance due to "genetic complexities" (presumably mostly dominance variance) which was 15% of the total genetic variance and 9% of the phenotypic variance for abdominal bristles. Other experiments show that, after subtraction of the additive and special environmental variance, only 14% (MADALENA and ROBERTSON 1975) or 6% (LOPEZ-FANJUL *et al.* 1989) of the phenotypic variance remains unexplained. Hence, the maximum V_D would be about 26 or 11% of the total genotypic variance, respectively, and 14 or 6% of the phenotypic variance, respectively. Thus, quantitative genetic variation for bristle traits is mainly additive and it is expected to be nearly neutral (ROBERTSON 1967). With artificial selection for bristle number, however, some decline in fitness is expected, as some deleterious (even lethal genes) may increase in frequency if their effect on the heterozygote is very large. This decline is usually observed in selection experiments (see HILL and CABALLERO 1992), but other factors such as inbreeding depression could also be considered as causes of this decline. However, inbreeding depression for bristles would be small or nonexistent if dominance were nondirectional. This seems to be confirmed by experiments on accumulation of spontaneous mutations, where directional dominance for new mutations affecting bristle number appears to be absent. Furthermore, inbreeding depression for bristle number has not been observed in segregating populations (*e.g.*, KIDWELL and KIDWELL 1966).

With parameters from experiments on accumulation of spontaneous mutations, intermediate equilibrium heritabilities are obtained with different distributions of mutant effects (see Figure 6). The quantitative variation for bristle number is generally controlled by genes with very small effects on bristles and large pleiotropic deleterious effects on fitness (Table 4). These seem to be rather unlikely properties of segregating genes for a trait such as bristle number, known to be nearly neutral and with segregating genes with substantial effect. Another implication of assuming these parameters is that, as ϵ_s is very small, estimates of $h_{M_p}^2$ would have nearly no bias (KEIGHTLEY *et al.* 1993) which, again, is very unlikely. For example, many mutants detected in artificial selection experiments from an isogenic base are lethal homozygotes with a large effect on bristles in the heterozygote (LOPEZ and LOPEZ-FANJUL 1993b) and thus, estimates of $h_{M_p}^2$ from the response to selection are necessarily biased. It is possible that the true distribution of effects of spontaneous mutations on bristle number is much more leptokurtic than assumed, or that the distribution is discontinuous with the majority of mutations having

infinitesimally small or no effect on the trait, as it is effectively assumed in the set of parameters from *P* element insertions.

It is possible to estimate the amount of variation exclusively due to *P* element transposition in *P* cytotype natural populations, where there are about 50 *P* element copies per genome and the rate of transposition is about 0.005/element/generation [MLJ, obtained from EGGLESTON *et al.* 1988]. This gives a total rate of transposition of about 0.125 per haploid genome per generation. To this rate of mutation, the genomic instability generated by *P* elements already inserted in the genome (namely, deletions and chromosomal rearrangements) should be added as a source of variation. Hence, it is expected that the amount of variation due to mutation in *P* cytotype strains is much higher than in *M* strains. This is in accordance with the estimate of h_M^2 for bristle number in *D. melanogaster* obtained from *P* strains being about four times larger than that from *M* strains (KEIGHTLEY *et al.* 1993). Thus, if we use an estimate of $h_M^2 = 10^{-2}$ for *P* strains and, for example $N = 10^4$ and a Wishart distribution of effects, the predicted equilibrium variance is 7.9, and the equilibrium heritability is 0.76, compared to 2.1 and 0.45, respectively, for *M* strains with the same model and population size.

A heritability of about 10% is predicted for viability using the spontaneous mutation parameter set, and this is independent of the population size. This is within the range of estimates obtained from laboratory experiments [TANTAWY and EL-HELW (1970): 9–16%; LOPEZ-FANJUL and VILLAVARDE (1989): 10%; GARCIA *et al.* (1994): 29%] and within the range of estimates for other life-history traits (ROFF and MOUSSEAU 1987; CHARLESWORTH 1987). It should be borne in mind that the equilibrium heritabilities for both bristles and viability have been obtained using the experimental estimate of V_E which was measured in the highly uniform environment of a laboratory. Heritabilities in the wild must, therefore, be much smaller. The values given can be regarded as those which would be obtained when the heritability is estimated in the laboratory.

Additive variation for viability is predicted to be caused mainly by mutants with effects $-0.1 < s < -0.01$ and substantial effect in the heterozygote. The results obtained by GARCIA *et al.* (1994) on the effects of inbreeding and artificial selection on viability in a natural population suggest the segregation in the base population of few loci with additive effects and a number of recessives at low initial frequencies.

Dependence of the equilibrium variance on the population size: Pleiotropic models are based on observed features of the genes, but have two important properties from a practical and theoretical point of view. The variance increases indefinitely with population size (KEIGHTLEY and HILL 1990) (see Figure 4) and the amount of apparent stabilizing selection might not be large

FIGURE 7.—Equilibrium heritability plotted against population size (N), using a Wishart distribution modified with parameter δ (see text).

enough (BARTON 1990; KONDRASHOV and TURELLI 1992).

Stabilizing selection models predict finite equilibrium genetic variance even with infinite populations (LATTER 1960; LANDE 1975; TURELLI 1984). Pleiotropic models, however, predict increases in variance without limit with increasing N [unless $\rho = 1$, in which case the model is similar to pure stabilizing selection, or a model such as that proposed by COCKERHAM and TACHIDA (1987) and ZENG and COCKERHAM (1993), where a house-of-cards mutation model is considered]. For the values of ρ and the distributions of effects assumed in this paper, nevertheless, the rate of increase in V_G is rather slow.

By restricting the fitness effects to a certain maximum, the model can be modified so that, while ρ is still intermediate, V_G reaches a limiting value. With the Wishart distribution used in this study, there is a small but non-zero probability that mutations of large effect are effectively neutral. This seems to be contrary to the observations from spontaneous and *P* element-induced mutations: mutants with extreme effects appeared to be invariably deleterious (although the number of mutants studied was relatively small). A function relating the effect on the trait (a) and the effect on fitness (s) can be fitted such that, for a given a , values of s can only be smaller than the value of the function. The particular function used was $l = -[|a| - \delta(1 - e^{-|a|/\delta})]$, such that for a given value of a , coefficients of selection $s > l$ were not allowed. This function has a parabolic shape such that the higher the gene effect, the larger the value of $-l$. The parameter δ gives the scale of the function.

Figure 7 shows the equilibrium heritability as a function of N with a Wishart distribution, additive model and different values of δ . The upper curve ($\delta \rightarrow \infty$) is the unmodified Wishart. The effect of the modification is very drastic in causing V_G to reach a limit. For example, with $\delta = 2^{10}$, the function is nearly flat: for mutants with an effect of 1 or $2\sigma_p$, only mutants with coefficients of selection between 0 and -0.001 or 0 and -0.004 , respectively, would not occur. It would of course not be possible to distinguish experimentally these coefficients of selection from strict neutrality.

As suggested by A. GARCIA-DORADO (personal communication), the effects caused by the above modification

TABLE 8

Proportion of the additive variance (V_A) for bristle number contributed by different types of mutant in a population of size $N = 10^4$ for different values of the strength of superimposed stabilizing selection, V_s

$-Ns$	$V_s \rightarrow \infty$		$V_s = 200$		$V_s = 20$	
	Λ	V_A	Λ	V_A	Λ	V_A
0-1	38	58	27	8	17	2
1-5	42	17	53	38	34	9
5-10	33	16	37	12	39	12
10-30	84	8	87	18	87	20
>30	1403	1	1396	24	1423	57
a	Λ	V_A	Λ	V_A	Λ	V_A
0-0.125	1039	7	1036	14	1026	23
0.125-0.25	265	20	266	35	279	32
0.25-0.5	203	31	201	35	197	28
0.5-0.75	57	13	60	11	61	11
>0.75	36	29	37	5	37	6

Λ , number of mutants per generation; s , coefficient of selection; a , absolute effect on bristles in σ_P units. A Wishart distribution of mutant effects was assumed with parameters: $\epsilon_a = 0.36$, $\epsilon_s = 0.20$, $\rho = 0.38$, additivity.

were shown to be equivalent to those produced by adding weak stabilizing selection to the pleiotropic model. This was made by adding to the coefficient of selection of the mutant an additional coefficient $s = -a^2/4V_s$ (ROBERTSON 1956), where V_s measures the width of the curve relating phenotype with fitness (see TURELLI 1984). Thus, a similar curve to, for example, that observed with $\delta = 2^{10}$ in Figure 7, was obtained by superimposing stabilizing selection with strength $V_s = 400$. This model of stabilizing selection superimposed on the present pleiotropic model might be plausible, as discussed by KONDRASHOV and TURELLI (1992). Its main implications concerning the nature of the quantitative variation are shown in Table 8, in which P element insertion parameters are assumed. Cases of $V_s \rightarrow \infty$ (no stabilizing selection), $V_s = 200$ ("weak" stabilizing selection) and $V_s = 20$ ("strong" stabilizing selection) are considered. The asymptotic additive variance predicted for the three cases are 2.04, 0.96 and 0.33, respectively. Note that the predicted genetic variance for strong stabilizing selection ($V_s = 20$) is low. The stronger the stabilizing selection, the fewer nearly neutral mutants ($0 \leq -Ns < 1$) appear and these only have small effects on the trait. The consequence is that, contrary to what was found before ($V_s \rightarrow \infty$), most of the variance is due to segregation of deleterious alleles ($-Ns > 5$). Moreover, mutants of very small effect on the trait ($a < 0.125\sigma_P$) contribute proportionally more variance than found with the pleiotropic model alone.

Apparent selection: A fitness advantage of intermediate phenotypes is observed for many quantitative traits (ENDLER 1986) and interpreted as stabilizing selection (LANDE 1975; TURELLI 1984). Stabilizing selection models define a rigid connection between trait values and

fitness. Pleiotropic effects on other quantitative traits also subject to stabilizing or directional selection would further increase the strength of this connection (LANDE 1980; TURELLI 1985; WAGNER 1989). In the pleiotropic model, the effects of mutants on all other traits are condensed into a single overall fitness effect, however. The pleiotropic model can also produce apparent stabilizing selection (KEIGHTLEY and HILL 1990; BARTON 1990). KONDRASHOV and TURELLI (1992) have analyzed the amount of apparent stabilizing selection produced by these models and have concluded that this is smaller than experimentally observed. GAVRILETS and DE JONG (1993), however, have shown that a class of pleiotropic models including epistasis can generate large amounts of apparent stabilizing selection.

The observed selection on a quantitative trait is often quantified as the standardized change in mean or phenotypic variance (variance selection differential) between early and late stages of the life cycle, *e.g.*, between progeny and adults (ENDLER 1986). A reduction in the phenotypic variance implies either directional or stabilizing selection on the trait itself, or as a result of pleiotropy, while an increase in variance implies disruptive selection. In a review of the distribution of directional and variance selection differentials in natural populations, ENDLER (1986) concluded that natural selection is often as strong as artificial selection, and that stabilizing selection is less common in nature than directional selection.

With additive gene action, a reduction in the genetic variance of a quantitative trait by directional selection is associated with a temporary build up of negative disequilibrium between linked and unlinked alleles in the parents which is partially recovered by recombination and segregation in the progeny (BULMER 1971). The proportion by which the variance is reduced is the inverse of the non-optimal strength of stabilizing selection, V_s (BULMER 1989). With recessive gene action a further change in variance across the life cycle can result from the selective loss of parents homozygous for deleterious recessive alleles, which reappear in the progeny with restoration of Hardy-Weinberg proportions. The difference in behavior between additive and recessive pleiotropic models is illustrated in Figure 8 which shows the proportional reduction in the phenotypic variance as a function of population size. Results were obtained by Monte Carlo simulation of a multilocus model without linkage at a balance between mutation, selection and drift using a Wishart distribution of mutant effects with the P element insertion parameters of Table 1 (KEIGHTLEY and HILL 1990). Results from two values of the correlation parameter, ρ , are shown. With complete correlation ($\rho = 1$), the reduction in variance is very small because the heritability maintained in the trait is very low (*cf.* Table 4). With the correlation parameter more appropriate to bristle number ($\rho = 0.4$), although the heritability

FIGURE 8.—Proportional reduction in the phenotypic variance (V_p) as a function of population size (N) for two values of p . Mutant effects have a Wishart distribution with recessive or additive gene action, $\epsilon_a/\sigma_p = 0.2$, $\epsilon_r = 0.2$ and $\lambda = 0.1$.

slowly increases with population size (Figure 5), the reduction in variance quickly reaches an asymptote and remains tiny for both additive and recessive gene action.

Bristle traits in *Drosophila* are peripheral traits (ROBERTSON 1967), at least for the range of numbers observed in natural populations, although they may show strong apparent stabilizing selection (KEARSEY and BARNES 1970; FOWLER 1984). Selection may not, however, be directly on bristle number but on the pleiotropic effects of the genes on larval competition (SPIERS 1974). Finally, the selection coefficients obtained by MLJ and used in our calculations could have been larger if measured in high density conditions (such as those used by KEARSEY and BARNES 1970), giving a larger strength of apparent stabilizing selection.

The aim of this work has been to investigate genetic variation under a pleiotropic model with parameter values from experimental sources. A complete analysis is not possible because there are gaps in our knowledge of the relevant parameters. Information on the joint distribution of effects of spontaneous mutations and fitness traits would be particularly interesting. It will be possible to test predictions of the different models as information on effects and frequencies of loci contributing to standing variation in natural populations will come from quantitative trait locus mapping experiments with molecular markers. It may not be possible, however, to obtain relevant information on the pleiotropic effects of the loci on fitness traits, a key feature of the models, as such pleiotropic effects are expected to be very small.

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