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DEVELOPMENTAL MODELS AND POLYGENIC CHARACTERS

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A comprehensive understanding of evolution requires an appreciation of the mechanisms by which genes affect phenotypes. It is generally accepted that genetic variation produces phenotypic variation through changes in developmental processes, and a number of investigators have sought ways to introduce developmental information into evolutionary models (Riska 1986; Atchley 1987; Slatkin 1987; Wake and Larson 1987). Nonetheless, a general understanding of how development mediates between the genetic and phenotypic levels of evolution remains elusive. Toward improving this understanding, we have explored the consequences of a simple nonlinear model of development based on the mechanism believed to be responsible for the determination of eyespot patterns on the wings of butterflies (Murray 1989; Nijhout 1991).

Models of pattern formation in development (such as positional information, lateral inhibition, reaction-diffusion, diffusion gradient and threshold) make precise predictions about how form will vary with variation in parameters of the model (Meinhardt 1982; Edelstein-Keshet 1988; Murray 1989; Nijhout 1990). Moreover, many models allow us to relate certain parameter values specifically to gene activity. For instance, in ordinary and partial differential equation models, the rate constants can often be directly equated with gene "activity," because genes code for enzymes that control reaction rates. Different values of a rate constant can represent different alleles of a gene that code for enzymes with different catalytic efficiencies. Developmental models can, therefore, make certain predictions about the relation between genetic variation and phenotypic variation.

Developmental models, however, are always about the individual, whereas evolutionary theory is about populations. Thus, for developmental models to be useful for the study of microevolution, they need to be stated in populational terms (Atchley and Hall 1991). To date, attempts to integrate developmental information into microevolutionary models have been done in the context of quantitative genetics by assuming that developmental parameters such as the growth rate of a tissue and the timing of its growth can be treated as quantitative genetic traits (Atchley 1987, 1990; Slatkin 1987). Atchley (1987) has developed a model that assumes that natural selection can act directly on these developmental

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parameters, whereas Slatkin's (1987) model assumes that the value of developmental parameters per se does not affect individual fitness but that any change in a parameter comes about through a correlated response to selection on the emergent phenotype. Such studies have begun to yield some insight into the effects that heterochrony and variation in developmental parameters can have on the pattern of phenotypic evolution. An alternative approach to integrating developmental models into population genetics would be to treat developmental parameters as if they were controlled by single genes and then model the change in allele frequencies of those genes under selection (Slatkin 1987). Here we explore the behavior of such a population genetic model of development.

THE DEVELOPMENTAL MODEL

We have used a one-dimensional diffusion gradient and threshold model with six parameters. A point source of value (*Source*) produces a diffusible substance with a diffusion coefficient (*Diffusion*) and a decay constant (*Decay*). The diffusion gradient that is produced is read at time (T_{end}) by a threshold (*Threshold*). In addition, all cells have a low autonomous background rate (*Background*) of production of the diffusible substance. The state of this system after an arbitrary period of time is shown in figure 1. The character measured is the linear distance between the source and the threshold value of the diffusible substance. Diffusion gradient and threshold models of this sort are used in developmental biology to explain the regulation of the position of parts, the sizes of parts, and the linear distance between parts. The dynamics of growth, regeneration, pattern formation, and pattern regulation in many developmental systems behave as predicted by such a gradient model (Child 1941; Wolpert 1969, 1981; Murray 1989; Lawrence 1992). Although gradient models are of general use in understanding developmental systems, recent studies on pattern formation in butterflies and moths have shown that a simple gradient model as the one we use here provides accurate representations of the mechanisms responsible for the formation of bands and eyespots in the color patterns on the wings (Toussaint and French 1988; Nijhout 1991, 1992; Carroll et al. 1994; Monteiro et al. 1994; Brakefield and French 1995).

Each of the six parameters of this model is regulated by a single gene, and we assume these genes to be unlinked. We assumed two alleles for each of these hypothetical genes, producing a high and a low value (given in parentheses here) for the developmental parameter they control, as follows: *Source* (3,000, 800); *Decay* (0.008, 0.001); *Diffusion* (1.0, 0.1); T_{end} (200, 50); *Threshold* (400, 250); *Background* (1.0, 0.1). Although it is likely that each of the six variables in the model is affected by more than one gene (the threshold mechanism, e.g., is itself nonlinear and likely to involve at least three gene products; Lewis et al. 1977; Nijhout 1991), we assume that we can select a region of parameter space in which only one gene has a major effect on the value of the developmental parameter. We assume a diploid organism and simple additivity (codominance) of the two alleles with respect to the developmental parameter value. The value of the quantitative trait, P, is therefore produced by the interaction among the six genes, as they affect the dynamics of the model in figure 1. The solution for P is obtained

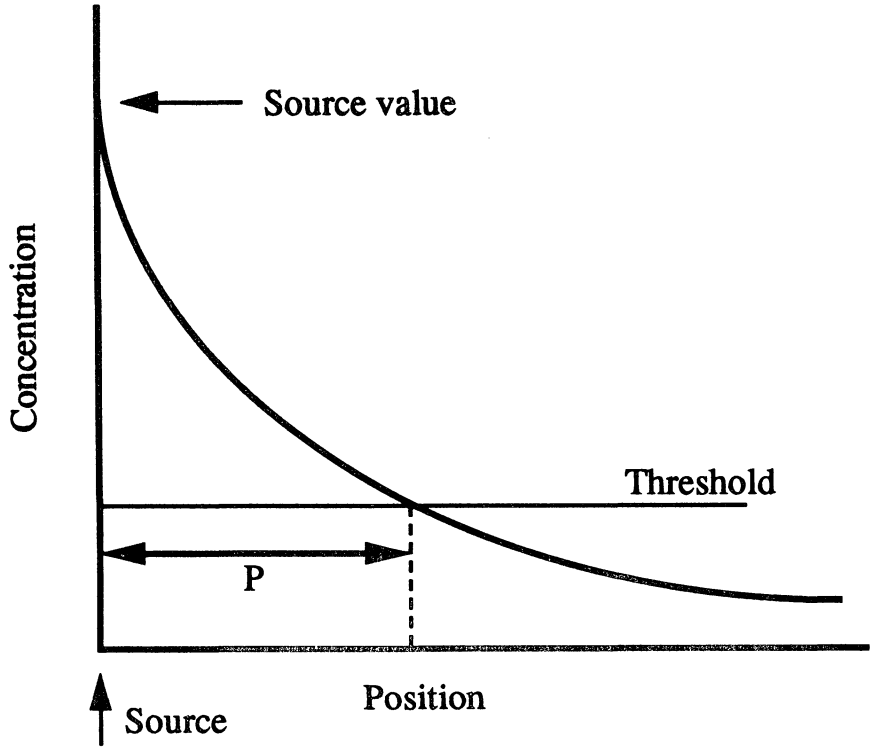

FIG. 1.—Diffusion gradient-threshold model for generating a quantitative character. A morphogen is produced at the location marked *Source*, where its concentration is maintained at steady state. The morphogen decays with time and diffuses away from the source site, producing a concentration gradient shown by the thick curved line. This gradient gradually rises with time. The phenotype, *P*, is the size of the domain where the morphogen concentration is above a threshold value.

by numerical simulation of the diffusion equation in one dimension (Crank 1975), given specific values for the alleles at each of the six genes.

The boundary conditions of the diffusion threshold model are such that it cannot yield a closed-form solution. It is therefore impossible to express the phenotype as a mathematical function of the genetic parameters. The phenotype is calculated by computer simulation for each set of parameter values. In a real developmental system, genes control the values of developmental parameters, which in turn provide the rate constants, timing events, and thresholds in the developmental process.

RESULTS

Genotype and Phenotype

To calculate the relationship between genotype and phenotype, we assume that for each gene there exists a range of alleles in the population that produce varia-

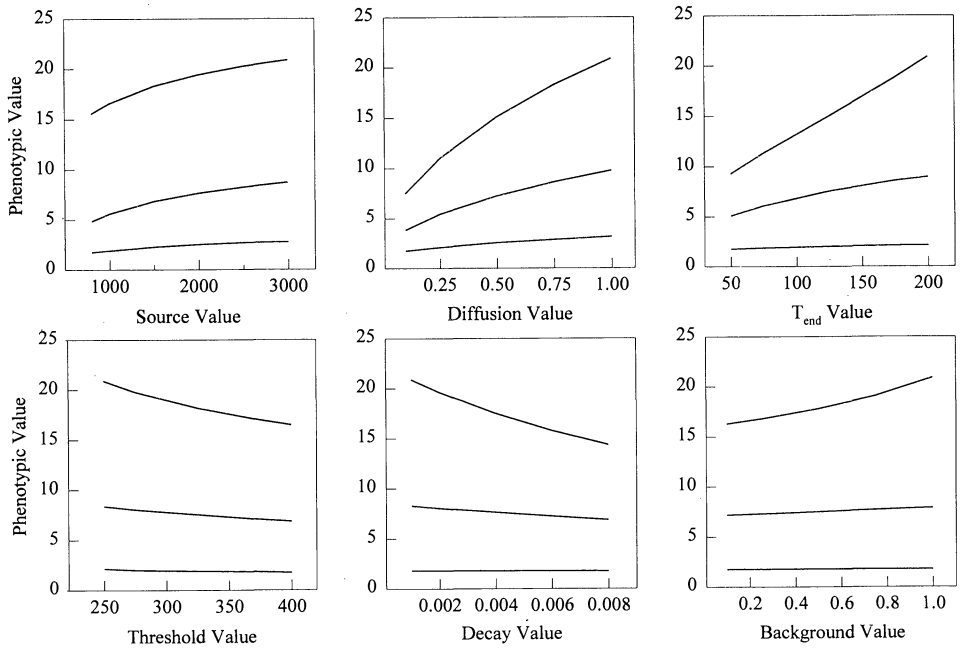

FIG. 2.—A sensitivity analysis of the effects of variation in each of the six genes on the phenotype while all other genes that affect the phenotype are held constant. Lower curves represent phenotypes produced by variation in the value of a gene when all other genes are fixed (homozygous) for their lowest allele; the upper curves, when all other genes are fixed for their highest allele (see text). The area enclosed by the upper and lower pair of curves represents the range of phenotypes possible by variation in that gene, depending on the values of alleles at the other genes. The intermediate curve on each graph represents the range of phenotypes produced by variation in each gene when all other genes are fixed for an allele with a value exactly halfway between the maximal and minimal values. In the absence of dominance with respect to the phenotype, each curve would be a straight line. In the absence of epistasis, each curve within a panel would have the same shape, and the middle curve would lie exactly halfway between the upper and lower curves.

tion in the developmental parameters, with the maximum and minimum values cited earlier. These values yield a range of P's from 1.8 (homozygous for all alleles with lowest effect) to 20.9 (homozygous for all alleles with highest effect). We computed how the phenotype, P, varied with variation in each developmental parameter when the allelic composition of the other five genes was held constant (fig. 2). In each panel in figure 2, the lower curve shows the sensitivity of the phenotype to variation in a given developmental parameter, in a background in which the other genes produce their lowest phenotypic effect. The upper curve in each panel shows the effect of the same developmental parameter in a background in which the other genes produce their highest phenotypic effect. The upper and lower curves thus bound a space that defines the relationship between genotype and the phenotype for this system. The relationship between genotype at each locus and the phenotype is weak; one genotype can correspond to a broad

range of phenotypes and vice versa, depending on the values of the other genes. The slopes of the curves in figure 2 describe the effects of allelic substitution (or mutation) on the phenotype in different genetic backgrounds.

Phenotypic values generally do not change linearly with genotypic values. Log transformation of the data does not linearize the curves in figure 2, though nonlinear transforms may exist that will. In genetic terms, this nonlinearity means that the alleles of a gene are not acting additively; dominance is an emergent property of the model. The actual degree of dominance of a given pair of alleles can be calculated from these curves by the method described by Falconer (1989, p. 112). For instance, suppose there are two alleles for the *Source* parameter corresponding to the extremes of the upper curve in figure 2. The phenotypic values produced by homozygosity at these alleles are 15.6 and 20.9, and their mean is 18.25, so the genotypic value of the *Source* gene, a (expressed as the deviation from the mean), is 2.65. The phenotypic value of the heterozygote is read from the curve at its midpoint and is 18.9. The degree of dominance, d, is the difference between this value and the mean of the homozygotes, in this case, 0.65. The intermediate curves in figure 2 are the phenotypic values produced when all background alleles are fixed at a value exactly halfway between the two extremes. If all genes had equivalent and additive effects on the phenotype, we would expect these curves to lie exactly halfway between the upper and lower curves, and we would expect all three curves to have the same shape. That they do not signifies that a substantial amount of epistasis exists in the system, a consequence of the interaction among the gene products.

The graphs in figure 2 demonstrate the indirect connection between a single-locus genotype and the phenotype that emerges from even a very simple model of development. All genes have a much smaller effect on P when placed in a background in which all others produce their lowest phenotypic effect (fig. 2, *lower curves*) than they do in a background where other genes produce their greatest phenotypic effect (*upper curves*). The sensitivity of P to variation in genetic value when all other genes are high differs considerably for different genes. Within the parameter ranges defined earlier, the T_{end} and *Diffusion* genes have the largest effect, and the *Background* and *Threshold* genes have the smallest effect on variation in P. Under a model of genetic determinism, one would call the T_{end} and *Diffusion* genes major genes and the *Background* and *Threshold* genes modifiers, for P. In a background in which all genes produce their lowest effect, the relationships are different. In those conditions, the *Diffusion* and *Source* genes have the greatest effect on P, and the *Decay* and *Background* genes have the least effect. The relationship between genes and the phenotype is highly context dependent, and little can be said about the effects of variation in any gene without specifying the genetic background (Wright 1968, 1982). A gene that has a major effect in one background may have little or no effect in another. This context dependency has some interesting consequences for the genetic response to selection on the phenotype.

The Response to Selection

To examine the genetic response to selection on the phenotype, we established a randomly breeding sexual population by computer simulation. Each of the six

genes was represented by two alleles that produce the two extremes of developmental parameter values listed earlier. The population was started with the alleles that produce a low value of P at a frequency of 0.9. The genotypes of 1,000 pairs of diploid parents were created by selecting randomly from this frequency distribution, and 10 random diploid offspring were produced from each pair. Offspring whose phenotype exceeded the mean phenotypic value minus one-half of the standard deviation of the parental generation were saved. From these, 1,000 pairs were randomly selected to be parents for the next generation, and so forth. Figure 3*A* illustrates the phenotypic response to this regime of truncating selection. The phenotype of the population responded readily to selection with an almost linear increase in the mean phenotypic value over time.

The genetic response to selection is shown in figure 3*B*. While all genes eventually went to fixation for the allele that produces the highest phenotypic value, each exhibited a distinctive response to selection. Two genes (*Source* and *Diffusion*) responded rapidly and went to fixation after about 10 generations. The remaining genes responded more slowly, and their high alleles generally remained at relatively low frequencies until the more rapidly responding genes were nearly fixed.

Evolution of Developmental Parameters

In our developmental model, the values of the parameters are not directly subject to selection. Thus, the change in each developmental parameter is largely determined by its covariance with the emergent phenotype (Slatkin 1987). The change in gene frequency produced by the correlated response of each developmental parameter is, however, better understood intuitively by examining the correlation of each developmental parameters with the emergent phenotype.

We calculated the additive genetic correlation between each developmental parameter and the phenotype for each gene during the course of selection through parent-offspring regression (fig. 3*C*). This correlation is a predictor of gene frequency change as shown in figure 4. The two genes that responded most rapidly to selection (*Source* and *Diffusion*) were those that initially had the highest correlation with the phenotype, but as selection progressed, their correlations with the phenotype decreased. As these genes went to fixation and their contribution to genetic variation was eliminated, the correlations of the remaining parameters increased in such a manner that each gene in turn assumed, for a brief period during selection, the highest correlation with the phenotype (fig. 3*C*). Selection also produced linkage disequilibria among the alleles; however, the genetic correlation between developmental parameters produced by these associations remained small. In spite of large rapid changes in the correlation of genes with phenotype, the narrow-sense heritability of the phenotype remained close to 1 throughout the period of selection. The variance of the phenotype rose gradually during the first half of the selection period and then remained high until the generation before the last alleles went to fixation.

Selection in the opposite direction, starting with the alleles that produce a high value for P at a frequency of 0.9 and selecting each generation for a phenotype smaller than the parental mean plus one-half of the standard deviation, produced a qualitatively similar genetic response (fig. 5). The initial phenotypic response to selection is more rapid, presumably because of the higher differential effects

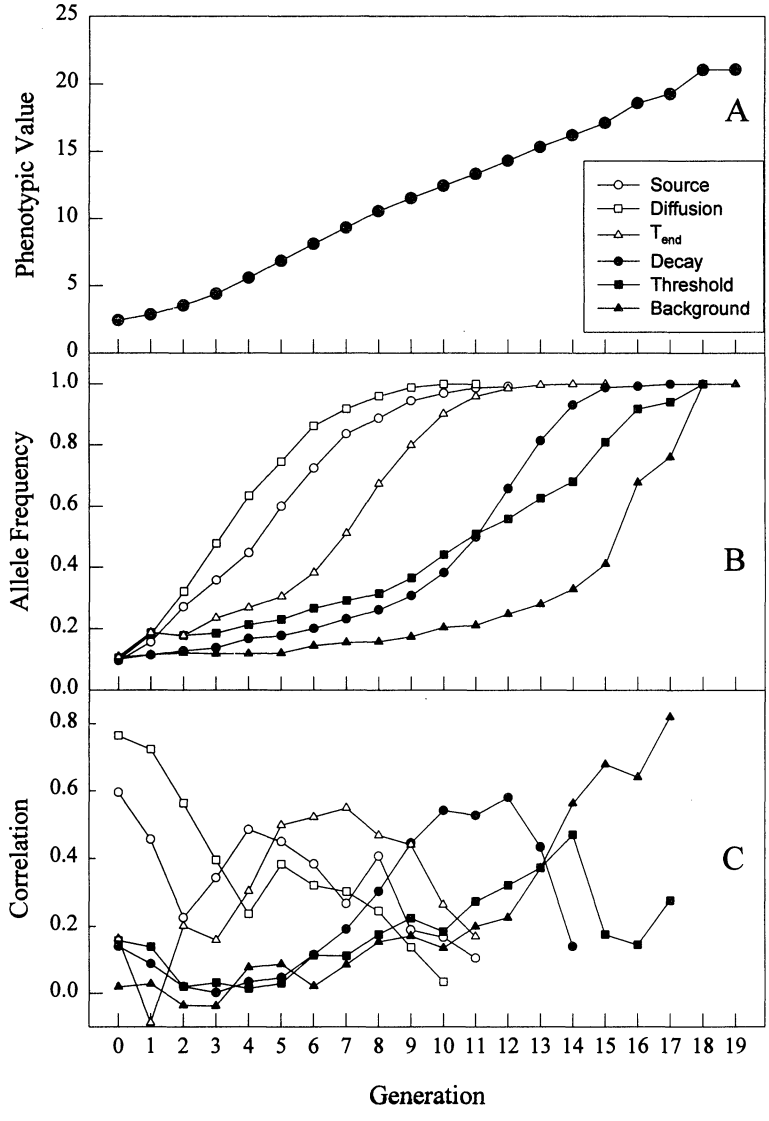

FIG. 3.—*A*, Response of the phenotype to truncating selection for a larger value. In each generation, individuals with phenotypic values below the mean minus one-half of the standard deviation of the previous generation were removed from the breeding population. *B*, Genetic response to truncating selection on the phenotype. *C*, Genetic correlations of the six developmental parameters with the phenotype during selection. The plot shows absolute values; the *Decay* and *Threshold* correlations are actually negative (see fig. 2).

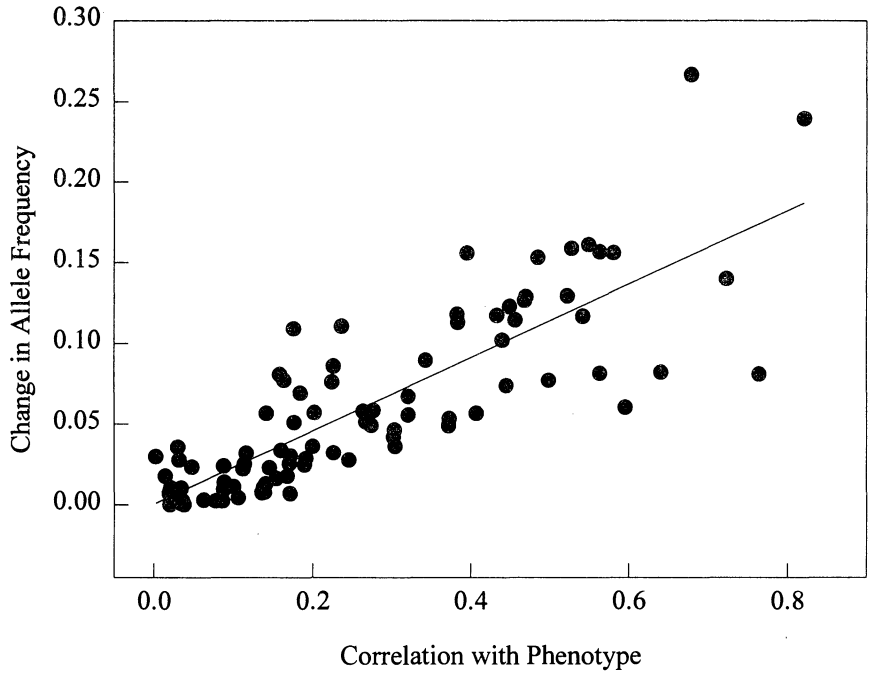

FIG. 4.—Plot of the correlations between each developmental parameter and the phenotype and change in gene frequency in the next generation.

of the genes at high phenotypic values. Downward selection on the phenotype, however, did not simply reverse the genetic response sequence from that found in the upward selection. During the second half of the selection process, when the phenotype changed relatively little, there continued to be an orderly genetic response to selection (fig. 5*B*) even though the genetic correlations with the phenotype were very low (fig. 5*C*).

DISCUSSION

We have examined the properties of a simple developmental model that uses a diffusion gradient and threshold mechanism to establish the dimension of a quantitative character. In this model, as in nature, genes affect the values of developmental parameters, and the developmental parameters in turn affect the phenotype. Our results show that even in a very simple developmental system genetic background has a large effect on the relationship between a gene and the phenotype. Variation in a given gene can have little or no effect on the phenotype in one genetic background, yet that gene can come to have a dominant effect on the phenotype when the frequencies of alleles at other loci change. Thus, whether a particular gene is perceived to be a major gene, a modifier gene, or even a neutral gene depends entirely on the genetic background in which it occurs, and this apparent attribute of a gene can change rapidly in the course of selection on

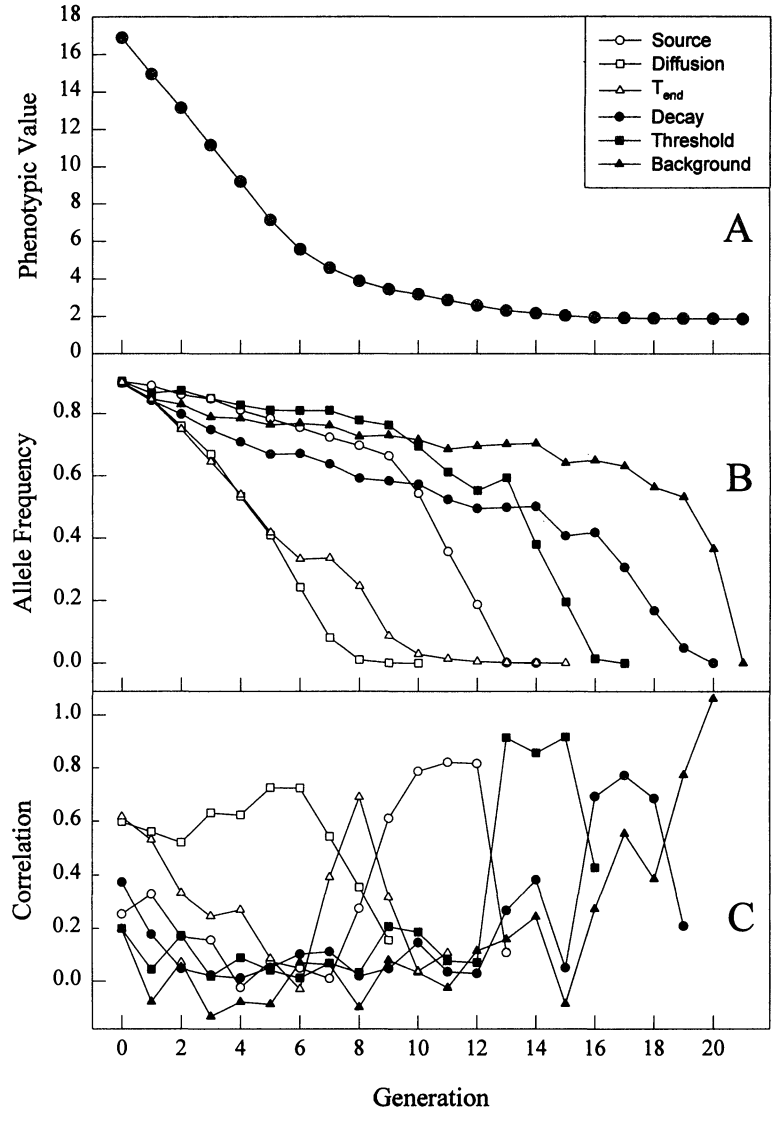

FIG. 5.—*A*, Response of the phenotype to downward-truncating selection. In each generation, individuals with phenotypic values above the mean plus one-half of the standard deviation of the previous generation were removed from the breeding population. *B*, Genetic response to truncating selection on the phenotype. *C*, Genetic correlations of the six developmental parameters with the phenotype during selection. The plot shows absolute values; the *Decay* and *Threshold* correlations are actually negative (see fig. 2).

the phenotype. Single-locus models for the evolution of complex phenotypes may, therefore, be of limited general value because they may apply only as long as gene frequencies do not change appreciably.

With selection acting exclusively on the phenotype, the genes responded differentially. Genes for developmental parameters with the higher initial correlation to the final phenotype responded more rapidly than those with lower correlations, which is what one would expect. Genes with low correlations to the phenotype appeared to be neutral early in the selection process (perhaps "pseudo-neutral" would be a preferable term, to distinguish such genes from those that can truly not have an effect on the phenotype under selection). These genes became highly correlated with P and subject to effective selection only after the first set of genes had gone to fixation. Small changes in gene frequencies were accompanied by large changes in the correlation of some genes with the phenotype, which suggests that it would be interesting to investigate whether in nature such correlations change as rapidly as this model suggests.

Is there a way to predict the sequence of the genetic response to selection? At the genetic level, it is most appropriate to define the effect of a developmental parameter on the phenotype in terms of the average effect of the genes that underlie that developmental parameter. The influence of a gene on the phenotype is often expressed as the average effect of gene substitution, α, which is given as

$$\alpha = a + d(q - p),$$

where a is the genotypic value of a homozygote for the gene in question, d is the degree of dominance among the two alleles, and p and q are the allele frequencies (see, e.g., Falconer 1989). In this system, there is no overdominance or underdominance, and d is always much smaller than a, which means that α is determined largely by a. Thus, if we can determine a, we have an approximate way of predicting which developmental parameter is most important in controlling variation of the phenotype.

The phenotypic values of homozygotes for any two alleles for a gene can be read from the graphs in figure 2, and from this the genotypic value, a, can be calculated. The difference in the phenotypic values of homozygotes for the high and low alleles is a measure of the effect of allelic substitution and therefore of the average effect of that gene. The appropriate genotype-phenotype curve can be determined empirically when the frequencies of the interacting genes are known. In figure 2, for instance, we have calculated curves for three specific genetic backgrounds. All other genetic backgrounds produce a fan-shaped array of nonintersecting curves that lie between the upper and lower curves in each panel of this figure.

The genotype-phenotype relations in figure 2 thus provide a rough heuristic tool for predicting which genes will respond early in the selection process and which genes will be relatively late responders. The gene with the greatest difference between its high and low alleles is the one that is most highly correlated with the phenotype and whose frequency responds most rapidly to selection. When all high alleles are at a low frequency, the genotype-phenotype curves lie

close to the lower extremes in figure 2, so the predicted order of genes (based on the mean slopes of the lower curves) is *Diffusion* > *Source* > T_{end} = *Threshold* > *Decay* > *Background*. Thus, one would expect *Diffusion* and *Source* to respond most rapidly to upward selection, as indeed they do. As selection proceeds, these genes eventually become fixed and no longer contribute to variation in the phenotype. At that point, other genes frequencies will have changed a little also, and the genotype phenotype relations will be closer to the intermediate curves in figure 2. The sequence of genes (with the first two gone to fixation) now is *Diffusion* > *Source* = T_{end} > *Threshold* > *Decay* > *Background*. As the next most rapidly responding genes (T_{end} and *Threshold*) go to fixation, they no longer contribute to variation in the phenotype, and the remaining genes (*Decay* and *Background*) become subject to selection in the order predicted by their effect on the phenotype. By the same line of reasoning, figure 2 predicts that downward selection on the phenotype (starting with gene frequencies as in fig. 5*B* and genotype-phenotype relations approximating the upper curves in fig. 2) would produce a sequence of genetic response beginning with *Diffusion* and T_{end} and followed by *Source* and *Threshold*. This pattern is indeed what we found.

In conclusion, we think that we have provided an easily understandable demonstration of the genetic behavior of a quantitative trait. It seems that even in a relatively simple developmental system, the phenotypic effect of variation at a single locus depends critically on the allelic values at the other genes and the frequencies of the various alleles in the population. We illustrate how the genetic response to selection depends on the correlation of each developmental parameter with the phenotype. This correlation changes rapidly in the course of selection and depends on the frequencies of all interacting genes. Our findings imply that for these kinds of systems, the effect of genetic background is sufficiently severe that only a small fraction of the genes that affect the development of a trait may be identifiable in any single sampling of a population. Furthermore, the fact that during selection the heritability of the phenotype remained close to 1 and the phenotypic variance remained high indicates that additive genetic variance was maintained despite the elimination of genetic variation. Presumably this is due to recruitment of previously pseudo-neutral loci whose effect on the phenotype became manifest as the genetic background changed.

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