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The genetics of phenotypic plasticity. II. Response to selection

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Abstract

We selected on phenotypic plasticity of thorax size in response to temperature in *Drosophila melanogaster* using a family selection scheme. The results were compared to those of lines selected directly on thorax size. We found that the plasticity of a character does respond to selection and this response is partially independent of the response to selection on the mean of the character. One puzzling result was that a selection limit of zero plasticity was reached in the lines selected for decreased plasticity yet additive genetic variation for plasticity still existed in the lines. We tested the predictions of three models of the genetic basis of phenotypic plasticity: overdominance, pleiotropy, and epistasis. The results mostly support the epistasis model, that the plasticity of a character is determined by separate loci from those determining the mean of the character.

Introduction

One of the central goals of evolutionary biology is to understand the processes by which organisms adapt to complex environments. One part of the Modern Synthesis has been aimed at the building of adequate theoretical models, testing those models experimentally, and verifying them in nature. Of necessity, the models and experimental studies have started with the simplest sets of conditions and built to more complex situations with the ultimate goal of approaching the conditions of

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the natural world. In this regard there has been a recent upsurge in theoretical models (Caswell, 1983; Via and Lande, 1985, 1987; Lynch and Gabriel, 1987; Castillo-Chavez et al., 1988; Gillespie and Turelli, 1989) and experimental studies (a sample from 1988: Gebhardt and Stearns; Groeters and Dingle; Kuiper and Kuiper; Lechowicz and Blais; Macdonald et al.; Newman; Schlichting and Levin; Taylor and Aarssen) on the effects of multiple environments on adaptation, although these concerns certainly have a long history (e.g. Wright, 1931; Schmalhausen, 1949; Johnson et al., 1955; Falconer 1960; Tantawy and Mallah, 1961; Levins, 1963; Bradshaw, 1965).

In particular phenotypic plasticity, the modification of developmental events by the environment, has received increasing attention (Schlichting, 1986). Most phenotypic plasticity studies fall into one of three categories. (1) Genetic models: after a long history of verbal descriptions and one- and two-locus models of the evolution of phenotypic plasticity there have been three recent quantitative genetic models developed (Via and Lande, 1985, 1987; Lynch and Gabriel, 1987; Gillespie and Turelli, 1989). (2) Experimental studies: recently several experiments have examined environmental modification of gene expression (Perkins and Jinks, 1973; Service and Rose, 1985; Clark, 1987; Scheiner et al., 1989). (3) Surveys: studies of variation in phenotype as a function of the environment have had a long history, notably the plant studies of Clausen et al. (1940). In recent years these surveys have been done specifically in the context of notions about phenotypic plasticity and the estimation of the magnitude of genotype-environment interaction variance (e.g. Scheiner and Goodnight, 1984; Via, 1984; Gebhardt and Stearns 1988; Groeters and Dingle, 1988).

The most serious lack in our understanding of phenotypic plasticity is experimental studies on its genetic basis (cf. Jinks and Pooni, 1988). Is the plasticity of a character a trait which can respond to selection? To what extent is this response independent of the response to selection on the mean of the character? What does this information tell us about the underlying genetic basis of plasticity, its genetic architecture? How can we use this information to build more realistic models of the evolution of phenotypic plasticity? Which is a more likely outcome to selection on adaptation to a complex environment, the evolution of genetic differentiation and specialized genotypes or the evolution of phenotypic plasticity and a single generalized genotype? It is this series of questions that we address in this paper and the ones to follow in this series.

We present the results of artificial selection on phenotypic plasticity of thorax size in response to temperature in *Drosophila melanogaster*. We used a family selection scheme to select on the trait of phenotypic plasticity of thorax size in response to temperature. That is, the phenotype of a group of full-sibs as expressed in two environments was the selected trait (see below for details). We realize that this form of selection will not be the usual form of selection in nature. However, the purpose of this experiment was to explore aspects of the genetic basis of the trait rather than to mimic natural selection. Nonetheless, some types of population structure, particularly when individuals interact most with full-sibs, will lead to forms of natural group selection on plasticity that are similar to our artificial family selection (Wilson, 1983; Fagen, 1987).

Previous selection experiments on plasticity and canalization have been done (Waddington, 1960; Kindred, 1965; Waddington and Robertson, 1966; Druger, 1967; Scharloo et al., 1972; Thompson and Rook, 1988) but were limited by not including parallel selection on the plasticity of the character and the character itself. Thus, they fail to reveal the extent to which these two aspects of the character are evolutionally independent. One exception was a joint selection experiment on mean performance and plasticity (Brumpton et al., 1977; Jinks et al., 1977).

Information on independence will reveal, in part, which of three polygenic models of the genetic basis of plasticity are correct. Model 1: plasticity is a function of homozygosity, the overdominance model (Lerner, 1954; Gillespie and Turelli, 1989). This model assumes the amount of change in phenotypes across environments is a decreasing function of the number of heterozygous loci with the result that heterozygotes have the highest fitness (Gillespie and Turelli, 1989). Balancing selection leads to the maintenance of potentially high levels of additive genetic variation in natural populations. Model 2: plasticity is a function of differential expression of the same gene in different environments, the pleiotropy model (Falconer, 1981; Via and Lande, 1985, 1987; Via, 1987). This model assumes the expression of an allele in one environment is independent of its expression in a different environment, selection is weak and stabilizing within environments, and selection is uncorrelated among environments (Via and Lande, 1987). If the genetic correlation among environments is not $|1|$, then the equilibrium additive genetic variance is the balance between mutation and stabilizing selection. A correlation of $|1|$ can lead to disruptive selection and an increase in the additive genetic variation. Model 3: plasticity is due to genes that determine the magnitude of response to environmental effects which interact with genes that determine the average expression of the character, the epistasis model (Lynch and Gabriel, 1987; Jinks and Pooni, 1988; Scheiner and Lyman, 1989). This model assumes the trait mean and the environmental variance are two independent characteristics (Lynch and Gabriel, 1987). Additive genetic variation is maintained at equilibrium only if there is a cost of plasticity. The models are not mutually exclusive. We note that our use of the terms overdominance, pleiotropy, and epistasis differs from the usual. In the present context the terms refer to effects that are manifest across environments only, not within a single environment.

In order to distinguish among the models we looked at the following evidence. First we examined the direct response to selection on plasticity. The overdominance model predicts that the response will plateau as maximal heterozygosity or homozygosity is reached because plasticity is a function of the number of heterozygous loci. The pleiotropy model predicts a weak response to selection on plasticity because there is no directional selection on the character itself and the distribution of allelic expressions in different environments is independent. The epistasis model predicts a response to selection proportional to the heritability of plasticity because there exist independent plasticity genes.

Second we examined the correlated response of plasticity to directional selection on the character itself. The overdominance model predicts an increase in plasticity in all lines as directional selection causes fixation of loci and homozygosity. The

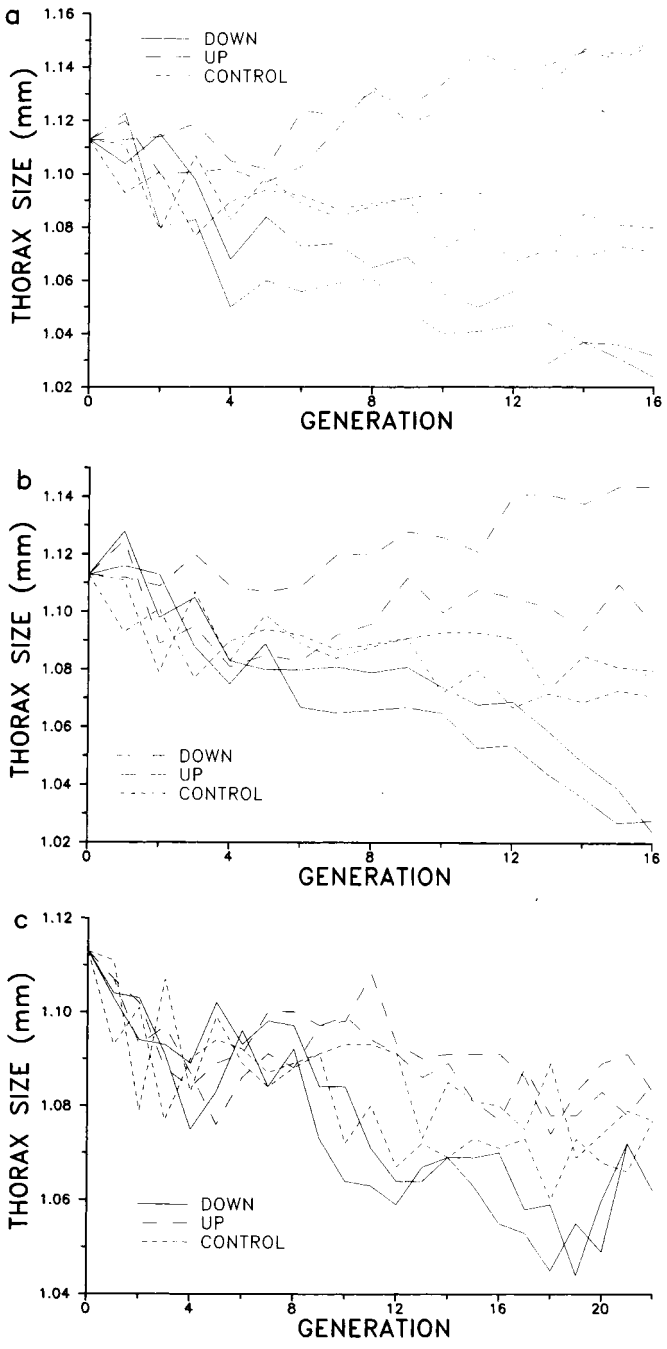

Fig. 1. Change in thorax size at 19° C in response to selection. (a) Direct response to selection at 19° C. (b) Indirect response to selection at 25° C. (c) Indirect response to selection on plasticity.

pleiotropy model predicts strong correlated responses because genetic correlations among environments less than |1| lead to an increase (decrease) in plasticity as trait means in the two environments diverge (converge). The epistasis model predicts a weak correlated response because the two types of traits (mean and plasticity of the character) are determined by different genes.

Third we examined changes in genetic variance during selection. The overdominance model predicts that plasticity will increase or decrease in proportion to the amount of genetic variation or heterozygosity. Selection for increased (decreased) plasticity will decrease (increase) genetic variation because selection is effectively on amount of heterozygosity. The pleiotropy model predicts selection for both increased and decreased plasticity will increase genetic variation of the trait because of selection for different alleles in each environment (see Via and Lande, 1987, Fig. 1A). The epistasis model predicts no change because selection on plasticity acts on genes other than those determining the mean of the trait.

Fourth we examined changes in the cross-environment genetic covariance during selection. The overdominance model makes no prediction. The pleiotropy model predicts a decline in the covariance when selecting on plasticity because of loss of antagonistic alleles with positive effects in one environment and negative effects in the other environment. It predicts a rise in the covariance when selecting on the trait mean in a single environment because of an increase in antagonistic alleles (see Via and Lande, 1987, Fig. 1C, D). The epistasis model predicts a decline in the covariance when selecting on plasticity because of a loss of genetic variation in the plasticity loci with the fixation of high or low plasticity alleles. It predicts no change in the covariance when selecting on the trait mean in a single environment because selection is operating on loci different from the plasticity loci.

The predictions made by the three hypotheses are not always mutually exclusive and some of the differences in predictions are of degree rather than kind. Also, there is no reason that nature in its perversity will not provide us with contradictory results. Finally, all three models could be correct to some degree. Thus, we do not mean to imply that with the present data we will be able to definitively decide which is correct. Future papers in this series will deal with additional predictions about correlations with plasticities and fluctuating asymmetries of other traits and about localization of effects on different chromosomes.

Materials and methods

Origin of lines

A population line was established with 301 individuals captured over a one month period in several locations in DeKalb Co. Illinois. The flies were maintained in mass culture at 21° C for two to three months prior to the start of the experiment. Each line was begun from 50 randomly chosen pairs. There were six selection regimes, increased and decreased plasticity, increased and decreased thorax size at 19° C, increased and decreased thorax size at 25° C, plus a control regime of random selection. Each regime was duplicated for a total of 14 lines.

Selection protocol

Because phenotypic plasticity is the property of a genotype, not an individual, a family selection scheme was used. For the purposes of selection, phenotypic plasticity was measured as the difference in mean thorax size of full-sibs raised at 19° C and 25° C. The variance among families of this measure is equivalent to the genotype-environment interaction variance in a full-sib analysis (Scheiner and Lyman, 1989).

For each line 50 females were collected as virgins and randomly paired with single males. Each pair was placed in a separate numbered vial with food, allowed to oviposit for 48 hrs, then transferred to new vials every 24 hrs for the next three days. The food was standard cornmeal-molasses-agar supplemented with live yeast. Each of two vials were placed in incubators at 19° C and 25° C, four vials per family, immediately following transfer of the adults to the next vial. They were placed in the two treatments on alternate days (eg. first vial in 19° C, second vial in 25° C) with half of the families having the first vial in one treatment and half in the other to avoid any confounding of day of laying and temperature. After emergence thorax length was measured on three etherized females from each vial, six flies per family per temperature, using a LASICO ocular filar and S-4A Auto-processor with a Wild stereomicroscope. From the 50 original families, 40 were used for selection. Generally, five or six pairs would either fail to mate or not produce enough offspring for measurement. The selection intensity was 50% with the top, or bottom, 20 families chosen to provide individuals for the next generation; selection was random in the control lines. We picked this selection intensity to maximize the maintenance of genetic variation. The flies for the next generation were taken from the 19° C treatment for all selection regimes in order to standardize any maternal effects; measurements of the base population indicated that such effects were small (Scheiner and Lyman, 1989). In general, the selected flies were siblings of those measured although in rare cases the same individuals were used. Each of the 20 families supplied three females and three males from which the 50 pairs of the next generation were chosen. All pairings were random with no attempt to avoid brother-sister matings resulting in an effective population size of 40.5 (Falconer, 1981, p. 64). Sixteen generations of selection were carried out on the lines for increased and decreased thorax size. Twenty-two generations of selection were carried out on all but one of the lines for increased and decreased plasticity and the control lines. For one line selecting for decreased plasticity only 21 generations of selection were carried out. The additional generations beyond 16 were done to test for limits to selection on plasticity (see below).

Evaluating the lines

After 16 generations of selection stock cultures of each line were established with 50 males and 50 females from all 40 families in the line placed in mass culture in half-pint milk bottles. After mass mating for at least one generation a half-sib

mating scheme was established within each line by collecting males and females as newly eclosed adults. The flies were aged for one day. Each male was allowed to mate for 24h with three females. The females were separated and allowed to oviposit for six days, being given new food vials daily. The vials from alternate days were placed at either 19° C or 25° C such that each male-female combination produced three vials at each temperature. After emergence thorax size was measured on three females from each vial, nine flies per family per temperature, using the method described above.

For the data analyses we tried to balance the data as much as possible. To do this we eliminated all dams that did not have at least three offspring in each temperature and all sires that did not have at least two dams. Final sample sizes were 34 to 58 half-sib families per line, a mean of 2.6 dams per sire, and a mean of 7.5 offspring per full-sib family per temperature for a total of 12345 flies from the 19° C treatment and 12264 flies from the 25° C treatment.

Statistical analysis

All analyses were done with either SAS (SAS Institute Inc., 1985) or SYSTAT (Wilkinson, 1988). The regressions and analyses of variance were done using SAS procedure GLM. Variance components within each treatment were calculated using procedure NESTED. Variance components for the two-way ANOVA were calculated using the MIVQUE0 method of procedure VARCOMP. Experience has shown this method to give virtually identical results to maximum-likelihood estimates. Standard errors for the heritability estimates were calculated as outlined in Scheiner and Lyman (1989). Trends in variances, covariances, and correlations during selection were tested using the MGLH module of SYSTAT. Genetic variances were log-transformed before analysis; cross-environment correlations were arcsine-square root transformed before analysis.

Results

Direct effects of selection

As expected there were significant responses over 16 generations to selection on thorax size at 19° C and 25° C (advances of 0.036 mm [1.85 SD] and 0.037 mm [1.65 SD] for increased size at 19° C; advances of 0.089 mm [4.69 SD] and 0.081 mm [4.14 SD] for decreased size at 19° C; advances of 0.018 mm [0.89 SD] and 0.002 mm [0.10 SD] for increased size at 25° C; advances of 0.089 mm [4.19 SD] and 0.088 mm [4.19 SD] for decreased size at 25° C) (Figs. 1a and 2a). The slopes of the responses to selection ranged from 2.85 to 5.14 ($\times 10^{-3}$) and were all significantly different from 0 (Table 1). In contrast, selection on plasticity resulted in much weaker responses over 22 generations (advances of 0.037 mm [1.64 SD] and 0.007 mm [0.31 SD] for increased plasticity; advances of 0.015 mm [0.68 SD]

Table 1. Slopes (± SE) of the responses to selection on thorax size at 19° C and 25° C and plasticity of thorax size (in mm/generation × 10^{-3}). Significance was determined by regression.

Selection regime		Rep.	Trait: Size at 19° C	Trait: Size at 25° C	Trait: Plasticity
19° C	up	1	2.85*** ± 0.18	2.49*** ± 0.19	0.36 ± 0.19
	up	2	3.39*** ± 0.21	2.98*** ± 0.20	0.41 ± 0.23
	down	1	−5.14*** ± 0.19	−4.43*** ± 0.20	−0.71*** ± 0.20
	down	2	−4.13*** ± 0.20	−3.41*** ± 0.20	−0.72*** ± 0.19
25° C	up	1	2.54*** ± 0.20	3.29*** ± 0.18	−0.75*** ± 0.22
	up	2	1.10*** ± 0.19	3.10*** ± 0.20	−2.00*** ± 0.21
	down	1	−5.25*** ± 0.18	−5.05*** ± 0.20	−0.20 ± 0.21
	down	2	−4.71*** ± 0.19	−4.26*** ± 0.20	−0.45* ± 0.20
Plast.	up	1	−0.64*** ± 0.11	−1.82*** ± 0.13	1.18*** ± 0.13
	up	2	−0.68*** ± 0.11	−1.15*** ± 0.12	0.47*** ± 0.12
	down	1	−1.94*** ± 0.12	0.98*** ± 0.13	−0.96*** ± 0.12
	down	2	−2.72*** ± 0.13	0.96*** ± 0.13	−1.76*** ± 0.14
Control		1	−0.88*** ± 0.11	−0.05 ± 0.12	−0.84*** ± 0.12
		2	−1.48*** ± 0.11	−1.37*** ± 0.11	−0.11 ± 0.12

*$P < 0.05$; ***$P < 0.001$

and 0.017 mm [0.75 SD] for decreased plasticity) (Fig. 3a) with slopes of the responses ranging from 0.47 to 1.76 (× 10^{-3}) (Table 1). After 16 generations of selection all lines selected on thorax size at 19° C and three of the four lines selected on thorax size at 25° C differed significantly from the control lines (Table 2). The lines selected for increased plasticity differed significantly from both control lines, but those selected for decreased plasticity differed from only one of the lines (Table 2).

An examination of Fig. 3a suggests that there may be a lower bound to selection on plasticity. We succeeded in decreasing plasticity so that flies raised at 19° C were the same size, on average, as flies raised at 25° C. That is, plasticity was reduced to zero. In theory, plasticity should have been reversible, larger flies at 25° C than at 19° C. However, we failed to push the lines below zero plasticity. To test this observation we compared the slopes of the response to selection from generation 1 to 11 with the slopes from generation 12 to 22. We found that lines selected for decreased plasticity had slopes that were significantly greater in magnitude during the first half of selection (Rep. 1: $MS_{slope \times half} = 0.0028$, $P < 0.02$; Rep. 2; $MS = 0.0142$, $P < 0.0001$). During the first 11 generations the slopes differed significantly from 0 (slopes (× 10^{-3}) = −1.59 ± 0.36, $P < 0.0001$,

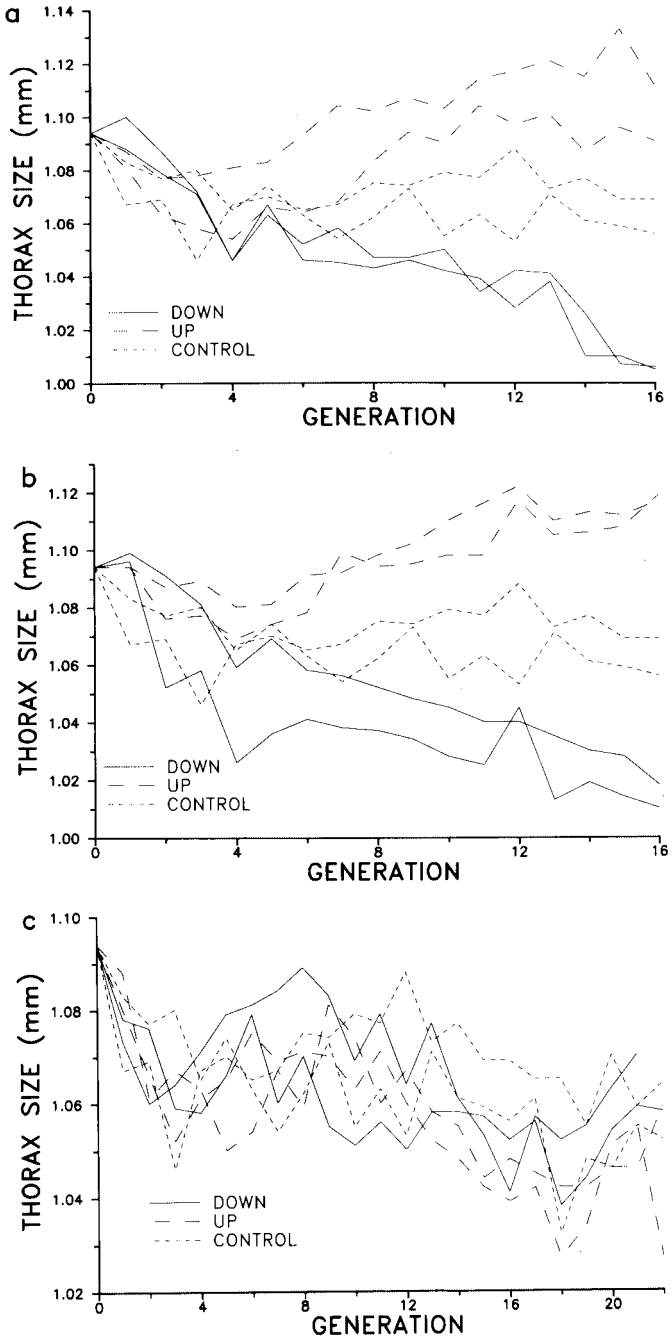

Fig. 2. Change in thorax size at 25° C in response to selection. (a) Direct response to selection at 25° C. (b) Indirect response to selection at 19° C. (c) Indirect response to selection on plasticity.

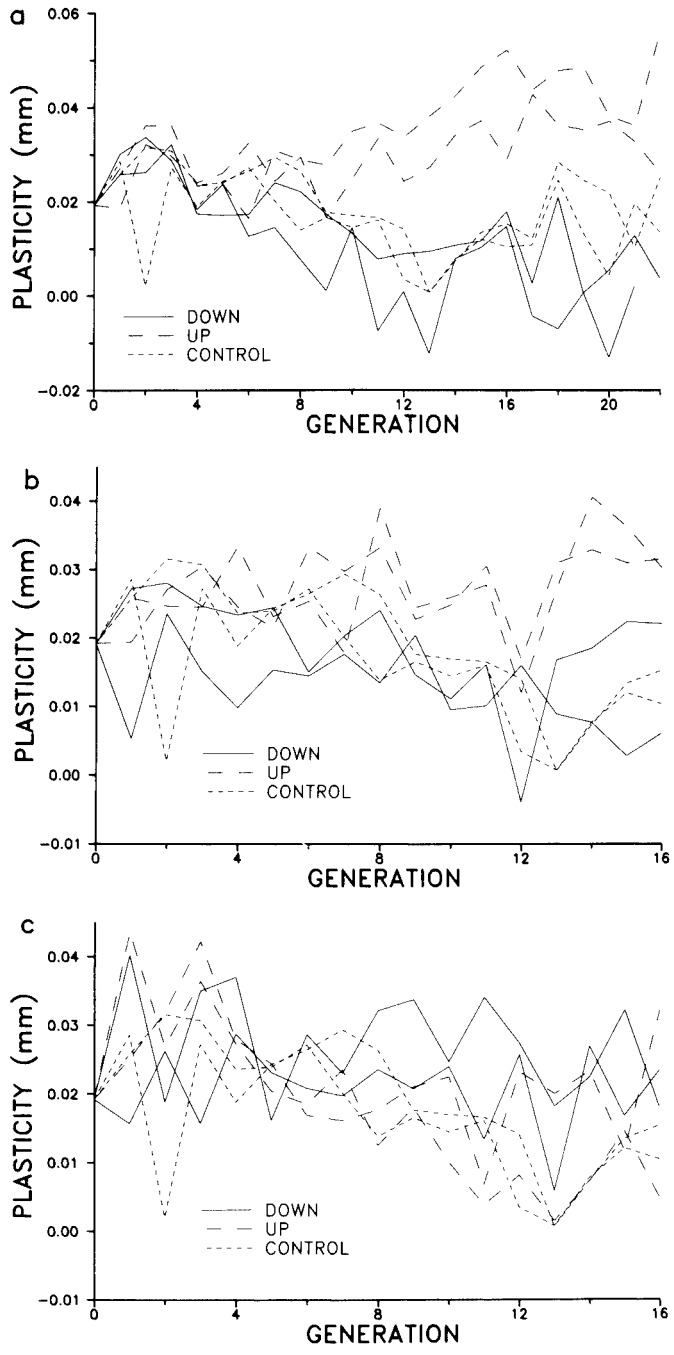

Fig. 3. Change in plasticity of thorax size in response to selection. (a) Direct response to selection on plasticity. (b) Indirect response to selection at 19° C. (c) Indirect response to selection at 25° C.

Table 2. Full-sib family mean (± SD) thorax sizes at 19° C and 25° C and plasticities (in mm) of the 14 lines after 16 generations of selection. Means within each column with different superscripts are significantly different ($P < 0.05$) based on a Student-Newman-Keuls test.

Selection regime	Rep.	Trait: Size at 19° C	Trait: Size at 25° C	Trait: Plasticity
19° C up	1	$1.146^{A} \pm 0.018$	$1.107^{B} \pm 0.022$	$0.0391^{A} \pm 0.0195$
up	2	$1.131^{B} \pm 0.022$	$1.102^{B} \pm 0.022$	$0.0288^{BC} \pm 0.0211$
down	1	$1.027^{H} \pm 0.017$	$1.012^{G} \pm 0.019$	$0.0144^{DE} \pm 0.0187$
down	2	$1.027^{H} \pm 0.016$	$1.011^{G} \pm 0.020$	$0.0155^{DE} \pm 0.0172$
25° C up	1	$1.134^{B} \pm 0.015$	$1.115^{A} \pm 0.018$	$0.0189^{DE} \pm 0.0187$
up	2	$1.094^{C} \pm 0.018$	$1.075^{C} \pm 0.017$	$0.0196^{DE} \pm 0.0183$
down	1	$1.021^{H} \pm 0.015$	$0.999^{H} \pm 0.019$	$0.0226^{CD} \pm 0.0193$
down	2	$1.034^{G} \pm 0.019$	$0.993^{H} \pm 0.026$	$0.0409^{A} \pm 0.0259$
Plast. up	1	$1.078^{DE} \pm 0.020$	$1.038^{F} \pm 0.021$	$0.0399^{A} \pm 0.0222$
up	2	$1.079^{DE} \pm 0.015$	$1.044^{EF} \pm 0.020$	$0.0343^{AB} \pm 0.0201$
down	1	$1.068^{F} \pm 0.017$	$1.048^{DE} \pm 0.019$	$0.0194^{DE} \pm 0.0177$
down	2	$1.069^{F} \pm 0.020$	$1.056^{D} \pm 0.022$	$0.0127^{E} \pm 0.0194$
Control	1	$1.084^{D} \pm 0.018$	$1.071^{C} \pm 0.023$	$0.0129^{E} \pm 0.0190$
	2	$1.074^{EF} \pm 0.017$	$1.052^{DE} \pm 0.018$	$0.0221^{CD} \pm 0.0199$

and -3.41 ± 0.34, $P < 0.0001$) but did not differ significantly from 0 during the last 11 generations (slopes ($\times 10^{-3}$) = -0.43 ± 0.36, $P < 0.23$, and -0.65 ± 0.45, $P < 0.15$). In contrast, lines selected for increased plasticity had no difference in slopes (Rep. 1: MS = 0.0007, $P < 0.25$; Rep. 2: MS = 0.0004, $P < 0.37$).

Partially confounding the estimates of response to selection was natural selection for smaller flies, especially at 19° C. Thorax size declined significantly over 22 generations in the control lines (changes of 0.036 mm [1.85 SD] and 0.036 mm [1.83 SD] at 19° C and 0.030 mm [1.47 SD] and 0.042 mm [2.12 SD] at 25° C) (Table 1). Because natural selection was stronger at 19° C than 25° C there was also apparent selection on plasticity (changes of 0.006 mm [0.26 SD] and 0.006 mm [0.27 SD]). The estimated intensity of natural selection (Falconer, 1981, p. 176), based on the changes in the control lines and calculated as the geometric mean of the intensities of the two lines, was -0.189 for thorax size at 19° C, -0.039 for thorax size at 25° C, and -0.135 for plasticity of thorax size. The intensity of artificial selection, using a 50% selection criterion, was + or -0.782 for increased and decreased traits, respectively.

Realized heritabilities were calculated after correcting selection intensities for natural selection using the formula:

$$h^2 = R(i\sigma_p)^{-1}$$

where R is the slope of the response to selection, i is the sum of the intensities of artificial and natural selection, and σ_p is the phenotypic standard deviation (Falconer, 1981, p. 175). Phenotypic standard deviations did not change significantly during selection so the mean values over all generations were used for each line. Mean realized heritabilities for thorax size at 19° C and 25° C were very similar (0.250 and 0.242, respectively) and much larger than heritability of plasticity of thorax size (0.061) (Table 3). These values are 64%, 74%, and 32%, respectively, of the narrow-sense heritabilities measured in the base population using dam means (see Scheiner and Lyman, 1989, Table 3); they are 77%, 78%, and 58%, respectively, of the pooled estimates of the narrow-sense heritabilities of the lines after 16 generations of selection (Table 4). The pooled estimates of the narrow-sense heritabilities were very similar to the estimates made before selection (Table 4, Scheiner and Lyman [1989] Table 3). The estimate of the realized heritability of plasticity is conservative because of the selection limit discussed above. If the slope of the response for only the first 11 generations is used for the lines selected for decreased plasticity then the realized heritabilities are raised to 0.076 ± 0.017 and 0.163 ± 0.016 with a mean realized heritability over all four lines of 0.088 ± 0.027. This value is 45% and 84% of the heritabilities estimated before and after selection.

Table 3. Realized heritabilities and genetic correlations. Standard errors of the individual heritabilities are based on regression. All heritabilities are significantly different from 0 at the $P < 0.001$ level. Standard errors of the means are based on the 4 estimated heritabilities or 8 estimated correlations.

Selection regime		Rep.	Trait		
			19° C	Size at 25° C	Size at Plasticity
19° C	up	1	0.247 ± 0.015	0.816	0.235
	up	2	0.255 ± 0.016	0.951	0.246
	down	1	0.279 ± 0.010	0.912	0.265
	down	2	0.217 ± 0.010	0.776	0.309
25° C	up	1	0.737	0.219 ± 0.012	−0.410
	up	2	0.338	0.211 ± 0.013	−1.118
	down	1	1.231	0.289 ± 0.012	0.083
	down	2	1.175	0.247 ± 0.011	0.217
Plast.	up	1	−0.357	−0.945	0.046 ± 0.006
	up	2	−0.608	−0.984	0.084 ± 0.006
	down	1	0.973	0.448	0.081 ± 0.009
	down	2	0.962	0.345	0.032 ± 0.008
Mean h^2			0.250 ± 0.013	0.242 ± 0.018	0.061 ± 0.013
			19–25	25–PL	19–PL
Mean r_g			0.867 ± 0.009	-0.296 ± 0.230	0.253 ± 0.195

Table 4. Narrow-sense heritabilities (SE) of thorax size at 19° C, thorax size at 25° C, and plasticity of thorax size based on sib correlations of the 14 lines following 16 generations of selection. The line estimates for thorax size are based on individual measures; the line estimates for plasticity and the pooled estimates are based on dam means. Significance was determined by ANOVA. Standard errors for individual measures were calculated as by Becker (1984, p. 60); standard errors for the dam means were calculated as described in Scheiner and Lyman (1989).

Selection regime		Rep.	Trait		
			19° C	Size at 25° C	Size at Plasticity
19° C	up	1	0.231^{+}	0.202*	0
			(0.144)	(0.142)	
	up	2	0.538***	0.590***	0.186*
			(0.192)	(0.189)	(0.046)
	down	1	0.174	0.413***	0.172
			(0.154)	(0.169)	(0.056)
	down	2	0.290*	0.418**	0.049
			(0.158)	(0.178)	(0.093)
25° C	up	1	0.367***	0.115^{+}	0.124*
			(0.121)	(0.107)	(0.036)
	up	2	0.372***	0.211*	0.007
			(0.175)	(0.134)	(0.061)
	down	1	0.462***	0.298*	0.014
			(0.151)	(0.135)	(0.039)
	down	2	0.145	0.206^{+}	0.037
			(0.132)	(0.134)	(0.052)
Plast.	up	1	0.640***	0.295**	0.193*
			(0.206)	(0.144)	(0.062)
	up	2	0.219*	0.316*	0.242**
			(0.131)	(0.162)	(0.059)
	down	1	0.428**	0.558***	0.176*
			(0.183)	(0.216)	(0.099)
	down	2	0.378**	0.426**	0.063*
			(0.202)	(0.207)	(0.055)
Control		1	0.079	0.402*	0.147*
			(0.116)	(0.187)	(0.046)
		2	0.359**	0.222	0.124
			(0.180)	(0.160)	(0.060)
Pooled			0.331***	0.326***	0.105***
			(0.013)	(0.049)	(0.013)

$^{+}P < 0.10$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

Indirect responses to selection

Selection on thorax size at 19° C and 25° C resulted in correlated changes in thorax size in the other environment as expected (Figs. 1b and 2b). A comparison of the lines showed that these indirect responses at a given temperature were generally of a smaller magnitude than the direct responses to selection at that temperature (Table 1) although enough to separate the selected lines from the control lines in all cases (Table 2). One of the lines selected for increased thorax size at 25° C did not differ significantly from one of the control lines at 25° C but did differ significantly at 19° C. Selection on plasticity of thorax size lead to significant differences from the control lines only for thorax size at 25° C in the lines selected for increased plasticity (Table 2, Figs 1c and 2c). Lines selected on plasticity were always intermediate in thorax size to lines selected on thorax size. In contrast, selection on thorax size resulted in significant changes in plasticity of thorax size (Figs 3b and 3c). This response was asymmetrical with significant increases in plasticity as a consequence of selection for increased thorax size at 19° C and decreased thorax size at 25° C. The converse selection had no effect on plasticity. Thus, selection for more extreme phenotypes and a less than equivalent correlated response in the other environment resulted in changes in plasticity equal in magnitude to selection directly on plasticity.

The correlated responses to selection were used to calculate realized genetic correlations for each pair of triats using the formula:

$$r_A = CR_y(i_x h_x h_y \sigma_{py})^{-1}$$

where CR_y is the slope of the correlated response to selection, i_x is the intensity of direct selection, h_x is the square root of heritability of the selected trait, h_y is the square root of heritability of the correlated trait, and σ_{py} is the phenotypic standard deviation of the correlated trait (Falconer, 1981, p. 286). The realized heritability estimated for each line was used for the directly selected trait while for the correlated trait the mean realized heritability from the other lines directly selected was used. Again, the mean phenotypic standard deviation was used. The assumptions for these calculations were not strictly met in that natural selection on the correlated trait was also occurring. However, the mean correlations are a relatively unbiased estimate of the true correlation because they were calculated over both increased and decreased selection for both traits canceling out the confounding effects of natural selection. The mean realized genetic correlation of thorax size at 19° C and 25° C was 0.867 (Table 3) somewhat larger than the additive genetic correlation based on sib-correlations estimated in the base population, 0.522 ± 0.168, and from the pooled lines after 16 generations of selection, 0.725 ± 0.015. This result supports the consistent overestimate of the heritability of plasticity since a correlation of 1.0 indicates zero heritability of plasticity if genetic variances are the same in both environments. During selection the correlation of full-sib family mean thorax sizes measured at 19° C and 25° C each generation did not change significantly (pooled estimate of slope $(\times 10^{-4}) = 4.50 \pm 16.95$, $P < 0.89$). Plasticity of thorax size was genetically correlated with thorax size at

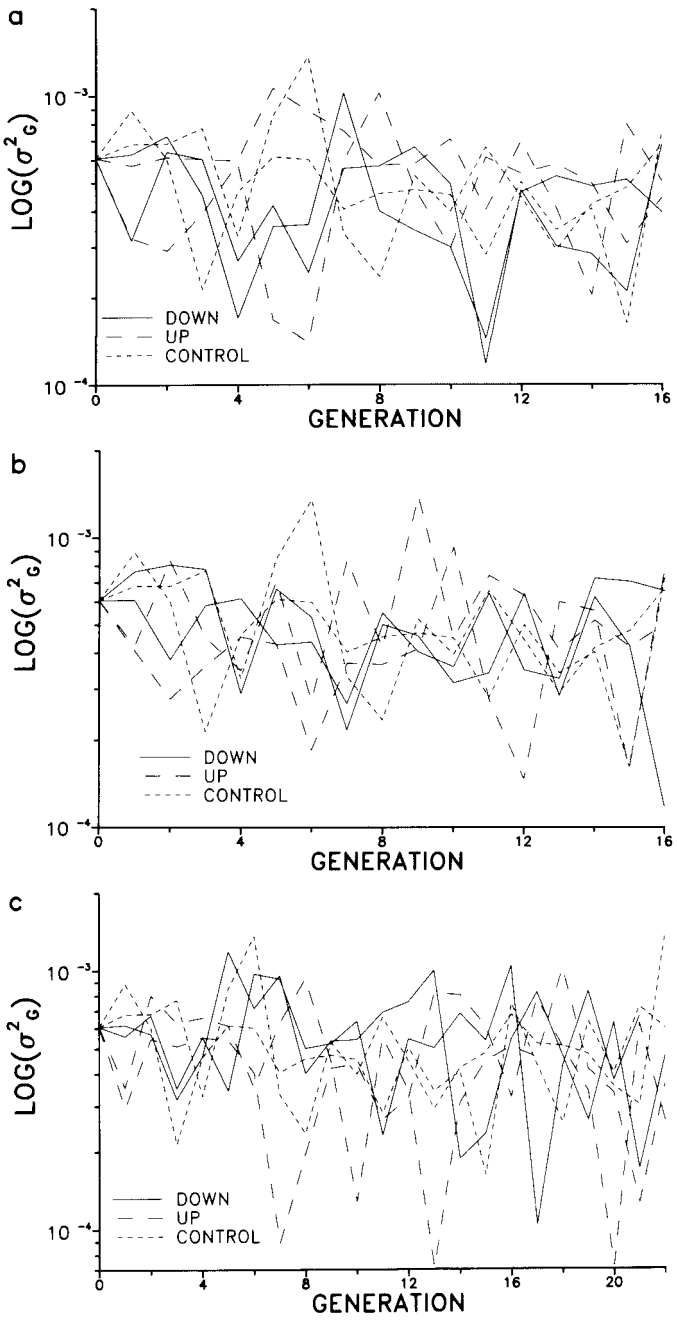

Fig. 4. Change in total genetic variance of thorax size at 19° C in response to selection. (b) Direct response to selection at 19° C. (c) Indirect response to selection at 25° C. (c) Indirect response to selection on plasticity.

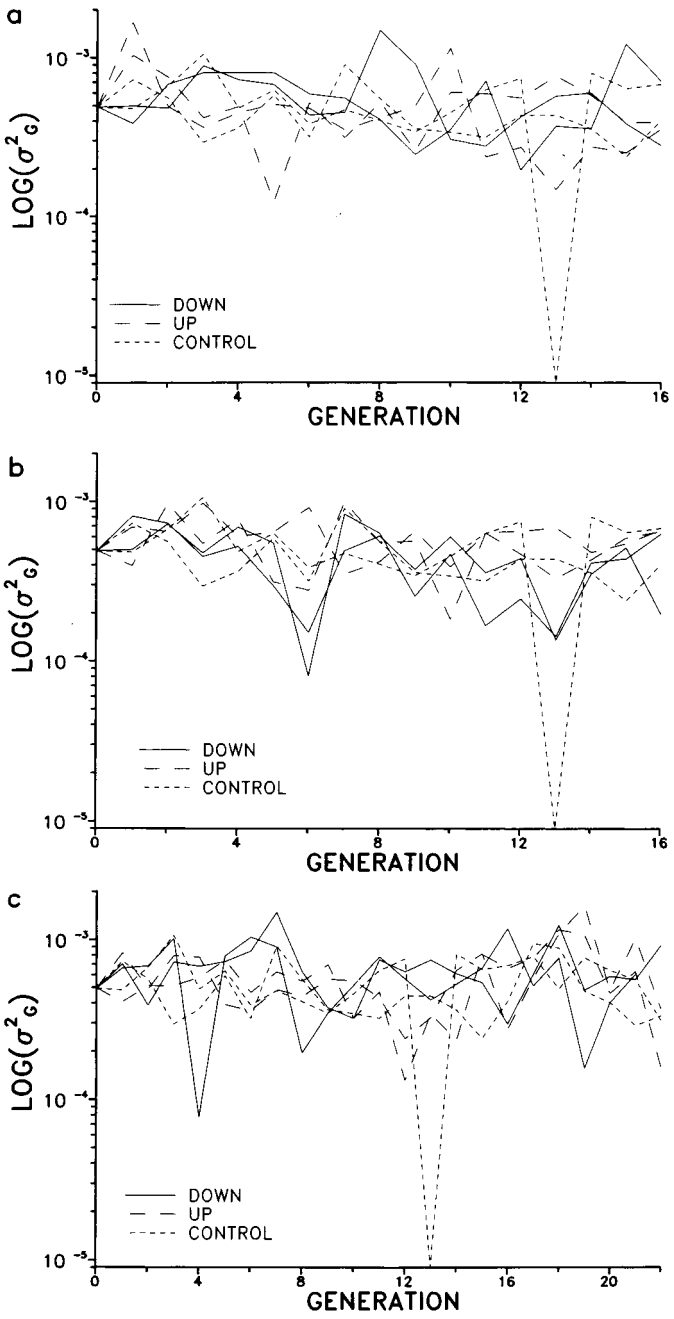

Fig. 5. Change in total genetic variance of thorax size at 25° C in response to selection. (a) Direct response to selection at 25° C. (b) Indirect response to selection at 19° C. (c) Indirect response to selection on plasticity. (Fig. 6).

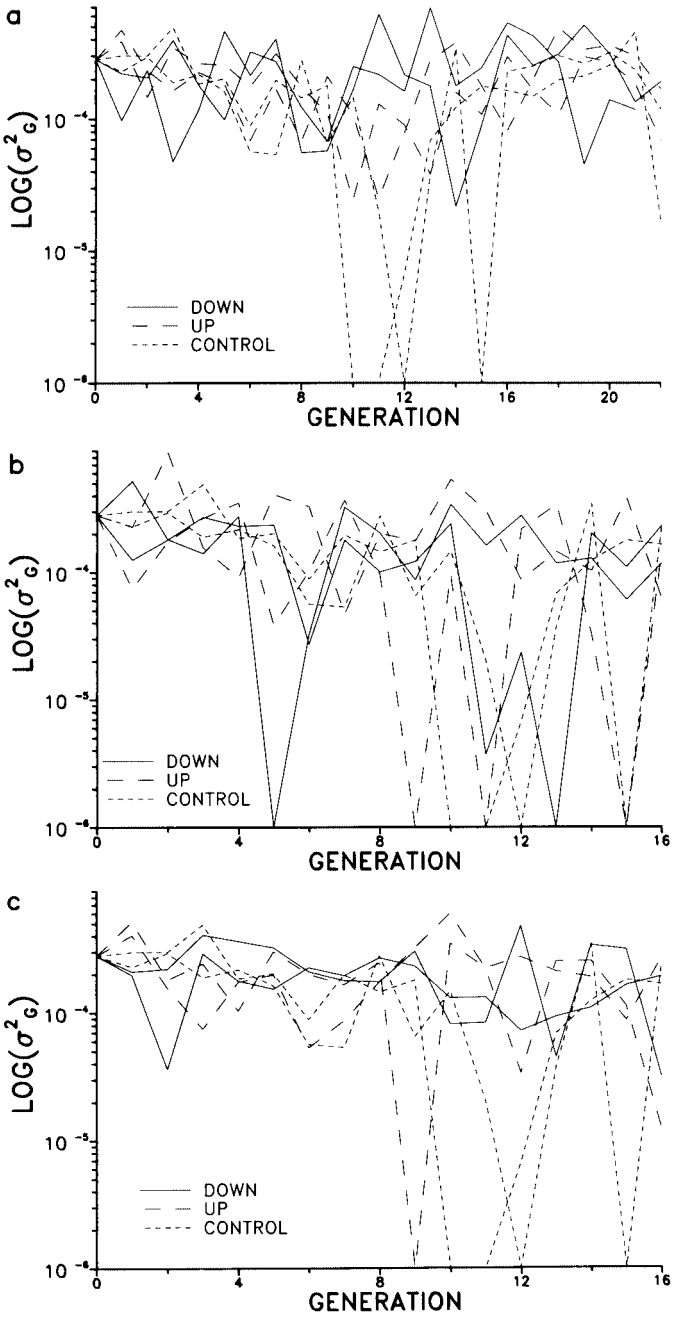

Fig. 6. Change in total genetic variance of plasticity of thorax size in response to selection. (a) Direct response to selection on plasticity. (b) Indirect response to selection at 19° C. (c) Indirect response to selection at 25° C. Values plotted as 10^{-6} are actually 0.

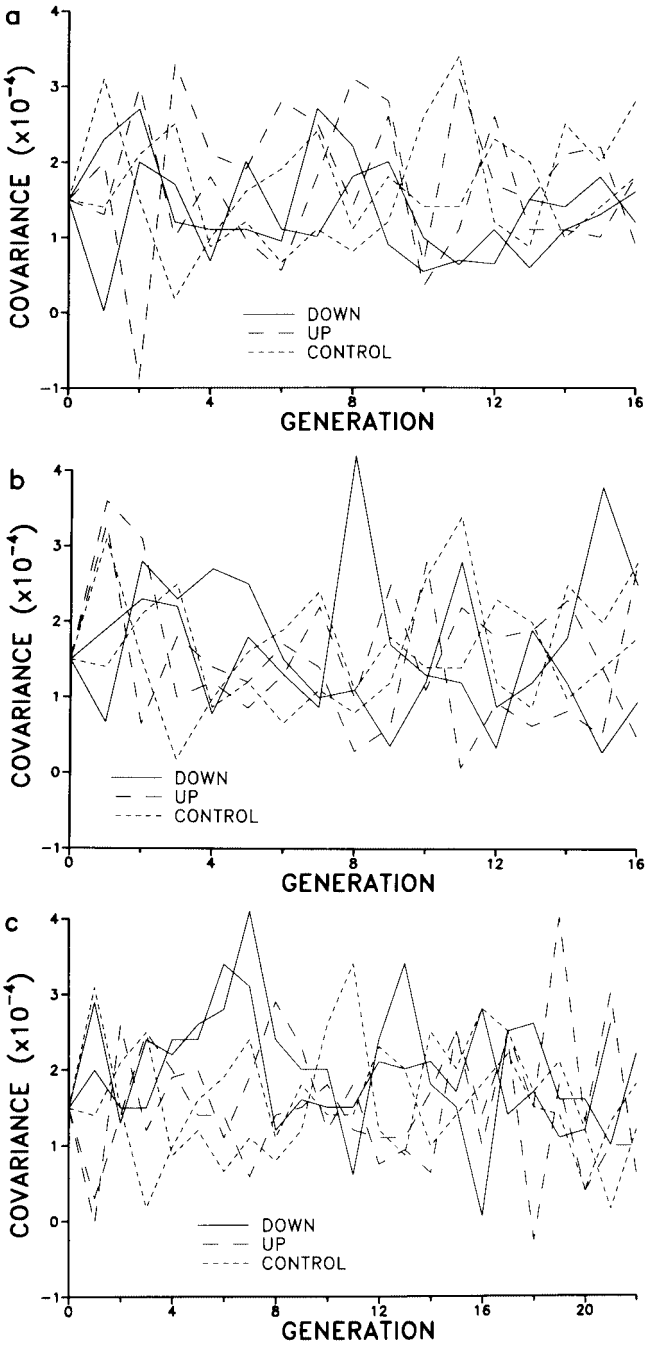

Fig. 7. Change in family mean covariance of thorax size at 19° C and 25° C in response to selection. (a) Response to selection at 19° C. (b) Response to selection at 25° C. (c) Response to selection on plasticity.

19° C, 0.253, and 25° C, −0.296, and lower than most estimates based on sib-correlations before and after selection, 0.502 ± 0.225 and 0.227 ± 0.047 for size at 19° C and -0.476 ± 0.253 and -0.506 ± 0.073 for size at 25° C, respectively. However, the large standard errors on the mean realized correlations and the correlations measured before selection suggest that the estimates are not significantly different.

Effects on variances and covariances

Because, of necessity, data were gathered by family we were able to track changes in broad-sense genetic variances and covariances during selection (Figs. 4–7). There was a significant decline in genetic variance over the course of selection on thorax size at 25° C (pooled estimate of slope ($\times 10^{-6}$) $= -17.36 \pm 7.81$, $P < 0.033$) (Fig. 5a) but not for selection on thorax size at 19° C (slope ($\times 10^{-6}$) $= -4.54 \pm 5.77$, $P < 0.41$) (Fig. 4a) or for selection on plasticity of thorax size (slope ($\times 10^{-6}$) $= 1.12 \pm 2.40$, $P < 0.62$) (Fig. 6a). In contrast, for correlated characters, that is the trait measured in the other 8 selection lines and 2 control lines, there was a marginally significant decline in genetic variation of plasticity for lines not selected on plasticity (slope ($\times 10^{-6}$) $= -4.57 \pm 1.90$, $P < 0.05$). Genetic variance for thorax size at 19° C and 25° C as correlated characters did not decline significantly (slopes ($\times 10^{-6}$) $= -1.72 \pm 3.02$, $P < 0.12$, and -0.98 ± 3.02, $P < 0.29$, respectively). A comparison of the narrow-sense heritabilities measured after 16 generations confirmed these observations. For thorax size measured at 19° C we found no significant difference between the heritabilities of the lines selected at 19° C and the other lines (Mann-Whitney $U = 25$, $P > 0.20$, two-tailed test). For thorax size measured at 25° C we found significantly smaller heritabilities in the lines selected at 25° C compared to the other lines ($U = 35$, $P < 0.025$, one-tailed test). In contrast, for plasticity of thorax size we found significantly greater heritabilities in the lines selected for plasticity compared to the other lines ($U = 34$, $P < 0.05$, one-tailed test). The covariance of family mean thorax size measured at 19° C and 25° C did not change significantly during selection for any line (pooled estimate of slope ($\times 10^{-6}$) $= -1.32 \pm 0.92$, $P < 0.06$; range of slopes = 3.97 to −7.85, $P \geqslant 0.12$) (Fig. 7).

Discussion

Response to selection

We have demonstrated that phenotypic plasticity is a trait that can respond to selection. This response is partially independent of change in the mean of that trait; selection on plasticity of thorax size did not result in a change in mean thorax size but selection on mean thorax size did change plasticity. The complex pattern of direct and correlated responses to selection show that the phenotypic plasticity of a

trait can be considered a character upon which evolution can act but in ways which will interact with selection on the mean of the trait.

Selection for increased thorax size at 25° C (Fig. 2a) and decreased plasticity (Fig. 3a) both resulted in a response to directional selection opposite the intended direction for the first few generations. These results suggest the presence of multiplicative (epistatic) genotype and genotype-environment interactions effecting thorax size (Gimelfarb, 1986) and that plasticity is due to the interaction of different types of genes.

We reached a selection limit for decreased plasticity (Fig. 3a) while there were still substantial amounts of additive genetic variance (Table 4). One simple explanation is that genes for plasticity of thorax size are linked to lethal genes or are themselves lethal at negative plasticities. Reeve and Robertson (1953) concluded that linkage to lethals was responsible for a lack of advance in selection for long wings in *D. melanogaster*. However, in the present case we did not see a decrease in viability or fertility in lines selected for decreased plasticity as would be expected if lethality was preventing advance. If the effect were due to linkage 11 generations would have been sufficient for recombination for all but very tight linkage. Thus, we conclude that the lack of advance was not due to effects of lethal loci. Rather, we explain the lack of advance by an epistatic model of plasticity (see below).

Although not central to the questions addressed in this paper, our data on change in genetic variation during selection is relevant to the current discussion on the maintenance of genetic variation. We found that genetic variances did not decrease during selection. Sampling error alone, genetic drift, was predicted to decrease genetic variance by 18% in 16 generations, 5.1% per generation, and 24% in 22 generations, 3.4% per generation (Falconer, 1981, p. 60). Yet, in the control lines the greatest decline in variance was for thorax size at 19° C, 0.6% per generation, and none of the trends were significant. A decline as great as that predicted would have been detected as significantly different from zero. Even the one case where variance declined in concordance with selection, thorax size at 25° C, it was only 2.5% per generation. Based upon assumptions of additivity among many genes of small effect (Fisher, 1930), two quantitative genetics models have been developed recently to explain the maintenance of genetic variation in natural populations, a weak selection, high mutation rate model referred to as the "continuous alleles" model (Lande, 1976) and a strong selection, low mutation rate model referred to as the "house-of-cards" model (Turelli, 1984). The models are different approximations of a more general continuous alleles model (Kimura, 1965). The "continuous alleles" model predicts that in small populations over short periods of time selection will always result in a decrease in genetic variation, contrary to our results. In contrast, Keightley and Hill (1989) show that a "house-of-cards" model can result in no decline or an increase in genetic variation in the initial generations of strong directional selection following strong stabilizing selection. This result occurs because under a "house-of-cards" model most alleles are rare; directional selection results in initially moving gene frequencies towards 50% increasing genetic variation.

Non-additivity can also result in increased genetic variation during selection. Goodnight (1988) shows how changes in gene frequencies at one locus can act to convert non-additive variance at a second locus into additive variance. Although modeled with respect to a genetic bottleneck, a similar effect could occur during the course of selection. Thus, the lack of a decrease in genetic variation during our selection experiment suggests either a "house-of-cards" additive model with moderate to strong stabilizing selection in nature or a non-additive, epistatic, model. These possibilities are not mutually exclusive.

Other investigators have selected on plasticity using a variety of selection schemes confirming our results that plasticity is a selectable trait. Selection experiments on the plasticity of various traits in *D. melanogaster* include: eye size (Waddington, 1960; Waddington and Robertson, 1966; Thompson and Rook, 1988), wing length (Waddington, 1960); wing vein length (Waddington, 1960; Scharloo et al., 1972), aristae morphology (Waddington, 1960), and scutellar bristle number (Kindred, 1965; Druger, 1967). All of the experiments examined the effects of temperature on the various traits. A family selection procedure, as used in this study, was performed in the studies on scutellar bristle number, aristae morphology, and one on eye size (Waddington, 1960). Alternating selection was used to select for eye size, wing length, and wing vein length by Waddington (1960). Individual selection done simultaneously in both experiments was used by Waddington and Robertson (1966), Scharloo et al. (1972), and Thompson and Rook (1988). A significant response to selection in both directions was achieved by Waddington and Robertson (1960), Druger (1967), and Scharloo et al. (1972). Kindred (1965) had a significant decrease in plasticity but not a significant increase. Waddington (1960), selecting only for decreased plasticity, had a significant response in eye size and aristae morphology but not wing length or wing vein length. Similarly, Thompson and Rook (1988) had a significant decrease in the plasticity of eye size but did not select in the reverse direction. There was no general pattern in the mode of the response with the means of the characters changing in only one environment in some studies (Waddington, 1960, aristae morphology; Kindred, 1965), the means changing in both environments but in the same direction in others (Waddington and Robertson, 1966; Scharloo et al., 1972), and the means changing in opposite directions in still others (Waddington, 1960, eye size; Druger, 1967; Thompson and Rook, 1988). In none of the studies were the effects of selection on plasticity contrasted with the effects of simple directional selection.

One study looked at the effects of joint selection on mean performance and plasticity of two traits, flowering time and height, in *Nicotiana rustica* in response to sowing date for all four combinations of high and low performance and high and low plasticity (Brumpton et al., 1977; Jinks et al.; 1977). Response to selection on plasticity was weak. Mean performance and plasticity were positively genetically correlated and the strong response to selection on the mean overwhelmed selection on plasticity when it was opposite to the correlation.

The indirect effects on plasticity by directional selection on a trait have been investigated. Similar to the results of this experiment, directional selection for body size in response to diet in *D. melanogaster* (Robertson, 1960a, b, 1964) and in

response to temperature in *D. pseudoobscura* (Druger, 1962) and selection on wing length in response to temperature in *D. melanogaster* and *D. simulans* (Tantawy et al., 1964) all resulted in increased plasticity due to incomplete carry-over effects in the alternate environments. Also, directional selection on scutellar bristle number in *D. melanogaster* (Gibson, 1970; Schnee and Thompson, 1984), growth rate in a fungus, *Schizophyllum commune*, (Jinka and Connolly, 1973, 1975), and height in tobacco, *Nicotiana rustica* (Jinks and Pooni, 1988) resulted in only partial response in the alternate environment. Similar to the present experiment, in four systems (Druger, 1962; Tantawy et al., 1964; Jinks and Connolly, 1973, 1975; Jinks and Pooni, 1988) the changes in plasticity were asymmetrical occurring mostly during selection for more extreme phenotypes. One experiment, selection on 6-week body weight in mice (Baker and Cockrem, 1970), failed to produce changes in plasticity.

Genetic basis of plasticity

To what extent are the predictions of each of the three models, overdominance, pleiotropy, and epistasis, met by our data? In general, the results tend to support the epistasis model but some paradoxical results suggest that reality may be even more complex than originally envisaged.

The strongest negative evidence comes with regard to the overdominance model. The only prediction met by the model was the plateau in response for decreased plasticity. With regard to other predictions, selection for increased plasticity did not plateau, there were correlated responses between plasticity and expression of the trait mean, and there was no evidence for a correlation between amount of genetic variation and plasticity (genetic variation at 19° C: Spearman rank correlation $r_s = 0.152$, $P > 0.50$; genetic variation at 25° C: Spearman rank correlation $r_s = -0.429$, $P < 0.20$). All of these results are contrary to the predictions of the model.

The evidence differentiating the pleiotropy model and the epistasis model is more equivocal. The direct response to selection on plasticity was weak, but the estimated narrow-sense heritability was low. These data contradict neither model. The correlated responses between thorax size and plasticity of thorax size were weak and asymmetrical. These data contradict the pleiotropy model but not the epistasis model. The genetic variance of the trait did not change during selection on plasticity. These data contradict the pleiotropy model but not the epistasis model; however this conclusion is weak because even direct selection on thorax size did not decrease the genetic variance substantially. The between environment covariance did not change during selection on either plasticity or the trait means. These data contradict both models for selection on plasticity and the pleiotropy model for selection on the trait means. Thus, four of the five predictions were met for the epistasis model and only one of the five predictions were met for the pleiotropy model.

The one aspect of the data not explained by any of the models was the lack of advance to selection for decreased plasticity after generation 11 despite the presence

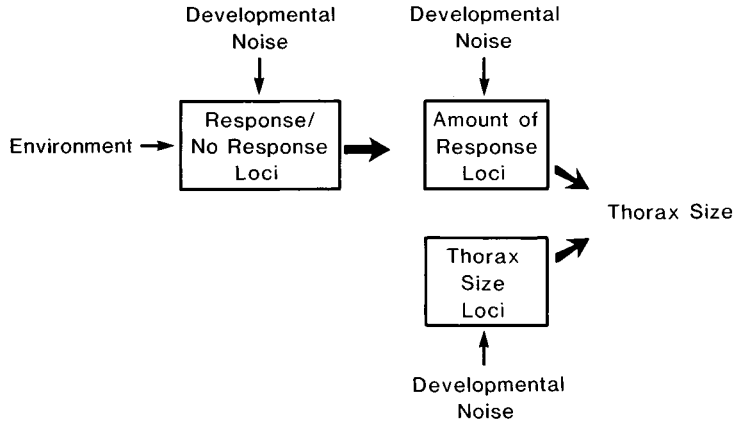

Fig. 8. An epistatic model of phenotypic plasticity. Thorax size is determined by the interaction of loci that determine mean thorax size and loci that determine the response to the environment. The plasticity loci in turn consist of two types, one set of loci determining response/no response and one set of loci determining the amount of response. Developmental noise in the expression of the first set will allow genetic variation in the second set to be expressed, but not the reverse.

of heritable variation. The lack of advance can be explained by constructing a more elaborate, and admittedly rather cumbersome, epistatic model of phenotypic plasticity (Fig. 8). We postulate that a plastic response to the environment has two components, a response/no response component and a magnitude of response component, the slope of the norm of reaction. Our model is similar in outline to that of Wagner (1989) for traits within a single environment. His model postulates the existence of two sets of loci. The "developmental" loci, the equivalent of our response/no response loci, act early in development and epistatically constrain the expression of the "polygenic" loci, our magnitude of response loci.

Our model explains several puzzling aspects of the data, why genetic variation remained at the selection limit, why selection on thorax size tended to decrease genetic variation for plasticity and, why the heritability of plasticity was consistently overestimated more than estimates of the heritability of thorax size. The consistent overestimate of the heritability based on sib-correlations suggests substantial amounts of epistatic variation. In particular, the consistent overestimate would result if selection operated primarily on only one of the two components of plasticity, response or magnitude, while measures of genetic variation included both components. It is reasonable to suppose that selection to decrease plasticity acted primarily upon genes responsible for response/no response tending to fix alleles for "no response" to the environment. In contrast, selection on thorax size might act on genes affecting the magnitude of the response but would not act on the response/no response loci. This second result would occur if the magnitude of response was, in part, a function of the differential expression of alleles in the two environments as assumed by the pleiotropy model. We postulate that after selection for decreased plasticity there remained additive genetic variation for the magnitude

of the response, but little or no genetic variation for the response/no response component. At the selection limit the response reaction was due to developmental noise but then, given that some flies were cued to respond, the genetic variation for plasticity was expressed. Conversely, after selection on thorax size estimates of the heritability of plasticity would decrease since variation in response would be unexpressed if variation in magnitude were zero.

Admittedly, our model of plasticity is rather *ad hoc*. Further experiments are necessary to determine the validity of this model. Such experiments would include: (1) reversing selection after the limit at zero plasticity was reached, (2) selecting on thorax size until genotype-environment interaction variation declined to zero then selecting on plasticity, and (3) crossing lines selected on thorax size and plasticity of thorax size to see if genetic variation for both components could be restored.

Other investigations of genotype-environment interaction variation have found substantial amounts of epistatic genetic variation although the amount was trait and environmental variable specific (Westerman, 1970a, 1970b, 1970c; Perkins and Jinks 1973; Jinks et al., 1973; Connolly and Jinks, 1975; Pooni et al., 1978; Via, 1984; Pooni et al. 1987). Jinks and Pooni (1988), summarizing a series of studies on the genetics of phenotypic plasticity in *Nicotiana*, concluded that the amount of plasticity in performance, environmental sensitivity in their terminology, was determined by loci different from those determining mean performance.

Specialists vs generalist

The final question raised in the introduction was whether, in a complex environment, the evolution of genetic specialization or a single, generalized genotype was more likely. This experiment suggests that, in the case of thorax size and temperature, it is the former, given the assumption of equal selection intensities. The heritability of thorax size was greater than the heritability of plasticity of thorax size. More importantly, there were constraints on the evolution of plasticity such that some phenotypes, larger flies at 25° C than at 19° C, were unattainable. Finally, the genetic basis of phenotypic plasticity appears to be a complex interaction between several different types of genes.

To what extent do these results hold for other species? We conducted a brief survey of recent papers which have estimated genotype and genotype-environment interaction variance components. Most systems were found to have more genotype than genotype-environment interaction variation for either the additive genetic components (Westerman, 1970a, 1970b, 1970c; Crosbie et al. 1977; Via, 1984; Pooni et al., 1987) or the total genetic components (Antlfinger, 1981; Antlfinger et al., 1985; Shaw, 1986; Rossiter, 1987; Gebhardt and Stearns, 1988; Groeters and Dingle, 1988; Macdonald et al., 1988). A few cases were found in which there was greater genotype-environment interaction variation (Newman, 1988; Taylor and Aarssen, 1988), although this conclusion depended on the trait and population (Scheiner and Teeri, 1986; Takano et al., 1987). Thus, for most systems specialists would likely evolve rather than generalists. In the one experimental study of joint

selection, the realized heritability of mean performance was greater than the realized heritability of plasticity and selection on plasticity was generally ineffective (Brumpton et al., 1977; Jinks et al., 1977). However, more sophisticated models will need to be developed and the dynamics of gene frequency changes will need to be explored in order to more fully understand and better predict the evolution of phenotypic plasticity in natural populations.

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