ARTIFICIAL SELECTION ON A FITNESS-COMPONENT IN
DROSOPHILA MELANOGASTER

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Recently there have been a number of studies concerning the quantitative genetics of components of fitness (e.g., Istock et al., 1976; Derr, 1980; review by Istock, 1983). This constitutes a return to an experimental approach which was once widespread (e.g., Robertson, 1957; review by Falconer, 1960), but fell from favor with the adoption of electrophoretic and related techniques in population genetics (Lewontin, 1974). Unfortunately, frustration has greeted most attempts to relate electrophoretic genotypes to fitness or fitness-component phenotypes, with only a few exceptions (e.g., Richmond et al., 1980). Taking a different approach, evolutionary ecology has endeavoured to dispense with genetic information in treating fitness-components such as fecundity and survivorship, usually referred to as life-history (Stearns, 1977). But this research strategy also has attendant shortcomings, especially in the difficulty of inferring genetic constraints on evolution from phenotypic correlations (cf. Charlesworth, 1980; Stearns, 1980; Rose and Charlesworth, 1981a). The present return to quantitative genetics research on fitness-components can to some extent be seen as an attempt to find a middle ground on which genetic variation and fitness-phenotype variation can be related to one another.

But this new return to the quantitative genetics approach has by no means been entirely free of difficulties. Perhaps the most puzzling development is the apparent ubiquity, though not universality,

of significant additive genetic variances for fitness-components (Istock et al., 1976; Dingle et al., 1977; Mukai, 1977; van Noordwijk et al., 1980; Rose and Charlesworth, 1981a, 1981b). These results are in ostensible contrast to Fisher's (1930) Fundamental Theorem, which has as its foremost corollary that the additive genetic variance of fitness should fall toward zero in the neighborhood of selective equilibria (Istock, 1978, 1983). (Though the Fundamental Theorem does not hold with exactitude under most conditions [Karlin, 1975], it does apply to a leading order of magnitude for genes of small effect, given stable population age-structure and multiplicative fertilities [Nagylaki, 1977].)

However, it has been shown formally that the additive genetic variance of a fitness-component need have no direct relationship with the additive genetic variance of fitness (Falconer, 1977; Rose, 1982). In particular, large values of fitness-component additive genetic variance can arise at selective equilibria at which the additive genetic variance of fitness itself is in turn zero. This pattern depends on the existence of antagonistic pleiotropy, or genetic "trade-offs," between fitness-components. With such antagonistic pleiotropy, additive genetic variance for fitness components may be preserved either because of a special pattern of fitness effects (Rose, 1982), such as overdominance at diallelic loci, or because of selective neutrality (Rose, 1983).

Evidence for the existence of antagonistic pleiotropy of the kind required by either version of this hypothesis has not been lacking (e.g., Caspari, 1950; Simmons et al., 1980). In particular, recent experiments on a long-standing, outbred,

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laboratory *Drosophila melanogaster* population have turned up evidence for antagonistic pleiotropy coupled with high additive genetic variances for fitness-components (Rose and Charlesworth, 1980, 1981a, 1981b). The population in question had been kept under stable conditions for many generations, with uncontrolled mating. Therefore, it seemed likely that the estimated high additive genetic variance of early fecundity, for example, was not a result of genetic or selective disequilibrium. Thus this population was used in the experiments reported here, since it seemed to constitute a model natural population at, or near, evolutionary equilibrium.

The major experimental manipulation was artificial selection for increased early fecundity, with selected lines, control lines, and relaxed selection lines. These experiments were designed to elucidate the factors responsible for the ostensible maintenance of heritable fitness-component variation. The first major point the experiments were designed to address was whether or not the earlier results found for this population were artifactual. This in turn led to two subsidiary questions. First, can characters of this kind be handled like other characters in quantitative genetics? (There are those who, in effect, argue that they cannot, such as Lints and Hoste [1977].) Second, if the results are interpretable in terms of quantitative genetics, are they consistent with the results of earlier work on the population, especially that reported in Rose and Charlesworth (1981a)? The second major point concerned the role of antagonistic pleiotropy in the evolution of the experimental population, particularly whether it gave rise to neutral or selectively maintained genetic variability, or perhaps played no role at all.

MATERIALS AND METHODS
General

Standard cornmeal and molasses medium was used for stock maintenance and larval rearing. CO_2 was used in handling the flies. Population maintenance and character assay were performed at 25 C, 12L:12D, and uncontrolled humidity. Handling was done at air-conditioned room temperatures (20–22 C) under illumination. Female fecundity was assayed by placing females paired with males in individual cells of 96-cell tissue culture plates, as described by Engels and Preston (1979), except that the females were not aged with Canton-S males and the assay was for 6 h L, instead of 72 h, on the 14th day from oviposition.

Experimental Population

All experimental lines were derived from the population described by Rose (1979) and Rose and Charlesworth (1980, 1981a, 1981b). Separate selection and control lines were derived from a large outbred sample of this population ($N >$ 2,000) which had been maintained for seven generations in eight population cages, with random distribution of eggs, laid in tissue culture plates, over all eight cages in each generation. Each experimental line was initiated in "Generation 1" by sampling from the eggs laid by adult females from a single cage. Four of these lines were subjected to selection and four were kept as controls.

Selection Experiment

In each generation, adults from the four selected lines were sampled for a total of up to 96 male-female pairs. Twenty eggs from the 14 females with highest measured fecundity were chosen to be reared together in their own vial in the line's population cage. The four control lines were handled identically, simultaneously with the selected lines, except that the 14 females chosen as the parents of the next generation were picked arbitrarily, subject to the constraint of a minimum fecundity of 20 eggs.

In Generation 8, four relaxed-selection lines were obtained from the four selected lines by sampling arbitrarily, without regard to the choice of progeny for the next selected generation. (That is, over-
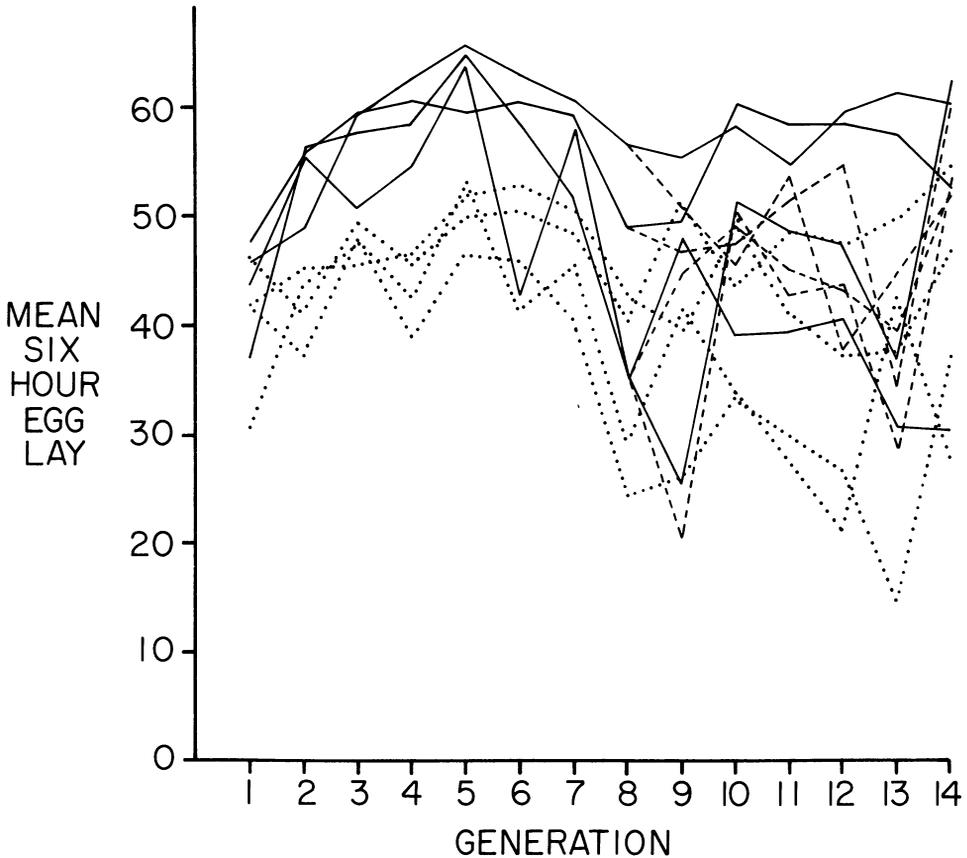
F<small>IG</small>. 1.   Mean 6-h egg lay for each line plotted against the successive generations indicated. Solid lines: selected. Dotted lines: controls. Dashed lines: relaxed.

lap was neither avoided nor sought.) From Generation 8 on, these lines were handled exactly as the controls were.

In Generation 14, 20 eggs from each of 16 females were chosen from each line as parents of the next generation, with selection in the case of the selected lines. Within each of the three experimental treatments (selection, relaxed-selection, control), the progeny of four females from each cage were placed in every cage of that treatment, thereby crossing all lines of a treatment together. The generation of mixed progeny derived from "pure line" cages was designated "Generation X0," with subsequent Generations X1, X2, etc. The selection line progeny ob-

tained from Generation X0 were sampled without selection in order to forestall selection against adults derived from Generation 14 cages which had depressed fecundity. Subsequent X Generations were handled in the same fashion as Generations 1–13, with the three treatments continuing as before.

Viability

Throughout the experiment, a total adult population count on the day of assay was made for each cage, giving an absolute viability measure of progeny derived from populations subject to each of three treatments. In addition, control-line and selected-line progeny from Gen-
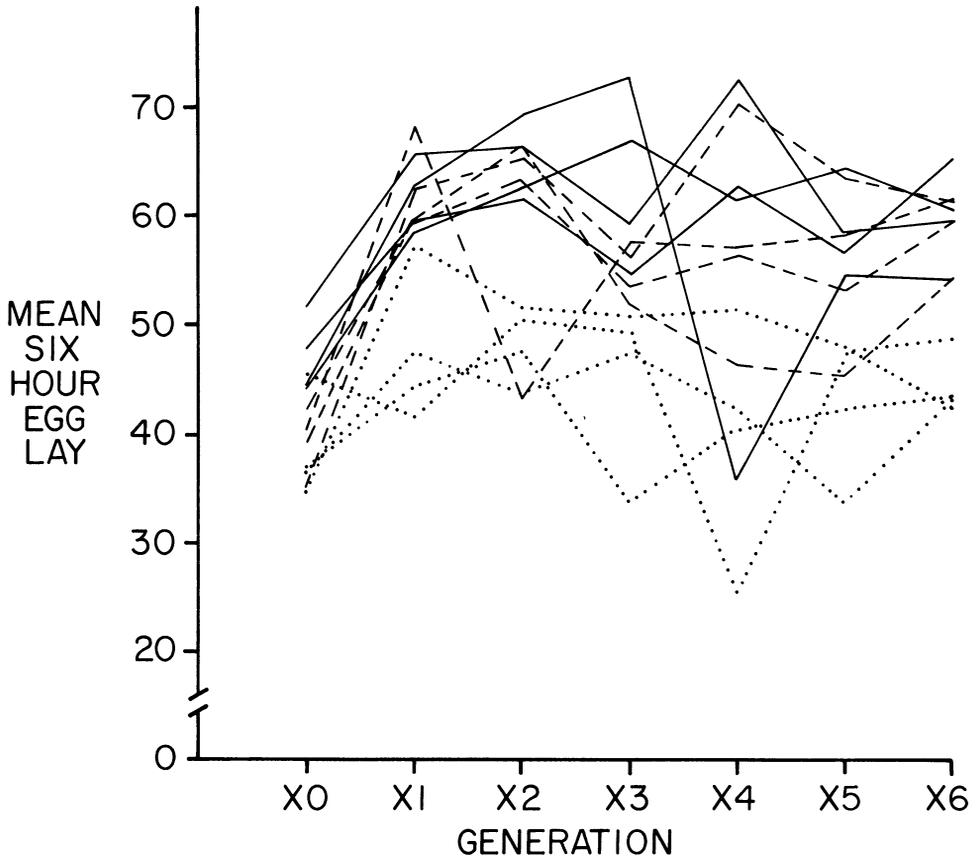
FIG. 2. Mean 6-h egg lay for each line plotted against the successive generations indicated. Solid lines: selected. Dotted lines: controls. Dashed lines: relaxed.

eration X2 were sampled and reared in separate tubes. Progeny from each of the eight lines were obtained in 58 groups of 20, in the same fashion as, and in conjunction with, the routine sampling of progeny for Generation X3. The number of living adults in each of the rearing tubes was then counted on the 14th day from oviposition, the day of fecundity assay, as was done for the population cage counts throughout the experiment.

RESULTS

Fecundity

The overall course of the experiment is shown in Figure 1 and Figure 2. Figure 1 suggests that, after rising quickly during Generations 1–5, mean selection-line fe-

cundity falls. The control lines seem to exhibit a long-term decline in mean fecundity. The relaxed selection line means seem to be spread out over the range of selected and control line means. Between-line within-treatment variance appears to increase over Generations 1–14. Figure 2 indicates that crossing within treatments increased mean fecundity over all lines, as suggested by the marked increase in fecundity from Generation X0, before crossing, to Generation X1, the first crossed generation. Moreover, it seems as if crossing raised the mean fecundity of the relaxed-selection lines to roughly the level of the selection lines.

Table 1 gives the analysis of variance using these data. The analysis bears out

the general pattern just outlined, with few inconsistent generations. Table 2 gives the results of analysis of variance on groups of days, checking for overall consistency. Even with a more stringent significance threshold ($P < .01$), the adduced patterns are statistically significant.

To begin with the response to selection, the results seem to be anomalous. The conventional expectation is of a consistent generation-to-generation response to selection over a period, perhaps ending with a plateau of response, at which point the selected lines should significantly differ from the controls (Falconer, 1960). This did not occur. After Generation 7, it is no longer possible to distinguish the selected lines from the controls, even though there was an initially significant response to selection.

One explanation for this loss of selection response detectability is inbreeding depression due to homozygosity of severely deleterious alleles. There are four sources of support for this hypothesis. First, if an effective population size of 30 is assumed, then the inbreeding coefficient increases by about 1.67% per generation, giving an inbreeding coefficient of about 20.97% after 14 generations (Falconer, 1960 p. 64). (This would be increased with significant variance in male mating success.) Thus inbreeding depression could have been predicted at the outset, as fitness-components are known to be depressed when outbred populations are inbred. Second, linear regression of pooled control line mean fecundities on generation number for Generations 1–14 gives a slope of $-.678$ ($P < .01$), corroborating the a priori expectation of inbreeding depression. Third, as shown in Table 3, the between-line within-treatment variance increases to a statistically significant degree, as is theoretically expected (Crow and Kimura, 1970) and experimentally commonplace (Wright, 1977 p. 4–137) upon inbreeding. Fourth, and perhaps most critically, the increase in fecundity over all treatments in Generation X1 indicates the hybrid vigour which is expected upon cross-

TABLE 1. Analysis of pairwise treatment differences in each generation.

Genera-tion	Selected vs. controls		Selected vs. relaxed		Relaxed vs. controls	
	Sig.	Obs.	Sig.	Obs.	Sig.	Obs.
1	—	561				
2	*	743				
3	*	684				
4	*	703				
5	*	686				
6	—	708				
7	*	731				
8	—	726				
9	—	684	—	694	—	654
10	—	736	—	733	—	721
11	—	727	—	720	—	721
12	—	704	—	721	—	707
13	—	701	—	682	—	703
14	—	675	—	715	—	724
X0	*	744	*	750	—	744
X1	*	728	—	709	*	721
X2	*	753	—	746	—	755
X3	*	696	—	730	—	702
X4	—	718	—	722	—	738
X5	*	724	—	744	—	744
X6	*	695	—	678	*	713

* $P < .05$.
All analysis of variance was based on hierarchical random-effects models, with the sole exception of the analysis of treatment differences between selected and relaxed lines in Generation 9, which treated the difference between the relaxed derivative of a selected line and that selected line as a fixed effect (cf. Kempthorne, 1957; Mendenhall, 1968).

ing lines that have been subjected to inbreeding depression due to recessive deleterious alleles (Crow, 1948; Falconer, 1960 p. 278; Wright, 1977 p. 6–43).

There is only one piece of evidence ostensibly contradictory to the interpretation of the results in terms of inbreeding depression. As shown in Table 3, the within-line variance does not decrease to a statistically detectable degree through the course of the experiment, as it eventually must with sustained inbreeding. The question is whether or not there can be significant inbreeding depression without sufficient exhaustion of genetic variation for statistical detection. Inbreeding depression requires only that recessive deleterious alleles be homozygous more often than in the outbred condition. If not all individuals in a line are homozygous for such alleles, as they need not be in the initial phases of inbreeding, this phenomenon will not de-

TABLE 2. Aggregate analysis of pairwise treatment differences.

Generations	Treatments	Signifi-cance	Observations
2–7	Selected vs. controls	**	4,255
8–14	Selected vs. controls	—	4,953
10–14	Selected vs. relaxed	—	3,571
9–14	Relaxed vs. controls	—	4,230
X1–X6	Relaxed vs. controls	**	4,373
X1–X6	Selected vs. relaxed	—	4,329
X1–X6	Selected vs. controls	**	4,314
X0 vs. X1	Selected-relaxed-controls	**	2,198

** $P < .01$.

All analysis was based on hierarchical random-effects models, excepting only the comparison of X0 and X1 Generations in which the generation effect was taken as a fixed effect and a mixed model was used (cf. Mendenhall, 1968).

crease that part of the genetic variance due to such loci, and may increase it, because the nondominant phenotype is expressed more frequently. Of course, at other loci, there may be variance-reducing fixation, but inbreeding depression does not require it to be of such magnitude to be detectable.

As there is no firm evidence against the hypothesis that inbreeding depression affected the fecundity of the experimental lines after the initial generations, and several lines of evidence for, it seems worth proceeding with the analysis of the results accepting it provisionally. In particular, in this light the results may be used to address two questions. First, what was the extent of the additive genetic variability segregating in the base population? Second, what was the effect of selection relaxation upon the gains achieved by artificial selection?

With regard to the first question, the results indicate that there was heritable genetic variation for fecundity. More quantitatively, the experimental data provide means of estimating the heritability of fecundity, as assayed. An unbiased procedure for both the estimate itself and its standard deviation (cf. Hill, 1972) is to calculate the heritabilities for arbitrary pairs of selected and control lines separately, with net differences between responses and net cumulative selection differentials used in place of absolute responses and differentials

(Rutledge et al., 1973 p. 712). The mean heritability and its standard error can then be obtained using these heritabilities as "raw data." This was done using selected-control pairs chosen according to their experimental labelling (1s-5c, 2s-6c, 3s-7c, 4s-8c), which was arbitrary. Three such heritability estimates were calculated, for Generations 1–5, Generations 1–10, and Generations 1–14, giving $h^2 \pm$ SE equal to .283 ± .109, .008 ± .053, and .035 ± .053, respectively. Evidently, only the first estimate is significantly different from zero ($P < .05$). However, there is no reason to expect the upward selection response of a character like fecundity to withstand inbreeding. Upon inbreeding, large homozygous effects of recessive deleterious alleles could readily obviate differences in allelic composition at other loci. (The validity of this hypothesis is readily checked by comparing the overall mean of the crossed selected lines in Generation X1 with that of the earlier peak in selection response in Generation 5: both are in the range 60–65 eggs/6 h.) Thus, it can be reasonably argued that the best estimate of the realized heritability for the fecundity of this population, as assayed, is .283 ± .109.

Turning to the second question, the results suggest that upon crossing (Generations X1–X6) there was no material difference between selection and relaxed-selection treatments, though both were significantly different from the controls.

TABLE 3. Variances within and between selected and control lines.

| | Variances | |
Generation	Individuals within lines	Lines within treatments
1	251	1,443
2	209	1,050
3	238	854
4	210	978
5	324	653
6	251	4,577
7	199	1,543
8	267	8,030
9	253	11,329
10	224	6,862
11	287	7,546
12	288	9,749
13	241	19,095
14	298	14,390
Mean	252.88	6,292.73
Regression slope	3.38	1,210.21
t-statistic for slope	1.44 (not sig.)	6.18 ($P < .01$)

Linear regression indicates that between-lines variance increases while within-line, or individual phenotypic, variance does not.

(On the proposed quantitative genetic explanation for the results as a whole, the lack of difference between any of the treatments during Generations 10–14 is attributable to inbreeding, and thus may not be used to support this conclusion.) Thus, the results suggest no erosion of the response to artificial selection upon relaxation of artificial selection, during Generation 9.

Viability

The average population production values of lines subject to each treatment are shown in Table 4. Statistical analysis indicates that there are no significant vi-

TABLE 5. Average absolute viabilities of selected and control lines with standard errors.

| | Average absolute viability | |
Line	Controls	Selected
1	.57 ± .03	.55 ± .03
2	.66 ± .02	.63 ± .02
3	.64 ± .02	.61 ± .03
4	.61 ± .02	.62 ± .03
Overall mean	.618 ± .013	.602 ± .014

Hierarchical analysis of variance indicates that there were no significant absolute viability differences between control and selected lines ($P > .05$). There were significant line-within-treatment differences ($P < .05$).

ability differences between selected and control lines over 20 generations. There were fewer data points available concerning the relaxed-selection lines, which were also on average intermediate between selected and control lines. Accordingly they were not analyzed statistically.

The results from the comparison of absolute viability differences between control and selected progeny derived from Generation X2 are given in Table 5. There were no significant treatment differences, but there was evidence of line heterogeneity within treatments. One interpretation of this result would be differentiation due to genetic drift. Alternatively, it could have been due to common cage environment effects on the mothers of the progeny obtained from each cage.

DISCUSSION

Early fecundity under artificial selection was found to have an initial realized heritability of .283 ± .109, an estimate which accords reasonably well with the sib analysis estimate of .371 obtained

TABLE 4. Average population production from 280 eggs with standard errors.

Generations	Controls	Selected	Relaxed
2–8	207.11 ± 4.02	200.71 ± 3.50	—
9–14	203.83 ± 4.70	201.17 ± 3.38	204.09 ± 4.77
X1–X6	207.92 ± 8.42	198.63 ± 2.68	207.21 ± 3.56
All (2–X6)	206.33 ± 3.40	200.20 ± 1.88	205.65 ± 3.02

Selected and control lines were compared statistically over all generations using hierarchical analysis of variance. Neither treatment nor generation differences were statistically significant ($P > .05$).

previously (Rose and Charlesworth, 1981*a*). Inbreeding was found to depress early fecundity, much as it appears to in other species (cf. Bowman and Falconer, 1960), and to increase variability between lines. Crossing inbred lines produced the typical hybrid vigour which is expected if inbreeding depression is due to recessive deleterious alleles (Crow, 1948; Falconer, 1960 p. 278; Wright, 1977 p. 6–43). However, it should be emphasized that these conclusions hinge upon the hypothesis that inbreeding depression arose after the first few generations of the experiment. Though evidence supporting this hypothesis was adduced, it remains open to reasonable criticisms.

More substantively, the magnitude of the realized heritability for early fecundity found in this experiment suggests that significant additive genetic variance for fitness-components can be maintained in populations which have not been subject to inbreeding (cf. Istock, 1978; Rose and Charlesworth, 1981*a*, 1981*b*; Rose, 1982, 1983). With regard to this point, further discussion of the biological material and the methods used may be appropriate. The population discussed here had been maintained in the laboratory for over 120 discrete generations, with culture reproduction every 13–15 days by means of a period of 3–8 hours of mass egg-laying on medium and no more than moderate resultant larval densities. The selection regime then used was designed to correspond to this method of culture reproduction as closely as possible, with the sole exception of a much smaller effective population size. The intent was to select on a character which had for many generations been a component of fitness in a base population at or close to evolutionary equilibrium. Limitations of experimental procedure undoubtedly prevented complete success in achieving this goal, but it seems likely that it was approached reasonably closely. Thus the hypothesis that additive genetic variability for fitness-components might have been preserved in this population under relatively static conditions seems to be worth some discussion.

If this hypothesis is in fact essentially correct, then population genetics is left with the problem of accounting for a phenomenon which ostensibly contradicts Fisher's Fundamental Theorem, as discussed at the outset. This is a problem with a variety of well-founded solutions. One is that there is antagonistic pleiotropy among fitness-components which leads to protected polymorphism as a result of the configuration of net fitnesses (Rose, 1982 and references therein). Another is that antagonistic pleiotropy gives rise to neutral polymorphism (Rose, 1983). (The evolutionary effects of antagonistic pleiotropy, which is a hypothesis concerning allele action, should be distinguished from the analogous effects of negative additive genetic correlation in artificial selection experiments. In particular, the latter may be due to linkage disequilibrium, while the former cannot be.) If the first theory is correct in the present case, then perturbations to gene frequencies by artificial selection should be opposed by natural selection once artificial selection has ceased, causing a return to the original selective equilibrium, or movement toward a new one if the limits of the basin of attraction of the original equilibrium have been exceeded. In either case, selection-relaxation should usually result in evolution away from the phenotype distribution produced by artificial selection. But if the second theory is correct, selection-relaxation should have little effect.

As discussed, selection-relaxation had no apparent effect, upon removal of the inferred effects of inbreeding: the relaxed lines were not significantly different from lines which had been subject to continued selection. Therefore, these results ostensibly support the second theory, that the genetic variability for fecundity found here is neutral.

But there is a major qualification which must be made to this conclusion. The experimental lines had effective population sizes on the order of 30, if not less,

and there was evidence of significant inbreeding. Therefore, it is conceivable that either the allelic variation required for natural selection to act was simply no longer present or linkage disequilibrium due to finite population size effects prevented its expression in appropriate gametic combinations.

It should also be noted that there was no evidence of selection-relaxation response after the relaxed lines were crossed. Therefore, the hypothesis of depauperate genetic variation must also have the auxiliary hypothesis that all four selected lines were virtually fixed for the same relevant alleles or gametes. This in turn requires the assumption that only a few loci, on the order of ten or less, were involved in the selection response. This is not inconceivable, but it is somewhat peculiar in that it in turn implies that these genes must be of relatively large effect on fecundity, in order to generate the detected additive genetic variation for the character.

Another possibility is that there are many nearly-neutral alleles involved, such that natural selection acts only with extreme slowness in returning the population to selective equilibrium. If it is assumed that alleles of this kind predominate in the determination of fecundity, in this population, then genetic drift must play a substantial role in preserving additive genetic variability for fecundity, much as if these alleles were neutral, whatever the qualitative pattern of genotypic fitnesses (Crow, 1972, 1976). Thus a qualified neutralist hypothesis is entailed, one that is not markedly distinct from a more thorough-going neutralism.

A further possibility is that the basic supposition on which all these interpretations are based, the achievement of evolutionary equilibrium in the base population from which the experimental lines were derived, is false. If that is the case, then another 100 or so generations in the laboratory may see the complete exhaustion of additive genetic variability for early fecundity in the population.

Finally, it could be argued that the best estimate of the heritability for early fecundity is that obtained using all 14 generations, .035 ± .053, and therefore there is no statistically significant selection response which requires evolutionary interpretation. This view is tenable only if its proponents are willing to adopt other hypotheses to explain the statistically significant fecundity differences between selected and control lines during Generations 2–7 and X1–X6.

Thus the results chiefly lead to unsettled questions, rather than firm answers. Further research addressed to the alternative hypotheses discussed here will have to be on a scale large enough to avoid the possibility of confounding effects due to inbreeding.

SUMMARY

The apparent maintenance of significant additive genetic variances for components of fitness is one of the major puzzles to have come out of recent research on the quantitative genetics of fitness. This issue was addressed by means of artificial selection for increased early fecundity in a *Drosophila melanogaster* population which had been maintained under stable conditions for over 100 generations. An initial direct response to artificial selection indicated that this population could be maintaining the genetic variability for fecundity which had been detected earlier by means of sib analysis, but the response was not sustained in later generations. Crossing selected with selected lines and control with control lines resulted in the recovery of the initial response to artificial selection, suggesting that inbreeding may have had significant effects. The results of selection-relaxation provided no evidence of natural selection acting to erase the gains achieved by artificial selection. A variety of hypotheses for explaining these results are tenable. Deciding between them requires further experimentation. In particular, it did not prove possible to test the antagonistic pleiotropy hypothesis for the maintenance of genetic variation for fitness-components.

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