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MULTIPLE GENETIC MECHANISMS FOR THE EVOLUTION OF SENESCENCE IN *DROSOPHILA MELANOGASTER*

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Abstract.—We present the results of selection experiments designed to distinguish between antagonistic pleiotropy and mutation accumulation, two mechanisms for the evolution of senescence. Reverse selection for early-life fitness was applied to laboratory populations of *Drosophila melanogaster* that had been previously selected for late-life fitness. These populations also exhibited reduced early-age female fecundity and increased resistance to the stresses of starvation, desiccation, and ethanol, when compared to control populations. Reverse selection was carried out at both uncontrolled, higher larval rearing density and at controlled, lower larval density. In the uncontrolled-density selection lines, early-age female fecundity increased to control-population levels in response to the reintroduction of selection for early-age fitness. Concomitantly, resistance to starvation declined in agreement with previous observations of a negative genetic correlation between these two characters and in accordance with the antagonistic-pleiotropy mechanism. However, resistance to stresses of desiccation and ethanol did not decline in the uncontrolled-density lines during 22 generations of reverse selection for early-life fitness. The latter results provide evidence that mutation accumulation has also played a role in the evolution of senescence in this set of *Drosophila* populations. No significant response in early-age fecundity or starvation resistance was observed in the controlled-density reverse-selection lines, supporting previous observations that selection on *Drosophila* life-history characters is critically sensitive to larval rearing density.

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The modern evolutionary theory of senescence rests upon the argument that the force of natural selection decreases with advancing age (Medawar, 1946; Hamilton, 1966; Charlesworth, 1980). That is, increments or decrements in viability or fecundity that are confined to later ages have relatively little impact on lifetime fitness. Two genetic mechanisms of senescence, consistent with this evolutionary argument, have been proposed. Medawar (1946) suggested that senescence may result from mutations with deleterious effects confined to later ages. Such alleles will be maintained at relatively high equilibrium frequencies (Charlesworth, 1980 p. 218), and they will tend to accumulate in populations (Edney and Gill, 1968). We will refer to this as the mutation-accumulation mechanism (Rose and Charlesworth, 1980). A second mechanism of senescence, also suggested by Medawar (1946) and developed by Williams (1957), is antagonistic pleiotropy. According to this

mechanism, senescence results from selection for alleles that have beneficial effects on fitness early in life but later, deleterious effects. Decline with age in the force of selection increases the likelihood that such alleles will have positive net effects on fitness.

If the evolutionary interpretation of senescence is correct and there is appropriate genetic variation, it should be possible to alter patterns of senescence by selection on experimental populations. If only old individuals are allowed to produce each subsequent generation, selection will favor alleles that enhance survivorship and late-age reproduction; that is, selection will act to forestall senescence. Conversely, if only the youngest individuals are allowed to produce subsequent generations, alleles contributing to senescence will be shielded from adverse selection.

These methods have been used successfully in a number of experiments to produce lines of *Drosophila* with divergent mean longevity (Wattiaux, 1968; Rose and Charlesworth, 1981b; Rose, 1984; Luckinbill et al., 1984; Luckinbill and Clare, 1985). However, other attempts to alter lifespan in *Drosophila* by selection in the laboratory have not been successful (Lints and Hoste, 1974; Lints et al., 1979; Luckinbill and

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Clare, 1985). The absence of response to selection in these latter cases is almost certainly due to the fact that selection was applied to flies that were reared at a larval density of 10 per shell vial. In contrast, a response to selection has occurred when flies were reared at less controlled and, consequently, higher (approximately one order of magnitude) larval densities (Rose and Charlesworth, 1981*b*; Rose, 1984; Luckinbill and Clare, 1985). Phenotypic differentiation of major alleles affecting longevity is apparently suppressed at low rearing densities, making selection on those alleles difficult if not impossible. This interpretation is supported by additional observations of density effects. When longevity comparisons are made between populations that have been previously differentiated by selection at high density, the apparent difference between the populations is a function of the density at which assayed flies are reared (Clare and Luckinbill, 1985; Luckinbill and Clare, 1986). Specifically, the differences in longevity between differentiated lines are much less when assayed flies are grown at low density.

In those cases where selection on lifespan in *Drosophila* has been successful, there have been concomitant changes in female fecundity patterns. Increased longevity is associated with relatively lower fecundity early in life and increased fecundity late in life (Rose and Charlesworth, 1981*b*; Rose, 1984; Luckinbill et al., 1984, 1987). This trade-off between early-life and late-life fitness components supports the antagonistic-pleiotropy mechanism for the evolution of senescence.

There have been several tests of mutation accumulation in *Drosophila*. Rose and Charlesworth (1980, 1981*a*) evaluated the additive genetic variance of daily fecundity as a function of age. If the mutation-accumulation mechanism were correct, additive genetic variance of a fitness component, such as daily fecundity, should have increased with age. They found no age-specific trend in genetic variance for daily fecundity. However, Clark (1987) suggests that tests of this sort may suffer from lack of sensitivity. Kosuda (1985) showed that variance in male mating activity among chromosome-substitution lines was much greater for old flies

than for young. Furthermore, the reduction in mating activity due to second-chromosome homozygosity, relative to heterozygosity, was greater at older ages than at younger ages. Lastly, there was no correlation among lines between early-age and late-age mating activity. Taken together, these results are consistent with mutation accumulation. Mueller (1987) compared early-age and late-age fecundity of *D. melanogaster* populations that had been maintained either through reproduction by young females (*r*-selected), or through reproduction by females of indefinite age (*K*-selected). Although early-age fecundity did not vary between *r*- and *K*-selected lines, the *r*-selected lines were significantly less fecund than the *K*-selected lines at the later age. These results are also consistent with the notion that absence of natural selection at older ages in the *r*-selected lines permitted the accumulation of alleles with deleterious late-age effects.

In this paper, we propose an additional test of the mutation-accumulation mechanism and present the experimental results of such a test. This test involves selection for late-life fitness, followed by reverse selection for early-life fitness. The outcomes of reverse selection for early-life fitness are different under antagonistic pleiotropy and mutation accumulation (Table 1). For simplicity of illustration, we assume a single diallelic locus affecting any arbitrary trait. Under both genetic mechanisms, allele A_2 enhances late-life fitness relative to the effect of A_1 . Under antagonistic pleiotropy, A_1 is relatively beneficial for early-life fitness, but under mutation accumulation, A_1 and A_2 are neutral with respect to early-life fitness. Selection for late-life fitness favors A_2 in both mechanisms. Subsequent reverse selection would increase the frequency of A_1 if the locus in question stands in an antagonistic-pleiotropic relationship with early-life and late-life fitness. However, under mutation accumulation, reverse selection favors neither allele, and we would expect to see no change in the population mean value of the trait in question.

Genetically increased longevity in *D. melanogaster* is associated with increased adult resistance to starvation, desiccation, and lethal concentrations of ethanol vapor

TABLE 1. Genetic models of senescence. Plus and minus signs indicate the effect of each allele relative to the other on either early-life or late-life fitness. Circles indicate neutrality.

Trait	Antagonistic pleiotropy		Mutation accumulation	
	Allele		Allele	
	A ₁	A ₂	A ₁	A ₂
Early-life fitness	+	-	○	○
Late-life fitness	-	+	-	+

(Service et al., 1985). If long-lived flies are subjected to selection for increased early-life fitness, different outcomes are expected, depending upon whether antagonistic pleiotropy or mutation accumulation is operating, as just explained. If alleles that increase adult stress resistance have antagonistic-pleiotropic effects on early-life fitness, then selection for increased early-life fitness will result in decreased stress resistance. On the other hand, under mutation accumulation, selection for increased early-life fitness should have negligible effects on stress resistance.

MATERIALS AND METHODS

Populations

Five of the populations used in this study had been maintained in discrete generations of two-weeks' duration for approximately five years. These populations, referred to as B₁-B₅, had, therefore, been subjected to strong selection for early-life fitness. The remaining five populations (O₁-O₅) had been cultured in discrete generations of ten-weeks' duration and had, consequently, been under selection for late-life fitness. These ten populations were derived simultaneously from a common ancestral population that had been maintained for the preceding five years under conditions favoring early-life fitness. The history and details of the selection procedures and culture conditions of the B and O populations are given by Rose (1984) and Service et al. (1985). The divergent selection pressures have resulted in a number of differences between B and O populations. For approximately the first two weeks of adult life, B females have greater fecundity than O females, after which the relative fecundities are reversed (Rose, 1984). O-popula-

tion males and females have greater longevities than do B-population flies (Rose, 1984). In addition, O-population flies are more resistant than B-population flies to stresses of starvation, desiccation, and ethanol vapor (Service et al., 1985). Thus, increased longevity is associated with increased resistance to several potentially important causes of mortality.

Reverse Selection

Uncontrolled Larval Density.—Five reverse-selection populations, designated R₁-R₅, were started by obtaining approximately 2,000 eggs from O₁-O₅, respectively. The R populations were then handled in exactly the same way and at the same time as the B populations; that is, they were subjected to natural selection for early-life fitness. Every two weeks, adult flies were allowed to oviposit en masse in fresh 8-dram shell vials until an adequate number of eggs were laid. Egg densities were estimated to vary between 100 and 200 per vial. If too many eggs were laid, the excess was removed by scraping the surface of the medium. Other than that, no attempt was made to regulate larval density. After oviposition, adult flies were discarded or used for assays of selection response (see below). Twenty-two R generations were obtained (21 generations of selection). Population sizes were generally between 1,000 and 2,000 each generation.

Controlled Larval Density.—Other studies have shown that selection on *Drosophila* life-history characters can be strongly affected by larval rearing density (Clare and Luckinbill, 1985; Luckinbill and Clare, 1985). Therefore, we established ten additional experimental populations in order to assess the effects of rearing density on natural selection for early-life fitness. Five controlled-density reverse-selection populations were started by sampling 600 eggs or larvae from each O population and transferring them to fresh food in 8-dram shell vials at a density of 30 per vial. These five populations were designated RC₁-RC₅. In order to provide a standard against which to assess any selection response, five controlled-density B populations (BC₁-BC₅) were similarly established. The RC and BC populations were maintained in two-week

discrete generations. Each subsequent generation was produced by sampling eggs from the current generation and transferring them to 20 rearing vials per population at a density of 30 per vial. Thus, each generation produced something less than 600 adult flies per population. Of these, 100 females per population were used for assays of selection response (see below), leaving somewhat fewer than 200 females as parents for each subsequent generation. The procedure was carried out for 12 generations.

Assays of Selection Response

Uncontrolled-Density Selection.—Four characters were tested for response to selection for early-life fitness in the R populations: early-age female fecundity and resistances to starvation, desiccation, and ethanol vapor. Fecundity was measured when flies were 4–5 days old. Fifty female/male pairs per population were placed in vials containing charcoal medium covered with a suspension of live yeast and allowed to oviposit for one 24-hr period. The procedures for testing starvation, desiccation, and ethanol resistance were similar to those used by Service et al. (1985). Forty females (6 days old) per population were used to assay each stress-resistance character.

Flies used for phenotypic assays were either taken directly from the experimental populations or were the second-generation descendants of flies sampled from the experimental populations. These latter flies were the product of two generations of controlled-density rearing (30 eggs per 8-dram shell vial) under conditions designed to forestall selection for early-life fitness components. The procedures for controlled-density assays are intended to reduce or eliminate unwanted environmental causes of variance, including possible maternal effects resulting from systematic differences in culture conditions between selected and unselected lines. All previous phenotypic assays of the B and O populations (Rose, 1984; Service et al., 1985) have used two generations of controlled-density rearing. However, Luckinbill et al. (1984) have demonstrated that response to selection for early-life and late-life fitness can be reliably detected when assayed flies are taken directly from experimental populations. In

fact, phenotypic divergence between early- and late-selected lines is more marked in uncontrolled-density assays (Clare and Luckinbill, 1985). The crucial difference between controlled- and uncontrolled-density rearing of flies used for phenotypic assays is probably not control per se, but the fact that uncontrolled density generally means much higher density. Thus, while we shall adopt the practice of referring to our two types of assays as uncontrolled density (for flies taken directly from the experimental populations) or controlled density (for grandchildren of flies in the experimental populations), it should be borne in mind that the important distinction is probably high versus low density, respectively. Controlled-density assays were done on the grandchildren of flies from every other generation of selection, beginning with the first and ending with the eleventh. Uncontrolled-density assays were done on alternate generations, beginning with the second generation and continuing through the twenty-second.

Controlled-Density Selection.—Early-age fecundity and female starvation resistance were assayed for each generation, using flies taken directly from the experimental populations. Fifty flies were used per population for each character. Since the experimental populations (RC_1 – RC_5 and BC_1 – BC_5) were maintained at controlled density, these are controlled-density assays.

Method of Data Analysis

We analyzed our results by least-squares linear regression of population means on generation. For example, the mean starvation resistance level of the R_1 population in the eighth generation was taken as a single datum (R_{18}). In order to mitigate the effects of uncontrolled environmental variation, the means of individual reverse-selected lines in a generation were divided by the average level of the appropriate B controls for that generation. Therefore, one of our calculations involved the linear regression of the ratio $R_{1j}/B_{.j}$ on generation, where subscript j refers to generation and $B_{.j}$ is the mean of the five B populations in the j th generation. Tests of our hypotheses centered on tests of the significance of regression coefficients. However, because of our replication of re-

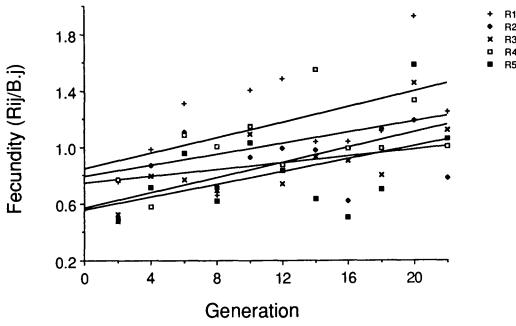


FIG. 1. Response of early-age fecundity to reverse selection for early-life fitness with uncontrolled larval rearing density and using uncontrolled-density assays. Each line is the linear least-squares regression on generation of a population mean value (R_{ij}), divided by the overall mean of the control populations (B_{ij}). Subscripts i and j refer to population and generation, respectively. The different symbols refer to the five reverse-selection populations.

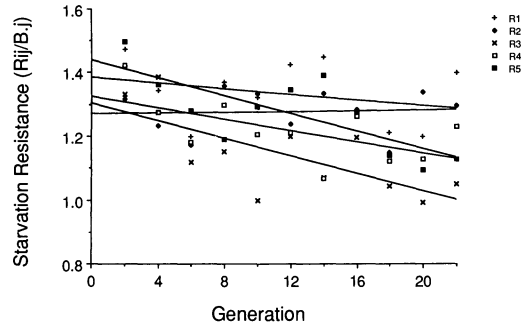


FIG. 2. Response of starvation resistance to reverse selection for early-life fitness with uncontrolled larval rearing density and using uncontrolled-density assays. Explanation of lines and symbols is as for Figure 1.

verse-selection lines and the problem of genetic sampling effects (Hill, 1971), we used each slope as a data point and performed t tests for the significance of deviation from zero of a set of five regression slopes. Since the appropriate alternative statistical hypothesis is for response to selection in the direction of the B-population controls, one-tailed P values are given.

One assumption of the regression model is that the error terms, ϵ_i , associated with the several values of the independent variable, X_i , are themselves independent random variables. This assumption can be violated in time-series data when the error terms become positively autocorrelated. Such autocorrelation is likely to arise if important variables that are correlated with

time are omitted from the model (Neter and Wasserman, 1974 p. 352). In the present case, we could imagine some environmental trend in the laboratory. However, unless the control and selected populations reacted in different ways to such “missing” environmental factors, use of control lines to “standardize” the trait values in the selected lines should have eliminated or reduced the effects of such factors.

RESULTS

Fecundity and Starvation Characters

Uncontrolled-Density Selection. — Figures 1 and 2 show the results of 22 generations of uncontrolled-density reverse selection for the fecundity and starvation characters, respectively, using uncontrolled-density assays. Fecundity increased significantly over the course of selection, while starvation resistance decreased sig-

TABLE 2. Responses to reverse selection. Tabled values are mean regression coefficients with t statistics in parentheses, and significance levels are associated one-tailed probabilities (4 *d.f.*).

Line, assay, and generation	Fecundity	Starvation	Desiccation	Ethanol
Uncontrolled-density selection				
<i>Uncontrolled-density assay</i>				
22 generations	0.021 (7.63) ^c	-0.008 (2.99) ^b	-0.003 (1.24)	-0.005 (0.35)
12 generations	0.037 (6.06) ^c	-0.012 (2.35) ^a	0.012 (1.91)	0.025 (0.64)
<i>Controlled-density assay</i>				
11 generations	0.018 (1.65)	-0.035 (2.53) ^a	-0.001 (0.13)	-0.018 (1.79)
Controlled-density selection				
12 generations	-0.005 (0.90)	-0.0002 (0.03)	—	—

^a $P \leq 0.05$.
^b $P \leq 0.025$.
^c $P \leq 0.005$.

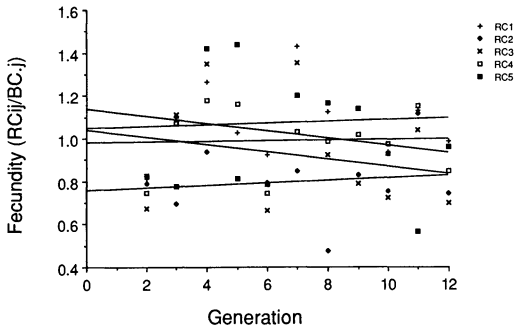


FIG. 3. Response of early-age fecundity to reverse selection for early-life fitness with controlled larval rearing density and using controlled-density assays. Each line is the linear least-squares regression on generation of a population mean value (RC_{ij}) divided by the overall mean of the control populations ($BC_{.i}$). Subscripts i and j refer to population and generation, respectively. The different symbols refer to the five reverse-selection populations.

nificantly (Table 2). The former is only to be expected, given the reintroduction of selection for early fertility. The latter is evidently a reflection of antagonistic pleiotropy between starvation resistance and some early-life fitness component(s). Service and Rose (1985) estimated a large-magnitude negative genetic correlation between early fecundity and starvation resistance, suggesting that fecundity itself might be the key character whose rise depresses starvation resistance.

Controlled-Density Selection.—Figures 3 and 4 show the comparable results of reverse selection with controlled larval rearing densities over twelve generations for fecundity and starvation resistance, respectively. In contrast to the results for uncontrolled-density selection, there was no statistically significant change in either character over the generations studied (Table 2). This difference between the results for uncontrolled- and controlled-density selection cannot be attributed to the fewer generations in the latter experiment. Analysis for the corresponding 12 generations of reverse selection upon uncontrolled-density lines still indicates a statistically significant response to selection (Table 2). One interpretation of this is that it might reflect problems of assay sensitivity at lower rearing densities (cf. Clare and Luckinbill, 1985). However, the controlled-density assay of the

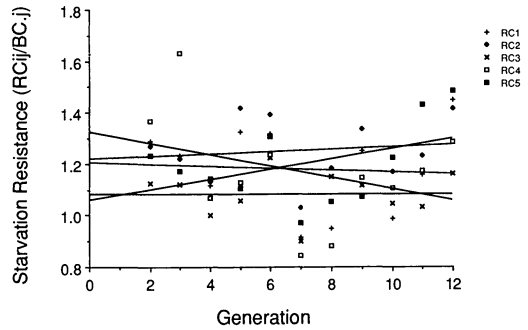


FIG. 4. Response of starvation resistance to reverse selection for early-life fitness with controlled larval rearing density and using controlled-density assays. Explanation of lines and symbols is as for Figure 3.

uncontrolled-density lines reveals a statistically significant decrease in starvation resistance (Table 2). Therefore, the lack of response to reverse selection seems to reflect a difference in selection response, rather than an assay artifact.

Desiccation- and Ethanol-Resistance Characters

Figures 5 and 6 show the effects of 22 generations of reverse selection upon the desiccation- and ethanol-resistance characters in the uncontrolled-density selection lines, using uncontrolled-density assays. There was no consistent significant change over the period studied. Assays with controlled and uncontrolled larval rearing densities were not different (Table 2); in both cases, there was no significant change. These results do not accord well with an interpre-

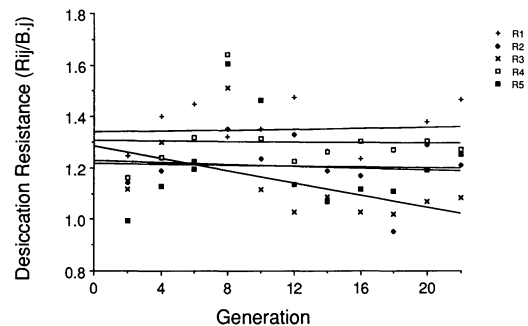


FIG. 5. Response of desiccation resistance to reverse selection for early-life fitness with uncontrolled larval rearing density and using uncontrolled-density assays. Explanation of lines and symbols is as for Figure 1.

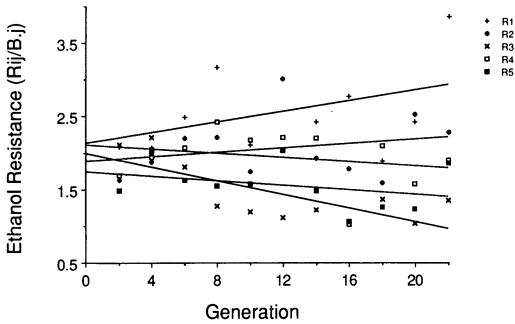


FIG. 6. Response of ethanol resistance to reverse selection for early-life fitness with uncontrolled larval rearing density and using uncontrolled-density assays. Explanation of lines and symbols is as for Figure 1.

tation of antagonistic pleiotropy, as we discuss below.

DISCUSSION

The foregoing results seem to us to be significant in four respects. Firstly, we have obtained independent evidence that the starvation-, desiccation-, and ethanol-resistance characters in our populations are not controlled by a single physiological mechanism. These results support the findings of Service (1987) and further suggest that the life-history differences between the B and O populations have a polygenic basis.

Secondly, we have corroborated the findings of Luckinbill and Clare (1985, 1986) and Clare and Luckinbill (1985): selection response in *Drosophila* life-history experiments can be critically dependent on larval rearing density. In particular, low rearing densities seem to reduce responses to selection (cf. Lints and Hoste, 1974; Lints et al., 1979).

Thirdly, we have still more evidence for antagonistic pleiotropy in the fall of starvation resistance upon a return to selection for early fertility and a relaxation of selection for later fertility. The rapid rise of fecundity upon reverse selection also suggests the existence of genetic antagonism between early reproduction and later reproduction, which must have been reducing early reproduction in our longer-lived late-reproduced stocks. These results are entirely consistent with previous work on these populations (Rose and Charlesworth, 1981a, 1981b; Rose, 1984; Service and Rose, 1985).

Fourthly, and of more interest, the results with respect to desiccation and ethanol resistance suggest that these characters can respond to selection for later reproduction in such a way that there is little or no antagonistic response in early-life fitness components. At the level of gene action, this suggests that there are alleles that enhance survival to, or reproduction at, later ages that do not have deleterious effects at early ages. This is a third line of evidence in support of mutation accumulation as a population-genetic mechanism for the evolution of senescence in *Drosophila* (see also Kosuda [1985] and Mueller [1987]). In the context of our experiments, we interpret these results to indicate that selection for early-life fitness in the ancestral fly population allowed alleles with adverse effects on desiccation and ethanol resistance to achieve relatively high frequencies. Subsequent selection in the O populations for late-life fitness reduced the frequencies of these deleterious alleles. Finally, during the relatively short period of reverse selection, allele frequencies in the R populations remained at O-population levels because of effective neutrality under conditions favoring early-life fitness.

There is one major problem with this line of interpretation: the possibility that the original longer-lived populations could have been fixed for the alleles enhancing resistance to desiccation and ethanol. There are two arguments against this alternative interpretation. Firstly, it is likely that there were many loci contributing to the genetic variance that underlay the response to selection for late-life fitness. In the large populations that we have used, it is unlikely that all the relevant alleles would have proceeded to fixation in the course of selection. This argument is not necessarily inconsistent with the estimate by Luckinbill et al. (1987) of a low number of effective factors controlling senescence in *D. melanogaster*. Their method of estimation (Wright, 1968; Lande, 1981) is based on the assumption that all factors have equal effect. Violation of this assumption will underestimate the number of effective factors, in some cases seriously (Wright, 1968 pp. 384–386). Secondly, if there were a few loci having fixed alleles of large effect that also exhibited an-

tagonistic pleiotropy with respect to early- and late-life fitness, then they should have made their effects manifest by preventing a return to control levels of early-life fitness characters. The one such character that we observed, early-age fecundity, exhibited a return to the control level (Fig. 1), as would be expected if there were no fixed alleles that had depressed it in the longer-lived populations.

There may, of course, be other, unexamined early-life fitness components that did not return to control-population levels, so our argument against antagonistic pleiotropy and, by implication, for mutation accumulation as the mechanism for the evolution of desiccation and ethanol resistance is necessarily qualified. Also, the pattern of selection and reverse-selection responses that we have attributed to mutation accumulation could result from epistatic interactions in a system initially characterized by antagonistic pleiotropy. Lenski (1988) has shown that fitness costs associated with phage resistance in *E. coli* can be partly overcome by changes at loci not initially involved in the evolution of phage resistance. In the present context, the retention of enhanced desiccation and ethanol resistance in the R lines together with a return to control levels of early-life fitness (early-age fecundity) might have been due to changes at "modifier" loci. Pursuing this argument, the antagonism or neutrality, with respect to early-life fitness, of major alleles controlling desiccation and ethanol resistance would be a function of genetic background: ancestral versus O (or R) populations, respectively.

Despite these potential alternatives to the interpretation of mutation accumulation, we feel that the weight of evidence in the present experiments supports the conclusion that both mutation accumulation and antagonistic pleiotropy are important mechanisms for the evolution of senescence. Both now have multiple, independent lines of evidence for their action. However, both are attested to primarily by work with *Drosophila* and, therefore, stand in need of evaluation with other species (Rose and Service, 1985). It is worth commenting that the fecundity character used by Rose and Charlesworth (1980, 1981a) to test the mu-

tation-accumulation mechanism appears, from the present results, to be a poor character for the evaluation of the mechanism. There is evidently a great deal of additive genetic variance for the character at early ages—genetic variance that is tied up with an antagonistic-pleiotropy mechanism or mechanisms (Rose, 1984; Service and Rose, 1985). Tests of mutation accumulation based on age-dependence of genetic variance in a fitness component require that antagonistic pleiotropy be virtually absent. The present type of test does not require this, nor does that of Mueller (1987). On the other hand, the present test is weakened in that the argument for mutation accumulation is based on a negative result. As antagonistic pleiotropy is undoubtedly common in the evolution of senescence (Rose and Service, 1985), coupled selection and reverse-selection experiments, when practical, should be considered in conjunction with overall tests of genetic variation and covariation (sib analyses) in future work on population-genetic mechanisms of senescence.

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