GENETICS OF LIFE HISTORY IN *DROSOPHILA MELANOGASTER*. I. SIB ANALYSIS OF ADULT FEMALES

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Manuscript received January 20, 1980
Revised copy received October 24, 1980

ABSTRACT

A sib analysis of adult life-history characters was performed on about twelve hundred females from a laboratory *Drosophila melanogaster* population that had been sampled from nature and cultured so as to preserve its genetic variability. The following results were found. There was no detectable trend with age in additive or dominance genetic variances for age-specific fecundity. Environmental variance for age-specific fecundity increased with age. The genetic variance for fecundity characters was primarily additive. The genetic variance for longevity was primarily dominance variance. There were negative genetic correlations between early fecundity and lifespan, as well as between mean egg-laying rate and longevity.

QUANTITATIVE genetic variation in fitness is of central importance in evolution. Since viability, fecundity, and longevity characters together constitute life history, their underlying genetic structure in turn composes that of fitness. Most research on Drosophila fitness components has dealt with the quantitative genetics of egg-to-adult viability (*e.g.*, MUKAI *et al.* 1974), although there has been some work on early fecundity (ROBERTSON 1957; RICHARDSON and KOJIMA 1965), longevity (CLARKE and MAYNARD SMITH 1955; MAYNARD SMITH 1959) and combinations of the three characters (GILBERT 1961, ANDERSON and WATANABE 1974). The only detailed studies of the genetics of late female fecundity in Drosophila are those by GOWEN and JOHNSON (1946) and GIESEL (1979), using *D. melanogaster* inbred lines.

This neglect of later life-history characters is understandable, because they can not be accommodated within the framework of conventional, discrete-generation, population genetics theory (*cf.*, CROW and KIMURA 1970). But the recent development of genetical theory for age-structured populations, reviewed by CHARLESWORTH (1976, 1980), has overcome such limitations. Furthermore, this theory shows that the action of natural selection on later adult life-history characters is quantitatively different from that on early life-history characters, with important implications for the evolution of senescence (WILLIAMS 1957; HAMILTON 1966; CHARLESWORTH and WILLIAMSON 1975; CHARLESWORTH 1980).

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Research carried out while the senior author was a Commonwealth Scholar.

The present report is concerned with the genetic variation for *D. melanogaster* female age-specific fecundity and female longevity in a randomly mating population. The nature of this variation was ascertained by means of analyses of variance and covariance between full-sib and half-sib families (FALCONER 1960). Selection experiments checking the results of this sib analysis are described in an accompanying article (ROSE and CHARLESWORTH 1981).

MATERIALS AND METHODS

A. *The experimental population*: The population of *D. melanogaster* used in these experiments was derived from 200 males and 200 females collected by P. T. IVES in August, 1975, near South Amherst, Massachusetts. The methods of collection are described in IVES (1970). The South Amherst population of *D. melanogaster* is among the best known natural populations of Drosophila, having been studied more or less continuously since 1931 (IVES 1970). From these studies, it seems likely that the South Amherst population has been continuously endemic since 1930.

In the laboratory, the flies underwent their entire life cycle at 25° in 10 to 16 1/3 pint milk bottles, each with about 1 inch of Lewis medium and some powdered, live yeast. Discrete generations of 13 to 15 days were maintained, with regular mixing of adults among bottles. The total adult population count never fell below that of the original sample and was typically well into the thousands.

B. *Sib analysis*: The main experiment was replicated as a whole seven times, from April 1977 to June 1978. Virgin females were sampled from the base population at short intervals over a 24-hr period, ensuring that they were within one day of the same age from pupal emergence. Nine groups of up to 10 females were mated to single males of the same age during the period before egg-laying of the phenotypes to be assayed. Two lots of larvae were collected simultaneously for rearing, in separate tubes, from each mated female. Sufficient time was allowed for larval eclosion to preclude the possibility of developmental-rate bias in larval collection. A single adult female was finally harvested at random for assay from each of the rearing tubes. Thus, common environmental effects on full-sibs were limited to those on eggs immediately before laying and larvae just after emergence. (See Figure 1.) The total number of progeny assayed in each replicate of the experiment, or "block", was about 180.

This procedure introduced a significant *divergence* of full-sib phenotypes after collection for different rearing tubes, because the collection of the first lot of larvae did not require much scraping of the laying surface, while the second collection did. Since the surface of the laying medium was treated with yeast paste, this resulted in an additional quantity of yeast in the second larval rearing tube. As ROBERTSON and SANG (1944) have shown, improvement in larval nutrition increases the early fecundity of the adult female.

The magnitude of all such rearing-tube effects was estimated in a separate experiment, using the procedures of the sib analysis itself except for the following differences in the method of obtaining the adult phenotypes. Eighteen females were mated to 18 males as pairs. Two samples of larvae were collected for rearing, in separate tubes, from each mated female, as in the sib analysis. Three adult females were harvested for assay from each of these rearing tubes.

C. *Phenotype assay*: All handling was performed at room temperature, using CO_2 anaesthesia. All flies were kept in the same incubator at 25° under constant illumination.

All flies were within 48 hr of age from their oviposition as eggs in the standard laying tube. These laying tubes were plastic, stoppered with cotton wool and 2.5 × 8 centimeters. Each contained high-agar medium, with sucrose and yeast as nutritional sources, and charcoal powder added for coloring. The laying tube surface was covered with yeast paste to which a small amount of dilute acetic acid had been added.

Forty-eight to 72 hr after the start of oviposition, the medium was removed intact for collection of larvae. Groups of 10–20 larvae were collected from the surface of the medium, using a paper cup in a glass tube. (The number collected did not reflect the total number laid in the

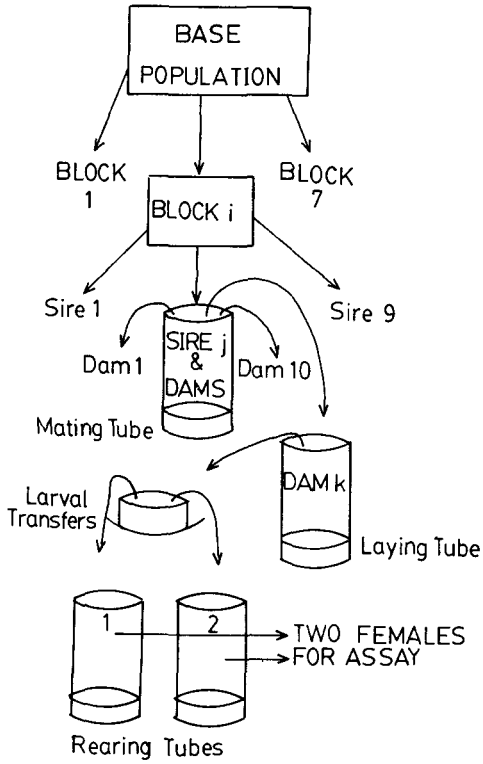

FIGURE 1.—Sib analysis procedure for generating the phenotypes that were measured. The entire procedure was repeated for seven samples of the base population, as shown, producing 160 to 180 phenotypes for each replication of the experiment, or "block". About 1200 female phenotypes were assayed for most characters, although some characters, such as longevity, were not assayed for Block 1. See MATERIALS AND METHODS, part B, for further explanation.

original laying tube.) The paper cup was then ejected into a plastic tube containing Lewis medium and powdered yeast. These tubes were incubated for 7 days, and then newly emerged adult females were harvested at intervals to within 32 hr of the same age from eclosion.

These females were provided with males and kept as pairs for two days, to allow mating. (From fertility tests, virtually all females laying eggs after this point had been successfully mated.) After mating, each pair was provided with a new laying tube every 24 hr until the death of the female was recorded. All dead males were replaced by others of the same age. New males were provided for all females every two weeks. All eggs laid on the medium surface or on the sides of the laying tubes were counted at 24-hr intervals after the mating period.

ANALYSIS

A. *General analysis of variance*: The normal analysis of variance for unbalanced full and half-sib experimental designs is given in KEMPTHORNE (1957, pp. 421–423). The experiment discussed here requires a different analysis of variance, because of its division into sequential blocks and the confounding tube effect. In fact, the expected mean-square formulae for this experiment were not available and had to be derived from the basic equations for the unbalanced

hierarchical analysis of variance, following KEMPTHORNE (1957, pp. 238–243). The derivations and resulting formulae are extremely cumbersome, as may be seen in ROSE (1979); they will not be given here. From these formulae, it was possible to obtain all the source variance components. Then the phenotypic variance components were estimated using the conventional formulae for sib analyses (*cf.*, FALCONER 1960, pp. 172–174).

Sampling variances of estimates of variance components from unbalanced data are not known in general. Only comparatively recently have they been found for the three-way hierarchical, or random effects, model (MAHAMUNULU 1963). The sampling variances for the variance components of the model for the present sib analysis are not known. In the case of the estimate of the additive genetic variance for daily fecundity, *ad hoc* confidence intervals were estimated, using three times the nominal standard deviation for the estimated parameter, under the assumption of negligible tube effects, as obtained from the formulae of MAHAMUNULU (1963). Confidence intervals for the dominance variance for longevity were obtained by assuming an approximately balanced design and negligible tube effects, reasonable assumptions for that case, following MENDENHALL (1968, pp. 350–352). While other confidence intervals could have been obtained by these approximations, or others, the repetition of the experiment over a number of days allows a more empirical assessment of the estimation accuracy. Since exact confidence intervals are not available, the estimates found must be viewed with caution in any case.

B. *Analysis of tube effects*: The procedure used to estimate the tube effects requires the analysis of variance given in KEMPTHORNE (1957, p. 255). Since some observations were missing, the average over the available progeny from the ith larval sample of the jth parent's progeny, when progeny from both parents were present, was used as the basic observation. Linear regression on estimated daily fecundity tube effects was used to smooth out the day-to-day variation in these estimates. The predictor values provided by this linear regression were then used in the formulae for the variance components of the sib analysis.

C. *Analysis of daily fecundity*: The analysis of daily fecundity covered assay days 1–25, with the total number of daily observations fluctuating between 1153 and 396. Toward the end of life, the average egg-laying of individual females fails completely. This gives rise to a reasonably unimodal distribution near the mean daily fecundity and a sharp spike at zero fecundity. This spike becomes steadily higher as the assayed group ages, causing a trend of increasing deviation from normality with age from assay days 1 to 25. To remove this biasing factor, all fecundity data was taken to be conditional on non-zero fecundity. That is, zero fecundity was taken to represent a missing data point. The absence of low 24-hour fecundity values, other than zero, indicates that this procedure is biologically appropriate.

Another problem with the fecundity data is that the mean decreased with age. This complicated the analysis of variance because the standard deviation and the mean had a correlation coefficient of 0.904 ($p < 0.001$) over days 1–25. Fortunately, there is a general method for transforming data to remove such

scale effects (WRIGHT 1952, 1968, pp. 230–236). The required transformation was found to be $X^t = \log_e (X + 23.81)$, and was applied to each datum individually, before the analysis of variance. It must be emphasized that such transformations are the only means of making comparisons, between variance components, that are scale-independent.

D. *Analysis of aggregate characters*: The large amount of data collected for each phenotype allowed the specification of a number of aggregated characters. The characters to be discussed here are: (a) *fecundity over an interval of days* conditional only on laying at some point during the interval, (b) *longevity* defined as the last day of assay on which the female was still alive, and (c) the *last day of laying*, abbreviated as "last day", defined as the last day of assay on which the female was still alive and had laid eggs, and (d) the *laying rate*, as given by the total egg-count divided by the last day of lay.

In addition to the analysis of variance for these characters individually, an analysis of covariance between characters was also performed. The method outlined in KEMPTHORNE (1957, pp. 264–265) was used. For characters x and y, this involved the analysis of variance for the linear function $(x + y)$, as well as x and y confined to phenotypes with both x and y characters. The components of covariance were then estimated using the general formula $2\,\mathrm{Cov}(x,y) = \mathrm{Var}(x + y) - \mathrm{Var}(x) - \mathrm{Var}(y)$.

RESULTS

A. *Daily fecundity*: Table 1 gives means and linear regression statistics for $\hat{V}_P$ (estimated phenotypic variance), $\hat{V}_A$ (estimated additive genetic variance), $\hat{V}_D$ (estimated dominance genetic variance), $\hat{V}_E$ (estimated environmental variance), and $\hat{h}^2$ (estimated heritability) from the daily fecundity data for assay days 1–25. Figures 2, 3, 4 and 5 provide plots of $\hat{V}_P$, $\hat{V}_A$, $\hat{V}_D$, and $\hat{V}_E$, respectively, together with their best estimators or means. The linear regressions are unweighted.

These results indicate that V_A and V_D do not change with age in a constant fashion, while V_P and V_E on the whole increase with age. It is fairly clear that V_A, V_E, and V_P are greater than zero overall, but there is no evidence that V_D is

TABLE 1

Mean and regression statistics for variance components and heritability for daily conditional fecundity using transformed data from days 1 to 25

	$\hat{V}_A$	$\hat{V}_D$	$\hat{V}_E$	$\hat{V}_P$	$\hat{h}^2$
Mean	0.02925264	0.00001152	0.06552056	0.09478352	0.311204
Regression slope	—0.00002222	—0.00072778	0.00210457	0.00135438	—0.00461977
Intercept at day zero	0.02954150	0.00947266	0.05816115	0.07717658	0.37126101
t-statistic for regression	—0.0599	—0.9435	3.3807	5.8677	—1.3516
Degrees of freedom	23	23	23	23	23
Two-tailed statistical significance of regression fit	none	none	$P < 0.01$	$P < 0.001$	$(P < 0.2)$

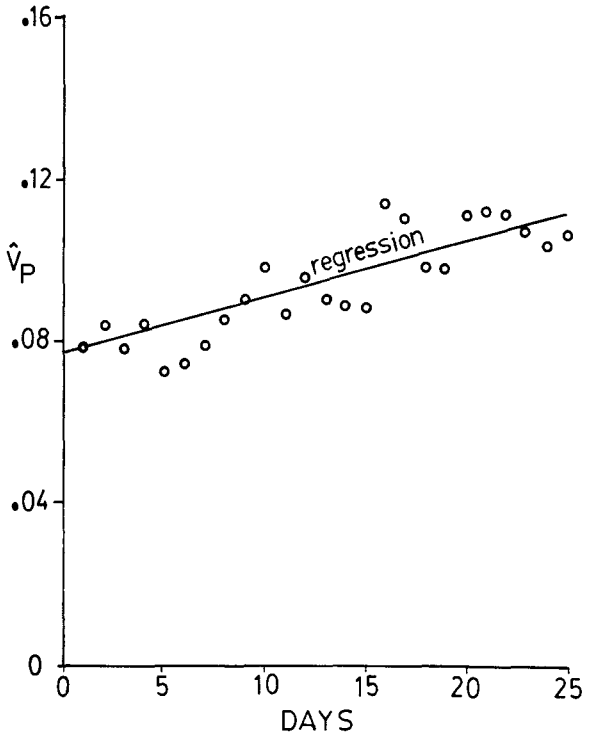

FIGURE 2.—Estimates of the phenotypic variance, V_P, for daily conditional fecundity when transformed so as to be independent of the mean conditional fecundity. The estimates are plotted against the day of assay. Table 1 shows that the least-squares linear regression of $\hat{V}_P$ on day of assay is significant, so that the regression line is plotted with the daily estimates.

greater than zero. Though it is probably never exactly zero at any age, the evidence does seem to indicate that V_D is an order of magnitude smaller than V_A. If V_A and V_D for daily fecundity are in fact independent of age over assay days 1–25, the mean values over the entire period are their best known estimators. Since V_D is estimated by four times the difference between dam and sire components of variance in the sib design, the fact that its mean estimate is so close to zero indicates that maternal effects play little role in the determination of fecundity.

B. *Aggregate characters*: Table 2 gives the variance components for the aggregate characters, untransformed, under the assumption of significant V_D (part A.) and negligible V_D (part B.). Both analyses were conducted because of the quite low levels of $\hat{V}_D$ for all egg-laying characters, aggregate or daily. The decline in $\hat{V}_A$ for egg-laying totals is a scaling artifact.

The most notable feature of Table 2 is the large value of $\hat{V}_D$ for longevity: 22.34. Making the simplifications discussed above allows the calculation of a 95% confidence interval lower bound of 3.81 for V_D, almost twice the size of $\hat{V}_A$.

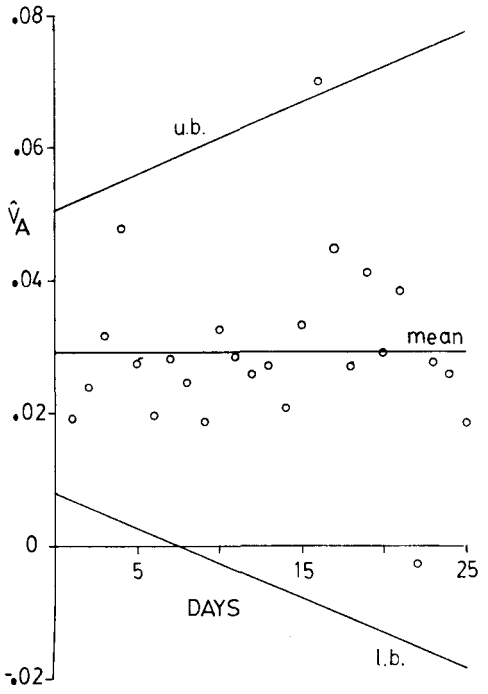

FIGURE 3.—Estimates of the additive genetic variance, V_A, for daily conditional fecundity when transformed so as to be independent of the mean conditional fecundity. The estimates are plotted against day of assay. Table 1 shows that the least-squares linear regression of $\hat{V}_A$ on day of assay is not significant, so that the regression line is not plotted. Instead, the mean value over days 1–25 is plotted. *Ad hoc* confidence-interval bounds are plotted above and below the mean. These were obtained by linear regression on the daily sampling variance estimates for additive genetic variance estimates, as explained in the ANALYSIS section, part A.

Table 3 gives the additive genetic and phenotypic correlations (r_A and r_P, respectively) among those character pairs for which mortality did not substantially bias the results. (Thus, late fecundity data, which is not available for phenotypes that die early, was not used.) Longevity and the last day of laying appear to be closely related characters, both genetically and phenotypically, suggesting that they may be lumped together as "lifespan". Both early fecundity and the egg-laying rate appear to have an antagonistic relationship with lifespan. Fecundity at intermediate ages has a more ambiguous relationship with the other characters. While this set of statistics is suggestive, the sampling variances are evidently large, as indicated by the underestimate of one of the r_A by at least 0.431. Therefore, these results must be regarded skeptically, viewed by themselves. In any case, it is notable that the $\hat{r}_A$ and $\hat{r}_P$ results generally do not correspond, except when $\hat{r}_A$ is of large magnitude. This suggests that r_P estimates need not be a good guide to underlying genetic constraints to, and consequences of, evolution, because r_E appears to have no necessary similarity to r_A.

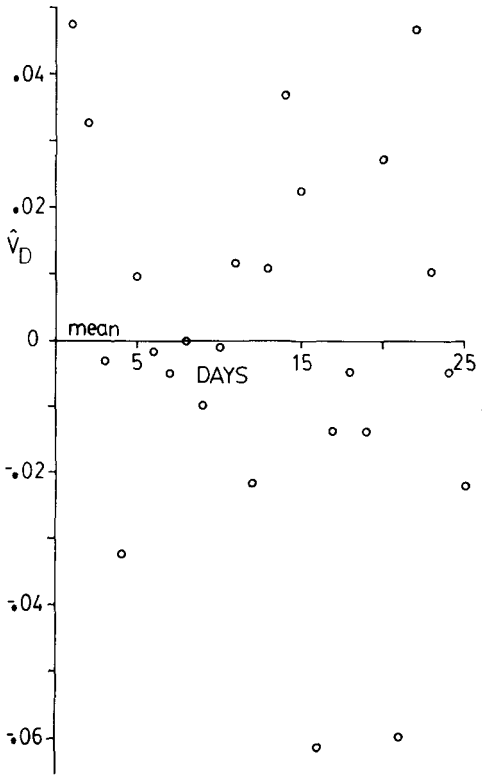

FIGURE 4.—Estimates of the dominance genetic variance, V_D, for daily conditional fecundity when transformed so as to be independent of the mean conditional fecundity. The estimates are plotted against the day of assay. Table 1 shows that the least-squares linear regression of $\hat{V}_D$ on day of assay is not significant, so that the regression line is not plotted. Instead, the mean value over days 1–25 is plotted. In this case, the mean value is indistinguishable from the zero axis.

DISCUSSION

A. *The genetics of life-history characters*: The results indicate that there is abundant genetic variability for *D. melanogaster* adult female life-history characters, and that there *may* be substantial pleiotropy among genes affecting such characters. In the case of age-specific fecundity, this variability appears to consist primarily of additive genetic variance, which is constant in magnitude over most of the adult lifespan once scale effects are removed. By contrast, there appears to be substantial dominance variance for longevity, and little additive variance, although the small number of observations suggests cautious interpretation. Both of these results are also subject to confounding epistatic variance components (FALCONER 1960), which were assumed to be negligible without supporting evidence. Additive genetic correlation estimates suggest the presence of antagonistic gene effects on egg-laying and lifespan, but these estimates lacked confidence intervals for statistical assessment.

Previous work on *D. melanogaster* early fecundity has yielded a variety of

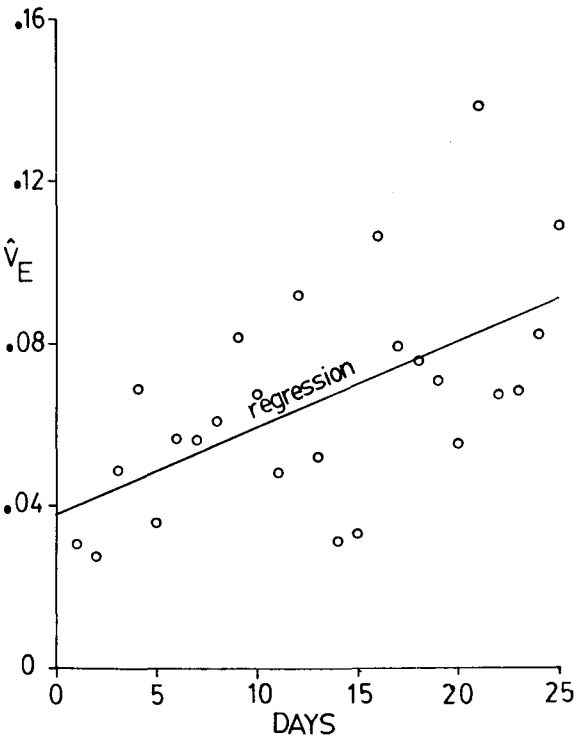

FIGURE 5.—Estimates of the environmental variance, V_E, for daily conditional fecundity when transformed so as to be independent of the mean conditional fecundity. The estimates are plotted against day of assay. Table 1 shows that the least-squares linear regression of $\hat{V}_E$ on day of assay is significant, so that the regression line is plotted with the daily estimates.

heritability estimates. ROBERTSON (1957) found a value of 0.18 in experiments based on a population derived from a single impregnated female. Other laboratory stocks have given fecundity heritability estimates below 0.10 (TANTAWY and EL-HELW 1970). TAIT and PRABHU (1970) studied several populations and estimated heritability as 0.680 in one case, with other populations having heritabilities in the 0.5 to 0.20 range. The present experiments suggest that, in the absence of inbreeding, the heritability of fecundity, when transformed to be scale-independent, falls from about 0.3–0.4 at early ages to 0.2–0.3 at later ages, due to increasing environmental variance. Without transformation, this fall is enhanced by scale effects, with a higher initial value of heritability. The significance of the increase in environmental variance with age is open to a number of theoretical interpretations. However, it might be due entirely to handling methods and therefore be irreproducible. Thus, it seems prudent to await the results of comparable experiments on this matter.

GOWEN and JOHNSON (1946) found negative correlations between what amounted to egg-laying rate and longevity among inbred lines of *D. melanogaster*, corresponding to the present negative additive genetic correlation esti-

TABLE 2

Genetic analysis of aggregate characters

Character	$\hat{V}_A$	$\hat{V}_D$	$\hat{V}_E$	$\hat{V}_P$	$\hat{h}^2$	Number of observations
(A) Assuming $V_D \neq 0$.						
Egg-laying:						
Days 1–5	4762.60	768.50	2108.28	7639.40	0.6234	1177
Days 6–10	2933.40	76.00	6913.11	9922.51	0.2956	1145
Days 11–15	3224.40	231.36	6740.04	10195.80	0.3162	1039
Days 16–20	3833.20	—6363.44	11362.34	8832.10	0.4340	840
Days 21–25	284.28	926.28	5852.70	7063.26	0.0402	596
Days 1–10	14603.92	—8992.72	28001.89	33613.09	0.4345	1177
Longevity:	2.0272	22.3416	48.6775	73.0463	0.0278	962
Last day:	5.3092	3.3744	59.2228	67.9064	0.0782	956
Laying rate:	64.868	—19.592	186.023	231.299	0.2805	956
(B) Assuming $V_D = 0$.						
Egg-laying:						
Days 1–5	5146.86	0	2492.54	7639.40	0.6737	1177
Days 6–10	2971.40	0	6951.11	9922.51	0.2995	1145
Days 11–15	3687.12	0	6508.68	10195.80	0.3616	1039
Days 16–20	651.48	0	8180.62	8832.10	0.0738	840
Days 21–25	747.42	0	6315.84	7063.26	0.1058	596
Days 1–10	10107.56	0	23505.53	33613.09	0.3007	1177
Last day:	6.9964	0	60.9100	67.9064	0.1030	956
Laying rate:	55.072	0	176.227	231.299	0.2381	956

TABLE 3

Estimated genetic and phenotypic correlations

Characters	$\hat{r}_A$	$\hat{r}_P$
Egg-laying days 1–5 *and*		
Longevity	—1.431	—0.215
Last day of egg laying	—0.132	0.024
Egg-laying days 6–10	—0.162	0.663
Egg-laying days 11–15	—0.478	0.495
Longevity *and*		
Egg-laying rate	—0.708	—0.339
Last day of egg laying	0.768	0.874
Egg-laying days 6–10 *and*		
Longevity	0.300	0.171
Last day of egg laying	—0.633	0.222
Egg-laying days 11–15	0.508	0.541
Egg-laying days 11–15 *and*		
Longevity	—0.712	0.210
Last day of egg laying	—0.502	0.467

mate for these two characters. GIESEL (1979) performed an experiment on lines that were more heavily inbred than those of GOWEN and JOHNSON (1946). Ostensibly in exact contradiction to the results found here and by GOWEN and JOHNSON, GIESEL found strong *positive* genetic correlations for characters like fecundity and longevity. Nonetheless, these results do not fundamentally disagree. The fitness components of heavily inbred strains depend on the number and severity of recessive deleterious alleles that have been fixed by inbreeding (WRIGHT 1977, pp. 41–43). For alleles of this kind, positive correlations in fitness effects is to be expected. TEMIN (1966) found that complete sterility was positively correlated with reduced viability for Drosophila chromosomes. Likewise, MUKAI and YAMAZAKI (1971) found no evidence of negative genetic correlation between viability and developmental time among newly arisen mutations, but none of these results necessarily reflect the genetic correlations to be expected among alleles that are not deleterious.

Two studies illustrate this point clearly. HIRAIZUMI (1961) found that chromosomes that depressed fitness exhibited positive correlation in their effects on two fitness components, while high fitness chromosomes had negative correlations. Similarly, SIMMONS, PRESTON and ENGELS (1980) found that newly arisen mutations with deleterious effects on viability also reduced other fitness components, but in the case of an equilibrium population, alleles that depressed viability *enhanced* other fitness components. GIESEL (1979) has provided a survey of low fitness correlations, while the present study provides a survey of those correlations that quantitatively predominate in outbred populations. The disparity between the genetic correlation results in the two cases is to be expected from what is known of Drosophila populations, those of other species, and evolutionary theory generally (WRIGHT 1977, *passim*).

There are two complications to the interpretation of the results from the present experiment. First, the population studied had been in the laboratory for some time, so that its genetic variability cannot be taken as representative of that of the natural population from which it was derived. Indeed, the population was maintained in the laboratory for so long that there seems little doubt that it had largely adapted to the culture conditions and was at, or close to, genetic equilibrium. But this presents no fundamental difficulty if the results are understood as pertaining only to what *may* occur in a large outbred population, albeit not one in the field.

Second, it has been assumed that linkage is of negligible effect in the present results. If the population studied possessed predominantly "congealed" or "highly structured" chromosomes due to substantial linkage disequilibrium and epistasis, then the genetic variance estimates would be of no validity, and the genetic correlations results could not be used to infer pleiotropy, as is usually done in the absence of inbreeding (FALCONER 1960, pp. 312–313). Fortunately, there seems to be little question that large, outbred Drosophila populations exhibit relatively little linkage disequilibrium (see MUKAI 1977). Therefore, there should be a reasonable correspondence between the estimated genetic parameters and the underlying pattern of genetic variability, subject to sampling error.

B. *The evolution of senescence*: It has been theoretically established that the intensity of natural selection on age-specific fitness components declines with age after the onset of reproduction (MEDAWAR 1952; WILLIAMS 1957; HAMILTON 1966; CHARLESWORTH and WILLIAMSON 1975; CHARLESWORTH 1980). This may give rise to senescence by one or both of two distinct evolutionary pathways. (1) Deleterious mutations that have effects only on later ages may accumulate because of their virtual neutrality (MEDAWAR 1952; EDNEY and GILL 1968). (2) Alternatively, alleles that have large deleterious effects at later ages may be favored by natural selection because of smaller beneficial effects at early ages (WILLIAMS 1957).

All other things being equal, the first of these theories implies an increase with age in the additive genetic variance of fitness components, because selection-mutation equilibrium frequencies for deleterious genes rise with age (CHARLESWORTH 1980, p. 218). However, it is at least conceivable that genes affecting late fecundity, for example, have smaller effects than those acting at earlier ages. If the magnitude of such effects fell no faster than the mean fecundity, then the transformation used in the analysis of the data (see above), which removed scale effects due to the mean, would have compensated for them in the case of the present experiment. Nonetheless, given carefully chosen assumptions about changes in the magnitude of allelic effects, calibrated so that the effects remain sufficient to depress mean fecundity to the extent observed, it might be possible to explain the absence of an increase in additive genetic variance without rejecting the mutation-accumulation theory.

While this sort of *post hoc* escape is possible for any scientific theory, it is generally not acceptable. Accordingly, the absence of any trend towards increased additive genetic variance for fecundity constitutes *prima facie* evidence against the mutation-accumulation theory of senescence.

On the other hand, if the negative additive genetic correlation values for early fecundity and lifespan are at least qualitatively correct, that alone would be sufficient to preclude the possibility that mutation accumulation is solely responsible for senescence in *Drosophila melanogaster*. If this is indeed the case, substantial indirect responses to selection on individual life-history characters should occur, with changes in early fecundity and lifespan proceeding in opposite directions. This possibility is tested in ROSE and CHARLESWORTH (1981).

The authors thank D. S. FALCONER, R. L. FRANKHAM, J. MAYNARD SMITH and J. H. SANG for discussions that aided the planning and interpretation of the experiments. J. F. CROW and J. J. RUTLEDGE made helpful comments on the manuscript.

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Corresponding editor: W. W. ANDERSON