Genet. Res., Camb. (1983), **42**, *pp.* 137–149
Printed in Great Britain

The number of loci affecting a quantitative trait in *Drosophila melanogaster* revealed by artificial selection

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(*Received 14 February 1983 and in revised form 18 July 1983*)

SUMMARY

Individual and within-full-sib family selection for low sternopleural bristle number was carried out for 17 generations, with six replicate lines for each selection method. Our results can be summarized as follows: (1) the response to selection was exhausted very quickly, (2) the additive variance of the selected lines declined rapidly, (3) the variation in response to selection decreased as selection progressed, (4) genetic differences among replicates at the selection limit were small, (5) individual selection resulted in a higher initial response than within-family selection, but similar limits were achieved with both procedures. These observations are consistent with the hypothesis that the pattern of response to selection is due to the segregation in the base population of only a few loci with large effects, at intermediate frequencies.

1. INTRODUCTION

Under the infinitesimal model of many genes of very small effect, with additive gene action and independent loci, the expected genetic gain per generation for individual selection is larger than that for within-full-sib family selection. This is always the case, unless there is a large component of variance due to environmental causes of resemblance among family members for the selected trait (Falconer, 1981). This prediction assumes that lines of infinite effective size starting from the same base population are selected by either method with the same intensity. These conditions imply that the phenotypic and genetic variances of the trait remain constant over generations.

Under the same genetic model but with finite population size, it has been shown by Dempflé (1975) that selection within full-sib families implies a relatively lower rate of decay of the genetic variance compared to individual selection. This more efficient use of variation may result in a higher selection limit than that reached by the former method. Furthermore, the effective population size of lines subjected to individual selection has been shown to be smaller than the actual number of parents (Robertson, 1961). This effect does not occur with selection within families, as this regime guarantees an equal representation of all families in all generations. Consequently, the genetic variance available for individual selection will be eroded

more rapidly and the selection limit achieved will then be smaller than that attained by selection within families.

However, these predictions may not hold for a trait whose genetic variation is controlled by a small number of loci of large effects, segregating at intermediate frequencies. Unless the population size and/or the intensity of selection are very small, both selection methods should now lead to the same limit, as the probability of fixation of the desirable allele at all loci is then nearly one. Young & Skavaril (1976) have used computer simulation to show that the presence of major genes at initially low frequencies may also reverse the predictions made from the infinitesimal model, particularly when the effective population size is small.

In the present experiment, individual and within-full-sib family selection have been carried out for low sternopleural bristle number in *Drosophila melanogaster*. The response and the limits attained by both selection methods were compared in order to provide practical evidence on the theoretical predictions detailed above.

2. MATERIAL AND METHODS

The Dahomey base population was founded in 1973 from an initial sample comprising about 1000 individuals, and has been subsequently maintained in a cage at 25 °C in the Institute of Animal Genetics (Edinburgh). In 1978 a cage was established and maintained at 25 °C in this laboratory, starting from a sample obtained from Professor Alan Robertson.

A sample of eggs was collected from the population cage and a total of 72 individual pair matings were made using the emerging adults. Selection for low bristle score on the two sternopleural plates was practised in twelve lines, each of them starting from six matings chosen at random from the 72 made. In each line, 10 males and 10 females from each of six full-sib families were scored every generation.

Individual selection was carried out in six replicate lines (denoted I_1 to I_6) by selecting the most extreme six males and six females from the 60 of each sex recorded. Selection within full-sib families was also carried out in six replicate lines (denoted F_1 to F_6) by selecting the most extreme male and female of each family. Thus, the total number of individuals scored per generation and the proportion selected (10%) were the same for each of the two selection methods. Selection was continued for 17 generations.

Within a line, matings were always made individually and at random, each family being kept in a separate vial at 25 °C. Spare matings were kept to replace unsuccessful ones. All lines were contemporaneous during the experiment.

The lines were examined cytologically at the end of the experiment and all of them were found homozygous for the standard order.

3. RESULTS

(i) *Base population*

The mean, variance, coefficients of asymmetry and kurtosis, and heritabilities, estimated both by regression of offspring on mid-parent and by realized heritability

in the first generation of selection, are shown in Table 1. Estimates of the same parameters from a different experiment (López-Fanjul & Domínguez, 1982) are also shown for comparison. The distribution of the trait is both slightly asymmetric and leptokurtic, the corresponding coefficients being significantly different from zero in both sets of data. The design used to estimate the regression coefficient

Table 1. *Parameters of the base population*

No. scored	Mean	Variance	Asymmetry	Kurtosis	Heritability ± S.E.	
					Estimated	Realized*
1440†	19·2	5·9	0·5 ± 0·07	0·3 ± 0·14	0·59 ± 0·04	0·47 ± 0·05
1600‡	18·8	6·4	0·6 ± 0·06	0·5 ± 0·12	0·61 ± 0·04	0·39 ± 0·03

* Realized heritability in the first generation of selection pooled over replicates ± empirical standard error.

† Present experiment.

‡ From López-Fanjul & Domínguez (1982).

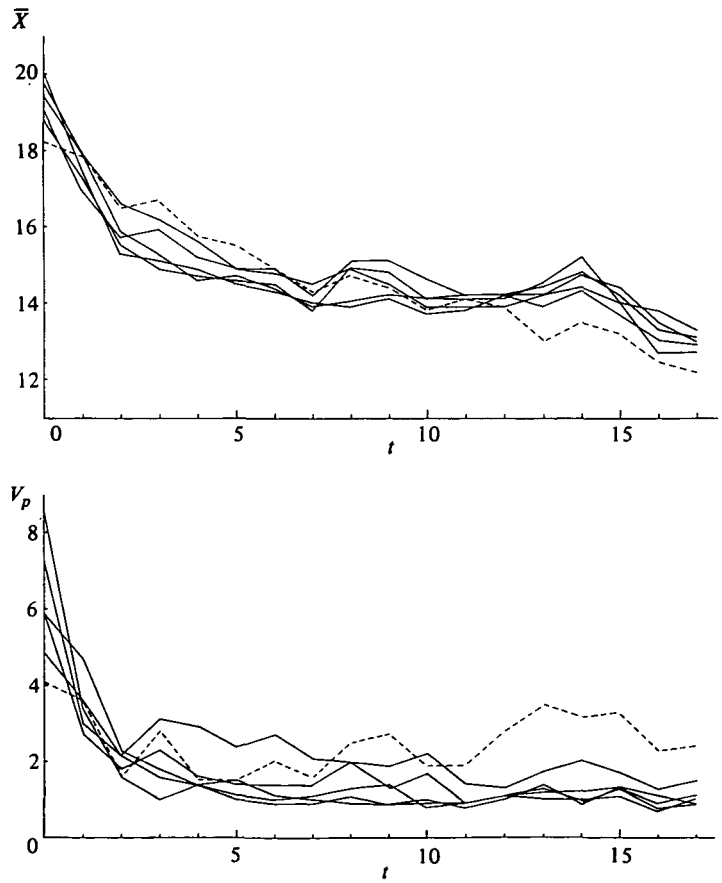

Fig. 1. Mean sternopleural bristle number ($\bar{X}$) and phenotypic variance (V_p) of the replicates under individual selection (the broken line corresponds to replicate I_2).

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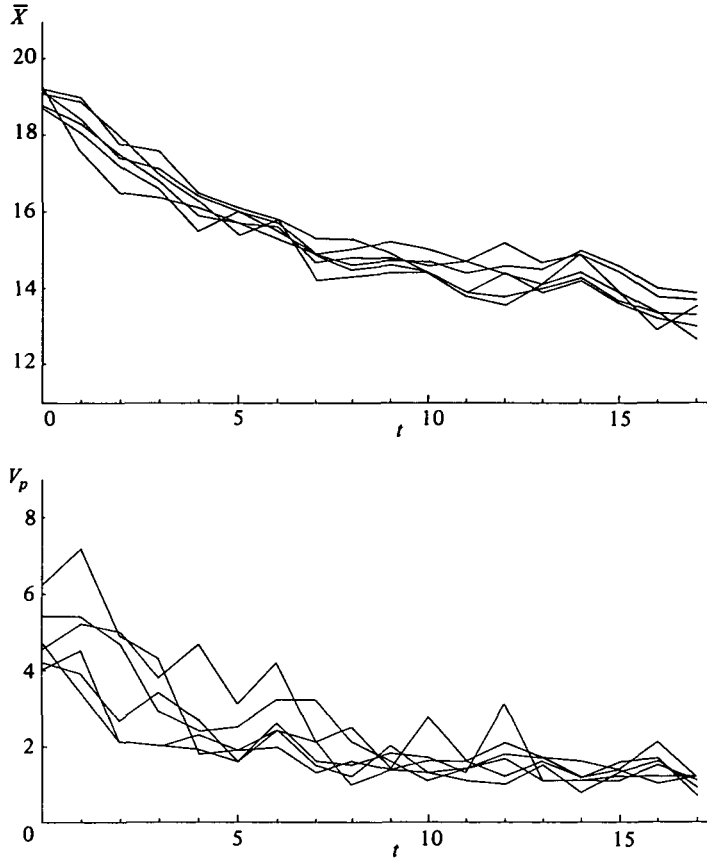

Fig. 2. Mean sternopleural bristle number ($\bar{X}$) and phenotypic variance (V_p) of the replicates under within-family selection.

included assortative mating (Reeve, 1961) and divergent selection of the parents (Hill, 1970) to reduce the standard error of the estimate. Realized heritabilities were significantly lower than base population estimates in the two experiments. No evidence was found of asymmetry of response, or of non-linearity of offspring–parent regression. No satisfactory explanation can be offered for this phenomenon, despite the apparent repeatability of the results.

(ii) *Evolution of means and variances*

The changes of the mean and the phenotypic variance of the selected replicates are shown in Figs. 1 and 2. The average changes over replicates for each selection method are shown in Fig. 3. All replicates selected by the same method behave in a similar manner, the only exception being replicate I_2, which will be considered separately (section vii).

The pattern of initial response was quite different for each selection method. Response to individual selection was very pronounced at the beginning, one-half of the final response being made in the first two generations. Conversely, selection

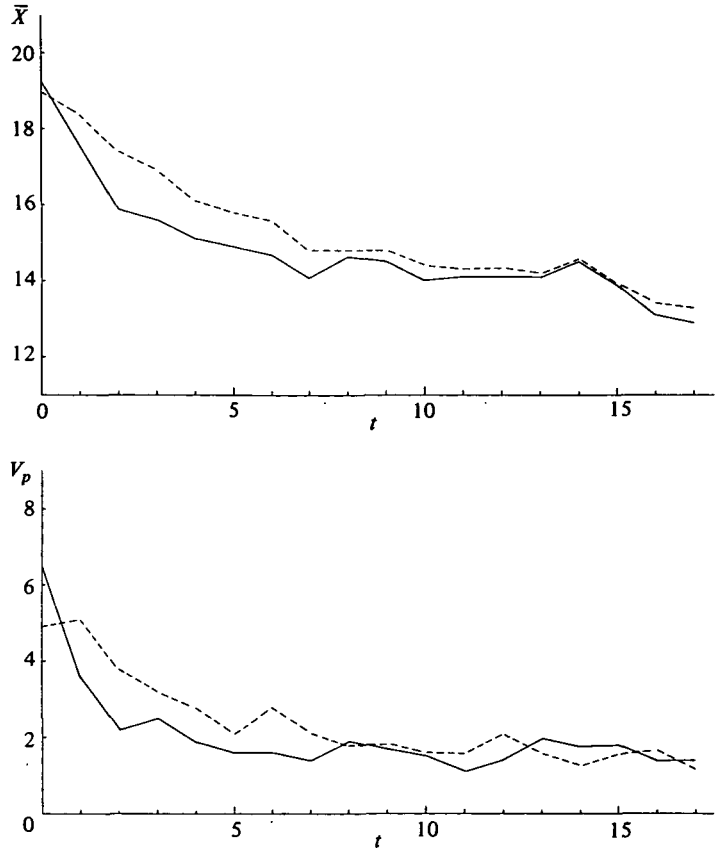

Fig. 3. Average response over replicates ($\bar{X}$) and within-replicate phenotypic variance (V_p) under individual (continuous line) and within-family selection (broken line).

within families resulted in a more gradual change of the mean. On the other hand, a similar plateau was reached by all replicates when selection was terminated at generation 17, and three-quarters of the final response had been attained at generation 7 by both selection methods. The original extreme lowest phenotype (14 bristles) was barely exceeded at generation 17 in both instances. The decrease of the mean observed during the last three generations of selection may be attributed to an unidentified environmental trend, as it was experienced by all lines after a former period of stability lasting for seven generations.

The phenotypic variance followed parallel changes to those observed for the mean. Individual selection resulted in a drastic decrease of the variance to one-third of its original value in the first two generations. On the other hand, the variance of the lines selected within families declined gradually. However, by generation 8 all lines had similar phenotypic variances of about one-quarter of the value in the base population, which remained stable to the end of the experiment.

Heritability estimates obtained from full-sib correlation analysis were calculated for each line and generation. This procedure seems justified given the additive nature of the trait, although there may be culture effects resulting in an upwards

bias, perhaps of the order of the residual variance obtained in later generations. These estimates had also been shown to be biased downwards as the choice of the parents is not random (Ponzoni & James, 1978), but in our case the bias involved is negligible (less than 2%). A pooled heritability was also calculated for each selection system and generation, and by multiplying it by the corresponding within-replicate phenotypic variance an estimate of the overall additive variance

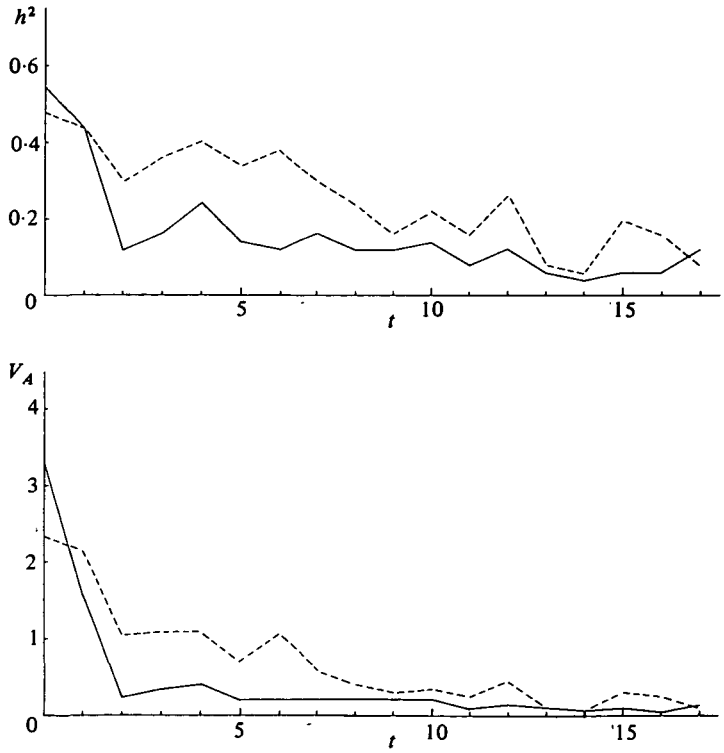

Fig. 4. Heritability (h^2) estimated from twice full-sib correlation and corresponding additive genetic variance (V_A) pooled over replicates under individual (continuous line) and within-family selection (broken line).

of the lines selected by each method was obtained. The evolution of these parameters is shown in Fig. 4. The pooled additive variance under individual selection was rapidly reduced to 7% of its original value within two generations and remained stable thereafter. Selection within families also resulted in a decline of the additive variance but in a more gradual way, reaching about 15% of the initial value by generation 8 and remaining practically unchanged afterwards. The observed changes of the additive variance paralleled those experienced by the mean, periods of no response being associated with exhaustion of the additive variance.

(iii) *Selection intensities*

Selection intensities were estimated per line and generation as the applied selection differential in phenotypic standard deviation units of the corresponding

generation. Their average values for each group of replicates remained constant during the whole experiment a 1·23 and 0·99 for individual and within-family selection, respectively. A designed intensity of selection was calculated from the mean of the initially selected parents in each generation prior to their partial substitution by spare individuals with the nearest scores. Their average values over replicates and generations were 1·47 and 1·23 for individual and within-family selection, respectively, and these values were considerably lower than expected (1·71 and 1·54, Becker, 1975).

Table 2. *Percentage of initially selected matings that failed per generation period and selection method*

	Generation period			
Selection method	0–3	4–7	8–11	12–16
Individual	18·1	47·2	43·1	33·3
Within families	20·8	30·4	34·8	39·8

Table 3. *Effective population size per generation period and selection method*

	Generation period			
Selection method	0–3	4–7	8–11	12–16
Individual	9·7	13·0	11·4	12·5
Within families	23·0	22·5	20·0	15·7

The difference between the expected and designed intensities of selection may be primarily attributed to departures from normality of the phenotypic distribution of the trait. This distribution, initially asymmetric, approached symmetry as selection progressed. On the other hand, the initial degree of leptokurtosis remained stable during the whole experiment.

The discrepancy between the designed and the observed intensities of selection can be mainly ascribed to fitness deterioration of the lines induced by the selective process. As the family size could always be kept at ten males and ten females in all lines, natural selection had to act mainly through unsuccessful matings which were replaced by spare flies. The percentage of originally selected matings that failed per generation period and selection method is shown in Table 2. Failures increased as selection continued, indicating a progressive decay of the fitness of the lines.

(iv) *Effective population sizes*

Effective population sizes were calculated by the 'percentage of genes' method (James, 1962*a*, *b*) for all lines and generations. Average values over replicates are shown in Table 3 for each selection method and generation period.

The number of families in lines selected individually could always be kept at the intended number of six. Nevertheless, a reduction of the effective size to 80 % of its expected value calculated from the number of parents (12) was observed during the first three generations, the period in which most of the response was

achieved. This is in close agreement with Robertson's (1961) prediction. From generation 4 to the end of the experiment the average effective size of the lines selected individually was practically the same as that expected without selection.

For the lines selected within families, expected (23) and observed effective sizes were very close to each other for the first seven generations. A decrease of the observed values compared to those expected was detected thereafter. This corresponds with the loss of families that occurred from generation 5. Notwithstanding the fact that up to seven spare matings per family were kept for substitution, the intended number of families could only be achieved in one replicate and was reduced to 2–3 families in four replicates by the end of the experiment.

Table 4. *Pooled realized heritability* (b) *and standard error estimated: empirically* ($\sigma_{\bar{b}}$), *from regression theory* (σ_b), *corrected (Hill, 1972)* (σ_c), *for each selection method*

Selection method	b	$\sigma_{\bar{b}}$	σ_b	σ_c
Individual	0·37	0·08	0·18	0·22
Within families	0·32	0·004	0·04	0·08

(v) *Short-term response to selection*

This analysis has been arbitrarily restricted to the first six generations of selection, although the response can be considered linear in terms of selection differentials during the first two or seven generations for individual or within-family selection, respectively.

Table 4 shows the realized heritabilities pooled over replicates (b) estimated by regression of the average cumulative response on the average cumulative selection differential. These heritabilities are 30–40 % lower than those estimated in the base population. Three different standard errors of the realized heritabilities are given: (a) from regression theory (σ_b), (b) corrected by the method proposed by Hill (1972) (σ_c), (c) empirical, from the realized heritabilities estimated in single replicates ($\sigma_{\bar{b}}$). For both selection methods $\sigma_{\bar{b}} < \sigma_b < \sigma_c$, which disagrees with the predictions made from the infinitesimal model (Hill, 1972). Similar results have been reported by López-Fanjul & Domínguez (1982), selecting for the same trait in the same population. Our results also show that the variability of response to selection decreased as selection progressed, contrary to the predictions made from the infinitesimal model, with or without selection (Hill, 1974, 1977).

(vi) *Selection from crosses between lines*

At generation 17 two-way crosses were made between replicates previously selected by the same method. Thus, two groups of three synthetic lines each were formed (denoted $SF_1 = F_1 \times F_2$, $SF_2 = F_3 \times F_4$, $SF_3 = F_5 \times F_6$; $SI_1 = I_1 \times I_3$, $SI_2 = I_4 \times I_5$, $SI_3 = I_4 \times I_6$). Line I_2 had been previously shown to be segregating for a lethal allele affecting bristles (section vii) and it was therefore excluded from the crosses. From each of the two parental lines the five males and five females with the lowest bristle counts from 25 males and 25 females scored were put together

in the same bottle, and the resulting synthetic population was mass selected for a further seven generations for low bristle number, with intensity 10/50 of each sex. The evolution of the mean of the selected synthetics is shown in Fig. 5. On the average, only a small significant response to selection was detected, amounting to 0·12 and 0·14 bristles per generation for the SI and SF groups of synthetic lines, respectively.

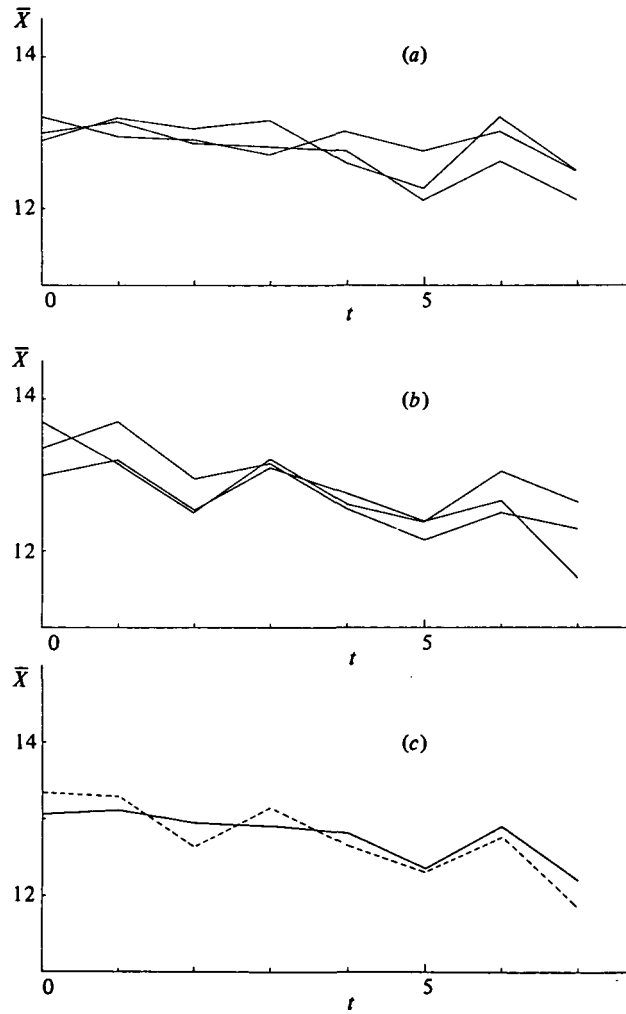

Fig. 5. Mean steropleural bristle number ($\bar{X}$) of synthetics formed by crossing lines previously selected: (*a*) individually (SI), (*b*) within families (SF), under individual selection. (*c*) Average for both groups of selected synthetic lines.

(vii) *Line* I_2

A delayed response to selection was observed in this line starting at generation 12 and it was accompanied by a threefold increase in variance that was maintained thereafter. This late response was associated with the presence of a letal allele H^{St}

https://doi.org/10.1017/S0016672300021601 Published online by Cambridge University Press

(Gallego, García-Dorado & López-Fanjul, 1982) at the Hairless locus (location 3–69·5, Lindsley & Grell, 1968). H^{St} heterozygotes can be easily distinguished from wild-type homozygotes as vein L5 does not reach the wing margin. In addition H^{St} heterozygotes show suppressions of ocellar, dorsocentral, scutellar and post-orbital bristles.

The phenotypic distributions of sternopleural bristle number for wild-type homozygotes and H^{St} heterozygotes do not overlap, the mean of the latter being 2·2 bristles lower. From generation 13 onwards all selected individuals in line I_2 were H^{St} heterozygotes. The presence of allele H^{St} can be tentatively traced back to generation 6. In this generation an individual scoring nine bristles – three bristles less than any other scored in this experiment up to that time – was selected and it happened to be a common ancestor of all individuals scored in the line at generation 9. Our results would therefore suggest that allele H^{St} was not initially present in the base population. Unfortunately, line I_2 was accidentally lost and the pertinent tests could not be performed.

4. DISCUSSION

Under the infinitesimal model, the relative efficiency of within-family compared to individual selection at the limit depends on the magnitude of the effective population size of the lines. A decline of the effective size with individual selection is expected (Robertson, 1961), resulting in a smaller variance exposed to selection. On the other hand, selection within families should result in a more efficient use of the variance than individual selection (Dempflé, 1975). These two causes, which would theoretically determine the long-term level of superiority of within-family selection, could only be shown to be operating in the short-term. Robertson's effect ceased after three generations, and the conditions required for the completion of Dempflé's effect were only met in the early generations. Gains by both selection methods practically stopped after seven generations and the final responses achieved were similar. These results suggest that the segregation of a small number of loci of large effects and at appreciable frequencies in the base population determined a high proportion of the genetic variation of the selected trait. Evidence in favour of this hypothesis is examined below.

Phenotypic variances declined strongly during the early generations of selection, attaining values of about one-third to one-quarter of that in the unselected base population. Although a scale effect can be shown to be involved it was not the only explanation, as reductions of the order of 30–40 % of the original variance were still found after logarithmic transformation of the data. On the other hand, the heritability estimated every generation by full-sib correlation analysis also declined rapidly to 7–15 % of its initial value. This drastic decrease was of similar magnitude on the logarithmic scale. A large reduction of the additive variance with selection was thus apparent, which can in principle be attributed to gene-frequency changes and to the build-up of negative linkage disequilibrium between the loci affecting bristle number, both caused by selection. Under the infinitesimal model with infinite population size, small reductions of about 10–20 % for both the phenotypic variance and the heritability are predicted (Bulmer, 1971). A larger decrease is

expected if a small number of loci at substantial frequencies, and consequently with a large proportionate effect, contribute significantly to the genetic variance (Sorensen & Hill, 1982). Further reduction can result from inbreeding, but this would be negligible and would not account for the sharp decline of the additive variance observed in the selected lines.

Several predictions follow from a model with a small number of genes. First, the response to selection will be exhausted very quickly (Robertson, 1960). This is in agreement with the half-life of the selection process being attained in two and four generations for individual and within-family selection, respectively. Secondly, the variation in response to selection will be small. Our results show that the between-replicate variance was smaller than predicted under the infinitesimal model with or without selection (Hill, 1977). Furthermore, the means of the replicates converged as selection progressed. Consequently, the empirical estimates of the standard errors of the realized heritabilities were smaller than their expectations under the infinitesimal model (Hill, 1972), as the predicted variation of the response to selection was larger than observed.

Our results are therefore in sharp contrast to most previously reported work. It is a common feature of selection experiments that replicate differentiation increases with time, which is interpreted as being caused by genetic drift acting on a trait determined by a large number of loci (Hill, 1974, 1977; Falconer, 1981). Previous mass-selection experiments for sternopleural bristle number exhibit this pattern (McPhee & Robertson, 1970; López-Fanjul & Hill, 1973; Madalena & Robertson, 1975). The final limits attained in these works were remarkably close to those found in the present experiment, although in the former cases they were reached in a more gradual manner as the between-replicate variation in those experiments was considerably larger. Compared to individual selection, mass selection may result in the effective population size of the lines being considerably smaller than expected from the number of selected parents. Therefore, drift effects will be more important than assumed, and will increase with time.

A model with a small number of genes of large effects will also imply that the probability of fixation of the favourable allele at each locus should be practically unity for a wide range of effective population sizes and selection intensities. Genetic differences among replicates at the selection limit should then be small. The means of the replicated lines selected by either method did not significantly differ from each other at the end of the experiment, suggesting their genetic similarity. This argument is strengthened as the synthetic populations formed by crossing replicates in pairs at the selection limit responded very little to selection. On the other hand, the limits attained by both methods are expected to be equal. This is also in agreement with our results. All these observations together indicate that the genetic variation of sternopleural bristle number in the Dahomey population of *D. melanogaster* is essentially due to segregation at a small number of loci. Robertson (1967, 1968) has also proposed this model in the Kaduna population based on different considerations.

Little can be said on the possible general value of the above model except that it is not contradicted by the scarce data available concerning the number of loci affecting quantitative traits. It is nevertheless suggestive that a trait such as body

weight in mice, previously thought to be controlled by perhaps a few hundred loci (Comstock, 1969), is now considered to be determined by a small number of loci, based also on the genetic similarity of selected replicates at the limit (Falconer, 1973).

This work was supported by a grant from Comisión Asesora de Investigación Científica y Técnica. We are indebted to Drs L. Dempflé, W. G. Hill and L. Silvela for helpful comments. We also wish to thank R. Díez for technical assistance.

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