MASS SELECTION FOR POST-WEANING GROWTH IN MICE[1]

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MEASUREMENT of population change resulting from selection has been one of the useful approaches in the study of quantitative inheritance (see, for example, MATHER and HARRISON 1949; MACARTHUR 1949; LERNER and DEMPSTER 1951; BELL, MOORE and WARREN 1955; FALCONER 1955; ROBERTSON 1955; CLAYTON, MORRIS, and ROBERTSON 1957; MARTIN and BELL 1960; FRASER and KINDRED 1960; THODAY and BOAM 1960; WOLFE 1961; and LENG 1962). Moreover, it is quite clear that there is more to be learned from good selection experiments. For general discussions of selection studies, see LERNER (1958) and FALCONER (1960).

The data to be reported in this paper were obtained in a study initiated in 1957. The most recent data included were collected in October, 1962, and reflect selection practiced during 17 successive generations. From the outset, long-term objectives have been: (1) To determine with all reasonable assurance, the maximum increase in average post-weaning growth that could be achieved by recurrent mass selection in the population to be described, and (2) To identify the cause (or causes) for ultimate cessation of response. Most specifically, the object in this connection is to provide unambiguous evidence for overdominance if there is any. This will be attempted through analysis of consequences of selection for combining ability with one or both of the foundation inbred lines. Such selection is to be initiated when it appears that response to mass selection has ceased. The critical phase of the experiment with respect to these objectives has not been reached.

This paper deals with effects of selection (through 17 generations) and various related issues. It should be noted that the experiment being discussed provided the information reported by RAHNEFELD, BOYLAN and COMSTOCK (1962).

DESCRIPTION OF EXPERIMENT

Two populations of mice have been employed in the main phase of the experiment; they will be referred to as the S and A lines.

The S line was formed from the reciprocal crosses of two unrelated inbred lines. Each of these lines traced to one pair of full-sibs resulting from 25 or more gen-

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erations of continuous full-sib mating, and both lines have been maintained. Random members of the two F_1's (reciprocals) were used equally in matings to produce an F_2 generation. This F_2 was designated generation zero of the S line. In view of the way this line was originated, it is reasonable to suggest (1) that its original genetic variation was less than would have been achieved in a population formed from a broader genetic base and (2) that linkage disequilibrium was initially high. On the other hand, the manner of origin provides useful information concerning the genetics of the line. First, original gene frequencies at most of the segregating loci must have been near to 0.5. Second, more than two alleles per locus must, at most, be restricted to a small fraction of all loci.

Selection for one trait, post-weaning growth, has been practiced in the S line beginning with selection of breeders from animals of Generation 1. The measure of growth was weight increase from 21 to 42 days of age in Generation 1 and from 18 to 42 days of age in all later generations. Mice were weaned at 21 days in Generation 1 and at 18 days thereafter. Selection has been based entirely on growth of the individual, no attention being paid to growth of relatives or to any trait other than growth. Animals selected have been those with greatest post-weaning growth subject to the restriction that no more than two (in a very few instances, three) male offspring of the same sire have been employed. This restriction was aimed at minimizing inbreeding in the line. Selected animals have been mated at random. Complete pedigree information has been recorded but inbreeding coefficients have not yet been computed.

The A line is a derivative of a standard laboratory inbred (BALB/c). It traces to one pair of full-sibs produced by over 60 generations of continuous full-sib mating. Sibbing is not now practiced in this line; it has been handled as a closed random breeding population since the beginning of the experiment. However, the inbreeding coefficient of the line is in excess of .99 so there is reason to assume that its genetic variance is low.

The A line has been employed throughout as a control population. Breeding animals have been chosen randomly except that males have usually been prechecked in trial matings for "effective fertility."

There has been no overlapping of generations in the S line. A-line animals have been raised in parallel with every generation in the S line but generations have overlapped. For convenience a generation in the S line and the contemporary A-line mice are referred to collectively as a cycle of the experiment. After some initial variation in the first five or six cycles, generation time in the A line was stabilized at one per 2½ generations in the S line. Only the first litters of A-line females have been used to provide "control" data, but age at parturition since the sixth cycle has averaged to be double that of S-line females.

Matings made each cycle have been as follows: (a) Each of 20 to 25 S males with three S females and two A females. All S × A litters have been raised to 42 days. Sometimes all S-line litters are raised and in other instances they have been reduced to two by each sire. (b) A-line matings. The goal has been to raise 40 or more litters on which to base "control" values for growth and other traits. Because of difficulty in obtaining conception in these matings the goal was not

achieved in all cycles. Numbers less than 40 were 17, 27, 11 and 22 in Cycles 1, 2, 4 and 5, respectively.

All matings in each cycle were made during the same (shortest possible) time interval to minimize environmental differentials in performance of the different kinds of mice. Crossbred mice from S × A matings were raised to obtain evidence concerning effect of selection in the S line on performance of crossbred offspring. This aspect of the experiment will be reported in another communication.

The main phase of the experiment has been supplemented in two ways. First, in Cycles 8–13, S-line offspring of parents selected for slow (instead of fast) growth were also raised. In each case, two or three litters from each of five to eight sires were involved. The purpose was to provide additional information on heritability of growth. The slow-growth parents were always selected from the same group as fast-growth parents, i.e. from the progeny of fast-growth parents. No offspring of slow-growth parents were ever used as breeding animals. Second, a new population was established from the same inbred lines used in forming the S line and by the exact procedure followed in the first instance. It is called the S′ line. At Generation zero its genetic constitution should have been nearly identical to that of the S line at generation zero. The S′ line has been managed the same in all respects as the S line. The purpose was to obtain, by comparison of the two lines, another measure of response to selection in the S line. The time lag between the two, with respect to selection practiced, was 15 generations. Comparisons to date have been of S_{16} with S'_1, S_{17} with S'_2 and S_{18} with S'_3.

Each litter has been maintained as a group in one container until 42 days of age. Water and a standard laboratory chow have been provided *ad libitum*. Animals were identified by a toe clipping system. The laboratory has an exhaust fan and temperature control. Management has been as uniform as possible for all mice in all cycles. No disease problems have so far been encountered.

Data recorded have been sex, 18- and 42-day weights, litter size at weaning and at 42 days, and feed consumption by litters in the post-weaning (18–42 day) period.

PROCEDURES IN STATISTICAL ANALYSIS

Growth of males and of females have been considered as potentially different manifestations of genotype. Justifications are (a) the sex difference with respect to endocrine environment and (b) actual differences in means and variances. Accordingly, growth data from males and females have been treated separately in all statistical analyses and attention has been directed to estimation of the genetic correlation between growth in the two sexes. This aspect of results will be treated elsewhere. It will suffice to note here that a comparatively high genetic correlation has so far been indicated. This is not surprising, but the situation may change as selection continues. The issue is touched on here to explain choices that have been made in treatment of data.

Intra-cycle analyses of variance provided estimates of the sire component of variance (paternal half-sib covariance), the litter and within litter components of variance and the total phenotypic variance. As usual four times the sire com-

ponent was taken as an estimate of additive genetic variance. Bias due to selection of sires will be considered later.

Parent-offspring regression was also used as a source of information concerning additive genetic variance. In line with the decision to treat male and female growth as separate traits, the regressions employed were of male offspring growth on growth of sires and female offspring growth on growth of dams. Estimated regression coefficients were multiplied by twice the observed phenotypic variance to obtain estimates of additive genetic variance.

Averages of estimates were frequently computed. In all cases, weighted averages were employed, the weights used being inversely proportional to the estimated variances of quantities averaged. Computation of these estimated variances will be described.

The nature of the intra-cycle analyses of variance is set out below.

Source of variation	*Degrees of freedom*	*Mean square*	*Mean square Expectation*
Sires	f_1	M_1	$W + k_2D + k_3S$
Litters in sires	f_2	M_2	$W + k_1D$
Within litters	f_3	M_3	W

W = within litter variance; D = dam (litter) component of variance; S = sire component of variance.

The mean square expectations listed assume independence in distribution of the "effects." The possibility that this assumption is not valid for these data because of intra-litter competition will be discussed later. Composition of the k's has been indicated by various authors but was set down again by RAHNEFELD *et al.* (1962). The estimate of S was

$$\hat{S} = \left[M_1 - \left(\frac{k_2}{k_1}\right) M_2 + \left(\frac{k_2 - k_1}{k_1}\right) M_3 \right] \Big/ k_3$$

and accordingly the variance of $\hat{S}$ was taken to be

$$V(\hat{S}) = \left[V(M_1) + \left(\frac{k_2}{k_1}\right)^2 V(M_2) + \left(\frac{k_2 - k_1}{k_1}\right)^2 V(M_3) \right] \Big/ k_3^2$$

where $V(M_i)$ is variance of M_i. Given normal distribution of "effects,"

$$V(M_i) = 2(E\,M_i)^2/f_i$$

where EM_i is expectation and f_i, the degrees of freedom for the ith mean square. It is common procedure to substitute observed mean squares for their expectations in computing estimates of $V(\hat{S})$. An unfortunate result is positive correlation between estimates of S and $V(\hat{S})$ so that when several values of $\hat{S}$ are obtained, the larger ones, on the average, are judged less reliable than proper, relative to smaller ones. To avoid this, the following procedure was followed in connection with estimates of S from data of single cycles. Analyses for all cycles were pooled to provide a single estimate of S based on all data. Then this was used in obtaining a numerical approximation to $E\,M_1$ for each of the individual cycles. More specifically, the estimates of W and D from the particular analysis, the k_2 and k_3

appropriate to that analysis and the overall estimate of S were substituted in $W + k_2D + k_3S$ to obtain the value to be substituted for EM_1 in computation of the estimate of $V(\hat{S})$.

The parent-offspring regression based estimate of additive genetic variance was $2bP$ where b symbolizes the appropriate parent-offspring regression coefficient and P is the estimate of total phenotypic variance. $4P^2V_b$ was used as variance. Here V_b symbolizes the estimated variance of the regression coefficient (b). This procedure treats P as a constant but this was judged satisfactory since, by comparison with b, P was extremely well estimated.

In parent-offspring regression computations, the unweighted mean of growth by all sons (or daughters) of a sire (or dam) was employed as the dependent variable and each parent-offspring pair of values was given equal weight. The decision to proceed in this way was made after investigation of gain in precision likely to be achieved by unequal weighting (see KEMPTHORNE and TANDON 1953). It appeared to us that "optimum" weighting would not be worth the extra labor in computation it would require.

RESULTS

Evidence concerning genetic stability of the A line: Satisfactory measurement of temporal variation in effect of environment in terms of performance of a control population rests on absence of genetic change in the control. The A line was highly inbred even at the beginning of the experiment but this does not guarantee absolute homozygosity. Moreover, significant accumulation of genetic variation via mutation during the course of the experiment must be considered as a possibility. It seemed desirable therefore to examine the A-line data for evidence of (1) additive genetic variance and (2) selection that could have caused genetic change in growth of the line if a nontrivial amount of genetic variation were present.

(1) *Additive genetic variance of post-weaning growth in the A line:* An estimate of the sire component of variance was computed from the data of each cycle. This was done to see if any indication of increase in additive genetic variance (during the course of the experiment) would be discovered. A time trend was not found so the several analyses were pooled to obtain a single set of variance component estimates for each sex. Degrees of freedom in the two pooled analyses were as follows:

	Degrees of freedom	
Source of variation	*Males*	*Females*
Sires	192	195
Litters in sires	800	878
Within litters	1360	2238

The difference between sexes reflects an unequal sex ratio which has been a consistent feature of the line. More females were weaned in each of the 18 cycles. The variance component estimates are listed in Table 1.

The pooled intra-cycle parent-offspring regression estimates were:

Regression	*Estimate*
Son on sire	—.048 ± .055
Daughter on dam	.042 ± .030

Estimates of additive genetic variance representing information from all data of the 18 cycles are listed in Table 2.

TABLE 1

Estimates of variance components (A line)

Component	Symbol	Estimates	
		Males	Females
Sire	S	.035 ± .028	—.027 ± .015
Dam (litter)	D	.64	.51
Within litter	W	.58	.52
Total	P	1.26	1.00

TABLE 2

Estimates of additive genetic variance (post-weaning growth in the A line)

Source of estimate	Estimates	
	Males	Females
Sire component of variance	.140 ± .112	—.108 ± .060
Parent-offspring regression	—.120 ± .138	.084 ± .059
Average	.037 ± .087	—.012 ± .042

Heritability estimates, computed using average values from Table 2 and estimates of P from Table 1, are .029 ± .069 and —.012 ± .042 for growth of males and females, respectively. In view of standard errors shown, these do not establish complete absence of additive genetic variance. On the other hand, they provide no positive evidence for genetic variation in the line.

Analogous estimates of heritability were made using data from only the last five cycles of the experiment. They were —.046 ± .090 and .053 ± .065 for males and females, respectively. Again the size of standard errors prevents conclusion that there was no additive genetic variance. More important, however, there was no indication that genetic variation in the A line had increased with time.

(2) *Selection in the A line:* The magnitude of selection differentials would have no bearing on genetic change in the A line if genetic variance is actually absent. However, since the latter cannot be assumed with absolute certainty, the actual differentials are of interest. The intent was to select A-line parents entirely at random. Differentials that occurred would therefore be entirely due to chance or to some unsuspected nonrandom mechanism.

The difference between mean post-weaning growth of animals selected (that actually left offspring) and the mean for all animals of the same sex was com-

puted each cycle. When this difference was averaged for all cycles the result was 0.11 g in the case of male parents and −.01 g in the case of female parents. Since the generation interval in the A line was no less than two cycles when the whole experiment and both sexes are considered, it appears safe to say that the average selection differential per cycle was virtually zero.

It should be added that for Cycles 7–12 the mean growth of selected A-line animals was also computed weighting by number of actual offspring. Values obtained were very nearly the same as the unweighted means.

Response to selection in the S population: Mean values of post-weaning growth in successive cycles are listed in Table 3. They are simple averages of means

TABLE 3

Average post-weaning growth (in grams) by cycles

Cycle	S population	A line	Difference
1	10.97	9.35	1.62
2	10.32	8.09	2.23
3	10.52	8.00	2.52
4	12.13	9.74	2.39
5	12.99	10.31	2.68
6	12.19	8.99	3.20
7	11.81	9.34	2.47
8	12.74	9.08	3.66
9	13.36	9.95	3.41
10	13.78	10.10	3.68
11	13.44	8.82	4.62
12	14.32	8.96	5.36
13	15.34	10.00	5.34
14	14.60	9.95	4.65
15	15.26	9.57	5.69
16	14.96	9.40	5.56
17	15.61	9.84	5.77
18	14.86	9.41	5.45

computed separately for males and females. As noted earlier, growth in Cycle 1 was measured from 21 to 42 days of age while in all other cycles the period was 18 to 42 days. In an effort to adjust, the actual mean values observed in Cycle 1 were increased by one seventh to obtain those listed in Table 3.

Variation in A line means is assumed to be nongenetic in origin. On this premise, the difference between the S- and A-line means provides an appropriate criterion of genetic change in the S-population mean. Inspection of these differences leaves no doubt of an increase during the course of the experiment. However, the actual sequence of values suggests nonlinearity. In particular, the successive values give the impression of accelerated response to selection in the interval from Cycle 8, 9, or 10 to Cycle 12 or 13 followed by reduced response thereafter. This was checked by a fifth-degree regression analysis using orthogonal polynomials (ANDERSON and HOUSEMAN 1942). The linear term, as expected, was

found highly significant while all of the nonlinear terms fell far short of statistical significance.

The linear regression of the S-A difference on cycle number (i.e. on S-population generation time) was chosen as the estimate of response to selection from these data. It was found to be .252 ± .020 grams. Multiplication by 17 gives 4.28 ± .34 as estimated total response to all the selection preceding Cycle 18.

An alternate estimate is provided by comparison of mean growth in the S and S′ populations. This comparison was available in Cycles 16, 17 and 18. Since the S′ population lagged behind the S population by 15 generations and since selection was practiced in S′ in the same way as in S, the difference in mean growth between them estimates response from 15 generations of selection. Means are listed below.

	Mean post-weaning growth (grams)		
Cycle	*S-population*	*S′-population*	*Difference*
16	14.96	10.55	4.41
17	15.61	10.87	4.74
18	14.86	11.03	3.83
Average	15.14	10.82	4.32

Adjusted from 15 to 17 generations, this estimate becomes 4.90 g, which is in very reasonable agreement with the 4.28 ± .34 arrived at by running comparison with the A line.

Total selection differentials for the 17 generations in the S population were 36.28 g for males and 16.14 g for females, the average being 26.21 g. Using this with the two estimates of total response, .187 and .163 ± .013 are obtained as estimates of realized heritability.

Additive genetic variance and heritability in the S population: Realized heritability (see preceding section) provides information concerning additive genetic variance. However, it may reflect factors other than the ratio of additive genetic to total variance. Independent estimates are required as part of the basis for deciding whether this was the case.

The increase in population mean that occurred during the experiment guarantees that there were also changes in gene frequencies. There can be little doubt that there was associated change in additive genetic variance, but there is no *a priori* basis for confident prediction that such change should have been large or trivial, positive or negative. First attention was given to checking whether a significant time trend could be discerned.

As a preliminary, the within litter and dam variance component estimates obtained from data of individual cycles were examined for time trends. Variation in each case appeared random with reference to time. Regressions (linear) on generation time were computed and found nonsignificant for both variances in both sexes. As a result overall estimates of phenotypic variance were employed in computing the parent-offspring regression based estimates of additive genetic variance for individual generations. These were 2.31 and 1.49 for males and females, respectively.

Next the two estimates (from the sire component of variance and from parent-

offspring regression) were averaged to get one estimate of additive genetic variance for each sex in each generation. As was to be expected, these were extremely variable. Stated differently, the data from any one generation were not sufficient to provide a good estimate. Regression analyses (both linear and quadratic) failed to establish significant time trends of any sort. These were weighted analyses in which the separate estimates of additive genetic variance received weight inversely proportional to the estimates of their sampling variances. It must be emphasized, however, that the evidence does not suffice to preclude the possibility that real change of biologically significant magnitude did in fact occur. This is well illustrated by the following condensations of the evidence. Linear regression coefficients (generation time being the independent variable and estimate of additive genetic variance the dependent variable) were .043 ± .036 and .010 ± .024 for male and female growth, respectively. Obviously, neither a positive nor a negative time trend is precluded. While these coefficients suggest that additive genetic variance increased from what it was at the outset, the evidence is very weak. Another view is provided when information is pooled for early, intermediate and late generations. The estimates obtained are listed in Table 4. They suggest an increase followed by a decrease. However, none of the period differences are statistically significant and no firm conclusions concerning change or lack of change over time are justified.

TABLE 4

Estimates of additive genetic variance by six-generation periods

Generations	Estimates for	
	Male	Females
1–6	.30 ± .31	.08 ± .24
7–12	.75 ± .26	.61 ± .20
13–18	.54 ± .34	.39 ± .18
Average	.56 ± .17	.39 ± .12

Using average estimates of additive genetic variance from Table 4 heritability estimates obtained for male and female growth are .243 ± .074 and .264 ± .078, respectively.

Further information is available from results of divergent selection practiced in Generations 7 to 12. However, separate estimates of heritability for male and female growth cannot be obtained. Let X and Y symbolize mean growth of parents and offspring, respectively, and let subscripts be used as follows: M to indicate males; F to indicate females; H to indicate selection for fast growth; and L to indicate selection for slow growth. Then, if

$$D_p = \tfrac{1}{2}\,[X_{MH} + X_{FH} - X_{ML} - X_{FL}], \text{ and}$$
$$D_o = \tfrac{1}{2}\,[Y_{MH} + Y_{FH} - Y_{ML} - Y_{FL}],$$

the ratio D_o/D_p is an estimate of the regression of offspring growth on mean growth of parents that has been used as an estimate of heritability. If heritability,

phenotypic variance and selection were all equal for the two sexes, the expectation of D_o/D_p would be $h^2[\frac{1}{2} + (r/2)]$ where h^2 is heritability and r is genetic correlation between the sexes. Previously recorded estimates indicate that h^2 is similar, if not the same, for males and females and the net impact of actual differences in selection and phenotypic variance would be very small. Thus it will suffice to consider D_o/D_p as an estimate of $h^2[\frac{1}{2} + (r/2)]$. The estimates are as follows:

Generation (parents)	D_o/D_p
7	.133
8	.182
9	.198
10	.254
11	.262
12	.288
Average	.220 ± .024

The standard error was estimated from variation among the six separate estimates and hence is based on only five degrees of freedom. The heritability estimate is very close to others obtained. Since this one pertains to the middle set of six generations, it indicates either (a) that the estimates of additive genetic variance listed in Table 4 for that period are too high or (b) that the genetic correlation between the sexes is considerably less than perfect.

Heterosis in the F_1 of foundation inbred lines: During the initial phase of the experiment when crosses were being made to establish the S population, data were collected for comparison of post-weaning growth in the foundation inbreds with growth in the reciprocal F_1 crosses of the two inbred lines. Four rather small crops of mice were raised in which representatives of both lines and of both F_1's were grown concurrently. The F_1 minus midparent difference in growth was estimated as follows for each crop. A mean for each sex in each of the four groups was computed. Averages were then taken of the two F_1 means and of the two line means. The difference between these two averages was taken as a measure of heterosis in the F_1. Finally the four differences were averaged weighting inversely to variances. These final estimates of the F_1 minus midparent difference were 2.20 ± .30 and 1.34 ± .27 g for males and females, respectively.

At the time the data were collected, mice were still being weaned at 21 days; hence these estimates are in terms of post-weaning growth between 21 and 42 days of age.

Reciprocal crosses of the S and S′ populations: These were grown in Cycles 16 and 17. The numbers of litters were as follows:

Cycle	$S\,♀ \times S'\,♂$	$S'\,♀ \times S\,♂$
16	36	32
17	39	38

The prime objective was to discover whether the increase in post-weaning growth of the S population was partly due to a change in maternal effect on post-weaning growth. If this were the case, growth of crossbreds should have been best when

the female parent was S. Another purpose was to determine the hybrid vigor, if any, exhibited in the cross. Average growth rates were as follows:

	Males		*Females*	
Cycle	$S♀ \times S'♂$	$S'♀ \times S♂$	$S♀ \times S'♂$	$S'♀ \times S♂$
16	14.34	14.30	11.47	11.23
17	14.31	14.93	11.54	11.78
Average	14.33	14.62	11.50	11.50

The advantage, if any, appears to lie with animals from S′ dams. However, there were two small biases working in that direction. In Cycle 16 the S′ × S cross was slightly favored by selection of parents and in both cycles the S′ × S litters were smaller on the average than S × S′ litters. A negative regression (−.12 g) of growth on litter size had been found using S-population data from Cycles 14–18. Using the difference in selection differentials multiplied by heritability to adjust for the difference in selection and the above regression estimate times the average litter size difference to adjust for litter size, adjusted means favor the S × S′ cross by .18 g and .47 g in the case of males and females, respectively. It seems safe to conclude that the fraction of change in post-weaning growth of the S population that should or could be attributed to change in maternal effect is small at most.

An appropriate measure of hybrid vigor in the cross is obtained by comparing the mean of growth averages for the two crosses with the mean of growth averages for the two populations. These comparisons are shown below.

	Males		*Females*	
Cycle	*Parent mean*	*Cross mean*	*Parent mean*	*Cross mean*
16	14.12	14.32	11.39	11.35
17	14.54	14.62	11.89	11.66
Average	14.33 g	14.47 g	11.64 g	11.52 g

The cross mean is one percent higher in the case of males but one percent lower in the case of females. Standard errors of the mean differences were not computed exactly but would have been no greater than .15 g and .12 g for males and females, respectively. Thus, in addition to the fact that no hybrid vigor was indicated, it can be stated that the chance that more than a very small amount would have been revealed by more extensive testing is a remote one.

Correlated response in litter size: RAHNEFELD *et al.* (1962) obtained, using data from 13 generations in the S population, an estimate (.15) of the genetic correlation between post-weaning growth and litter size. The estimate was not significantly different from zero but the regression on generation time of the difference in litter size between the S and A lines was estimated as .082 ± .035. From the two pieces of evidence it was concluded that a positive genetic correlation did exist. Further evidence is now available.

The litter size regression on time (over 18 generations) was .105 ± .033 and the difference in mean litter size of the S and A lines was larger in the 18th generation than in all but one of the preceding ones.

Further evidence is available from the difference in litter size between the S and S′ populations, data being available in Cycles 16–18. Observed means were as follows:

	Mean litter size		
Cycle	*S population*	*S′ population*	*Difference*
16	7.35	5.74	1.61
17	8.02	6.40	1.62
18	8.82	7.44	1.38
Average	8.06	6.04	1.54

Remembering that the time-lag between the two populations was 15 generations, division by 15 provides an estimate of change per generation of selection. The result is .103 which is almost identical with the regression estimate.

DISCUSSION

It appears safe to conclude that the control population, a highly inbred line, has provided in this instance a satisfactory measure of nongenetic variation in time. Estimates from the accumulated data indicate that heritability of growth in the control population may be very close to zero and is, at the very least, much smaller than in the population under selection. In addition, the total selection differential for growth in the control population was trivial compared to that in the selected population. The possibility of genetic change in mean growth resulting from natural selection and genetic correlation between reproduction and growth seems rather remote in view of the fact that the observed trend in litter size (as measured by regression on cycle time) was very small, $-.008 \pm .032$. There remains the possibility outlined by BRAY, BELL and KING (1962) that, given both (1) a time trend in environment and (2) genotype × environment interaction, a control population genetically different from the selected population will provide a faulty measure of the effect of the environment trend on the selected population. This, they noted, would be most likely in the case of an inbred line control because of the narrow and possibly unique range of genotypes involved. The close agreement between the two estimates of progress (one by comparison with the control, the other by comparison with a second population originated in the same way from the same inbred source materials as the first selected population) indicates little error due to genotype-environment interaction in this instance. It is worth remembering that, when environment is random relative to time, genotype × environment interaction variance may inflate the variance over time of the mean difference between two populations but will not bias the observed time trend of such a difference.

Biases in estimates of additive genetic (G) variance deserve some attention. The upward bias due to additive × additive types of genetic variance (COCKERHAM 1954, and KEMPTHORNE 1954) is now widely recognized. It is also well known that sire variance estimates may be biased upward by genotype-environment interaction when obtained *via* intra-time period analyses of variance (COMSTOCK 1955). On the other hand, it is intuitively obvious that there is a downward bias involved in the sire component procedure when applied using data from

animals having sires selected in one direction for the trait being studied. The selection practiced makes the sires genetically more uniform than random animals, hence the variance of their contributions to offspring phenotype, which is the variance estimated, will also be smaller.

Let g = breeding value of a sire, i.e. the additive genetic value of the sire's genotype, $s = g/2$ = effect of a sire on offspring phenotype, p = phenotype of a sire, S = variance of s for random males, P = phenotypic variance for random males, and G = additive genetic variance so that $h^2 = G/P$ = heritability. The effect, s, can be represented in terms of regression on p as follows

$$s = \beta_{sp}(p - \bar{p}) + x$$

where β_{sp} = regression of s on p, $\bar{p}$ = population mean of p, and x = deviation of s from regression on p. Then variance of s is

$$S = \beta_{sp}^2 P + V_x$$

when sires are unselected or

$$S' = \beta_{sp}^2 P' + V_x$$

when sires are selected and P' is phenotypic variance of the selected sires. Ignoring epistatic variance, $S = G/4$ and $\beta\, sp = h^2/2 = G/2P$. Hence

$$G/4 = (G^2/4P) + V_x$$
$$V_x = G(1 - h^2)/4$$
$$\text{and } S' = G[1 - h^2\,(1 - P'/P)]/4$$
$$= S\,[1 - h^2\,(1 - P'/P)].$$

In the growth data of this experiment $P = 2.31$ and $P' = .79$. Taking $h^2 = .25$, in line with estimates obtained, $h^2\,(1 - P'/P) = .16$. In view of the potential upward biases which in this case cannot be assessed, estimates were not adjusted for the downward bias from selection of sires. The subject has been discussed to emphasize that the sire component estimates of additive genetic variance may not be overestimates in this instance.

In discussion of procedure, it was noted that mean square expectations employed assume independence in distribution of effects. Since littermates were reared together in the same cage, the assumption may be invalid. Intra-litter competition seems likely. Its effect would be to create negative covariance among the within litter effects of littermates. The only impact of consequence is believed to be downward bias in estimates of the dam component of variance (D). If so, the issue is not a critical one.

The data provided two estimates of realized heritability for growth, .187 and .163. These are both smaller than the estimates, .243 ± .074 and .264 ± .078, of the heritability of male and female growth obtained from evidence other than response to selection. Two things should be noted. First, the estimates of realized heritability do not deviate by statistically significant amounts from the other estimates. Nevertheless they are smaller, and the difference may reflect a biological reality. Second, however, such reality would not of necessity imply any deficiency in ordinary quantitative genetic theory. Treating growth in males and females as distinct traits but accepting otherwise all the premises required for the prediction

that response equals selection differential times heritability it can be shown that the expectation of realized heritability as here computed is

$$\tfrac{1}{2}\left[\left(\frac{d_1}{d_1+d_2}\right)\left(1+r\sqrt{\frac{G_2}{G_1}}\right)h_1^2+\left(\frac{d_2}{d_1+d_2}\right)\left(1+r\sqrt{\frac{G_1}{G_2}}\right)h_2^2\right]$$

where h^2 = heritability, d = selection differential, G = additive genetic variance, r = genetic correlation between male and female growth, and subscripts distinguish males (1) from females (2).

Assuming $h_1^2 = h_2^2 = h^2$ since estimates were so nearly the same, the expression becomes

$$\frac{h^2}{2}\left[\left(\frac{d_1}{d_1+d_2}\right)\left(1+r\sqrt{G_2/G_1}\right)+\left(\frac{d_2}{d_1+d_2}\right)\left(1+r\sqrt{G_1/G_2}\right)\right].$$

Substituting actual values of d_1 and d_2 and our estimates of the ratios, G_1/G_2 and G_2/G_1, we obtain

$$h^2\ (.5 + .47r).$$

If one supposed that $r = .75$, the .187 estimate of realized heritability would convert to an estimate of h^2 equal to .22. In view of the lack of significant difference between estimates of realized heritability and other estimates of heritability, nothing would be gained by pressing the matter further. However, recognizing that genetic correlation between growth in the sexes is almost certainly not perfect, makes it clear that the two kinds of estimates are in better agreement than is at first suggested by the actual numbers. This is not to suggest a similar explanation for difference between realized and otherwise estimated heritability in other cases. When data for the two sexes are analyzed together to obtain one estimate of heritability, the impact of the genetic correlation is such that the answer obtained is more nearly appropriate to the ordinary prediction procedure.

The data reported provide only limited information concerning details of the genetic mechanism for growth in the material. However, the following observations deserve attention: (1) Hybrid vigor, measured as the difference between mid-parent mean growth (average of mean growth in the two parent inbreds) and average growth in the F_1 was about 2.0 g when the average for male and female growth is considered (adjusted for fact that the data were on 21 to 42 day weight). (2) Increase in growth from the F_2 level has been about 4.5 g in the S population. Assuming the F_2 mean would have been about midway between mid-parent and F_1 means, present mean growth must be about 3.5 g above the F_1 level. (3) Change in average growth over the 17 generations has been about six times the additive genetic standard deviation (in both males and females). (4) Concurrently additive genetic variance appears to have remained at much the same level.

The original hybrid vigor indicates that at some loci the allele favorable to growth was at least partially dominant. The reverse is not excluded for all loci, but loci where the plus allele was dominant in some degree must have been the more frequent. On the other hand, the fact that present performance is above the F_1 level by an amount greatly in excess of the original hybrid vigor indicates that

on the average dominance was far from complete. Following COMSTOCK and ROBINSON (1948, 1952), level of dominance will be symbolized as a, where

$a = 1$ indicates complete dominance of the plus allele,
$0 < a < 1$ indicates partial dominance of the plus allele,
$-1 < a < 0$ indicates partial dominance of the minus allele,

and so on. The results suggest that on the average a is quite small, probably closer to zero than to 0.5. Considering all loci, it is reasonable to visualize individual a-values distributed around this average. Whether this distribution is broad or narrow is of extreme interest but, unfortunately, cannot now be inferred. It may be very narrow, or so broad as to include a biologically significant number of both loci with overdominance and loci where the plus gene is almost completely recessive, or anything in between.

It was noted earlier that initial gene frequencies in the S line must have been in the neighborhood of 0.5 at almost all segregating loci. Additive genetic variance from loci segregating independently (or in linkage equilibrium), with a-values equal to or greater than zero, and not involved in epistasis, would decrease as frequencies of plus alleles increase from 0.5. Thus the fact that no obvious decrease in total additive genetic variance accompanied the substantial change in the population mean is of interest. A correct and complete explanation would involve inferences concerning number of gene pairs pertinent to growth, the distribution of a-values for these pairs, the pattern through generation time of linkage disequilibrium and the pattern of epistasis. The actual data support only one firm conclusion, that the genetic variation is not to be explained in terms of a small number of independently segregating genes.

There is no firm basis for predicting how long response to selection will continue. However, additive genetic variance appears to be as great as in the early generations and there is no indication that a situation in which artificial selection for growth would be counterbalanced by natural selection for fitness (LERNER 1954) is being approached. On the contrary, positive genetic correlation between growth and reproduction (as measured by litter size) is still indicated. The fact that most gene frequencies were originally near 0.5 has probably minimized loss of variation due to random drift (ROBERTSON 1960). Chance loss of alleles will probably be greater as time goes on. However, it appears reasonable to predict that selection will remain effective in the generations immediately ahead.

SUMMARY

Selection for post-weaning growth of mice, in a population derived from the cross of two highly inbred lines, was continued for 17 consecutive generations. Separate estimates of the change in mean growth that resulted from the whole of the selection were 4.90 and 4.28 grams. This increase was about six times the additive genetic standard deviation and about 43 percent of the original mean growth. Deviations of response estimates from linear regression on generation time were not statistically significant.

Additive genetic variance in growth was estimated separately for males and females. Linear regression of these estimates on generation time was positive, but nonsignificant for both sexes. Overall heritability estimates were .243 ± .074 and .264 ± .078 for males and females, respectively. Two-way selection in generations 7 to 12 provided another estimate, .220 with five percent confidence range .159–.281.

Gross realized heritability was .187 or .163 depending on the estimate of total genetic change employed. Neither figure deviates by an amount that is statistically significant from any estimate listed in the preceding paragraph. Unless perfect genetic correlation between growth in males and females is assumed, these realized heritabilities are most properly to be compared with the estimate from two-way selection (see DISCUSSION).

The F_1 cross of the progenitor inbred lines showed hybrid vigor, but final mean growth in the selected population was about 3.5 g greater than in the F_1. It thus appears that average dominance is (1) in the direction of alleles favorable to growth and (2) far from the complete dominance level.

Positive correlated response in litter size (0.1 mouse per litter per generation) was observed. Indefinite continuation is not anticipated, but the data to date do not suggest any decrease in the genetic correlation between growth and litter size that is indicated by the correlated response.

Supplementary work established that correlated response in maternal effect on post-weaning growth was absent or very small in magnitude.

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