

GROWTH AND REPRODUCTION IN MICE SELECTED FOR RAPID BODY WEIGHT GAIN

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SEVERAL investigators have reported the results of selecting for measures of growth rate or body size in mice (GOODALE 1938; MACARTHUR 1944, 1949; FALCONER 1953; RAHNEFELD *et al.* 1963; ROBERTS 1967). Direct response to selection has been substantial in each of these cases. Litter size has been shown to increase in several of the lines, the increase in the experiment reported by RAHNEFELD *et al.* (1966) being nearly three mice per litter. This suggested the possibility that litter size might be increased more rapidly by indirect selection, for body weight gain, than by direct selection, particularly since results of selection for litter size have indicated quite low heritability for this trait (FALCONER 1960; DALTON and BYWATER 1963). A line selected for rapid post-weaning gain was therefore included in an experiment in which the effects of selecting for litter size and its components were being studied. This permitted a direct comparison of the effects of these two kinds of selection, using the same base population and selecting contemporarily within the same laboratory.

Results from this project of selecting for litter size and for its components have been reported (BRADFORD 1968, 1969). The present paper reports the direct and correlated responses to selection in the rapid gain line and lines derived from it. The results suggest a complex relationship between body size and reproduction in the mouse, and provide additional evidence on the nature of the genetic control of litter size.

MATERIALS AND METHODS

The base population was a cross of four inbred lines (C57BL/6J, AKR/J, C3H/J, DBA/2J). Details of the formation of the stock and of the management of the colony are given in an earlier paper (BRADFORD 1968). The diet used was commercially prepared "White Diet" with specified minimum protein and fat contents of 24% and 7% respectively.

The strain selected for rapid post-weaning gain was designated line G. Eighteen males were each mated to two females each generation. Litters were counted the day of birth, and sexed at two days of age when litters of more than 10 were reduced to 10; there was no augmentation of litters with fewer than 10. Young were weaned, weighed, and ear notched at 21 days and caged, by sex, 4 to 7 per cage to 42 days of age when they were reweighed. Those individuals with the greatest weight increase between the two weighings were selected, regardless of litter, litter size or coat color genotype. Normally more than the necessary 18 males and 36 females were kept at six weeks, but only those numbers were mated except in the latest generations when numbers were increased slightly. Matings were made at approximately nine weeks of age, thus producing four generations per year. Males remained with the females for 7-10 days in the early part of

the experiment, and 14-17 days in the later generations. Beginning in generation 6, selected mice were weighed at mating. An unselected control (C), in which one daughter of each dam and one son of each sire were randomly selected each generation, was mated contemporarily throughout the experiment. There were 18 males and 36 females in each generation in this line also.

In both lines, generation 1 litters were from 4-way cross parents. The first selections were made from these litters. Results are presented through generation 24, i.e. for 23 generations of selection.

Females from generations 10, 13, 17 and 22 were sampled and autopsied at 16 days gestation to determine ovulation rate and embryo survival.

As indicated in the introduction, this experiment was part of a larger project in which the primary objective was to study means of effecting genetic change in litter size and its components. As will be shown, one of the results of selecting for gain in this experiment was a marked increase in phenotypic variation in litter size. This suggested that line G mice might be a useful population in which to select for litter size. Lines selected for large and for small litters were therefore initiated from generation 8 litters of line G, and selected for eight generations. For the initial selection, randomly sampled mice from within the larger litters were used to initiate the high line, designated GN⁺; mice similarly chosen from the smaller litters formed the base for the low line, GN⁻. All litters contributed to one or the other line. Selection to continue line G was carried out among those remaining. Corresponding lines, designated CN⁺ and CN⁻, were derived from line C one generation later, and were also selected for eight generations. All four lines as well as the parent lines were evaluated with respect to ovulation rate and embryo survival at the time the N⁺ and N⁻ lines were terminated.

RESULTS

1. *Change in gain and body weights:* Three- and 6-week weights for generations 1-24 of lines C and G are graphed in Figure 1, with Figure 2 depicting the

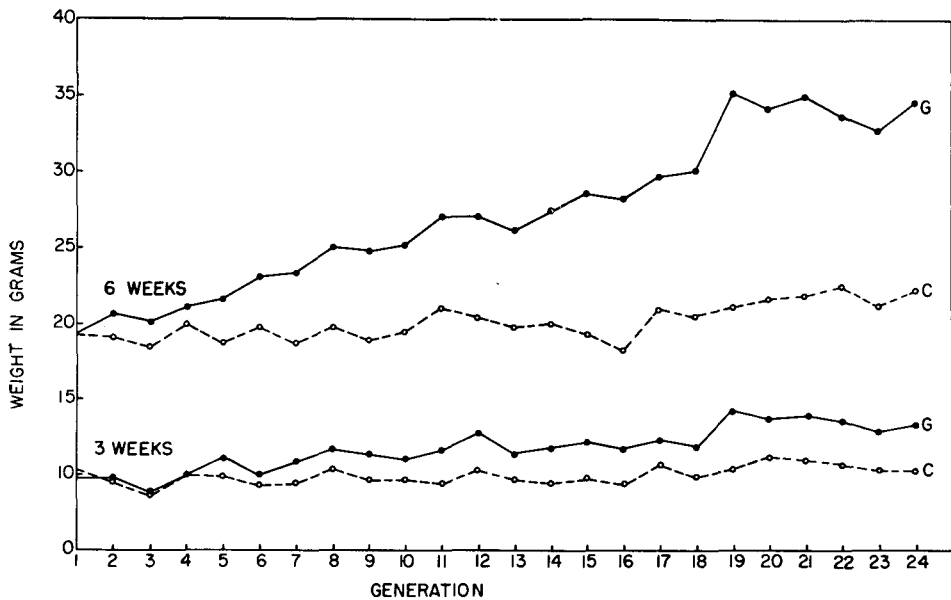


FIGURE 1.—3-week weight and 6-week weight of selected (G) and control (C) lines of mice. Average of male and female means.

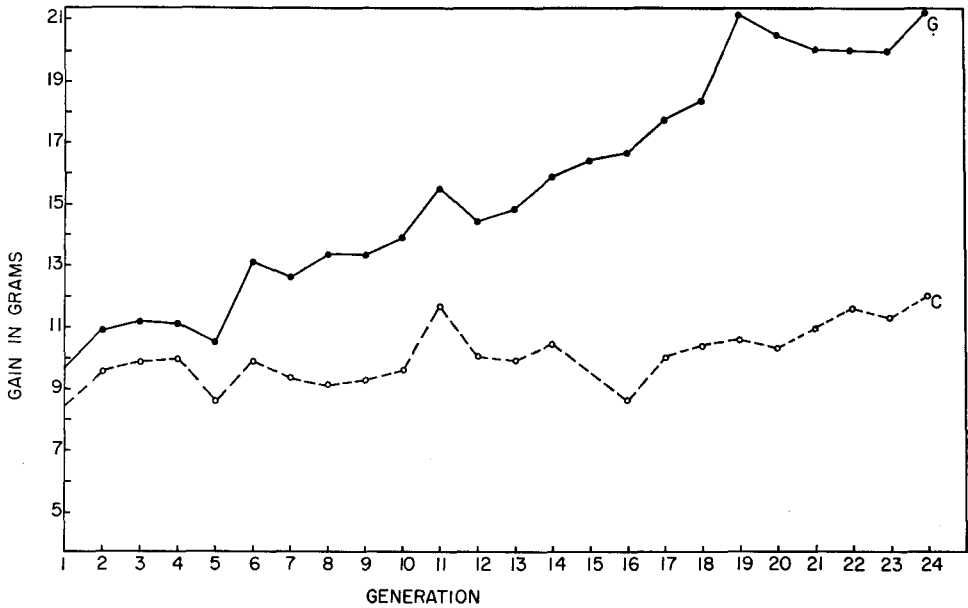


FIGURE 2.—Direct response to selection. Gain between 3 and 6 weeks of selected (G) and control (C) lines. Average of male and female means.

gains from 3–6 weeks, the values used for the graphs being unweighted means for males and females in all cases. The gain nearly doubled during this period, with the proportionate increase being very similar in the two sexes. The means in grams for males in generation 24 were 10.5 and 13.5 for 3-week weight; 24.6 and 37.8 for 6-week weight; and 14.1 and 24.3 for gain, for lines C and G, respectively. For females, the corresponding figures were 10.1 and 13.2; 20.2 and 31.3; and 10.0 and 18.1. As indicated in Figure 2, line G gain was in fact double that of line C in generations 19 and 20. In the succeeding generations, line G maintained the same level whereas line C increased slightly.

TABLE 1

Selection differentials for gain and for 3-week weight, 6-week weight and litter size

Line	Generations	Mean intended (I) and realized (R) selection differential per generation.							
		Gain* (grams)		3-week weight† (grams)		6-week weight† (grams)		Number born/litter†	
		I	R	I	R	I	R	I	R
G	1–8	2.43	2.43	–0.10	–0.09	2.32	2.32	0.65	0.69
	9–16	2.16	2.16	–0.07	–0.21	2.04	1.90	1.00	1.16
	17–23	2.24	1.96	0.26	0.21	2.14	1.80	0.90	0.45
C	1–8	–0.04	–0.09	0.28	0.26	0.01	0	0.26	0.30
	9–16	–0.09	–0.03	0.44	0.40	0.31	0.21	0.22	0.27
	17–23	0.08	0.21	0.22	0.19	0.16	0.13	0.27	0.16

* Primary selection differential.

† Secondary selection differentials.

Selection differentials for gain are shown for the two lines in Table 1, for three periods during the experiment. Both intended and realized (weighted) differentials are presented, the realized differentials being the differential for each individual weighted by the number of its progeny weaned. With one exception, the two differ little from each other, indicating in general no tendency for differential reproduction between more and less extreme individuals with respect to weight gain, in either the control or selected line. The one exception is the final period for line G, where realized differentials were slightly less than those intended. This suggests that the line may be reaching a point where natural selection is opposing the selection for increased gain. The small decrease in selection differential in line G for the second period compared to the first resulted from random sampling of individuals from this line for other experiments, prior to selection. Selection differential for line G was also lowered some in period 3 by the infertility encountered in generations 18–23 (Figure 4).

Secondary selection differentials measured for 3- and 6-week weights and number of young born per litter are included in Table 1. Selection differentials for gain are not exactly equal to the difference between those for 3- and 6-week weights because of a few death losses after 3 weeks, and in line C, normally only a random two or three of each sex were kept from each litter at weaning and weighed at six weeks.

It may be noted that while the selected individuals in line G were average or below average in 3-week weight, the line actually increased about 30% in this parameter. This suggests that the genetic correlation between weaning weight and post-weaning gain is fairly strongly positive, whereas the phenotypic correlation is zero or slightly negative. The latter is probably due in large measure to the influence of milk supply on preweaning growth, and the ability of animals whose pre-weaning growth is limited by milk supply to exhibit compensatory growth following weaning.

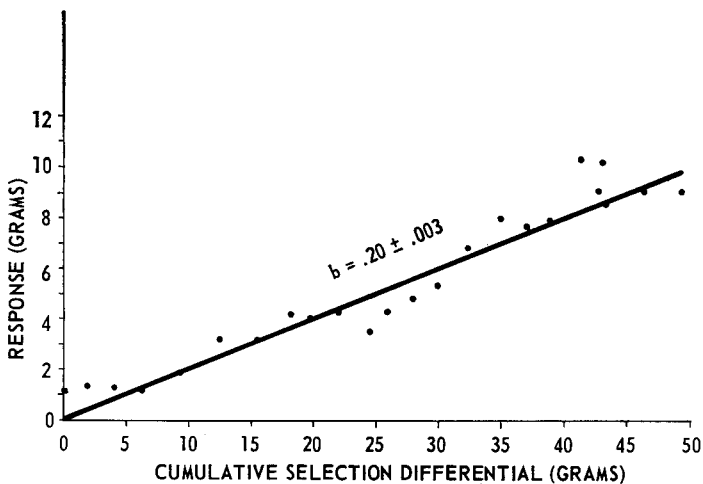


FIGURE 3.—Response to selection plotted against cumulative selection differential. Line G mean minus line C mean for each.

Other points to be noted from Table 1 are: 1. Small positive selection differentials for 3-week weight in line C, due most probably to greater post-weaning mortality in mice which were very small at weaning; 2. Substantial positive selection for litter size in line G. The latter is presumably due to two factors, one being the availability of more mice in larger litters, i.e. "automatic" selection for litter size (which was avoided insofar as possible, but not completely, in line C, by selecting replacements from each litter), and the second being compensatory growth mentioned above. Mice in large litters would obtain less milk prior to weaning, consequently would be smaller then but would tend to gain more after weaning and hence would have a higher probability of being selected in this line.

Selection response, measured as deviation of the line G mean from line C mean, is plotted against cumulative realized selection differential in Figure 3. The selection differentials used were also the difference between those for line G and line C, although the latter were very close to zero as shown in Table 1.

Regression of generation mean on cumulative selection differential for gain provides an estimate of realized heritability. The estimate from these data is 0.20 ± 0.003 . The estimate obtained after 19 generations was 0.24, the decline over the next four generations reflecting a possible cessation of response as mentioned earlier and indicated in Figure 1.

Mice in line G continued to gain more weight than those in line C after six weeks of age, as evidenced by weights taken at mating at approximately nine weeks of age. Direct comparison between the lines is not possible, since only selected mice were weighed at mating in line G, whereas line C mice were a random sample of the line. Males and females in line C typically gained 6–7 and 3–4 grams, respectively, between 6 and 9 weeks; corresponding values for the selected individuals in line G in the later generations were 12 and 8 grams, respectively, leading to weights at mating averaging about 50 grams for males and 40 for females. Following weaning of first litters, nonpregnant line G females typically weighed 50–60 grams, with some higher. Males of this age weighed 60–70 grams, with individuals recorded to 80 grams. The appearance, particularly of the males, was one of some obesity at these older ages. The mice were always quite active, however, and particularly at ages up to six weeks, appeared to be fully as active as the much smaller line C animals.

2. *Reproduction*: Proportion of females producing litters in lines C and G is shown in Figure 4. In line C, this measure of fertility was rarely less than 0.9, and in eight of the 24 generations it was 1.0. Line G also maintained a high fertility for the first 10 generations, and then was generally somewhat below line C for the next seven. From generations 18–20, it dropped precipitately, to 42% of females mated producing litters, and then by generation 24 had returned in a similar pattern to approximately the generation 10–17 level.

Concurrent with the decline in fertility beginning in generation 11, a delay in birth of the litters in line G was noted. Line C typically had 90% or more of the litters within four days of birth of the first, with a sharp peak on day 3; line G litters tended to spread over a two-week period, with no peak. This was due at least in part to less regular cycles, and a gestation period nearly a full day longer.

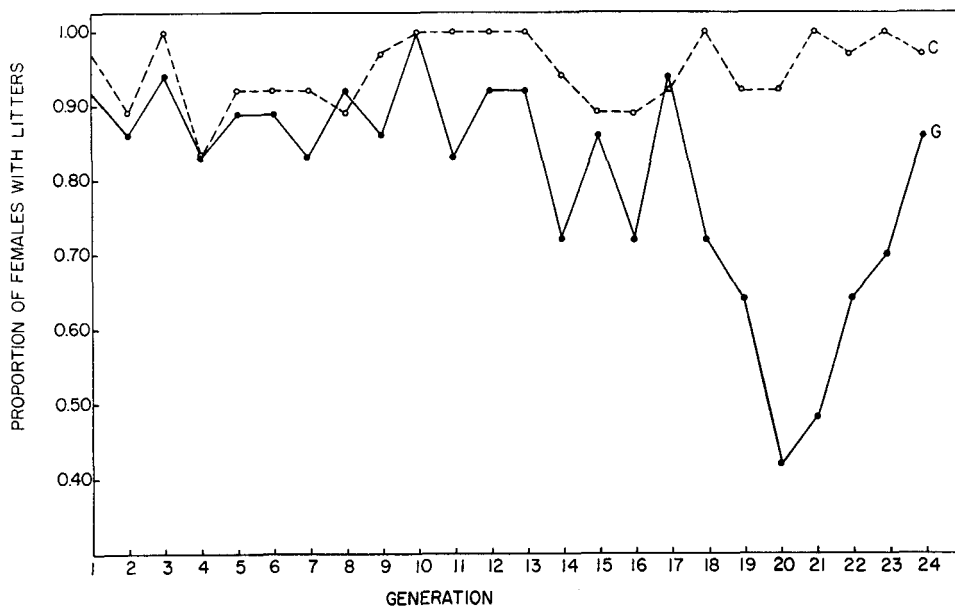


FIGURE 4.—Fertility of selected and control lines.

Mean total number of young born in first litters of line G and line C females is shown in Figure 5. In contrast to the results reported from several studies cited earlier, mean litter size in line G did not increase, although there is some

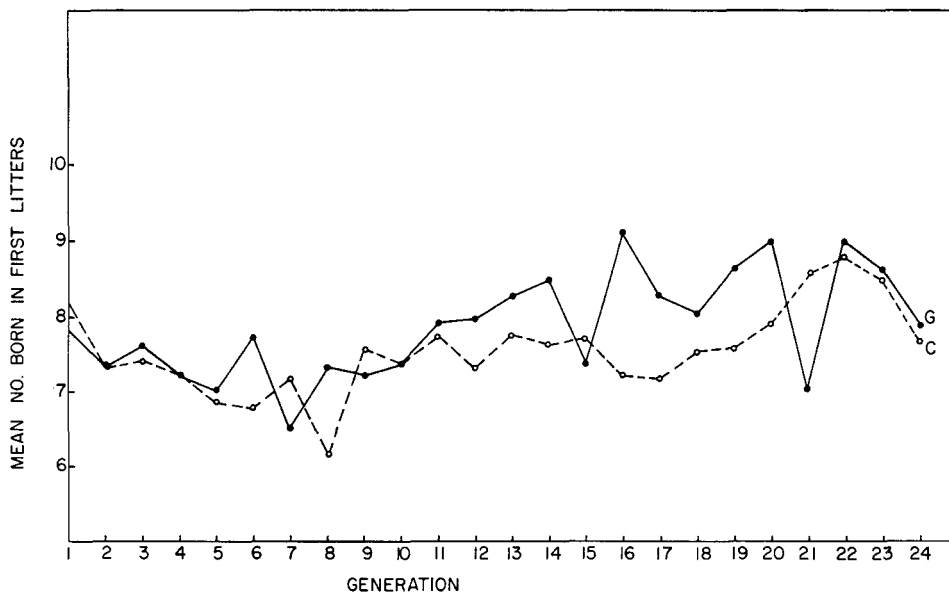


FIGURE 5.—Litter size of selected and control lines.

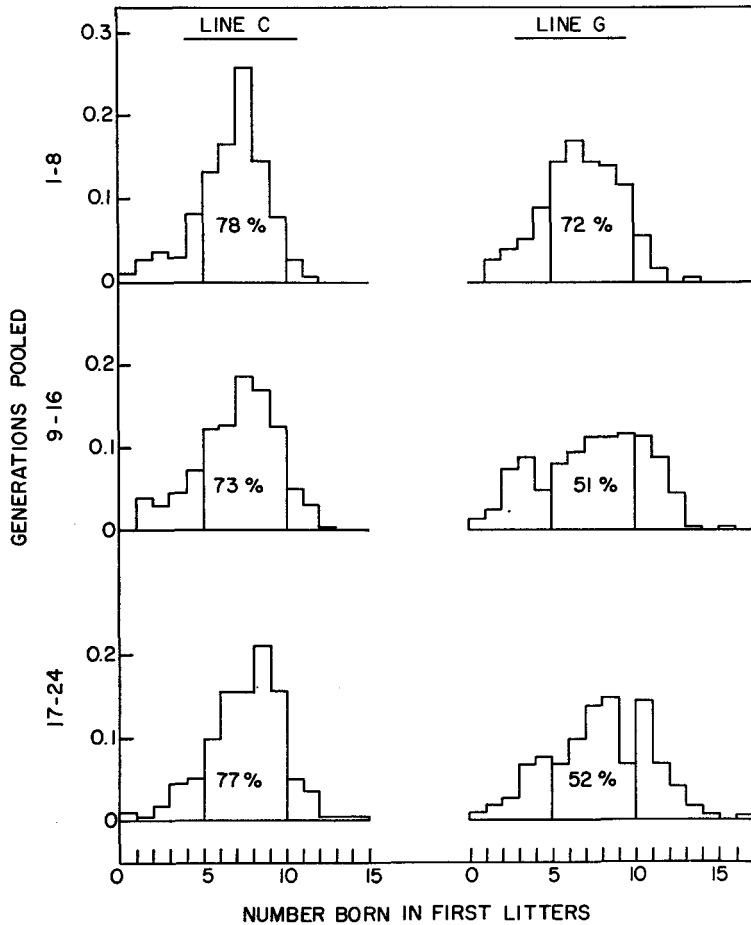


FIGURE 6.—Distribution of litter sizes of selected and control lines by 8-generation periods. Histograms based on 216–277 litters, each converted to a total frequency of 1.0.

evidence of increased inter-generation variability in the latter half of the experiment.

Although mean litter size did not increase, a marked increase in intra-generation variability in this parameter was noted early in the experiment, and persisted throughout. This is shown in Figure 6, in which the frequency distributions of litter sizes (converted to a total frequency of 1.0) for the two lines are depicted for the three 8-generation periods of the experiment. These distributions therefore include inter-generation as well as intra-generation variability. Line C had a mode of either 8 or 9, approximately three-fourths of the litters of sizes 6, 7, 8, 9 or 10, and only four litters of more than 12, out of a total of over 800 litters. Line G, in contrast, had no definite modal class, only about half the litters in the 6–10 range, and as many as 17. Within some generations the distribution of litter size was bimodal, with a relatively high frequency of 3 and 4 and of 11 and 12;

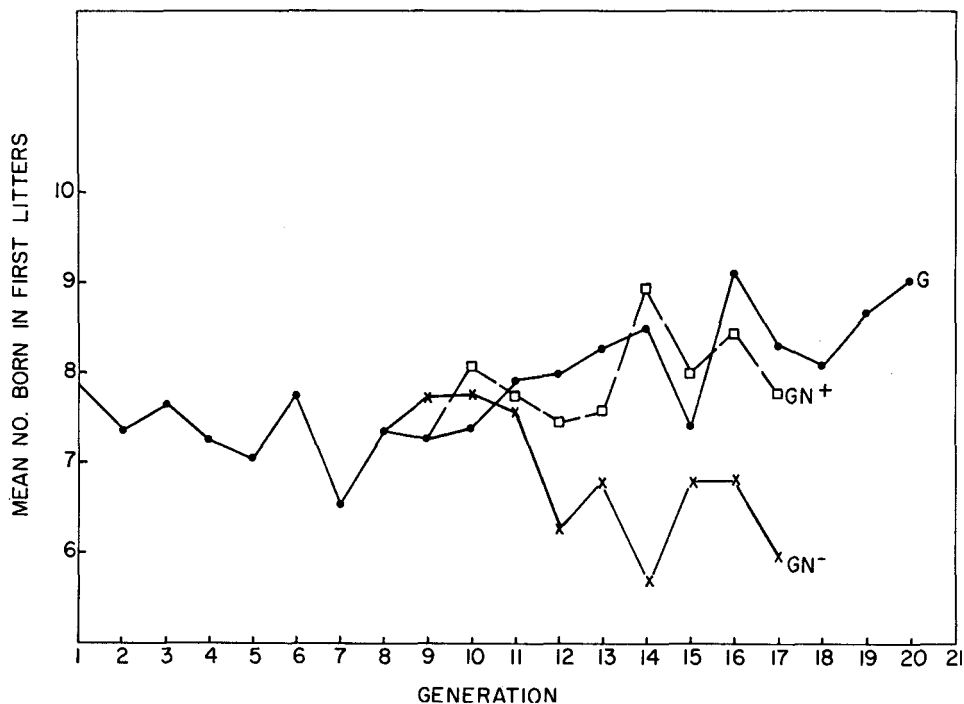


FIGURE 7.—Litter size of line G, selected continuously for 3–6 week gain, and lines derived from it selected for large (GN⁺) or small (GN⁻) litter size.

this tendency is suggested by the pooled data from generations 9–16 in Figure 6.

Sib mating pairs of mice from the smallest and largest litters in generations 7 and 8 provided no evidence for segregation of a recessive lethal gene, the litter size in matings of mice from the smallest litters being slightly superior on the average to that of matings from the larger litters.

The results of eight generations of selection for large and small litter size in lines derived from generation 8 of line G are depicted in Figure 7. Selection for small litter size was effective, but that for large litters was not. The same pattern was observed in corresponding lines derived from line C (Figure 8).

TABLE 2

Ovulation rate and pre- and postimplantation losses in selected (G) and control (C) lines, and lines derived from them selected for litter size

Line	Number of females	Corpora Lutea (CL)	Implants (I)	Mean number of		
				CL-I	Normal fetuses (N)	I-N
G	31	14.4 ± 0.51	11.4 ± 0.70	3.0 ± 0.39	8.5 ± 0.60	2.9 ± 0.43
GN ⁺	39	12.2 ± 0.39	9.6 ± 0.45	2.6 ± 0.49	8.0 ± 0.49	1.5 ± 0.30
GN ⁻	43	11.5 ± 0.44	7.8 ± 0.42	3.7 ± 0.45	5.8 ± 0.41	1.9 ± 0.29
C	25	10.6 ± 0.36	9.4 ± 0.35	1.2 ± 0.25	7.8 ± 0.44	1.7 ± 0.40
CN ⁺	29	10.7 ± 0.38	9.0 ± 0.48	1.7 ± 0.35	7.7 ± 0.51	1.3 ± 0.24
CN ⁻	30	10.7 ± 0.37	9.1 ± 0.32	1.6 ± 0.44	6.2 ± 0.50	2.9 ± 0.35

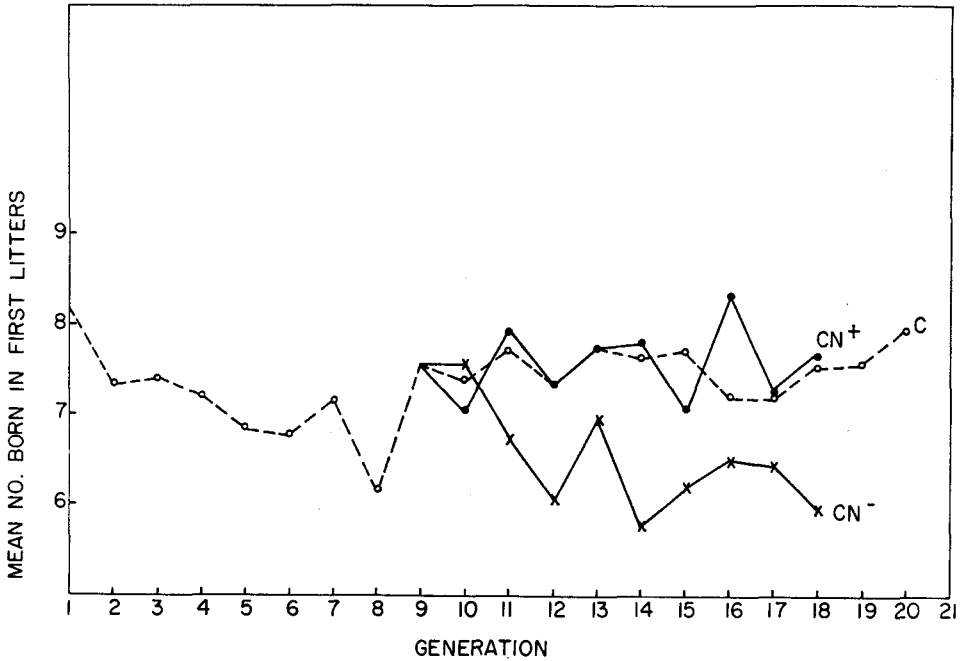


FIGURE 8.—Litter size of control line C, and lines derived from it selected for large (CN⁺) or small (CN⁻) litter size.

Mean values for the components of litter size in these lines measured on generation 8 females are summarized in Table 2. Values for contemporary line G and line C females are included. Ovulation rate declined, relative to line G, in both lines GN⁺ and GN⁻. Prenatal loss, particularly post-implantation, also declined in line GN⁺, leading to no net change in litter size. In line GN⁻ the response to selection was due mainly to the decrease in ovulation rate, total prenatal loss remaining about the same in absolute amount. These comparisons refer of course to line G at generation 17, not at generation 8 when the litter size lines were derived from it. However, the data recorded at generation 10 (and at 13, BRADFORD and NOTT, 1969) on components in this line, and the variability in litter size shown in Figure 6, indicates that the performance depicted for line G in Table 2 was characteristic of the line by generation 10 or before.

In lines CN⁺ and CN⁻, no changes in ovulation rate occurred. The response in line CN⁻ was due largely to an increase in post-implantation loss, in contrast to line GN⁻ where, as noted, the response was due to a decline in ovulation rate, and the proportionate increase in embryo loss was in the pre-implantation stage.

Weights of mice at mating are plotted for lines G, GN⁺, GN⁻ and C in Figure 9. The unweighted average of male and female means was used in each case. Weights at mating rather than six weeks were used because 6-week weights were not recorded for the N⁺ and N⁻ lines. The weights for line G are for individuals selected on their own 3-6 week gain, hence are higher than had they been taken on a random sample of the line. Those for lines GN⁺ and GN⁻ are also for

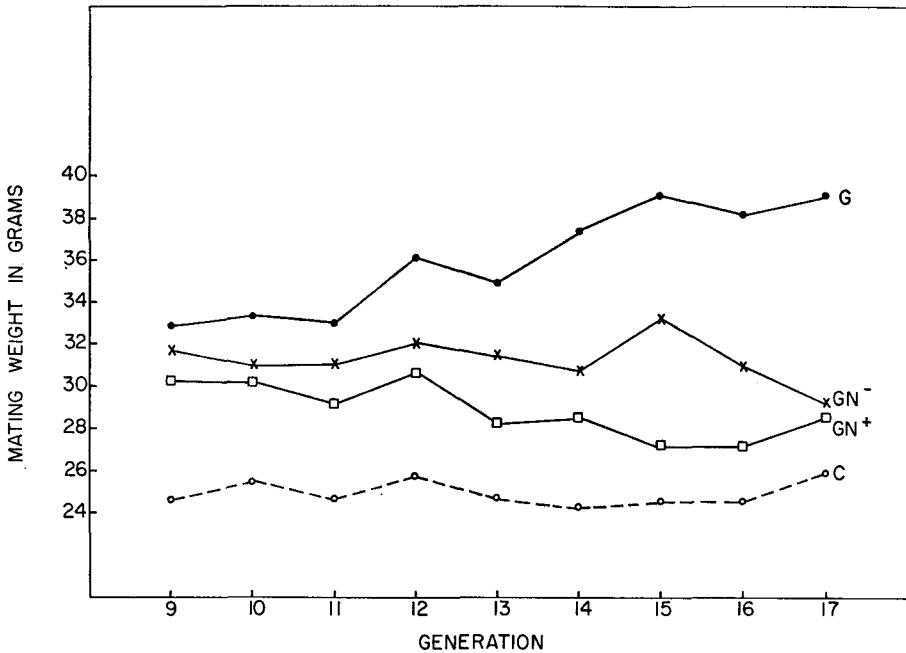


FIGURE 9.—Average body weight at mating (9 weeks) of mice from four lines (see Figures 5, 7). Average of male and female means.

selected individuals, i.e. raised in large and in small litters, respectively, except for the final point on the graph for each, which was based on the random sample of females autopsied to provide the results in Table 2, and their mates. From this sample, weight had decreased in both lines, the average deviation of the two from the control being 6.3 grams initially and 2.6 grams after eight generations of selection. Since this regression of more than half the distance to the control level occurred in both lines, it appears it is due to relaxation of selection for body weight rather than to genetic correlation between litter size and body weight.

The pair of lines derived from line C again showed a different pattern, line CN⁺ changing little relative to line C for all eight generations, with CN⁻ also changing little until generation 8, when a decrease in weight occurred.

DISCUSSION

The most notable result from this experiment is the absence of any correlated response in mean litter size following selection for rapid body weight gain. This was in spite of an accumulated secondary selection differential of approximately 18 for number born per litter. The experiment was carried out to test whether indirect selection for litter size, via selection for weight gain, was more effective than direct selection. Evidence for a positive correlation between the two traits comes from experiments reported by MACARTHUR (1949), FALCONER (1953), FOWLER and EDWARDS (1960), RAHNEFELD *et al.* (1966) and ELLIOTT, LEGATES

and ULBERG (1968). RAHNEFELD *et al.* (1966) obtained an estimate of 0.89 for the genetic correlation between litter size (weaned) and post-weaning gain. The results reported here clearly represent an exception to the general pattern.

Absence of a correlated response cannot be attributed to failure to obtain direct response to selection. The increase in gain and in 6-week weight in this experiment was at least as great as in any of the experiments cited (see also ROBERTS 1966) and was probably greater than in most when the comparison is made over the same number of generations.

Examination of the correlated response in litter size in some of the previous experiments reveals that although the direction of the correlated response has been consistent, the magnitude and pattern have not. The increase in litter size in MACARTHUR's large line all occurred in the first five generations; in FALCONER's, in the first six. FALCONER and KING (1953) suggest from this that the correlation between body size and fertility may depend on pleiotropic effects of relatively few genes. On the other hand, RAHNEFELD *et al.* (1966) reported a correlated response over 29 generations which did not differ significantly from linearity. It is true that in that experiment direct response has occurred over a much longer period of time than in any other such experiment and that the correlated increase in litter size ceased while direct response was still continuing (COMSTOCK, personal communication). It may also be noted that, although the correlated response over 29 generations did not depart from linearity, the data presented by RAHNEFELD *et al.* (1966) in fact suggest a leveling off at about generation 21.

In the present experiment, variance in litter size increased over the first nine generations of selection, and changed little thereafter. The pre-implantation loss also changed little after this time, and the rate of increase in ovulation rate was less than it had been early in the experiment. Direct response to selection for gain, however, continued undiminished at least through 19 generations of selection. A possible explanation, in physiological terms, is that "uterine capacity", either the physical capacity or the endocrine system necessary for support of pregnancy, is limiting at the outset or becomes limiting early in the development of a high body weight strain. Thus while ovulation rate can increase for some time, litter size cannot. This is consistent with LAND's (1970) conclusion that ovulation rate shows a more consistent genetic connection with body weight than does litter size.

It is obvious that the difference in correlated response in litter size between the present experiment and those reviewed is not due to ovulation rate but to pre-natal loss. Such losses could be due to fertilization failure, failure of embryos to implant, or death after implantation. Fertilization rate was estimated on 30 females each for lines C and G from segregation 14; the values were similar for the two lines. Thus this does not appear to be the source of the difference. Total pre-implantation loss in line G was above three per litter in generation 10 and in each generation measured thereafter, i.e., 13, 17 and 22. Post-implantation loss increased over this period, from 2.1 to 3.8. The change in the former therefore appears to be due to some change in the line which occurred early and thereafter

remained fairly constant; the latter is probably due to density dependent embryo mortality which is known to occur at this stage of pregnancy in mice (McLAREN and MICHIE, 1959). Why no increase in number of young carried to term occurred in this line whereas it has in others is not known. Lack of genetic variation in uterine capacity or adverse environmental factors appear to be ruled out, since contemporary lines from the same base population have mean litter sizes of about 11.5 and 12 (lines E and S1, BRADFORD, 1968, 1969 and unpublished).

Of the derived lines selected for litter size, the performance of line GN⁺ is of particular interest. Clearly, the large phenotypic variance in litter size in line G did not make it a good base population from which to select for large litter size. It is also obvious that the line behaved differently with respect to components than other lines selected for litter size. FALCONER (1960), BATEMAN (1966) and BRADFORD (1969) have each reported that response to selection for large litters occurred as a result of an increase in ovulation rate. In line GN⁺, however, ovulation rate declined. FOWLER and EDWARDS (1960), McLAREN (1962) and LAND (1970) have presented evidence for two components of ovulation rate—pituitary gonadotrophin level and ovarian sensitivity to such hormone(s). The former tends to show the stronger association with body weights. The results from line GN⁺, in which body weight was declining during the course of selection for litter size, suggest that where the pituitary output and ovarian sensitivity paths are operating counter to each other, the former exerts the overriding influence.

Selection for smaller litter size was about equally effective in lines GN⁻ and CN⁻, again indicating no particular advantage for selection purposes of the more variable base population. However, the components involved in the response were quite different in the two lines (Table 2). The decline in embryo survival in line CN⁻ is similar to that reported by FALCONER (1960).

Lines GN⁺ and GN⁻ maintained a larger standard deviation in litter size than lines CN⁺ and CN⁻ through most of the eight generations, characteristic of the parent line. However, as body weight declined in GN⁺ and GN⁻, variability in litter size also gradually declined, suggesting that the increased variance in litter size in line G was in fact associated with the increased body weight and not due, for example, to chance fixation of genes affecting variability in litter size in this strain.

The failure of line CN⁺ to respond to selection for larger litters, in either litter size or its components, was unexpected. A line (S1) selected for large litter size from the same base population but initiated eight generations earlier increased by 1.4 mice per litter (BRADFORD 1968) over a comparable period. The most obvious difference between line S1 and line CN⁺ is that selection in the former was initiated among progeny of a 4-way cross of highly inbred lines, and linkage disequilibrium would have been much greater then. However, other data from this laboratory, including the continued response of line S1, do not support this as an explanation of the difference.

It is concluded that the genetic correlation between body weight and ovulation rate holds generally in the mouse. Litter size will increase with an increase in

body weight provided ovulation rate is the component limiting litter size in the base population or, alternatively, uterine capacity increases as body weight and ovulation rate increases. However, LAND and FALCONER (1969) and BRADFORD (1969) have shown that genetic improvement in ovulation rate as a result of selection for this trait may not lead to an increase in litter size. The results of the present experiment indicate that some component of uterine capacity as defined earlier may be limiting even in large mice. Obesity of the large mice could contribute to an endocrine imbalance affecting support of pregnancy. Thus the genetic correlation between body weight and litter size is much less consistent than that between body weight and ovulation rate, and may be zero.

It is also concluded that the selection history of a strain can have a marked effect on the response to selection not only for the trait for which selection has previously been practiced, but for other traits as well. The pattern of response to selection for litter size which had been shown to hold in three earlier experiments with unselected base populations did not apply to a strain previously selected for large body weight.

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SUMMARY

Weight gain from 21–42 days in a line (G) derived from a 4-way cross stock of mice was nearly doubled by 23 generations of selection for this trait. Realized heritability was 0.20 ± 0.003 . Proportion of fertile matings declined in the later generations. Mean litter size did not change, but variability in litter size increased markedly due to an increase in ovulation rate, and an increase in prenatal loss which affected some females more than others. Selection for large litter size in a line (GN⁺) derived from line G after seven generations of selection was ineffective in changing the mean, but did affect the components, ovulation rate and prenatal loss both declining. This is in contrast to the usual result of selecting for large litter size, which is an increase in ovulation rate with little change in prenatal survival. Selection for low litter size in a corresponding line (GN⁻) was effective, due primarily to a decrease in ovulation rate. Body weight declined in both lines GN⁺ and GN⁻ when selection for gain was replaced by selection for litter size. It is concluded that a positive genetic correlation between body weight and ovulation rate holds generally in this species, but that prenatal loss is not predictably associated with body weight. Consequently, the genetic correlation between body weight and litter size may be positive, as reported for several experiments, or near zero, as found in this case.

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