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Direct and Correlated Responses to Selection for Increased Postweaning Gain in Mice[1]

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Summary. Mass selection for increased body weight gain from 21 to 42 days of age was practiced for 12 generations in four replicate lines of ICR-albino mice. Response to selection averaged 0.56 ± 0.03 g. per generation. This response represented an increase of 7.0 genetic standard deviation units and 3.4 phenotypic standard deviation units in 12 generations. The realized heritability pooled over the four replicates was 0.24 ± 0.02. Sizable positive correlated responses were found for 42 and 56-day weight and gain from 42 to 56 days. Much smaller positive correlated responses were noted for 12-day litter weight and 12-day individual weight. Neither litter size nor weaning weight were significantly altered by selection for increased postweaning gain. Reproductive efficiency measured as percent fertile matings declined significantly in the selected lines.

Rahnefeld *et al.* (1963) suggested that early postweaning body weight gain may serve as a more useful criterion for the study of selection for growth in mice than six week body weight since it seemed to be fairly independent of maternal influences, was moderately heritable and could be accurately and easily measured. Successful selection experiments utilizing either mature weight or postweaning gain have been reported (MacArthur, 1949; Falconer, 1953; Rahnefeld *et al.* 1963; Roberts, 1966, and Bradford, 1971). While the results of direct response to selection have generally been consistent among these reports, correlated responses in other growth traits and in reproductive and maternal traits have varied. Additionally, these experiments have suffered variously from lack of adequate genetic and environmental control, small population size and subsequent rapid increases in inbreeding or from linkage disequilibrium resulting from crossing inbred lines immediately prior to the initiation of the experiment.

The purposes of this study were: 1) to assess the relative rate of response to selection for increased postweaning gain among replicated lines of laboratory mice; and 2) to examine genetic changes in other growth, reproductive and maternal traits associated with response to selection for the primary trait.

Experimental Procedure

Laboratory Procedures. The foundation population (ICR-Albino) was obtained from a large, random mating colony at the Institute for Cancer Research, Philadelphia. After one generation of random mating to allow for acclimation to this laboratory and to expand the original base population of 100 females and 50 males, individuals were randomly divided into six lines. Each line consisted of 30 paired matings each generation. Mass selection was practiced for increased body weight gain from 21 to 42 days of age in four replicate lines (S11, S12, S13, and S14), while two replicate lines (C01 and C02) were maintained as unselected controls. Generations were contemporary in all six lines throughout the 12 generations of selection reported in this paper. All animals were randomly mated in generation zero, and selection was practiced for the first time in the selected lines in generation one.

Matings were made when dams were eight to ten weeks of age. Selected individuals were mated at random with the exception that no full-sib or first cousin matings occurred. Males were in the mating cages for 16 days, after which females in individual cages were checked twice daily for litters. Only first parity litters were used. Number of live young born (litter size) was recorded at birth and the litters were standardized to eight (four males and four females) at five days of age. Litters of less than eight were augmented with foster mice which were subsequently discarded at weaning.

At 12 days of age the young were permanently identified by toe clipping and both the total litter weight (eight mice) and the weight of each individual was recorded. The young were weighed individually and weaned at 21 days of age with four randomly allotted animals of like sex placed together in polypropylene cages. Individual body weight was also recorded at 42 and 56 days of age. All weights were recorded to the nearest tenth of a gram.

The mice were fed Old Guilford breeder pellets during mating and lactation and were fed Purina Laboratory Chow during the postweaning growth phase. The laboratory was maintained at approximately 22 °C with 12 hours of artificial illumination and 12 hours of darkness each day.

Statistical Procedures. Both expected and realized selection differentials were calculated. Expected selection differential was calculated for each line as the difference between the total line mean and the mean of those selected to be parents within a generation. The realized selection differential was the mean difference between the total line mean and the mean of those selected pairs which actually produced a litter. Realized heritability was calculated as the deviation of selected line mean from

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Table 1. *Means (g), Standard Deviations, and Regressions of Means on Generations Number for Gain from 21 to 42 Days* †

Gen	C01	C02	S11	S12	S13	S14
0	13.3 ± 3.2	14.6 ± 3.2	13.8 ± 3.3	13.5 ± 3.7	13.6 ± 3.6	13.1 ± 3.6
1	14.8 ± 6.6	15.2 ± 7.1	13.8 ± 6.6	13.4 ± 6.1	14.3 ± 6.3	13.7 ± 6.2
2	15.2 ± 3.7	14.6 ± 4.0	14.9 ± 3.9	15.0 ± 3.9	16.2 ± 3.8	15.6 ± 3.8
3	14.2 ± 5.6	14.2 ± 3.9	15.4 ± 3.7	15.5 ± 4.0	16.6 ± 3.9	15.2 ± 4.1
4	16.4 ± 4.3	15.9 ± 4.0	18.7 ± 3.8	18.3 ± 4.4	18.6 ± 4.9	18.3 ± 4.2
5	16.0 ± 3.8	15.7 ± 4.1	20.5 ± 4.6	17.6 ± 4.3	20.6 ± 4.4	18.5 ± 4.9
6	15.6 ± 4.0	14.8 ± 3.5	18.5 ± 4.1	17.4 ± 4.0	18.2 ± 3.7	17.9 ± 4.3
7	15.1 ± 3.4	14.7 ± 3.4	18.5 ± 4.2	17.8 ± 4.3	18.6 ± 3.7	18.5 ± 3.7
8	14.4 ± 3.2	14.3 ± 2.8	17.2 ± 2.6	16.7 ± 3.2	17.0 ± 3.2	16.9 ± 3.2
9	17.1 ± 3.7	16.6 ± 3.6	23.1 ± 4.0	21.1 ± 3.9	21.5 ± 4.2	21.9 ± 4.5
10	15.8 ± 3.8	15.1 ± 3.5	21.6 ± 4.1	20.5 ± 3.7	21.3 ± 4.0	20.5 ± 4.3
11	15.2 ± 3.0	15.2 ± 3.2	21.1 ± 3.6	19.5 ± 3.5	20.8 ± 3.5	20.4 ± 3.5
12	14.9 ± 3.5	15.5 ± 3.1	22.1 ± 3.6	21.5 ± 3.6	22.6 ± 3.5	20.6 ± 4.2
Regression coefficients	0.10 ± .07	0.09 ± .06	0.72 ± .12**	0.63 ± .09**	0.64 ± .10**	0.63 ± .10**

** Statistically significant ($P < 0.01$).

† Standard deviation not corrected for sex differences.

the control regressed on the accumulated selection differential (Falconer, 1960). Direct response to selection was measured as the regression of the deviation of selection line generation mean from control line generation mean on generation number. Correlated responses were measured in the same manner. Homogeneity of response (regression) across replicate lines was determined by methods outlined by Steel and Torrie (1960).

Results and Discussion

Response to Selection. Generation means, standard deviations and regressions of generation mean on generation number are presented in Table 1. Trends in the replicated control lines were strikingly similar. The small positive regressions of gain on generation number were virtually identical for the control lines and were not significant. Lack of differences between the lines in either the trends or the fluctuation about the trends suggested that either line would have served as an adequate control. Trends in the selected lines in Table 1 were similar and were significantly positive, with an average increase of about 0.65 gram per line per generation in 21 to 42 days gain. Although selection for increased body weight gain might be expected to increase the phenotypic variance as a consequence of the correlation between the mean and the variance (Falconer, 1960), the standard deviations in Table 1 showed little tendency to change appreciably.

Response to selection for increased body weight gain from 21 to 42 days is depicted in Fig. 1 and 2 as deviations from the unweighted mean of the two control lines. Except for a slight discrepancy in generation five, the four lines were very similar in response. No significant differences were detected among the four selection response curves. There were no significant deviations from linearity in the selected lines. Therefore, the pooled regression (0.56 ± .03) of selection line mean deviations from control gave

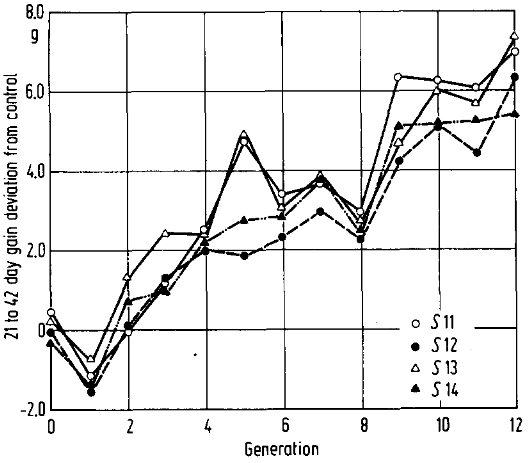

Fig. 1. Response to selection for increased postweaning gain in the four replicate lines expressed as deviation from the pooled control

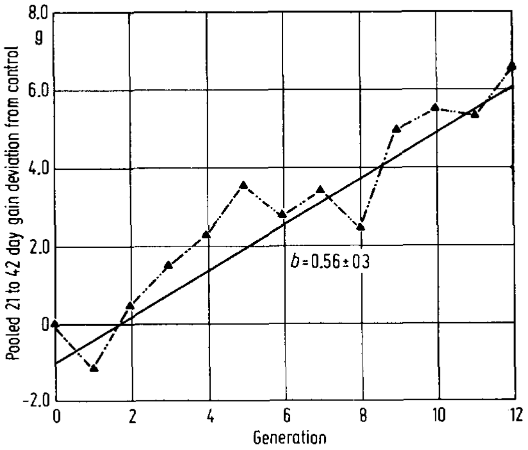

Fig. 2. The regression of deviation of the pooled selection lines from the pooled control for gain from 21 to 42 days

an estimate of genetic advance per generation. This rate of genetic advance is greater than the rate of advance found by others (Rahnefeld *et al.*, 1963; Bradford, 1971) who used similar selection procedures and population sizes. The differences may be due in part to the fact that mice used in the present study were from a large random mating base population developed from a broad genetic base while those used in previous studies were derived from crossing from two to four inbred lines and hence were from a more restricted genetic base which was likely in linkage disequilibrium.

The cumulative pooled estimate of genetic advance was 6.72 grams. Jara-Almonte and White (1973) used the same control population (C 01 and C 02) in a large population study and found the additive genetic standard deviation to be 0.96 and the sex adjusted phenotypic standard deviation to be 1.96 for 21 to 42 day gain. Using these values, the progress made in selection for increased postweaning gain was 7.0 times the genetic standard deviation and 3.4 times the phenotypic standard deviation and represented a 54% increase in rate of postweaning growth over the rate of growth in generation zero.

The response to selection was also homogeneous among males and females (Table 2). The results in Table 2 illustrate the need for replication in selection experiments. If only lines S 11 and S 12 had been included, a tendency toward sexual dimorphism in selection response would have been indicated when in fact the overall response was virtually identical between the sexes.

Table 2. *Homogeneity of Regression Coefficients for Male and Female Response to Selection for Postweaning Gain*

Line	Males b ± s.e.	Females b ± s.e.
S11	0.67 ± 0.09	0.60 ± 0.08
S12	0.58 ± 0.07	0.52 ± 0.04
S13	0.55 ± 0.10	0.55 ± 0.06
S14	0.52 ± 0.06	0.58 ± 0.04
Pooled	0.57 ± 0.03	0.55 ± 0.03

Cumulative expected and realized selection differentials and the ratios of realized to expected selection differentials are presented in Table 3. The realized selection differential should reflect any positive or negative effect of natural selection acting upon the selected mates (Falconer, 1960). Since the ratio of realized to expected cumulative selection differential was very near unity for all lines, it is unlikely that natural selection had any effect upon the selection response within the period covered by this study. Similar results were reported by Bradford (1971) and by Falconer (1953) when selecting for 42-day body weight.

Table 3. *Cumulative Realized and Expected Selection Differentials and the Ratio of Realized to Expected Values for 21 to 42 Day Gain*

Line	Expected	Realized	Realized expected
C01		2.2	
C02		1.9	
Pooled		2.0	
S11	27.2	27.0	.99
S12	26.1	24.9	.95
S13	27.4	27.4	1.00
S14	29.1	29.3	1.01
Pooled	27.4	27.2	.99

Table 4. *Realized Heritabilities for 21 to 42 Day Gain in Selected Lines*

Line	Realized heritabilities b ± s.e.
S11	0.28 ± 0.04**
S12	0.26 ± 0.03**
S13	0.24 ± 0.03**
S14	0.22 ± 0.02**
Pooled	0.24 ± 0.02**

** Statistically significant ($P < 0.01$)

Realized heritabilities are presented in Table 4. The pooled estimate of 0.24 ± 0.02 compared favorably with the expected heritability of 0.19 ± 0.08 which was determined from the base population of mice used in this study by Jara-Almonte and White (1973). The realized heritability estimates for the individual lines were not significantly different and were very similar to those reported from similar experiments (Rahnefeld *et al.*, 1963 and Bradford, 1971).

Correlated Response in Growth and Maternal Traits. Jara-Almonte and White (1973) utilized the C 01 and C 02 mice in a large population study designed to estimate genetic parameters associated with growth and maternal ability. Their estimated genetic correlations between gain from 21 to 42 days and 12-day litter weight, 12-day individual weight, 21-, 42-, and 56-day body weight and gain from 42 to 56 days were −0.31 ± 0.40, −0.12 ± 0.72, 0.04 ± 0.32, 0.80 ± ± 0.11, 0.80 ± 0.12 and 0.29 ± 0.29, respectively. From these results, correlated responses would not be expected to be sizable for the preweaning traits, but should be appreciable for the postweaning traits.

The realized correlated responses are presented in Table 5. Neither the differences between C 01 and C 02 nor among the selected lines shown in Table 5 were significant. That is, the trends in the control lines for all correlated traits were homogeneous as were the correlated responses in the selected lines. There were no significant deviations from linearity for the correlated growth traits. Therefore, the pooled correlated responses are shown in Fig. 3, 4 and 5.

Table 5. *Regression of Various Body Weights and Weight Gain on Generations*

Line	12-Day litter *wt* $b \pm$ s.e.	12-Day indiv. *wt* $b \pm$ s.e.	21-Day *wt* $b \pm$ s.e.	42-Day *wt* $b \pm$ s.e.	56-Day *wt* $b \pm$ s.e.	42 to 56-Day gain $b \pm$ s.e.
C01	−0.96 ± 0.19**	−0.11 ± 0.03**	−0.24 ± 0.004**	−0.15 ± 0.09	−0.09 ± 0.09	0.05 ± 0.05
C02	−0.98 ± 0.15**	−0.12 ± 0.02**	−0.25 ± 0.03**	−0.15 ± 0.06*	−0.07 ± 0.07	0.10 ± 0.05
Pooled	−0.97 ± 0.12**	−0.12 ± 0.01**	−0.24 ± 0.02**	−0.15 ± 0.03**	−0.08 ± 0.05	0.07 ± 0.04
S11	0.05 ± 0.20†	0.01 ± 0.02	0.02 ± 0.05	0.65 ± 0.06**	0.87 ± 0.05**	0.22 ± 0.04**
S12	0.22 ± 0.11	0.03 ± 0.02	0.07 ± 0.03	0.60 ± 0.06**	0.74 ± 0.05**	0.13 ± 0.04**
S13	0.28 ± 0.15	0.03 ± 0.02	0.04 ± 0.05	0.59 ± 0.05**	0.76 ± 0.05**	0.17 ± 0.05**
S14	0.49 ± 0.17*	0.06 ± 0.02**	0.02 ± 0.06	0.59 ± 0.07**	0.80 ± 0.06**	0.20 ± 0.05**
Pooled	0.26 ± 0.09**	0.03 ± 0.01**	0.04 ± 0.02	0.61 ± 0.03**	0.79 ± 0.03**	0.18 ± 0.02**

† Deviation from mean of both controls each generation.
* Statistically significant ($P < 0.05$).
** Statistically significant ($P < 0.01$).

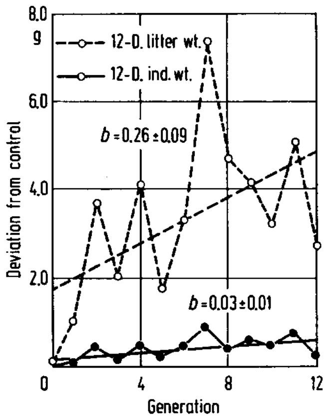

Fig. 3. Correlated responses in 12-day litter weight and 12-day individual weight pooled over replicates

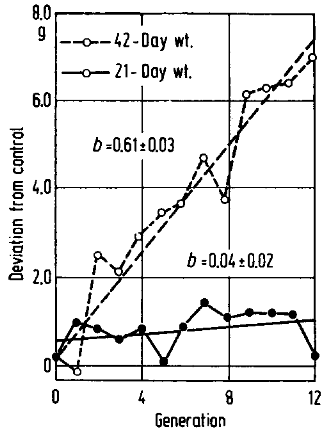

Fig. 4. Correlated responses in 21-day weight and 42-day weight pooled over replicates

The negative trends in the control lines for the preweaning traits could have arisen through increased inbreeding or certain consistent environmental trends From the effective population size, the average increase in inbreeding per generation was predicted at 1.0% or 12% after 12 generations. White (1972) has shown in a crossfostering study that 12 and 21-day individual weight decreased at the rate of about 0.20 and 0.25 grams per 10% increase in inbreeding, respectively. Therefore, inbreeding depression certainly could not completely account for the negative trends in the controls. Since this experiment was initiated within six months after the laboratory was constructed, it is possible that a gradual build-up in some type of detrimental pathogen causing diseases such as sub-clinical juvenile diarrhea which would reduce preweaning growth may have contributed to the negative trends. Even though the trend in the controls was slightly negative at 56 days, the regression was not significant. Therefore, the negative trends in the preweaning traits were likely caused by both inbreeding depression and some unidentified but consistent environmental effect during the preweaning period which could be overcome after weaning by compensatory growth.

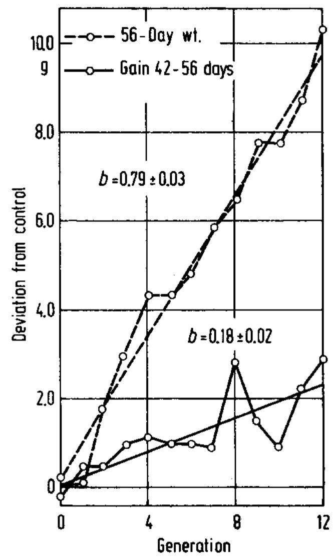

Fig. 5. Correlated responses in gain from 42 to 56 days and 56-day weight pooled over replicates

Although Jara-Almonte and White (1973) reported negative genetic correlations between gain from 21 to 42 days and 12-day litter weight and 12-day individual weight (-0.31 ± 0.40 and -0.12 ± 0.72, respectively), the pooled realized correlated responses for both traits were positive and significant (Fig. 3). However, the regressions (Table 5) were not significant in three of the four replicate lines. Even though the pooled regression was significant, the magnitude of the correlated response for 12-day litter weight was small and quite variable (Fig. 3) representing an accumulated mean change of less than 5% over 12 generations. These results agree with those of Eisen et al. (1970) who found a significant correlated response in 12 to 42-day gain in only one of four replicates when selecting for increased 12-day litter weight.

No significant correlated responses were noted for 21-day body weight, indicating that weaning weight and early postweaning body weight gain were uncorrelated. These results agree with the predicted genetic correlation (-0.04 ± 0.32) reported by Jara-Almonte and White (1973).

The correlated responses in the postweaning traits were sizable and consistent (Fig. 4 and 5) as would be expected from the predicted genetic correlations (Jara-Almonte and White, 1973). In fact, the magnitude of the correlated genetic change in 42-day body weight (0.61 ± 0.03) is considerably higher than the direct responses to selection for increased 42-day weight reported by Falconer (1953) and Roberts (1966) who used within-family selection schemes and mice derived from crosses among inbred lines.

Correlated Responses in Reproductive Traits. Number of live offspring per litter at birth and percent fertile matings measured as the percent of females exposed to males that littered were used as measures of reproductive fitness. Table 6 shows the trends in the control lines and the correlated responses in the selected lines. There were no significant trends in the control lines for either litter size or percent fertile matings and the regressions for the two lines were homogeneous.

Table 6. *Regression of Litter Size and Percent Fertile Matings on Generations*

Line	Litter size b ± s.e.	Percent fertile matings b ± s.e.
C01	−0.01 ± 0.06	−0.77 ± 0.40
C02	0.05 ± 0.05	−0.80 ± 0.40
Pooled	0.03 ± 0.03	−0.78 ± 0.26
S11	0.08 ± 0.04†	−2.06 ± 0.97
S12	0.09 ± 0.07	−1.34 ± 0.54*
S13	0.06 ± 0.08	−0.92 ± 0.65
S14	0.00 ± 0.05	−2.46 ± 0.69**
Pooled	0.06 ± 0.03	−1.69 ± 0.36**

† Deviation from mean of both controls each generation.
* ($P < 0.05$) ** ($P < 0.01$).

Although none of the regression coefficients was significant (Table 6), there was an indication of a slightly positive correlated response in litter size (Fig. 6). Fig. 6 shows that litter size in all four lines was one to two mice larger than controls in generation two and then tended to level off at about an average deviation from control of one mouse with no apparent tendency to increase further. These results are in agreement with those of Eisen *et al.* (1970) and Bradford (1971) who also found very slight increases in litter size when selecting for increased 12-day litter weight and increased 21 to 42-day gain, respectively. The magnitude of the regression coefficients for lines S 11 and S 12 in Table 6 are similar to those of Rahnefeld *et al.* (1963) who reported the regression of litter size on generation number to be .105 ± .033 mice per generation.

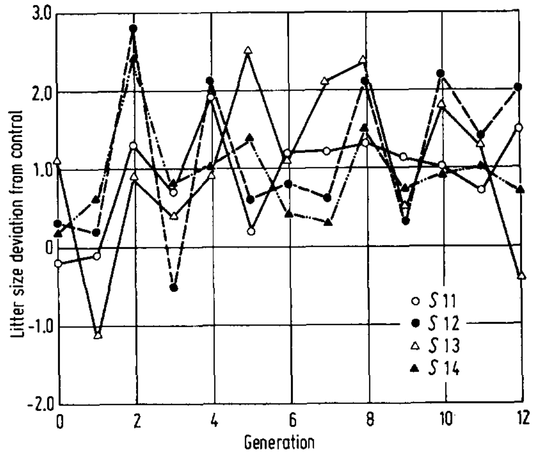

Fig. 6. Correlated responses in litter size

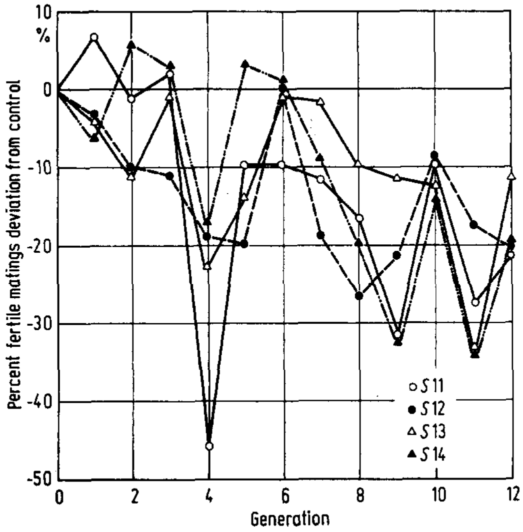

Fig. 7. Correlated responses in percent fertile matings

There was a significant reduction in the percent fertile matings in two of the selection lines (Table 6), and the pooled regression of -1.69 ± 0.36 was highly significant. Fig. 7 shows the percent fertile matings for each generation for the four selection lines deviated from the pooled control. In contrast to the results of Bradford (1971) who did not observe sizable reductions in fertility until after 11–12 generations of selection, reproductive difficulties occurred in the fourth generation of selection in all four selected lines in this experiment. Although there did appear to be some recovery of reproductive fitness in generations 5, 6, and 7, a reduction in percent fertile matings ranging from 10 to 30% persisted from generation eight to 12. This trend was consistent across the four replicates and is likely a general dhenomenon to be expected from selection for increased growth in mammals. As noted in Table 3, there was no tendency for the more rapidly gaining females to be less fertile. Therefore, reduced fertility in the selected mice was a general problem which affected all mice in the selected lines.

General Discussion

The direct response to selection for increased postweaning gain was considerably larger than had previously been reported (Bradford, 1971; Rahnefeld *et al.* 1963; Roberts, 1966). Additionally correlated responses in 42-day body weight were markedly greater in this study than direct response to selection for increased 42-day body weight reported by Falconer (1953) and Roberts (1966). The greater responses in this study are likely associated with the genetic constitution of the base population, population size and the selection procedure utilized. The base population utilized in this study was the non-inbred ICR-albino population which was originally developed from intercrossing among many lines with divergent genetic backgrounds, while previous base populations have been developed from crossing two to four inbred lines resulting in a rather restricted genetic background. The replicate size (30 paired matings) used in this study was larger than most previous studies. This resulted in minimal increases in inbreeding and allowed for greater selection intensity and larger selection differentials. The use of mass selection rather than within-litter selection resulted in the utilization of all rather than approximately one-half the additive genetic variance (Falconer, 1953).

Both direct response to selection and correlated responses in weaning weight and weight at 42 and 56 days agreed well with theoretical parameters derived from the base population by Jara-Almonte and White (1973). However, correlated responses in 12-day litter weight and 12-day individual weight were not consistent with expected values. The predicted genetic correlations reported by Jara-Almonte and White (1973), were not estimated with a great deal of precision which may account for the discrepancy. Secondly, regression in only one of the four replicates was significant indicating the difficulty in accurately detecting the very small variable response. Therefore, the genetic relationship between 12-day litter weight and gain from 21 to 42 days is likely positive but very small in magnitude.

As has been shown by previous workers, there was a slight increase in litter size in the selected lines. However, the increased litter size occurred in the second generation of selection and remained rather constant thereafter. These results did not totally agree with those of Bradford (1971) who detected no increase in litter size until generation 12 and Rahnefeld *et al.* (1963) who noted a rather consistent increase in litter size through 17 generations. The value of sufficient replication is illustrated by the regression coefficients for litter size shown in Table 6 and the plotted values in Figure 7. Had either S 13 or S 14 alone been included, there would have been very little if any indication of an increase in litter size; whereas if either S 11 or S 12 alone had been included, there would have been a definite indication of increased litter size.

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