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Direct and Correlated Responses to Selection for Post-weaning Weight Gain on ad libitum or Restricted Feeding in Mice

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Summary. Selection for post-weaning weight gain in mice from 21 to 42 days, on either a full or restricted feeding level during this period was carried out for seven generations. Control lines were maintained for each feeding level. The rate of selection response was higher on full feeding due to a higher heritability and a larger phenotypic variance. Realised heritabilities of 0.29 ± 0.05 and 0.19 ± 0.04 for selection on full and restricted feeding respectively, were in close agreement with base population estimates.

Selection on full feeding led to positive correlated responses in 21 day weight, 42 day weight, food intake and efficiency between 21 and 42 days, and 42 day tail length, but with little change in reproductive performance.

Correlated responses to selection on restricted feeding were reduced 21 day weight, but an increase in 42 day weight and increased efficiency from 21 to 42 days. However, overall reproductive performance fell.

Key words: Mice – Selection – Growth rate – ad libitum feeding – Restricted feeding

Introduction

Growth rate, efficiency of growth, food intake and body composition are important characters in many animal breeding programs and knowledge of the interrelationships among these characters is essential for predicting the consequences of any selection scheme. For example, if one alters the way an animal grows by increasing the growth rate, what changes can be expected in body composition at any particular weight or age, or if efficiency is improved, how is food intake affected?

Under ad libitum feeding, most of the genetic variation in growth rate is associated with genetic variation in food intake. Selection for growth rate results in a large increase in voluntary food intake (see recent review by Roberts 1979). On the other hand, there were indications from the work of Falconer and Latyszewski (1952), that selection in mice for body weight at six weeks of age on a restricted feeding regime may exert more selection pressure on genes controlling the partition of energy into protein and fat. However, the results of McPhee et al. (1980) do not support this suggestion. The selection program described in this paper was initiated to further investigate this question, and to provide more information on the interrelationships between the growth characters mentioned above. Yüksel et al. (1980) have emphasised that it is very important to have a clear picture of the progress of response to selection in experiments of this type. The main purpose of this paper is to provide such a picture for both direct and correlated responses to selection for post-weaning gain. Detailed investigations of the growth and body composition of the lines on both levels of feeding are described by Hetzel and Nicholas (1983 a, b).

Materials and Methods

Two selection lines were established, each with its own control line, and selection was continued for seven generations. The four lines were designated:

SF – *S*elected for weight gain on ad libitum or *F*ull feeding
CF – Unselected *C*ontrol on *F*ull feeding
SR – *S*elected for weight gain on *R*estricted feeding
CR – Unselected *C*ontrol on *R*estricted feeding.

Mass selection was practised for weight gain from 21 to 42 days of age in both selection lines. The feeding treatment was imposed only during this 3 week period, i.e. at other times all mice were fed ad libitum. The food restriction was in amount only, with all mice being fed about 83% of the average intake of unselected mice of the same age on full feeding. Expressed on a daily basis, the food allocation in the restricted lines was 3.5 g for days 21 to 24, 4.5 g for days 25 to 28, 5.0 g for days 29 to 34, and 5.5 g for days 35 to 42. Mice were caged and fed individually so that individual food intake could be recorded on full feeding, and to ensure that the intake for all mice on restricted feeding was essentially equal.

The lines were initiated by randomly sampling progeny from 80 single pair matings. The parents had been taken from a large random mating population (Quackenbush strain), and were as unrelated as possible. At weaning, one male and one female offspring from each litter were allocated to each selection line, and from every fourth litter, one male and one female were used to constitute each control line.

From the 160 mice measured in each selection line, the best 10 males and 20 females were selected as parents. Two selected females were allocated randomly to each selected male. Because of infertility, and because of the inability of some males to mate successfully with two females, reserve matings amongst the next best males and females were also set up. In most generations, between 12 and 15 males were required to produce 20 litters. From each of these litters, four male and four female offspring were recorded, making a total of 160 mice recorded in each selection line in each generation. The control lines comprised 10 single pair matings each generation, which were arranged such that one male and one female selected at random from each family, contributed to the next generation. In theory, the variance in family size was therefore zero in the control lines, thus doubling the effective population size. Full-sib and half-sib matings were avoided, and generations were contemporaneous throughout. Two males and two females were recorded from each control litter each generation, making a total of 40 mice measured per control line per generation.

Mice were mated at between seven and ten weeks of age, and were weighed at mating. Males were removed after 17 days. In the selection lines where two dams were mated to each sire, females were then placed into individual cages. Litters were checked daily. At birth, the number of live young born was recorded and the number of days from joining to littering calculated. When litter size exceeded 12, it was reduced to 12 (wherever possible to 6 of each sex). Litters of less than 8 were supplemented with foster mice born on the same day. Foster mice were identified by removing 3–4 mm from the tip of their tail, and were discarded at weaning. From generation four onwards, litters were also weighed at birth. Only first parity litters were used except for generation seven, when there was high post-natal mortality in first litters. Two days after birth, litters were reduced at random to 8 (4 of each sex).

Mice were weaned at 21 days of age, weighed and placed in individual plastic cages. Individual food intake was measured between 21 and 42 days of age using a glass feeding jar designed to eliminate spillage of the food. A metal disc with holes was placed over the food which was finely ground. Mice were fed a standard laboratory chow (Allied Feeds) every two days. At 42 days of age, all mice were weighed, measured for tail length and given excess, cubed food until selection was carried out. Efficiency was calculated as weight gain/food intake from 21 to 42 days.

As there was a very high degree of consistency between the sexes for all lines, all results were pooled across sexes. Both direct and correlated responses to selection were estimated as the linear regression of the deviations of a selection line from its own control against generation number. Variance of response was estimated according to Hill (1977).

Realised heritabilities were calculated as the regression of cumulated response on cumulated selection differential where both were measured as deviations from control. Realised genetic correlations between weight gain and the correlated characters were estimated after Falconer (1954) using the formula

$$r_G = \frac{C_Y h_X \sigma_{P_X}}{R_X h_Y \sigma_{P_Y}}$$

where R_X and C_Y are the direct and correlated responses in X and Y respectively, h_X and h_Y are the square roots of the heritabilities for X and Y, and σ_{P_X} and σ_{P_Y} are the phenotypic standard deviations for traits X and Y. Base population heritability estimates were taken from results of preliminary experiments described by Hetzel (1978). Approximate standard errors of the genetic correlations were calculated after Hill (1971).

Inbreeding coefficients at generation seven were estimated using the coancestry method of Cruden (1949).

Results

The average performance of the control lines in the base generation for all characters measured is given in Table 1. The effect of the restricted diet was to decrease weight gain from 21 to 42 days by nearly one third and to reduce the variance of weight gain by a factor of almost three.

(i) Direct responses: Direct responses to selection for weight gain are shown in Fig. 1. There were marked fluctuations from generation to generation in both control lines, presumably caused by environmental factors, in particular variations in food quality. Regressions of mean weight gain on generation number were –0.12 ±0.14 and –0.04 ±0.24 for CF and CR respectively, indicating no overall trend for the control lines over the seven generations of selection. Expressed as the deviation of a selection line from its control (Fig. 2), response was much higher on full feeding, 0.79 ± 0.15 g/generation, as compared with 0.37 ± 0.08 g/generation on restricted feeding. The predicted rates of response using base population estimates of heritability, phenotypic variance and the expected selection intensity were 1.42 g/generation and 0.57 g/generation for SF and SR respectively. Actual responses were therefore about 40% lower, due mainly to reduced selection differentials caused by infertility.

Table 1. Average performance of control lines in the base generation

	CF		CR	
	Mean	Variance	Mean	Variance
Growth characters				
Birth weight[a]	1.59	0.02	1.64	0.02
21 day weight	13.9	2.0	13.8	2.1
42 day weight	28.8	12.5	24.3	3.1
Weight gain (21 – 42 days)	14.9	8.0	10.5	3.1
Food intake (21 – 42 days)	121.6	78.4	100.5	–
Feed efficiency (21 – 42 days)	0.12	0.0004	0.10	0.0003
42 day tail length	8.1	0.3	7.7	0.1
Reproductive characters				
Days from joining to littering	25.7	17.1	26.1	18.2
Litter size	13.3	10.3	14.3	5.0
Littering %	85.0	–	85.0	–

[a] From generation four

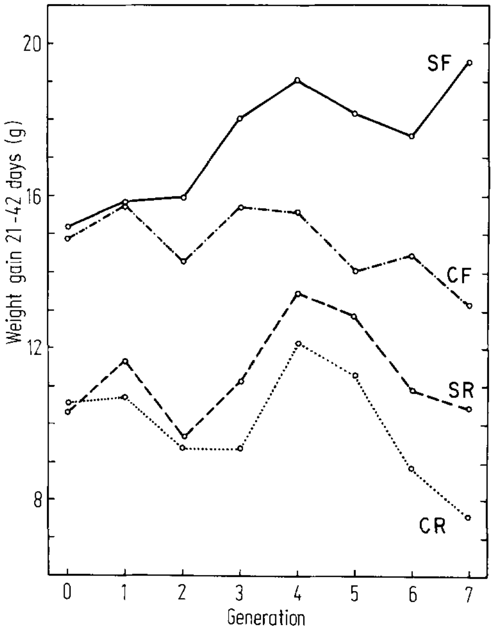

Fig. 1. Generation means for weight gain from 21 to 42 days

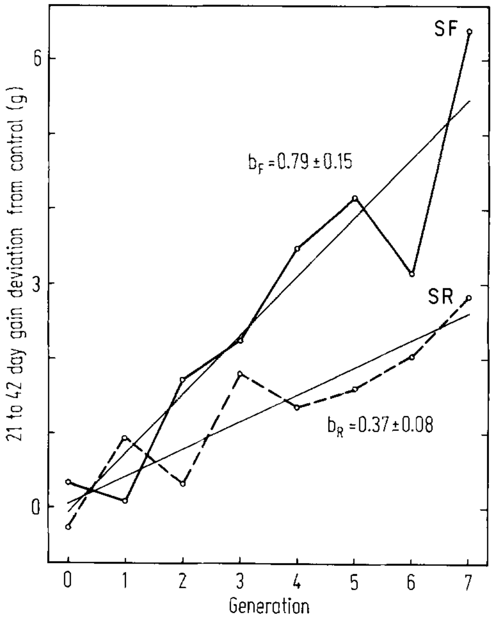

Fig. 2. Direct response to selection for weight gain from 21 to 42 days on full feeding (SF) and on restricted feeding (SR)

Cumulated selection differentials (CSD) and realised heritabilities are given in Table 2. Due to the larger variance in weight gain on full feeding (almost three times larger), CSD was greater for SF than SR. CF had a small negative CSD presumably due to chance. CR had a consistently small positive selection differential each generation, resulting in an overall positive CSD. This may have been an effect of the restricted diet such that heavier individuals, i.e. those with a higher weight gain, had a greater chance of contributing offspring to the next generation.

Realised heritability of weight gain was higher on full feeding than on restricted feeding. Both estimates agree very closely with estimates from the base population of 0.33 ± 0.09 and 0.22 ± 0.07 for full and restricted feeding respectively (Hetzel, 1978).

(ii) Correlated responses: (a) Growth characters: There was no significant change in either control line for any character over the seven generations of the selection experiment. Correlated responses are presented in Table 3 and in Fig. 3 to 6. Variances of correlated responses estimated from the variance of the regression coefficient are biased downwards since the contribution of genetic drift has been ignored (Hill 1971).

Table 2. Cumulated selection differentials (CSD) at generation seven and realised heritabilities (h_R^2)±standard error

Line	CSD	h_R^2
SF	+ 17.07	0.29 ± 0.05
CF	− 1.39	–
SR	+ 14.88	0.19 ± 0.04
CR	+ 2.12	–

Table 3. Correlated responses per generation to selection ± standard error, for those characters not illustrated in Fig. 3 to 6

	SF	SR
Growth characters		
Birth weight	0.02 ± 0.02	− 0.02 ± 0.01
42 day tail length	0.09 ± 0.03	0.04 ± 0.03
Reproductive characters		
Days from joining to littering	0.10 ± 0.35	0.47 ± 0.17
Littering %	1.24 ± 2.12	− 1.83 ± 1.41
Litter size	0.05 ± 0.08	0.14 ± 0.13

Birth weight, which was recorded only from generation four onwards, was not significantly different between lines, nor did it show any change with selection. 21 day weight showed no significant overall trend in either SF or SR, but as can be seen from Fig. 3, there was a definite increase for SF after generation four. However, SR was significantly lighter than its control at 21 days in all generations except generation zero and two. Therefore, while the rate of change in 21 day weight was not significant, selection on restricted feeding appears to have established and maintained a significantly lower weaning weight.

42 day weight steadily increased in both selection lines (Fig. 4) although in the case of SR, at a much slower rate than SF. Food intake of the SF line changed very little over the first three generations, but

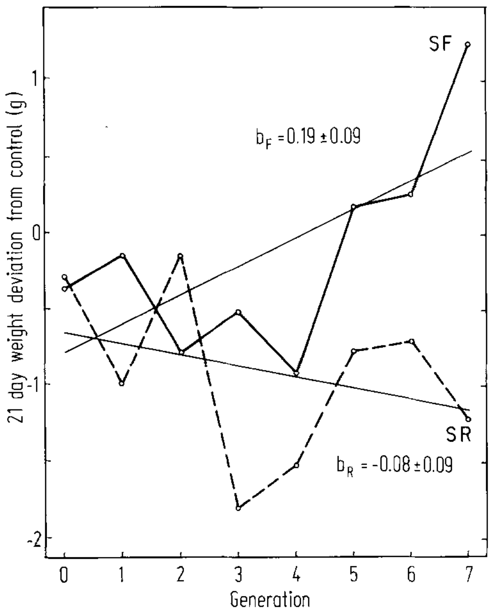

Fig. 3. Correlated responses in 21 day weight

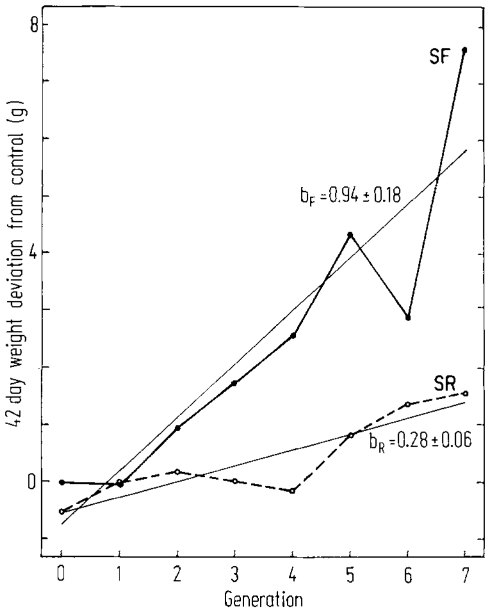

Fig. 4. Correlated responses in 42 day weight

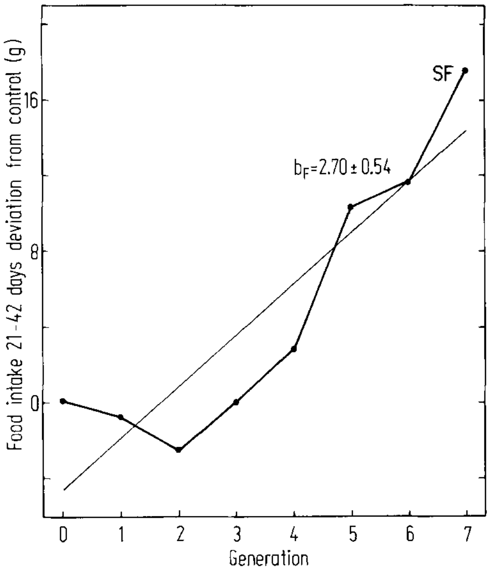

Fig. 5. Correlated responses in food intake from 21 to 42 days

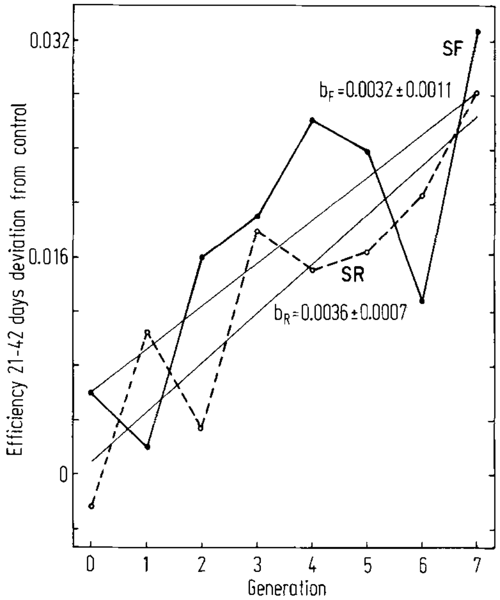

Fig. 6. Correlated responses in efficiency from 21 to 42 days

thereafter increased at a rapid rate (Fig. 5). Therefore, for the first three generations, selection response for weight gain was realised with little change in voluntary food intake, as was achieved by Eisen (1977) using a restricted selection index. Efficiency increased in both selection lines at about the same rate (Fig. 6) but there was appreciable variance about the regression lines. This may have been caused by the variations in food quality suggested earlier.

Although the overall trend in 42 day tail length was positive for both selection lines (Table 3), it was only significant in the case of SF. Thus, skeletal size increased with selection on full feeding, while on restricted feeding, it showed very little change.

Realised genetic correlations and standard errors are presented in Table 4, together with the estimates from the base population as given by Hetzel (1978). On restricted feeding, the two estimates are not significantly different and are of the same sign. In contrast, the correlated responses predicted from the base population estimates on full feeding are vastly different and in most cases in the opposite direction to those realised. However, as was pointed out by Hetzel (1978), the base population estimates on full feeding are very different

Table 4. Realised genetic correlations (realised r_G) and base population estimates (base r_G) ± standard errors, between weight gain and the other growth characters on the two feeding levels

		21 day weight	42 day weight	Food intake	Efficiency
Full	realised r_G	0.83±0.10	0.83±0.04	2.09[a]	0.79±0.07
feeding	base r_G	-0.71±0.16	-0.20±0.33	-0.12±0.26	0.75±0.12
Restricted	realised r_G	-0.39±0.18	0.55±0.08	–	0.95±0.04
feeding	base r_G	-0.96±0.03	0.13±0.26	–	1.00±0.01

[a] Standard error could not be calculated because estimated $r_G > 1$

to other published values, probably because of compensatory growth following the abnormally low weaning weight of some mice.

(b) Reproductive characters: The correlated responses in some fitness related traits are given in Table 3. The controls showed no significant changes for these characters with the exception that CR declined in litter size at a rate of -0.33 ± 0.12 mice per generation. All lines were approximately the same age and weight at mating until generation three after which SF mice were always heavier. Control mice were always quicker to mate than mice from either of the selection lines probably because only one female was mated with each male. However, relative to CR, SR mice took longer to mate, presumably as a consequence of selection on the restricted diet. Litter size in the SR line also decreased, the reduction being partly obscured by the drop in the control line mentioned earlier. Therefore, overall reproductive performance fell in the SR line. On the other hand, SF reproductive performance remained fairly steady relative to its control.

The mean inbreeding coefficients at generation seven were 10.3%, 7.5% 10.9% and 9.7% for SF, CF, SR and CR respectively, with an average standard deviation of 2.8%. The observed levels of inbreeding were close to the expected value of 8.7% (1.25%/generation) for the controls, but were considerably lower than the predicted value of 13.1% (1.87%/generation) for the selection lines. This was due to the fact that in the selection lines, more than 10 males contributed offspring to the next generation as described in the Material and Methods section above. At generation seven, these fairly low levels of inbreeding would have had only a small effect on reproductive performance.

Discussion

Selection for post-weaning weight gain on full feeding was effective at increasing the mean weight gain by 49% or two phenotypic standard deviations in only seven generations. This was a faster rate of response than reported by others (Dalton 1967, Bradford 1971, Lasalle et al. 1974, Frahm and Brown 1975) and was due to a greater selection intensity particularly in males, and a higher heritability. There are several possible reasons for the higher heritability. Firstly, the founder mice for this experiment were sampled from a large random mating population rather than from a 3 or 4 way cross of inbred lines and therefore additive genetic variance would probably be higher, Secondly, the individual housing of the mice could be expected to reduce environmental variance caused by behavioural interactions, thereby increasing heritability. In addition, the use of reasonably large population sizes reduces the probability of unfavourable chance changes in gene frequency, which may lower the rate of response as well as the selection limit eventually reached.

On restricted feeding, selection increased weight gain by 37% or 1.5 phenotypic standard deviations. The lower rate of response as compared with full feeding was a result of the lower phenotypic variance of weight gain on restricted feeding and a lower heritability. The higher heritability on full feeding is the result of the contribution of extra genetic variance in food intake to the total genetic variation in weight gain.

Falconer and Latyszewski (1952) reported a higher heritability of six week body weight in mice on a restricted diet, even though both genetic and phenotypic variances were lower than on full feeding. However, the difference between the two estimates was not significant. Subsequent studies with pigs (Fowler and Ensminger 1960), rats (Park et al. 1966) and mice (Korkman 1961) showed heritability of body weight or weight gain always to be higher on full feeding.

The correlated increases in 42 day weight, food intake, efficiency and tail length on full feeding were in agreement with almost all other similar experiments (Rahnefeld et al. 1963, Baker and Cockrem 1970, Sutherland et al. 1970, Timon and Eisen 1970, Bradford 1971, Lasalle et al. 1974, Baker and Chapman 1975, Frahm and Brown 1975). The upward trend in weaning weight has also been a common finding in these studies. In most cases the correlated responses in this study were different than those predicted from base population estimates of genetic correlations among the characters. A possible reason put forward was the abnormally low weaning weights of mice involved in the base population estimates (see Hetzel, 1978), causing a different genetic relationship between weight gain and other growth characters. These correlations must therefore be regarded as unreliable.

On the other hand, correlated responses on restricted feeding were largely in agreement with changes predicted from base population parameters. Higher weight gains were achieved by a reduction in 21 day weight as well as an increase in 42 day weight. Tail length did not increase, contrary to the finding of Falconer and Latyszewski (1952) where selection was for the closely related character, six week body weight. Due to food intake being held constant throughout the experiment, efficiency of growth increased.

On full feeding, reproductive performance was relatively stable. Rahnefeld et al. (1963) reported a correlated increase in litter size while Lasalle et al. (1964) found no significant change. However, Morris and Lineweaver (1972) reported a downward trend. Bradford (1971) showed that while ovulation rate was increased as a correlated response to selection for weight gain, uterine capacity was not, so that litter size remained unchanged.

Reproductive performance deteriorated with selection on restricted feeding. Mice took longer to mate, littering percentage dropped slightly and litter size decreased. In the only other reported study of correlated responses to selection for the closely related character, six week body weight on restricted feeding, Falconer and Latyszewski (1952) found no such decrease. Inbreeding was not sufficiently high in this study to account for any marked reduction in reproductive performance.

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