Two-way within-family and mass selection for 8-week body weight in different mouse populations

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SUMMARY

Two mouse populations, randombred albino mice and a cross of four inbred strains, were divergently selected for high (H_8) and low (L_8) 8-week body weight over 18 generations using within-family and individual selection. The crossbreds showed asymmetry of selection response and realized heritabilities (H_8 0.29 ± 0.01; L_8 0.17 ± 0.01). In the randombred population realized heritabilities were symmetrical (H_8 0.23 ± 0.01; L_8 0.22 ± 0.02). Over the first nine generations individual selection was nearly 40 per cent better than within-family selection, as was expected from the full sib correlation in both populations. As selection progressed, within-family selection reached 82 % and 61 % of the responses obtained with individual selection in the crossbreds and randombred respectively. Correlated responses for 3-week (weaning) and 5-week body weights agreed with observations made on direct responses, but selection for L_8 did not reduce weaning weight. Selection for L_8 decreased and selection for H_8 increased first litter size at birth. However, mass-selected L_8-pairs had a higher life-reproduction and life-span than H_8-pairs.

1. INTRODUCTION

Using the laboratory mouse as experimental animal, quantitative characters have been intensely studied by single-trait selection studies (Roberts, 1965; Eisen, 1974; McCarthy, 1982). In almost all experiments either mass or within-family selection was applied. The relative merits of these selection methods were compared in several computer simulation studies (Dempfle, 1975; Young & Skavaril, 1976; Willeke, 1982) but less information is available from experimental work. The present experiment is conducted as the control of a selection experiment for antagonistic traits. The data collected allow comparison of the effectiveness and consequences of mass selection and within-family selection with regard to direct and correlated response. Also, it is of interest to study repeatability of rate and pattern of selection response in genetically different populations. Therefore two mouse populations, one originating from a 4-way cross, the other from an established randombred colony, were used.

2. MATERIALS AND METHODS

(i) *Laboratory procedures*

Two foundation populations were used, a cross of four inbred lines (crossbred) and randombred albino Swiss mice (randombred). Two generations of random mating among the stocks elapsed before each population was divided into eight selection lines, divergently selected for 8-week body weight – two up, two down – by mass selection (MS) or intra-litter selection (ILS) and three randombred control lines (CL). The lines were reproduced from eight single-pair matings in each generation. On average, 25 per cent were selected in each line.

Litters were standardized within 24 h of birth in crossbreds to eight and in randombreds to ten pups. Mice were weaned at 21 days, separated by sex and distributed into cages. Individual weights were recorded to the nearest one-tenth of a gram at 21, 35 and 56 days of age. The mice were fed ad libitum with Altromin Lab Chow and reared in controlled environment at 22 ± 1 °C and 55 ± 5 % relative humidity.

(ii) *Estimation of realized genetic parameters*

Realized selection differentials were weighted with the number of offspring measured. Calculations were carried out separately for males and females and their un-weighted average was used for further calculations. In the ILS lines the selection differentials calculated were the mean differences in 8-week weight between the selected individuals and the mean of their same-sex litter-mates. In the MS lines realized selection differentials were obtained as deviation of the mean of the selected individuals from the mean of all recorded individuals in each generation. In the control lines selection differentials were calculated to check randomness of selection.

Realized heritabilities were estimated by the regression of the cumulative selection responses on the cumulative selection differentials. Heritability of intra-litter variation is given by $h_w^2 = h^2 (1-r)/(1-t)$ in contrast to the heritability of deviations from the population mean $h^2 = (V_A)/(V_T)$, as given by Falconer (1981), where r is the within-family relationship – $1/2$ in this case – and t the phenotypic correlation between litter-mates.

Hill (1971) and Avery & Hill (1977) have pointed out that estimates of variance of realized heritability, obtained by using standard regression techniques, are biased downwards, since genetic drift and linkage disequilibrium are neglected. Variance between replicates provides an estimate of the variance of realized heritability. As Falconer (1973, 1976) has pointed out, no assumption is necessary here. For computation of empirical standard errors realized heritabilities from the ILS lines were corrected to heritabilities pertinent to mass selection [$h^2 = h_w^2 (1-t)/(1-r)$]. Average realized heritability estimates were obtained by pooling the adjusted values from within-family selection and from mass selection. The empirical variance estimate is based on four degrees of freedom (four lines selected upwards and four lines selected downwards).

3. RESULTS

(i) *Estimates of phenotypic and genetic parameters in the foundation populations*

Phenotypic parameters for first litter size at birth and body weights at 3, 5, and 8 weeks of age in the two base populations are given in Table 1. Randombred animals produced a higher first litter size and had heavier body weights ($P \leqslant 0.05$) than crossbreds. Significant effects ($P \leqslant 0.05$) of sex and litter size were found for

Table 1. *Foundation populations – first litter size and body traits* ± s.d. *(g)*

	Crossbred	Randombred
Progenies	1347 (667 ♂; 680 ♀)	1338 (641 ♂; 697 ♀)
Full-sib families	170	132
First litter size (152 females)	9·4 ± 2·2	11·6 ± 2·9
3-week weight	10·0 ± 1·3	10·9 ± 1·8
5-week weight	19·5 ± 1·9	24·2 ± 2·3
8-week weight	23·5 ± 2·0	30·8 ± 2·9

Table 2. *Foundation populations – heritability estimates* (± s.d.) *for 8-week body weight*

Analysis	Crossbred[a]	Randombred[b]
Full sib	0·40 ± 0·05	0·56 ± 0·06
Daughter–dam	0·29 ± 0·08	0·38 ± 0·06
Son–sire	0·26 ± 0·08	0·34 ± 0·08
Offspring–midparent[1]	0·27 ± 0·07	0·33 ± 0·05

[1] Adjusted for the sex-difference in variance.
[a] 1347 prog./170 full-sib families.
[b] 1338 prog./132 full-sib families.

all body weight traits in both populations. Heritability estimates for 8-week body weight are given in Table 2. In both populations estimates from full sib correlations and from female parents are higher than those from male parents, presumably because of maternal effects. Heritability estimates from offspring–midparent regressions gave values of 27 % and 33 % for the crossbreds and randombreds respectively.

(ii) *Control lines*

During the first 18 generations linear regression coefficients of average 8-week body weight on generation number were not significantly different from zero in either control population. However there was a small reduction in 8-week weight in both populations which could be due to inbreeding. Inbreeding coefficients as calculated by a method given by Cruden (1949), increased at a rate of about 3·1 % per generation and reached 51 % in the 18th generation. Small cumulative 'selection differentials' of 0·14 g and 0·06 g for the crossbreds and the randombreds, respectively, indicate that selection for 8-week body weight was negligible. Therefore the average performance of all CL served as unselected control.

(iii) *Direct selection responses*

(a) Crossbred population

Direct responses for the MS and ILS lines derived from the crossbred population are shown in Fig. 1. In general all lines progressed under selection. As given in Table 3, linear regression analysis of weight response on generation number was significant and agreement between replicates was good. However, responses were
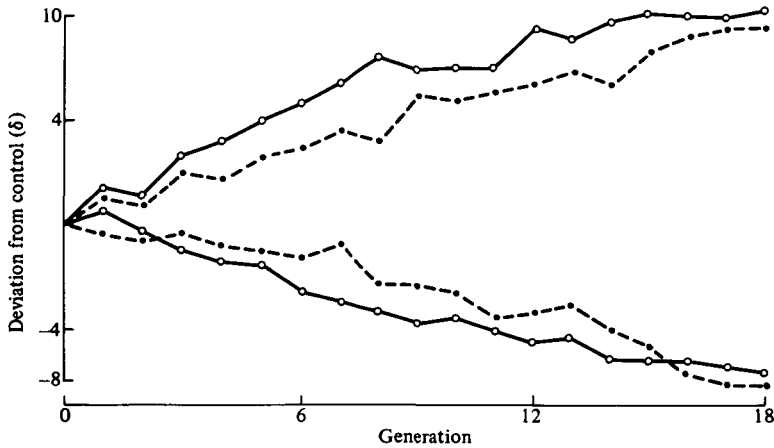

Fig. 1. Crossbred population: two-way within-family and mass selection for 8-week body weight (pooled over replicates). ○———○, Mass selection; ●----●, within-family selection.

Table 3. *Direct responses – linear regression on generation number of deviations of selected line mean from control*[1]

Selection method	Direction	Replicate	Crossbred		Generation		Randombred	
			1–9	10–18	1–18	1–9	10–18	1–18
MS	H_8	1	0·79	0·50	0·65	0·62	0·59	0·61
		2	0·73	0·52	0·63	0·71	0·68	0·69
	L_8	1	−0·41	−0·44	−0·42	−0·93	−0·60	−0·76
		2	−0·31	−0·35	−0·33	−0·84	−0·57	−0·71
ILS	H_8	1	0·56	0·48	0·52	0·32	0·44	0·38
		2	0·42	0·40	0·41	0·57	0·49	0·53
	L_8	1	−0·18	−0·28	−0·23	−0·34	−0·27	−0·30
		2	−0·22	−0·34	−0·28	−0·23	−0·31	−0·27
ILS/MS	H_8		0·64	0·86	0·74	0·66	0·73	0·70
	L_8		0·55	0·78	0·67	0·32	0·49	0·38

[1] All responses significantly different from zero ($P \leqslant 0.01$).

asymmetrical. Both selection methods resulted in immediate asymmetry. During the first nine generations, downward selection achieved about half as much as upward selection. Up to generation 18 the asymmetry was slightly reduced, but it still exists. Comparison of the effectiveness of within-family and mass selection (Table 3) shows that the response obtained with ILS selection was about 60% of

that obtained with MS selection up to generation 9. From generation 10 to generation 18 ILS selection achieved 82 % of the response by MS selection, in either direction.

(b) *Randombred population*

Fig. 2 shows the direct selection response for the selection lines derived from the randombred population. In this population MS and ILS behave differently. In the first nine generations downward MS responded more, while with ILS response was
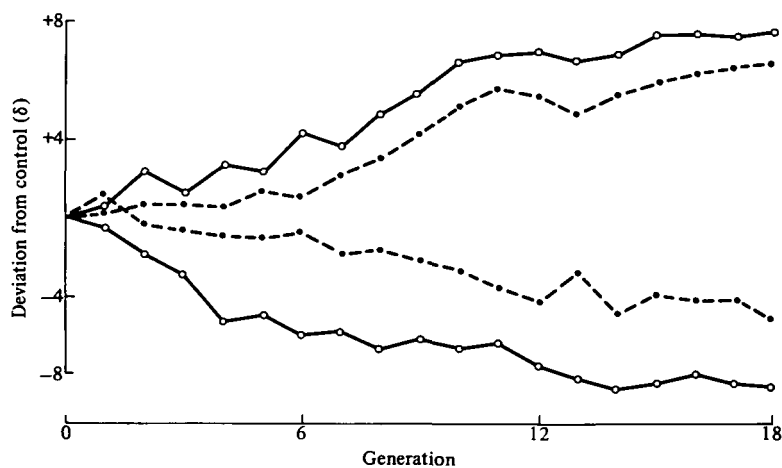

Fig. 2. Outbred population: two-way within-family and mass selection for 8-week body weight (pooled over replicates). ○——○, Mass selection; ●----●, within-family selection.

greater upwards (Table 3). From generation 10 to generation 18 no significant difference between the opposite directions was observed with MS, while ILS continued to show asymmetry. Success obtained by ILS was about 66 % and 32 % upward and downward MS, respectively, up to generation 9. From generation 10 to generation 18 ILS improved relatively to 49 % of MS in the downward direction and to 73 % in the upward direction.

(iv) *Realized heritabilities*

Estimates of realized heritabilities for 8-week body weight obtained by regressing selection responses on cumulative selection differentials and their standard errors over the entire 18 generations are presented in Table 4. Heritabilities from intra-litter selection (ILS) were adjusted to individual selection (MS). In the crossbred population realized heritabilities of upward and downward selection are significantly different (Table 4, $P \leqslant 0.01$). In the randombred population up-and-down selection resulted in nearly equal heritabilities and no evidence of genetic asymmetry becomes apparent. There is a slight contradiction between MS and ILS. Under MS the high lines respond a bit less (insignificantly) than the low lines but the differences are reversed under ILS, and these are formally significant.

Table 4. *Realized heritabilities – generation 1 to generation 18*

Selection method	Direction	Crossbred		Randombred	
		R_1	R_2	R_1	R_1
MS[1]	H_8	0.29 ± 0.02	0.28 ± 0.01	0.20 ± 0.02	0.23 ± 0.03
	L_8	0.19 ± 0.02	0.14 ± 0.03	0.26 ± 0.03	0.24 ± 0.02
ILS[1,2]	H_8	0.32 ± 0.01	0.28 ± 0.02	0.22 ± 0.01	0.29 ± 0.02
	L_8	0.17 ± 0.02	0.20 ± 0.01	0.18 ± 0.03	0.19 ± 0.02
Pooled[3]	H_8	0.29 ± 0.01		0.23 ± 0.01	
	L_8	0.17 ± 0.01		0.22 ± 0.02	
	Divergence	0.23 ± 0.02		0.22 ± 0.01	

[1] Standard errors of the regression coefficients. [2] $\left(h^2 = \dfrac{1-t}{1-r} h_w^2 \right)$. [3] Empirical standard errors (4 D.F.).

Table 5. *Correlated responses (pooled over replicates) – linear regressions on direct response in 8-week weight scaled by the phenotypic standard deviations*[1]

Selection method	Direction	Crossbred		Randombred	
		3-week	5-week	3-week	5-week
		body weight		body weight	
MS	H_8	0.53	0.84	0.59	0.99
	L_8	-0.12n.s.	-0.56	-0.21n.s.	-0.77
ILS	H_8	0.61	0.71	0.56	0.83
	L_8	-0.10n.s.	-0.62	-0.11n.s.	-0.62

[1] Responses significantly different from zero ($P \leqslant 0.05$); n.s.: not significantly different from zero.

(v) *Inbreeding coefficients*

Mean inbreeding coefficients, averaged over replicate lines, were 54% (MS) and 27% (ILS) for the crossbreds. In the randombred population inbreeding coefficients reached 56% under MS and 31% under ILS. Within-family selection has effectively reduced inbreeding to half the level to the lines with mass selection. In nearly all lines the actual inbreeding rates were slightly higher than expected, mainly because the number of parents was sometimes less than eight pairs due to sterility.

(vi) *Correlated response in body weights*

Two additional body traits were measured in all lines, weaning weight at 3 weeks and 5-week body weight. Correlated standardized responses were regressed on standardized direct responses in 8-week body weight. The regression coefficients pooled over replicates are presented in Table 5. In the crossbred lines asymmetry of correlated response is evident. Downward MS and ILS selection moved 5-week weight about 25% as far as upward selection. Weaning weight at 3 weeks of age, which is mainly a maternal trait (Eisen, 1974), was significantly increased in the up-lines but did not respond to downward selection. This is in general agreement

with observations by Falconer (1973) on divergent selection for 6-week body weight.

In the randombred population divergent mass selection for 8-week body weight showed significant correlated responses in 5-week body weight. However, downward mass selection affected 5-week weight less than upward selection. With ILS, however, asymmetry of correlated responses became evident.

Similar to the results previously noted in the crossbred population, downward selection for 8-week body weight did not reduce weaning weight.

Table 6. *Correlated response for fertility traits of selected pairs*
(pooled over replicates)[1]

Selection method and direction		Crossbred			Randombred		
		DL	IM	LS	DL	IM	LS
CL[2]		$0.02^{n.s.}$	$0.001^{n.s.}$	-0.02	$0.01^{n.s.}$	$0.002^{n.s.}$	-0.06
MS[3]	H_8	0.02	0.001	0.23	0.04	0.003	0.28
	L_8	0.02	0.002	-0.15	0.04	0.002	-0.24
ILS[3]	H_8	0.02	—	0.15	0.02	$0.002^{n.s.}$	0.18
	L_8	0.01	—	-0.08	0.04	$0.002^{n.s.}$	-0.12

DL: days between mating and littering; IM: proportion of infertile matings; LS: first litter size at birth.

[1] Responses significantly different from zero ($P \leqslant 0.05$), n.s.; not significantly different from zero.

[2] Linear regression on generation number.

[3] Linear regression on generation number of deviations of selected line means from control.

(vii) *Correlated response of fertility traits of selected parents*

Fertility traits of selected parents measured in all lines were: days between mating and littering (DL), proportion of infertile matings (IM) and first litter size at birth (LS). Table 6 shows the changes over the entire 18 generations, expressed as deviations from control, and calculated by linear regressions on generation number. Controls of both populations showed no significant change for days between mating and littering (DL) and for the proportion of infertile matings (IM). However, the changes observed are in the direction expected if inbreeding depression occurs. Litter size (LS), was significantly reduced, perhaps as a result of the inbreeding. DL increased significantly in all selected pairs, which parallels observations of several experiments (Bradford, 1971; Eisen, Hanrahan & Legates, 1973). IM increased in all lines, except in the ILS lines derived from the crossbred population, where no infertile mating occurred during the first 18 generations (Table 6). H_8 selection increased and L_8 selection decreased LS, which is expected from the favourable correlation between litter size and adult body weight in mice (Eisen, 1974). In the crossbred lines correlated asymmetrical response for LS became evident, greater response being obtained in the up-lines, similar to the direct and correlated responses of body weights.

(viii) *Lifetime reproduction of the MS-strains*

After 12 generations two-way mass selection for 8-week body weight, lifetime reproduction was tested on a random sample of mice. In each strain 32 pairs of mice were used. Litters were recorded within 24 h of birth and thereafter discarded to avoid delayed implantation due to lactation. All pairs had a first litter size.

Table 7. *Life-reproduction and life-span* ± s.d. (32 *single pair matings in each strain*)

Trait	Crossbred			Randombred		
	C	H_8	L_8	C	H_8	L_8
FLS	8·7 ± 1·7	10·2 ± 2·6	6·9 ± 2·7	10·6 ± 3·2	12·2 ± 3·4	7·6 ± 2·4
NL	8·6 ± 2·7	6·9 ± 2·2	10·4 ± 3·1	5·5 ± 3·2	5·8 ± 2·5	8·4 ± 2·3
TB	72·1 ± 15·9	53·8 ± 12·3	73·2 ± 9·3	51·6 ± 12·1	51·9 ± 13·3	67·9 ± 12·1
MLS	8·4	7·8	7·0	9·4	8·9	8·1
MLIS	557 ± 63	498 ± 71	535 ± 93	471 ± 75	431 ± 58	501 ± 87

FLS, first litter size at birth; NL, mean number of litters; TB, mean number of total young born; MLS, mean litter size at birth (TB/NL); MLIS, mean life-span (days).

Selection for high 8-week weight increased first litter size while selection for low 8-week weight decreased it, which response was expected. The H_8-pairs, however, had a shorter reproductive life-span. In both populations, L_8 strains produced more total young than the H_8 strains; in the randombred population they were even superior to the control strain. This agrees with the experience of Roberts (1961), who observed that mice selected for small size had a higher reproductive rate than mice selected for large size. In both populations L_8 breeding pairs showed a longer life-span than H_8 pairs; in the randombred population, as noticed before for TB, they were even superior to the control strain.

4. DISCUSSION

One aim of the present experiment was to compare the effectiveness of within-family and mass selection. Over the first nine generations individual selection was nearly 40 per cent better than within-family selection, which was expected from the full sib correlation in both populations. As selection progressed, within-family selection reached 82 per cent of the response obtained with mass selection in the crossbred population. In the randombred population, the difference in response between MS and ILS was slightly reduced as selection progressed. The long-term differences in direct selection response among the ILS and MS lines can be caused by loss of desirable alleles due to genetic drift. Both total response and duration of response should be reduced if selection is carried out in a small population with a fairly high rate of inbreeding. The advantage of within-family selection in later generations therefore should come chiefly from the reduced rate of inbreeding which also became evident in computer simulation studies (Dempfle, 1975).

It is quite evident that the response of the crossbred population was asymmetrical

while realized heritabilities in the two opposite directions were for all practical purposes equal in the outbred population. The asymmetry in the crossbred population is statistically significant, and one may ask for the causes of this asymmetry.

The crossbred foundation is derived from four inbred lines, survivors of many inbreeding attempts and, therefore, strongly selected. As evident also in this investigation, small mice tend to have more offspring during their lifetime (Table 7). It appears reasonable to assume, therefore, that genes causing mice to be small were of high frequency in the crossbred base population, a contention supported by their much smaller body weight (Table 1). One may assume then that high frequency of genes for low body weight is the cause of the asymmetry – low realized heritability in the downward selected lines. In most other experiments asymmetry was found reversed – lower heritability in the upward selected lines (Falconer, 1953; Legates & Farthing, 1962; Falconer, 1960; Sutherland, Biondini & Haverland, 1968).

The correlated response of 5-week weight follows rather closely the direct response of 8-week weight. However, response in individual weaning weight is virtually absent in the downward selected lines. This may have to do with decreased litter-size of smaller mice and more ample milk supply to the fewer offspring. The reproductive performance and life-span of the mass-selected lines seems to support the notion that body-size optimum for lifetime production is closer to the size of the low body weight lines. While in the smaller lines derived from the crossbred foundation life-production and -span of downward selected lines is equal to that of controls, in the larger lines derived from the randombred base controls are equal to the upward selected line (Table 7). It should be mentioned that H_8 mice are significantly fatter at 8 and 26 weeks of age than L_8 mice (Walter *et al.* 1983). The level of inbreeding of the lines was nearly alike. Therefore, the differences in life-production and -span are to be attributed to the changes brought about by selection for 8-week weight.

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