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Long-term restricted index selection in mice designed to change fat content without changing body size

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Abstract The objective of this study was to determine if low secondary selection differentials, caused by selecting within full-sib families, may have accounted for the failure of an intended restricted selection index to reduce epididymal fat pad weight (EF) without changing body weight (BW) in mice. Replicate lines that had been selected within full-sib families for high (HE) or low (LE) EF, while holding BW constant, were crossed. After two generations of random mating, two replicates were sampled and selection initiated for the same restricted index criteria except that mass selection was used to increase the selection differentials. In both phases of selection the HE restricted index selection, designed to increase EF without altering BW, was in agreement with expectation. In contrast, the LE index, designed to decrease EF without changing BW, did not agree with theory since BW increased while EF decreased only slightly. Therefore, reduced selection differentials could not explain the deviation from theory. A possible explanation may reside in the restricted selection index being more sensitive to changes in genetic parameters due to shifts in gene frequency as a consequence of the selection applied. However, linkage disequilibrium and genetic drift can not be ruled out as contributing factors to the asymmetry of response.

Key words Selection index · Restricted index · Fat · Mice

Introduction

Restricted index selection is expected to maximize genetic gain in the aggregate breeding value of a subset of traits while holding genetic change to zero in a second subset (Kempthorne and Nordskog 1959). An experiment designed to test this theory, by developing divergent mouse lines for fat content while holding body weight unchanged, involved eight generations of replicated within full-sib family selection (Eisen 1992a, b). Selection was based on an index for high or low 12-week epididymal fat pad weight (EF) while holding genetic change in body weight (BW) to zero. Although realized heritabilities of index units (I) were symmetric, the correlated responses in component traits of the restricted index lines were asymmetric. Realized genetic responses for EF and BW in the high-fat restricted index lines (HE) were in agreement with expectation, but responses in the low-fat restricted index lines (LE) did not agree with expectation because EF failed to respond downward and BW increased.

The objective of the present study was to determine if the discrepancy resulted from low selection differentials in the LE replicates caused by selection within families. The approach taken was to attempt to increase the selection differentials by changing from within-family selection to mass selection. Preliminary reports have been presented elsewhere (Eisen 1994a; Eisen et al. 1994).

Materials and methods

Following eight generations of within full-sib family selection, based on the restricted selection index for either high or low fat content without changing body size, the two replicates of each selection treatment were crossed to each other. For the high fat replicates, HE1 (high-fat replicate 1) was crossed to HE2 (high-fat replicate 2), and

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similarly for the low-fat replicates (LF1, LF2) and control replicates (RS1, RS2). The purpose of crossing the replicates was to eliminate inbreeding depression effects which may have occurred within replicates and to remove genetic-drift effects between replicates.

Progeny within each F_1 population (HE, LE and RS) were allowed to random mate without selection for two generations to reduce linkage disequilibrium effects which would be expected to be present due to selection and crossing. In generation 11, two new replicates, consisting of 15 full-sib families each, were randomly chosen from each synthetic population to continue the same selection treatments. These replicates were designated HE4, HE5; LE4, LE5; and RS4, RS5. In the HE and LE replicates, selection was continued for the same restricted index using mass selection instead of within-family selection. To avoid a high degree of inbreeding, at least eight families had to be represented in each replicate. This requirement had only a small effect on reducing the selection differentials. The restricted selection index was derived as $I=11.93\ P_{BW}–0.3323\ P_{EF}$, where P_{BW} and P_{EF} are phenotypic values representing a deviation from the mean for BW and EF, respectively. Replacement animals in the control line were randomly selected within families, as in the earlier generations. Approximately 60 males were scored per replicate selected line in each generation while 30 males were measured in each control-line replicate.

The procedure for collecting data has been described previously (Eisen 1992a, b). Principals of approved laboratory animal care have been followed. Briefly, matings were made at about 9 to 10 weeks of age. Males were euthanized at 12 weeks of age at which time BW and EF were recorded. Only the right epididymal fat pad was weighed because the correlation between right and left fat pads is high (0.98). The right hind-limb subcutaneous fat pad (SF) was dissected as a correlated fat component. EF and SF were adjusted for body weight in two ways: as a percentage of body weight (EF%, SF%) and by using body weight as a covariate (EFADJ, SFADJ). Litter size at birth (LS) and littering rate (LR), the number of females giving birth as a percentage of those mated, were recorded in each generation. Litters were standardized to ten pups at 1 day of age in order to minimize the effect of litter size on the growth of the progeny. All males received Purina Laboratory Chow 5001 (Purina Mills, Richmond, Ind.) *ad libitum* from weaning at 3 weeks to 12 weeks of age.

In generation 20, 40 males were sampled from each replicate-line subgroup to obtain feed-intake and feed-efficiency data. Males were weaned at 3 weeks of age, and two siblings were caged together to make up the experimental unit. Males were fed *ad libitum* Purina Laboratory Chow 5001. Mice were weighed at 3 and 6 weeks of age, and 3 to 6 week postweaning gain, feed intake and feed efficiency (body weight gain/feed intake) per mouse were recorded. Feed intake/$\overline{BW}$ where $\overline{BW}$ is the mean body weight at 3 and 6 weeks of age of the two males caged together, was calculated to adjust feed consumed for maintenance requirements. Feed intake/metabolic body size, where each body weight was raised to a power of 0.75, gave similar results and is not reported.

Primary selection differentials for index units and secondary selection differentials for EF and BW were calculated as the difference between the mean of selected males and the mean of all males. Selection differentials were calculated on an unweighted basis and also weighted by the number of progeny of each selected male measured for the selected trait in the next generation. Selection differentials were halved in each generation since selection was applied to males only. Realized index weights were calculated using the method of Dickerson et al. (1954).

Methods used to estimate direct and correlated responses have been presented previously (Eisen 1992a, b). Data from generations 11 to 19 were used to estimate direct and correlated responses to selection as the regressions of selected-line means on generation number. The selected-line means were deviated from control-line means in each generation to account for environmental effects. Realized heritabilities of index units in generations 11 to 19 were estimated as the regressions of generation mean responses on cumulative selection differentials. Responses and realized heritabilities were also based on divergence between high and low index lines (Falconer 1989). Realized responses and realized heritabilities estimated from generations 0 to 8 and 11 to 19 were pooled to obtain overall values. Hill (1972) has shown that the standard errors of these least-squares regression coefficients are biased downward because of a positive correlation between generation means. Therefore, standard errors were estimated from the variation between replicates or approximated by the methods of Hill (1972).

Data on feed intake and feed efficiency in generation 20 were analyzed using a model that included a fixed effect of selection treatment, a random replicate effect, selection treatment×replicate interaction, and a random residual. The interaction mean square was used to test for selection effects. Orthogonal comparisons were used to test for selection divergence (HE–LE) and asymmetry of selection response (HE+LE–2∗RS).

Results

Phenotypic statistics for the control-line replicates pooled within generations 11 to 19 (Table 1) were similar to those in generations 0 to 8 (Eisen 1992a). Epididymal fat pad weight was considerably more variable (CV=37.38%) than body weight (CV=9.25%). The regressions of index units and component traits on generation number were not significantly different from zero in the control replicates.

Phenotypic statistics in the selected lines for index units and the component traits are given in Table 2. Phenotypic variances for I and EF and the phenotypic covariance and phenotypic correlation between BW and EF were larger ($P< 0.01$) in HE compared to LE. The phenotypic variance for BW did not differ significantly ($P>0.05$) between the HE and LE lines. The LE lines did not differ ($P>0.05$) from the unselected controls (RS) for any of these statistics (data not shown).

Cumulative weighted primary selection differentials were consistently less than unweighted selection differentials, the ratios being 0.97, 0.90, 0.89 and 0.93 for HE4, HE5, LE4 and LE5, respectively. The absolute values of the primary (index units) and one of the secondary (EF) weighted cumulative selection differentials were larger in HE than in LE, being 1.8 times greater for I and 6.4 times greater for EF (Table 3). This result can be explained by the larger phenotypic variances observed for I and EF in the HE replicates, compared with the LE replicates, which was caused by a positive correlation between the mean and variance of I and EF, respectively. In contrast, the secondary selection differentials for BW did not differ between the selected lines.

The primary selection differentials were 1.74- and 1.25-times greater in HE and LE, respectively, for mass selection (generations 11 to 19) than for the within-family selection practiced in the earlier generations (Eisen 1992a). The selection secondary differentials for EF were 2.70- and 1.33-times greater in HE and LE, respectively, for mass selection than for within-family selection.

The realized index weights were close to expectation for all lines except HE5, where the relative weight for BW was less than intended (Table 3). The mean relative index weight applied to body weight in the LE replicates based on mass selection (35.0) was less than that observed for within-family selection (48.0) (Eisen 1992a). The relative index weights for BW in the HE lines based on mass se-

Table 1 Control-line means, phenotypic standard deviations ($\sqrt{V_p}$), coefficients of variations (CV), and regressions of generation means on generation number±standard error (b±SE)

Trait^{a}	Mean^{b}	$\sqrt{V_p}$^{b}	CV^{b}	b±SE^{c}
I	337.0	37.99	11.27	–1.91±1.21
BW, g	37.3	3.45	9.25	–0.01±0.15
EF, mg	325.0	122.45	37.38	5.48±5.63

[a] I, Index units; BW, 12-week body wt; EF, 12-week epididymal fat pad wt
[b] Pooled within replicate controls (RS4, RS5) and generations 11 to 19 (*n*=532)
[c] Pooled within replicate controls

Table 2 Estimates of phenotypic statistics in selected lines for index units and component traits^{a}

Line	Phenotypic variance^{d}			Phenotypic covariance (BW, EF)	Phenotypic correlation (BW, EF)
	I	BW, g^2	EF, mg^2		
HE	3754^{b}	15.88^{b}	68333^{b}	763.81^{b}	0.73^{b}
LE	1453^{c}	14.32^{b}	14030^{c}	269.24^{c}	0.60^{c}

[a] Pooled within replicates (HE4, HE5; LE4, LE5) and generations 11 to 19 (*n*=1036 for HE and *n*=1032 for LE)
[b,c] Statistics within a column with no superscript in common differ ($P< 0.01$)
[d] See Footnote^{a} in Table 1 for definition of traits

Table 3 Primary (I) and secondary (BW, EF) weighted cumulative selection differentials (WCSD) and realized relative index weights (RRIW) from generations 11 to 19

Line	WCSD^{b}			RRIW	
	I	BW, g	EF, mg	BW	EF
HE4	–280.77	5.45	1017	31.78	–1
HE5	–292.56	8.96	1125	24.13	–1
LE4	147.56	7.78	–166	33.60	–1
LE5	168.77	9.07	–168	36.40	–1
Intended^{a}				35.90	–1

[a] Based on restricted selection index using mass selection
[b] Values are halved because selection was only applied to males

Table 4 Regression coefficients±SE of index units and component means on generation number (generations 11 to 19)

Line	Trait		
	I	BW, g	EF, mg
HE4^{a}	–11.72±2.70**	–0.24±0.13	26.1± 8.1**
HE5^{a}	–11.67±2.70**	0.62±0.13**	57.5± 8.1**
Pooled^{b}	–11.69±0.03**	–0.19±0.43	41.8±15.7*
LE4^{a}	11.08±2.70**	0.36±0.13**	–20.4± 8.1**
LE5^{a}	12.41±2.70**	1.04±0.13**	0.4± 8.1**
Pooled^{b}	11.75±0.67**	0.70±0.34*	–10.0±10.4*
Divergence 4^{a}	–22.80±2.84**	–0.61±0.13**	–46.5±12.3**
Divergence 5^{a}	–24.08±2.84**	–0.42±0.13**	57.1±12.3**
Pooled^{b}	–23.44±0.64**	–0.51±0.09**	51.8± 5.3**
Asymmetry^{b}	0.06±0.69	0.89±0.77	31.8±36.8

* $P< 0.05$, ** $P< 0.01$
[a] Standard errors estimated by least-squares
[b] Standard errors estimated from variance between replicates
[c] See footnote^{a} in Table 1 for definition of traits

lection (28.0) and within-family selection (26.7) (Eisen 1992a) were in close agreement.

Direct selection responses for index units from generations 11 to 19 were significant for HE and LE with no evidence of asymmetry (Table 4), and they were larger than the respective pooled responses for the first eight generations based on within-family selection (–5.48±2.48 for HE, and 4.40±1.74 for LE; Eisen 1992a). Pooled divergence in index units was significant ($P< 0.01$). While the statistical tests for asymmetry in the components of the index (BW, EF) were not significant, there was clear evidence of asymmetry from the slopes pooled across generations (Table 5) and the plots of generation means against generation number (Fig. 1b, c). In the HE replicates, the pooled correlated response in BW was not significant while that for EF increased ($P< 0.05$). In contrast, the correlated response in BW increased ($P< 0.05$) whereas that for EF did not change in the LE replicates.

Generation means, as a deviation from the control, pooled over replicates are plotted in Fig. 1a–c for index units and the components traits. Table 5 gives the responses per generation and per additive genetic and phenotypic standard deviation, pooled across all generations of selection. The standard deviations were taken from the control populations as being representative of the base-population values. Pooled responses per generation were consistent with the responses in generations 11 to 19. The overall responses in index units were about 6 additive genetic and 3.5 phenotypic standard deviations for the HE and LE replicates. In the HE line, epididymal fat pad weight increased 5.8 additive genetic standard deviations while BW did not change significantly. Thus, epididymal fat pad weight as a percentage of body weight (EF%) increased. The LE line had no significant change in EF, but BW increased 3.8 additive genetic standard deviations. As a result, EF% decreased in LE.

Realized heritability estimates for index units in generations 11 to 19 and the earlier generations 0 to 8 are given in Table 6. The realized heritabilities in the earlier generations have been converted to a mass selection basis. These realized heritabilities were similar for the HE and LE lines. In the HE line, realized heritability decreased in the later generations whereas the reverse was found in the LE line. The LE line had a higher realized heritability than HE in the second phase of the study; this asymmetry was highly repeatable across replicates: HE4=0.34±0.08, HE5=0.31 ±0.07, LE4=0.58±0.14, LE5=0.58±0.12. The asymmetry in realized heritability was a result of a higher selection differential in HE than in LE accompanied by similar selection responses in index units in each line. The realized

Table 5 Direct and correlated responses per generation (R/gen.), per additive genetic standard deviation ($R/\sqrt{V_A}$), and per phenotypic standard deviation ($R/\sqrt{V_P}$), pooled over all generations[a]

Trait	HE			LE		
	R/gen. ± SE	($R/\sqrt{V_A}$)	($R/\sqrt{V_P}$)	R/gen. ± SE	($R/\sqrt{V_A}$)	($R/\sqrt{V_P}$)
I	−8.59 ± 1.24	−6.32	−3.62	8.07 ± 0.93	5.93	3.41
BW, g	0.11 ± 0.36	0.77	0.51	0.54 ± 0.17	3.78	2.48
EF, mg	29.7 ± 8.6	5.77	4.05	−4.9 ± 5.8	−0.95	−0.67
EF%	0.070 ± 0.010	5.69	4.01	−0.021 ± 0.011	−1.71	−1.20

[a] Pooled across replicates and generations 0 to 8 and 11 to 19

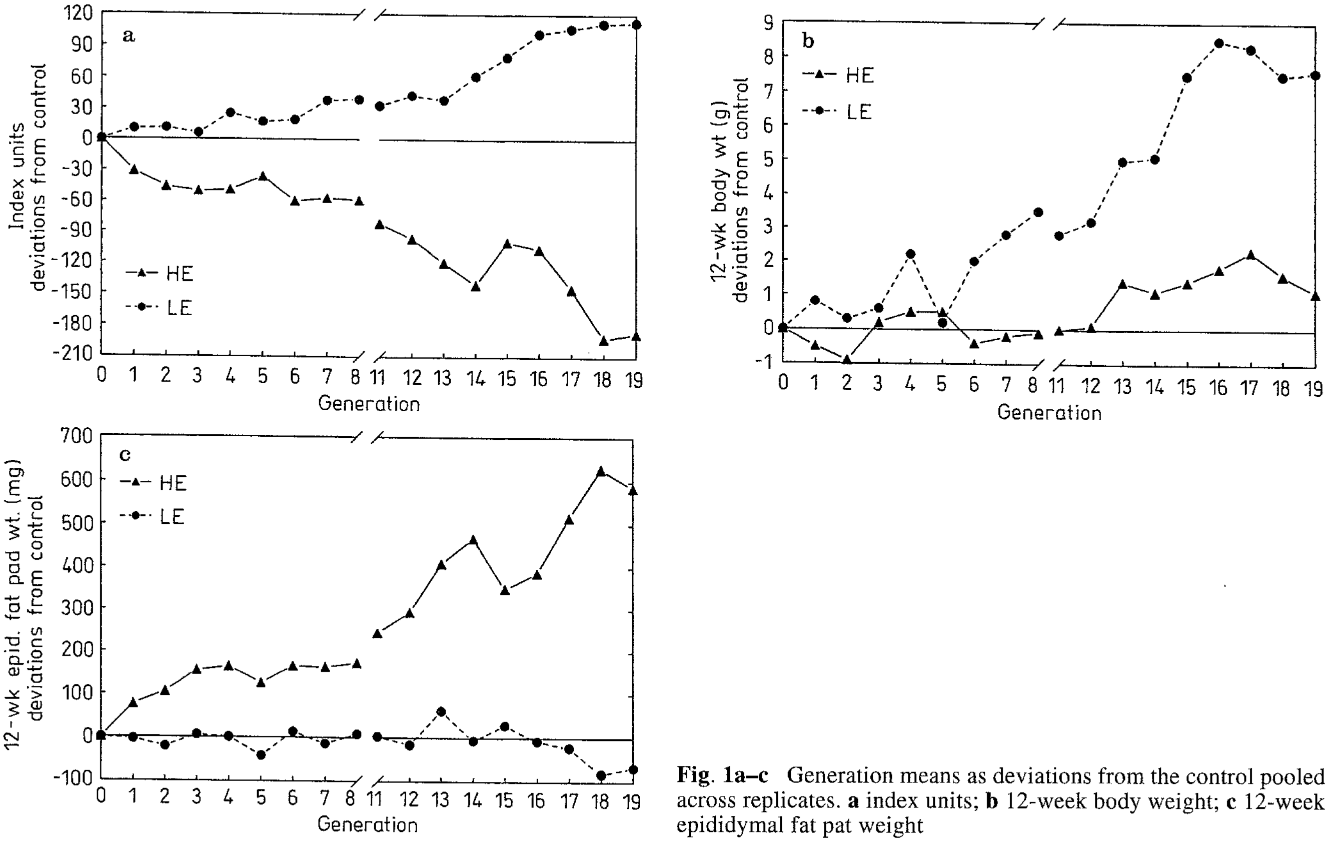

Fig. 1a–c Generation means as deviations from the control pooled across replicates. **a** index units; **b** 12-week body weight; **c** 12-week epididymal fat pat weight

Table 6 Realized heritability estimates ± SE for index units pooled over replicates

Generations	HE	LE	Divergence
0–8[a]	0.42 ± 0.20	0.44 ± 0.19	0.42 ± 0.05
11–19	0.32 ± 0.01	0.58 ± 0.002	0.41 ± 0.003
Pooled[b]	0.35 ± 0.10	0.56 ± 0.10	0.41 ± 0.03
Son-sire regr.[c]	0.33 ± 0.10		

[a] Eisen (1992a)
[b] Weighted by inverse of the variance
[c] Eisen and Prasetyo (1988)

heritability for divergence was similar in the two phases of the study. The pooled realized heritability for divergence and for HE was not significantly different from the base-population estimate.

When epididymal fat pad weight was adjusted for the covariate body weight (EFADJ), the selection lines diverged symmetrically with HE increasing and LE decreasing from generations 11 to 19 (Table 7). A similar result was found for the adjusted subcutaneous fat depot (SFADJ). When the fat depots were expressed as a percentage of body weight (EF%, SF%), there was again a tendency for asymmetry, although it was not statistically significant. The increase in EF% and SF% in the HE lines was greater than the decrease in EF% and SF% in the LE lines.

Littering rate (LR) and litter size (LS) were monitored for changes in fitness as a result of selection (Table 7). Littering rate had no significant overall trend. Litter size had a small decrease ($P < 0.05$) in HE and a nonsignificant increase ($P > 0.05$) in LE.

Least-squares means of growth traits in males of generation 20 are given in Table 8. LE males had greater ($P < 0.05$) 3- and 6-week body weights and postweaning gains than HE males. Six-week body weight and postweaning gain of HE males did not differ from the RS controls. LE males consumed more ($P < 0.05$) feed than HE males,

Table 7 Regression coefficients ± SE of correlated trait means on generation number (generations 11 to 19)

Line	Trait					
	EFADJ, mg	EF%	SFADJ, mg	SF%	LR%	LS
HE4[a]	34.6 ± 8.0**	0.074 ± 0.018**	10.7 ± 4.2*	0.023 ± 0.010*	0.39 ± 0.49	–0.046 ± 0.070
HE5[a]	31.6 ± 8.0**	0.113 ± 0.018**	19.5 ± 4.2**	0.062 ± 0.010**	–1.18 ± 0.49*	–0.023 ± 0.070
Pooled	33.1 ± 1.5**	0.094 ± 0.019**	15.1 ± 4.4**	–0.042 ± 0.019	–0.39 ± 0.78	–0.034 ± 0.011**
LE4[a]	–34.5 ± 8.0**	–0.054 ± 0.018	–14.8 ± 4.2**	–0.023 ± 0.010*	–0.02 ± 0.49	–0.015 ± 0.070
LE5[a]	–47.5 ± 8.0**	–0.020 ± 0.018	–13.1 ± 4.2**	–0.006 ± 0.010	–0.61 ± 0.49	0.074 ± 0.070
Pooled[b]	–41.0 ± 6.5**	–0.037 ± 0.017*	–14.0 ± 0.9**	–0.009 ± 0.14	–0.31 ± 0.29	0.030 ± 0.040
Divergence[a]	69.1 ± 10.9**	0.128 ± 0.025**	25.5 ± 7.0**	0.046 ± 0.012**	–0.40 ± 0.53	–0.031 ± 0.077
Divergence[a]	79.1 ± 10.9**	0.133 ± 0.025**	32.6 ± 7.0**	0.056 ± 0.012**	–0.57 ± 0.53	–0.097 ± 0.077
Pooled[b]	74.1 ± 5.0**	0.131 ± 0.003**	29.1 ± 3.5**	0.051 ± 0.005**	–0.08 ± 0.48	–0.064 ± 0.033
Asymmetry[b]	–7.9 ± 8.1	–0.057 ± 0.036	1.2 ± 5.3	0.033 ± 0.034	0.71 ± 1.08	–0.005 ± 0.055

* $P<0.05$, ** P, 0.01

[a] Standard errors estimated by least-squares

[b] Standard errors estimated from variance between replicates

[c] EFADJ, SFADJ are epididymal and subcutaneous fat pad weights, respectively, adjusted for the covariance body weight, EF%, SF% are epididymal and subcutaneous fat pad weights, respectively, as a percentage of body weight; LR is littering rate; LS is litter size at birth

Table 8 Least-squares means ± SE of growth traits in males of generation 20

Trait	Line[c]			SE
	HE	LE	RS	
3-week body wt, g[a]	12.9	14.5	13.6	0.18
6-week body wt, g[a, b]	30.4	35.2	31.0	0.52
Postweaning gain, g/d[a, b]	0.83	0.98	0.83	0.020
Feed intake, g/d[a]	6.67	7.25	7.17	0.11
Feed intake/$\overline{\mathrm{BW}}$[a, b]	0.234	0.226	0.247	0.0033
Feed eff., g/g[a, b]	0.125	0.136	0.116	0.0025

[a] Divergence (HE – LE) is significant at $P<0.05$

[b] Asymmetry (HE + LE – 2*RS) is significant at $P<0.05$

[c] Pooled across replicates; each line-replicate mean was based on 20 cages with two male mice per cage

but feed intake per unit body weight was actually lower in HE than LE males. The feed efficiency of LE males exceeded ($P<0.05$) that of HE males, and HE males were more ($P<0.05$) efficient than RS males. Asymmetric correlated responses ($P<0.05$) were found for 6-week body weight, postweaning gain, feed intake/$\overline{\mathrm{BW}}$ and feed efficiency.

Discussion

In an earlier experiment, it had been shown that within full-sib family restricted index selection for high or low epididymal fat pad weight, holding body weight constant, led to asymmetric correlated responses to selection. Selection in HE for high EF, holding BW unchanged, was successful across eight generations, but selection in LE for low EF, holding BW unchanged, was not. In the latter case, EF did not change while BW increased. One possible cause for the unexpected results in LE was relatively weak cumulative selection differentials which may have led to the positive response in BW and the lack of response in EF because of genetic drift (Eisen 1992a). The realized relative index weights applied to BW in the LE replicates were greater than expected, which may also have contributed to the unexpected findings.

It was reasoned that mass selection using the same index would overcome this problem and result in a symmetric response. Therefore, the replicates were crossed to minimize genetic drift and inbreeding effects, and two new replicates were sampled to initiate mass selection for the index within each selection-treatment population. The responses for EF and BW in the HE and LE lines in the later generations were qualitatively the same as those in the earlier generations. Responses per generation were greater in the later generations, as expected, because of the higher realized selection differentials.

Based on these results, other explanations for the asymmetry are necessary. Hill and Meyer (1984) showed that poor estimation of parameters may cause the actual response in the restricted variable to differ markedly from intended. However, this would not explain the fact that selection was asymmetric, with selection in one direction agreeing closely with expectations. It is unlikely that genetic drift can explain the responses in the LE replicates since the asymmetry was repeatable across both phases of the study.

Eisen (1977) suggested that restricted index selection may be more sensitive to changes in genetic parameters than single-trait selection. Mortimer and James (1987) reported simulation results in which restricted index selection is more sensitive to changes in genetic parameters due to shifts in gene frequency. Analytical and computer simulation studies of single-trait selection indicate that asymmetrical correlated responses can be expected frequently due to asymmetry of the genetic covariance between the

Table 9 Least-squares means of selected lines at 12 weeks of age

Line[f]	BW, g	EF, mg	EF %
HE	35.9 ± 0.4^{a}	590 ± 19^{a}	1.63 ± 0.04^{a}
LF	36.5 ± 0.5^{a}	171 ± 19^{b}	0.46 ± 0.04^{b}
RS	36.2 ± 0.6^{a}	329 ± 26^{c}	0.91 ± 0.06^{c}
HF	42.0 ± 0.5^{b}	816 ± 19^{d}	1.93 ± 0.04^{d}
LE	42.5 ± 0.4^{b}	249 ± 19^{e}	0.58 ± 0.04^{e}

[a, b, c, d, e] Means within the same column with no superscripts in common are different ($P<0.05$)

[f] Each line mean was based on 40 to 50 mice

two traits (Bohren et al. 1966). The situation obviously will be more complex for a restricted selection index. Also, under the infinitesimal model, asymmetry in correlated responses to selection can be caused by linkage disequilibrium (Villaneuva and Kennedy 1992).

Although the restricted selection-index results in the LE line did not agree with expectation, there still was a reduction in epididymal fat pad percentage because of the increased body weight and a small reduction in epididymal fat pad weight. This result contrasts with many reports of positive correlated responses in fat percentage due to selection for increased adult body weight or postweaning weight gain (Robinson and Bradford 1969; Timon et al. 1970; Eisen and Roberts 1981).

One purpose in developing selected lines having a different fat content at similar body weights and ages was to provide unique genetic models to study the genetic basis of energetic efficiency, rate of fat and lean deposition, and maintenance requirements (Eisen 1989, 1992a, b). A contemporary comparison of the HE, LE and RS lines with lines selected directly for high (HF) and low (LF) epididymal fat pad percentage indicates that this goal has been attained (Table 9). Here we have two sets of lines that differ in fat content at the same body weight and age (HE vs LF and HF vs LE) with the latter set having a higher growth rate than the former. Thus, energetic efficiency can be compared in HE vs LF and HF vs LE, respectively, without the confounding effects of body weight and age, which are generally used as covariates when comparing lines differing in fat- or lean-tissue growth rate.

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