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Mixed model analysis of a selection experiment for food intake in mice

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Summary

Data from 23 generations of mice selected for increased and reduced appetite were analysed by Restricted Maximum Likelihood fitting an animal model with litters as additional random effects. Traits considered were food intake between 4 and 6 weeks of age adjusted for 4-week body weight (AFI), the selection criterion, and body weight at 6 weeks (6WW). Selection was carried out within families. A high and a low selection line and a control were maintained in each of three replicates. Analyses were performed for each replicate separately taking subsets of the data spanning different numbers of generations. Overall estimates of heritabilities were 0·15 for AFI, which agreed well with realized heritability estimates, and 0·42 for 6WW. The litter variance, expressed as a proportion of the phenotypic variance, was 0·21 for both traits, yielding intraclass correlations of full-sibs of 0·29 and 0·42, respectively. Similar results were obtained for variances of each trait using univariate and multivariate analyses. From the latter, estimates of correlations between the two traits were 0·46 for additive genetic, −0·19 for litter and 0·31 for residual effects, resulting in a phenotypic correlation of 0·23. Analyses of data from generations 2–7, 8–13 and 14–23 separately showed a marked decrease in genetic variance and heritability in later generations for both traits. Heritabilities of AFI, for instance, were 0·24, 0·10 and 0·07, respectively. These changes could not be attributed to the effects of inbreeding or of selection in an infinitesimal model and suggested that some change in variance due to change in gene frequency had occurred during the course of the experiment.

1. Introduction

Traditionally, data from selection experiments have been analysed by relating selection responses to selection differentials, and estimating realized heritabilities and correlations (Falconer, 1989*a*). Although covariances among animals within generations are largely ignored in such analyses, in a number of situations the simple regression of (cumulated) response on selection differential may be almost as efficient as a more cumbersome maximum likelihood estimator (Hill, 1972).

Statistical methods using mixed models have come to dominate the analysis of data from livestock improvement schemes, both in the prediction of breeding values and the estimation of genetic parameters. Recently, a model of analysis which defines additive genetic effects for all animals individually and accounts for all variances and covariances among them, 'animal model', is being increasingly used. It allows parents without records to be included and thus information on all known relationships to be incorporated, so the correct correlation structure for animals across many generations is used.

For data from selection experiments, initial applications of mixed models have been to evaluate response to selection. Sorensen & Kennedy (1984*a*) compared least squares and mixed model estimates of selection response. Blair & Pollak (1984) suggested that mixed models may reduce the need for a control population when estimating genetic trend. It has been shown, however, that estimates of realized heritabilities from such analyses depend on the assumed values of genetic variances (Thompson, 1986).

Maximum likelihood (ML) estimation provides a framework to accommodate the estimation of variance components, the estimation of fixed effects and the prediction of realized values of random effects under a mixed model. Moreover, if all information determining selection decisions is incorporated in the analysis, it can provide estimates unbiased by selec-

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tion. Thompson (1977) considered ML estimates of heritability for data from several generations. Sorensen & Kennedy (1984*b*) demonstrated that use of the relationship matrix with the animal model would account for drift and selection and allowed estimates of the additive genetic variance in the base population to be obtained. This does, however, assume the infinitesimal model (Bulmer, 1980), i.e. very many unlinked additive genes such that their frequencies do not change as a result of selection.

Lines of mice were established in this laboratory and selected divergently for traits of growth, either lean mass, proportion of fat, or food intake adjusted for body weight (Sharp *et al.* 1984). The objectives of this paper are twofold: to examine the scope of the animal model in the analysis of data from a long-term selection experiment in mice, using partial data and relationship information to assess changes in additive genetic variance and covariance during the course of the experiment, and thereby to investigate the inheritance of food intake and aspects of its association with body weight. This analysis is restricted to the lines selected on adjusted food intake from 4 to 6 weeks of age (A lines) and to this trait and 6-week weight (6WW), for it was feasible only to conduct bivariate analyses.

2. Material and methods

(i) *The experiment*

Records were obtained for body weight at 4 and 6 weeks of age and food intake between 4 and 6 weeks for a total of 10941 mice from 23 generations of selection. The foundation of the lines, basically from a three way cross of two inbred and an outbred stock, and results for the first 11 generations are described by Sharp *et al.* (1984). Means for all lines at generation 20 are given by Hastings & Hill (1989).

Selection was carried out within families, selecting for adjusted food intake (AFI), namely food intake (FI) corrected for 4-week body weight (4WW) by phenotypic linear regression within sex. The regression equations used were: $AFI = FI + 1{\cdot}65\ (16{\cdot}1 - 4WW)$ for females, and $AFI = FI + 2{\cdot}21\ (17{\cdot}8 - 4WW)$ for males, with all units in grams (Sharp *et al.* 1984). Three replicates were established from the same base population with 16 full-sib families each. Each replicate comprised a line selected for high (H) AFI, a line for low (L) AFI and a random bred control (C). All lines were maintained with 16 full-sib families each up to generation 8, and 8 families subsequently. Litter sizes were standardized to 6–12 young by culling and cross-fostering. Up to 8 progeny per litter, 4 of each sex, were recorded in the H and L lines but only 2 of each sex in the C lines. Recording of the control stopped after generation 20 while that in the selection lines continued to generation 23. Records from generations 0 and 1 were not utilized because there was a subsequent change in diet.

(ii) *Analyses*

Traits analysed were AFI, the selection criterion, and 6WW. Uni- and bivariate analyses were carried out by Restricted Maximum Likelihood (REML) fitting an animal model with litters as an additional random factor. Estimates were obtained using a derivative-free algorithm employing the Simplex method to locate the maximum of the log-likelihood function (Meyer 1989, 1990). Fixed effects fitted were generations (2–23), line (H, C, L) sex (male, female) and a litter-size class (7 levels, for 6–12 mice reared).

Data were analysed one replicate at a time, selecting various subsets of the data. Since data structure and numbers of records were similar for all replicates, overall estimates of variances were obtained simply as arithmetic means over replicates. Better estimates could have been obtained by combined likelihood analyses, and tests of differences among replicates made, but this would have greatly increased computing requirements. Pooled estimates of genetic parameters were then calculated from the mean variance components.

In the first set of *univariate analyses (I)*, generation 2 always comprised the first generation of records but the number of generations taken was increased successively to give 7 data sets. Pedigree information for generations 0 and 1 was included in the analysis to link the three selection lines within each replicate. For analyses including records from all generations, solutions for animal and fixed effects were obtained at convergence.

In the second set of *univariate analyses (II)* consecutive subsets of the data, namely generations 5–7, 8–13 and 14–23, were taken. Each of these was carried out firstly, including all pedigree information available back to generation 0, and, secondly, utilizing only pedigrees on animals in the data, i.e. treating parents born in generations 4, 7 or 13 as unrelated base animals. In analyses omitting data from earlier generations, parents had been selected on AFI but the data on which selection decisions were based were not used, so estimates were expected to be biased by selection. To overcome this problem, Graser *et al.* (1987) suggested that these parents be treated as fixed (i.e. not randomly sampled). All analyses of later generation data sets were therefore repeated treating parents without data as fixed.

For comparison, estimates of realised heritabilities within full-sib families were obtained for both sets of univariate analyses as regression of response on cumulative selection differential. Selection differentials were calculated within litter and sex, as average difference of selected mice from their respective litter means. Responses were taken as the deviation between

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means of the selected lines and the corresponding control lines. Estimates were obtained for each selection line and from the divergence between high and low lines for each replicate. As for variance components, pooled estimates were obtained as simple arithmetic means over replicates.

Multivariate analyses of AFI and 6WW were carried out for the complete data and the subsets comprising generations 2–7, 8–13 and 14–23. As for univariate runs, pedigrees for generations 0 and 1 were included in the analysis for data sets starting with generation 2. For simplicity, analyses of the other two data sets ignored back pedigrees and all animals were treated as random.

3. Results

Characteristics of the data structure for the various subsets are summarized in Table 1. Although analyses were carried out for one replicate at a time, numbers were nearly the same in each replicate and are given separately only for the complete data (generations 2–23). For analyses omitting data from earlier generations, use of back pedigree information greatly increased the number of animals included in the analysis when all animals were treated as random effects. When parents without records were regarded as fixed, however, the total number of animal effects to be fitted was the same, whether or not earlier pedigree information was included. When pedigrees for fixed animals were included, the additional parents without random progeny 'dropped' out of the analysis since there were no covariances linking them to animals with records.

Overall means changed little over time (Table 1) for selection responses high and low were about equal. The standard deviations (S.D.) shown were calculated across selection lines within replicates and thus increased when records for later generations were included due to increasing divergence between lines, but there was little trend up to about generation 20 in within line and generation S.D.s. For both AFI and 6WW, total variation tended to be slightly lower between generations 6 and 14. For AFI in particular though, S.D.s showed an increase in the last few generations which was accompanied by a reduction in line means.

(i) *Univariate analyses I*

Results from univariate analyses including data from increasing numbers of generations are given in Table 2. For both traits, estimates of the additive genetic variance (σ^2_A) decreased slightly but consistently as more data from later generations were considered. The low value for AFI for generations 2–4 included an estimate of 0 for one replicate, so that all variation between litters was assigned to the estimate of the variance due to common environment (σ^2_C) which was correspondingly increased. With only three generations of data this was presumably an expression of sampling error. In a full-sib family structure, the two components, σ^2_A and σ^2_C, have a high negative sampling correlation, particularly when the data span few generations (Meyer, 1989), so their sum and the covariance of full sibs are estimated quite accurately.

Estimates of σ^2_C for both traits varied little between analyses, except for the outlier discussed above. Error components (σ^2_E) showed a slight increase for 6WW and a more marked increase for AFI for analyses including data from generations 17 or later, corresponding to the pattern observed for S.D.s within lines and generations. Differences between analyses in estimates of phenotypic variances (σ^2_P), heritabilities (h^2), so-called c-squared effects ($c^2 = \sigma^2_C/\sigma^2_P$), and intra-class correlations of full-sibs ($t = h^2/2 + c^2$) then reflected those in the components from which they were derived. Estimates of additive genetic variance ranged from 3·6 to 4·5 g^2 and of heritability from 0·13 to 0·17 among replicates at generation 23, i.e. were within 15% of their mean.

For 6WW, σ^2_P changed little over generations, decreasing slightly with σ^2_A. Estimates of h^2 dropped from 0·48 to 0·42, while c^2 remained more or less constant at a value of 0·22 and so t was reduced very little. For AFI, estimates of σ^2_P increased for analyses of records from generations 2 to 19 and, even more markedly, generations 2 to 23 due to an increase in σ^2_E in the last generations. As a result, h^2 decreased proportionally more than σ^2_A, from an estimate of 0·24 for records up to generation 7, to 0·15 for the complete data and although σ^2_C showed no trend over time, c^2 decreased from 0·24 to 0·21 and t from 0·35 to 0·29.

Estimates of the realised heritability within full-sib families for AFI from the divergence between high and low lines are given in Table 3. Corresponding within family heritabilities from REML analyses were calculated as $(\sigma^2_A/2)/(\sigma^2_A/2 + \sigma^2_E)$. Except for analyses including only the first few generations, when sampling errors are obviously higher, they agreed well with their counterparts from REML analyses. Patterns for estimates for high and low lines separately (not shown) were similar. On average, realized heritabilities were slightly higher than REML values. The opposite would have been expected if all data from selected lines had been utilized (Juga & Thompson, 1989), but in this analysis data from the first two generations were omitted.

Mean additive genetic (breeding) values of animals predicted from the model using all data are shown in Fig. 1. Response in AFI appears to have been very similar for all replicates. Predictions depend on the estimates of variance components, so the slightly larger divergence in replicate 1 could partly be attributed to a higher heritability estimate for this

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Table 1. *Number of records, total number of animals in the model (i.e. including those in the pedigree without records) and number of litters summed over replicates, together with overall means and standard deviations (S.D.) within and between lines, averaged over replicates, for the subsets of data analysed. Values for individual replicates are given for the complete data*

Data set	No. of records	No. of animals	No. of litters	6-week weight		Adjusted food intake	
				Mean (g)	S.D. (g)	Mean (g)	S.D. (g)
2–4[a]	2391	3016	407	23·8	3·52	62·3	5·90
2–7	4847	5474	816	24·4	3·59	62·7	6·37
2–10	6060	6698	1091	24·7	3·68	62·6	6·43
2–13	7242	7882	1294	24·8	3·71	62·3	6·59
2–16	8441	9012	1496	24·9	3·77	62·4	6·90
2–19	9682	10328	1701	24·8	3·80	62·5	7·27
2–23	10941	11593	1907	24·8	3·91	62·7	7·88
Rep. 1[b]	3582	3782	636	24·6	3·96	63·2	8·30
Rep. 2	3660	3881	626	25·1	3·71	63·1	7·27
Rep. 3	3699	3930	645	24·8	4·07	61·9	8·06
5–7	2456	2732[c] 3905	409	25·0	3·54	63·1	6·70
8–13	2395	2677 4674	478	25·6	3·81	61·3	6·91
14–23	3699	3845 6759	613	24·8	4·27	63·7	9·85

[a] Generations included.
[b] Replicate.
[c] No. of animals for analyses excluding back pedigrees or treating all animals as fixed (first row) and including back pedigrees and treating all animals as random (second row).

Table 2. *Estimates of additive genetic* (σ^2_A), *common environmental* (σ^2_C), *error* (σ^2_E) *and phenotypic* (σ^2_P) *variance components, pooled over replicates, from univariate analyses of data sets including data from increasing numbers of generations; with resulting estimates of heritabilities* (h^2), *'c-squared' effects* (c^2) *and the intraclass correlation of full sibs* (t)

Data set	σ^2_A	σ^2_C	σ^2_E	σ^2_P	h^2	c^2	t
			Adjusted food intake (g)				
2–4	2·79	6·84	13·91	23·57	0·118	0·290	0·349
2–7	5·66	5·66	12·69	24·00	0·236	0·236	0·354
2–10	4·71	5·74	13·26	23·81	0·198	0·241	0·340
2–13	4·08	5·85	13·52	23·44	0·174	0·250	0·337
2–16	4·11	5·94	13·95	24·00	0·171	0·248	0·333
2–19	4·35	5·81	14·35	24·50	0·178	0·237	0·326
2–23	4·05	5·76	17·41	27·22	0·149	0·212	0·286
Rep. 1	4·52	5·16	17·28	26·95	0·168	0·191	0·275
Rep. 2	3·61	6·17	18·14	27·91	0·129	0·221	0·286
Rep. 3	4·03	5·95	16·82	26·80	0·151	0·222	0·298
			6-week weight (g)				
2–4	3·73	1·81	2·76	8·31	0·449	0·218	0·442
2–7	3·96	1·72	2·53	8·21	0·482	0·210	0·451
2–10	3·90	1·65	2·50	8·05	0·484	0·205	0·447
2–13	3·75	1·70	2·55	8·00	0·469	0·213	0·447
2–16	3·44	1·87	2·50	7·81	0·440	0·239	0·460
2–19	3·38	1·70	2·74	7·82	0·432	0·217	0·434
2–23	3·34	1·66	2·96	7·95	0·420	0·209	0·419
Rep. 1	3·61	1·74	2·32	7·66	0·471	0·227	0·463
Rep. 2	2·93	1·77	3·41	8·11	0·362	0·218	0·399
Rep. 3	3·47	1·46	3·15	8·08	0·429	0·181	0·396

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Table 3. *Estimates of the realized heritabilities within full-sib families for adjusted food intake from divergence between high and low selection lines, together with corresponding within-family heritabilities derived from REML estimates of variance components*

Data Set	No. of points	Replicate no. 1	Replicate no. 2	Replicate no. 3	Mean
2–4	2	1·014[a]	0·206	0·219	0·480
		0·168	0	0·098	0·091
2–7	5	0·417	0·304	0·245	0·322
		0·205	0·212	0·128	0·182
2–10	8	0·221	0·177	0·202	0·200
		0·174	0·140	0·133	0·151
2–13	11	0·174	0·114	0·131	0·140
		0·153	0·119	0·118	0·131
2–16	14	0·160	0·119	0·132	0·137
		0·150	0·120	0·114	0·128
2–19	17	0·149	0·134	0·165	0·149
		0·146	0·118	0·130	0·132
2–23	21	0·132	0·125	0·142	0·133
		0·116	0·090	0·107	0·104
5–7	2	0·638	0·366	0·035	0·350
		0·187	0·262	0·251	0·183
8–13	5	0·079	−0·046	0·034	0·027
		0·041	0·163	0·008	0·085
14–23	9	0·060	0·077	0·077	0·070
		0·029	0·029	0·085	0·039

[a] First line, realized heritability; second line, REML estimate.

data set. For all replicates, the rate of response to selection seemed to fall after about generation 16. Correlated responses in 6WW were markedly less homogeneous; for replicate 2 there appeared to be little genetic difference between the C and L lines.

In order to compare predicted generation means from the analysis with the observed means, predictions for each generation and line were calculated as the sum of estimates of line and generation effects and the mean additive genetic value of animals. These are given in Fig. 2 for the H and L lines together with the corresponding phenotypic means, both expressed as deviations from the control. On the whole, predictions agreed well with the observed values, suggesting that the model of analysis used fitted the data reasonably well.

(ii) *Univariate analyses II*

Table 4 contains estimates from analyses of parts of the data omitting records from earlier generations. Differences between estimates from analyses including and excluding pedigree information back to generation 0 were similar for both traits, so the latter are not shown for 6WW. As expected, estimates of σ_A^2 utilizing all pedigree information were consistently higher than those ignoring back pedigrees. For the latter, parents (without records) of the first generation of animals with records were treated as if they were unrelated, so animals were implicitly assumed to be less inbred than they really were and the estimate of σ_A^2 was biased downwards. For both traits, this bias was less when treating parents without records as fixed than when treating them as random. On average, estimates of σ_A^2 were somewhat higher when parents without records were treated as fixed. This difference was larger for AFI, the trait under selection, than for 6WW, suggesting that the procedure may indeed have reduced bias due to selection of parents.

Estimates of σ_C^2 differed little between the four analyses for each subset while, on average, estimates of the residual variance (σ_E^2) tended to be slightly lower when treating base animals as fixed than when treating all animals as random. Resulting estimates of the variance within full-sib families (σ_W^2), calculated as $\sigma_A^2/2+\sigma_C^2+\sigma_E^2$, showed very little difference between analyses, indicating that fluctuations in the three individual components were mainly due to sampling. Differences in estimates of σ_P^2, h^2, c^2 and t reflected those in their constituents.

The most striking feature of Table 4, however, is the large decline in estimates of the additive genetic variance after generations 7 or 13, from 7·2 to 2·5 g² for AFI and 4·3 to 2·3 g² for 6WW. Analyses including more and more data had already indicated an increase in residual variances in later generations, which is confirmed for both traits. For AFI, in particular, estimates of σ_E^2 for generations 14–23 increased to about twice their value in generations 2–4 (Table 2) and 5–7. This reduced h^2 for AFI from 0·30 to 0·07 while h^2 for 6WW dropped from 0·53 for data from generations 5–7 to 0·30 for data from generations 14–23. Realized within-family heritabilities for AFI for generations 14–23 were also considerably lower than in earlier generations, decreasing to 0·07 from an average of 0·14 for generations 2–13 (Table 3), although the decline was less marked than in the REML analyses.

There is evidence that the environmental sensitivity of selected animals increases over time. In many selection experiments the phenotypic variance did not decline with the genetic variance, which implies an increase in environmental variation (Falconer, 1989, p. 222), but in this study the phenotypic variance and the residual variance increased substantially. Considering data from generations 14–20, the average estimates of σ_E^2 and σ_P^2 for AFI were 17·70 and 27·40, respectively, i.e. higher in comparison to estimates from generations 8–13, but substantially lower than when records from generations 21–23 were included. This suggested that results were, in part at least, affected by health problems of animals.

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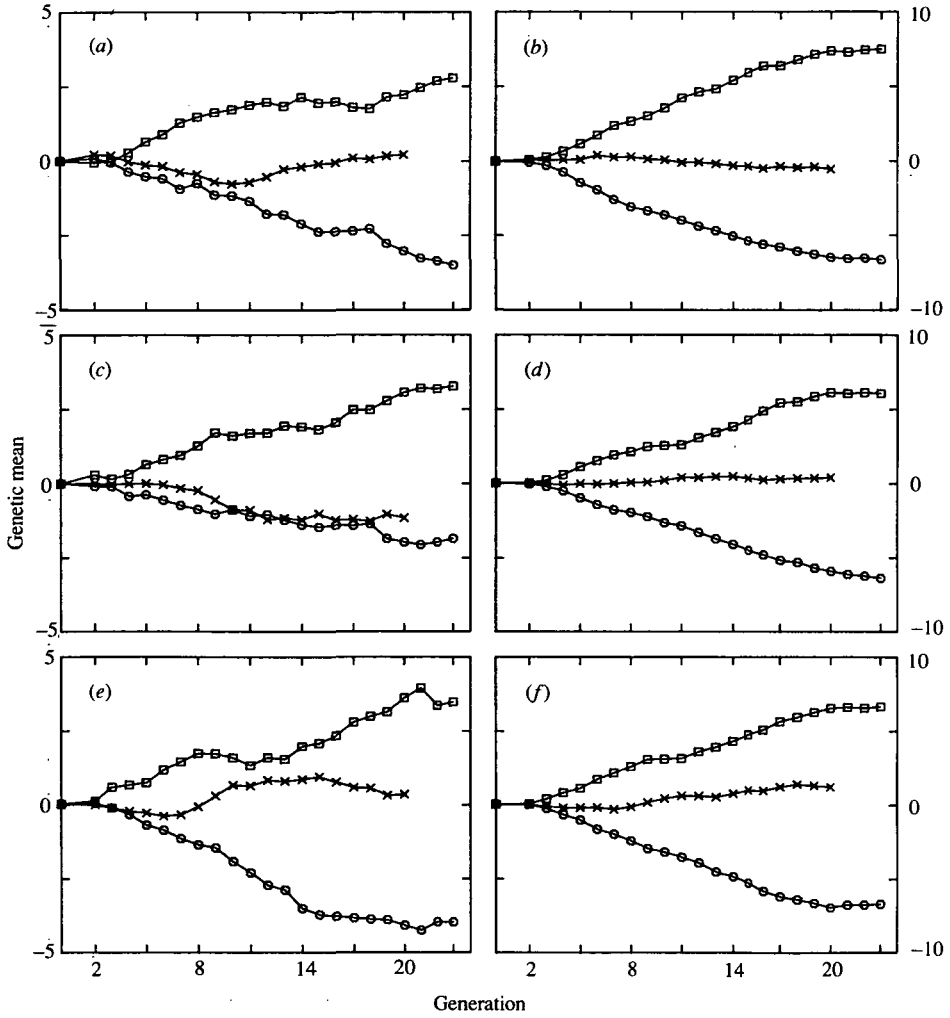

Fig. 1. Mean estimated additive genetic effects for animals each generation for high (□), control (×) and low (○) selection lines, for 6-week weight [(*a*), (*c*), (*e*) for replicates 1, 2 and 3, respectively] and adjusted food intake [(*b*), (*d*), (*f*) for replicates 1, 2 and 3].

(iii) *Multivariate analyses*

Results from multivariate analyses of data from generations 2–23 are given in Table 5. Estimates of variance components were very close to those from corresponding univariate analyses, both for the complete data and analyses considering subsets only (not shown). Estimates of correlations varied considerably more between replicates than those for h^2 and c^2. Overall, the genetic correlation (r_A) between AFI and 6WW was 0·46. Because estimates of the additive genetic covariance decreased less than the corresponding variances for analyses including data only from later generations (see Table 4), r_A increased from 0·38 for data from generations 2–7 and 8–13 to 0·63 for generations 14–23.

Estimates of the environmental correlation of sibs (r_C) were low and negative, the pooled value being −0·19. Litter effects presumably reflect maternal effects which are not removed by correction for litter size, included in the model to adjust for differences in levels of nutrition till weaning. Estimates of the residual environmental correlation (r_E) were positive, 0·31 overall, despite the fact that AFI includes a negative regression on 4WW, yielding a low phenotypic correlation (r_P) of 0·23 between the two traits. Estimates of r_E and consequentially r_P were consistently higher for records from generations 14–23 than for earlier data. As the increase in residual variances occurred in later generations (Table 4), this could in part be explained by sickness of animals which reduced both AFI and 6WW.

4. Discussion

In the model fitted it was assumed that gene action was additive and that all maternal effects were accounted for by random litter effects and systematic differences due to litter size. In principle, the method of analysis extends easily to accommodate additional random effects such as maternal genetic effects or dominance effects and their covariances, but in practice it is difficult to ensure that the data structure provides sufficient contrasts for the different effects to be distinguished. The experiment reported here was not designed to facilitate estimation of genetic

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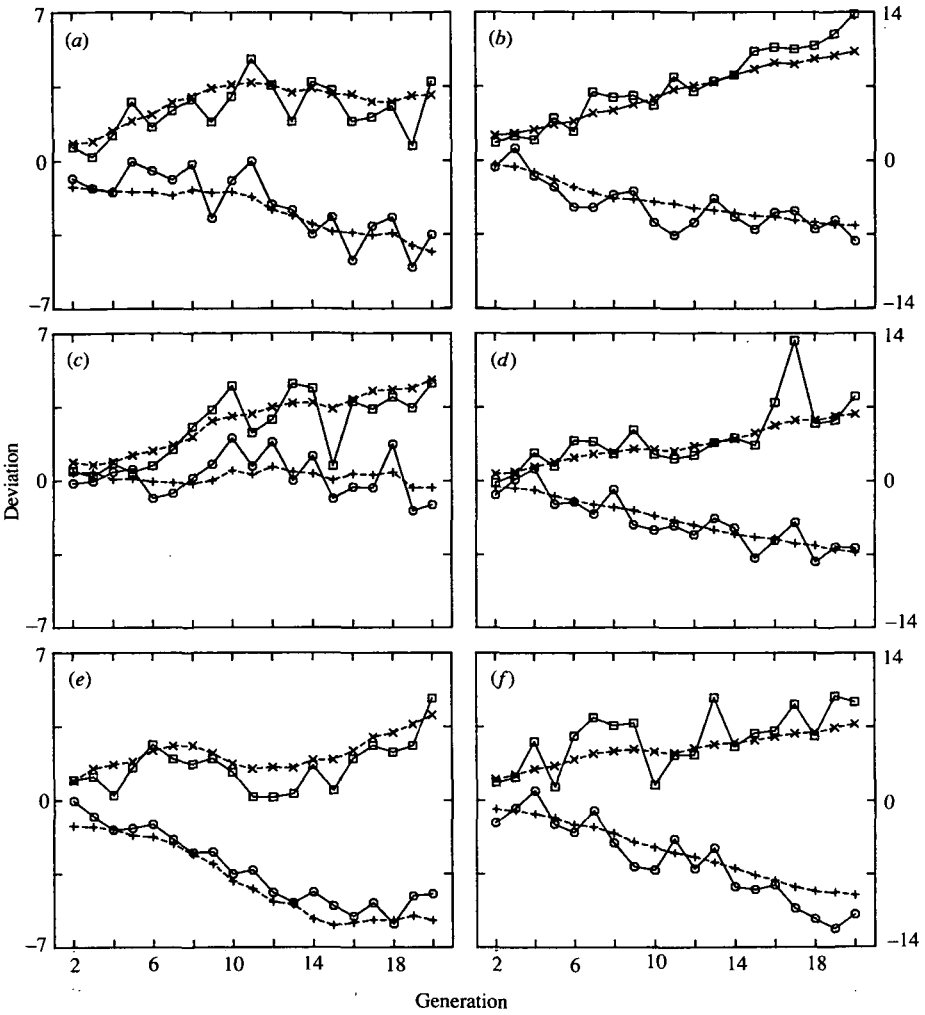

Fig. 2. Mean predicted value and phenotypic mean, both deviated from control, each generation for high and low selection lines, for 6-week weight [(*a*), (*c*), (*e*) for replicates 1, 2 and 3, respectively] and adjusted food intake [(*b*), (*d*), (*f*), respectively; with ' × ' and ' + ' depicting predicted values for high and low lines, respectively, and ' □ ' and ' ○ ' depicting the corresponding observed values.

parameters but to achieve genetic changes in animals, so additional random effects were not fitted. For the family structure used, dominance variance would have been included in the non-additive genetic covariance between full sibs, σ^2_C.

Analyses by REML as carried out here implicitly assume a multivariate normal distribution of the data which, in genetic terms, is equivalent to the assumption of an infinitesimal model (Bulmer, 1980). Invoking this model, traits are considered to be determined by infinitely many unlinked additive genes each of small effect, and gene frequencies are assumed not to change due to selection. Consequently, genetic variances are expected to remain constant except as a result of inbreeding, with the amount defined by the inbreeding coefficient, and of selection causing linkage (gametic) disequilibrium among unlinked loci. Hence all estimates of σ^2_A from analyses considering successively more generations of data were expected to be identical if the infinitesimal model held. With inclusion of pedigree information back to generation 0 and all records on which selection decisions were based, the estimates should be of the variances in the base population. Data from generation 1 were not utilized here so that estimates of σ^2_A were somewhat biased downwards due to selection of parents in that generation, but as selection was practised within families, this bias was likely to be very small.

Estimates of σ^2_A decreased with increasing number of generations of data, suggesting that the infinitesimal model was not appropriate and that variances changed as a consequence of change in gene frequencies due to selection. Similarly, in the absence of selection, estimates from analyses omitting data from earlier generations but including pedigree information back to generation 0 are expected to give an estimate of the variance in the base population. The marked decline found in estimates of σ^2_A over time (Table 4) was too large to be attributed to the effects of selection causing disequilibrium among unlinked genes. The lines were founded from a three-way cross, but linkage would have been expected to yield a progressive reduction in genetic variance over early generations which persisted, rather than the reduction observed in later

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Table 4. *Estimates of additive genetic* (σ^2_A), *common environmental* (σ^2_C), *error* (σ^2_E), *within full-sib family* (σ^2_W) *and phenotypic* (σ^2_P) *variance components, pooled over replicates, from univariate analyses of data sets omitting records from earlier generations; with resulting estimates of heritabilities* (h^2), *'c-squared' effects* (c^2) *and the intraclass correlation of full sibs* (t)

	Adjusted food intake						6-week weight		
Data[a]...	5–7		8–13		14–23		5–7	8–13	14–23
Back[b]...	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes
σ^2_A R[c]	5·22	5·66	2·45	2·59	1·84	2·03	4·16	2·89	1·97
F[d]	7·00	7·15	2·00	2·10	2·42	2·51	4·32	2·45	2·30
σ^2_C R	4·76	4·74	5·55	5·60	5·78	5·81	1·58	1·81	1·67
F	4·80	4·78	5·57	5·55	5·87	5·96	1·61	1·68	1·65
σ^2_E R	12·84	12·64	13·92	13·91	25·54	25·00	2·28	2·79	3·87
F	12·00	11·95	14·11	14·08	25·30	25·46	2·22	2·99	3·74
σ^2_W R	20·22	20·22	20·69	20·81	33·06	32·43	5·95	6·04	6·53
F	20·29	20·31	20·68	20·68	32·38	32·68	5·98	5·90	6·54
σ^2_P R	22·83	23·05	21·91	22·10	33·15	33·44	8·03	7·48	7·51
F	23·79	23·88	21·68	21·73	33·59	33·93	8·14	7·12	7·69
h^2 R	0·229	0·246	0·112	0·117	0·056	0·061	0·518	0·386	0·262
F	0·294	0·299	0·092	0·097	0·072	0·074	0·531	0·344	0·299
c^2 R	0·208	0·206	0·253	0·253	0·174	0·174	0·197	0·242	0·222
F	0·202	0·200	0·257	0·255	0·175	0·176	0·198	0·236	0·215
t R	0·323	0·328	0·309	0·312	0·202	0·204	0·456	0·435	0·354
F	0·349	0·337	0·303	0·304	0·211	0·213	0·463	0·408	0·364

[a] Comprising records from generations.
[b] Including information from back pedigrees.
[c] Analyses treating all animals as random.
[d] Analyses treating parents without records as fixed.

generations. Terms for variance from new mutations were not included in the model, but as variances declined, mutational variance was presumably negligible.

Simulation of normal deviates was employed to investigate the pattern of changes of the additive genetic variance due to inbreeding and selection expected under an infinitesimal model. Breeding values of individuals were computed as the mean of those of their parents with an increment due to segregation, normally distributed with variance (1-F) σ^2_{A0}, where σ^2_{A0} is the variance in the base population and F the mean inbreeding coefficient of the parents. Figure 3 shows the variance of simulated additive genetic values per line and generation, using the exact family size and relationship structure of replicate 2. Points given represent means over 2000 replicates for $h^2 = 0{\cdot}40$ and $\sigma^2_P = 100$. To assess the importance of selection, simulation was carried out both by selecting the best in each family to mimic the selection strategy in the experiment and by selecting at random.

As Fig. 3 illustrates, σ^2_A declined from close to 40 to about 25 in generation 23, somewhat more than expected from the average inbreeding coefficient of 0·27 in the last generation. For a heritability as high as 0·40, selection reduced variance in the H and L lines after generation 4 by about 2 units below that of the C line, but the difference decreased in later generations. The simulation was repeated for a heritability of 0·15, a value comparable to the overall estimate for AFI, and the effects of selection on the genetic variance were then negligible.

Results from the simulation therefore indicated that, under the infinitesimal model, little effect of selection on variance would be expected in this experiment in which AFI, the selected trait, had a low heritability and selection was practised within families. This could explain why variance component estimates for 6WW, which was not under direct selection but had a genetic correlation of 0·46 with AFI, showed no consistent differences between univariate analyses and multivariate analyses, and why estimates of genetic variance of AFI from analyses omitting data from earlier generations differed little whether parents without records were treated as fixed or random.

Sorensen & Kennedy (1986) simulated a selection experiment with 5 generations and obtained unbiased estimates of σ^2_A when ignoring data from the first three generations of selection but including pedigree information back to the base population. This was surprising, because some information contributing to selection decisions had been ignored. Extending the simulation for up to 10 generations, however, Van der Werf & De Boer (1990) clearly demonstrated that use of back pedigree information did not fully account for selection based on records not included in the analysis,

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Table 5. *Estimates of the additive-genetic* (σ_{Aij}), *common environmental* (σ_{Cij}), *error* (σ_{Eij}) *and phenotypic* (σ_{Pij}) *variance and covariance components from bivariate analyses of data from generations 2–23 of adjusted food intake* (*trait 1*) *and 6-week weight* (*trait 2*), *together with resulting estimates of heritabilities* (h_i^2), *'c-squared' effects* (c_i^2) *and genetic* (r_A), *common environmental* (r_C), *residual* (r_E) *and phenotypic* (r_P) *correlations. Results from pooled replicates of the univariate analyses are given for comparison*

Analysis...	Multivariate				Univariate
Replicate...	1	2	3	Pooled	Pooled
σ^2_{A1}	4·51	3·59	4·14	4·08	4·05
σ_{A12}	1·63	1·24	2·28	1·72	
σ^2_{A2}	3·81	3·25	3·37	3·48	3·34
σ^2_{C1}	5·24	6·22	6·06	5·84	5·76
σ_{C12}	−0·62	−0·30	−0·85	−0·59	
σ^2_{C2}	1·77	1·75	1·48	1·67	1·66
σ^2_{E1}	17·25	18·14	16·72	17·37	17·41
σ_{E12}	1·86	2·90	1·84	2·20	
σ^2_{E2}	2·21	3·24	3·19	2·88	2·96
σ^2_{P1}	27·00	27·96	26·29	27·29	27·22
σ_{P12}	2·87	3·84	3·27	3·33	
σ^2_{P2}	7·79	8·25	8·04	8·03	7·95
h^2_1	0·167	0·129	0·151	0·150	0·149
h^2_2	0·489	0·394	0·419	0·433	0·420
c^2_1	0·194	0·223	0·225	0·214	0·212
c^2_2	0·228	0·213	0·184	0·208	0·202
r_A	0·393	0·362	0·611	0·456	
r_C	−0·204	−0·089	−0·282	−0·189	
r_E	0·302	0·378	0·251	0·311	
r_P	0·198	0·253	0·225	0·225	

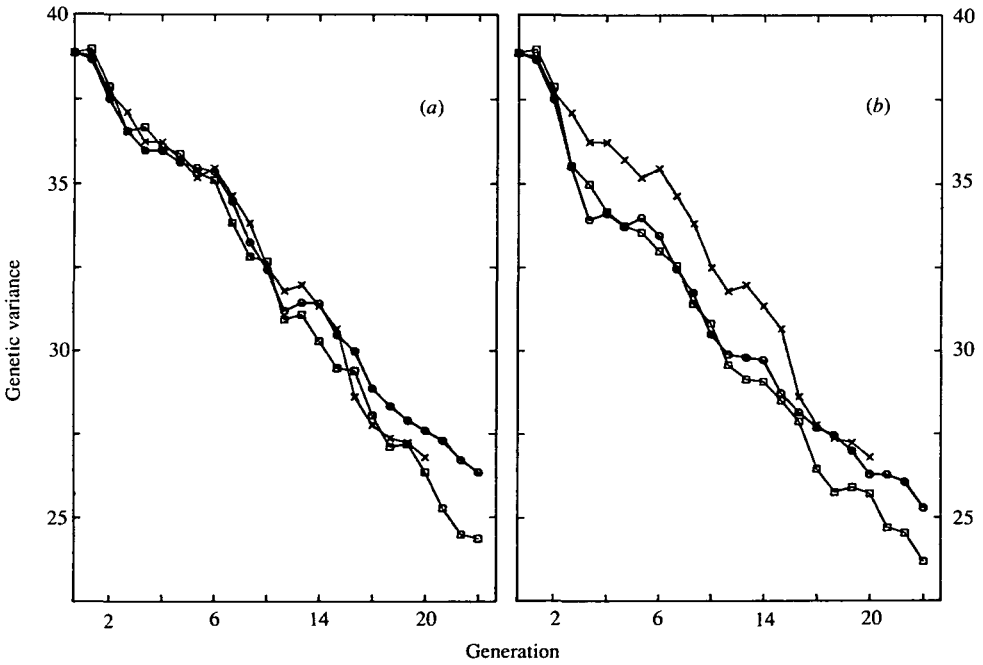

Fig. 3. Additive genetic variance each generation for high (□), control (×) and low (○) lines, using simulated data under an infinitesimal model for replicate two. (*a*) Random selection within families in all lines, (*b*) selection as in the experiment. Each point represents a mean over 2000 replicates.

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although the observed selection bias was considerably less than expected from normal theory. Further research is required to better understand how information from different sources is used and combined in this kind of analysis.

Regarding selected animals as fixed is equivalent to using only the proportion of variance among their progeny independent of the fixed parents to estimate the genetic variance, so only variance arising from Mendelian sampling in the progeny and subsequent generations is considered. This is logically appealing and has been employed in analyses of dairy data under a sire model when treating proven sires as fixed (Van Vleck, 1985), but the properties of this approach with an animal model analysis are not yet fully understood. Preliminary simulation results with the animal model suggest that, provided inbreeding is correctly taken into account, the estimate of the within-family variance is unbiased, whereas its partition into additive genetic and environmental variance may not be.

An alternative to the anlyses in this study, in which attempts were made to draw inferences about the genetic variance in the base population, would have been to estimate the current genetic variance in individual generations throughout the experiment. As outlined by Sorensen & Kennedy (1984*b*), the genetic variance in generation t can be estimated from records of generations, t, $t+1$ and later by treating animals in generation t as unrelated and non-inbred. If records for all animals in generation t are included, under the infinitesimal model estimates of the additive genetic variance are then only affected by inbreeding and selection prior to generation t, and all animals in the analysis can be treated as random.

In spite of some open questions concerning the expectations of variance components when records are missing but pedigree information is available, results from this study indicate selection for appetite in mice has reduced the genetic variance over and above the effects of inbreeding and selection. Increased levels of disease could have caused the increases in phenotypic variances in later generations, but not the reduction in environmental variance. Mixed model methodology, in particular an animal model REML analysis, appears to provide useful tools to allow a better understanding of results from selection experiments.

The analysis enabled unbiased estimates of genetic and environmental parameters to be obtained both for the trait under selection and for a correlated trait. Selection led to an increase in 6WW (28·6, 24·2 and 21·2 g for H, C and L, respectively, averaged over replicates at generation 20) and relatively smaller changes in 4WW (16·8, 15·2 and 14·7 g, respectively) (I. M. Hastings, personal communiction). This indicates that the phenotypic correction applied to 4WW in computing adjusted feed intake was insufficient. It is seen (Table 5) that the genetic correlation of AFI, and thus presumably of unadjusted food intake, is considerably higher that the phenotypic correlation in each replicate. This is brought about because, while both the genetic and environmental correlations of AFI and 6WW were positive, as might be expected as larger and faster growing mice eat more, the common environmental (litter) correlations were negative. A possible explanation is that mice in litters which, because of poor maternal care or nutrition, were of low weight at 4 weeks of age, would compensate and achieve higher 6WWs with relatively low food intake as maintenance rather than gain accounts for most of the energy utilized. A more detailed investigation would require a multivariate analysis of 4 and 6WWs, food intake and body composition, for it is notable that the high lines in the present experiment were leaner than the low lines (Hastings & Hill, 1989), in contrast to lines selected for high food intake without adjustment for weights which became fatter (Biondini *et al.* 1968). Such multivariate analyses require heavy computations to maximize likelihoods with respect to many parameters, but the same principles apply.

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