The genetic basis of response in mouse lines divergently selected for body weight or fat content. I. The relative contributions of autosomal and sex-linked genes

IAN M. HASTINGS[1]* AND ROEL F. VEERKAMP[2]

[1] *Institute of Cell, Animal and Population Biology, University of Edinburgh, West Mains Road, Edinburgh EH9 3JT, Scotland*
[2] *Genetics and Behavioural Sciences Department, Scottish Agricultural College, West Mains Road, Edinburgh EH9 3JG, Scotland and AFRC Roslin Institute, Roslin, EH25 9PS, Scotland*

Summary

Lines of mice have been divergently selected for over forty generations on either body weight or fat content. Reciprocal crosses were made between the divergent lines and the offspring backcrossed to the parental lines. The resulting data allowed us to investigate the genetic basis of response, including two features of particular interest: (i) the relative contribution of autosomal and sex-linked genes and whether any significant Y chromosome or cytoplasmic effects were present (ii) the mechanism of gene action, whether predominantly additive or whether significant dominance effects were present. A large additive sex-linked effect was observed in lines selected on body weight which accounted for approximately 25% of the divergence. The remaining 75% of the divergence appeared to be autosomal. There was no apparent sex-linked effect in lines selected on fat content and the response appeared to be entirely autosomal and additive.

1. Introduction

In nature, inherited characters which vary continuously over a range of values (for example, height, weight, wing-span) are classed as 'quantitative traits'. Their genetic basis is attributed to the effects of a large number of autosomal genes, each of which has only a very small, additive effect on the character. A large body of theory has been developed on this premise. It underlies genetic studies of the evolutionary process and has been of immense practical importance in the application of genetics to livestock production (e.g. Falconer, 1989). While it is recognized that this paradigm is an oversimplification, there are few estimates of the contribution of genes with other modes of action. Divergently selected lines are a useful resource to test the assumptions underlying the genetic basis of their response: the means of crosses between such lines provide information on the mode of gene action, and the variance and higher moments of the crosses provide evidence to discriminate between polygenic and monogenic gene action. Gene actions investigated in this study were: (i) autosomal, sex-linked, mitochondrial and Y chromosomal, (ii) additive or dominant, (iii) direct or maternal (i.e. direct gene action affects the trait of the animal itself,

whereas maternal gene action affects the trait in offspring). The results of a complementary study designed to detect the presence of genes with large effects ('major genes') are presented elsewhere (Veerkamp *et al.* 1993).

The lines investigated here are lines of mice selected for over 40 generations on either body weight or fat content. They were derived from a common base population, and are replicated. Selection was restricted to males for the first 20 generations of selection on body weight, and for the entire 43 generations of selection on fat content. When selection is restricted to males, sex-linked genes are hemi-zygous and are expressed without the complications of dominance which arise in autosomal genes; under these circumstances sex-linked genes may be expected to make a disproportionate contribution to the response (Griffing, 1965; Charlesworth, Coyne & Barton, 1987). There has also been recent conjecture that divergence in sex-linked loci between populations, possibly in response to differing selection pressures, may eventually contribute to genetic isolation, and ultimately speciation (Coyne & Orr, 1989; Coyne, 1992). One of the primary aims of this study was therefore to estimate the relative contributions of autosomal and sex-linked genes in response to selection.

* *Corresponding author.*

12

2. Materials and methods

The mouse lines used in this study were selected either on body weight (the 'P' lines) or on fat content (the 'F' lines) and their origin has been described by Sharp, Hill & Robertson (1984). Briefly, the lines were derived from an outbred base, split into three replicates, and males selected at 10 weeks of age on an index either of lean mass (P lines) or of fat content (F lines); females were not selected. After 20 generations the three replicates within each criterion/direction were crossed to form new lines and the original replicates maintained without selection. For example the three replicates selected for low body weight (designated PL1, PL2 and PL3) were crossed to form the new line PL6; similar crosses were made to form the PH6 (from replicates selected for high lean mass), FH6 (from replicates selected for high fat content) and FL6 (from replicates selected for low fat content; Hastings, Yang & Hill, 1991).

The selection criteria were changed slightly. The index of lean mass used to select the P lines was genetically very highly correlated with body weight (Sharp, Hill & Robertson, 1984; Beniwal *et al.* 1992*b*) so the P6 lines were selected on body weight at 10 weeks of age in both sexes. The selection index in the F6 lines was changed to the ratio of dry weight to body weight at age 14 weeks which has a close phenotypic correlation with fat content (Hastings & Hill, 1989; unpublished data from F6 generation 43); as before, selection was restricted to males. At the time of this experiment the lines differed approximately five fold in fat content (4·5% *vs.* 22%) with no difference in the underlying fat-free body weight (unpublished observations).

The method used to investigate the genetic basis of response was to make a reciprocal cross between the divergently selected lines and backcross the offspring to both parental lines. In all crosses, care was taken to make all possible reciprocal crosses to allow for the effects of the X chromosome: there were two reciprocal halves in the hybrid cross, each of which was reciprocally crossed to both parental lines giving a total of eight types of backcross (a glance at Tables 1–3 should clarify the procedure). Details specific to the P and F lines are as follows.

(i) *P lines*

Each of the 16 families from the P6 parental lines at generation 31 were, as nearly as possible, equally represented in the F1. Ten families were set up in each reciprocal half of the cross i.e. high × low and low × high (in the terminology used here the first parent is the male). Care was taken to ensure equal representation of each reciprocal half of the F1 in each backcross and equal representation of each family within this restriction. All individuals were weighed at 6 and 10 weeks of age. The number of families in each group of the backcross was reduced to five, from each of which eight individuals were kept; where possible this consisted of four from each sex. At generation 38 another reciprocal cross was set up as part of another experiment. As before, 10 families were set up in each reciprocal half of the F1 and all offspring weighed at 6 and 10 wks of age; no backcrosses were set up.

Subsequent analyses of these experiments (see later) suggested a significant sex-linked effect was present. Reciprocal F1 crosses were made in the separate P1, P2 and P3 lines at generation 44 to ascertain whether the sex-linked effect was present in all replicates or in a single replicate. As in the P6 crosses, ten families were set up in each reciprocal half of the cross and all offspring weighed at 6 and 10 weeks of age.

(ii) *F lines*

Fifteen families were set up in each reciprocal half of the backcross and 10 in each group of the backcross. The lines had been selected on the proportion of water in the carcass, a character that could only be measured on dead individuals. Thus not all individuals in the F1 could be measured as some were required as parents for the backcrosses. Where possible 20 individuals of each sex within each group of the backcross were measured; these 20 were selected to ensure, as closely as possible, equal contributions from each family.

There were differences in the magnitude of variance between the lines. The statistical analyses were performed on data transformed to minimize this effect: the 10 week body weights (BW) measured in the P6 lines were log transformed (TBW) and the percentage dry weight to body weight (FAT) measured in the F6 lines were transformed (TFAT) as log(FAT-24). The Genstat 5·2 Residual Maximum Likelihood (REML) option (Genstat 5 Committee, 1988; Patterson & Thompson, 1971) was used to estimate the effects of independent variates (Table 4). This treatment is similar to that employed for the analysis of diallel crosses (for example: Jinks (1956); Hayman (1960), references therein). A random effect of sire was included in the REML analyses to account for the common environmental and genetic effects between observations within full-sib families (although most generations were composed of groups of full-sibs, a few males sired more than one family). Analyses of P6 lines included generation as a fixed effect (three levels: parental, F1 and backcross) and litter size as a linear covariate. Data from the parental lines contemporaneous with the F1 and backcrosses were recorded to reduce the effects of environmental fluctuations. Analyses of F6 included generation as a fixed effect with two levels (the F1 and backcross; parental generation could not be fitted because of environmental fluctuations caused by alterations in cage type

Table 1. *Mean body weight at age 10 weeks (number weighed) and mean standard errors of groups from P hybrid crosses. Data for pure-bred H × H and L × L are from the contemporaneous parental lines. In the crossing nomenclature the male parent is represented first*

	H × H	L × H	H × L	L × L	Mean s.e.
REPLICATE 6					
gen 31					
Female	42·9 (49)	28·6 (22)	29·9 (30)	19·4 (51)	0·6
Male	50·4 (57)	36·6 (19)	31·1 (31)	22·7 (45)	0·6
gen 38					
Female	39·6 (49)	26·3 (28)	26·4 (36)	16·7 (51)	0·5
Male	44·7 (48)	33·4 (30)	28·9 (39)	20·2 (40)	0·6
REPLICATE 1					
Female	31·2 (35)	25·5 (26)	26·1 (30)	18·8 (23)	0·5
Male	37·6 (30)	36·1 (33)	29·5 (33)	21·4 (37)	0·5
REPLICATE 2					
Female	26·1 (29)	25·8 (23)	23·2 (27)	21·7 (25)	0·5
Male	31·4 (34)	33·8 (22)	26·0 (27)	26·4 (23)	0·6
REPLICATE 3					
Female	31·7 (19)	27·4 (34)	26·8 (21)	19·0 (33)	0·6
Male	41·9 (20)	37·1 (36)	29·1 (36)	24·0 (24)	0·7

Table 2. *P6 backcrosses and contemporaneous parent lines. The X chromosome genotype is also shown; where the X chromosomes contain genes from both lines (due to recombination in F1 females) it is represented as H/L*

(i) High backcross

Cross	F1 × H				H × F1				H × H	
Source of F1	H × L		L × H		H × L		L × H		—	—
Sex	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
X genotype	LH	H	HH	H	H(H/L)	H/L	H(H/L)	H/L	—	—
10 wk wt	33·3	42·0	36·0	42·6	33·2	39·8	33·2	37·3	43·0	49·5
S.D.	1·82	3·04	3·56	2·78	2·89	3·51	3·77	4·62	3·66	4·48
S.E.	0·47	0·81	0·86	0·64	0·58	0·73	0·86	1·03	0·51	0·59
n	15	14	17	19	25	23	19	20	51	57

(ii) Low backcross

Cross	F1 × L				L × F1				L × L	
Source of F1	H × L		L × H		H × L		L × H		—	—
Sex	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
X genotype	LL	L	LH	L	L(H/L)	H/L	L(H/L)	H/L	—	—
10 wk wt	23·1	27·6	24·6	26·8	23·1	29·0	23·0	30·4	19·4	23·6
S.D.	2·02	2·97	3·07	2·75	2·51	2·89	3·15	2·40	1·68	2·59
S.E.	0·44	0·70	0·69	0·61	0·56	0·65	0·70	0·54	0·24	0·38
n	21	18	20	20	20	20	20	20	47	47

(Hastings & Hill, 1993)) and litter size as a linear covariate. Dry weights were obtained in 9 different batches across the different crosses, so batch was included as fixed effect in the analysis of FAT and TFAT.

Crossbreeding effects were estimated with the model for crossbreeding parameters shown in Table 4. Sex and interactions between sex and crossbreeding effects were also fitted, to allow for different expression of genes in the two sexes.

3. Results

The results of the P6 and F6 hybrid cross and backcross are shown on Tables 1–4. There is a large sex difference in the reciprocal halves of the F1 in the P lines: female offspring from both reciprocal crosses are the same weight but the weight of male offspring was biased towards that of the female parent. If this was a maternal effect it would be expected to affect both sexes equally but the weight of females is midway

12-2

Table 3. *F6 backcross and contemporaneous parental lines. The X chromosome genotype is also shown; where the X chromosomes contain genes from both lines (due to recombination in F1 females) it is represented as F/L*

(i) Hybrid cross

Cross	L × L		F × L		L × F		F × F	
Sex	Female	Male	Female	Male	Female	Male	Female	Male
DW/BW (%)	31·4	30·7	35·3	36·8	36·4	37·5	45·9	48·6
S.D.	1·5	1·5	2·0	1·8	1·7	2·4	4·4	3·4
S.E.	0·3	0·3	0·4	0·6	0·3	0·3	0·8	0·6
n	28	26	25	10	37	50	29	28

(ii) Fat backcross

	F1 × F				F × F1				F × F	
Source of F1	F × L		L × F		F × L		L × F		—	—
Sex	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
X genotype	LF	F	FF	F	F(F/L)	F/L	F(F/L)	F/L	—	—
DW/BW (%)	36·0	41·1	38·2	43·5	36·9	38·3	38·2	41·6	42·8	43·5
S.D.	2·9	3·1	2·9	3·5	2·9	2·8	3·6	5·7	3·2	3·8
S.E.	0·6	0·8	0·7	0·8	0·7	0·7	0·8	1·3	0·7	1·0
n	20	17	20	18	18	17	21	20	19	15

(iii) Lean backcross

	F1 × L				L × F1				L × L	
Source of F1	F × L		L × F		F × L		L × F		—	—
Sex	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
X genotype	LL	L	LF	L	L(F/L)	F/L	L(F/L)	F/L	—	—
DW/BW (%)	31·8	31·9	32·0	33·3	32·0	33·1	31·9	33·3	31·4	31·5
S.D.	1·2	1·6	1·5	2·0	1·7	2·1	1·5	1·9	3·5	3·8
S.E.	0·3	0·4	0·3	0·4	0·4	0·5	0·4	0·4	0·8	0·9
n	18	20	20	20	20	20	18	19	20	18

Table 4. *Average crossbreeding effects for the different crosses*

Cross[1]	Mean	Both sexes					Females		Males	
		A[2]	D	Am	Dm	Mito	As	Ds	As	Ychr
H × H	1·0	1·0	0·0	1·0	0·0	1·0	1·0	0·0	1·0	1·0
L × L	1·0	−1·0	0·0	−1·0	0·0	−1·0	−1·0	0·0	−1·0	−1·0
L × H	1·0	0·0	1·0	1·0	0·0	1·0	0·0	1·0	1·0	−1·0
H × L	1·0	0·0	1·0	−1·0	0·0	−1·0	0·0	1·0	−1·0	1·0
H × (LH)	1·0	0·5	0·5	0·0	1·0	1·0	0·5	0·5	0·0	1·0
H × (HL)	1·0	0·5	0·5	0·0	1·0	−1·0	0·5	0·5	0·0	1·0
(LH) × H	1·0	0·5	0·5	1·0	0·0	1·0	1·0	0·0	1·0	−1·0
(HL) × H	1·0	0·5	0·5	1·0	0·0	1·0	0·0	1·0	1·0	1·0
L × (LH)	1·0	−0·5	0·5	0·0	1·0	1·0	−0·5	0·5	0·0	−1·0
L × (HL)	1·0	−0·5	0·5	0·0	1·0	−1·0	−0·5	0·5	0·0	−1·0
(LH) × L	1·0	−0·5	0·5	−1·0	0·0	−1·0	0·0	1·0	−1·0	−1·0
(HL) × L	1·0	−0·5	0·5	−1·0	0·0	−1·0	−1·0	0·0	−1·0	1·0

[1] Genotype of the male parent given first.
[2] Abbreviations: A = direct additive autosomal, D = direct dominance autosomal, Am = maternal additive autosomal, Dm = maternal dominance autosomal, As = direct additive sex-linked, Ds = direct dominance sex-linked (zero in males), mito = mitochondrial, Ychr = Y-chromosomal (zero in females).

between that of the parental lines in both halves of the reciprocal cross. A major difference in genotype between the sexes is that males receive only a maternal X chromosome, so initial inspection of the data suggested that this chromosome may have a significant effect on body weight (Hastings, 1990).

A sex-linked effect of similar magnitude was noted in the original P replicates and in another hybrid cross made at generation 38 of the P6 line (7 generations after the original cross), Table 1.

The results from the REML analyses of gene action are presented in Table 5. Direct additive autosomal

Table 5. *REML estimates (± standard errors) for the gene effects, separated for males and females*

		BW (g)	TBW	FAT (%)	TFAT
A[1]	Female	8.7 ± 1.0	2.6 ± 0.3	5.7 ± 1.1	0.46 ± 0.07
	Male	9.7 ± 1.1	2.6 ± 0.3	8.6 ± 1.1	0.66 ± 0.08
D	Female	1.3 ± 1.4	0.7 ± 0.4	-2.4 ± 0.8	-0.04 ± 0.06
	Male	0.4 ± 1.2	0.5 ± 0.3	-1.5 ± 0.6	0.09 ± 0.05
As	Female	2.4 ± 0.9	0.7 ± 0.2	0.7 ± 1.0	0.07 ± 0.07
	Male	3.3 ± 0.7	0.9 ± 0.2	0.0 ± 0.8	0.01 ± 0.06
Ds	Female	-0.4 ± 0.8	-0.1 ± 0.2	-0.7 ± 0.6	-0.05 ± 0.04
Mito	Female	0.0 ± 0.4	0.0 ± 0.1	0.4 ± 0.4	0.03 ± 0.03
	Male	-0.3 ± 0.4	-0.1 ± 0.1	0.5 ± 0.4	0.02 ± 0.03
Ychr		-0.1 ± 0.4	0.0 ± 0.1	-0.6 ± 0.5	-0.05 ± 0.03
Am		0.3 ± 0.6	0.1 ± 0.2	-0.4 ± 0.5	-0.02 ± 0.04
Dm		-0.4 ± 0.6	-0.1 ± 0.2	-0.3 ± 0.5	-0.02 ± 0.03
Effect (male–female)		5.7 ± 0.3	1.6 ± 0.1	1.1 ± 0.3	0.05 ± 0.03
Litter size regression		-0.5 ± 0.1	-0.1 ± 0.03	-0.2 ± 0.1	-0.02 ± 0.01

[1] Abbreviations see Table 4.

gene action explained most of the differences between cross types in body weight (both for BW and TBW). The direct additive autosomal effect explained 17·4 g and 19·4 g of the total difference of approximately 22 g and 24 g in BW between the high and low lines in the females and the males, respectively. Additive sex-linked gene action was significant in analyses of both BW and TBW, explaining 4·8 g and 6·6 g of the difference in BW between the high and low lines in females and males, respectively. There was no significant evidence for dominant gene action or for maternal, mitochondrial or for Y-linked effects. There was a significant effect of litter size on weight at 10 weeks, with pups being 0·5 g lighter for each extra pup in the litter. Males were 5·7 g heavier than females on average over all the crosses. Estimates of the importance of all effects were in good agreement between BW and TBW.

Direct additive autosomal effects also explained most of the line differences in fatness (11·3 and 17·3 percentage points of difference between the high and low lines in FAT for females and males, respectively). A significant negative direct dominance effect was estimated for FAT ($-2·4$ for females and $-1·5$ percentage points for males) but dominance was not significant for TFAT. None of the other gene effects examined were of importance for either FAT or TFAT. Males were fatter than females and extra pups per litter reduced the fatness at 14 weeks.

4. Discussion

Only autosomal and sex-linked additive genes out of all the gene effects examined had a significant influence on BW. Direct dominance was not significant in this data-set, this is in agreement with results from some authors (e.g. Bandy & Eisen, 1984), although others did find heterosis affecting body weight (e.g.

Bandy & Eisen, 1984; Roubertoux, Semal & Ragueneau, 1985). Maternal effects were not significantly different from zero in this analysis. In contrast, Veerkamp (1991) reported negative maternal heterosis for body weight analysing the same data set, but omitted litter size as a covariate.

Heterosis for litter size in females from crosses between selected lines of mice has been reported (e.g. Mausolf, Horst & Schlote, 1983) and Bandy & Eisen (1984) reported a negative effect of litter size on subsequent body weight. Hence, F1 dams have bigger litters but smaller pups per litter. In this data-set the mean litter size of the backcrosses with parental dams was 9·85 pups and for the backcrosses with F1 dams the litter size was 11·46 and this likely resulted in the negative maternal heterosis estimate for body weight obtained by Veerkamp (1991).

REML Analysis of the data set suggested that 25 % (equivalent to about 5 g) of the divergence in the P6 line was due to a large sex-linked effect with the remainder explicable by additive autosomal genes. The entire response in the F6 could be explained by the actions of autosomal additive genes. These results were unaffected by eliminating non-significant effects, such as Y chromosomal, from the model. The residual mean squares obtained from this reduced model was 98 % of that obtained from a model fitting cross by sex interactions and it is therefore very unlikely that other significant gene effects are present. A similar lack of epistasis between different modes of gene action was noted in these lines by Hastings, Bootland & Hill (1993) who found that a mutation disrupting growth hormone production had similar effects in both the High and Low P6 lines.

On the basis of the data presented here, it is impossible to distinguish whether the large effect of the X chromosome in the lines selected on body weight is due to a single sex-linked major gene or whether the X chromosome contains a number of

segregating alleles at loci affecting body weight. The X chromosome is associated with approximately 25% of the high/low divergence although it accounts for only around 5% to 6% of the haploid DNA in mice (Ohno, 1967). Sex-linked genes are hemizygous in the males so an increased selection pressure on these alleles may account for the skewed distribution of effects towards the X chromosome, particularly since selection was practised only on males during the first 20 generations.

There are two possible explanations for the observation that a significant X-linked effect was apparent in the lines selected on body weight but not in lines selected on fat content. First, body weight and fat content have qualitatively different metabolic bases. Growth is a general, systemic character while fat content is a small, distinct part of metabolism. Thus the number of sex-linked loci affecting fat content may be lower than the number affecting body weight. Secondly, a sex-linked major gene affecting body weight could have been present in the base population (Veerkamp *et al.* 1993) but no such gene affecting fat content was present.

The large sex-linked effect appears in crosses of all three of the original replicates (Table 1). This suggests that the effect did not arise as a single spontaneous mutation in one of the replicates but that if due to a single gene it must have been present in the base population. The magnitude of the effect appears similar in all replicates despite the additional 11 or 19 generations of selection in the P6 replicates (selection in the original P1, P2 and P3 replicates ceased at generation 20). This suggests that if the X chromosome effect was due to many sex-linked genes, the original sex-linked variation must have been essentially fixed by generation 20 so that no further disproportionate response was possible. The analysis of Beniwal *et al.* (1992*a*) revealed a rapid decrease in additive genetic variance after the initial few generations of selection in the original P replicates. This is consistent with the presence of a major gene in the base population as genetic variance would have been high while it is segregating but falls on fixation. However it is also consistent with the rapid fixation of a number of sex-linked genes.

The large sex-linked effect noted in the P lines is apparently not deleterious as no fitness differences were observed between crosses or sexes (apart from the normal effect that larger females have larger litters). The first stage of genetic isolation is believed to be the appearance of Haldane's rule. This rule states that of the two sexes the heterogametic sex (males in this case) are more likely to be infertile or inviable, an effect generally attributed to sex-linked genes (Coyne & Orr, 1989; Coyne, 1992), however the large phenotypic effect associated with sex-linked gene(s) in the P replicates is not associated with a correlated reduction in fertility or viability (data not shown).

Bhuvanakumar *et al.* (1985) crossed lines of mice divergently selected for 6 week body weight. The high/low divergence in body weight at 6 weeks was by a factor of 1·9, exactly that of the P6 lines although their lines were slightly lighter (approximately 2 g). They found reciprocal differences of 1·6 g or 12% of divergence at 6 weeks. Unfortunately the sexes were not treated separately so any differences between males from the two reciprocal halves would have been obscured. If, however, we assume maternal effects to be negligible (as in this study) the only difference between the reciprocal halves was the X chromosome content of the males. Under this assumption, the X chromosome then accounts for 24% of the divergence, exactly the estimate obtained earlier in the P6 lines. However, other studies, for example White, Eisen & Legates (1970) and Bakker, Nagai & Eisen (1976), failed to find any evidence of sex-linked effects in mice selected on 6 week body weight. It therefore appears that the genetic basis of response in mouse lines (specifically the contribution of sex-linked genes) may differ between experiments even when selection is on the same character.

The bias which appears to exist towards sex-linked alleles has an interesting methodological implication. The heritability of a trait is a property of a population in a specific environment and most researchers do not explicitly acknowledge that its value may differ between sexes; for example, when selection is applied on one sex, realized heritability is calculated as twice the regression of response on cumulated selection differential (Falconer, 1989). However sex-linked genes are hemi-zygous in the heterogametic sex (males in mammals) so selection on recessive or semi-dominant alleles on the sex chromosomes will be more effective, and their contribution to response proportionally larger than, autosomal alleles. Extending the results to both sexes will therefore overestimate the heritability. The proportion of DNA in the sex chromosome and its gene content is similar in all mammalian species (Ohno, 1967; Lalley & McKusick, 1985) so differences noted in mice lines may be significant in other, commercially important species.

References

Bakker, H., Nagai, J. & Eisen, E. J. (1976). Average genetic and heterotic effects on growth in mice selected for large six week body weight on rapid post weaning gain. *Journal of Animal Science* **43**, 1145–1155.

Bandy, T. R. & Eisen, E. J. (1984). Direct and maternal genetic differences between lines of mice selected for body weight and litter size: traits of offspring. *Journal of Animal Science* **59**, 908–921.

Beniwal, B. K., Hastings, I. M., Thompson, R. & Hill, W. G. (1992*a*). Estimation of changes in genetic parameters

in selected lines of mice using REML with an animal model. I. Lean mass. *Heredity* **69**, 352–360.

Beniwal, B. K., Hastings, I. M., Thompson, R. & Hill, W. G. (1992*b*). Estimation of changes in genetic parameters in selected lines of mice using REML with an animal model. II. Body weight, body composition and litter size. *Heredity* **69**, 361–371.

Bhuvanakumar, C. K., Lynch, C. B., Roberts, R. C. & Hill, W. G. (1985). Heterosis among lines of mice selected for body weight. 1. Growth. *Theoretical and Applied Genetics* **71**, 44–51.

Charlesworth, B., Coyne, J. A. & Barton, N. H. (1987). The relative rates of evolution of sex chromosomes and autosomes. *American Naturalist* **130**, 113–146.

Charlton, H. M. (1984). Mouse mutants as models in endocrine research. *Quarterly Journal of Experimental Physiology* **69**, 655–676.

Coyne, J. A. (1992). Genetics and Speciation. *Nature* **355**, 511–515.

Coyne, J. A. & Orr, H. A. (1989). Two rules of speciation. In *Speciation and its Consequences* (ed. D. Otte and J. A. Endler). Sinauer Ass., Mass. USA.

Genstat 5 committee (1988). *Genstat 5 Reference Manual.* Oxford: Oxford University Press.

Falconer, D. S. (1989). *Introduction to Quantitative Genetics* 3rd ed. Essex: Longman.

Griffing, B. (1965). Influence of sex on selection. I. Contribution of sex-linked genes. *Australian Journal of Biological Science* **18**, 1157–1170.

Hastings, I. M. (1990). An investigation of mouse lines selected on body weight for the presence of major genes. *Proceedings of the 4th World Congress of Genetics Applied to Livestock Production* **XIII**, 317–320.

Hastings, I. M., Bootland, L. H. & Hill, W. G. (1993). The role of growth hormone in lines of mice divergently selected on body weight. *Genetical Research* **61**, 101–106.

Hastings, I. M. & Hill, W. G. (1989). A note on the effects of different selection criteria on carcass composition in mice. *Animal Production* **48**, 229–233.

Hastings, I. M. & Hill, W. G. (1993). The effect of cage type on murine body composition. *Mouse Genome* **91**, 329–330.

Hastings, I. M., Yang, J. & Hill, W. G. (1991). Analysis of lines of mice selected on fat content. 4. Correlated responses in growth and reproduction. *Genetical Research* **58**, 253–259.

Hayman, B. I. (1960). The theory and analysis of diallel crosses. III. *Genetics* **45**, 155–172.

Jinks, J. L. (1956). The F2 and backcross generations from a diallel cross of *Nicotiana rustica* varieties. *Heredity* **10**, 1–30.

Lalley, P. A. & McKusick, V. A. (1985). Report of the committee on comparative mapping. Eight international workshop on human gene mapping. *Cytogenetics and Cell Genetics* **40**, 536–566.

Mausolf, M., Horst, P. & Schlote, W. (1983). Existence and exploitation of maternal and multiparous animals. *Proceedings of the 5th World Congress on Animal Production* **1**, 284–286.

Ohno, S. (1967). *Sex Chromosomes and Sex-linked Genes.* New York: Springer.

Patterson, H. D. & Thompson, R. (1971). Recovery of inter-block information when block sizes are unequal. *Biometrika* **58**, 545–554.

Roubertoux, P., Semal, C. & Ragueneau, S. (1985). Early development in mice: II. Sensory motor behaviour and genetic analysis. *Physiology and Behaviour* **35**, 659–666.

Sharp, G. L., Hill, W. G. & Robertson, A. (1984). Effects of selection on growth, body composition and food intake in mice. I. Responses in selected traits. *Genetical Research* **43**, 75–92.

Veerkamp, R. F. (1991). An investigation for the presence of a major gene in mouse lines selected on body weight. *Ingenieur's Thesis.* Wageningen Agricultural University, The Netherlands.

Veerkamp, R. F., Haley, C. S., Knott, S. A. & Hastings, I. M. (1993). The genetic basis of response in mouse lines divergently selected for body weight or fat content. II. The contribution of genes with a large effect. *Genetical Research* **62**, 177–182.

White, J. W., Eisen, E. J. & Legates, J. E. (1970). Sex-heterosis interaction. Heterosis and reciprocal effects among mice selected for body weight. *Journal of Animal Science* **31**, 289–295.