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Evidence for a major gene for rapid postweaning growth in mice

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SUMMARY

Mice gaining 3 or more standard deviations above the mean were noted beginning in generation 25 in a line selected for high 21–42 day weight gain. The exceptional growth rate appears to be due to an autosomal recessive gene, based on the following: (1) the exceptional individuals appeared suddenly, in only one of 2 closely related sublines; (2) mating high growth individuals to unrelated, normal size strains produces relatively uniform F_1's with mean gains below the mid-parent average; (3) F_2's have a distribution markedly skewed towards high gain and a coefficient of variation approximately double that of F_1's; (4) true breeding high growth strains can be established in one generation by intermating the largest F_2's; (5) intermating normal F_2's produces progenies with a distribution similar to the F_1 except for a few large segregates; (6) high growth segregates have been obtained in F_2's from each of 4 successive backcrosses to the C57BL/6 inbred line. The symbol *hg* (high growth) is proposed for the postulated gene, which appears to be completely recessive. Frequency of positively identified segregates in F_2's and backcrosses is on average less than 25 and 50 %, due probably to some overlap of *Hg-* and *hg hg* distributions. Gain of *hg hg* individuals from 21–42 days is 30–50 % higher than of *Hg-* contemporaries; mature weight is also much higher, while 21-day weight of *hg hg* individuals in segregating litters is slightly lower. Fertility of homozygotes ranges from normal to as much as 40 % lower than for comparable *Hg-* mice; *hg hg* mice are not obese. The gene may provide a useful model for study of regulation of mammalian growth.

INTRODUCTION

There is evidence for a large amount of genetic variation in growth rate between and within breeds or strains of mammals, much of it explained by differences in mature size. This variation is generally found to be quantitative in nature and of moderate heritability. In mice, the evidence comes from selection experiments and from differences among inbred lines and their crosses; the subject has been reviewed by Roberts (1966), Eisen (1974) and McCarthy (1982). There is also discontinuous variation, in the form of dwarf and obese mutants (Green, 1981).

In cattle, the gene for double muscling has some effect on growth rate but the effect is more on degree and kind of muscling and on stress susceptibility (see review by Hanset, 1982). A major gene with similar effects, the halothane sensitivity (*hal*)

gene, occurs in pigs (e.g. Smith & Bampton, 1977; Webb *et al.* 1982). Individual loci associated with a large increase in size and weight of the musculo-skeletal system of mammals without a marked change in body composition have apparently not been reported.

Mice with an exceptionally rapid postweaning growth rate occurred in an experimental stock in our colony. Based on the sudden appearance of very large animals in one litter and the results of crossing such exceptional individuals with several different stocks, we have concluded that the rapid growth is the result of a single autosomal recessive gene (proposed symbol *hg*) with nearly complete penetrance. We present here the evidence for this conclusion.

MATERIALS AND METHODS

A strain of mice (G) with rapid postweaning growth rate was developed by selection for gain from 21–42 days from a base population produced by crossing four common inbred lines (AKR, C3H, C57BL/6 and DBA/2). Gain relative to that of an unselected control (C) was doubled in 20 generations (Bradford, 1971), and some further increase occurred thereafter (Barria & Bradford, 1981*a*). Weaning weight at 21 days showed a correlated increase in the early generations and remained above that of line C. Fertility of line G matings declined beginning about generation 10 (Barria & Bradford, 1981*b*), and by generation 20 had reached a level which prompted splitting off a subline (G′) at generation 21, to reduce the risk of losing the stock. Line G′ was also selected for 21–42 day gain, with the only difference in management or treatment being slightly earlier mating age (7–8 weeks) than in lines G and C (9 weeks).

The management and mating plans for lines G and C were described by Barria & Bradford (1981*a*). Briefly, all lines were maintained by mating a minimum of 18 pairs or trios, usually more, per generation. All stocks were kept in a room maintained at 23 ± 2 °C with lights on 14 h (0500–1900) per day. Mice were fed white diet (Simonsen Laboratories, Gilroy, CA) with a guaranteed analysis of a minimum of 24 % CP and 6 % fat and a maximum of 3·5 % crude fibre. Litters were counted the day of birth, and those with more than 10 were reduced to 10 at 2 days. Young were weaned and weighed to the nearest 0·1 g at 21 days with weaned young caged at $\leqslant 4$ per cage to 42 days. Mice were weighed again at 42 days and selected on the basis of 21–42 day gain without adjustment for litter size. Matings were made at 8–9 weeks of age with males left with the female throughout the production cycle or removed when the female was obviously pregnant. Matings in which the female had not produced a litter and was not pregnant 4–5 weeks after mating were discarded.

In generation 29 a male with a gain of 41·3 g, compared with a previously recorded maximum of 33·9 g, was observed in line G′, and one of 38·4 g occurred in generation 30. We speculated that these might be the result of a favourable epistatic combination of genes produced by the long-term selection for gain. Sib mating was therefore initiated at generation 31 in an attempt to fix the exceptional phenotype. However, fertility of the line in general and of the very large individuals in particular was low and although some exceptionally large individuals

continued to segregate in most generations, the frequency never exceeded 30 % and was usually less than 20 %. The sib lines were crossed at generation 36 and again at generation 40. Random mating was resumed at generation 40. However, fertility and maternal performance continued to decline, and in generation 53 only one litter was produced. The gains of individuals in this litter were above the usual modal class for the line, though not as high as the extremes observed in some generations.

To avoid loss of the stock and to investigate further the mode of inheritance of the exceptionally high growth, each of the 9 individuals in generation 53 was mated to an individual from line W, a gain selected stock carrying 50 % line G inheritance (Spearow, Neira & Bradford, 1976). W mice were nearly equal in gain to line G but on average more fertile. Five litters were produced from the G′ × W matings, and these formed the foundation of a new line, H.

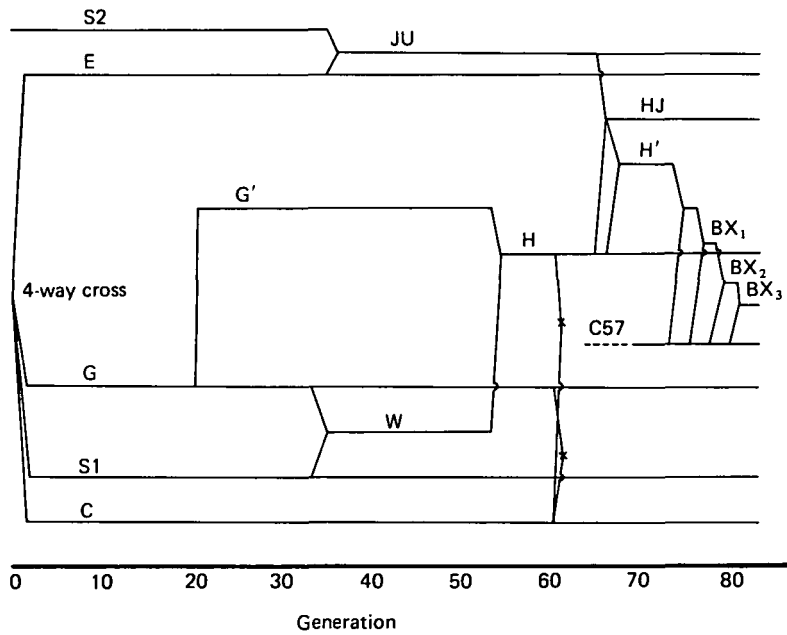

Fig. 1. Relationships of stocks involved in the experiment. Lines derived from cross of AKR, C3H, C57BL/6, DBA/2: C, Control; G, Gain; S1, Large Litters; E, High Embryo Survival; G′, subline of G. hg mutation apparently occurred in this line prior to generation 25. W, from cross of G and S1 at generation 33; selected for gain. S2, Line selected for large litters, from 8-way cross base. C57, C57BL/6 inbred. Lines G′, H, HJ, H′ and the backcrosses to C57 carried the hg mutant.

Line H was selected for rapid gain and was used in crossing experiments with lines G and C at generation 7, and with line JU (Eklund & Bradford, 1976) at generation 14. A line (H′) derived from the backcross to H, i.e. H(JU·H) from the latter experiment, was later used in a backcrossing experiment with the C57BL/6 (referred to hereafter as C57) inbred line.

The relationships among the various lines and the generations at which the events occurred are diagrammed in Fig. 1. The following is a brief summary of information on the lines represented in that figure:

Line	Description	Postulated genotype with regard to *hg* gene
C	Unselected control	*Hg Hg*
S1, S2	Selected for large litter size	*Hg Hg*
E	Selected for high prenatal survival	*Hg Hg*
JU	High litter size	*Hg Hg*
G	Selected for high 21–42 day weight gain	*Hg Hg*
W	Selected for high 21–42 day weight gain	*Hg Hg*
G′	Selected for high 21–42 day weight gain	Segregating
H	Selected for high 21–42 day weight gain	Segregating (*hg hg* after gen. 12)
HJ	Selected for high 21–42 day weight gain	(*hg hg* after gen. 5)
H′	Selected for high 21–42 day weight gain	*hg hg*
C57BL/6	Standard inbred	*Hg Hg*

RESULTS

(1) *Line G′*

The mean gains and coefficients of variation for lines G and G′ for generations 22–52 are presented in Fig. 2. Although the first exceptional individual noted at the time of weighing was in generation 29, the first 'mutant' individuals may have been 3 females and a male in a litter of 6 in generation 25. The 21–42 day gains in this litter were 21·0, 24·5, 23·8 and 25·5 g for females, and 27·7 and 31·7 g for males. The means for the line in that generation were 18·3 g ($n = 73$) and 25·1 g ($n = 87$) for females and males respectively. The mean intra-generation standard deviations for generations 22–24 were 2·0 g for females and 2·2 g for males. Thus, 3 of the 6 individuals exceeded the mean by 3 base standard deviations, and a fourth was $2{\cdot}7\sigma$ above the mean. Also, 3 of the six exceeded the previously recorded maximum gains of 24·4 g for females and 30·6 g for males (Table 3). Three of the 4 females and the 31·7 g male were selected and mated; none was fertile.

The proportion of individuals with gains exceeding the mean by 2 standard deviations (based on the mean for generations 22–24) is given for different periods of the experiment in Table 1. The choice of plus 2 standard deviations as the threshold to be exceeded admittedly is arbitrary; it was chosen to provide a measure of the increase in proportion of extreme individuals.

Fertility, defined as proportion of females producing litters, is shown in Table 2 by mating type for generations *22–30*, *31–40*, and *41–52*. All individuals were selected on the basis of gain, but the selected individuals showed a wide range of gains. Selected individuals of each sex were classified into one of two classes: 'normal', and 'large', i.e. 2 or more base standard deviations above the mean, making for 4 types of matings. The results confirm a low level of fertility for the extreme individuals. Matings between normal males and females resulted in 68 % fertility, compared to 53 % when either the male or the female was large, and only 25 % when both were extreme.

(2) *Results of crossing G′ × W*

The mean, standard deviation, range and coefficient of variation in gain, by sex, for the G′ and W parental generations and the G′ × W F_1 and F_2 are presented in

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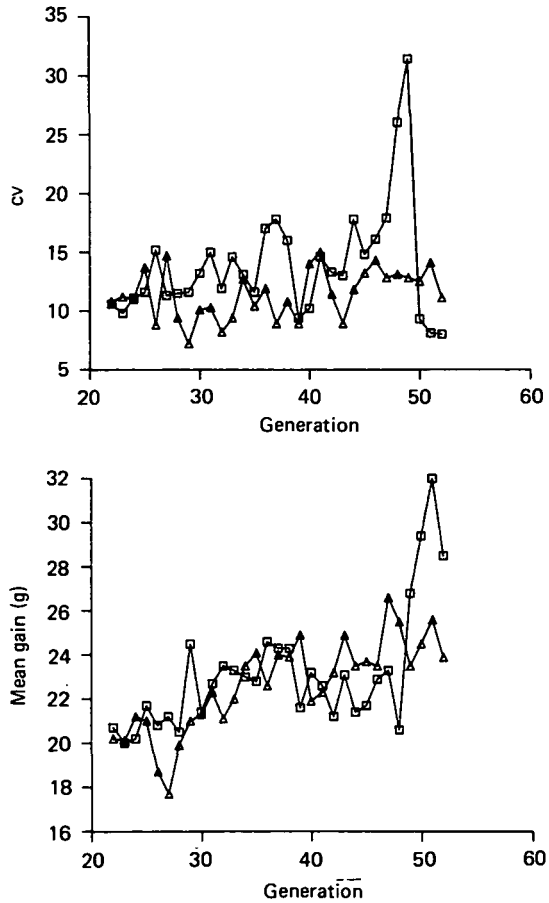

Fig. 2. Unweighted mean of male and female 3 to 6 week gain (g) and coefficient of variation (c.v.) for lines G (△) and G′ (□).

Table 1. *The proportion of individuals in G′ whose 3–6 week gain (g) exceeded the generation mean by two base (generation 22–24) phenotypic standard deviations*

	Males					Females				
Generations	N	Mean (g)	CV	Range	% Exceeding $\bar{X}+2\sigma$	N	Mean (g)	CV	Range	% Exceeding $\bar{X}+2\sigma$
22–24	284	23·5	9·4	16·1–30·6	2	241	17·0	11·9	10·6–24·4	1
25–31	546	25·2	14·4	17·4–41·3	8	497	18·7	12·1	12·9–28·1	4
32–35 (Inbred)	290	26·6	11·7	19·2–39·2	13	265	19·6	13·4	12·5–30·2	12
36–40 (Inbred)	418	27·4	15·2	13·5–45·6	17	375	20·0	18·4	12·2–32·9	9
(Non-inbred)	78	28·8	13·9	22·1–46·9	19	95	20·6	12·8	14·2–31·3	8
41–52	578	26·5	16·0	14·7–44·1	15	656	19·3	14·9	8·1–31·4	12

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Table 3. As noted previously, line G′ produced only one litter in generation 53, and the gains of these individuals, which were highly inbred, were not exceptionally large, especially for females.

A marked increase in the range and the coefficient of variation in the F_2 over the F_1 was shown by both sexes, suggesting segregation of an autosomal recessive gene in the cross. The distributions of gains in the F_2 (Fig. 3) are markedly skewed, and suggest a bimodal distribution for males, with those in the second group gaining much more than any F_1's. On the other hand, the lower limits of the F_1 and F_2 distributions were virtually identical for both sexes.

Table 2. *Fertility of matings of G′ males and females less than (normal) and more than (large) 2 base standard deviations above the generation mean*

Mating type		Generations					
		22–30		31–40		41–52	
Male	Female	No. matings	% Fertile	No. matings	% Fertile	No. matings	% Fertile
Normal	Normal	301	73	390	63	146	71
Normal	Large	17	47	29	48	37	59
Large	Normal	52	62	95	47	86	53
Large	Large	4	50	42	26	36	25

Table 3. *Mean and variation in 3–6 week gain (g) in G′, W and the G′ × W F_1 and F_2*

Sex	Line or generation	N	Mean	SD	CV	Range
Females	G′	4	21·9	0·5	2·5	21·1–22·3
	W	26	22·4	1·9	8·6	19·9–27·6
	F_1	20	21·1	2·6	12·4	16·1–25·0
	F_2	59	23·5	4·4	18·8	17·1–33·9
Males	G′	5	35·4	2·5	7·0	32·4–38·1
	W	24	26·5	2·5	9·3	21·8–31·5
	F_1	19	29·5	2·6	9·0	24·3–33·7
	F_2	53	31·2	5·0	15·9	24·2–42·8

Fertility of matings among F_1 individuals was 100 % and among selected (large) individuals from the F_2 was 54 %. Because of this poor fertility, the desire to maintain a stock with good population size, and some overlap of phenotypes between individuals homozygous for the alleged gene and those heterozygous or homozygous for the normal allele, it took several generations of selection to fix the gene in the line (H) derived from this cross.

We propose the symbol *hg* (high growth) for the postulated gene. On the hypothesis advanced, the extra rapid gaining individuals are of genotype *hghg*, while *HgHg* and *Hghg* are normal and not distinguishable from each other on the basis of gain. As indicated in Fig. 3, there is some overlap of phenotypes between *Hg-* and *hg hg*.

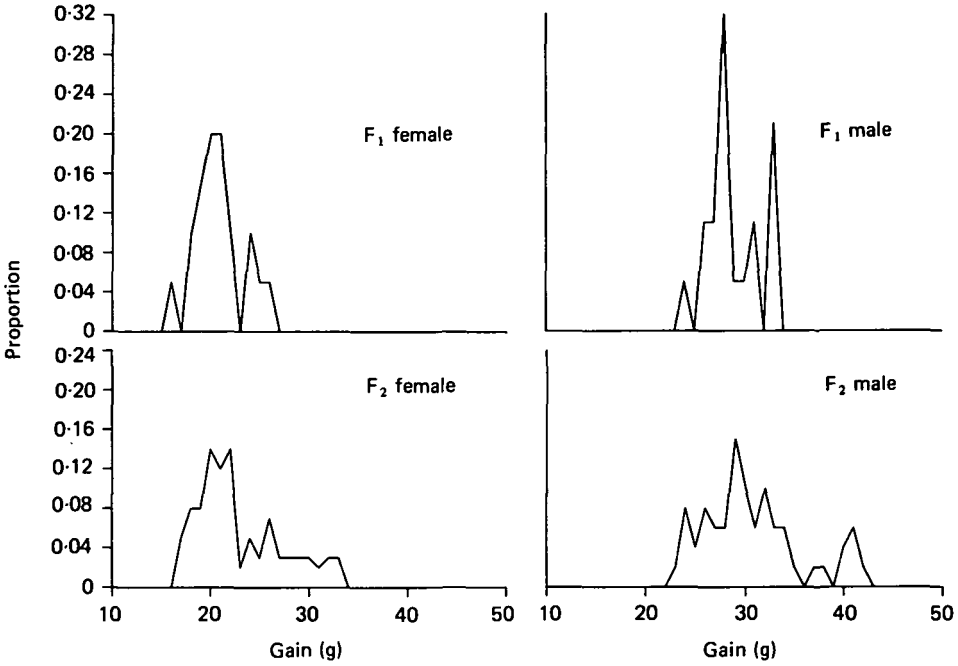

Fig. 3. Distribution of 3 to 6 week gain (g) of F_1 and F_2 males and females of the G′ × W cross.

(3) *Crosses between H and C and G and C*

Lines H and G each were crossed reciprocally with line C at generation 6 of line H and generation 57 of lines G and C. These crosses were made to determine if G also carried the postulated gene, and if the gene could be extracted from a cross with a strain not selected for growth rate. The results are presented in Table 4. Line H was not homozygous *hg hg* at this time, so an expected proportion of segregates in the F_2 and backcross could not be stated. However, the data provide two important conclusions:

(1) The gene does segregate following a cross with a line that has not been selected for rapid gain, as indicated by the markedly increased coefficient of variation in the CH F_2 and H(CH) backcross.

(2) The gene is not present in line G, based on the similar coefficients of variation for C, G, CG F_1 and F_2, and C(CG) and G(CG) backcrosses.

The CH F_1's of both sexes were below midparent average in gain, consistent with the hypothesis of the presence in line H of individuals homozygous for a recessive gene for rapid gain.

Fertility of matings in this experiment are shown in Table 5. As reported by Barria & Bradford (1981*b*), line C has very high fertility, with line G lower. Matings within line H were much lower still, and the crosses confirm that fertility of both males and females of this line is impaired. Matings involving both CG and CH F_1's, either males or females, had good fertility, and crossing appeared largely to overcome the infertility problems of both lines G and H.

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Table 4. *Mean and variation in 3–6 week gain (g) of mice from lines C, G, H and crosses*

Line or cross	Males			Females		
	No.	$\bar{X}$	CV	No.	$\bar{X}$	CV
C	115	13·0	12·3	123	9·8	16·3
G	70	28·9	8·0	57	23·5	11·1
H	57	32·0	18·1	72	23·5	15·7
F_1						
CG	106	20·3	8·9	99	16·2	10·8
CH	154	20·5	12·2	119	15·5	12·3
F_2						
CG	131	20·2	11·4	116	15·7	12·1
CH	116	20·4	20·1	115	15·8	19·0
Backcross						
G(CG)	65	24·6	11·4	55	19·9	13·1
H(CH)	86	26·0	18·5	68	19·1	19·9
C(CG)	67	16·3	11·7	67	12·9	14·7
C(CH)	71	16·6	10·8	68	12·9	11·6

Table 5. *Percent females producing litters in matings involving lines C, G, H and crosses*

Male line or cross	Female line or cross									
	C		G		H		CG F_1		CH F_1	
	No.	%	No.	%	No.	%	No.	%	No.	%
C	38	100	19	68	27	56	9	100	8	100
G	20	100	25	80	—	—	9	100	—	—
H	23	74	—	—	51	51	—	—	10	90
CG F_1	9	100	12	92	—	—	30	97	—	—
CH F_1	9	100	—	—	12	100	—	—	30	97

(4) *Crosses between H and JU*

Because of the continuing infertility problems of *hghg* individuals (line H), it was decided to cross line H with a highly fertile, high litter size line, JU. This line originated from a cross between lines selected for high litter size (S2) and high embryo survival (E) and had been selected for 6 generations for high birth weight (Eklund & Bradford, 1976). Litter size increased as a result of selection for high birth weight. Following termination of that experiment, the line was maintained by random selection and mating, with the exception that a small amount of selection for litter size was practiced. For the 5 generations prior to being crossed with line H, JU had a fertility of 100% and a mean number born in first litters of 13·24.

The crosses were made at generation 14 of line H, when the latter showed no evidence of segregation and was therefore judged to be homozygous *hghg*. In addition to producing F_1's, F_2's and backcrosses to both parent stocks, an experiment was carried out to test whether the *hg* gene: (1) is expressed when the

proportion of 'weight-selected' genes in the background is reduced to 25%, and (2) is completely recessive. A one-generation two-way selection experiment was carried out among the progeny of the JU(JU·H) backcross, by intermating the highest 20 and the lowest 20 pairs based on gain.

The results are presented in Table 6. The results in the F_2 and backcross are reasonably consistent with the hypothesis of a single recessive gene for rapid gain, although the proportion of individuals segregating was below expectation if penetrance is high, particularly in the H backcross. The F_1 mean was markedly below that of the midparent average, as expected if gain in the H line parents was elevated by homozygosity for a recessive gene for high growth rate. Standard deviation and coefficient of variation of the F_2 were more than double those in the F_1, and the F_2 and H(JU·H) backcross distributions (not presented) were similar to those shown in Fig. 3 with regard to skewness and tendency to bimodality.

Selecting and intermating the 20 males and 20 females (out of 67 and 92 respectively) of the JU(JU·H) backcross with the highest gain produced offspring of which 6% were above the parental generation limit, while the 20 pairs with the lowest gain produced none which exceeded the parental group limit. The expected proportion in each, neglecting the effects of the one generation of selection, is 0·0625 times the penetrance. Thus the proportion of segregates averaged over both groups is a little lower than expectation, if penetrance is high, but well within expected limits of sampling variation. The most striking result is the difference in frequency of segregates in the progenies of the plus- and minus-selected parents, which was highly significant ($\chi^2 = 8{\cdot}0$, d.f. = 1). Among possible explanations for this result are:

(*a*) The gene is not completely recessive.

(*b*) The expression of the major gene is dependent on other 'plus' genes for growth, and the reduction in number of alleles with a quantitative effect on growth by the two crosses to JU and the negative selection put the stock below the necessary threshold number.

Presumed *hghg* individuals were selected from the F_2 and from the backcross to H, to form lines HJ and H′ respectively, which were propagated from the largest individuals each generation. Line H′ was apparently fixed (*hg hg*) in the first generation, but HJ had both normal (similar to F_1) and large (similar to the largest F_2's) progeny for 3 generations. The difference in pattern between H′ and HJ in this respect lends support to the hypothesis of an effect of background genotype. However, by F_5 HJ also was apparently homozygous *hg hg* based on absence of any smaller individuals, and has remained so. Continued selection of line HJ for high gain has produced a rapid response to selection as shown in Fig. 4.

Data on fertility of the matings in this experiment are presented in Table 7. In contrast to the results of crossing H with C (Table 5), matings between JU·H F_1's and line H, whether the latter were male or female, had below normal fertility. These results, in combination with those from subsequent generations of H′ and HJ, indicate that the high fertility of line JU did not overcome the adverse effects of *hghg* homozygosity on fertility.

Table 6. *Mean and variation in 3–6 week gain (g) of mice from lines JU, H and crosses*

	Males					Females				
Line or cross	No.	$\bar{X}$	CV	Range	% 'Segregates'	No.	$\bar{X}$	CV	Range	% 'Segregates'
JU	97	15·4	11·2	12·7–19·7	—	80	11·7	12·9	8·9–16·0	—
H	44	39·6	10·9	25·1–47·8	—	45	27·5	13·7	20·5–35·8	—
F_1	90	22·8	8·7	18·3–27·0	—	142	16·4	11·8	11·3–20·4	—
% Heterosis		−17·1 %					−16·3 %			
F_2	40	23·6	20·2	18·0–35·8	18*	84	16·8	23·4	10·9–30·0	18*
BX(H)	30	30·9	17·6	21·7–42·6	33†	43	23·0	16·4	16·9–31·4	26†
BX(JU)	67	18·7	14·8	12·7–27·7	—	92	14·2	14·5	9·0–18·7	—
BX(JU) intermated Selected for:										
High gain	63	20·0	17·0	14·4–33·7	3‡	70	15·0	18·8	9·7–24·6	9‡
Low gain	58	17·2	14·1	9·6–20·9	0‡	69	13·5	10·9	11·3–17·9	0‡

* Exceeded maximum F_1 gain. (Note similarity of minimum gain of F_1 and F_2.)
† Exceeded parental mean, $(\bar{F}_1+\bar{H})/2$, by more than 2 F_1 standard deviations.
‡ Exceeded maximum BX(JU) gain.

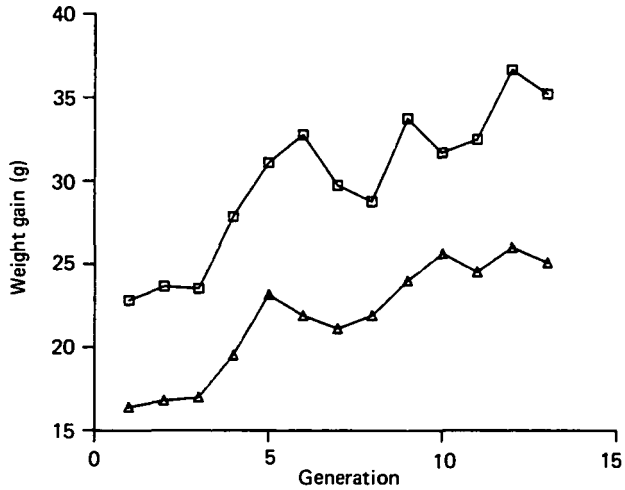

Fig. 4. Mean 3 to 6 week gain (g) of males (□) and females (△) of generations 1 through 13 of line HJ.

Table 7. *Percent females producing litters in matings involving lines JU, H and crosses*

	Female line or cross							
	JU		H		JU·H		Total	
Male line or cross	No. ♀♀	%	No. ♀♀	%	No. ♀♀	%	No.	%
JU	18	100	20	70	11	91	49	86
H	25	84	47	55	10	60	82	65
JU·H	12	100	7	57	19	95	38	89
Total	55	93	74	59	40	85		

(5) *Crosses between H′ and C57*

These crosses were undertaken with the objectives of: (a) putting the *hg* gene into a standard inbred line for studies of its physiology, and (b) studying the expression of the gene in the absence of other segregating genes.

Results are presented in Table 8 and Fig. 5. Contemporary pure line C57 and H′ stocks were not produced, but the distribution from other generations are included in Fig. 5 for reference. As in the previous crosses involving *hghg* mice, the F_1 was very uniform, and the F_2 showed a bimodal distribution. Two F_3's were produced, one by mating all individuals clearly in the upper mode of the F_2, and the other by selection at random from the lower mode but excluding individuals in the zone of overlap between the two distributions. The first of these bred true for *hg*, in contrast to line HJ. On the other hand, the frequency of *hghg* segregates from the normal group was less than 6·25%, again indicating less than 100% penetrance. However, the results of these matings provide some of the most convincing evidence for other than quantitative inheritance of growth rate, in that the realized heritability estimate provided by the means of the two groups of F_3 progeny was 0·92.

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Twenty males from each of the two F_3's were assigned at weaning to a feed intake study and are not included in the results in Table 8 and Fig. 5. Data on feed intake will be reported elsewhere, but it is of interest to note that the highest gain and 6-week weight in that trial came from an apparent *hghg* segregate from the normal parents.

Table 8. *Mean and variation in 3–6 week gain (g) of male and female mice from C57 × H′ crosses*

	Males					Females				
Generation	N	Mean	CV	Range	% Exceeding F_1 limit	N	Mean	CV	Range	% Exceeding F_1 limit
F_1	63	21·1	8·8	17·7–25·5	—	79	15·4	10·6	11·6–19·2	—
F_2	202	23·1	22·3	15·2–41·1	24	218	17·3	17·9	11·9–30·0	21
F_3(*hghg* × *hghg*)	51	31·7	9·8	23·9–39·7	96	71	21·4	13·7	10·9–28·1	80
F_3(*Hg_* × *Hg_*)	60	20·3	13·7	16·6–32·3	3	66	15·1	16·6	11·3–23·9	8

The *hghg* segregates from the F_2 were backcrossed to line C57, and the cycle repeated. Results are presented in Table 9. Results of the third cycle of this crossing, i.e. the second backcross to C57 and the 'F_2' from it, are also presented in Table 9. The pattern of increased variation and bimodal distribution in the F_2 from each of these backcrosses is again evident in these data. The frequency of clearly identifiable segregates is again less than 25 %. However, the proportionate effect of the gene, estimated from the two modes of each F_2 distribution, was very similar in each case to that in the first cycle of crossing with C57.

Fertility in most groups in this experiment, following the initial H′ × C57 matings, has been very good (Table 10). Matings involving *hghg* mice selected from the F_2's carrying 50 and 75 % C57 inheritance had 100 % fertility, while those segregated from the second and third backcrosses averaged 80 % (Table 10).

(6) *Characteristics of the mutant phenotype*

The identifying phenotype for the gene postulated is a marked increase in postweaning growth. Based on the two groups of F_3's from the C57 × H′ cross (Table 8) the average effect in the two sexes is an increase from 17·7 to 26·6 g (50 %) in gain between 21 and 42 days. If the obvious segregates from the normal parents are excluded, the mean of that group is 17·2 and the increase 54 %. The difference may have been augmented by the effects of quantitative genes, since in effect there was one generation of selection for gain. During the period of rapid response in line G, the average response was approximately 0·5 g per generation. Subtraction of this still leaves an effect of the *hghg* genotype in the C57·H′ F_3 of a 50 % increase in 21-day gain. In lines G′ and H the proportionate effect appeared to be less, about 30–35 %, but still substantial. In terms of phenotypic standard deviation units of an *Hg*-population, the estimated effect of homozygosity for *hg* ranges from 3·5–5·0σ in the different groups in this experiment.

A striking feature of the gene is that it causes no increase in weaning weight. In F_2's where all dams are *Hghg* and hence differential maternal effects are ruled

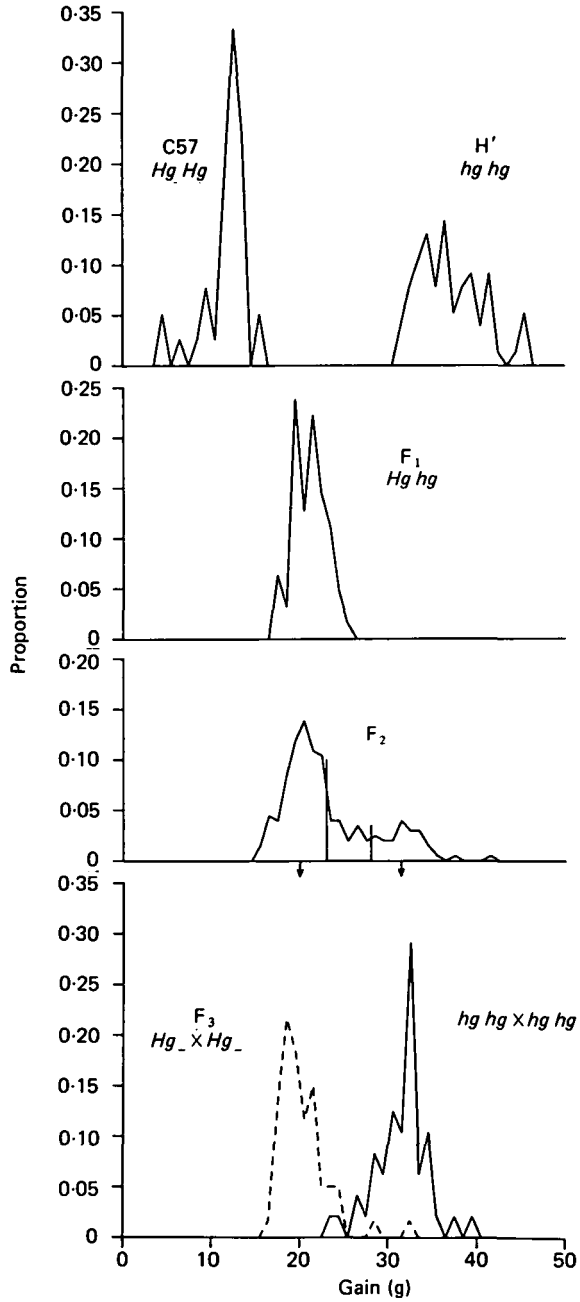

Fig. 5. Distribution of 3 to 6 week gain (g) in 3 generations of males of the H′ × C57 cross.

out, *hghg* young tend to weigh slightly less at 21 days, about 0·5 g on average, than their normal littermates.

Fertility of *hghg* mice, both males and females, is variable but on average lower than that of comparable *Hg-* individuals, as shown in Tables 2, 5, 7 and 10. The

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Table 9. *Mean and variation in 3–6 week gain of mice from first and second generations of successive backcrosses of C57 × H′ to C57*

Generation	Sex	N	Mean	CV	Range	% Exceeding BX limit
BX_1(C57)	F	73	13·7	10·9	10·8–17·4	—
	M	65	18·1	11·6	14·4–24·3	—
$F_2(BX_1(C57))$	F	90	15·0	18·7	10·0–23·3	17
	M	91	19·4	24·7	7·4–31·9	18
BX_2(C57)	F	114	14·1	9·2	11·1–18·0	—
	M	133	17·8	9·6	14·3–21·9	—
$F_2(BX_2)C57))$	F	423	14·6	19·2	9·0–24·3	15
	M	432	18·2	20·9	8·7–32·1	17

Table 10. *Percent females producing litters in matings involving H′, C57 and crosses*

Males		Females				
Group	Genotype	Group	Genotype	Litters	No. matings	% Fertile
H′	*hghg*	H′	*hghg*	H′	20	65
H′	*hghg*	C57	*HgHg*	F_1	15	60
C57	*HgHg*	H′	*hghg*	F_1	16	69
F_1	*Hghg*	F_1	*Hghg*	F_2	48	100
F_2	*Hg-*	F_2	*Hg-*	F_3	18	94
F_2	*hghg*	F_2	*hghg*	F_3	24	100
F_2	*hghg*	C57	*HgHg*	BX_1	24	88
BX_1(C57)	*Hghg*	BX_1(C57)	*Hghg*	$F_2(BX_1)$	20	95
$F_2(BX_1)$	*hghg*	C57	*HgHg*	BX_2	18	100
C57	*HgHg*	$F_2(BX_1)$	*hghg*	BX_2	8	100
BX_2(C57)	*Hghg*	BX_2(C57)	*Hghg*	$F_2(BX_2)$	112	93
F_2&$F_3(BX_2)$	*hghg*	F_2&$F_3(BX_2)$	*hghg*	F_3&$F_4(BX_2)$	65	80
F_2&$F_3(BX_2)$	*Hg-*	F_2&$F_3(BX_2)$	*Hg-*	F_3&$F_4(BX_2)$	52	98

basis of the impairment has not yet been established. The depression in fertility is greater in lines selected for gain (G′, H, H′, HJ) than in backcrosses to C57. It appears that both quantitative genes for gain and the *hg* gene in homozygous state depress fertility to some extent, and that in combination they interact to produce a more severe depression. Litter size of the *hghg* mice which are fertile is on average a little lower than for *Hg-* contemporaries, but generally within the normal range.

Appearance of the mice and body composition data (Calvert, Famula and Bradford (1984) indicate the gene does not cause obesity. All line G, G′, H and H′ mice are unusually susceptible to mites. A controlled comparison has not yet been made, but we do not believe that *hghg* mice are more susceptible than other mice from the gain selected lines. Lifespan of the *hghg* mice has not been measured. A very short life span is characteristic of line G mice (Eklund & Bradford, 1977), but it is not known if *hghg* mice age more rapidly than *Hg-* mice of the gain selected strains.

DISCUSSION

Although the segregation frequencies reported for the various crosses are in some cases lower than the 25% (F_2) or 50% (backcross) expected for a recessive gene, due to some overlap of the *hghg* and *Hg*-distributions, the results in general support the conclusion of an autosomal recessive gene causing a marked increase in postweaning growth rate. In the absence of a criterion for identifying *hghg* homozygotes other than gain, estimation of degree of penetrance is difficult. Overlap of the *Hg-* and *hg hg* distributions could occur with two consistently reproducible distributions whose means are not sufficiently different to separate them, or because in each generation a certain percentage of *hg hg* individuals do not express the phenotype typical of that genotype, i.e. incomplete penetrance in the traditional sense. Taking into account the results from all the crosses, and the fact that lines apparently fixed for and free of the *hg* gene have been extracted from several different crosses, leads to the conclusion that penetrance in the traditional sense is quite high, probably over 80% but possibly not complete.

The simplest hypothesis for the origin of the postulated *hg* gene is that it arose by mutation in line G′ or, if it arose in G, it was lost from that line before any homozygous individuals were produced. There remains the question as to whether or not the same mutation might occur in a strain not selected for gain, or whether its occurrence, expression or detection is dependent on a high frequency of quantitative genes with positive effects on gain. With an effect as large as the gene appears to have, one would expect such a mutation to be found if it occurred in any regularly observed experimental stock, and it has not been noted in any other of the many stocks in our colony. Roberts & Smith (1982), referring to obese and dwarf mutants in mice, state, 'it may be no accident that several of these mutants were found in lines selected for weight in the direction of the mutant effect'. The occurrence of a litter with 4 apparent dwarfs in the *hghg* F_4 from the H′ × C57 cross also raises the question as to whether there is some instability at a locus or loci affecting gain in the gain selected stocks.

The long delay in identifying the genetic basis of the exceptionally rapid growth merits some comment. In retrospect, it appears that the gene might have been identified and a true breeding strain established much earlier than in fact was done. A major impediment was of course the poor fertility of the homozygotes (Table 2). This coupled with the desire to maintain a large population size to permit further selection of the stock was an important factor. Without doubt the most important factor, however, was simply that a single gene with an effect of this magnitude on growth was not anticipated, and the appropriate experiment to test that hypothesis was not done at the early stages.

A question does remain as to whether the many generations of selection in a population with this gene segregating did in fact increase the frequency of modifiers which enhanced its expression and made its eventual identification easier. As pointed out earlier, the results of the JU(JU·H) backcross experiment suggest that an epistatic combination of genes may in fact be involved. The slight reduction in proportion of extreme individuals in successive backcrosses to a standard inbred (Table 9 and unpublished) supports this conclusion. Thus there is the possibility that the postulated gene may interact with one or more other genes for full

expression, as has been documented for other genes with large effect (see review by Roberts & Smith, 1982). However, the fact that segregates gaining 30–50% more than the parental generation maximum have been obtained from intermating individuals from each of 4 successive backcrosses to an inbred line of normal size provides very strong support for the single gene hypothesis proposed.

A gene with an effect of this magnitude offers new and potentially useful means of studying the physiology of mammalian growth. Assuming a specific product of the gene can be identified, the potential for cloning it, transferring it to other species and studying its expression there, as has been done for the human growth hormone gene (Palmiter *et al.* 1983), is also an intriguing possibility. The value of the gene for increasing growth of livestock species would be limited unless its adverse effects on reproduction, as shown in most of the stocks described here, could be overcome. Fertility in stocks such as HJ are not particularly encouraging as to the possibility of using selection to reduce adverse effects of the gene on fertility, but the C57 crosses (Table 10) suggest that fertility of homozygotes in some genetic backgrounds is sufficiently near normal to permit ready use of the gene as a model for study of regulation of growth.

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