

## The growth of mice selected for large and small size in relation to food intake and the efficiency of conversion

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### SUMMARY

Mice selected for large size show increases in both food intake and efficiency, and small mice show decreases in both. This is true whether the comparisons are made at the same age or at the same weight. Food intake and efficiency contributed more or less equally to the responses to selection for growth. Mice seem to regulate their food intake to a certain level of energy. On suspension of a period of food restriction, mice ate the same amount as others of the same strain that had not been restricted, and which were bigger. At the same time, they converted it more efficiently than the mice which had been full-fed throughout, because of a linear negative association between efficiency and body weight. Thus, following restriction, mice eat as much as bigger mice of the same age, and convert it as efficiently as younger mice of the same weight. The product of these two effects gives rise to rapid (compensatory) growth.

### 1. INTRODUCTION

If animals are selected to grow faster, it follows that they must do so by eating more, or by utilising the food more efficiently, or by some combination of the two. Typically, both voluntary food intake and efficiency of conversion change as positive correlated responses to selection for growth, as shown for a variety of species in a review by Yüksel (1979). The genetic correlation between the two component traits is usually small except in the pig, where the evidence is reasonably consistent that it is negative. In the mouse, the evidence is overwhelming that genetic variation exists both for voluntary food intake and for efficiency of conversion. Timon and Eisen (1970), Sutherland *et al.* (1970), Hayes & McCarthy (1976), Eisen, Bakker & Nagai (1977), Eisen & Bandy (1977) and McPhee *et al.* (1980) all agree that when mice are selected for increased weight gain, they both consume more food and convert it more efficiently, usually significantly so. A more detailed review of the mouse literature on this topic was provided by Roberts (1979). While the generality as stated can be defended, it is perhaps only fair to add that the magnitude of various changes in the two component traits is variable. The nature of the genetic variance in the system is not well understood.

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The purpose of this paper is to report on the changes in food consumption and in efficiency found in the lines of mice selected for growth described by Falconer (1973). The material is unusual in that it comprises 6 large lines, 6 small lines and 6 unselected control lines. Variation among replicates within size groups is largely attributable to genetic drift, which allows us to examine how much of the variation in food intake and in efficiency may stem from this cause alone. Unfortunately, it has not been possible to examine all the replicates systematically, as measuring food intake of individual mice is demanding of facilities and labour. This paper summarises the main findings of a series of trials, usually conducted on a small scale, over several years. The results, for ease of summary, are presented graphically and the main conclusions are evident without statistical refinement. Some aspects of the data will be developed in further papers, but for present purposes, the emphasis will be on the coherent features of the separate studies.

Three lines of enquiry will be presented sequentially. The first is purely descriptive: how much food do large and small mice eat, and how well do they convert it? The only novel feature of this study is that the observations were continued until well after maximum body weight had been reached. The second experiment examines the regulation of food intake when alternative sources of energy are available. In particular, do any of the strains respond differentially to a ready source of energy, such as glucose? Finally, how do different strains react to the same amount of food, and what happens when they revert to their normal intake?

## 2. MATERIALS AND METHODS

All mice in these studies were housed and fed individually. The pelleted food was given to them in especially constructed baskets. Attempts were made periodically to estimate any waste, by keeping mice in cages without sawdust and bedding and separating out any food crumbs. Very little waste was actually observed, less (and usually much less) than 5% of the amount eaten, confirming the general impression that wastage was not a problem.

For the first study, mice were taken at 3 weeks of age from each of the large, control and small lines from the 17th generation of three replicates (replicates B, C and D) of Falconer's (1973) Q stocks. Each of the 9 lines provided 11 male mice. This trial was not terminated until the surviving mice were 75 weeks old. By that time, numbers were falling in some groups, but 81 of the 99 mice set up were still alive after one year. Body weights and food intake were recorded every week.

The next study came from the 27th generation of the Q stocks, and two of the above replicates (C and D) were represented, each with its large, control and small lines. The mice this time were all females, and each line was divided between two treatments, differing in the liquid that was provided. One was the usual tap water, the second a 5% glucose solution. The glucose was introduced in an attempt to manipulate any glucostatic mechanism of appetite control, since preliminary trials had indicated that mice would drink glucose solution preferen-

tially. A 5% solution was taken because this is isotonic with mouse body fluids, removing any complicating effect of tonicity on appetite. In this study, an attempt was made to monitor blood glucose level on the different treatments, but the measurement was unsatisfactory and the results are omitted from this paper. There were six mice from each line on each treatment and the trial was conducted between the ages of 3 and 8 weeks.

The last study to be described came from the 37th generation, replicates B and D being represented but the small lines being excluded. The two large lines and the two controls were fed *ad libitum*; in addition, a sample of each large line was fed on a daily basis exactly what the corresponding control line (at the corresponding age) had eaten the previous week. The trial began when the mice reached three weeks of age, and the intention was to restrict the large line to not less than 80% of its normal weight. By six weeks of age, it was becoming clear that the effects of the restriction were becoming more severe than this, so full feeding was immediately resumed. The mice were killed at 26 weeks of age and the gonadal fat was excised and weighed. However, no difference in carcass composition was detectable by then, and the results are omitted from this paper. There were 10 male mice per group in this study.

### 3. RESULTS

#### *Growth, food intake and efficiency*

Mean growth curves of the mice used in the first study are shown in Fig. 1. Selection had been for weight at 6 weeks of age but as expected, the weights were different at all ages. Mice reach about 80% of their mature weight by 10 weeks of age. All sizes gradually gain weight until they are at least a year old, presumably in part through the accumulation of fat. The three large lines are very similar in weight at all ages; the control and small lines show rather more divergence among themselves, but the nine lines differentiate clearly into three size groups.

For simplicity, food consumption is shown (Fig. 2) as the average of the three lines within a size group. There is no doubt that large mice eat more than small ones, and it would be astonishing if they did not. This is particularly noticeable at or around the age of selection, at 6 weeks, after which age the difference becomes less because the large mice reduce their intake. Food intake per unit of body weight is summarized in Fig. 3, with more detail in Table 1. Avoiding consideration of what exact power of weight may be the most appropriate, we may conclude the following. When mice are weaned at 3 weeks of age, large and small mice eat the same amount per unit body weight, but thereafter, this measure of intake declines differentially between the two. Small mice when fully grown eat their own weight of food per week, whereas large mice eat only three-quarters of their own weight. The control lines are very similar to the large lines (on this measure) until around 6 weeks of age, and thereafter adopt a level intermediate between large and small.

Large mice eat more than the controls, and small mice less, not only at the same age but also at the same weight (Table 2). Only a limited range of overlapping

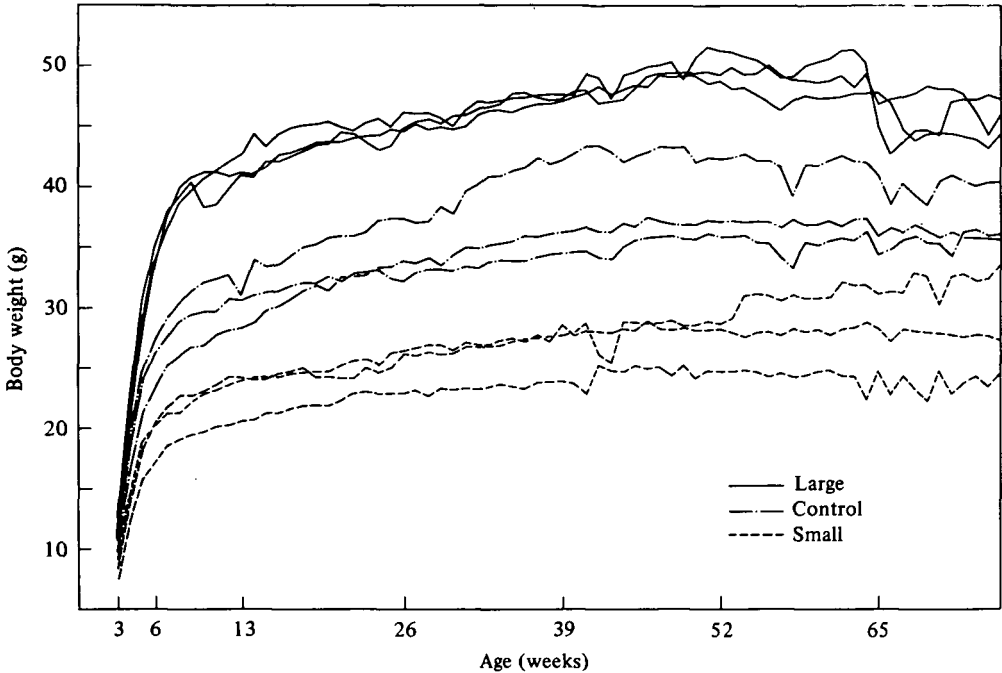


Fig. 1. Body weight in grammes of three replicates each of large (L), control (C) and small (S) mice, from 3 to 75 weeks of age.

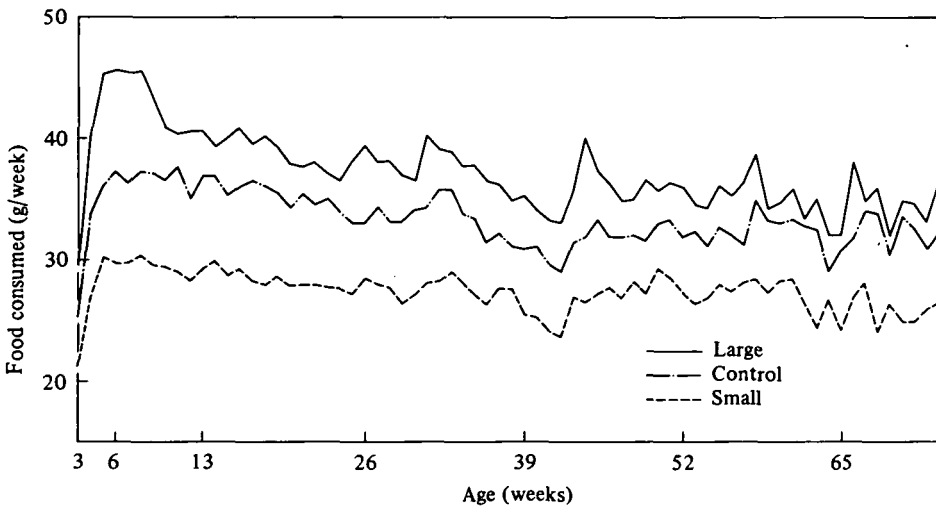


Fig. 2. Mean food consumption, in grammes per week, of the 3 replicates in each size group. L, C and S as in Fig. 1.

weights is available. Table 2 was constructed by determining the age at which each line reached 15 g and 20 g, and noting its food intake at those ages. The means for each size group are tabulated.

Efficiency of conversion was expressed as weight gain divided by food intake, a measure which declines to zero when growth stops. But over the growing period,

until about 8 weeks of age, there is no doubt that large mice are more efficient than the controls, and not so clearly, that the small mice are less efficient (Fig. 4). This is presumably related to the relatively higher maintenance requirement of the small lines, which is obvious at mature sizes (Fig. 3), as they require more food to maintain one unit of body weight. This is conventionally explained in terms of a higher surface area to mass ratio, with its implications for thermo-regulation and its energetic cost.

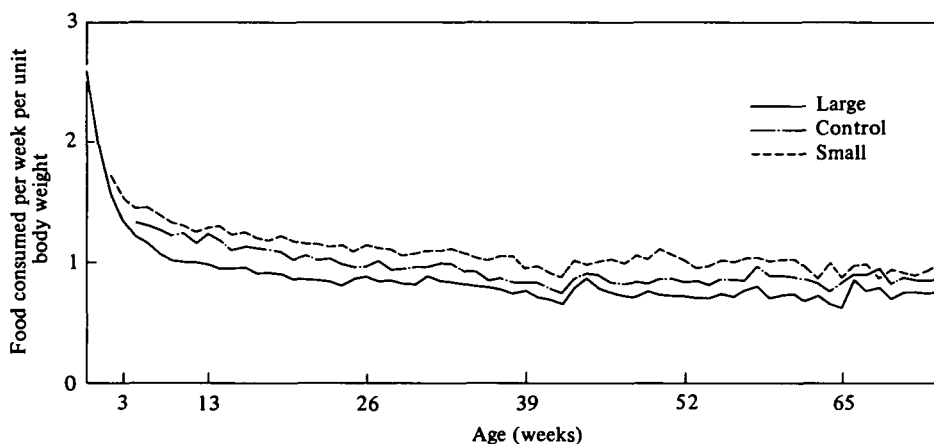


Fig. 3. Mean food consumption in grammes per week per unit body weight.

Table 1. *Food consumed per week per unit body weight at various ages. Averages for 3 replicates each of large (L), control (C) and small (S) mice*

Lines	Age in weeks							
	3	4	5	6	9	12	26	52
L	2.58	1.98	1.58	1.35	1.07	1.00	0.88	0.72
C	2.44	1.94	1.56	1.45	1.27	1.15	0.96	0.83
S	2.59	2.03	1.72	1.54	1.39	1.25	1.14	1.01

Table 2. *Average amount of food consumed by large, control and small mice at the same body weight*

Lines	At 15 g		At 20 g	
	Av. age (wk)	Food (g)	Av. age (wk)	Food (g)
L	3.2	33	3.8	37
C	3.6	31	4.4	34
S	4.3	28	7.1	30

We thus see that the effect of selection for growth has been to change both food intake and efficiency correspondingly. Since weight gain is the product of these two effects, we can compare the relative magnitude of their contributions to the change in weight. Table 3 shows the percentage changes of the large and small lines from their corresponding control line – each row indicating what

might have been observed in an unreplicated experiment. This, however, pays too much attention to the historical origins of large-control-small sets; genetic drift over generations means that the LB large line (for instance) has little more in common with the CB control line than it has with either of the other two controls. The best estimate of the relative contributions of food intake and efficiency to differences in body weight thus comes from the average of the three replicates, which shows the effects to be roughly equal. That one large line should have all of its response apparently attributable to improved efficiency, and one small line to reduced food intake, can be dismissed as accidents of drift, emphasizing that general conclusions cannot be drawn from single comparisons when lines are subject to drift.

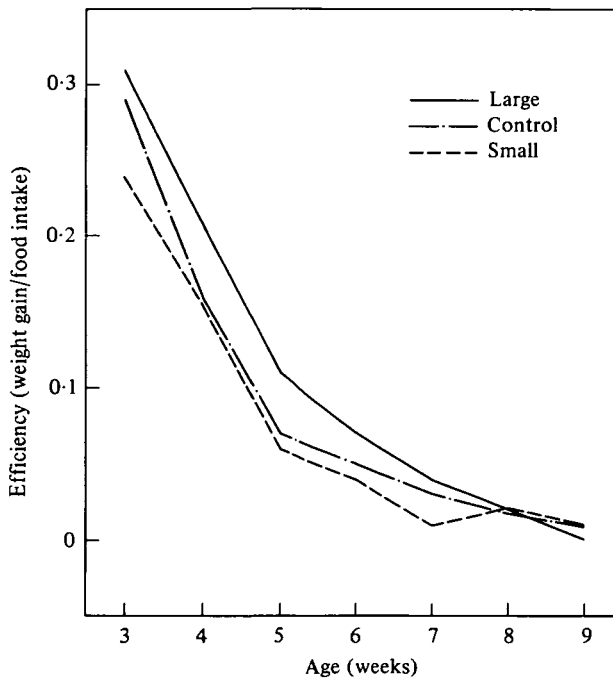


Fig. 4. Mean efficiency (weight gain/food intake) of the 3 replicates in each size group. L, C and S as in Fig. 1.

Table 3. Percentage changes, relative to control, in voluntary food intake and gross efficiency (ages: 3 to 6 weeks)

Rep.	Large lines		Small lines	
	Food intake	Efficiency	Food intake	Efficiency
B	+4	+46	-19	-19
C	+27	+28	-17	-1
D	+34	+30	-16	-14
Average	+22	+35	-17	-11

The conclusion from this study is therefore that selection for body weight changes both food intake and efficiency in the appropriate direction. The combination of genetic parameters in the two component traits is such that both can contribute more or less equally to the response.

*Regulation of intake*

The next study attempted to examine further the changes in voluntary food intake. Particularly, was the growth of large mice limited by their inability to ingest more food, or conversely, could their voluntary intakes be reduced by an alternative method of meeting their satiety requirements? We cannot enter here into detailed discussion of appetite control, but one simple theory (as described in standard biological text books) was amenable to test. This is the glucostatic

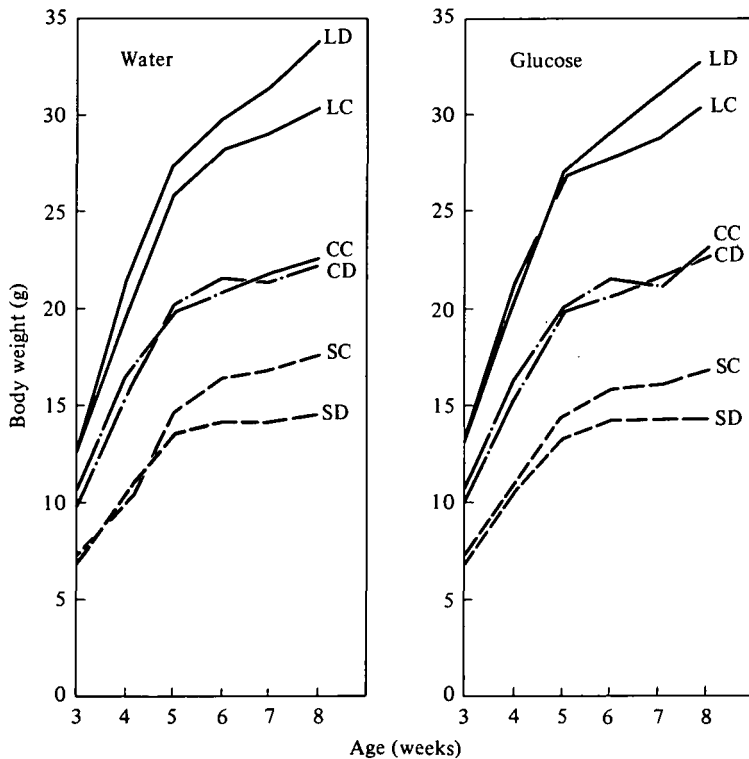


Fig. 5. Body weights (g) between 3 and 8 weeks of 2 replicates each of L, C and S mice. On left, when given ordinary water; on right, when water replaced by glucose solution.

theory of short-term appetite control. In simplified form, the theory states that the 'satiety centres', the ventromedial nuclei of the hypothalamus, respond to an elevated blood glucose level, and the animal stops eating until blood glucose drops again. The experiment asked a simple question: in view of the known predilection of mice to drink glucose solution in preference to ordinary drinking water, would this extra glucose in readily available form satisfy the satiety centre earlier, reduce food intake, and thus reduce growth? Or would it in fact provide extra energy to meet the energetic cost of protein synthesis (see Webster, 1977, for discussion) and thus allow the animals to grow more? To test this, each line was divided between two treatments, one being given ordinary tap water and the other a 5% glucose solution.

The glucose solution had no effect on weight gains – growth between 3 and 8 weeks was identical on the two regimes (Fig. 5). There were, however, obvious differences between lines in their glucose intake. The two large lines drank about  $2\frac{1}{2}$  times as much glucose solution as they did of water, while the two small lines showed only a slight increase (Fig. 6). The interpretation is complicated by the behaviour of the two control lines, which went one each way. This division suggested that the control lines might have been fixed for different alleles controlling glucose preference, possibly alleles at a single locus. To test this, further samples from the six control lines maintained in the laboratory (Falconer, 1973) were measured for glucose solution intake from 6 to 12 weeks of age. The weekly intakes for the C and D control lines (which had shown a difference in Fig. 6) are

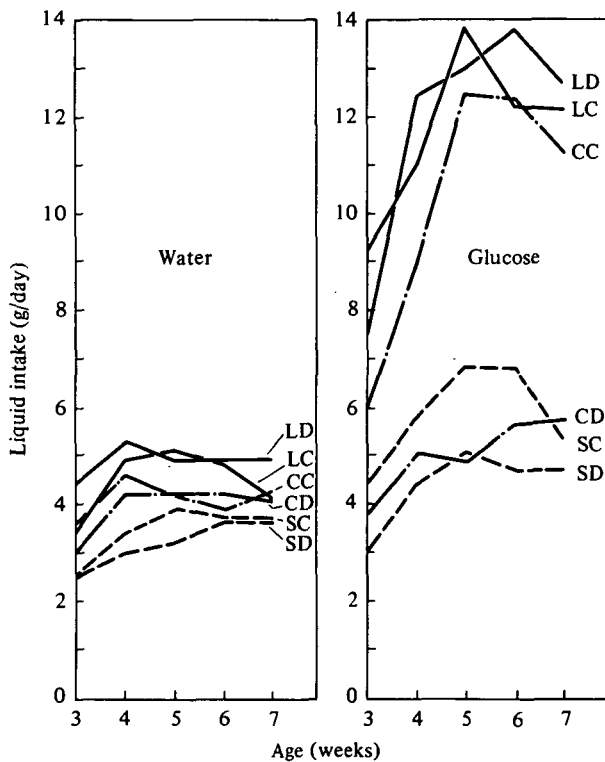


Fig. 6. Mean daily liquid intake (g) of water (on left) and glucose solution (on right) of L, C and S mice.

shown in Fig. 7. There is no hint of discontinuities in the distributions within lines, and unlike the previous sample, the mean intakes are not very different. The variation between individual mice was immense, and we can only suppose that the unfortunate difference between the controls in Fig. 6. was an accident of sampling small numbers. Given this, we shall treat the samples in Fig. 6 merely as two groups – glucose preferers and non-preferers.

The intake of solid food was reduced for the three lines that drank glucose solution copiously, compared to their intakes with normal drinking water, while



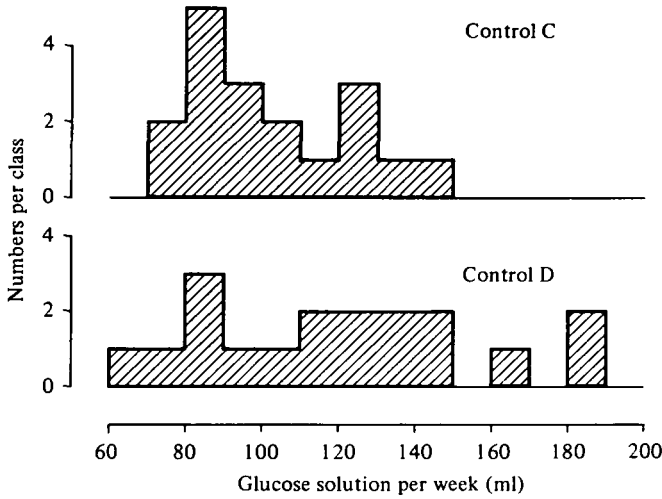


Fig. 7. Distributions of glucose intake within each of the two control strains, for the sixth week on trial.

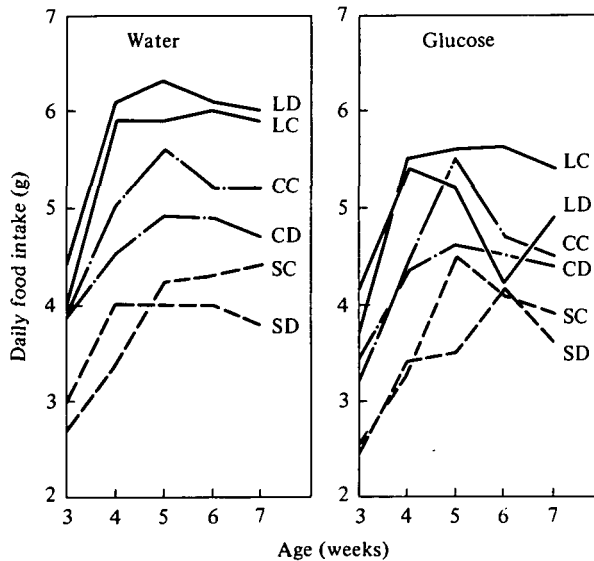


Fig. 8. Daily food intake (g) of mice when given water (on left) or glucose solution (on right).

that of the other three lines was affected much less (Fig. 8). The next step was to compare the total energetic intake from the two sources. The energetic value of glucose is available from standard text books, while that of our cubed diet was obtained by bomb calorimetry. The total energetic intake of mice of different strains was very similar whether they had water or glucose solution (Fig. 9). It is noticeable, though, that weekly fluctuations were greater among the three lines that drank glucose solution, as if they were having trouble with their glucostatic mechanism, but the overall impression is that of successful regulation of intake to

a given energy level. The regulation is too precise to be dismissed as a mere consequence of drinking so much glucose solution that they could not eat solid food.

The conclusion from this study was that whereas large mice may have a predilection for glucose solution, this does not induce satiety nor does it allow them to increase their total energetic intake. This suggests that the changes in appetite brought about by selection for increased growth are mediated, at least in the short term, through a mechanism related to total energetic requirements.

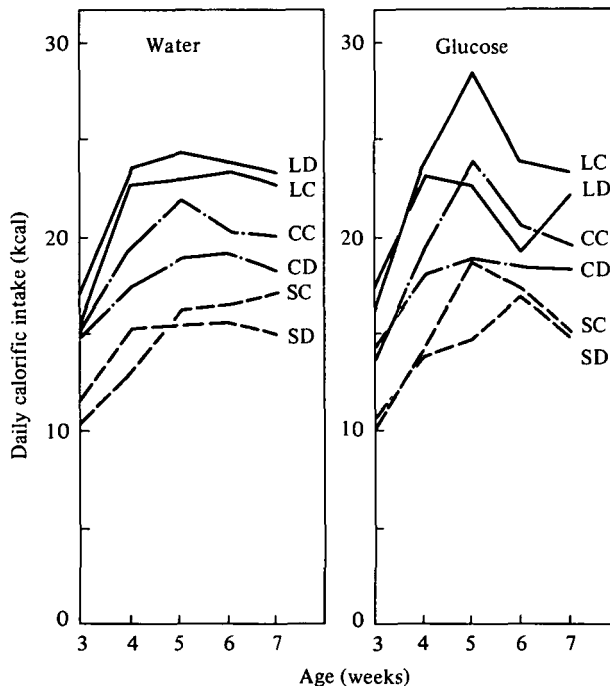


Fig. 9. Total daily calorific intake of mice when given water (on left) or glucose solution (on right).

#### *Food restriction and compensatory growth*

The final study involved restriction of food intake. If, as shown earlier, the large mice are more efficient than the controls, then on the same amount of food they ought to grow more. When this was tested, however, the large mice in fact gained less weight than the controls (Fig. 10) on the same amount of food, between the ages of 3 and 6 weeks. The amount fed to the large mice was the voluntary intake of the controls. This was barely sufficient to cope with their maintenance requirement, and at this level of feeding, the large mice were less efficient than the controls, unlike the situation under *ad libitum*. This reflects the complicated relationship between level of intake and efficiency, well-known to animal nutritionists. The result differs also from that reported by Stanier and Mount (1972). In a similar study, they fed both large and control mice the same amount of food

– 4 g per day. In their study, the large mice still grew better than the controls, though the differences between the two on *ad libitum* feeding were not fully realized under restriction. However, other differences between the two studies apart, the restriction imposed by Stanier and Mount was somewhat less severe for the large mice than the one used in this study, especially at younger ages, and that alone may be sufficient to explain the difference between the two results. Nevertheless, the finding that the large mice in this study gained less weight than the controls was unexpected.

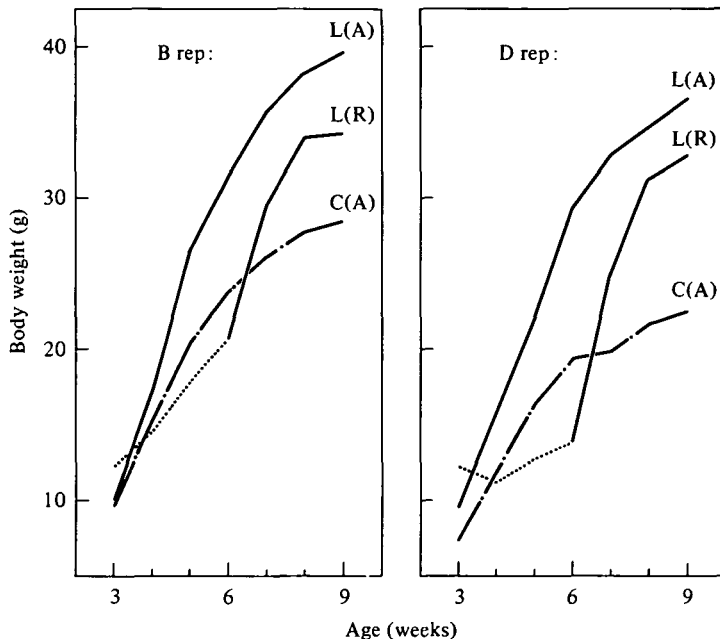


Fig. 10. Body weights (g) between 3 and 9 weeks of age in 2 replicates each of L and C lines. L(A) and C(A) were both fed *ad libitum*; L(R) was restricted to the food intake of the corresponding control, between 3 and 6 weeks of age.

At six weeks, the food restriction was terminated, and all mice were fed *ad libitum*. The two lines that had been restricted now showed the classical compensatory growth. Later weights are not shown in the interest of curtailing the graphs, but by 20 weeks of age, the restricted large line in the D replicate had caught up with the one fed *ad libitum* throughout. The B replicate seemed to settle down about 5 g less, but whether this was a difference between samples or a permanent effect of earlier restriction, we cannot tell.

The next question is how do animals achieve compensatory growth? Taking food intake first, the astonishing finding is that the very first week after being taken off restriction, the mice ate at least as much as those which had been full-fed (Fig. 11) and which were 60–100% heavier than they were. There may be an element of chance in such precise regulation of appetite, but using words loosely, the system behaves *as if* voluntary food intake were simply a function of age.

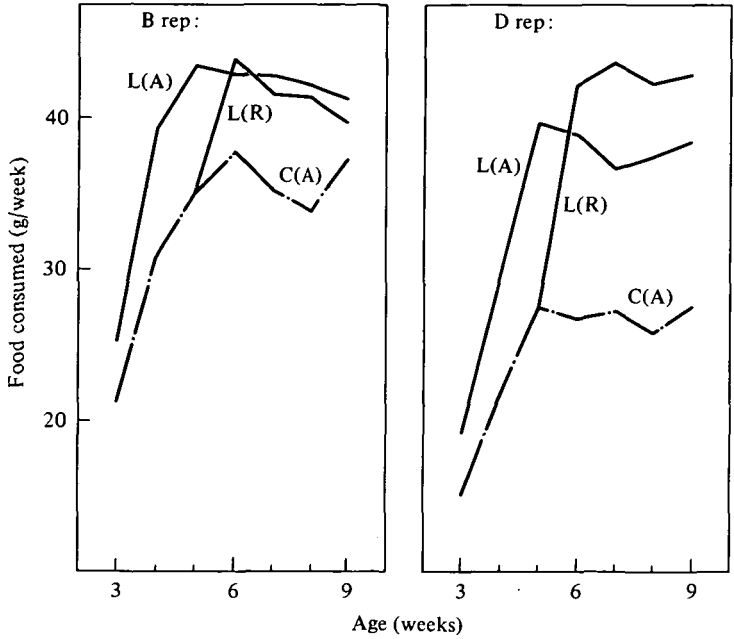


Fig. 11. Food consumption (grammes per week) of the lines shown in Fig. 9.

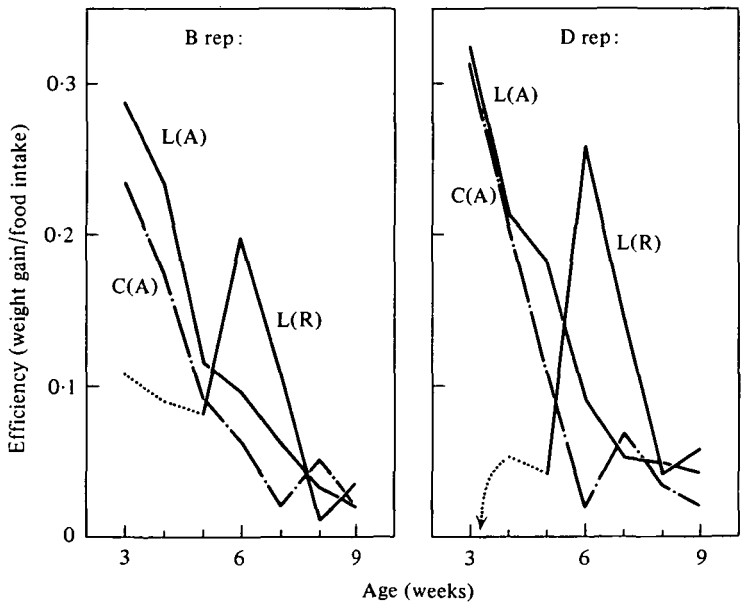


Fig. 12. Efficiency of conversion of the lines shown in Fig. 9.

Mice of the large lines, between 6 and 7 weeks of age, seem to eat a similar amount of food irrespective of whether they are 15 g or 30 g at the time.

Next, the lines that had been on restriction, as soon as they were taken off, show a large improvement in efficiency (Fig. 12), which then declines roughly in parallel to that of the full-fed mice. This spike in efficiency can be interpreted from the

following: the mean efficiency of the two large lines was plotted against their mean body weight at the time over weekly intervals between the ages of 3 and 10 weeks (Fig. 13). We see that efficiency declines as a remarkably linear function of body weight. When we superimpose on this plot those mice which had been restricted (marked as stars in Fig. 13) we see that they adopt the efficiency exactly appropriate to their weight at the time irrespective of their age.

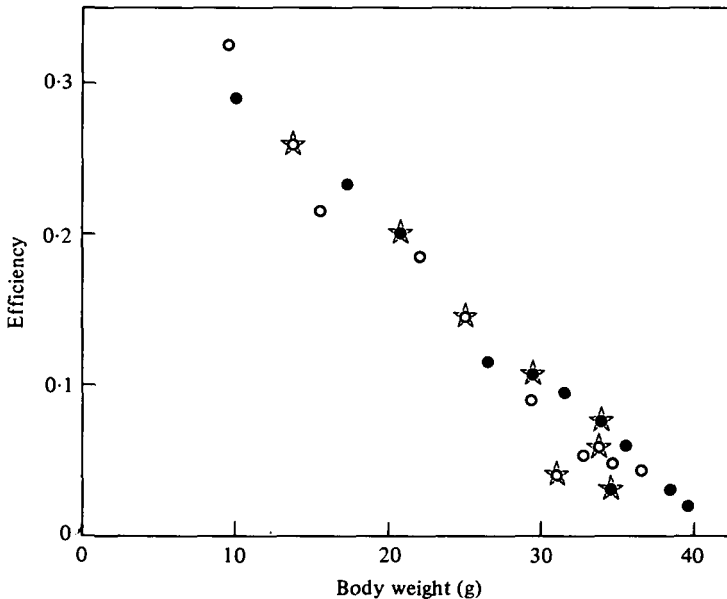


Fig. 13. The relationship, over successive weeks from 3 to 10 weeks of age, between efficiency and body weight at the time, for the two large lines fed *ad libitum*. Stars show the weekly efficiencies following restriction i.e. from 6 to 9 weeks.

It thus seems that, following a period of food restriction, mice have a bigger appetite than they normally would at that weight, and a higher efficiency than they normally would at that age. Because they are smaller and older, they benefit on both accounts, and the product of these two benefits is the rapid gain in weight known as compensatory growth.

In conclusion, one important consequence of selection should be noted. Selected large mice are more efficient than unselected controls at all body weights (Fig. 14), consonant with the earlier finding that they are more efficient even age for age, despite being bigger. The hint in Fig 14. that Large and Control mice differ in slope was not substantiated by a formal test.

#### 4. DISCUSSION

There is no doubt that selection for large size in the Edinburgh lines of mice led to an increase both in food intake and in efficiency, and that this is true whether the comparisons are made at the same age or at the same weight. The small mice, correspondingly, show decreases in intake and efficiency. What is

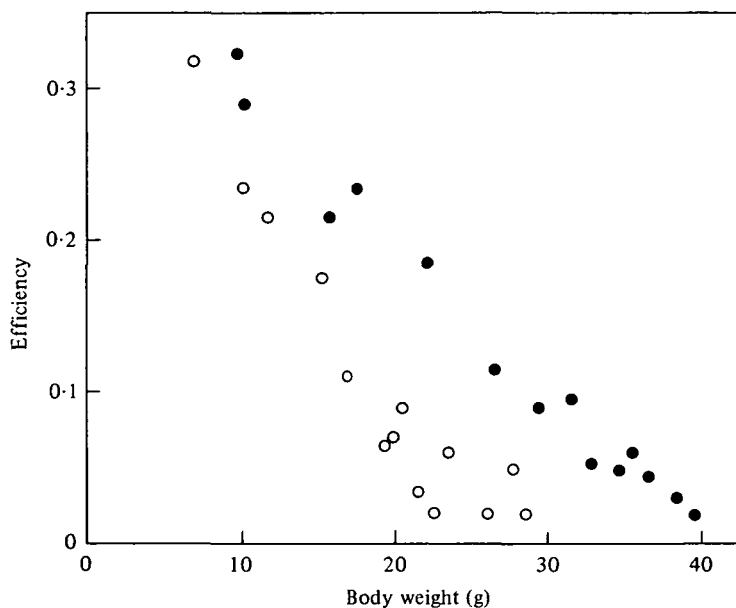


Fig. 14. The relationship between efficiency and body weight at the time, for the large and control lines, replicates pooled in both cases. Large, ●; control, ○.

more difficult to decide is to what extent the changes in the two component traits may be related. Other things being equal, an increase in food intake would be expected, at least over some range of intake, to lead to higher efficiency. If we subtract the maintenance requirement from a given intake, then what is left over is available for growth. Animals eating little more than their maintenance requirement will therefore not grow, and will be inefficient; those eating more will grow, and be more efficient. As we saw from the food restriction results, the amount eaten by the control lines was little above the maintenance requirement of large lines which explains why the large lines were very inefficient on the same feeding level as the controls.

However, the qualification for the mechanical relationship, stated above, was 'other things being equal', and they may not be. For a start, as we saw from the first study, small mice have a relatively higher maintenance requirement per unit body weight, seen clearly when all mice have stopped growing. This need not be wholly attributable to the higher surface area to mass ratio. Maintenance requirement covers not only thermoregulatory aspects but also protein turnover. Priestley and Robertson (1973), working with these strains, suggested that protein turnover was indeed slower in large mice than in small mice; small mice in fact had a higher rate of protein synthesis, but this was outweighed by even more rapid protein degradation. One of the effects of selection may thus have operated on protein turnover, which may explain why large mice are more efficient than the small mice when compared at the same body weight, despite the strong negative association (within a size group) between weight and efficiency.

It seems therefore that selection for weight is not simply selection for increased

appetite, and that appetite may in fact be some consequence of metabolic changes brought about by the selection. Radcliffe and Webster (1976), working on the rat, suggested that appetite control is linked to the animal's impetus for protein deposition, and that the retention of lipid and energy is of no consequence for appetite control. If we may suppose that this 'impetus' is the genetic regulation of body size (though that statement is no more precise) it then follows that the increased food intake of our large mice is a consequence of their more rapid growth. This may explain the precision of appetite control found here both in the glucose and in the restriction studies. It may also explain the curious hump in the food intake of the large lines around 6 weeks of age, following a period of very rapid growth. As growth slowed down the metabolic demands were reduced sufficiently to cut back their voluntary food intake to a lower level.

There are indications from studies on domestic livestock that the results reported here on the effects of restriction may have some generality. Saubidet and Verde (1976) reported that Aberdeen Angus steers, subjected to varying levels of restriction, all had very similar intakes once the restriction was removed. They note specifically that steers of the same age had very similar intakes, irrespective of their weights at the time. They also note that the restricted animals had a lower maintenance requirement because of their lower body weights, thus implying higher efficiency once restriction was removed. Somewhat similar effects were also found in sheep (Allden, 1968, 1970), but with the qualification that this depends on the ages over which the animals are restricted.

The implications of the mouse studies reported in this paper are that growth, food intake and efficiency are all inter-related whereby no single member can be fully understood independently of the other members. Ideally, carcass composition should also be included. Not only would this give a more complete picture of the input-output system, but it might also indicate genetic factors involved in the partitioning of metabolites to various destinations. It seems that selection for growth may have operated, at least in part, at the level of this partitioning.

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