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The limits to artificial selection for body weight in the mouse

II. THE GENETIC NATURE OF THE LIMITS

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1. INTRODUCTION

The first paper of this series (Roberts, 1966) examined the results of some earlier selection experiments for body weight in the mouse, conducted in this laboratory. The object was to determine the limits to selection that had been attained for this trait. Theoretical considerations of the experimental results led to the conclusion that the limits observed were compatible with a model based on the exhaustion of the additive genetic variance by fixation of loci contributing to the variation in weight. It was emphasized, however, that while no other explanation was necessary, other explanations were not specifically excluded by the analysis applied. This paper reports an experimental investigation of the genetic nature of the limits found in two of the selected lines included in the earlier study. The investigation establishes that in at least one of the two lines, total fixation was not an adequate explanation of the limit reached.

2. MATERIALS AND METHODS

It would obviously have been desirable to extend the experimental analysis of the limits to all seven lines described in the first paper. Unfortunately, the available cage space permitted only two of the lines to be studied in the way described here.

The two lines chosen for further study were the *CRL* and *CFS* lines, representing the large and small mice, respectively. These lines were first described by Falconer (1960), and their further progress under Dr Falconer's care was summarized in the first paper of this series. Both lines had been selected on growth between 3 and 6 weeks for thirty-one generations when I acquired them, and I am indebted to Dr Falconer for making these lines available to me.

The choice of these particular lines in preference to the others was governed by the following considerations. The *CRL* line was the largest of the four large lines that were available, and as it was to serve as a standard against which to assess methods of transcending the limit, it seemed a logical choice for a more detailed genetic study. The small *CFS* line did not meet this criterion so well, as it was the

largest of the three available small lines. However, the reproductive performance of the two smaller lines was by that time so poor that further work on them, which would require expansion of the stocks, presented serious practical difficulties. So the *CFS* line was preferred for continuation, as it had a better reproductive performance and also the added advantage of stemming from the same base population as *CRL*, the large line chosen. This would render any comparison between the large and small lines more meaningful.

Selection was continued in both of these lines, but from generation 32 onwards, the character selected was changed from growth between 3 and 6 weeks to 6-week weight itself. This was done for the sake of convenience, as Falconer (1955) had shown that the ranking of mice on the two measurements was virtually indistinguishable. But with the change in the selection procedure, the designations of the two lines were changed: *CRL* now became known in the laboratory as the *CL* line, while *CFS* became *CS*. This avoids confusion with Falconer's earlier (1960) study of these lines, while it also simplifies the designation of sublines drawn from the lines, as explained below. Frequent reference will be made to the *CL* and *CS* lines throughout the remainder of this series of papers. The selection was continued on a within family basis for a further twenty generations and more in each case; the sequential numbering of the generations was not broken.

Two offshoots were taken from each of the *CL* and *CS* lines. In one case, all selection was suspended, and the sublines became known as *CLR* and *CSR*, where the *R* stands for 'relaxed' selection. In the second pair of offshoots, the direction of the selection was reversed, and the sublines were called *CLB* and *CSB*, where the *B* stands for 'back' selection. In other words, *CLB* was the large line now selected for low body weight, while *CSB* was the small line selected for high body weight.

CLR was drawn at random from the 38th generation of *CL*. The remainder of the mice in that generation were selected as appropriate either to continue the *CL* line or to form the 1st generation of *CLB*, respectively. Similarly, *CSB* was derived from the 35th generation of the *CS* line while *CSR* was drawn at random from the 37th generation of *CS*. All of the lines were run on fifteen pair matings per generation.

3. RESULTS

(i) *Continued selection for body weight*

Though the character to which selection was applied was changed formally from post-weaning growth to weight at 6 weeks, there is no reason to suppose that the *CL* and *CS* lines had not attained the limit for 6-week weight by the time that I acquired them. This is amply confirmed in Fig. 1 which shows the progress of the two lines under selection from the time that they were formed. The dotted parts of the graphs summarize the weights up to generation 31, as discussed in the earlier paper. The solid lines represent the weights during the present study; these parts will be reproduced on a different scale in further figures, for the purposes of comparison with other studies, throughout the remainder of this series of publications.

Let us consider first the *CL* line. Under continued selection for 6-week weight, this line remained at much the same level as before (about 32 g.) for a further twelve generations. However, between generations 43 and 44, there was a marked increase in the mean body weight to 35 g., and the line has remained at this higher level for a further ten generations. Except for one sporadically high point at the 21st generation, the *CL* line is now running at a level that is clearly different from what it was before, after it had reached an apparent limit. The *CS* line, on the other

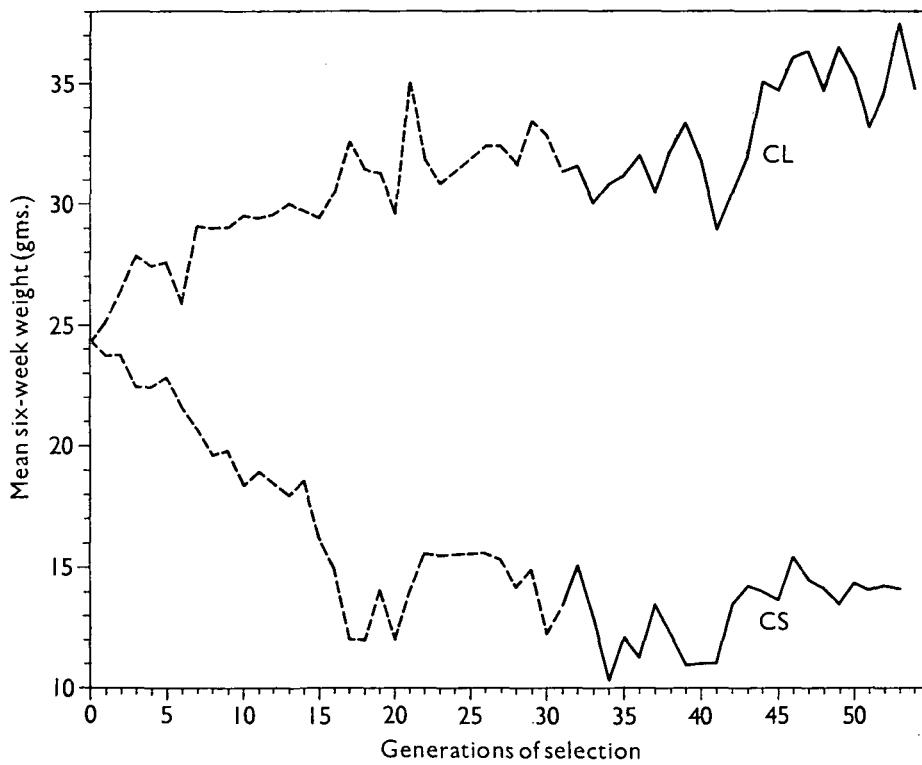

Fig. 1. Long-term responses to selection of *CL* and *CS* lines. Solid parts—weights during present study. Dotted parts—earlier responses, for comparison.

hand, does not arouse much suspicion of any major shift of a permanent nature in mean weight. Though its weights fluctuate over a range of about 5 g., there is no reason to revise the figure of 14 g. that was derived as the limit for this by generation 31 (see earlier paper).

It is important to decide whether the higher mean weights of the *CL* line from generation 44 onwards was of environmental or of genetic origin. Two factors might suggest an environmental cause. One is that the small (*CS*) line also showed an increase in weight at nearly the same time, i.e. at generation 42 of *CS*, which was contemporaneous with generation 43 of *CL*. The other reason is that the composition of the diet was modified at about that time, the modified diet being introduced

as *CL* mice of generation 43 and *CS* mice of generation 42 were approaching 6 weeks of age. There are, on the other hand, several reasons which cumulatively render it extremely unlikely that the change of diet was the cause of the increase in the *CL* line. Firstly, the modification of the diet was only slight, the main item being the replacement of miller's offal by ground wheat; the intention was to acquire a greater constancy of diet rather than to alter its nutritive value. Secondly, the increase in the *CS* line was not great compared to previous fluctuations in this line, and the increase occurred the generation before the large increase in *CL* was observed. Thirdly, no parallel increase in weight was shown by four other lines all derived from the *CL* line a few generations earlier (two of these lines are shown in Fig. 4). A dietary effect on weight would therefore have to be highly specific to the *CL* line, and from a recent review of the literature (Roberts, 1965) it would seem very improbable that genotype–environment interactions of this magnitude should appear in strains separated by only a few generations. For these reasons, it seems much more likely that the increase in weight of the *CL* line was of genetic origin, and this interpretation will be adopted in the evaluation of the data discussed in the remainder of this series of papers. It should be noted that the change occurred well after various offshoots of the *CL* line were propagated for other studies.

The genetic nature of the change in weight is open to several interpretations. The fact that it occurred, over three generations, after a depression of the mean weight to its lowest level for over thirty generations accords well with the model of selective peaks, separated by 'saddles', often expounded by Wright, and recently (1965) reviewed by him. This model is a fairly complex one whose main feature is genic interactions. At a simpler level, we could postulate a new mutation favourable to the direction of selection. Perhaps the most likely model would invoke a rare recombinational event as suggested by Thoday & Boam (1961), and confirmed by Thoday, Gibson & Spickett (1964), to explain similar shifts in the mean bristle counts of selected lines of *Drosophila*. With an organism like the mouse, there is at present little hope of being able to distinguish between these various models experimentally. The main point is that we do not lack plausible genetic explanations of the increase in weight of the *CL* line that are still consistent with a temporary limit to selection resulting from the exhaustion of the original additive genetic variance.

To summarize, two conclusions emerge from this section. Firstly, there is no evidence that a formal change in the character selected in any way affected the conclusions drawn earlier (Roberts, 1966) with respect to the limits of artificial selection for body weight in these two lines. Secondly, we have now a third instance (out of four possible cases) of a large line proving to be unstable with respect to body weight after it had apparently reached a limit. But whereas the two cases reported in the earlier study both showed a shift contrary to the direction of selection, and remain completely unexplained, the one reported here was in the direction of selection and is much more open to an acceptable genetic interpretation. One may ask, however, whether the shifts in all three lines may not have been different facets of a common phenomenon. In terms of Wright's model, is it possible that the two

cases which showed a decline in weight accidentally drifted to a lower peak? An opportunity for this to happen would stem from a lowering of selection pressures, which might result from the reduced fertility that frequently characterizes highly selected lines.

(ii) *Test for additive genetic variance in lines at the limit*

If all the loci affecting body weight in a line have been fixed by selection, then of course there will be no genetic variance of any description left in that line. This, however, is not very easy to test without special experimental programmes. But existing data can be utilized to see whether there is any heritable (or additive) variance available. If additive genetic variance is present, then this ought to be reflected in correlations between relatives which would lead to positive estimates of the heritability.

Maternal effects on body weight in the mouse are well known, and since these grossly affect estimates of genetic parameters (Falconer, 1964), relationships such as full sibs that involve a common dam are not of much use for present purposes. Regressions on sire, however, do not incur these complications, and although the number of sires used in any one generation was at the most fifteen, different generations can be pooled to obtain reasonably accurate estimates of the regression of offspring on sire. Data from generations 32 onwards have been employed to obtain estimates of the heritability of body weight in the *CL* and *CS* lines after they had reached their limits, with the following results:

$$CL \text{ line: Heritability} = 0{\cdot}194 \pm 0{\cdot}120$$
$$CS \text{ line: Heritability} = 0{\cdot}180 \pm 0{\cdot}092$$

The estimates of the heritability in the two lines are very similar in absolute terms. The estimate for the large line is not significantly different from zero, but that for the small line is on the borderline of formal statistical significance at the 5% level. This suggests that, in the small line at least, a substantial proportion of the variance in weight may be additive genetic. If this is so, it follows that the limit in the *CS* line is not fixed by the exhaustion of the genetic variance. This point will be amplified in section (iv) below.

(iii) *Relaxed and reversed selection in the large line*

The first effect of the cessation of selection for large size was a practical one that became immediately apparent, namely, that on account of their increased fertility, both the *CLR* and *CLB* lines became much easier to maintain than the parent *CL* line, in which selection for high 6-week weight was continued. Two aspects of this increase in fertility are summarized graphically in Figs. 2*a* and 3. Figure 2*a* gives the frequency distribution of the number of fertile matings, out of the fifteen that were set up in each generation in each line over the period of study. With two trivial exceptions, the *CLR* line regularly equalled or excelled the *CL* line over the sixteen generations that have elapsed since its formation. Its fertility on this

measure has been consistently high. The *CLB* line, on average, fell in between the other two, but it also never caused any concern on account of infertility. Figure 3 shows the number of live young at birth in the first litters on the three lines. Over the early generations, especially, the superiority of both the *CLR* and *CLB* lines over *CL* is unquestionable; in later generations, this superiority in litter size faded away.

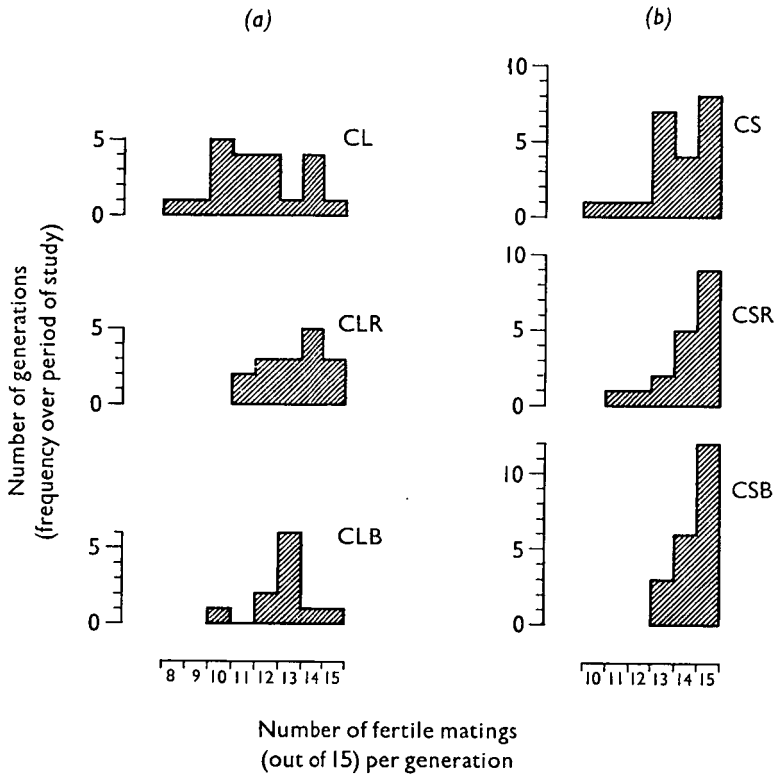

Fig. 2. Frequency distributions of the number of fertile matings (out of fifteen) in *CL* and *CS* lines from generation 32 onwards, and their derivatives.

While this increased fertility of the relaxed- and back-selection lines was a welcome feature on managemental grounds, it posed a problem with respect to the genetic interpretation of any changes in body weight. There is a well-known maternal effect on body weight in the mouse, as mice gestated and reared in large litters have their weights depressed as a consequence. In order to compare mice of different lines, it is therefore desirable to adjust the weights to a common litter size. By pooling data within generations, the expected negative regression of 6-week weight on number born was found in all lines, the depression of mean weight being in the region of 0·6 g. for each extra mouse born. This is considerably higher than the value of 0·34 found by Falconer (1964) in an unselected strain of the same origin. However, when the regression was calculated from the generation means, there was not the slightest evidence that the same relationship held. Using the generation

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means to regress body weight on litter size is not very accurate, as the degrees of freedom are limited, but cumulatively, the lines reported here and some others showed no hint of any consistency in the sign of the regression coefficients which, of course, individually never even approached statistical significance. It was therefore decided that the weights should *not* be corrected for litter size. This decision was helped by the fact that the within-generation regressions, when these were applied to generation means as a trial, generated such small corrections that no conclusion could possibly be affected.

The mean 6-week weights, plotted against generation number, are shown in Fig. 4. Disregarding the change in weight of the *CL* line, discussed earlier, neither

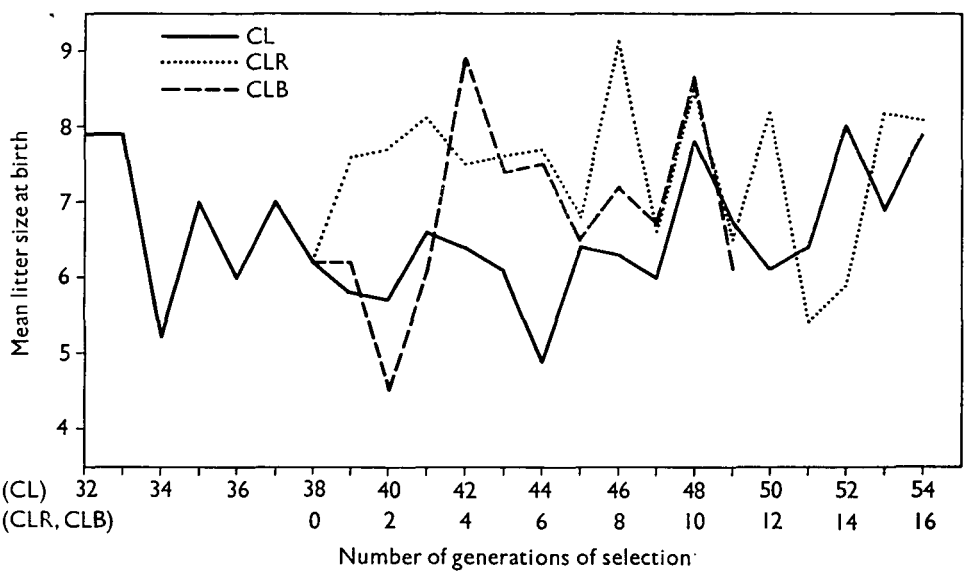

Fig. 3. Effects of relaxed and reversed selection in large line on number of live young at birth in first litters.

relaxed nor even reversed selection had any effect on body weight, and both sublines continued at precisely the old level of the *CL* line. The *CLB* line, the one selected for a reduction of body weight, accumulated a total selection differential of 15 g. over its eleven generations. When, in its 11th generation, it showed its highest-ever weight, and it had quite obviously failed to show any response to downward selection, it was discontinued. The *CLR* line was continued for other reasons; over its sixteen generations, it has accumulated a negligible positive selection differential of less than 2 g., pointing to the successful randomization of animals chosen as parents.

The heritabilities in the *CLR* and *CLB* lines were calculated from the regression of offspring on sires, pooled within generations, with the following results:

$$CLR \text{ line: Heritability} = -0{\cdot}016 \pm 0{\cdot}098$$
$$CLB \text{ line: Heritability} = +0{\cdot}084 \pm 0{\cdot}158$$

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These estimates obviously do not differ from zero, and confirm the conclusion from the back selection that no additive genetic variance remained in the *CL* line.

The conclusion from this section is clear: there was no additive genetic variance of body weight remaining in the *CL* line at the selection limit. The absence of additive variance, however, is not quite synonymous with the fixation of all loci affecting body weight. Overdominance could, in principle, lead to a situation where some loci segregated without showing any additive variance, if heterozygotes were selected on the basis of weight alone. Gene frequencies would then equilibrate at some intermediate level, and only after an accidental deviation from equilibrium

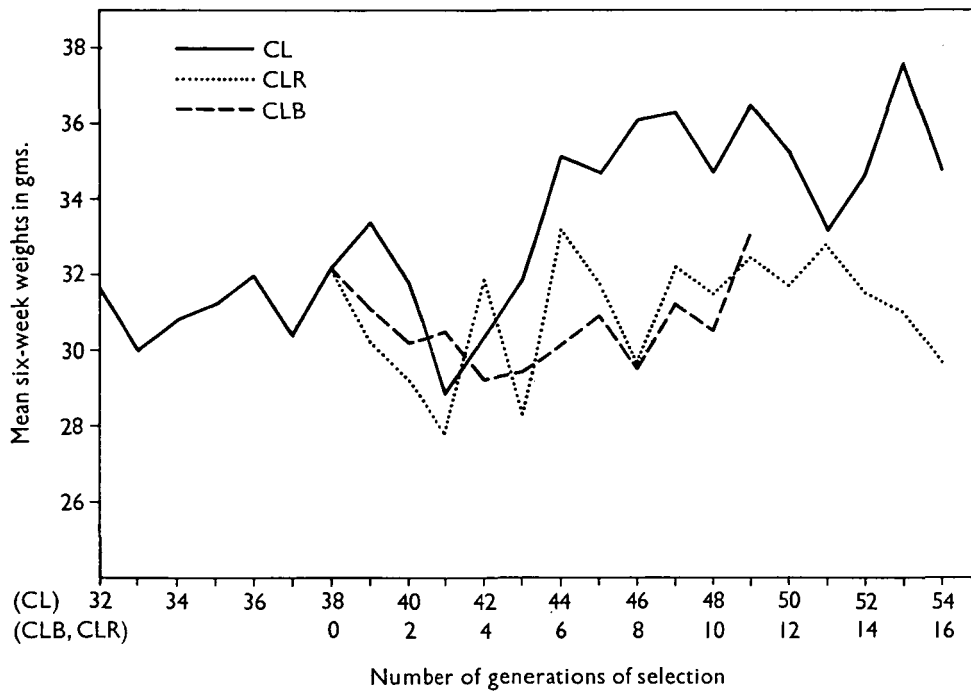

Fig. 4. Effects of relaxed and reversed selection in large line on mean 6-week weight.

could a response be obtained to reversed selection. Overdominance of this kind could be simulated by close linkage between pairs of genes; recombination between the members of such a pair was invoked earlier as a likely explanation of the increase in weight of the *CL* line. Overdominance of another kind was specifically excluded by the experimental results. This situation demands that natural selection should oppose the artificial selection; one homozygote would be rejected because of its effect on weight, while the other homozygote would tend to be either infertile or inviable, in which case the heterozygote might be fitter than either homozygote, under the conditions of the experiment. But under these conditions, while there would be no additive variance of overall fitness, there would be additive genetic variance of body weight. The fact that weight did not change when selection was

relaxed or reversed proves that if there were any overdominant genes, or linked pairs, still segregating, they caused a negligible amount of variance.

From the fact that all relevant loci were fixed, we can deduce something about the cause of increased fertility which, as mentioned earlier, followed the cessation of selection for large size. Since no genetic variance in body weight remained, this must mean that there was a negative environmental correlation between large size and fertility. The productivity of large mice will be examined in more detail, and in a more appropriate context, in a future paper.

(iv) *Relaxed and reversed selection in the small line*

When selection for low body weight was stopped, the effects on the fertility of mice of the *CS* line were again beneficial. The number of sterile matings fell, as shown in Fig. 2*b*, the reduction being more noticeable in the back selected (*CSB*)

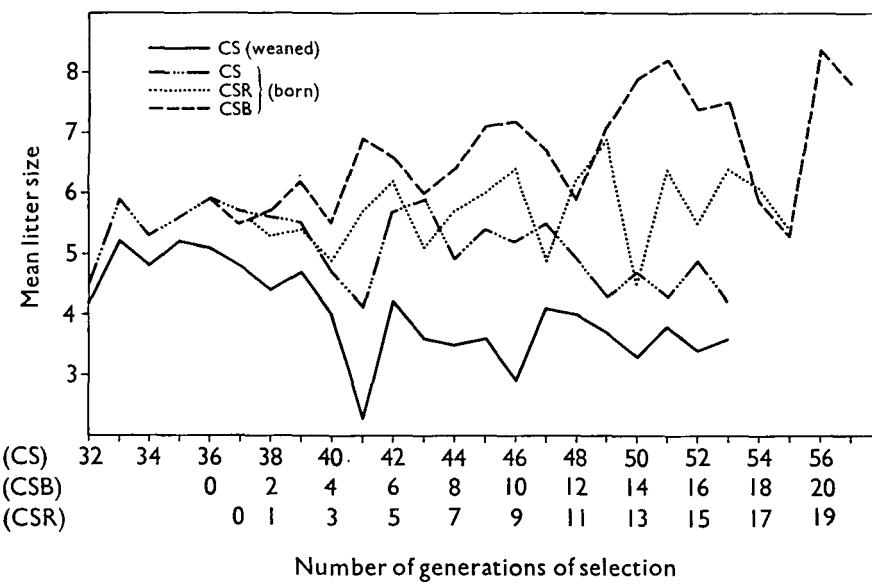

Fig. 5. Effects of relaxed and reversed selection in small line on number of live young at birth in first litters. Number weaned in *CS* line also shown.

line than in the relaxed (*CSR*) line. This is slightly different from the large lines, where the ranking of the relaxed and back-selected lines was reversed. As a general point, we may note also that sterility is commoner in large mice than in the corresponding small ones. The other criterion of fertility that was examined, namely the mean litter size at birth, also showed an improvement in both lines, and again the increase was more conspicuous in the *CSB* line than in the *CSR* line, as shown in Fig. 5. But for reasons given previously, these litter size differences were not employed to attach adjustments to body weights.

The effects of the relaxed and reversed selections on body weight are summarized in Fig. 6. Some violent changes in weight occur in all three lines from time to time; as usual in similar situations, some of the weight changes in different lines are

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synchronous, while others are not. However, despite the fluctuations, a fairly clear picture emerges. The relaxed line (*CSR*) gives a hint that it may have increased in weight slightly but there is no indication that the difference between it and its parental line (*CS*) has increased at all with time. The average difference between the two lines has been of the order of 1 g. or so for the last ten generations. The line in which the direction of the selection was reversed (*CSB*) shows quite a clear-cut result. Progress was made regularly over about thirteen generations of reversed selection, and the mice, weighing by now about 17 to 18 g., are no longer particularly small. But for the last eight generations, no further progress has been made, suggesting that probably a limit has now been reached for the reversed selection.

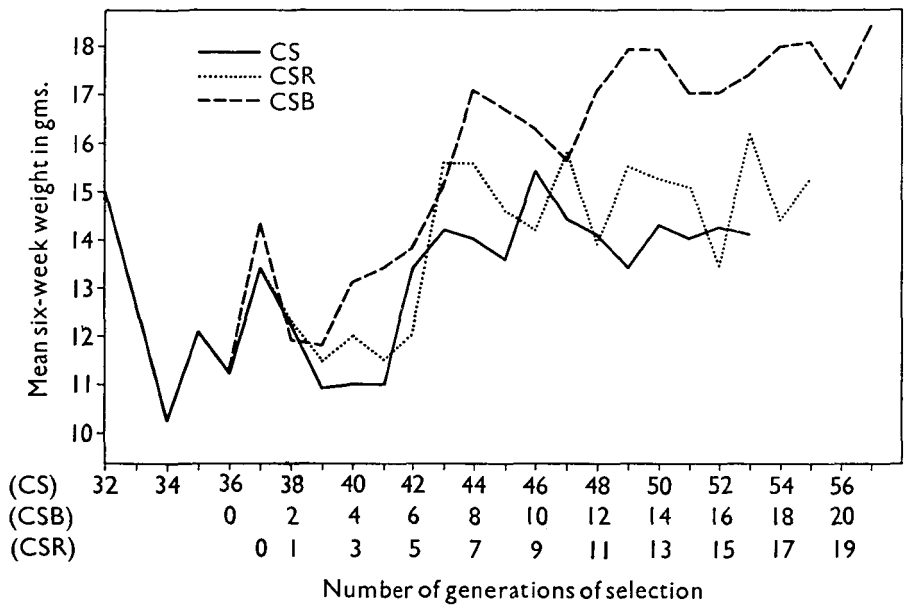

Fig. 6. Effects of relaxed and reversed selection in small line on mean 6-week weight.

Whether a limit has been reached or not, there is no doubt about the reality of the response to reversed selection. This accords with the heritability estimate given earlier, and proves that, unlike the corresponding large line the additive genetic variance in the small (*CS*) line had not been exhausted by thirty-six generations of selection for small size. For the previous twenty generations or so, the *CS* line had reached an apparent limit to downward selection, which indicates that some process had prevented at least some of the alleles affecting body weight from going to fixation.

The heritability estimated from the offspring-sire regression in the *CS* line was given earlier as $0{\cdot}180 \pm 0{\cdot}092$. Estimates derived in similar fashion from the *CSR* and *CSB* lines were the following:

$$CSR \text{ line: Heritability} = 0{\cdot}080 \pm 0{\cdot}078$$

$$CSB \text{ line: Heritability} = 0{\cdot}156 \pm 0{\cdot}088$$

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Though the estimate from *CSR*, on its own, is insignificant, the estimate from *CSB* agrees well with the one originally obtained from *CS*, while all three are consistent within the limits of their sampling errors.

It is well known that the heritabilities realized in practice may differ markedly from estimates derived in this manner. To test this, the heritability realized by selection in the *CSB* line was computed from the data summarized in Fig. 7, which shows a plot of generation means against the cumulated selection differential. The

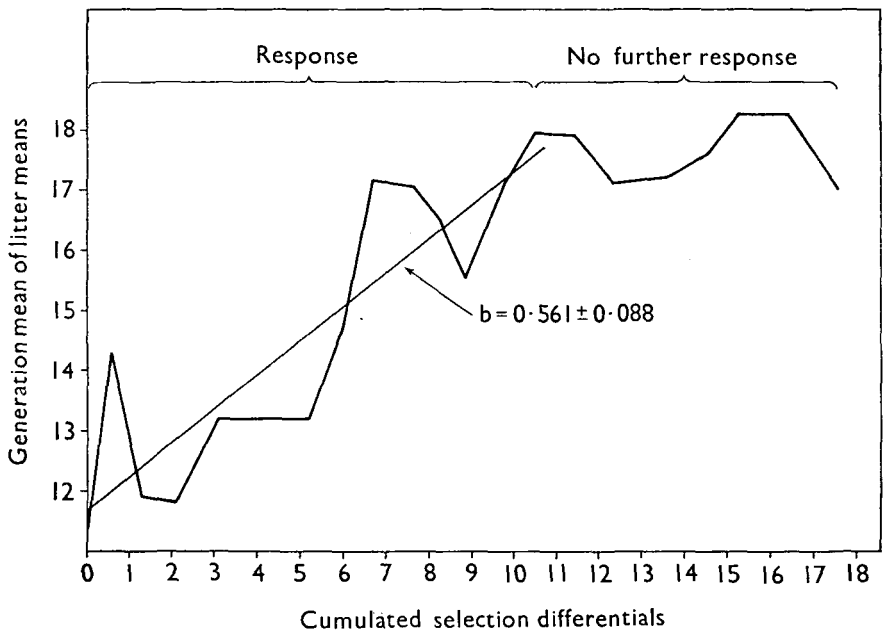

Fig. 7. Mean 6-week weight in *CSB* line plotted against cumulated selected differential. The straight line is the least squares regression line over the period of the response.

generation means have been calculated in a way slightly different from the ones given previously; this time, they are the means of litter means. This is a more appropriate measure for present purposes, as the selection differentials were calculated (the method of selection being within—families) as the mean deviation of selected animals from the means of the litters in which they were measured. Selection differentials were calculated separately for the two sexes and averaged, sterile animals being disregarded. The graph has been divided somewhat arbitrarily into two parts, one corresponding to the period of initial response (thirteen generations), and the other to a second period when there was no obvious response and which we suppose represents the limit to the reversed selection. Only the first part of the graph was utilized to calculate the realized heritability, which turned out to have the surprisingly high value of $0{\cdot}561 \pm 0{\cdot}088$. This value is probably inflated somewhat. *CSB* was taken off the 36th generation of *CS*, and as can be appreciated best from Fig. 1, this represents a low value for the *CS* line. Some of the apparent response,

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in absolute terms, of the *CSB* line may therefore have been due to environmental increases that occurred later. These difficulties could have been circumvented, in principle, by recording the response of the *CSB* line as a deviation from *CS*. Unfortunately, there was not sufficient contemporaneity between generations in the two lines to render this a satisfactory procedure. But if, instead, we take the final superiority of the *CSB* line over *CS* to be 3·5 g. (from Fig. 6), and that this had been achieved by the time the cumulated selection differential was 10·5 g. (from Fig. 7), it now gives us a realized heritability of 33%. Though well within the upper confidence limit of the original estimate obtained from *CS* line, it is still high when we consider that the additive genetic variance in the *CS* line, though obviously not exhausted, must surely have been severely depleted.

To what, then, must we ascribe the preservation of so much additive genetic variance in the *CS* line? An obvious factor to test is natural selection, but it becomes very difficult indeed to test this factor adequately. There are some indications that natural selection may oppose the artificial selection; the slight increase in weight noted when selection was relaxed could be interpreted in this way. It was also noted that fertility and litter size increased on relaxation, but there is no evidence that the sterility in the *CS* line has had any adverse effect on the selection process. This can be determined from a comparison of the expected and realized selection differentials. The expected selection differential is the mean superiority of selected individuals. The realized selection differential, for a within-family method of selection, is the superiority of animals that proved themselves fertile, and therefore had a litter measured in the next generation. The expected selection differential cumulated over the last twenty generations of the *CS* line was only 0·28 g. greater than the realized, or 0·014 g. per generation. This proves conclusively that natural selection did not operate through any differential fertility between the smallest mice and those not quite so small. This, however, takes no account of any natural selection that may have operated on viability between conception and the time when the animals were measured at 6 weeks of age. It is not possible, from the data available, to estimate the selection differential that may have been lost on account of mortality. It is, however, common laboratory experience that the losses are heaviest among the smallest mice within any one stock; indeed, the phenomenon is by no means confined to the mouse alone. Some indication of the extent of the mortality is shown in Fig. 5, which shows both the number born alive and the number weaned in the *CS* line. The loss between birth and weaning is frequently 20%, and sometimes 40%. This, of course, represents only a part of the total mortality. Much earlier in its history (generations 16 to 19), the reproductive performance of the *CS* line was examined by Fowler & Edwards (1960), who reported losses of 28% between ovulation and the recording of live births. The performance of the line would certainly not be expected to have improved since that time. It is therefore probable that fully half of the number conceived die before weaning time. Further losses occur before selection at 6 weeks of age. Over its last twenty generations, the *CS* line showed a mortality rate of 11% between 3 and 6 weeks of age, though the mean weaning weight of the animals that died was only about a tenth of a gramme less than the

weaning weight of the survivors. This apparently slight reduction, however, may mean a much greater reduction of selection differential in 6-week weight; there are complex relationships between the variance components of weights at successive ages, as discussed by Monteiro & Falconer (1966). As the total selection differential obtained was only about 0·6 g. per generation, any tendency for the smaller mice to die in the post-weaning phase may contribute a substantial proportionate effect on the selection differential.

If the failure to respond to artificial selection is to be attributed to the opposing effect of natural selection, acting through differential viability, then the mice selected among the eventual survivors must have a mean weight equal to what the mean weight would have been had all zygotes survived. In other words, the positive deviation of those rejected by artificial selection must have been counterbalanced by the negative deviation of those that failed to survive to 6 weeks. In view of the heavy mortality, and the fact that about a third to a half of the survivors were selected, this seems to be a reasonable postulate.

Though the evidence is only indirect, it seems justifiable to conclude that the limit to selection for small size in the *CS* line is due to natural selection opposing the artificial selection, and that further the natural selection operates through its effect on viability and not on the fertility of the survivors. The one slight difficulty is that, if the hypothesis of reduced viability is correct, the weights should increase so little when the artificial selection was relaxed. It appears as if the natural selection may not exist at all until body weight is reduced to some particular level. Some support for this idea may be derived from Fig. 1. The initial response to selection in the *CS* line was rapid and, if not linear, accelerating. But at generation 17 or so, it came to an abrupt halt, and failed to show any further response over the next thirty-five generations. This suggests strongly that the barriers to further progress were encountered at a particular weight, but that none of their effects were felt until that weight was reached. This is strongly reminiscent of F. W. Robertson's (1963) finding in *Drosophila*, that there is a critical larval weight below which pupation fails to occur. It is not wildly speculative to suppose that some analogous phenomenon may exist during the development and growth of the mouse, and that in the *CS* line, this critical low weight may have been reached.

4. DISCUSSION

It was seen in the preceding sections that the limit to artificial selection had been reached for very different reasons in the large and small lines. In the large line the additive genetic variance had been effectively exhausted. In the small line, however, a substantial proportion of the remaining variance was additive genetic, and a response to reversed selection was readily obtained.

It was explained earlier that only two of the seven selected lines available for study were subjected to further experimental investigation of the nature of the limits. However, Falconer (1955) reports some short-term studies of a similar kind

on two of the other five lines. Reversed selection was carried out from the small (*NS*) line on two separate occasions. The first (from generation 12) was at a time when the line was still responding, but by the second time (from generation 20) the line was approaching its ultimate limit. Over four generations, the response to the reversed selection was unmistakable. The other study described by Falconer was the relaxation of selection from the 24th generation of the large (*NF*) line, after the line had reached its limit. Over six generations, there was no indication that the relaxation of selection resulted in any separation from the line under continued selection.

Though the evidence just quoted is fragmentary, it does encourage some thought of the possible generality of the phenomena described in this paper, with respect to selection for body weight in the mouse, namely that selection for large size may lead to the exhaustion of the additive genetic variance whereas selection for small size may reach a limit despite the detectable presence of additive variance. If this is so, then the genetic nature of the limits were reversed from the ones that appear to obtain in *Drosophila*; in this organism, it is selection for *small* size that seems to lead to fixation. Reeve & F. W. Robertson (1953) described a strain, selected for fifty generations for long wings, in which the additive genetic variance was much greater than in the base population and from which relaxed and reversed selection yielded ready responses. F. W. Robertson (1955) reported a parallel but extended study, using thorax length as his criterion of size. After twenty generations of selection, the small flies failed to yield any response to further selection in either direction. The large flies, on the other hand, reached the limit to further selection after twelve to fifteen generations but quickly returned to the level of the base population on the reversal of selection. Detailed analyses in both of these *Drosophila* studies indicated to the authors that genetic mechanisms of some complexity operated to preserve heterozygosity in the lines selected for large size.

Another *Drosophila* study on the long-term effects of selection, this time for a bristle score, was reported by Clayton & A. Robertson (1957). Despite the highly additive genetic basis of the character selected, a limit to the response in either direction was still compatible with a considerable amount of residual genetic variance. In their high lines, the variability was attributable to the continued selection for lethal heterozygotes. In the low lines, the situation appeared to be particularly complex, lethal genes, infertility of extreme females and inversion heterozygotes all being invoked to explain some of the residual genetic variance.

The results so far available on selection limits suggest that models based on the exhaustion of the additive variance may not be sufficiently comprehensive to describe fully many of the situations derived in practice. They therefore underscore the need for more detailed investigations of specific cases, if we are to gain a deeper appreciation of the genetic nature of the limits to artificial selection. This objective may be less remote if organisms showing some diversity of biological organization could be included in such studies, which furthermore ought to include characters cast in different evolutionary moulds, if any generalities are to emerge.

SUMMARY

1. The effects of long-continued selection for body weight in two lines of mice, one large and one small, are described.

2. The large line showed a sharp increase in weight after remaining at an apparent limit for twenty generations. A rare combinational event is suggested as the most likely explanation.

3. Reversed and relaxed selection from the large line at the limit failed to yield any response. This indicates that effectively, the additive genetic variance in this line had been exhausted.

4. In contrast, the small line at the limit regressed slightly towards the base population when selection was relaxed. Reversed selection yielded a ready response until a new limit was apparently reached. Loci affecting body weight in this line had therefore not been fixed by selection.

5. Natural selection, operating on viability between conception and the time when the selection was made, appears to explain best the lack of fixation in the small line.

6. Attention is drawn to the necessity of more experimental work to elucidate the genetic nature of the limits to artificial selection.

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