Selection of mice for growth on high and low planes of nutrition

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INTRODUCTION

The choice of environment, when selection is to be applied for the improvement of farm animals, presents a problem that is still incompletely solved. Should the breeder subject the animals among which selection is to be made to a 'good' environment which gives maximal expression to the desired character? Or should he rather subject them to the conditions, whether good or bad, under which the improved breed is destined subsequently to live? Considerations of genotype-environment interaction, or the specialization of breeds, point to the latter course as likely to be the better, and this view can be supported by theoretical considerations of the genetic correlation between two characters (Falconer, 1952). Yet an experiment with mice (Falconer & Latyszewski, 1952) did not fully substantiate the theoretical expectations. The improvement made by selection under good conditions was not carried over when the animals were transferred to bad conditions, but the improvement made under bad conditions was retained when the animals were transferred to good conditions. Selection under bad conditions therefore produced animals that performed well under both good and bad conditions. This experiment, however, had several defects, and such unexpected results clearly needed confirmation by another experiment. The experiment described here was therefore undertaken with the object of exploring the problem afresh. It was designed so as to provide a test of the adequacy of the theory of selection from which predictions might be made of the responses to be expected when selection is made under different environmental conditions.

The theoretical considerations are based on the idea that if a character is measured under two different environmental conditions it may be treated not as one but as two different characters. For example, the growth of animals reared on a high plane of nutrition is one character and the growth of animals reared on a low plane of nutrition is another. The genetic similarity between the two characters is expressed as the genetic correlation between them. From a knowledge of the genetic correlation and of the heritability of each character it should be possible to predict the improvement to be expected in one character when selection is applied to the other; to predict, in other words, how much of the improvement made by selection in one environment will be carried over when the improved breed is transferred to another environment.

The general plan of the experiment was as follows. Two-way selection was applied to one pair of lines for growth-rate when the individuals were reared on a high plane of nutrition, and to another pair of lines for growth-rate when the individuals were reared on a low plane of nutrition, one line of each pair being selected for increased growth and the other for decreased growth. Some individuals in each generation were reared on the other nutritional plane, so that in every generation there was a measurement of the mean growth in both environments; or, in other words, a measurement of the mean of both characters. Thus a comparison of the correlated and direct responses could be made for both characters. Two estimates of the genetic correlation could then be obtained, in a manner to be explained in a later section, and if the responses were in accord with the theoretical expectations, these two estimates should be the same. This analysis of the responses in terms of the genetic correlation will be found at the end of the Results section.

EXPERIMENTAL PROCEDURE

Stock

The stock of mice used (known in the laboratory as the C-stock) was constructed in 1949 from crosses between Bateman's high-lactation line, a line selected for large size after a cross of MacArthur's with Goodale's large lines, and two stocks carrying a variety of mutant genes and having the inbred line C57BL/Fa in their ancestry. The stock was first used in another experiment (Falconer & Robertson, 1956), which, however, produced no detectable genetic change. The 'experimental' and 'control' lines of that experiment were crossed in 1952 to provide the foundation population of the present experiment. The foundation population was divided into two sets of twelve single-pair matings which constituted generation 0 of the selection programme. One set of twelve matings was the starting point of selection for one character and the other set for the other character.

Characters selected

All mice were weighed at 3 weeks and at 6 weeks of age, and selection was based on the growth during this period of 3 weeks. Selection was made both for increased growth and for decreased growth, so that the two sets of matings in generation 0 were further divided each into two lines, one selected upwards and the other downwards. The lines selected for increased growth (large lines) will be indicated by the symbol +, and those selected for decreased growth (small lines) by the symbol —. The mice of one large and one small line were reared on the standard cubed diet, which provided a high plane of nutrition. These will be referred to as 'high-plane lines', with the symbol H. The mice of the other pair of lines were reared on a specially prepared diet, to be described below, which provided a low plane of nutrition. These lines will be referred to as 'low-plane lines', with the symbol L. Thus the H-lines were selected for the character 'growth on high plane' and the L-lines were selected for the character 'growth on low plane'. These diets were administered to the first litters of all matings, and the selection

was made exclusively among mice born in these first litters. The mice of all second litters were reared on the other diet; that is to say, mice of the H-lines were reared on low plane, and mice of the L-lines on high plane. Thus, the second litters provided measurements of the correlated responses of the characters not directly selected. (An error in the routine for the exchange of diets between first and second litters was probably made at generation 11. The observed growth, seen best in Fig. 5, suggests that the second litters of both high-plane lines were
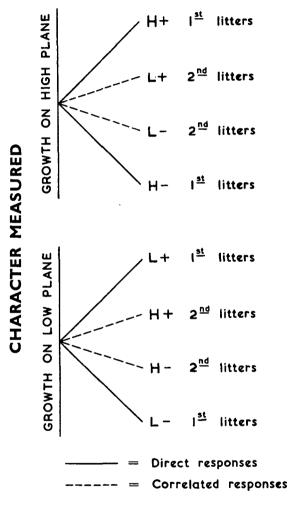

Fig. 1. Diagrammatic plan of the experiment.

reared on high plane instead of on low plane. The values are entered in the graphs as observed, but they are excluded from the computations). Table 1 summarizes the designations and treatments of the lines, and Fig. 1 summarizes the nature of the responses measured. The designations by which the lines are known in the laboratory, which for the sake of clarity are not used in this paper, are given also in Table 1.

Table 1. *Summary of designations and treatments of the lines*

Designation of lines		Direction of selection	Character selected	Diet administered	
In this paper	In the laboratory			1st litter	2nd litter
H+	CFL	Upward ⎫	Growth on high plane	High	Low
H−	CFS	Downward ⎬			
L+	CRL	Upward ⎫	Growth on low plane	Low	High
L−	CRS	Downward ⎬			

Method of selection

The method of selection was strictly within litters. That is to say, two mice were selected out of the first litter of each mating, one male and one female as far as possible. This method has two advantages; it reduces the rate of inbreeding, and it reduces the influence of maternal effects on the response to selection. Twelve single-pair matings were made in each generation of every line, the matings in all lines being made contemporaneously throughout. The theoretical rate of inbreeding under this system is 1·04% per generation. Litters were standardized at birth, by reduction or augmentation, as nearly as possible to eight young, four of each sex. The intensity of selection was thus about one out of four, which gives an expected selection differential of about one standard deviation. Litters were weaned at 3 weeks, males and females being stored separately. Litters to be reared on the low plane of nutrition were fed on the low diet from 3 weeks to 6 weeks and were then fed on the normal, high diet.

This programme of selection was carried on for thirteen generations, after which the procedure was changed as follows. The second litters of generation 14 were not measured in the usual way but were used instead for measurements of food-consumption. From generation 15 onwards, rearing on low plane was discontinued, and all lines were selected for growth on high plane. At the same time the number of matings was reduced to six in each line. The line selected for small size on low plane (L−) was discontinued after generation 16. The responses in the remaining three lines are presented here up to generation 22, even though after generation 13 they are not strictly relevant to the main problem.

It would have been desirable to keep unselected lines as controls and to measure them at every generation, but this would have necessitated a reduction in the number of mice reared and measured in the selected lines, because space was limited; and it was decided—perhaps wrongly—not to keep control lines. An unselected line was, however, measured contemporaneously with generation 7. This line, known as JC, was derived from the same base population and was in use as a control for another experiment. First-litter mice were used as controls for the direct responses, and second-litter mice for the correlated responses. Thus the controls are represented on the graphs by two points at generation 7.

Diets

The high plane of nutrition was the normal cubed diet used in the laboratory. Its analysis (for which I am indebted to Dr Ruth E. Fowler) was as follows: carbohydrate, 56·8%; protein, 18·5%; fat, 4·5%; water, 12·9%; ash, 7·3%. The low plane of nutrition was provided by a specially prepared cubed diet made from the ingredients of the normal cubes 'diluted' with 50% of indigestible fibre in the form of ground oat husks. This low diet was fed *ad lib.* over the 3-week period from 3 to 6 weeks, and it reduced the growth during this period by about 20%. A batch of 14 cwt. of this special diet was manufactured at the beginning of the experiment and was used throughout generations 0–9. It is almost inevitable that some changes of its nutritional value took place during this period of storage, and the controls measured at generation 7 indicated a reduction of 10% in the growth of mice fed on the low diet when compared with the beginning of the experiment. A second batch of special diet was manufactured later and put into use at generation 10. No general effect of this change was apparent. Measurement of the food-consumption of mice on each diet will be described later.

RESULTS

If this experiment can justifiably be regarded as a 'model', showing what might be expected to happen in the practice of livestock breeding, its results are very clear in the breeding policy to which they point. But, as a test of the adequacy of current theory for the prediction of the responses, its results are less clear. For this reason the theoretical analyses of the responses will be deferred till the end of this section and the results will be presented first in the form of a straightforward description.

Description of responses

The responses to selection are shown graphically in Fig. 2*a*. (Fig. 2*b* is for later use, in the analysis of the responses.) The points in these graphs show the mean growth in each successive generation, each point being the unweighted mean of males and females. Continuous lines show the responses to direct selection (i.e. selection for the character itself) and broken lines show the responses to indirect selection (i.e. the correlated responses to selection for the other character). There are four comparisons to be made between direct and indirect selection in respect of the progress made, referring respectively to growth on high plane and to growth on low plane in response to upward and to downward selection. The results depicted in Fig. 2*a* are as follows:

1. *Increase of growth on high plane.* Direct selection was more effective than indirect selection at the beginning, but not very much more effective. Toward the end, however, the correlated response caught up with the direct response. In the long run, therefore, indirect selection was just as effective as direct selection.

2. *Increase of growth on low plane.* Not much progress was made by either

method. Direct selection, however, did yield some progress, whereas indirect selection yielded none at all.

3. *Decrease of growth on high plane.* Direct selection was much more effective than indirect selection, which yielded hardly any progress.

4. *Decrease of growth on low plane.* Direct and indirect selection were equally effective, both yielding rapid progress.
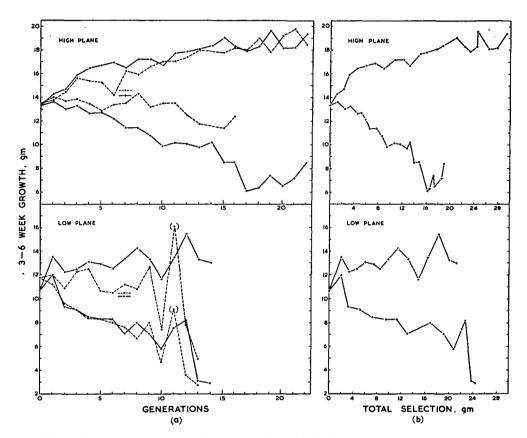

Fig. 2. Responses to selection in the four lines. Solid lines show the direct responses, broken lines the correlated responses. The horizontal lines at generation 7 are unselected controls, solid lines referring to first litters for comparison with direct responses, broken lines to second litters for comparison with correlated responses. The bracketed points are open to suspicion of error.

The responses to selection for increased growth (1 and 2 above) agree with the results of an earlier experiment (Falconer and Latyszewski, 1952) conducted on similar lines but on a smaller scale: growth on high plane was increased almost as much by selection on low plane as by selection on high plane, but growth on low plane was not increased at all by selection on high plane. In both experiments selection on high plane improved only growth on the high plane, but selection on low plane improved growth on both the low and the high planes. In practice there

must always be a certain range of environmental conditions to which any breed is subjected, and it should perform well under all. The breeding policy to which the results of these experiments point is, therefore, to subject the animals during selection to environmental conditions corresponding to the worst, rather than the best, under which the improved breed will be required to perform. This, if the results of the mouse experiments should prove to be general, will produce animals with the best all-round performance.

The first comparison made above, between the two large lines when grown on high plane, showed that direct and indirect selection were in the long run equally effective in increasing growth on high plane. This, however, is not the whole story. The mice of the low-plane line were heavier at 3 weeks, 6 weeks and at 12 weeks of age; and they were less fat than the mice of the high-plane line. Thus, indirect selection produced animals that were more desirable from the 'economic' point of view, if the mice are regarded as 'models' of farm animals. The data concerning these subsidiary aspects of the selection will be presented later.

Weaning weight

One of the advantages of the method of selection within families applied in this experiment is that no direct selective pressure is put on maternal performance. The maternal performance may nevertheless change as a correlated response following the changes of body size, and an increased or decreased maternal performance may influence the growth of the offspring as a maternal effect. Maternal effects as a possible complication of the responses of growth may be explored by an examination of the weaning weights (i.e. at 3 weeks) and of the connexion between weaning weight and subsequent growth. The weaning weights of the four lines are shown in Fig. 3. The large and small lines differentiated, as
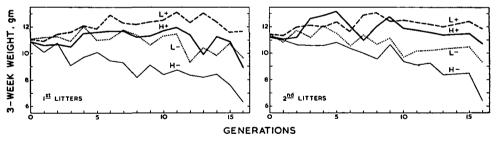

Fig. 3. Weaning weights of the four lines.

is to be expected, the large lines increasing and the small lines decreasing in weaning weight. But a more important, and unexpected, difference is found between the high-plane and low-plane lines. Both low-plane lines had higher weaning weights than the corresponding high-plane lines. The difference may have been partly a direct effect of the diet on the maternal performance of the females, because the difference is more apparent in first than in second litters, and

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because some difference was already apparent in the first generations. It cannot, however, have been entirely due to a direct effect of the diet, because the difference persisted after generation 14 when all mice were reared on high plane. (Additional estimates of the weaning weights of the two large lines were obtained in generation 19 and will be presented later.)

The connexion between weaning weight and subsequent growth may be assessed from the regression of growth on 3-week weight. Regressions were calculated both within litters and between litters, the latter from the components of covariance and variance between litters. The computed regression coefficients—pooled over all generations since they showed no consistent trends— are given in Table 2.

Table 2. *Regressions of growth (3–6 weeks) on weight at 3 weeks, computed within generations and pooled over generations 0–12. The between-litter regressions are computed from the components of covariance between litters, obtained from analyses of covariance. The standard errors of the within-litter regressions are given in italics*

	Growth on high plane				Growth on low plane			
	Large		Small		Large		Small	
	♀	♂	♀	♂	♀	♂	♀	♂
Between litters								
1st litters	−0·15	0·13	0·00	0·32	0·00	0·34	0·19	0·40
2nd litters	−0·17	−0·24	−0·33	0·13	0·08	0·29	0·38	0·43
Within litters								
1st litters	0·06	0·39	0·10	0·52	0·58	0·57	0·95	0·96
	0·07	*0·08*	*0·08*	*0·07*	*0·12*	*0·12*	*0·18*	*0·19*
2nd litters	−0·05	0·31	0·03	0·54	0·93	1·23	0·94	1·01
	0·07	*0·07*	*0·07*	*0·10*	*0·15*	*0·16*	*0·14*	*0·18*

Growth on high plane was very little influenced by weaning weight, but growth on low plane was fairly strongly influenced, particularly in the within-litter component. The responses were then replotted with growth adjusted to a standard weaning weight by means of the between-litter regression coefficients; but the graphs were barely distinguishable from the uncorrected responses. It may be concluded, therefore, that the responses of growth were not materially influenced by the changes of weaning weight.

Phenotypic variation

Fig. 4 shows the phenotypic variation within litters in all four lines on both high and low planes of nutrition. The variation of growth on high plane is expressed as the coefficient of variation, since this measure proved to be independent of the mean growth. The coefficient of variation of growth on high plane was substantially the same in all the lines and remained constant at about 10% over the whole experiment. Growth on low plane, however, is less straightforward because neither

the coefficient of variation nor the standard deviation was independent of the mean growth: the large and small lines differed inconsistently whichever way the variation is expressed. The standard deviation is shown in Fig. 4, and it may be seen to have changed markedly during the course of the experiment, though not in the same way in all lines. In one line it remained fairly constant over the whole
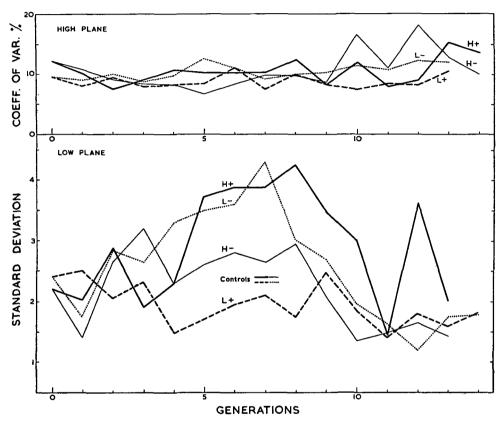

Fig. 4. Phenotypic variation within litters.

experiment. This is the line selected upwards for growth on low plane (L+). In all the other lines it increased to a maximum at about generation 7 and then decreased toward the end. The increase is most marked in the high-plane large (H+) and the low-plane small (L−) lines. It is perhaps noteworthy that these are the two lines that showed unexpectedly small correlated responses.

Susceptibility to the effect of the diet

An interesting comparison may be made between the four lines, which shows how each was affected by the low plane of nutrition. This comparison is made in Fig. 5, which shows the difference between growth on low plane and growth on high plane for each line in successive generations, the difference being expressed

as a percentage of the growth on high plane. The vertical axis thus shows the proportionate reduction of growth caused by the low-plane diet; or the 'suscepti-bility' of the line to the 'harmful' effects of the low-plane diet. From this view-point growth is regarded as a single character subject to the influence of a specific environmental difference, and the graphs show how the lines react to this environmental difference. In a limited sense they indicate environmental varia-bility of growth. The picture presented by the graphs is clear and simple. The reaction of the two high-plane lines to the dietary difference increased over the course of the experiment, and this may reasonably be attributed to a progressive
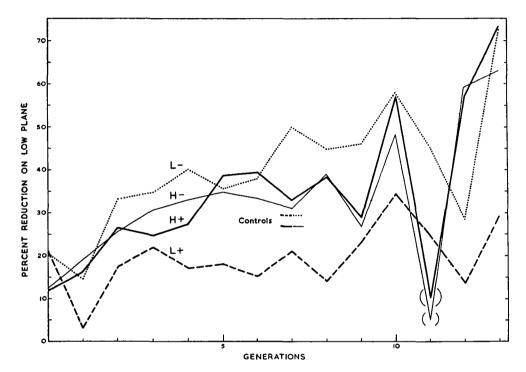

Fig. 5. Effect of the diet on the growth of the four lines in successive generations. The mean growth in each generation has been adjusted to a standard 3-week weight by means of the between-litter regression coefficients given in Table 2.

deterioration of the nutritive value of the low-plane diet. The two high-plane lines, large and small, remained virtually equal in susceptibility throughout the experi-ment, and we may conclude that their susceptibility was not influenced by the selection. The two low-plane lines, in contrast, changed, and changed differently. The low-plane large line (L+) decreased in susceptibility in comparison with the high-plane lines and with the controls in generation 7, whereas the low-plane small line (L−) increased in susceptibility. Selection on low plane appears therefore to have influenced environmental variability of growth, selection for increased growth having reduced it and selection for decreased growth having increased it. The

changes depicted in Fig. 5 parallel rather closely the changes of phenotypic variation of growth on low plane depicted in Fig. 4, and would do so even more closely if the variation of low-plane growth were expressed as a coefficient of variation. One can hardly avoid the conclusion that both graphs depict the same changes, namely, changes of sensitivity to differences of the dietary environment.

Food-consumption

Having presented the results of the selection we may now inquire into the nature of the two characters, 'growth on high plane' and 'growth on low plane', to which selection was applied. In particular it is desirable to know the nature of the restriction to growth imposed by the low plane of nutrition. For this purpose a small-scale study was made of the food-consumption and efficiency of gain of the four lines on both diets. The mice used for this purpose were males born in the second litters of generation 14. The mice were housed singly in cages with wood-wool for bedding but no sawdust. Every two or three days from 3 weeks to 6 weeks of age

Table 3. *Mean food consumption and efficiency of gain from 3 to 6 weeks, in males of generation 14. (The efficiencies given are means of individual ratios of gain to food consumed)*

	H+	L+	H−	L−
High-plane diet				
Number of mice	5	5	5	5
Gain, gm.	20·1	19·0	10·0	12·7
Food consumption (g).	111·0	116·1	78·7	91·6
Efficiency (%)	18·7	16·4	12·7	14·3
Food wasted (g.)	16·1	9·7	15·0	16·4
,, ,, (%)	12·7	7·7	16·0	15·2
Low-plane diet				
Number of mice	4	4	0	3
Gain (g.)	1·7	11·1	—	1·1
Food consumption (g.)	67·3	109·7	—	61·7
Efficiency (%)	2·6	9·3	—	1·2
Food wasted (g.)	124·3	92·8	—	93·6
,, ,, (%)	64·9	45·8	—	60·3

weights were taken of (*a*) the mice, (*b*) the unconsumed food in the food basket, and (*c*) the food wasted, i.e. unconsumed food on the cage floor after faeces and wood-wool had been removed by sieving. From these weights the gain in weight of the mice and the food consumed were obtained; and the efficiency of gain (gain in weight/food consumed) was calculated. Five mice were allocated to each group, but there were several deaths among the mice on low-plane diet, particularly among the small lines, and no mouse of the low-plane small line completed the test. These deaths, which occurred in the first week, can be attributed to the mice being housed singly. For the same reason the gains were less than under the normal procedure of housing five mice per cage. The results of the feeding tests are given

in Table 3. Despite the small numbers of mice tested the conclusions about the
diets are clear. It will be remembered that the low-plane diet consisted of the
ingredients of the high-plane diet diluted with 50% of indigestible fibre, and that
it was fed *ad lib*. The mice fed on the low-plane diet consumed less food than those
fed on the high-plane, but they wasted very much more. It appears, therefore,
that the mice ate selectively, rejecting the indigestible fibre. The nature of the
restriction to growth imposed by the low plane of nutrition was thus in the amount,
and not in the quality of the food ingested. The efficiency of gain was much less
on the low than on the high plane, presumably because more energy had to be
expended in getting the food. The four selected lines differ in a regular manner in
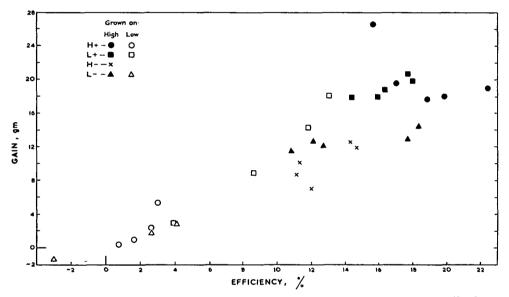their efficiency of gain. The greater the gain in weight the greater their efficiency

Fig. 6. Relationship between gain from 3 to 6 weeks and efficiency, i.e. gain/food-
intake. Solid points refer to mice reared on high plane, open points to mice
reared on low plane. Each point represents one individual.

of gain. This relationship is found also between the individuals within the groups
on both diets, as shown in Fig. 6. More detailed consideration of the relationship
between gain and efficiency would not, however, be justified with such small
numbers of animals in each group.

Further studies of the two large lines $(H+ \text{ and } L+)$

The responses to selection already presented showed that in the long run direct
and indirect selection had been equally effective in increasing growth on the high
plane of nutrition. Attention has already been drawn to the fact that this equality
of growth conceals important differences between the two lines. These differences
—of weight, and carcass composition—will now be described.

Body weight. In generation 19, twelve matings were set up in each of the two large lines, and most of the male offspring from both first and second litters were weighed at 12 weeks, in addition to the usual weighings at 3 weeks and 6 weeks. The weights and growth of the two lines are given in Table 4. The mice of the low-plane line were the heavier by about 3 g. at 3 weeks, at 6 weeks and at 12 weeks, though their gain in weight over the whole period was almost identical with the high-plane line. The weight of a litter at 3 weeks is more strongly influenced by the mother than by the intrinsic growth of the young. Therefore the difference of weight between the lines, appearing as it does at 3 weeks and remaining constant thereafter, must probably be attributed to a maternal effect. If this interpretation is accepted, it means that the difference in maternal performance must have arisen as a correlated response, since no direct selection was applied to maternal performance. Thus selection on low plane, though no more effective than selection on high plane when judged by the improvement of growth achieved, led to a more

Table 4. *Body weights of the two large lines, reared on high plane,*
measured in generation 19

	High-plane line (H+)		Low-plane line (L+)	
	1st litters	2nd litters	1st litters	2nd litters
Number of mice	37	26	30	17
Weight (g.): 3 weeks	10·7	11·5	13·7	14·1
6 weeks	30·7	32·1	34·0	34·9
12 weeks	42·7	41·6	45·9	45·2
Growth (g.): 3–6 weeks	20·0	20·6	20·3	20·8
6–12 weeks	12·0	9·5	11·9	10·3

'desirable' produce in respect of maternal performance. The cause of the inferred difference in maternal performance very probably lies in the difference of carcass composition next to be described.

Carcass composition. Selection for large size on a low plane of nutrition was found in the previous experiment (Falconer & Latyszewski, 1952) to result in mice with less fat than those produced by selection on a high plane of nutrition. This difference was found again in the present experiment. Measurements of fatness were made on male mice of the two large lines in generations 16, 18 and 19. Rearing on low-plane diet had ceased at generation 15. The mice of generation 16 were measured at 6 weeks of age, but in generations 18 and 19 the measurements were made at 12 weeks, when the differences of fatness would be expected to be accentuated. (See Fowler, 1958.) Fatness was measured by the weight of the abdominal-fat deposit, which is easily dissected out. In addition, carcass analyses were made on a few of the generation 19 mice by Dr R. E. Fowler, who kindly allows me to quote her results. The correlation between abdominal fat and total fat was high (0·98 in the high-plane line and 0·94 in the low-plane line), so the weight of abdominal fat provides a good measure of general fatness.

The results of the measurements of abdominal fat are given in Table 5. In all of the three generations sampled the mice of the low-plane line had less fat than those of the high-plane line. The samples taken in generation 16 and 18 were rather small and the differences between the lines are not significant. In generation 19, however, the samples were larger and the difference is clearly significant. The mice measured in generation 19 were derived from eleven litters of each line, and

Table 5. *Abdominal fat of males of the two large lines, reared on high plane*

| | | High-plane line (H+) | | | | Low-plane line (L+) | | | |
| | | | Body weight (g.) | Abdominal fat | | | Body weight (g.) | Abdominal fat | |
Generation	Age	Number		Weight (g.)	%	Number		Weight (g.)	%
16	6 weeks	8	32·5	0·46	1·36	15	33·8	0·42	1·24
18	12 weeks	10	39·2	0·70	1·78	9	42·2	0·54	1·28
19	12 weeks	37	42·7	0·86	1·96	30	45·9	0·67	1·45

there proved to be significant differences in the percentage of abdominal fat between the litters. For this reason the test of significance of the difference between the means of the two lines was based on the observed variance of litter-means. On this basis the difference between the means is 2·4 times its standard error, which with twenty degrees of freedom has a probability of 0·02. The analyses of variance yielded the estimates of the components of variance given in Table 6. From these

Table 6. *Mean squares and components of variance of percentage of abdominal fat. Males of generation 19 at 12 weeks, all reared on high plane*

| | High-plane line (H+) | | | Low-plane line (L+) | | |
	d.f.	M.S.	Component	d.f.	M.S.	Component
Between litters	10	0·785	0·127	10	0·488	0·110
Within litters	26	0·364	0·364	19	0·193	0·193
Total	36	0·481	0·491	29	0·295	0·303

figures it appears that the two lines differed in variability, particularly in the within-litter component, the low-plane line being less variable in the percentage of abdominal fat. Though the difference is significant only at the 20% level, it is probably real because a significant difference of variability was established by the carcass analyses described below, and the low-plane line was less variable, though not significantly so, also in the abdominal fat samples in generations 16 and 18.

The components of variance in Table 6 can be used to set upper limits to the heritability of the percentage of abdominal fat, though the estimates will not be at all precise when based on samples as small as these. The estimates obtained

are 52% in the high-plane line and 73% in the low-plane line. It is probable that much of the between-litter variance is environmental in origin, and the true values of the heritabilities are probably much lower than these figures.

The results of the carcass analyses made by Dr Fowler are given in Table 7. For the methods used, see Fowler (1958). These analyses were made on some of the mice of generation 19 whose abdominal fat was measured in the samples described above. In addition to the measurements of total fat, already mentioned, estimates of the water in the carcass were made as a measure of the protein content.

Table 7. *Carcass analyses of males at 12 weeks, made by Dr R. E. Fowler. All mice were reared on high plane*

	High-plane line (H+)	Low-plane Line (L+)	Significance of difference (P)
Number of mice	8	7	
Body weight	43·09	47·79	
Carcass weight	34·16	38·47	
Abdominal fat (g.)	0·72	0·70	
Total fat (g.)	5·47	4·53	
Water (g.)	20·24	24·39	
Total fat, as % of carcass weight	15·4	11·8	0·1–0·2
Water, as % of carcass weight	59·6	63·4	0·02–0·05
Standard deviation of % fat	4·50	1·46	0·01
Standard deviation of % water	3·82	2·10	0·2

The percentage of fat in the carcass was lower in the low-plane line than in the high-plane line, and the percentage of water, indicating protein, was higher. The latter difference is significant at the 5% level. The lower variance of the low-plane line was found again in the carcass analyses, the difference of variance of fat percentage being significant at the 1% level. In these samples the difference between the lines in the amount of abdominal fat was by chance rather less than in the larger samples referred to in Table 6. Consequently the differences of carcass composition between the lines are probably underestimated by these analyses.

Body-length and tail-length

In order to obtain some information about skeletal size, measurements of body-length and tail-length were made on some male mice of the two large lines in generation 19. The mice measured were all from second litters, and were measured at 12 weeks of age. I am indebted to Mr J. H. Isaacson for making these measurements. The means of the two lines are given in Table 8. The mice of the low-plane line had longer bodies and tails. But they were also heavier; and, since linear dimensions may be expected to vary in proportion to the cube root of weight, the comparison of the lines should be made from the ratios of body- or tail-length to the cube root of the weight. These ratios, given also in Table 8, show that the mice

of the low-plane line were proportionately longer in body and tail, but only slightly so.

Table 8. *Body-length and tail-length of males at 12 weeks, all reared on high plane*

	High-plane line (H+)	Low-plane line (L+)
Number of mice	26	18
Weight (g.)	41·6	44·7
Body-length (mm.)	108·5	113·0
Tail-length (mm.)	97·5	105·7
Body-length/(Weight)$^{\frac{1}{3}}$	31·31	31·84
Tail-length/(Weight)$^{\frac{1}{3}}$	28·14	29·78

Analysis of responses

The experiment was designed, as was explained in the Introduction, so as to provide a test of the adequacy of the theory of selection from which predictions of the responses might have been made. The prediction needed in practice is of the progress to be expected by indirect selection, relative to that expected by direct selection. For example, if growth on low plane is the character to be improved, will it be better to select for growth on high plane and achieve progress through a correlated response, or to select for growth on low plane itself and rely on the direct response? The prediction derived from the current theory of selection shows that the ratio of the improvement expected from indirect selection to that expected from direct selection should be as follows (Falconer, 1952):

$$\frac{CR_L}{R_L} = \frac{i_H}{i_L}\frac{h_H}{h_L}r_A. \tag{1}$$

(The meanings of the symbols used here and throughout this section are given in Table 9.) In the same way the expected responses of growth on high plane are given by the equation

$$\frac{CR_H}{R_H} = \frac{i_L}{i_H}\frac{h_L}{h_H}r_A. \tag{2}$$

The best test of the validity of these equations would have been to estimate the two heritabilities and the genetic correlation in the population before selection was applied and then see if the predictions were born out. This, however, would have required a separate experiment on a large scale, and instead a less direct test was applied. All the quantities in both equations can be estimated from the observed responses to selection, except the genetic correlation. The solution of each equation therefore yields an estimate of the genetic correlation, one estimate coming from a comparison of the change of low-plane growth according to the method of selection (equation (1)), and the other from a comparison of the change of high-plane growth (equation (2)). The two estimates ought to be the same if the theory is adequate.

There is, however, a difficulty in the application of this test, which should be faced at the outset. The equations are theoretically valid for the prediction of the initial response to selection applied to a single base population. But after some generations of selection the parameters involved, i.e. the heritabilities and the genetic correlation, must be expected to change; and the theory cannot predict the extent of the changes involved. Moreover, after some generations of selection

Table 9. *Meanings of symbols*

H	the character 'growth on high plane'
L	the character 'growth on low plane'
R	direct response of the character indicated by subscript
CR	correlated response of the character indicated by subscript. (CR_H = change of H resulting from selection for L CR_L = change of L resulting from selection for H)
i	intensity of selection (= selection differential in phenotypic standard deviations) applied to the character indicated by subscript
h^2	heritability of the character indicated by subscript
r_A	genetic correlation (i.e. correlation of breeding values) between the characters H and L

the parameters in the equations no longer refer to a single population but to two, i.e. the two lines under comparison. Therefore only the first few generations of the experiment can legitimately be used to test the validity of the theory. If the theory is upheld by the initial responses, then the later generations of the experiment can be used to answer the empirical question: how long will the prediction hold good?

Table 10. *Responses up to generation 7, judged as deviations from the control*

	Upward selection		Downward selection	
	Growth on high plane	Growth on low plane	Growth on high plane	Growth on low plane
Intensity of selection	$i_H = 0.83$	$i_L = 0.69$	$i_H = 0.80$	$i_L = 0.66$
Realized heritability	$h_H^2 = 0.26$	$h_L^2 = 0.31$	$h_H^2 = 0.42$	$h_L^2 = 0.25$
Direct response	$R_H = 2.26$	$R_L = 3.07$	$R_H = 2.80$	$R_L = 3.23$
Correlated response	$CR_H = 1.55$	$CR_L = 0.64$	$CR_H = 1.17$	$CR_L = 2.89$
Genetic correlation	$r_A = 0.75$	$r_A = 0.19$	$r_A = 0.66$	$r_A = 0.57$

Table 10 gives the data need for the solution of equations (1) and (2) from the responses up to generation 7, when a group of unselected animals were measured as controls. The responses given in the table are the total responses measured as deviations from the controls, first-litter mice being used as controls for the direct responses and second-litter mice for the correlated responses. The intensities of selection were calculated from the deviations of selected individuals from their

litter-means, weighted by the number of progeny measured in the next generation and divided by the phenotypic standard deviation within litters, males and females being averaged. The heritabilities were estimated as realized heritabilities from the ratio of total response to total selection differential. The realized heritabilities are depicted graphically in Fig. 2b, where the generation means are plotted against the cumulated selection differential. Four estimates of the genetic correlation between high-plane growth and low-plane growth are entered at the foot of Table 10. The estimate in each column is derived from the responses entered in the same column above it. For example, the estimate of 0·75 in the first column refers to the upward responses of growth on high plane and is obtained by equation (2) as follows:
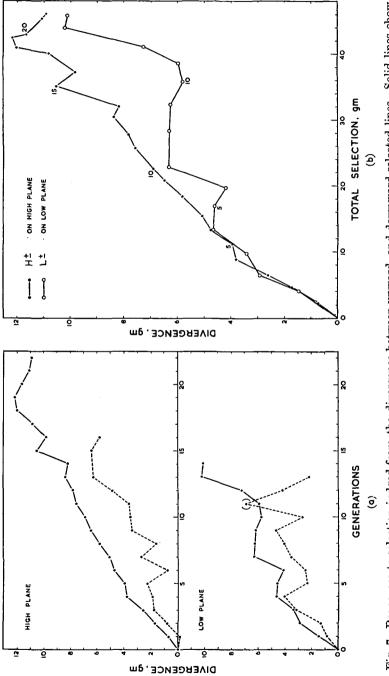
$$r_A = \frac{CR_H}{R_H} \frac{i_H}{i_L} \frac{h_H}{h_L}$$

$$= \frac{1·55}{2·26} \frac{0·83}{0·69} \sqrt{\frac{0·26}{0·31}}.$$

The estimates under the columns headed 'growth on low plane' refer to the responses of growth on low plane and are obtained in a similar way by equation (1). Three of the four estimates are in reasonably good agreement, only one being seriously discrepant. This is the one derived from the upward responses of growth on low plane. Over the first seven generations of selection, therefore, we may conclude that the observed responses are in reasonably good agreement with the theory of selection for correlated characters.

For the later generations of the experiment an examination of Fig. 2a is sufficient to show that the responses do not agree at all well with the theory, and, in the absence of unselected controls, it would be pointless to subject them to detailed analysis. Let us therefore see if anything can be discovered about the causes of the discrepancy.

Examination of the realized heritabilities depicted in Fig. 2b shows that there was asymmetry between the upward and downward responses, and that the realized heritabilities of high-plane growth changed. The realized heritability of growth on high plane over the first four or five generations was about 70% when selected upwards and about 20% when selected downwards; but thereafter it was about 12% upwards and 45% downwards. Growth on low plane, apart from irregularities in the first two generations, showed a fairly constant realized heritability of about 10% when selected upwards and about 20% when selected downwards. The asymmetry of the responses may have arisen from genetic causes or from changes of the environment: the former seems more probable for the responses of high-plane growth, and the latter, through deterioration of the diet, for the responses of low-plane growth. Whatever its cause, the asymmetry could not have been predicted on the basis of theory. The next step should therefore be to find out if the discrepancies of the correlated responses can be attributed to the asymmetry.

The complications introduced by the asymmetry of the responses can, in some

Fig. 7. Responses to selection judged from the divergence between upward- and downward-selected lines. Solid lines show the direct responses, broken lines the correlated responses. The figures alongside the graphs in (*b*) are generation numbers.

degree, be circumvented by consideration of the divergence between upward- and downward-selected lines. The responses measured as divergence are shown in Fig. 7, the generation means being plotted against generations in Fig. 7a and against the cumulated selection differentials in Fig. 7b. The correlated responses are now at least qualitatively in agreement with expectation over the whole experiment: in both cases the response to indirect selection (i.e. the correlated response) is less than the response to direct selection. This is what would be expected unless the heritabilities of the two characters, or the intensities of selection applied to them, were very different and the genetic correlation were very high.

In order to test the agreement quantitatively it is necessary to divide the experiment into parts, because neither the realized heritabilities nor the responses remained constant over the whole experiment. The responses were therefore divided at generation 4 into two parts, because this is the first point at which the heritabilities changed appreciably. Table 11 gives the results of the analyses made

Table 11. *Responses judged from the divergence between upward and downward selected lines. The columns headed 'H' refer to growth on high plane, the columns headed 'L' to growth on low plane. The genetic correlations in each column are estimated by equations (1) or (2) from the responses entered above in the same column*

| | Generations | | | | | |
| | 0–4 | | 4–13 | | 0–13 | |
	H	L	H	L	H	L
Intensity of selection (i)	1·66	1·40	1·65	1·52	1·66	1·48
Realized heritability (h^2)	0·41	0·36	0·22	0·13	0·30	0·20
Direct response (R)	0·90	1·20	0·53	0·46	0·69	0·70
Correlated response (CR)	0·48	0·98	0·46	−0·01	0·38	0·38
Genetic correlation (r_A)	0·67	0·65	1·25	−0·02	0·74	0·39

in the same way as was described above. Three analyses are given: up to generation 4; from generation 4 to generation 13; and over the whole experiment from generation 0 to generation 13. The realized heritabilities were computed from the regression of generation mean on cumulated selection differential and the responses from the regression of generation mean on generation number. Since the responses here are the divergence between lines selected in opposite directions, the regression lines were made to pass through the origin (i.e. no divergence at generation 0), except those referring to the period from generation 4 to generation 13.

The first four generations of selection yield two estimates of the genetic correlation that are in very good agreement with each other. Up to this point, therefore, the responses agree well with the theory of selection for correlated characters. After generation 4, however, the two characters yield widely discrepant estimates of the genetic correlation, and the responses do not agree well with the theory. Circumvention of the asymmetry between the upward and downward responses

by consideration of the divergence, though it brings the responses into qualitative agreement with the theory, does not go far towards removing the discrepancies.

The conclusion to be drawn from these analyses of the responses is that the theory of selection for correlated characters appears to be adequate for the prediction of the relative merits of direct and indirect selection over the first few generations. For the later generations, however, the theory does not adequately describe the responses. The reason for the discrepancy probably lies in the changes of the genetic parameters that took place during the course of the selection.

DISCUSSION

The conclusions drawn from the experimental results may be summarized as follows:

1. Selection for increased growth gave the same result as the previous experiment: growth on high plane was increased equally by selection on low plane as by selection on high plane, but growth on low plane was increased only by selection on low plane. The best 'all-round' performance was thus produced by selection on low plane.

2. Also in agreement with the previous experiment was the difference in carcass composition: the mice whose growth had been increased by selection on low plane were less fat than those whose growth had been increased by selection on high plane. The equality of growth was therefore reached by different physiological pathways.

3. Selection for decreased growth gave results that 'mirror-imaged' the results of selection for increased growth: growth on high plane was reduced only by selection on high plane, but growth on low plane was reduced equally by selection on high plane and selection on low plane. The best 'all-round' performance was thus produced by selection on high plane.

4. The results of selection in both directions may be generalized by saying that if good performance under a variety of conditions is desired, then selection should be made under the conditions *least* favourable to the desired expression of the character: if an increase is desired, the selection should be made under conditions that reduce the character, and vice versa.

5. These results, which refer to the final outcome of thirteen generations of selection, do not accord well with the theory of selection for correlated characters. Over the first few generations, however, the results were in reasonably good agreement with the theory. The discrepancies probably arose from changes of the genetic parameters which took place during the course of the selection.

How much reliance can be placed on these conclusions? In the first place, the absence of replicates must cast some doubt on the generality of the results, because little is known about how much the response to selection may be influenced by the special circumstances of a particular line or a particular experiment. The uniformity of response among the replicates of an experiment with *Drosophila* (Clayton, Morris & Robertson, 1957) was quite enough over the first ten generations

or so to justify the drawing of conclusions about the direct responses in an experiment without replicates, such as the present one. But the correlated responses may be less reliable, for reasons explained by Clayton, Knight, Morris & Robertson (1957), and the conclusions drawn from them—which are the main conclusions of the experiment—must be accepted only with some caution. On the other hand, selection for increased growth has produced the same results in two different experiments with mice, and the conclusions about upward selection are therefore more reliable.

In the second place, the lack of unselected controls, except at the seventh generation, weakens the theoretical analyses of the results. It does not, however, impair the reliability of the main conclusions, which are based on comparisons of two lines on the same nutritional plane.

The theoretical analyses are the least satisfactory feature of the experiment. They show that changes of the genetic parameters took place, which led to final responses that could not have been predicted from the parameters of the base population. But the precise nature of these changes and the way in which they affected the responses remain obscure. In short, the experiment shows pretty clearly *what* happened when selection was applied in two different environments, but not *why* it happened. There are, perhaps, some clues. Firstly, there is the asymmetry of the responses in opposite directions. The cause of this, which affects the direct responses, must be sought before we can hope to understand the correlated responses. Secondly, there are the changes of phenotypic variability, and of 'sensitivity' to the low-plane diet. These can be described by saying that selection on low plane affected the canalization of growth, whereas selection on high plane did not. But the changes of canalization need a genetical explanation no less than the changes of growth.

The problems raised and left unsolved by this experiment are partly genetical and partly physiological. I shall conclude by outlining the terms in which I believe the solutions should be sought. The concept of genetic correlation arises from pleiotropy as a property of genes. When two quantitative characters are under consideration, three classes of gene are postulated: A, genes that affect one character only; B, genes that affect both characters; and C, genes that affect the other character only. The segregation of genes of class A causes variation of the first character, class B of both characters, and class C of the second character. Selection applied to the first character changes the frequencies of the genes of classes A and B; the changes of the class B genes cause the correlated response of the second character. The physiological aspect of the problem consists of discovering how these three classes of gene affect the character. In the present experiment, for example, the genes of class A, say, affected fatness more than did those of the other two classes. A solution of the physiological problem would enable us to predict the qualitative differences between the products of selection in different environments. The genetic aspect of the problem consists of discovering how the genetic properties of the population change as the frequencies of the genes of the three classes change. Interaction between the genes of different classes seems

to be inescapable. For example, the effects of (i.e. the variation caused by) genes of class A, say, may be increased in the presence of plus alleles of the C class and reduced in the presence of minus alleles. The genetical problem is thus one of great complexity. Its solution seems hardly likely to be achieved until we have a wider empirical knowledge of the responses to selection in different environments, or of correlated responses in general.

SUMMARY

1. Two-way selection was applied to the growth of mice between 3 and 6 weeks of age when reared on a high plane of nutrition and, in another pair of lines, when reared on a low plane of nutrition. In each generation the growth of all four lines was measured on both high and low planes of nutrition.

2. Growth on the two planes of nutrition was treated as two different characters and the direct and correlated responses of each were estimated. The genetic correlation between the two characters was estimated from the responses of each of the four lines, and from the divergence between upward-and downward-selected lines. The different estimates should be the same if the theory of selection for correlated characters adequately accounts for the responses. Up to generation 7 the agreement was reasonably good, but in the later generations it was not. Four estimates of the genetic correlation up to generation 7 were: 0·75, 0·19, 0·66, 0·57.

3. There was asymmetry between the upward and downward responses, and the realized heritabilities changed over the course of the experiment; so also did the phenotypic variation. In all these respects the lines behaved differently.

4. The conclusions drawn from the final responses are summarized at the beginning of the Discussion.

5. The mice produced by selection for increased growth on low plane, but later reared on high plane, were compared with those produced by selection on high plane. Their growth was the same, but they were heavier, had less fat and more protein, and were better mothers.

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