AN ABSTRACT OF THE THESIS OF

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Title: AN ANALYSIS OF THE RESPONSE TO SELECTION FOR HIGH AND LOW RATE OF GAIN IN THE MOUSE, MUS MUSCULUS

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An experiment was conducted to examine the responses to selection for high and low rate of gain in the mouse under a system whereby inbreeding was maximized. Rate of gain was measured by an index designed to include gains in both the pre- and postweaning periods with the gains in the latter period emphasized over those of the former. The various components (weights and gains) of the index were also analyzed in relation to their response to selection for the index.

Data were collected on weight at 14, 24 and 32 days of age and litter size at 14 days of age.

Results of the analyses indicated that while a response to selection for high index was obtained, virtually no response to selection for low index occurred. Responses of the component parts of the

index (14, 24 and 32 day weights and gains between 14 and 24, 24 and 32 and 14 and 32 days) to selection for high index increased with increasing ages at which data were collected. Little if any response to selection for low index was obtained for the component parts of the index.

It is proposed that the lack of response in the low line was caused by the opposition of natural selection to the artificial selection pressures imposed, which also was effective in maintaining a degree of heterozygosity above that described by calculated inbreeding coefficients. The hypothesis was supported by data on litter size.

A disease which was widespread in the colony was found to have significantly reduced weights, gains and indexes in both the high and low lines. The disease was contributory in reducing the response to the two-way selection by effectively masking the phenotypic expression of genes for the several characteristics.

A depressing effect of inbreeding on litter size occurred in both lines. The effect on the high line was more severe than that noted for the low line despite an increase in body size in the high line over five generations of selection. Thus inbreeding directly reduced litter size rather than indirectly through a reduction in maternal size. The cause(s) of the reduction were not determined.

Random genetic drift due to small effective population sizes was hypothesized as the cause of the significant differences seen between replicates.

An Analysis of the Response to Selection for High and Low Rate of Gain in the Mouse, *Mus musculus*

by

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A special place is provided here for my sister, Susan Norblad, whose help, love and humor have sustained me throughout. Special note of her suggestion of a title for this thesis should be made, as it is very illustrative of selection experiments, in general:

"Mene, mene, tekel upharsin" (Daniel 5:25), meaning "numbered, numbered, weighed and divided."

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INTRODUCTION

The search for knowledge of the gene and genetic systems is in reality an extension of man's quest to survive. Whether the knowledge is translated into cures or calories, the basic motivation remains. It is on the side of calories that experimentation in animal breeding falls. As man has been unable to increase the area upon which his animals feed, thus enabling an increase in his own food supply, he has had to resort to an attempt at increasing the yield of the land available. It has been through selective manipulation of genes and genotypes that he has been able to succeed in his goal. However, dwindling land resources and an ever-increasing human population have necessitated that man further increase the efficiency of both crops and animals. To this end, extensive studies of selection methods and the responses of the organisms which are subjected to the selective pressures have been made.

It is known that response to selection is hampered by inbreeding due primarily to a general loss of vigor and fitness, most noticeable in early life traits. In the present study, interest is focused on the responses to selection of mice for high or low rate of gain, in a

manner which combines both pre- and postweaning gains, under a regimen of maximum inbreeding. It is expected that a certain degree of asymmetry should develop as selection in the direction of reduced gains should compliment the losses due to inbreeding. Selection in the direction of increased gains should either be ineffective or progress only slowly, if the selective pressures are strong enough to combat those presented by inbreeding. In addition to this primary goal, examination of the responses of the selected lines to the adverse stress of disease, which occurred in the colony, proved to be of interest.

Livestock producers rarely incur such high levels of inbreeding in their herds; however, a certain degree of inbreeding is often encountered. As animals are selected for specific traits over many generations, however, though the actual calculated coefficients of inbreeding do not reflect it, these will more nearly resemble an intensively inbred line, which has survived the debilitating effects of inbreeding than animals in the wild or unselected state. More frequently, various disease problems occur in domestic herds. Thus it is hoped that the examination of the responses to selection under such circumstances will be of benefit to those interested in increasing the efficiency and rate of production from our decreasing natural resources.

LITERATURE REVIEW

I. Genetic Analysis of Body Weight and Growth in the Mouse

The most important economic traits of livestock are liveweight gain and weight per day of age. The high costs of producing and maintaining most species of livestock almost prohibit their use for studies on the effects of inbreeding, selection, selection limits, and the other various factors affecting these traits. This may account for the great amount of work done in these areas on laboratory species, specifically the mouse, Mus musculus. Body weight and weight gains are relatively easy traits to measure which may be another reason for choosing these traits as traits for examination in quantitative genetic studies.

Selection for Body Weight and Growth

Early evidence of the existence of genetic variance of an additive nature was supplied by Goodale (1938). Using a form of progeny testing which he termed "genotypic selection," mice were selected for large body weight. Progress was reported over 14 "chronological groups" which very roughly corresponded to generations. Over this period, he was able to increase the weights of his mice from 25 g to 43 g at 60 days of age. Though at this time Goodale had the expectation of further response, by the time of his 1941 progress report which

covered selection done in a further 14 groups, he had more or less reached a selection plateau (Falconer and King, 1953). Goodale's work clearly established the feasibility of changing the phenotype by selecting for body weight in the mouse.

Goodale's experiment did not have any control population; therefore, environmental time trends could not be assessed. MacArthur (1944a, 1949) conducted a two-way selection experiment whereby the lines selected in opposite directions served as controls for each other. His results of 23 generations of selection for 60-day weight were reported in 1949. MacArthur used mass selection and specifically avoided inbreeding. By the 23rd generation, the large line mice were roughly three times the size (38 g) of the small mice (about 12 g) and at this time responses to further selection were already much reduced. Butler (1952), working with the same strains, reported that very little further progress had been made. A quite momentous offshoot of MacArthur's selection experiments was his report (1944b) of correlated responses to selection for weight which he discovered in his lines. He found that the lines had also diverged with respect to behavior, hair colors, relative length of the appendages and litter size. MacArthur himself attributed these differences, especially those related to color, to random genetic drift.

Falconer (1953a) reported the results of an experiment dealing with selection in the mouse, that was far more sophisticated than any

work previously published. Falconer selected for high and low 6-week weight thus permitting a shorter generation interval than that achieved by Goodale or MacArthur. He constructed his base population from a four-way cross of inbred strains which in terms of genetic variation, is equivalent to a single full-sib family from a random bred population. Falconer selected his animals on the basis of the within-litter deviation from the litter mean for the sex being selected. Animals were divided into families and each litter within a family contributed one male and one female as parents, which were randomly mated to produce the next generation (full-sib matings were avoided). This within-litter method of selection effectively excluded selection for maternal effects between litters. The within-family selection excluded differences between families. These methods simplified interpretation of the results and kept inbreeding to a minimum by doubling the effective population size (Falconer, 1960a).

Over the 11 generations covered in this first report, Falconer (1953a) found that the high and low lines diverged regularly; however, the responses were highly asymmetrical. The high line increased a total of 4 g whereas the low line increased by 7 g, with heritability estimates of 0.20 upward and 0.50 downward. An examination of this asymmetry along with results of further selection were given in a later paper (Falconer, 1955). Falconer concluded that 6-week weight can be divided into two component parts; weaning weight at 3 weeks, a

characteristic largely due to maternal environment, and post weaning growth. The maternal component was further divided into two parts, one being related directly to maternal size and having a positive effect on the young, and one negatively correlated, not with body weight but with the deviation of body weight from the original level in either direction. The net result was that the two components cancelled each other out when maternal weight increased; but there was a marked reduction in the maternal component when weight was reduced. Thus, Falconer assigned the asymmetry of response to asymmetry in the maternal component entirely.

In his earlier paper (1953a), Falconer argued that the asymmetry could be accounted for largely by an increase in the inbreeding coefficient, which had risen to 38% by generation 11. However, in a more detailed examination of the causes of asymmetry, Falconer (1953b) found that decreases due to inbreeding were insufficient to account for the asymmetry observed, and he concluded that it was a property of the genetic control of the character selected. He discussed in detail three forms of asymmetry in genetic systems: scale of measurement, unequal frequencies of alleles acting in opposite directions, and directional dominance. A conclusion reached concerning scale was that by representing response in terms of realized heritability, scale effects are removed. Unequal gene frequencies are a property of the initial population used, and directional dominance is an inherent property of

the genes segregating for the character under examination, and therefore there may or may not be asymmetry in a selection experiment. However, it is more common than not (Falconer, 1953b, 1955, 1960b). Recently, Falconer (1973) reported on 20 generations of two-way selection for body weight and found no significant asymmetry.

Apart from ideas on asymmetry, Falconer drew several conclusions from his extensive experimentation on body weight in mice:

(i) The small and large lines diverged by 16 times the original standard deviation.

(ii) The response to selection ceased in both lines after about 20 generation.

(iii) The realized heritability remained unchanged in both lines until the limit was reached.

(iv) Realized selection differentials equalled the expected differential in the high line but fell short of expected in the low line, indicating that natural selection impedes progress in that direction.

(v) Upon suspension of selection, the small line reverted towards the original level while the large line did not, corroborating the finding on natural selection.

(vi) A large number of loci with nearly equal effects control genetic variation of this trait.

(vii) Dominance is largely in the direction of increased size.

(viii) The large line had longer tails, higher 12-day and 3-week weights, and larger litter size than the small line; fertile matings and postnatal viability fell in both lines.

In a study initiated by Comstock, and reported by Rahnefeld et al. (1963), the above findings of Falconer are generally supported, though

the experiment differed in many respects. Their population was from a cross of two inbred lines, selection was based on postweaning growth and they used a mass selection procedure based on the individual's deviation from the population mean. Seventeen generations produced a change in mean growth of 4 to 5 g, which was about six times the original genetic standard deviation. Heritability estimates ranged from 22 to 26%. The response was linear and, at the time of this report, was not tending toward a limit.

Doolittle, Wilson and Hulbert (1972) made a comparison of multiple trait selection methods (index, minimum culling level and tandem) for the combined traits of litter size and postweaning gain (21-42 days of age). They found the index to be slightly though not significantly superior to the other methods. Increases made in weight gain were accompanied by increases in 42-day body weight while 21-day weight remained stable. Frahm and Brown (1973) examined weaning weight (WW line) and postweaning gain (ADG line) by selecting for each independently in separate lines and analyzing the resulting correlated response for the trait not selected. Within-litter selection was practiced for the trait of weaning weight to eliminate maternal influences while mass selection was practiced in the gain line. After 12 generations of selection, the average linear selection response per generation in the WW line equalled 0.17 g and 0.008 g per day for 21-day weight and 21-42 day rate of gain respectively while in the ADG

line corresponding values were 0.06 g and 0.027 g per day. Weight at 56 days also increased by 0.33 and 0.77 g per generation for WW and ADG lines respectively. The average correlation between the two traits was about 0.33, and realized heritabilities were 0.19 for weaning weight and 0.27 for average daily gain.

Limits to Selection and Genetic Variance

A somewhat uniform result of long-term selection experiments for growth or body weight in mice has been the plateaus or selection limits that have been reached. These limits have been extensively explored using mice from lines plateaued by selection. Assuming there is a finite number of loci affecting the trait being considered, then eventually, through the processes of selection, genetic drift and inbreeding (disregarding rare mutational events), alleles at these loci will become fixed, genetic variation will decline to zero and no further progress will be made. Also, when considering limits, one must consider physiological limits; for example, a mouse of weight zero will not exist and also, even though an animal has the genetic capacity to make faster gains, it may not be able to consume enough nutrients to do so.

Three most commonly used methods have been employed by various experimenters to test for the fixation of genes in lines plateaued by selection (Falconer, 1953a, 1955; Chai, 1966a; Roberts,

1966a, b, 1967a, b). If all genes for a trait have been fixed, there should be no genetic variance; all variance present should be due to environment. Chai (1966), using MacArthur's (1944a) small strain and Goodale's (1938) large strain, made a hierarchical analysis of variance for each generation with total variance divided into between matings, between litters within matings and within litters. The total and individual components of variance in the large strain showed no definite change among generations for either birth or 60-day weights. Weights of small mice drifted upwards and the coefficients of variation increased in later generations. These the author attributed to either recombination of linked polygenes or new mutations.

If genes are fixed for an upper or lower limit, then reversed or relaxed selection will be ineffective in changing the level the trait has attained through selection. Roberts (1966b), using mice previously selected for high and low postweaning rate of gain and which had plateaued in both directions (Falconer, 1960b), attempted both reversed and relaxed selection. No response was noted in the large line indicating exhaustion of additive genetic variance. In contrast, under relaxed selection the small line regressed slightly towards the level of the base population while reversed selection produced a ready response until a new limit was reached. Loci affecting body weight in this line had therefore not been fixed by selection. To explain these results, Roberts postulates that natural selection, operating on

viability between conception and the time when selection was made, favored individuals heterozygous at some loci.

In a continuation of the same study, Roberts (1967a) constructed crosses between high lines and between low lines previously plateaued by selection to determine if the genes fixed in each line were the same or different. In every case, the crossbred progeny exhibited heterosis as evidenced by an increase in body weight showing that all selected lines were differentiated with respect to genes affecting body weight. Further selection was made on the progeny of the crosses in the same direction of their previous selection. Selection of large line crosses produced a stock whose mean weight was 25% higher than the largest of the original lines at its limit. The response to selection of small lines was slow, and after 24 generations had failed to recover the low weights of the original lines. The evidence in this study points of linkage of genes affecting body weight. It has been shown by Hill and Robertson (1966) that linkage affects the chance of fixation of alleles under selection. An unfavorable allele at a locus is more likely to become fixed if it is linked to another locus with a greater effect on the character. When the effects are more nearly equal, the chance of fixation of the more favorable allele at each locus is reduced. The relative importance of linkage will be the amount of genetic variance due to linked loci in proportion to the total variance. In crosses between lines previously selected in the same direction, this ratio will be maximized (Roberts, 1967a).

In an attempt to create new variance in the plateaued lines, Roberts (1967b) irradiated males from the selected and plateaued lines. The results were negative and no further gain was achieved through selection. A second method, outcrossing to an unselected line and selecting from the cross, resulted in a clear gain over the original limit but nine generations were needed to even recover the limit. Relative to their use in livestock improvement, neither method was considered valuable.

In a later study of Goodale's strains (Wilson et al., 1971), results similar to those of Roberts (1966a) were obtained. Although estimates of heritability indicated that after 84 generations, genetic variance was not exhausted, the authors concluded that the long plateau indicated that the estimates were probably biased and no genetic variation for increased body weight was available for selection.

It has been noted by many experimenters that additive genetic variation was the preponderant component of the total genetic variation available in selection for body size or growth. The results of some workers suggest that non-additive genetic variance (including dominance and interaction variance) is virtually nil. Chai (1965b), in an analysis of crosses and backcrosses of large and small strains, found the effective size genes involved acted additively and that any dominance contributing to the total variability was trivial. Miller, Legates and Cockerham (1963), in an examination of non-additive hereditary

variance for several traits, found no evidence of such for the traits of 12-day litter weight, individual weaning weight, gain from 3 to 6 weeks, and individual 6-week weight.

In studies of the 60-day weight of crosses between small, medium and large mice of inbred and outbred groups, it was found that in all cases crossbred progeny were near the midparent average, indicating an additive type of inheritance and little, if any, heterosis (Warwick and Lewis, 1954).

Though non-additivity is generally considered a trivial source of variation, authors who have found dominance effects have determined that the direction of the dominance favors large size and rapid growth. Chai (1957), in a continuation of his previous studies, concluded that either a preponderant number of dominant factors or factors with preponderant dominance effects favored large over small mice. In 1961, the same author, in an attempt to isolate polygenes contributing to size variation, again found that the large genes appeared to be dominant over the small genes.

Very recently, by examining the efficacy of the use of recurrent selection and whether the use of this method would lead to the fixation of genes, or maintenance of some heterozygous loci, Comstock (1973) concluded that allelic interaction (dominance) was an attribute of one or more loci still segregating after 58 generations of selection for postweaning growth.

Interestingly, in a diallel analysis of weight from birth through 10 weeks, Kidwell and Howard (1969) found low values for general combining ability, indicative of a low proportion of additive genetic variance. Heterosis increased relative to the mean between birth and 4 weeks and declined thereafter but was significant at all ages. Significant specific combining effects, indicative of non-additivity were found for weeks 1 through 7.

Carmon (1963), in a complete diallel analysis between four strains, only one of which was highly inbred, found considerable heterosis for weight at both 21 and 45 days of age. The data were also analyzed with respect to general and specific combining ability (the former measures the average performance of a line in hybrid combination and the latter measures whether specific crosses deviate from expectation based on the average performance of parental lines, Roberts, 1965). He found a high amount of general but a trivial amount of specific combining ability.

Carmon's (1963) findings have relevance to the choice of selection schemes designed to exploit specific combining ability with respect to selection for body weight traits in the mouse. Comstock, Singh and Enfield (1963) crossed a strain selected for increased growth by Rahnefeld et al. (1963) to a long inbred line, at each generation of selection, to measure the effect of selection on combining ability. The crosses exhibited superior growth; however, they did not, at any

stage, differ significantly from half the increase observed in selected lines. They concluded that general combining ability, and thus additive genetic variance, is responsible and that their results provided no evidence of non-additivity of genes for growth. The originators of the line utilized, however, had found some non-additivity (Rahnefeld et al., 1963).

Hansson and Lindkvist (1962), using a recurrent selection scheme which is designed to increase specific combining ability by selecting animals on the basis of their crossing performance with an inbred tester, made no progress. In a study utilizing reciprocal recurrent selection, Newman (1960, as cited by Roberts, 1965) also made no progress after five cycles of selection in mice previously selected to the point where they were near the limit for body weight. Here, the additive genetic variance was theoretically exhausted and any progress would be due to non-additive variance. From these two studies, it can be noted that if any non-additive variance existed, it was not utilized. However, the results must be read in the context of a general doubt about the efficacy of the two methods.

It is generally accepted that traits controlled primarily by genes which act in an additive fashion will show little inbreeding depression while those which have a significant amount of dominance effects will be more severely affected by inbreeding. From the above discussion on additivity versus non-additivity one would expect that traits

such as postweaning gain and body weights taken at periods after weaning would show little inbreeding depression. This theory was verified by the work of Lewis and Warwick (1953) in an experiment involving two-way selection for 60-day weight in both inbred and outbred populations. Selection was effective in both populations and there was no evidence for inbreeding depression. Heritability was slightly lower for inbreds than for outbreds; 37% compared with 42%. Selection did not affect variability in the high lines. Variability in the low lines increased but this was due to the existence of a recessive dwarf gene in the low lines.

Chai (1968) conducted an experiment using the method of selection with repeated backcrosses. In the small lines, he found that those selected downward from an original backcross to a large line were larger than those selected for large size and the original large parental strain. His interpretation of these results was that rapid fixation of genes for large size occurred early after the start of inbreeding.

In a selection experiment for postweaning rate of gain, appetite and feed efficiency, it was found that even though their mice attained high levels of inbreeding, there was little depression of traits noted (Sutherland et al., 1970).

White (1972), in a study of inbreeding effects on growth and maternal ability, found a depressing effect of postnatal performance of the dam on postweaning growth of the young at high levels of

inbreeding of the dam. Thus maternal traits, which generally exhibit a greater degree of dominance and are more prone to inbreeding depression, will have effects upon the offspring.

Butler (1952) stated, "inbreeding without selection will not cause loss in genetic variability" (1, 156) but it will form a heterogeneous population of inbred lines. This divergence between inbred lines has been attributed primarily to genetic drift. Robertson (1961) has stated that in a population under artificial selection, the effective population size may be less than the actual number of parents selected, as there will be variation between families in the character under selection and consequently in the probability of selection. He found that this effect will increase in magnitude the more intense the selection and the higher the heritability of the selected character.

Bereskin, Shelby and Hazel (1969) and Bereskin (1972), employing the technique of computer simulation, noted more genetic separation between lines in the one-sire lines than in the two- or four-sire lines of the study. He attributed these results to large variances in selection effects mediated by random drift in small populations.

A similar design was utilized by Hanrahan, Eisen and Legates (1973) in an actual experiment using postweaning gain as the trait selected. Population sizes of 1, 2, 4, 8 and 16 pair matings were evaluated at selection intensities of 100%, 50% and 25%. Selection responses per generation increased as selection intensity increased.

Selection response per generation and realized heritability increased with an increase in population size. Replication variability in realized heritability was large at population sizes of 1, 2 and 4 pairs. Genetic drift was determined to be the primary factor causing reduced response and lower repeatability at small population sizes. In a further study to investigate genetic drift Eisen and Hanrahan (1973) ascertained that small effective population sizes tended to cause greater divergence among replicates. Linear regressions of line means of the traits investigated on the inbreeding coefficient were significant indicating a significant effect of inbreeding on the traits, which included both preweaning and postweaning weights and rate of gain.

Thus, as with the experiments designed to examine genetic variance, results from experimentation on the effects of inbreeding on growth and body weight, especially in the postweaning phases, are somewhat contradictory, and may depend upon the specific population of animals used and its previous selection history.

Maternal Effects on Body Weight

The influence of the mother on the development of her offspring is a major factor in animal husbandry, as it will affect many economic traits. Extensive investigations of these influences have been carried out in laboratory species, especially the mouse. While care must be taken when attempting to extrapolate the findings to large animals, all

the data are useful in defining general trends and relationships that exist.

Legates (1972) has differentiated between the terms "maternal effects" and "maternal influences." The former are the measured phenotypic expressions arising from influences of the mother on a trait measured in her offspring. The latter refers to those things which condition the expression of the maternal effects. These result from her genotype and associated environmental factors.

There are two periods into which maternal influences can be divided. Prenatal factors are associated with the uterine environment and include such things as uterine capacity, and gestational nutrition. Postnatal influences include those factors operating after parturition. While temperment and maternal instincts are important, the major factor affecting growth and development of the young is lactational output.

Variance due to prenatal versus postnatal effects has been analyzed using the technique of embryo transfer and cross-fostering. Brumby (1960) transferred ova from Falconer's large and small strains to unselected control line dams, allowing these foster dams to raise the resultant offspring. His results indicated that the prenatal influences were as important as or more important than postnatal influences on growth of offspring.

Using the same type of technique significant uterine effects at birth and for 2-week weight were detected by Moore, Eisen and Ulberg (1970). The least squares estimates of uterine effects were 3. 9% and 4. 5% respectively for the two measurements. For weights taken at weekly intervals thereafter, up to 10 weeks, estimates of uterine effects were less than 1% of the mean. Cox, Legates and Cockerham (1959) and Miller, Legates and Cockerham (1963) upon analysis of measurements in the above population of mice found no evidence of non-additive genetic effects. Therefore, prenatal genetic variance for individual weights and gains subsequent to 12 days can be assumed to be primarily additive.

Postnatal influences are often assessed using cross-fostering techniques. Forty-nine cross-fostering groups of three mothers and 18 young each were studied by Young, Legates and Farthing (1965) with respect to the traits of weights at birth, 12 days and 21 days, and gain from birth to 21 days. Prenatal variance declined from 38% of the total variance at birth to 11% at 12 days after which it remained stable. Postnatal variance varied between 61% and 65% for the three weights and gain traits involved. Analysis of pre- and postnatal components for later weights and gains (weight at 42 and 56 days and gains from 21 to 42 days) showed persistent effects of prenatal influences of between 13% and 18% and of postnatal influences of between 4% and 22%, with effects on gain being the lowest. As

preweaning weights are components of later postweaning weights, a carryover of maternal influences would be expected for data on weights.

Earlier results of Bateman (1954) indicated that only 32% of the variance of 12-day weight was due to postnatal influences which is considerably lower than that found in other studies. This may be due to strain differences. Chai (1956a) found maternal influences on preweaning body size, in F_1 hybrids from crosses between strains of different body sizes, to contribute more than one-quarter of the total variation, a larger source than the genetic contribution.

Young and Legates (1965) mated females that had been cross-fostered and allowed them to rear their own litters in an attempt to detect postnatal influences on litter size and 12-day weight of the litter from cross-fostered females. Prenatal influences were found to be 14% and 20% for the traits, respectively, while postnatal influences accounted for 0% and 1% of the variance. In this study, litter sizes were standardized to six young, thus eliminating variation due to litter size on lactational performance.

The question of standardization of litters to eliminate variation due to this component was investigated by Nagi (1971). He showed that for 6 or 8 young per litter, the postnatal component represented 65% and 66% of the variance respectively. There were important differences in milk yield among dams as measured by weight increase from

1 hour nursing of the young at 12 days; however, the relative importance of the growth potential of the young, milk yield of the mother and other maternal factors on 12-day weight have not been fully clarified.

In another cross-fostering experiment, Rutledge et al. (1972) obtained results of a similar nature to others mentioned. They examined the composition of the phenotypic variance of several traits with reference to pre- and postnatal influences derived from the logistic and Richards growth functions. Variance due to actual dams was initially large but from day 6 to day 49 varied between 10% and 15% of the phenotypic variance. After day 49, this component became relatively more important. Variance due to foster dams peaked at 68% of the phenotypic variance at day 12 and progressively diminished thereafter. Diminishing effects of maternal environment were also noted by Kidwell and Howard (1969) and Monteiro and Falconer (1966), though the effects peaked at the fourth week.

The study of the magnitude and nature of the effects of increasing levels of inbreeding upon growth of the young and upon maternal ability of the postnatal dam were the objectives of White (1972), using the reciprocal cross-fostering technique. Increasing the levels of inbreeding of the dam was found to linearly depress postnatal maternal performance while increases of inbreeding of the young significantly depressed birth weight and weights at 12, 21, 42 and 56 days. In a related study White, Legates and Eisen (1968) hypothesized that

selection for increased body weight had increased maternal performance while selection for decreased weight had decreased maternal performance. Falconer (1955) related this same phenomenon to the relatively different sizes of the mammary glands in lines selected for body weight.

Hetherington (1972), in a study of paternal genotypic influences on certain physiological, gestational and fetal characteristics, found that the mean fetal weight of inbred litters, following a hybrid pregnancy and after corrections for litter size, was less than the fetal weight of inbred litters following an inbred pregnancy. These results were discussed in terms of the immunological status of the dam caused by the sires of the first and second litters, and point out that paternal influences which are commonly ignored in studies of the types described, should not be overlooked.

Selection experiments for preweaning traits, such as individual 12-day weight or for litter weight at day 12, have been somewhat successful though heritability estimates are generally lower than those for weight or gains in later life phases. Reporting the results of within-family selection for increased 12-day litter weights in four replicate lines over ten generations, Eisen, Legates and Robison (1970) obtained a realized heritability estimate of 0.11 ± 0.02 and an observed genetic gain of 0.25 ± 0.04 g per generation. A slight downward trend was attributed to the effects of accumulated inbreeding.

Analysis of the components of variance indicated that direct additive genetic variance for genes controlling growth in the individual accounted for 22.2% of the variance while postnatal maternal genetic variance accounted for only 6.1%. The total postnatal maternal environment accounted for 56.2% of the phenotypic variance in individual 12-day weight.

The results of a two-way selection experiment conducted by Dr. Nigel Bateman and reported by Falconer (1955) indicated that response to selection for increased lactational performance was successful but of short duration. The overall heritability was about 50% but when measured directionally, it was found that heritability realized in downward selection was five times greater than that in upward selection. Response to selection lasted only six generations at which time it plateaued. Reverse selection after the plateau was reached yielded an immediate and large response. The total range covered by the response amounted to only twice the original genetic standard deviation. Falconer concluded that the results indicated that natural selection opposed selection in either direction and prevented fixation of genes at both the high and low levels. The small total range showed that only a few genes are concerned with the major portion of the response.

Genotype-Environment Interactions

A major feature of most selection experiments using laboratory species is that they are normally carried out in an environment which has been as stabilized as facilities will permit. This stabilization reduces variance due to environmental differences and thus permits more accurate selection based more nearly on genotype. Whereas this procedure is consistent with the goals of a more theoretical analysis of selection response, it fails to describe the situation of the livestock breeder, for whom selection experiments are ultimately intended. In the actual practice of livestock breeding, a great variety of environmental conditions are encountered and thus, in genetic terms, any genotype-environment interaction may have a large influence on the achievement of selective breeding, if a breed improved under one set of conditions is transferred to an environment of a totally different nature.

Several investigations into the nature and magnitude of such interactions have been conducted. The theoretical groundwork was layed by Falconer (1952) in which a phenotypic measurement in two environments was regarded as two distinct characters. Genes operating favorably in both environments would then mean that the two "characters" were genetically correlated, thus permitting prediction of the progress expected of a character selected in one environment when

transferred to another. The general conclusion reached by Falconer was that animals, destined to be raised in a certain type of environment should be selected in it.

To further test the theory, Falconer and Latyszewski (1952) selected animals for high 6-week weight from the same base population under two nutritional regimes; one was fed ad libitum while the other was restricted to about 75% of the normal intake. Weights of both strains were increased by selection over eight generations; however, the strain on a reduced intake was about 10% lighter at 6 weeks of age. At the fifth, seventh and eighth generations, animals selected on one regimen were raised on the other. Animals selected on the full diet but raised on the restricted diet were much inferior to animals selected and raised on that diet. On the full diet, the animals selected on it were superior to those selected on the restricted diet, but only slightly so. The results indicate that animals should be selected in the environment where they will be raised.

While his basic premises were substantiated, Falconer's data were not in complete agreement with theory, since his derivations had indicated a symmetrical correlated response. Thus under prediction, the strain selected under full feeding should have shown considerable improvement on a restricted diet. It did not. To explore this situation further, Falconer (1960b) designed a second experiment similar to the first, with the difference being two-way selection under both

nutritional regimes, and instead of restricting intake, the low-plane diet was a diluted one fed ad libitum which had the effect of reducing weight by 20%. The diets were exchanged for samples of each of the two high and low lines each generation. The anomalies found in the first experiment persisted. When tested on full diet, the large mice selected on either diet performed equally well, but on the diluted diet, the large mice selected on the full diet were inferior. The small strain mice produced a mirror-image effect. Thus the conclusions reached in the 1952 study were reaffirmed with the additional provision that if selection must be carried out in only one environment, then it should be done in the environment least favorable to the desired expression of the character, within the range of environments normally expected. A corollary found in the experiment was that when tested on full diet, mice selected on a high plane were much fatter, though no heavier, than those selected on a low plane.

The asymmetrical response encountered by Falconer in both experiments remained unexplained. However, Bohren et al. (1966) designed a computer simulation study to examine patterns of change of genetic covariance between two characters being selected. Upon examination of the conditions necessary for asymmetry to exist, they found that only in special instances would symmetry exist, i. e., asymmetry is the more usual case. The most frequent contributor to asymmetry, in practice, was thought to be from loci contributing

negatively to the covariance and having allelic frequencies other than 0.5.

A study of a similar design to that of Falconer and Latyszewski's (1952) was conducted by Korkman (1961). The low diet had only enough nutritional value to allow the animals to survive and reproduce. A considerable selection differential was accumulated for animals on the low plane but no response to selection for 40-day weight was obtained. A normal response was obtained for animals on the high plane with a heritability estimate of 0.22. Korkman found that performance was best improved by selection on the nutritional plane on which performance was subsequently measured. He also noted a differential postnatal mortality with respect to strain and sex. Mortality was higher in the strain selected in the low plane and also in males. The differences between strains is to be expected considering the quality of diet they were on; however, the fact that the males were more affected by environmental differences was of interest. Previously (1957), Korkman had conducted an experiment which somewhat explained these findings. Two-way selection for sex difference was practiced based upon weight at 90 days of age. The highest male and lowest female (within litters) and vice versa were selected as parents of the next generation for the respective lines. Full-sib matings were avoided. Sex was thus regarded as a part of the environment in which the animal lived. In the high male-low female line, he

increased the sex difference from 2.2 g to 4.3 g while in the low male-high female line there was no decrease in sex difference. He also found that males were more retarded on low feed than females and that the difference between the sexes with regard to weight rests mostly on differential growth rates between 30 and 60 days of age. Thus a less adequate diet in this period would more severely affect the more rapidly growing male.

Dalton and Bywater (1963) reported a similar study using a full and diluted diet with selection being for high total litter weight at weaning. Fourteen generations of selection produced no response and no correlated response was obtained when the diets were switched. A possible explanation for the lack of response is that the trait, total litter weight, includes various factors such as litter size, milking ability, and growth. When a selection trait is compounded of several distinct traits, selection pressure is reduced on all of them and total response will be reduced. Also, the factors included in "total litter weight" are generally lowly heritable which will also reduce total response.

The above are examples of the attempt to build in a genotype-environment interaction through selection in modified environments. Another method of investigation is that of screening existing genotypes in several environments. Young (1953) tested three inbred strains on two diets at two temperatures. His results were negative and no

significant differences were noted among the strains. Summarizing previous work, Barnett (1965) showed that inbred strains adapted differentially to cold environments (-3°C). In many strains a change to cold resulted in reduced weight; after many generations, mouse weight had attained the control level. The adaptation was thus cumulative and Barnett reflected that as heterozygosity confers resistance on animals to the effects of cold that perhaps a balanced heterozygosity had been attained in his populations.

Roberts (1965) concluded, in a summary of the subject, that as genotype-environment interactions do not seem to be of a high magnitude unless a severe modification of the environment is created, interactions of this sort might be ignored in formal studies. However, the fact that they do exist must be remembered in practical selection programs.

Correlated Responses to Selection for Weight

In practical selection experiments, it is often less laborious to measure one character than another or in some instance, it may not be possible to measure a character until later in an animal's life or at all. As examples: body weight is simply measured whereas feed efficiency requires more labor; measurements on lactation may not be taken until maturity is reached and then only in females; it is not

commonly feasible to make counts of ovulations in litter bearing species. If characters are found which are easily measured and genetically related or correlated to those of interest, then selection pressure applied to these will enable progress to be made in the trait of interest, with the magnitude of progress depending upon the degree of correlation. Correlated measurements can also be used for predictive purposes with the accuracy of prediction also depending on the degree of correlation.

The laboratory mouse has been utilized in several studies designed to investigate the underlying causes of genetic correlations and the feasibility of their utilization in selection programs. Goodale (1938), MacArthur (1944b, 1949) and Falconer (1953a) had all noted that certain other changes occurred in their animals as they selected for body size. These included characters such as coat color, temperment and lengths of appendages. Falconer (1954) set out to verify the theory that if certain relevant parameters are known, then the expected correlated change can be predicted from theory. He selected one pair of lines for high and low 6-week weight while another pair of lines from the same base population was selected for long or short tails, respectively. Both parameters were measured in each of the two pairs of lines, thus giving him two estimates of the genetic correlation (0.62 and 0.57) between weight and tail length, which were in excellent agreement.

Cockrem (1959) used the same two characters to see if traits which had been shown to be positively correlated could be successfully selected to increase one while decreasing the other. Expected body weight was estimated from a regression equation of weight on tail length and then selections were made for both positive and negative deviations from the regression line. In one line, animals with greater body weight and shorter tails were selected while in the second line lighter weight, longer tailed individuals were selected. Selection produced rapid response over six generations; males in the line selected for positive deviations had weights 3.5 g greater and tails 2 cm shorter than corresponding parameters in the other line. Thus, it was shown that though genetic correlations of a high order may exist, this fact does not preclude the possibility of successful selection for various combinations of the correlated traits.

Because selection in livestock is normally not only for increased weight but also for efficiency of food utilization, increased growth rate and quality of the carcass, several studies have been initiated to determine the correlations of these with body weight. Hanrahan, Hooper and McCarthy (1973), McCarthy, Byrne and Hooper (1973) and McLellan and Frahm (1973) have all directed their research towards describing the changes which occurred in muscle weight and structure concomitantly with response to selection for weight. Muscle weight was found to be significantly and positively correlated with body weight.

The primary cause of change was a corresponding change in the fiber number and diameter of the muscle in the direction of the change in weight. Fowler (1958, 1962), working with lines previously selected for high and low body size, found that animals of the high strain consumed more feed and utilized it more efficiently than low line animals during the period of most rapid growth. Fat deposition was found to contribute very little to gains prior to 35 days of age, after which time fat deposition was the primary cause of gains. Rahnefeld et al. (1965) obtained a high and nearly perfect negative correlation between growth and feed efficiency. Total response to selection for post-weaning gains was 4.6 g or 43% over 17 generations of selection. For feed per unit gain, adjusted for average test weight, the correlated response of feed efficiency was -.10 per generation or -1.84 for 17 generations. Similar results were obtained by Lang and Legates (1969) with the additional observation that males were more efficient than females. Their data indicated also that the increased growth rate of the high line mice could not be attributed to increased fat deposition. The low line mice exhibited a temporary retardation of maximum growth rate due, in part, to an extended depression in growth following weaning.

Sutherland et al. (1970) established three lines and selected for feed efficiency, feed intake and rate of gain, respectively, observing the correlated responses in the two traits not being selected in each.

Rate of gain increased more rapidly in the line selected for feed efficiency and increased least rapidly in the line selected for feed intake. Feed intake increased most in the line selected directly for it with correlated responses in the other lines being somewhat equivalent. Feed efficiency increased most rapidly in the line selected directly for it and least rapidly in the line selected for feed intake.

Voluntary feed intake and efficiency was measured by Roberts (1973) in mice previously selected for weight compared with an unselected control. Results indicated that selection for body weight had caused changes both in voluntary intake and efficiency with the former having a somewhat greater relative effect.

Correlations found between pre- and postweaning growth by Frahm and Brown (1973) have been mentioned previously; the estimated correlation obtained being 0. 33. Timon and Eisen (1969), upon comparison of the growth curves of mice, selected and unselected for postweaning gain, found that though selection had increased growth rate there had been no effect on the shape of the growth curve. In contrast Monteiro and Falconer (1966) had found that with respect to preweaning growth, animals with a good maternal environment and rapid growth in this period reached sexual maturity earlier and entered the asymptotic phase of the growth curve earlier while litters with slow early growth entered this phase late. They define this as

compensatory growth which is achieved either by curtailment or prolongation of the exponential phase of growth.

Young and Legates (1965) obtained data which suggest that many of the same genes are acting on gains in the preweaning and first postweaning (21 to 42 days) periods but that different genes are operating on gains later in life (42 to 56 days). Large, positive maternal correlations also existed between various weights but correlations were negative between pre- and postweaning gains indicating that high milk production in the dam, allowing early high gains contributed to lower gains later, or poor milking performance necessitated compensatory growth in the offspring in the postweaning phase. Eisen, Legates and Robison (1970) in an experiment designed to investigate responses to selection for 12-day litter weight arrived at many of the same conclusions.

The traits of weight and gaining ability in individuals have thus been related to each other and to the food intake and conversion efficiency. In an attempt to probe more deeply into the physiological factors controlling these related characters, Synenki et al. (1972) examined the thyroid activity in strains of mice previously selected for high and low body weight. Uptake and turnover of ^{131}I were examined at different ages and a positive correlation between body weight at 6 weeks and thyroid activity was discovered.

Computer simulation studies (Parker, McGilliard and Gill, 1969, 1970), examining genetic correlation and response to truncation selection, showed that selection caused genetic correlation between the primary selected trait and an unselected secondary trait to decrease in offspring selected to become parents under either an additive or complete dominance model. The amount of reduction depended upon the intensity of selection or the heritability of the trait selected for the two models, respectively.

II. Genetic Analysis of Fertility and Litter Size in the Mouse

Litter size, as with weight, is an easily obtainable character when measured by the number of individuals born or alive at a specified time. It is, however, a patently complex character, involving factors of maternal and paternal genotype and physiology, as well as the genotype of the individual and embryonic viability. In addition, litter size and fertility are greatly influenced by the environment. Both are also intrinsically important characters in livestock production in that they affect several economic factors of importance and also affect the selection pressure that can be applied to other traits.

Maternal Effects and Selection for Litter Size

In order to understand the genetic interpretations of experimental

data concerning litter size, the most important non-genetic source of variation in litter size, maternal environment, should be explored.

It has been known for some time that larger mice produce larger litters (MacDowell, Allen and MacDowell, 1929). The larger the litter, the smaller will be the individuals in the litter, due primarily to less milk available per mouse and decreased uterine space available per young. Animals from the large litter will then have smaller litters comprised of individuals who will themselves be larger, as a consequence of being reared in a small litter, and so forth. The net effect of this cycle would be a negative regression of litter size on the size of the litter in which the dam was born and reared. It would also seem plausible to expect a positive genetic pathway for litter size. Falconer (1955) calculated standardized partial regression coefficients linking litter size to maternal body weight and the size of litter in which the dam was born. As expected, the body weight of the dam was negatively correlated with the size of the litter in which she was born and positively correlated with the litter size she produced. The product of the two partial regression coefficients was -0.07 while the direct genetic pathway measured as the partial regression of litter size on maternal litter size (weight of dam constant) was +0.07. Thus the two paths are of equal magnitude and of opposite sign, giving the observed direct regression of zero for litter size on maternal litter size. These results were again realized in a more sophisticated

study by Falconer (1964) in which he concluded that the influence on litter size through body weight was an adequate explanation of observed maternal effects on litter size.

There are two possible areas where the above facts could be realized. Either there is a differential ovulation rate or a differential pre- or post-implantation mortality of embryos, associated with body size. Fowler and Edwards (1960) compared the fertility in two lines, each of which had previously been selected for high and low body weight. In one line, fertility in the small strain had been impaired by delayed estrus, failure to ovulate and failure of embryos to implant. Hormonal treatment was sufficient to alleviate the condition. In the other line, the number of eggs ovulated was correlated with body weight. The authors concluded that differences between the two lines rested in a differential pituitary activity.

Land and Falconer (1969) effectively selected for high and low induced and high and low natural ovulation rate. They concluded that additive variance was present with respect to rate of ovulation and that the increases in ovulation rate observed were due to increased FSH (follicle stimulating hormone) activity. Decreases were due to decreased ovarian sensitivity to FSH. The correlation between natural and induced ovulation rates was 0.33, which may indicate that different genes control the responses obtained. McLaren (1962) and Land (1970) have presented similar evidence. It is then hypothesized that

ovulation rate has two components: pituitary gonadotrophin level and ovarian sensitivity to such hormones. Bradford (1971a) states that it is the former which shows the stronger association with body weight. In the course of a selection experiment for litter size in which body weight was declining, results suggested that the paths of pituitary output and ovarian sensitivity were operating counter to each other, and the former exerted the overriding influence. Bradford (1971b) also presented evidence that selection affected the degree of prenatal loss but that this was not associated with changes in body weight. Previously, Bradford (1968) had obtained data indicating that the use of ovulatory hormones was ineffective in improving litter size through selection, as its use obscured the genetic effects.

Falconer (1955, 1960c, 1963, 1964), in a series of experiments designed to explore the various facets of selection for litter size, obtained a linear response over 20 generations which then remained relatively stable over a further 11 generations. At the limit, the high line averaged 9.2, the low 6.0 and the control 7.6 mice. The response was thus symmetrical; however, when looked at in terms of selection differential, the response was greater in the low line with a realized heritability of 23% versus 8% obtained for the high line. The divergence of 3.2 mice was 1.6 times the original phenotypic standard deviation and 3.3 times the additive genetic standard deviation. These then are very small when compared to responses to selection for body

weight. When the causes of the asymmetry were examined, it was found that progress in the high line was due to increased ovulation rate. However, the ovulation rate in the low line had also increased compared to that of the control. The reduction in litter size in the low line was attributed entirely to a marked increase in post-implantation death. Crosses between selected lines and the control indicated that the increased mortality was attributable to the dams and not to the embryos. Selection had most likely rapidly increased the frequency of deleterious recessives, that were initially at low frequencies. The increased ovulation rate in the low line females remained unexplained.

Another selection experiment was reported by Bateman (1966) which generally confirmed results obtained by Falconer. He also found that decreased litter size in his low line was due to failure of implantation, and that this was a property of the strain of dam. Dalton and Bywater (1963) selected for litter size at weaning on both normal and diluted diets. No response was obtained for either high or low selection, possibly indicating that the heritability was very much lower for litter size at this stage.

The Effects of Inbreeding and Components of Variance for Litter Size

Inbreeding depression and heterosis, with respect to reproductive processes, are consistent features in experiments dealing with

normally outbreeding species. The mouse is no exception. Castle (1926) and Gruneberg (1939) both noted the phenomenon that fertility is raised in crossbred animals. McCarthy (1965) reported an experiment specifically designed to measure the effect of crossing inbred lines on litter size and found, in three of his four crosses, an increase in litter size. The increases were all attributable to reduced frequency of early post-implantation losses and he interprets this in terms of heterosis of embryonic viability. In a similar study, Martin, Harrington and Hill (1963) crossed four strains in a complete diallel and found that the implantation rate was higher for crossbred litters. Crossbred dams had the same ovulation rate as purebred dams but thereafter the litter size was larger for crossbred dams at all stages of gestation. Interestingly, for pureline matings, 36% of the embryonic mortality occurred after implantation. In purebred dams with crossbred litters, the figure rose to 58% and when dams were crossbred the figure rose to 100%. Thus, crossbreeding in mice, which usually results in increases in litter sizes, is primarily associated to a greater extent with crossbreeding of the dam rather than crossbreeding of the litter. Roberts (1960a) agreed with this hypothesis stating that inbreeding may impose a limit on the dam's potential fertility and that no amount of heterozygosity in the young would increase litter size above a certain level. The heterosis observed suggests a greater degree of non-additive genetic variation in litter size than was previously noted for body weight and growth.

Martin, Harrington and Hill (1963) analyzed their F_1 data and found that specific combining ability was a more important source of variation than was general combining ability.

Miller, Legates and Cockerham (1963) partitioned the total variance for litter size into additive and non-additive components and found the latter to contribute 58% of the total genetic variance while only 42% was attributable to additive sources. However, an attempt by Bowman (1962) to exploit non-additive genetic variation, by the use of a recurrent selection scheme, determined that the increases gained were no more than would have been expected if all the variance present were of an additive nature. The initial hybrid generation was above the mid-parent average, so some dominance was indicated. Bowman concluded that either the recurrent scheme was ineffective or that no non-additive variance was present (apart from some dominance) in this stock. It seems then that although ample evidence of non-additivity in litter size exists, attempts to utilize it have been somewhat unsuccessful.

Examinations of the causes of inbreeding depression seen in litter size, which is often described as the "other side of the coin" from heterosis, have been made to further elucidate the situation. Braden (1957) found the incidence of abnormal eggs no higher in inbred than in non-inbred females. Inbreeding in the female parent increases the loss of eggs or early embryos between ovulation and implantation

but does not increase post-implantation losses. Pre-implantation losses were also not attributable to inbreeding of the sire. Again was noted a positive association between body weight and ovulation rate. As inbreeding increases, followed by a decrease of body weight, the number of eggs should also decrease. Therefore, genes influencing ovulation rate without influencing body size do not show directional dominance but genes affecting ovulation rate as a consequence of their effect on body size may show directional dominance (Falconer and Roberts, 1960). Bradford (197 la) agreed with this theory with the additional statement that genes controlling pre-implantation losses also showed some directional dominance, in that he found some heterosis for this character, while genes controlling post-implantation losses acted additively.

Bowman and Falconer (1960) conducted a simple selection experiment with full-sib matings for litter size. Only three lines survived 12 generations of selection. The surviving lines had lower litter sizes initially and showed no decline upon inbreeding. These lines were then subjected to three cycles of inbreeding and crossing. Litters produced by crossbreds were larger than the non-inbred control by two mice in the first cycle but no increase was obtained in the second or third cycles. The authors concluded that the behavior of these lines in the inbreeding and crossing experiment points to simple dominance rather than over-dominance at loci causing variation of litter size.

It appears that while the heterosis produced by crossbreeding affects the post-implantation stages of gestation, the depression of litter size by inbreeding is mediated through pre-implantation losses while ovulation rate is less affected by either and is more related to body size. For all phases, however, some form and degree of non-additivity is present, and may be the significant component of the total genetic variance.

MATERIALS AND METHODS

Animal Handling

Randombred, Swiss Webster (Sim/WS) mice obtained in January, 1971 from Simonsen Laboratories, Inc., Gilroy, California, were used to form the initial breeding population. The colony was housed in the Small Animal Laboratory, Oregon State University, Corvallis, Oregon. The facility was kept at 80°F in the winter months and varied with external temperatures during the summer months. Animals were fed, ad libitum, a pelleted laboratory mouse chow prepared by the Oregon State University Feed Mill. The formula for the chow was altered after data on animals of Generation 0 were obtained. The formulae for the two rations are listed in Table 1. Water was available at all times from standard dispensers. The breeding groups were placed in 7" x 7" x 9" cages having half-inch mesh fronts and bottoms. When females were in the later stage of pregnancy they were removed and placed in individual 7" x 7" x 9" cages having quarter-inch mesh fronts and bottoms. Littering cans, 4" in diameter and 3" high, filled approximately one-third full of dry sawdust, were placed in the littering cages. One or two food pellets were placed within the cans to lure the females in. Only in rare instances were litters born outside the cans. Pregnant females were checked at approximately the same time

Table 1. Ration formulations.

Ingredient	lb/T	%
Ration I[a]		
Alfalfa	140	7.0
Wheat	714	35.7
Barley	600	30.0
Soybean meal	300	15.0
Herring meal	100	5.0
Lard (tallow)	60	3.0
Molasses	60	3.0
Trace mineralized salt	10	0.5
Limestone	16	0.8
Vitamin A	1,200,000 IU/T	
Vitamin D	120,000 IU/T	
Bentonite	75 lb/T added as a binding agent	
Ration II[b]		
Alfalfa	200	10.0
Wheat	1200	60.0
Soybean meal	240	12.0
Herring meal	140	7.0
Dried whey	160	8.0
Lard (tallow)	40	2.0
Trace mineralized salt	10	0.5
Dicalcium phosphate	14	0.7
Vitamin A	1,000,000 IU/T	
Vitamin D	120,000 IU/T	

[a]Used through May, 1971.

[b]Used through the remainder of the study.

each day for new litters and the dates of birth were recorded. Initially, litter size and litter weight were also recorded; however, all litters handled in this manner were cannibalized by their dams. Litter size was obtained at 14 days of age and data on litter size include stillbirths and postnatal death. All mice within each litter were identified by dye spots (5 percent picramic acid in 95 percent ethyl alcohol) at 14 days of age. Mice were weaned at 21 days of age by removal of the dam, and they were sexed at 24 days of age. At 32 days of age, males and females were separated and they were subsequently housed by sex and litter until selection and mating. On the average, four to five mice were housed together from 32 days of age until mating. Matings were made at 75 to 80 days of age with the exception of mice in Generation 3, which were not mated until they were approximately 120 days of age. Matings in this generation were delayed in an attempt to alleviate a severe disease problem in the colony.

Selection and Design

Animals were weighed at 14, 24 and 32 days of age and the weights were recorded to the nearest 0.01 gram for each individual. In five instances, the date for weighing was miscalculated and weights were recorded at 25 or 26 days of age. For these litters, the following correction formula was applied to approximate the correct weights:

$$\text{24-day weight} = \left(\frac{\text{weight at day of weighing - 14-day weight}}{\text{number of days between day of weighing and 14 days}}\right)(10) + \text{14-day weight} \quad (10)$$

Selection of young to become parents of the following generation was based on an index calculated from the following formula:

$$\text{Index} = \left(\frac{\text{14-day weight}}{\text{14 days}}\right) + (4)\left(\frac{\text{32-day weight - 24-day weight}}{\text{8 days}}\right).$$

The index formula was designed to intensify selection pressure on genes for lean gain. Fowler (1958) reported that fat deposition contributed very little to gains in mice made prior to 35 days of age, but was primarily responsible for gains made thereafter. Young and Legates (1965) and Eisen et al. (1970) determined that many of the same genes for gain are acting in the preweaning and first postweaning (21 to 42 days of age) periods but that different genes are operating for gains later in life. It has also been shown that maternal effects are greatest in the preweaning period (Falconer, 1964; Young, Legates and Farthing, 1965; Young and Legates, 1965; El Oksh, Sutherland and Williams, 1967; Kidwell and Howard, 1969; Eisen, 1970; Rutledge et al., 1972; Stanier and Mount, 1972).

An attempt was made, therefore, to emphasize early postweaning gain by multiplying that portion of the index formula by a factor of 4. As the mice were weaned at 21 days of age, weights taken at 24

days of age allowed for a 3-day period during which weanlings could acclimatize to a total dry feed regimen. It was noted throughout the study that generally the young were already consuming a considerable amount of dry feed at the time of weaning.

From the initial purchased population, males and females were randomly selected to form 30 breeding pairs or replicates. Litters produced by these pairs constituted animals of Generation 0. Subsequent generations produced through selection are designated Generations 1 through 5.

Indexes were calculated for animals in Generation 0 and the highest male and female and the lowest male and female were selected within a litter to be progenitors of the next generation of the high and low lines of a replicate, respectively. After Generation 0, only the highest male and female within the litter were selected to be parents in the high line. The lowest male and female were selected to be parents in the low line. Each of 30 replicates thus, at Generation 1, consisted of two lines, high and low. Only full-sib matings were made, and generations were kept non-overlapping with all animals within a generation having the identical coefficient of inbreeding. Litters within a generation, however, were produced over a span of about 6 weeks. This span was caused by the occurrence of a severe disease problem which necessitated, in later generations, repeat matings.

The attempt was made at all times to use first litters. In some instances, this was not possible. From Generation 2 onward, secondary matings were made. For example, the highest male or two highest males would be mated to the two highest females. Because of the design of the experiment, only one breeding pair initially represented the high or low line of a particular replicate. If this mating proved sterile the line was lost. Secondary matings provided some insurance for line continuation. It was also noted that animals which had been severely affected by the disease were frequently sterile. Secondary matings again provided some insurance. When a litter was decimated by disease, the parents were remated. Therefore some second parity litters are represented in the data. If the second mating of the highest or lowest ranked parents proved sterile or the litter was again stricken by disease, the litter produced by the secondary mating was used for selection and line continuation.

Due to the sterility problems often encountered in a program utilizing close inbreeding which were compounded by the disease situation, only nine replicates of the original 30 were suitable for analysis at the termination of the experiment at Generation 5. The replicates used all had data for both high and low lines through the third generation. After that time, each generation is represented by differing numbers of replicates. Generation 5 data consist of information from three high lines and three low lines from five replicates.

All but one line each of high and low from separate replicates were lost after Generation 5.

Disease

A disease struck the colony during the growth period of the second generation. Litters produced in Generations 0 and 1 were seemingly free of symptoms although the disease was present in other populations kept in the Small Animal Laboratory. The specific pathogen was never definitely diagnosed and no medicinal treatments were ever prescribed by the laboratory supervisor beyond germicidal cleansers used in the normal processes of cage and water dispenser care.

The afflicted animals became noticeably ill by approximately 18 days of age. Early symptoms included rough fur, lethargy and loose feces. As the disease progressed, afflicted animals refused feed, lost weight or grew very slowly, moved only rarely and had a noticeably hunched stance. Generalized tremors were seen in about 50 percent of those severely affected. Animals which succumbed were usually comatose several hours before death and had much reduced body temperatures as measured by touch. In general, whole litters were affected, with varying degrees of severity within a litter. Severely affected litters had a mortality rate of from 60 to 100 percent. Surviving animals regained their health usually by 32 days of age.

The majority were stunted, often weighing one-half to two-thirds the amount that normal individuals of the generation weighed.

By the third generation, nearly all the animals of the entire colony were affected. At this time, animals were permitted a longer period of growth before being mated, extending the generation interval for this group. The litters produced by these animals (Generation 4) were much less affected; however, the disease again became widespread in Generation 5, at which time the experiment was terminated.

Statistical Analyses

Data collected on index, 14-day weight, 24-day weight, 32-day weight and litter size at 14 days were each subjected to a least squares analysis. The least squares model for the first four variables listed above is as follows:

$$Y_{r\ell giwpatk} = \mu + R_r + L_\ell + G_g + LG_{\ell g} + S_i + W_w + P_p + D_a + DL_{a\ell} + DG_{ag} + T_t + TL_{t\ell} + b(M-\overline{M}) + E_{r\ell giwpatk}$$

where:

$Y_{r\ell giwpatk}$ = index, 14, 24 or 32 day weight of the k^{th} individual of the i^{th} sex in the ℓ^{th} line in the g^{th} generation of a random or selected nature (r) born in the w^{th} season in the p^{th} litter of the dam affected or not affected by disease (a) in the t^{th} replicate

μ = the population mean

R_r = the effect common to random (Generation 0) or selected (Generations 1 through 5) individuals

L_ℓ = the effect common to the ℓ^{th} line

G_g = the effect common to the g^{th} generation (excluding Generation 0)

$LG_{\ell g}$ = the effect common to members of the ℓ^{th} line in the g^{th} generation

S_i = the effect common to the i^{th} sex

W_w = the effect common to individuals born either in the winter months (November through April) or in the summer months (May through October)

P_p = the effect common to individuals born in the first or second litter

D_a = the effect common to individuals affected or not affected by disease

$DL_{a\ell}$ = the effect common to members of the ℓ^{th} line affected or not affected by disease

DG_{ag} = the effect common to members of the g^{th} generation affected or not affected by disease

T_t = the effect common to individuals in the t^{th} replicate

$TL_{t\ell}$ = the effect common to individuals of the t^{th} replicate of the ℓ^{th} line

$b(M-\overline{M})$ = the partial regression of index, 14, 24 or 32 day weight on litter size at 14 days post partum

$E_{r\ell giwpatk}$ = random errors that are assumed to be independent and normally distributed with mean = 0 and common variance, σ^2

The least squares model for litter size 14 days post partum is as follows:

$$Y_{r\ell gwptk} = \mu + R_r + L_\ell + G_g + LG_{\ell g} + W_w + P_p + b_1(D-\overline{D})$$
$$+ b_2(DL_{1i} - \overline{DL}_1) + b_3(DL_{2i} - \overline{DL}_2) + b_4(DG_{1j} - \overline{DG}_1)$$
$$+ \ldots + b_8(DG_{5j} - \overline{DG}_5) + E_{r\ell gwptk}$$

where:

$Y_{r\ell gwptk}$ = the size of the k^{th} litter of the ℓ^{th} line in the g^{th} generation of a random or selected nature (r), born in the w^{th} season in the p^{th} litter of the dam in the t^{th} replicate

μ = the population mean

R_r = the effect common to random (Generation 0) or selected (Generations 1 through 5) litters

L_ℓ = the effect common to the ℓ^{th} line

G_g = the effect common to the g^{th} generation (excluding Generation 1)

$LG_{\ell g}$ = the effect common to litters of the ℓ^{th} line in the g^{th} generation

W_w = the effect common to litters born either in the winter months (November through April) or in the summer months (May through October)

P_p = the effect common to litters of first or second parity

$b_1(D-\overline{D})$ = the partial regression of litter size on the percentage of the litter not afflicted by disease

$b_2(DL_{1i}-\overline{DL}_1)$ and $b_3(DL_{2i}-\overline{DL}_2)$ = the partial regressions of litter size in the designated lines (1 or 2), where i = the litter size within the line, on the disease incidence

$b_4(DG_{1j}-\overline{DG}_1)$ through $b_8(DG_{5j}-\overline{DG}_5)$ = the partial regressions of litter size in the designated generations (1 through 5), where j = the litter size within the generation, on disease incidence

T_t = the effect common to litters in the t^{th} replicate

$TL_{t\ell}$ = the effect common to litters of the t^{th} replicate of the ℓ^{th} line

$E_{r\ell gwtpk}$ = random errors that are assumed to be independent and normally distributed with mean = 0 and common variance, σ^2

Litter means for the raw data were calculated and were used in the formulation of selection differentials for index and for 14, 24 and 32-day weights. This was done by calculating the mid-parent average for animals selected to become parents of the next generation and subtracting from it the mean of the litter from which the animals were selected. It was found that selection differentials for the high and low lines were generally of similar magnitude and opposite sign. Since the least squares analyses indicated that environmental factors exerted significant influences upon the individual indices and weight variables, it was deemed necessary to correct the raw data for the effects of these environmental factors. The appropriate least squares constants, obtained through the least squares analyses of variance, were utilized for this purpose. Data were corrected for the following effects: sex, season, parity, disease, disease x line interaction, disease x generation interaction, replicate and litter size.

From the adjusted data, gain in grams was obtained for the following periods: 14 to 24 days of age, 24 to 32 days of age and 14 to 32 days of age.

Selection differentials were calculated for 14, 24 and 32 day weights, gains during the periods between these weights and for index. The selection differentials were computed as the difference between the mean of the young selected from the litter to become parents of the next generation and the litter mean. These differences were then weighted by the number of offspring produced by the selected mice to account for any bias produced by (1) differential prolificacy between lines selected for high or low weight or (2) increased inbreeding (Falconer, 1953a).

The adjusted values for the seven variables were also used to calculate response obtained through selection from one generation to the next. This was done by finding the difference between the respective litter means.

The averages of the weighted selection differentials and responses for each of the seven variables were then obtained over all replicates for each generation. The cumulative weighted selection differentials and responses were obtained by summation across generations (Falconer, 1953a).

The values obtained for the divergence between lines were calculated by subtraction of the low line mean value from the high line

value within generation. Positive divergence indicates that the high line mean was larger than that of the low line for particular generation. A negative divergence describes the situation in which the low line mean for the generation exceeded that of the high line.

Coefficients of inbreeding were calculated by the method described by Wright (1922). The formula is as follows:

$$F_x = \Sigma \left[(1/2)^{n_1+n_2+1} (1 + F_A) \right]$$

where:

F_x = the coefficient of inbreeding of the individual of interest, x

F_A = the coefficient of inbreeding of the common ancestor, A

n_1 = the number of generations from the sire of x back to A

n_2 = the number of generations from the dam of x back to A

The summation sign signifies that contributions to inbreeding in the pedigree of all common ancestors should be totaled.

Effective population sizes were calculated using the formula from Li (1955):

$$N_e = \frac{N}{1 + F}$$

where:

N_e = the effective population size of the breeding population of a generation

N = the actual number of breeding individuals in a generation

F = the coefficient of inbreeding of the breeding individuals.

RESULTS AND DISCUSSION

Responses to Selection for Index and Related Variables

The least squares analyses of variance of index, 14-day weight, 24-day weight and 32-day weight are presented in Tables 2 through 5, respectively. From these tables it can be seen that the sources of variation affecting the variables were generally significant. The only exception was the disease x line interaction for all variables. Considering the magnitude of F-values for the sources of variation affecting 14, 24 and 32-day weights, no general trends in F-values are evident for generation, parity or replicate sources of variation. The unselected Generation 0 is significantly different from the subsequent selected generations for 14 and 32-day weights as shown by the high significance of the F-values for the random versus selected source of variation. However, the F-value lacks significance for the 24-day weight. This lack of significance may be due to the stress of weaning overshadowing differences due to feed change and the increase in inbreeding. The sex effect increases throughout the growth period. Nash and Gowan (1962) found that males were heavier at birth. This difference vanished by 12 days and reappeared at about 26 days. Thereafter, males gained at a more rapid rate.

The effect of season of birth decreased as the animals increased

Table 2. Least squares analysis of variance of sources of variation affecting index.

Source of variation	d. f.	Mean square	F
Total	585	--	--
Regression	37	2,456,426.32	337.136***
Mean	1	319,587.57	43.862***
Random vs. selected	1	379,056.15	52.024***
Line	1	512.25	0.070
Generation	4	137,879.96	18.924***
Line x Generation	4	18,215.78	2.500*
Sex	1	604,928.81	83.024***
Season	1	3,914.03	0.537
Parity	1	236,654.34	32.480***
Disease	1	1,256,204.42	172.410***
Disease x Line	1	1,148.31	0.158
Disease x Generation	4	122,936.51	16.873***
Replicate	8	85,036.76	11.671***
Replicate x Line	8	17,885.87	2.455*+
Litter size	1	58,799.47	8.070***
Error	548	7,286.16	--

*Significant at the 5.0 percent level of probability.

*+Significant at the 2.5 percent level of probability.

***Significant at the 0.5 percent level of probability.

Table 3. Least squares analysis of variance of sources of variation affecting 14-day weight.

Source of variation	d. f.	Mean square	F
Total	585	--	--
Regression	37	781.60	1,012.019***
Mean	1	1,067.40	1,382.068***
Random vs. selected	1	55.32	71.624***
Line	1	2.95	3.816+
Generation	4	14.06	18.206***
Line x Generation	4	6.37	8.254***
Sex	1	1.26	1.636
Season	1	56.22	72.795***
Parity	1	6.68	8.646***
Disease	1	10.89	14.102***
Disease x Line	1	0.02	0.028
Disease x Generation	4	1.14	1.476
Replicate	8	5.69	7.363***
Replicate x Line	8	4.39	5.690***
Litter size	1	179.59	232.538***
Error	548	0.77	--

+Significant at the 10.0 percent level of probability.

***Significant at the 0.5 percent level of probability.

Table 4. Least squares analysis of variance of sources of variation affecting 24-day weight.

Source of variation	d. f.	Mean square	F
Total	585	--	--
Regression	37	2, 991. 79	490. 682***
Mean	1	3, 713. 89	609. 113***
Random vs. Selected	1	9. 77	1. 603
Line	1	84. 39	13. 842***
Generation	4	148. 20	24. 392***
Line x Generation	4	33. 85	5. 552*+
Sex	1	87. 71	14. 386***
Season	1	394. 84	64. 757***
Parity	1	173. 56	28. 465***
Disease	1	143. 58	23. 549***
Disease x Line	1	15. 05	2. 469
Disease x Generation	4	12. 04	1. 975+
Replicate	8	27. 98	4. 589***
Replicate x Line	8	29. 22	4. 792***
Litter size	1	390. 02	63. 968***
Error	548	6. 10	--

+Significant at the 10. 0 percent level of probability.

*+Significant at the 2. 5 percent level of probability.

***Significant at the 0. 5 percent level of probability.

Table 5. Least squares analysis of variance of sources of variation affecting 32-day weight.

Source of variation	d. f.	Mean square	F
Total	585	--	--
Regression	37	6, 588. 27	724. 765***
Mean	1	4, 502. 05	497. 243***
Random vs. Selected	1	183. 47	20. 184***
Line	1	88. 46	9. 732***
Generation	4	72. 57	7. 984***
Line x Generation	4	13. 44	1. 479
Sex	1	640. 37	70. 446***
Season	1	315. 99	34. 761***
Parity	1	11. 10	1. 221
Disease	1	1, 147. 22	126. 204***
Disease x Line	1	12. 14	1. 336
Disease x Generation	4	26. 31	2. 895*
Replicate	8	89. 39	9. 833***
Replicate x Line	8	36. 20	3. 982**
Litter size	1	156. 23	17. 187***
Error	548	9. 09	--

*Significant at the 5. 0 percent level of probability.

**Significant at the 1. 0 percent level of probability.

***Significant at the 0. 5 percent level of probability.

in age. This is consistent with other work (Young, Legates and Farthing, 1965; El Oksh, Sutherland and Williams, 1967) which determined that effects of maternal environment decrease with increasing age of young.

Disease exerted a progressively greater influence on the weights as the animals grew, and also the disease x generation interaction increased as the mice became larger. While the symptoms of the disease were not apparent at 14 days of age, it is likely that the animals were in the initial stages of infection at this time. With the exception of Generation 4, more animals were afflicted in each succeeding generation, which would account, in part, for the trend in the magnitude of the interaction term. The effect of line generally increases while the effect of the line x generation interaction decreases as the animals increase in age. The magnitudes of the F-values for the replicate x line interaction decrease through the growing period. The causes for this decrease are not clear, as no trend can be noted for replicate, and the trend for the source of variation of line is an increasing one. There is a definite decrease in the effect of size of litter on weight of mice with increasing age from 14 to 32 days. It is generally recognized that the effects of maternal environment are decreasingly important as animals develop to maturity (Falconer, 1964; Rutledge et al., 1972).

The least squares means for lines, generations, and lines

within generations for the variables of index, 14-day weight, 24-day weight and 32-day weight are presented in Tables 6 through 9 and are illustrated in Figures 1 through 4, respectively. Means fluctuate greatly from generation to generation for all variables. With the exception of the data for index, the means for Generation 4 are highest. The animals of this generation were generally free of disease which may account for the increased values. For each of the variables, the pooled generation mean for the high line exceeds that for the low line, although the difference between the means lacks significance.

Full-sib matings were made each generation; consequently, the coefficient of inbreeding increased identically for all mice with each succeeding generation. Since full-sib matings were employed, the level of inbreeding is confounded with generations. This also means that inbreeding level is confounded with responses to selection. The values of the inbreeding coefficients for each generation, as calculated by Wright's (1922) method, are listed in Table 10.

In Table 11 are listed the means, standard deviations and coefficients of variation for index and 14, 24 and 32-day weights. The smaller coefficient of variation for 14-day weight can be explained on the basis that 14-day weight is partly a measurement of the nursing ability of the dam. Thus, less variation should be found within litters which might result in a reduction of overall variation.

Table 6. Least squares means of index by lines, generations, and lines within generations.

Generation	Line	
	High	Low
0[a]	202.3	202.3
1	192.4	179.3
2	347.4	325.1
3	243.8	252.2
4	272.5	223.7
5	192.9	246.0
0-5	241.9	238.1

[a]Generation 0 is random and unselected.

Table 7. Least squares means of 14-day weight by lines, generations and lines within generations.

Generation	Line	
	High	Low
0[a]	6.49	6.49
1	7.05	7.01
2	6.61	6.25
3	7.20	6.20
4	8.04	8.66
5	7.14	6.22
0-5	7.09	6.81

[a]Generation 0 is random and unselected.

Table 8. Least squares means of 24-day weight by lines, generations and lines within generations.

Generation	Line	
	High	Low
0[a]	14.27	14.27
1	15.25	14.61
2	11.85	11.07
3	14.75	11.74
4	18.15	16.98
5	15.72	12.17
0-5	14.99	13.47

[a]Generation 0 is random and unselected.

Table 9. Least squares means of 32-day weight by lines, generations and lines within generations.

Generation	Line	
	High	Low
0[a]	19.47	19.47
1	18.66	17.80
2	18.42	17.26
3	18.93	16.45
4	22.82	20.83
5	19.11	16.25
0-5	19.56	18.01

[a]Generation 0 is random and unselected.

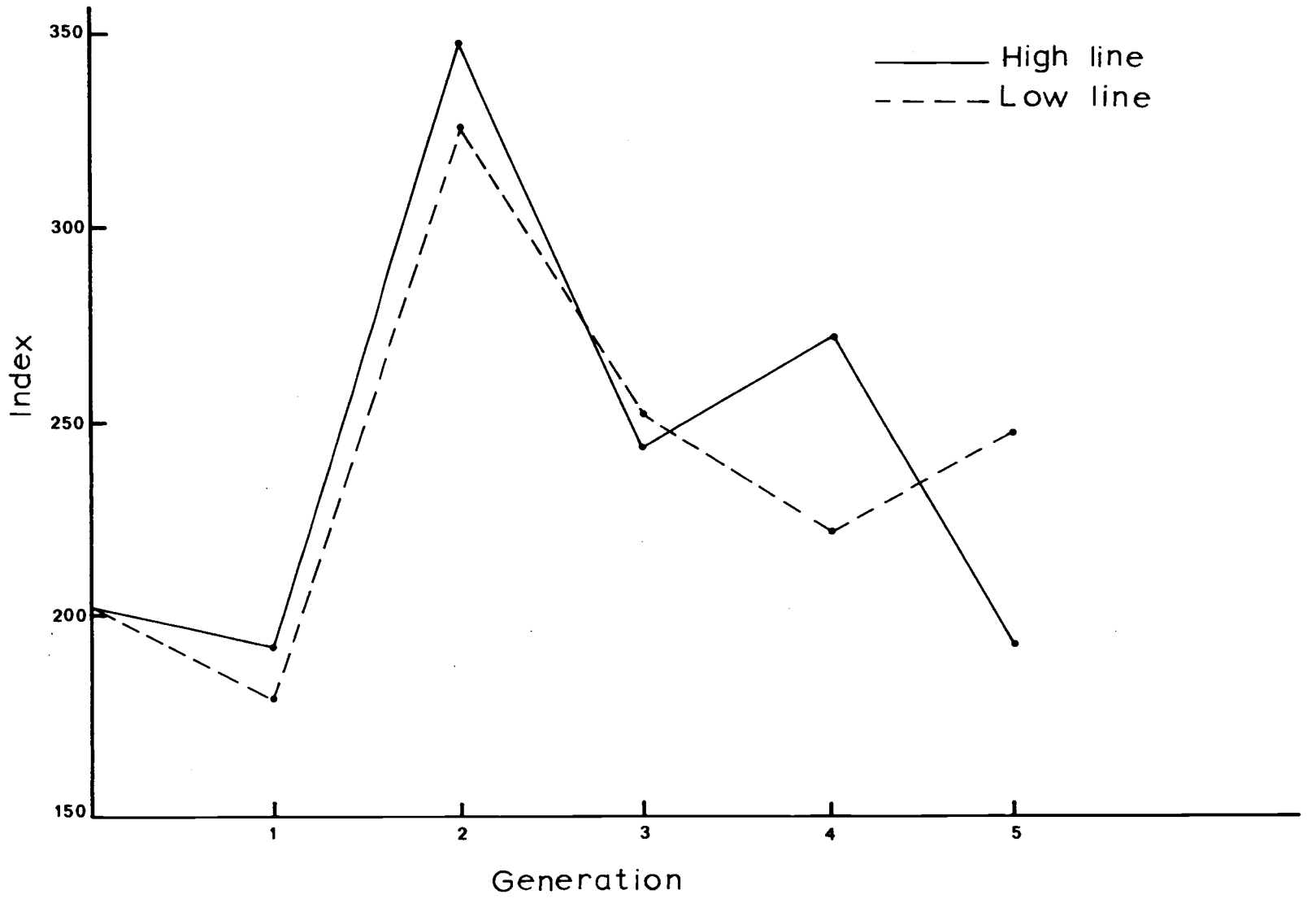

Figure 1. Mean index for high and low lines by generation.

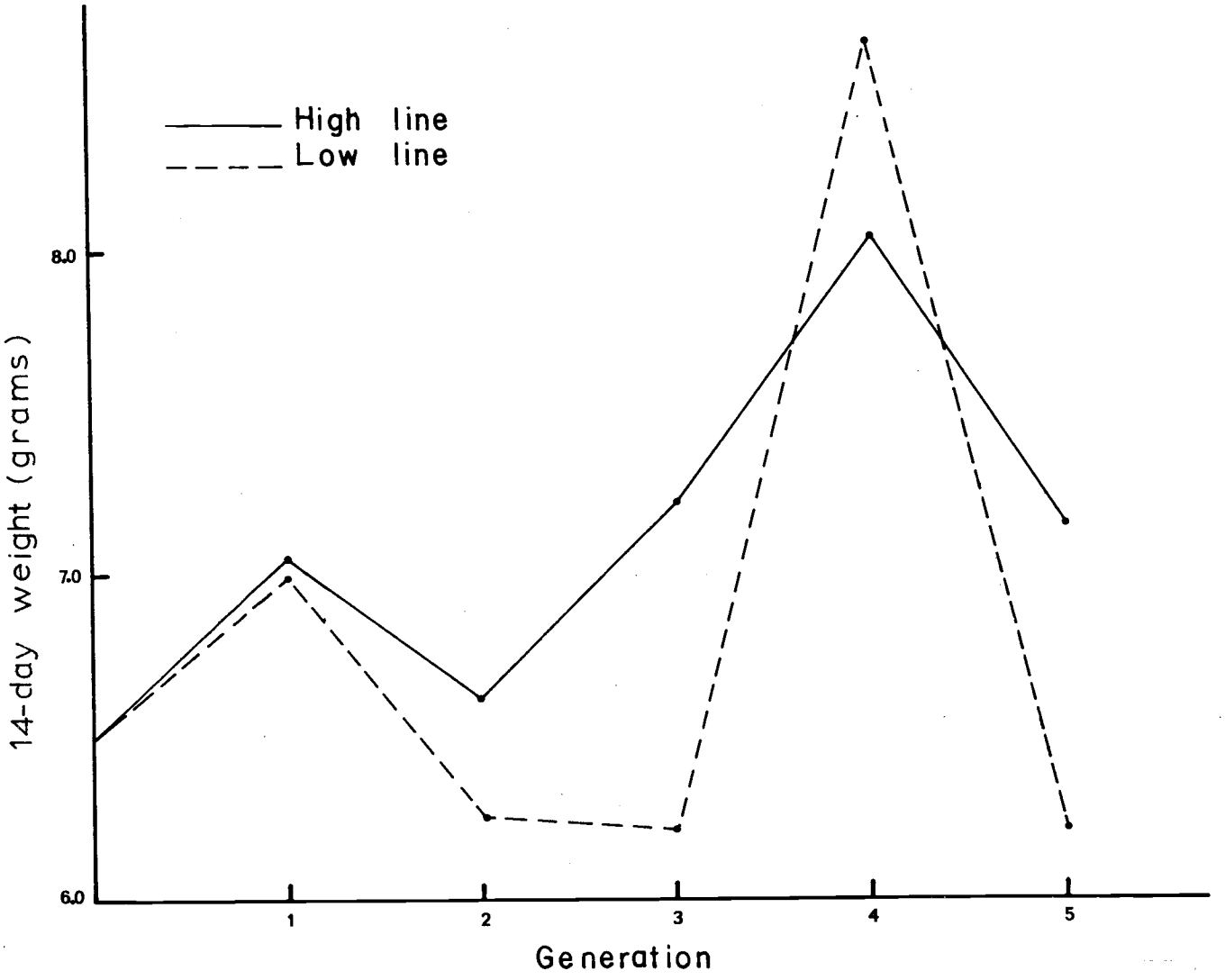

Figure 2. Mean 14-day weight for high and low lines by generation.

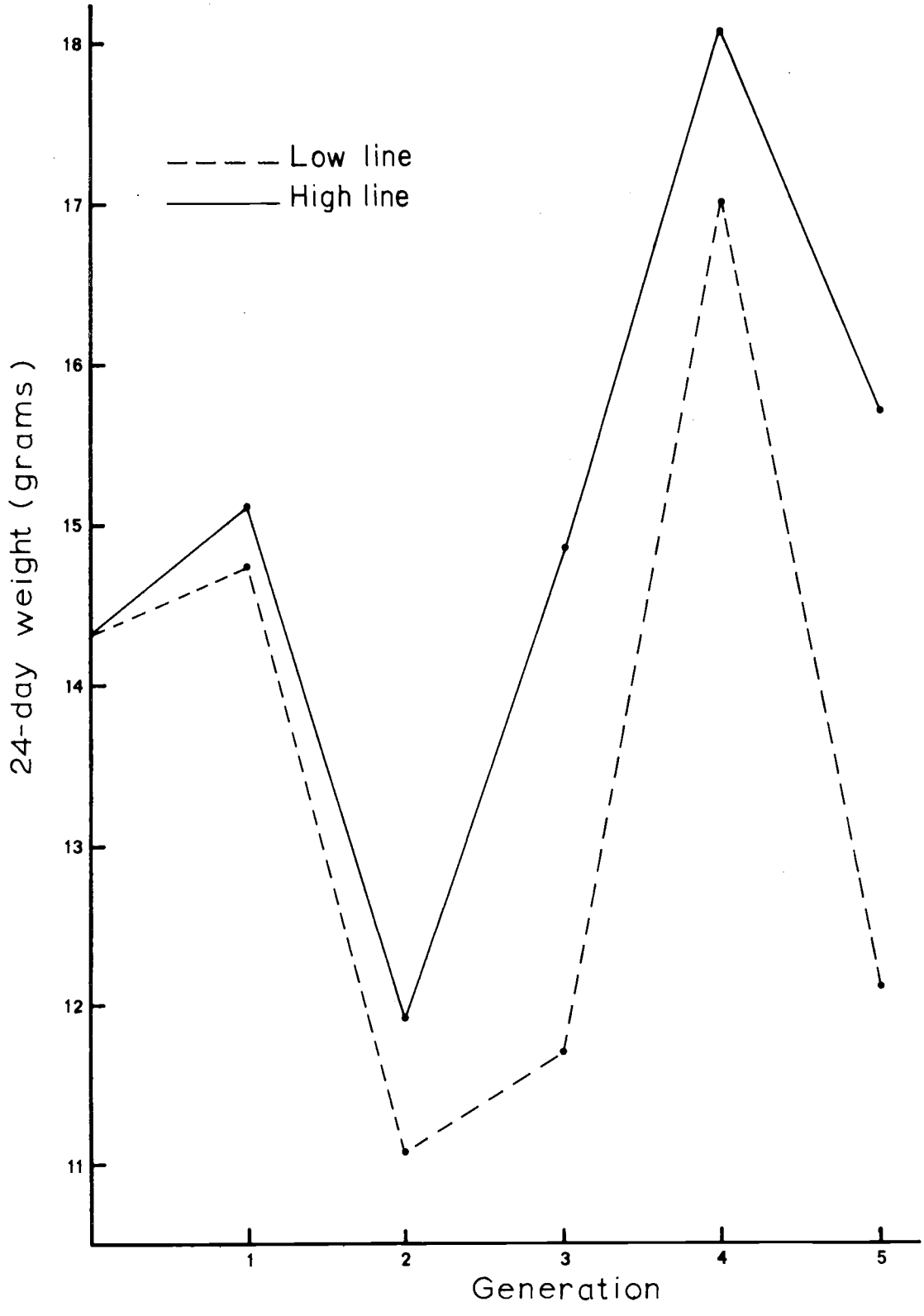

Figure 3. Mean 24-day weight for high and low lines by generation.

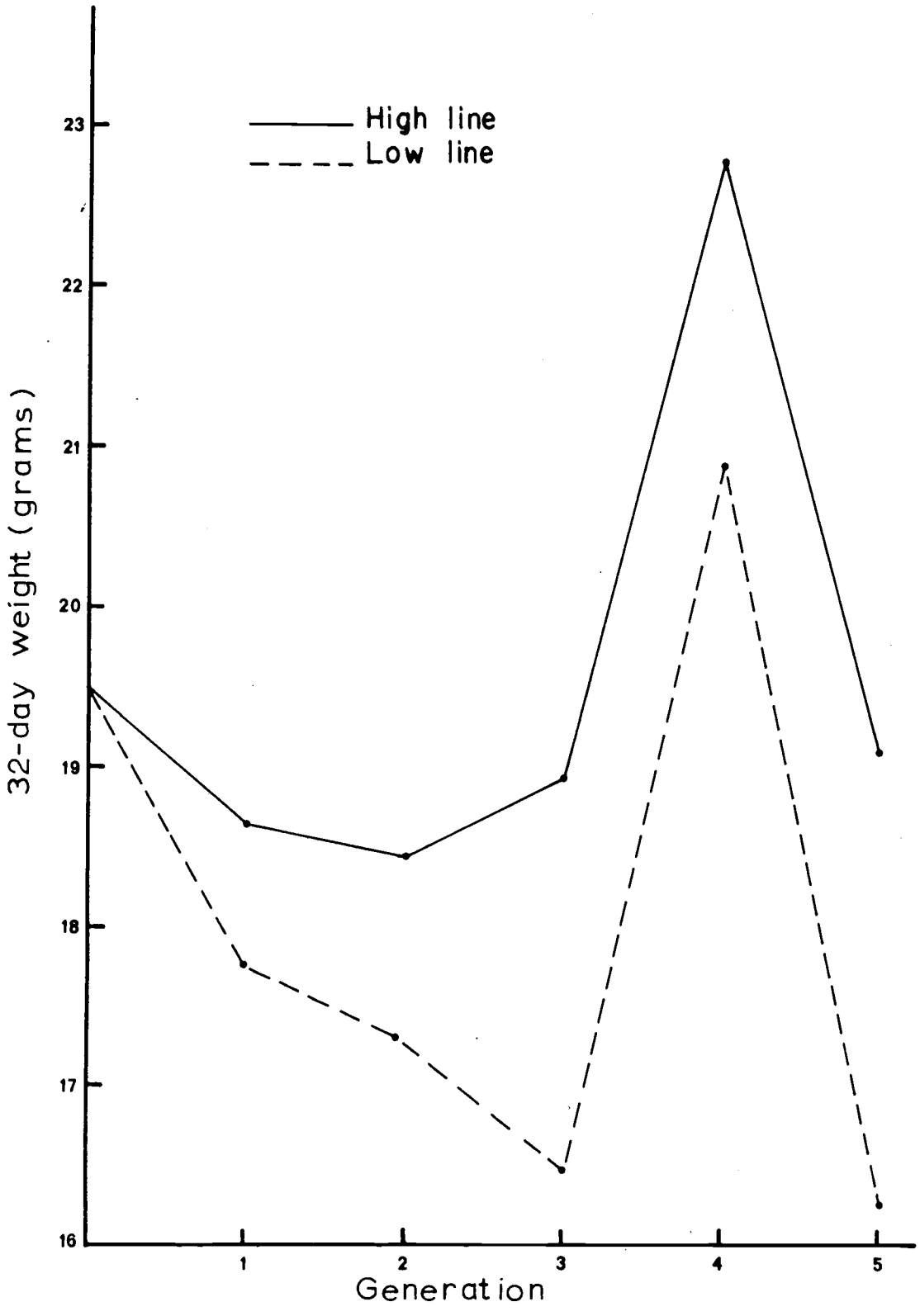

Figure 4. Mean 32-day weight for high and low lines by generation.

Table 10. Coefficient of inbreeding for all mice for each generation.

Generation	Coefficient of inbreeding
0	0.0000
1	0.2500
2	0.3750
3	0.5000
4	0.5938
5	0.6719

Table 11. Means and their associated variations for index, 14-day weight, 24-day weight and 32-day weight.

Parameter	Number of records	Mean[a]	Standard deviation	Coefficient of variation
Index	586	247.5	27.0	0.15
14-day weight	586	7.04	0.88	0.08
24-day weight	586	14.52	2.47	0.13
32-day weight	586	18.48	3.02	0.14

[a]Adjusted for actual average litter size of 9.13 offspring. It should be noted that the coefficients of variation were determined from the unadjusted means.

The index, as it was originally conceived, was meant to include values describing both pre-weaning and post-weaning gains with emphasis on the latter measurement. The emphasis or weighting by a factor of four of post-weaning gain would then emphasize the trait which had a higher heritability (0.09 for 12-day litter weight, Eisen, Legates and Robison, 1970; 0.35 for 6-week weight, Falconer, 1953a). This should theoretically result in a greater response to selection in the postweaning period.

The formula of the theoretical index was:

$$I = \frac{\text{14-day weight}}{\text{14 days}} + 4\left(\frac{\text{32-day weight - 24-day weight}}{\text{8 days}}\right)$$

or

$$I = \frac{\text{14-day weight}}{14} + \frac{\text{32-day weight - 24-day weight}}{2}$$

However, simple algebraic manipulation of the formula produces the following results:

$$I = 1/14\ (\text{14-day weight}) + 1/2\ (\text{32-day weight - 24-day weight})$$

$$= 1/14\ [\text{14-day weight} + 7\ (\text{32-day weight - 24-day weight})]$$

$$14I = \text{14-day weight} + 7\ (\text{32-day weight - 24-day weight})$$

$$= (1)\ (\text{14-day weight}) + 7\ (\text{32-day weight}) - 7\ (\text{24-day weight})$$

As all indexes were equally considered, the multiplier of 14 on index can be disregarded. Thus, by selecting for a high index value, as was done for high line mice, the 24-day weight was de-emphasized by a factor of 7 while the 14-day weight and 32-day weight were each emphasized by factors of 1 and 7, respectively.

The converse is true for low line selection. By selecting for a low index value, the 24-day weight was emphasized by a factor of 7 while the 14-day weight and 32-day weight were each de-emphasized by factors of 1 and 7, respectively.

An attempt was thus made to alter the basic growth patterns of the lines; selected high line mice were those with rapid early life growth, retarded growth from 14 to 24 days of age and rapid growth from 24 to 32 days of age. Selected low line mice were those exhibiting slow early life gains, rapid gains from 14 to 24 days of age and retarded gains from 24 to 32 days of age.

Direct response to selection for body weight at a fixed age invariably results in a correlated growth response at other points on the growth curve. Timon and Eisen (1969) found that selection for increased post-weaning gain increased the mean absolute growth rate over the entire growth curve but had no effect on the relative growth rate or shape of the growth curve. Full-sib analysis suggested high genetic correlations among weights at 5, 12 and 21 days of age and weekly thereafter to 14 weeks.

It would thus seem that the selection pressures applied to the animals in the present experiment were antagonistic. A depressed 24-day weight in the high line is not, however, necessarily antagonistic when one considers the events occurring between 14 and 24 days of age. The animals were weaned at 21 days of age forcing a nutritional

stress which could result in retarded growth. Also, animals which were diseased showed symptoms of infection generally between 18 and 22 days of age. In light of this, high line response to selection could still be expected.

Response to selection for low indexes presents problems, as one must assume that low line animals are equally stressed during the critical period just described. Both high and low lines for the index and all weight variables were equally depressed by the disease, as indicated by the non-significant F-values for the disease x line interaction term in the least squares analyses. Though there is no critical proof to indicate it, the stresses of weaning should be equal for both lines. Thus, a reduced 24-day weight would occur in the low line, as well as in the high, and not the converse as demanded by the selection criterion. Therefore, while selection for reduced 14-day and 32-day weights are compatible, expectation of an elevated 24-day weight is not. The consequence of this is that while high line selection could be expected to be effective, low line selection could be expected to be relatively ineffective.

In Table 12 are presented the mean weights of mice by line and disease classification over all generations. The data in Table 12 are illustrated in Figure 5. The values found in Table 13 are, in essence, slopes of the lines of each of the different periods illustrated in Figure 5. The values are calculated as gain in grams per day of the

Table 12. Mean weights of mice in grams by line and disease classification over all generations.

Age (days)	Disease classification	Line	
		High	Low
14	Normal	7.53	7.18
	Infected	6.89	6.55
24	Normal	16.58	14.75
	Infected	14.27	12.44
32	Normal	22.69	20.81
	Infected	16.14	14.26

Table 13. Rates of gain in grams per day by line and disease classification over all generations.

Age (days)	Disease classification	Line	
		High	Low
14-24	Normal	0.91	0.76
	Infected	0.74	0.59
24-32	Normal	0.76	0.76
	Infected	0.23	0.23

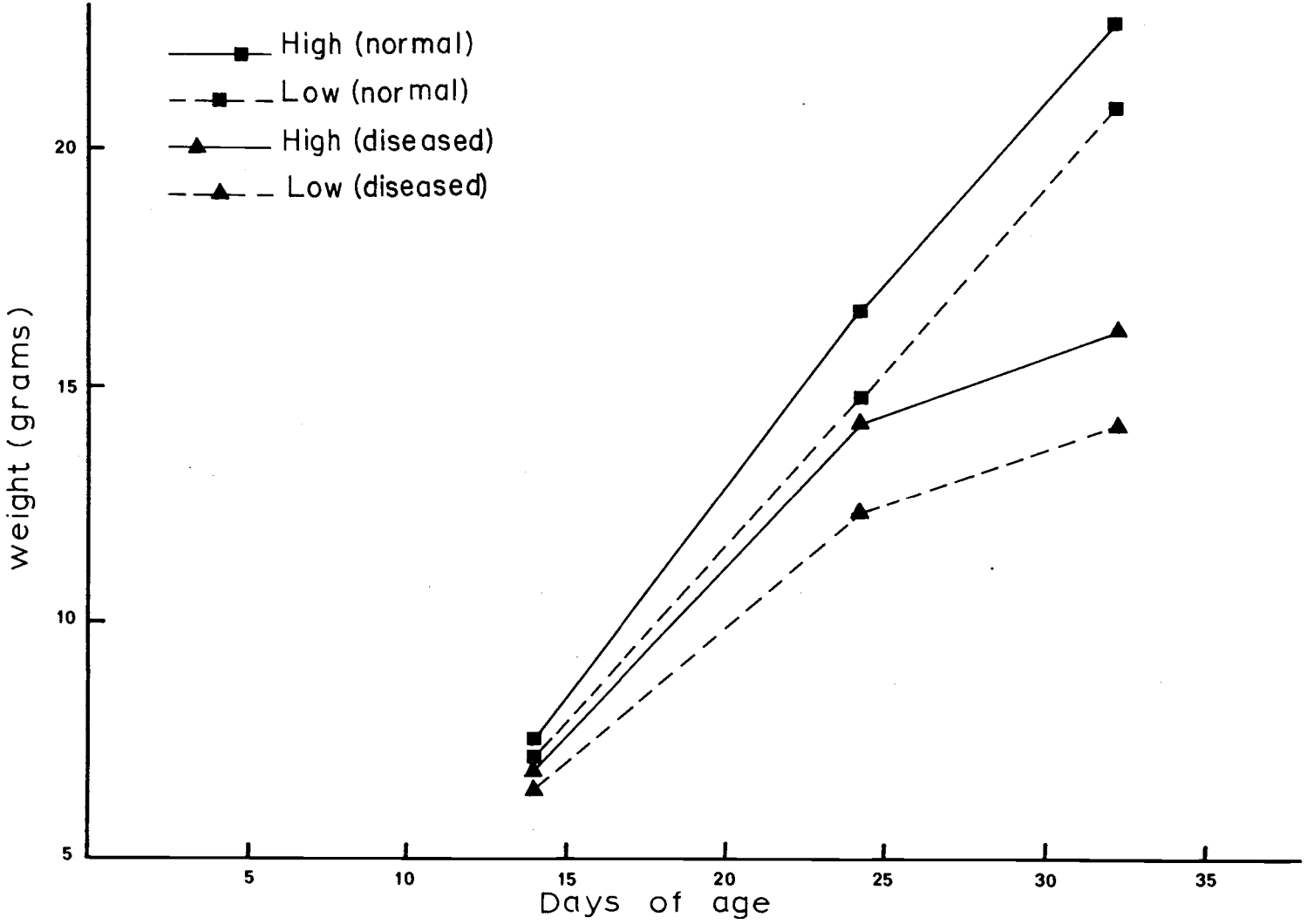

Figure 5. Growth curves by line and disease classification.

respective growth periods. From the above, the depressing effect of the disease is especially noticeable in the 24 to 32-day growth period. It is interesting to note also from Table 13 that there was no change in rate of gain over the two periods for non-infected low line mice (0.76 g/day) while a change did occur for high line mice (0.91 to 0.76 g/day). Also, rates of gain were identical for diseased high and low line mice in the later period.

Line and disease classification trends by generation for index, 14-day weight, 24-day weight and 32-day weight are illustrated in Figures 6 through 9. These trends are highly variable; however, high and low lines within disease classification generally follow the same pattern. A comparison of the figures indicates that 32-day weights were most affected by disease because a greater difference between the non-infected versus infected animals occurred in this trait.

Upon analysis of selection differentials for the actual data, it was found that differentials for the high and low lines were generally of similar magnitudes and opposite signs. However, as it was found that environmental effects exerted a significant influence and the response to selection was rather asymmetric, an adjustment of the data for environmental sources of variation was needed. The least squares constants, obtained through the least squares analyses of variance, were utilized for data adjustments. The constants are listed in Tables 14 through 20. Adjustments for each of the four variables

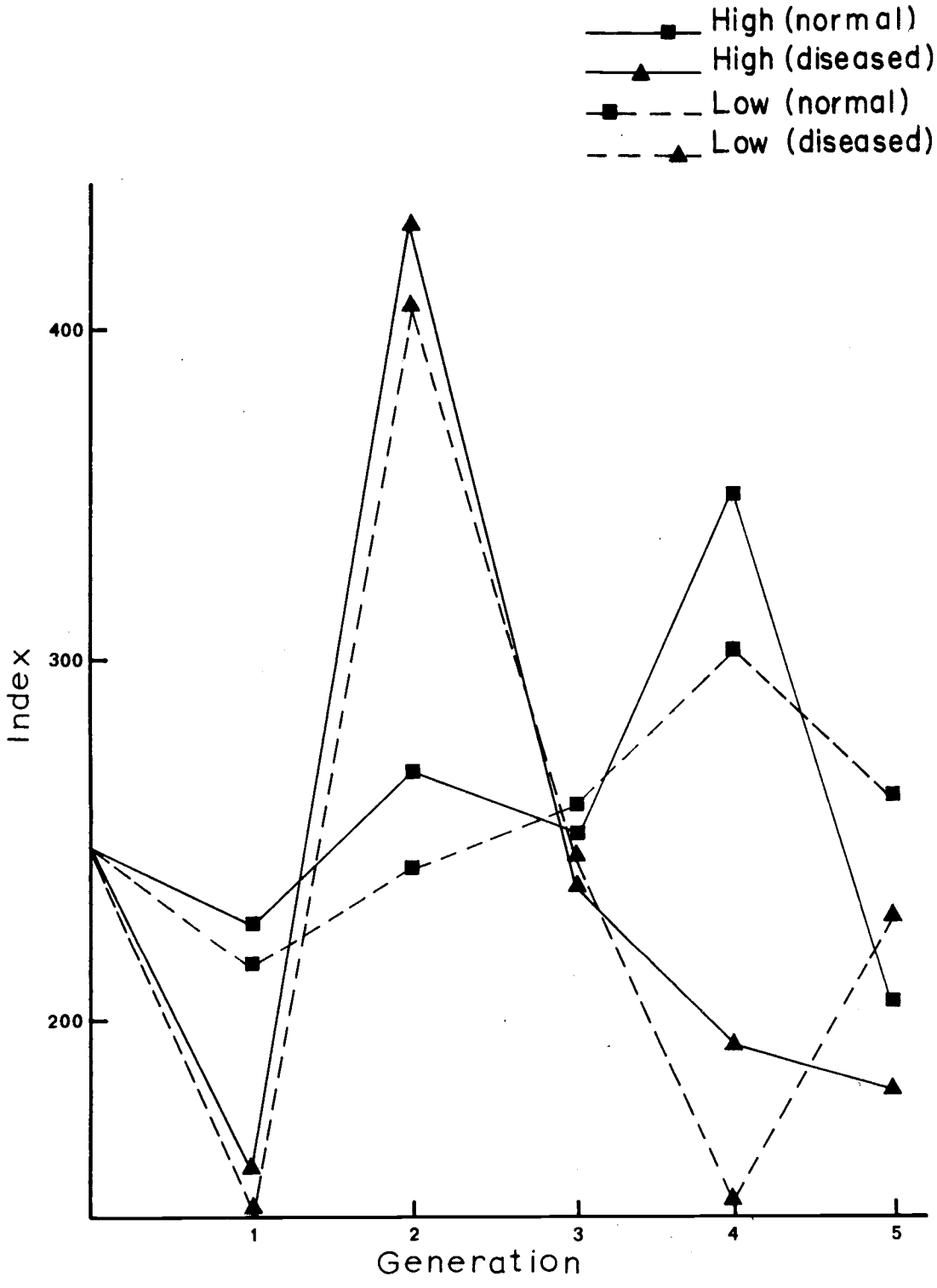

Figure 6. Mean index for line and disease classification by generation.

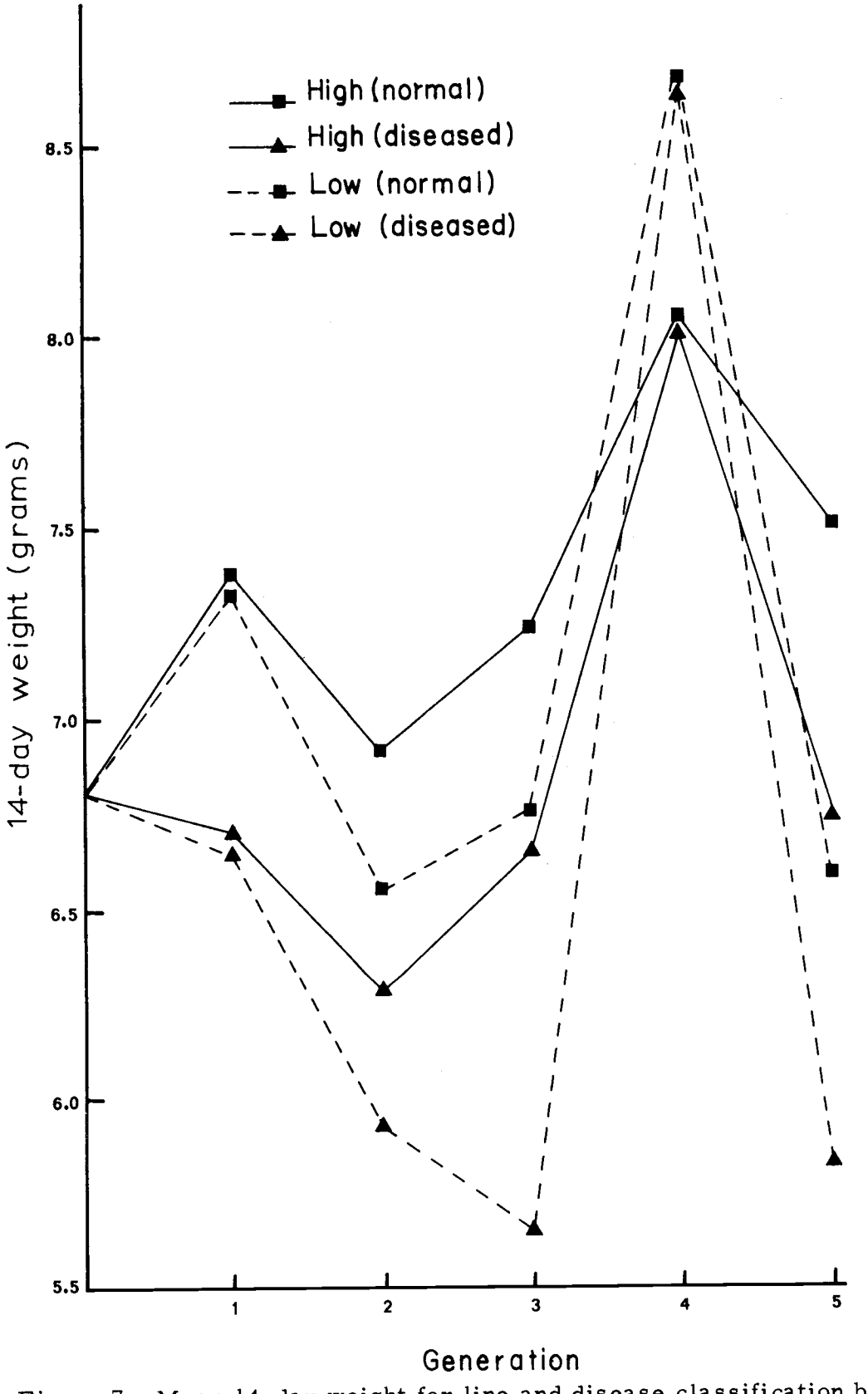

Figure 7. Mean 14-day weight for line and disease classification by generation.

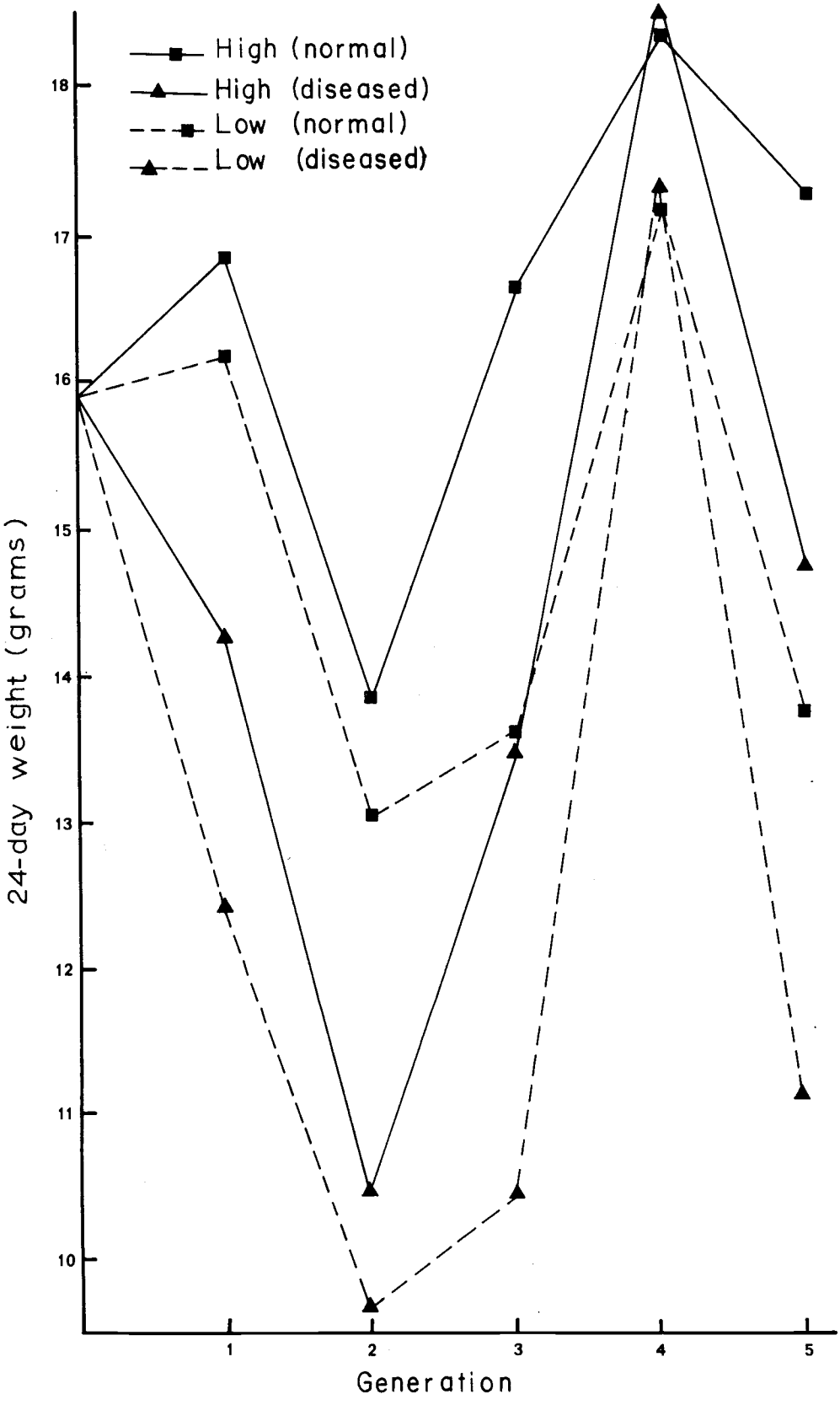

Figure 8. Mean 24-day weight for line and disease classification by generation.

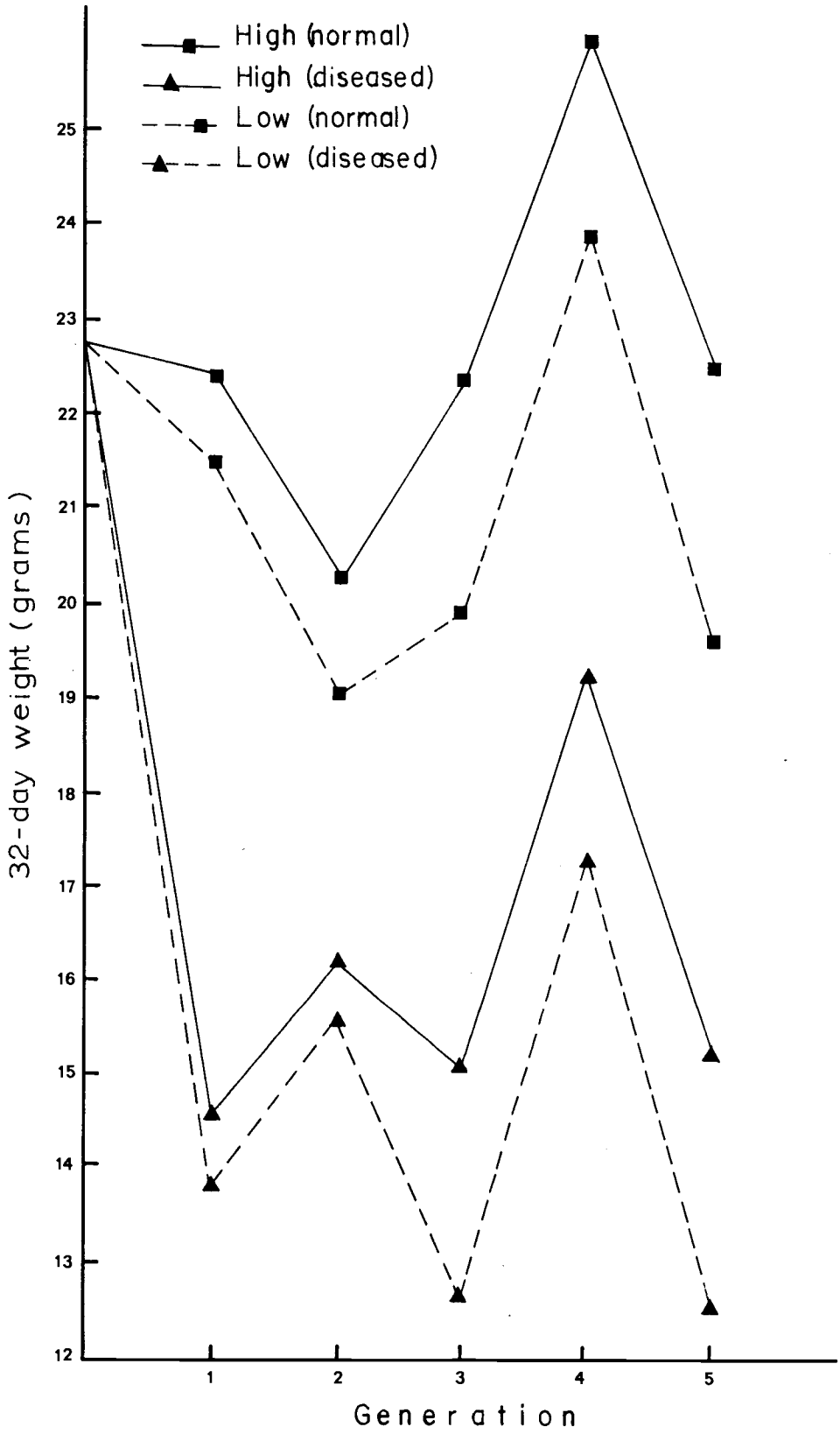

Figure 9. Mean 32-day weight for line and disease classification by generation.

Table 14. Least squares constants of the effects of random vs. selected line, sex, season and parity on index and 14-day, 24-day and 32-day weights.

Parameter	Random vs. selected	Line	Sex	Season	Parity
Index	49.23	2.26	32.90	4.10	41.06
14-day weight	0.55	0.17	0.05	-0.50	-0.22
24-day weight	0.23	0.92	0.40	-1.33	-1.11
32-day weight	1.00	0.94	1.07	-1.19	-0.28

Table 15. Least squares constants of the effects of disease and disease x line interaction on index and 14-day, 24-day and 32-day weights.

Parameter	Disease	Disease x Line
Index	0.01	-2.76
14-day weight	0.32	-0.01
24-day weight	1.16	0.32
32-day weight	3.27	0.28

Table 16. Least squares constants of the effects of generation on index and 14-day, 24-day and 32-day weights.

Parameter	Generation				
	1	2	3	4	5
Index	-61.68	88.69	0.47	0.58	-28.06
14-day weight	- 0.01	-0.61	-0.34	1.31	- 0.35
24-day weight	0.70	-2.77	-0.98	3.33	- 0.28
32-day weight	- 0.43	-0.80	-0.96	3.17	- 0.98

Table 17. Least squares constants of the effect of disease x generation interaction on index and 14-day, 24-day and 32-day weights.

Parameter	Generation				
	1	2	3	4	5
Index	25.71	-92.74	-4.53	68.50	3.06
14-day weight	0.02	0.00	0.22	- 0.30	0.06
24-day weight	0.13	0.54	0.44	- 1.22	0.12
32-day weight	0.60	- 1.29	0.34	0.05	0.30

Table 18. Least squares constants of the effect of replicate on index and 14-day, 24-day and 32-day weights.

Parameter	Replicates								
	1	2	3	4	5	6	7	8	9
Index	-101.59	38.71	23.60	-28.57	60.62	28.80	-41.66	4.79	6.30
14-day weight	0.01	-0.52	-0.65	0.10	0.54	0.38	- 0.23	0.25	0.13
24-day weight	- 1.25	0.16	-1.40	0.10	0.71	1.30	- 0.16	0.49	0.05
32-day weight	- 3.32	1.00	-0.83	- 0.54	1.84	1.72	- 0.92	0.59	0.46

Table 19. Least squares constants of the effect of replicate x line interaction on index and 14-day, 24-day and 32-day weights.

Parameter	Replicates								
	1	2	3	4	5	6	7	8	9
Index	-5.45	3.92	4.79	11.11	-65.13	31.42	27.78	-2.97	-5.47
14-day weight	0.54	0.10	0.16	-0.04	- 0.78	-0.63	-0.14	-0.38	1.17
24-day weight	1.39	0.67	0.40	-0.39	- 0.20	0.81	-0.42	-1.67	-0.59
32-day weight	1.19	0.78	0.54	-0.15	- 1.55	1.51	0.11	-1.81	-0.62

Table 20. Partial regression coefficients of index and 14-day, 24-day and 32-day weights on litter size.

Parameter	Coefficient
Index	7.05
14-day weight	-0.39
24-day weight	-0.57
32-day weight	-0.36

were made for the following effects: sex, season, parity, disease, disease x line interaction, disease x generation interaction, line and litter size. From the adjusted figures, gain in grams during the following periods was also obtained: 14 to 24 days of age, 24 to 32 days of age and 14 to 32 days of age.

Selection differentials for each of the seven variables were calculated as the difference between the mean of the young selected to become parents of the next generation and the mean of the litter from which they were selected, weighted by the number of offspring produced by the selected mice. Weighting by the number of offspring eliminates any bias produced by differential fertility between phenotypes for weight or increased inbreeding (Falconer, 1953a). Response was calculated as the difference between the litter mean of a generation and the litter mean of the preceding generation. The averages of the weighted selection differentials and responses for index,

weights, or gains were then obtained over all replicates for each generation. Cumulative weighted selection differentials and responses for each of the seven variables were obtained by summation across generations (Falconer, 1953a). The adjusted mean, weighted selection differentials by generation, average and cumulative total are listed in Table 21. The mean responses by generation and the cumulative total responses are listed in Table 22.

By plotting the difference between the adjusted generation means of the high and low lines against generation, divergence indicating a separation of lines, for each of the four variables across generations is illustrated (Tables 23 through 26, Figures 10 and 11). After the first generation, in which an increased divergence was obtained, the trend in divergence decreased for 14-day weight. The weights of high and low line mice at 14 days thus tended to become more alike with increasing generations despite selection for divergence. Weight at 14 days is more likely to be depressed by increases in inbreeding through the depression of postnatal maternal performance (White, 1972). Dams of animals in the first generation are not inbred and thus no depression would occur from that source, which could explain the high divergence found in the first generation. Subsequently, high performance in high line mice would be depressed. If differential effects of inbreeding occurred such that low line mice were less affected by inbreeding, this would contribute to a decreased divergence.

Table 21. Adjusted mean weighted selection differentials[a] by generation.

Parameter	Line	Generation					Average	Total[b]
		0	1	2	3	4		
Index (units)	High	+41.0	+47.9	+33.3	- 7.0	+19.1	+26.9	+134.3
	Low	-93.0	-41.0	-18.1	+47.0	-10.6	-23.1	-172.4
14-day weight (grams)	High	+ 0.08	+ 0.24	+ 0.19	+ 0.53	+ 0.05	+ 0.22	+ 1.09
	Low	+ 0.06	+ 0.15	+ 0.16	- 0.03	+ 0.39	+ 0.15	+ 0.73
24-day weight (grams)	High	+ 0.67	- 0.11	+ 0.80	+ 1.21	+ 0.43	+ 0.60	+ 3.00
	Low	+ 0.36	+ 0.38	+ 0.45	- 0.64	+ 0.52	+ 0.19	+ 0.97
32-day weight (grams)	High	+ 1.99	+ 0.70	+ 1.58	+ 1.76	+ 0.71	+ 1.35	+ 6.74
	Low	- 1.45	- 0.91	+ 0.22	+ 0.39	+ 0.34	- 0.28	- 1.41
14-24 day gain (grams)	High	+ 0.52	+ 0.26	+ 0.62	+ 0.69	+ 0.39	+ 0.50	+ 2.48
	Low	+ 0.20	-0.15	+ 0.22	- 0.61	+ 0.14	- 0.04	- 0.20
24-32 day gain (grams)	High	+ 1.34	+ 0.81	+ 0.45	+ 0.55	+ 0.39	+ 0.71	+ 3.54
	Low	- 1.68	- 0.71	- 0.21	+ 0.80	- 0.18	- 0.40	- 1.98
14-32 day gain (grams)	High	+ 1.90	+ 0.50	+ 1.62	+ 1.24	+ 0.67	+ 1.19	+ 5.93
	Low	- 1.42	- 0.50	+ 0.01	+ 0.20	+ 0.53	- 0.24	- 1.18

[a]Calculated as the difference between the litter mean and the mean of the selected young to become parents of the next generation and weighted by the number of offspring produced in the next generation.

[b]The cumulative total across generations.

Table 22. Adjusted mean response[a] by generation.

Parameter	Line	Generation 1	2	3	4	5	Total[b]
Index (units)	High	+55.5	+153.4	-139.1	+57.5	-84.6	+42.7
	Low	+13.4	+142.2	- 65.8	-40.5	- 6.5	+42.8
14-day weight (grams)	High	+ 1.48	+ 0.49	+ 0.64	+ 0.77	- 1.07	+ 2.31
	Low	+ 1.61	- 0.75	+ 0.32	+ 1.42	- 2.25	+ 0.35
24-day weight (grams)	High	+ 2.73	- 1.42	+ 3.04	+ 2.51	- 1.94	+ 4.92
	Low	+ 2.44	- 3.44	+ 0.92	+ 3.12	- 4.30	- 1.26
32-day weight (grams)	High	+ 2.97	+ 0.19	+ 0.08	+ 5.96	- 4.17	+ 5.03
	Low	+ 2.28	- 2.38	+ 0.34	+ 2.08	- 3.87	- 1.55
14-24 day gain (grams)	High	+ 1.25	- 1.91	+ 2.39	+ 1.74	- 0.88	+ 2.59
	Low	- 1.04	- 2.62	+ 0.60	+ 1.70	- 2.04	- 3.40
24-32 day gain (grams)	High	+ 0.24	+ 1.61	- 1.79	+ 3.45	- 1.80	+ 1.71
	Low	- 0.14	+ 1.03	- 1.22	- 1.31	+ 0.42	- 1.22
14-23 day gain (grams)	High	+ 1.63	- 0.30	+ 3.38	+ 5.19	- 3.11	+ 6.79
	Low	+ 1.53	- 1.66	- 0.54	+ 0.39	- 1.61	- 1.89

[a]Response was obtained by calculating the difference between the litter mean in the previous generation and the litter mean in the generation indicated. A plus sign indicates a larger while a minus sign indicates a smaller mean index, weight, or gain for the generation indicated than for the previous generation.

[b]The cumulative total across generations.

Table 23. Generation means and divergences for 14-day weight (grams).

Generation	Line	Mean	Divergence[a]
0	-	6.25	0
1	High	7.74	1.47
	Low	6.27	
2	High	7.79	0.99
	Low	6.80	
3	High	8.04	0.93
	Low	7.11	
4	High	8.95	-0.28
	Low	9.23	
5	High	7.88	0.90
	Low	6.98	

[a]Calculated as the difference between high and low line means. A minus sign indicates the low line mean exceeds that of the high line.

Table 24. Generation means and divergences for 24-day weight (grams).

Generation	Line	Mean	Divergence[a]
0	-	13.04	0
1	High	15.77	0.29
	Low	15.48	
2	High	14.00	2.37
	Low	11.63	
3	High	15.29	2.74
	Low	12.55	
4	High	17.79	0.76
	Low	17.03	
5	High	15.85	2.90
	Low	12.95	

[a]Calculated as the difference between high and low line means.

Table 25. Generation means and divergences for 32-day weight (grams).

Generation	Line	Mean	Divergence[a]
0	-	18.90	0
1	High	21.87	0.70
	Low	21.17	
2	High	21.26	2.72
	Low	18.54	
3	High	21.15	2.99
	Low	18.16	
4	High	24.72	3.18
	Low	21.54	
5	High	21.93	3.33
	Low	18.60	

[a]Calculated as the difference between high and low line means.

Table 26. Generation means and divergences for index (index units).

Generation	Line	Mean	Divergence[a]
0	-	135.2	0
1	High	190.7	40.8
	Low	149.9	
2	High	328.6	31.7
	Low	296.9	
3	High	211.2	-16.8
	Low	228.0	
4	High	229.3	41.9
	Low	187.4	
5	High	150.1	-68.8
	Low	213.9	

[a]Calculated as the difference between high and low line means. A minus sign indicates the low line mean exceeded that of the high line.

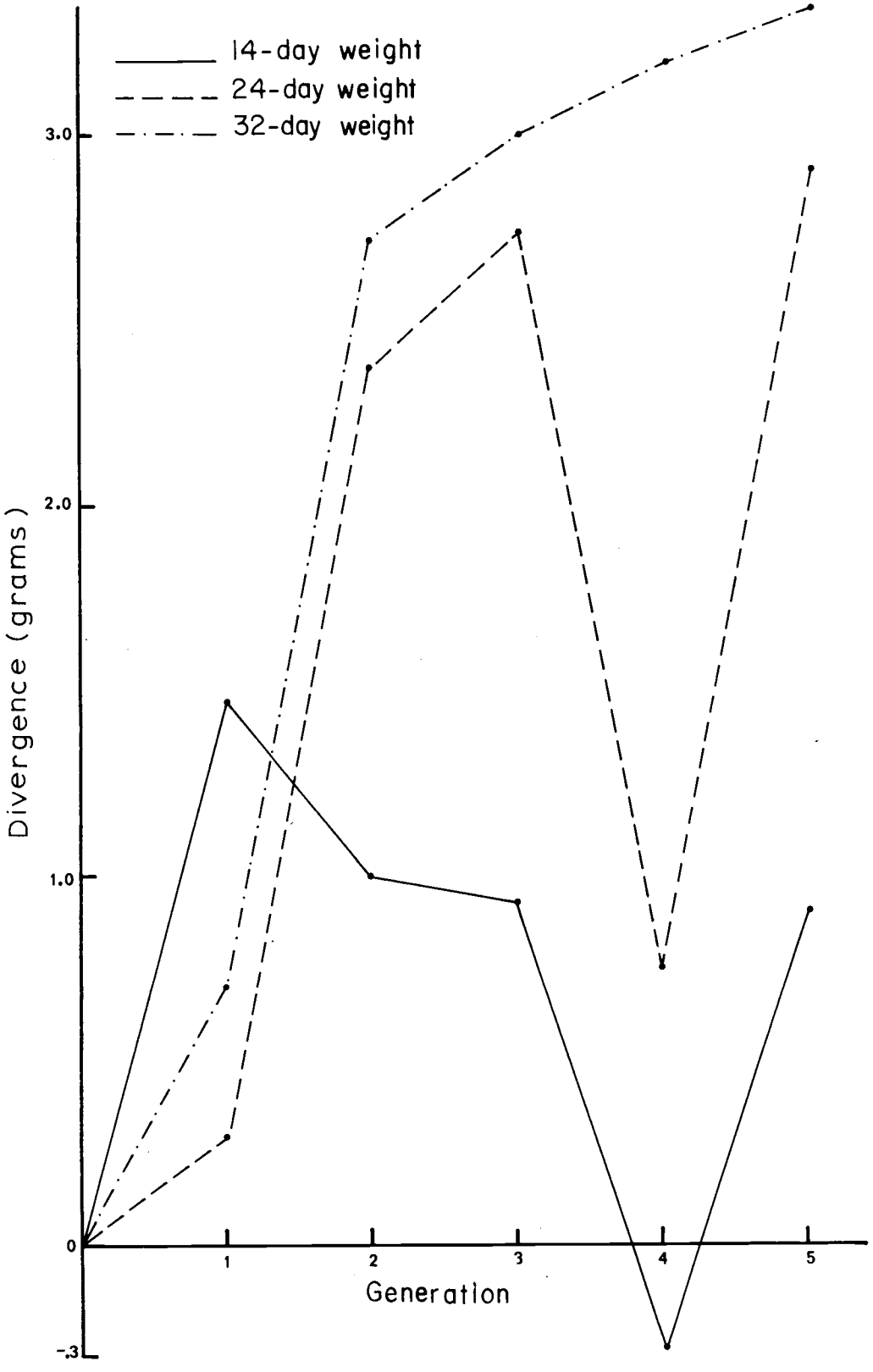

Figure 10. Divergence between lines by generation for 14, 24 and 32-day weights. A negative value indicates the low line exceeded the high line in weight.

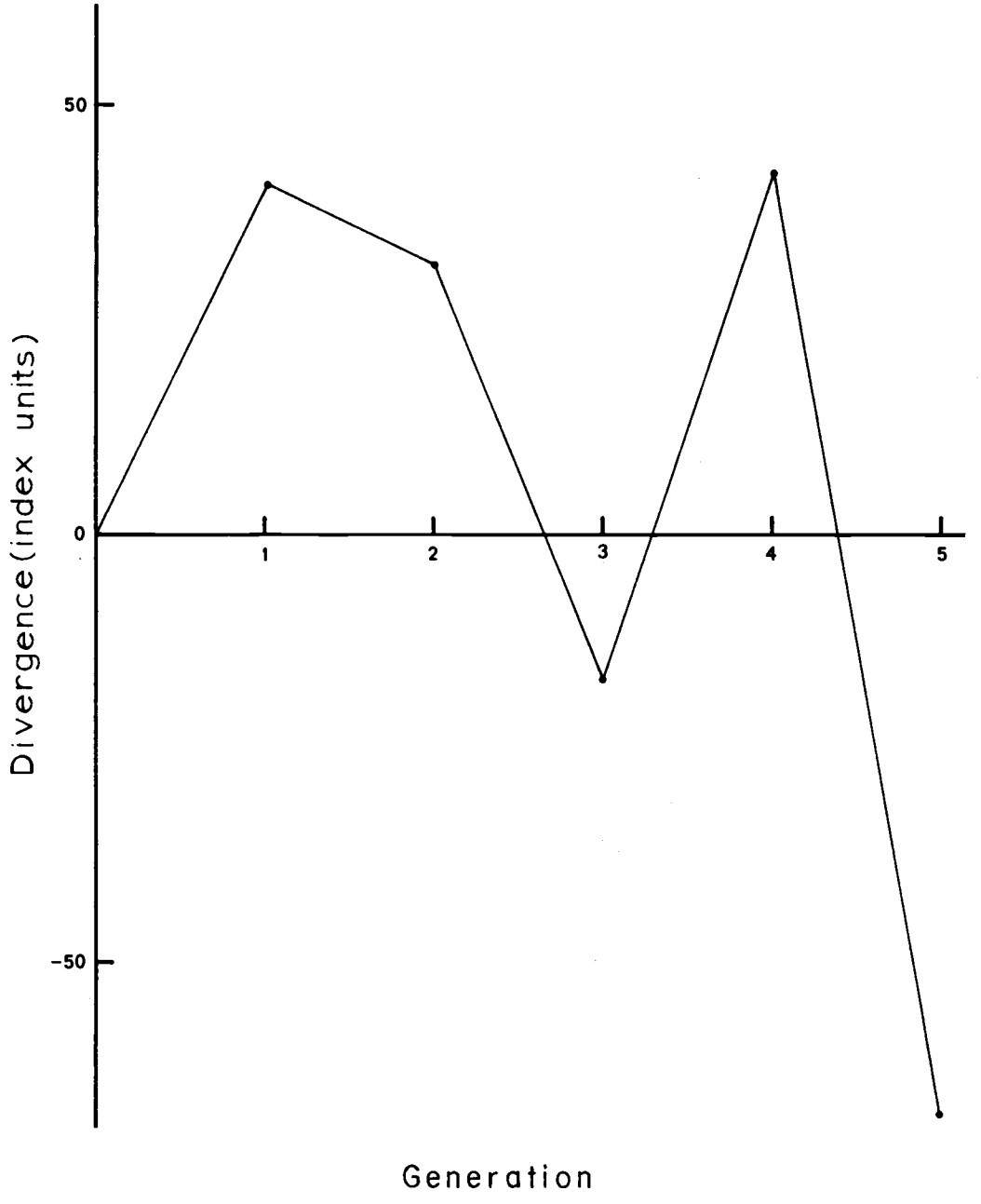

Figure 11. Divergence between lines for index by generation. A negative value indicates the low line exceeded the high line.

Selection pressure on 14-day weight was only one-seventh as great as that for the other variables, as previously noted. With the increasing degree of infection over generations, which was noticeable at later ages, selection pressure on 14-day weight could very well have been less than the theoretical one-seventh. With reduced selection, any progress initially obtained might have been lost.

Divergence increased generally across generations for 24 and 32-day weights with the exception of Generation 4 for 24-day weight. As the data used for this analysis have been corrected for disease and disease interactions, it would appear that another factor either related or unrelated to the disease problem has been omitted from the analyses, with regard to the generally anomalous characteristics of the Generation 4 data. An increasing divergence across generations indicates a response to selection, either in one line with the other remaining constant or in both lines.

The graph of the divergence of lines for the index (Figure 11) indicates that very little response to selection for the combined traits was obtained; variation across generations was approximately zero. The reasons for the lack of response in the index, while response was obtained in the variables from which the index was constructed, remain unclear.

An attempt was made to discover the causes for the anomalous divergence of lines for index by examining gains through 14 to 24 days,

24 to 32 days and 14 to 32 days. The divergences for these variables are found in Tables 27 through 29, and Figure 12, respectively. Increased divergence was obtained during the weaning period (14 to 24 days) in Generation 4, while the reverse was true in the adjacent period of growth (24 to 32 days). For the overall period measured (14 to 32 days) increasing divergence between lines, across generations occurred. The increasing divergence, which was obtained during the weaning period, is somewhat puzzling, in light of the theory presented previously on the relative selection pressures applied to each of the weight variables by using the index as the criterion of selection. However, divergence may be obtained by an increase in one line with the other line remaining at a constant level. Thus if the low line was unresponsive to selection due to physiological antagonisms, while for the high line, the negative pressure on the gains during the weaning period was negated by the positive pressures applied to 14 and 32 day weights, then the increasing divergence is tenable.

Conversion of the divergence data to the form of "growth curves" reveals some interesting information (Figure 13). The divergence between lines generally increased progressively as mice increased in age and with increasing generations. It may be noted that the curves for Generations 1 and 4 are at variance with those of Generations 2, 3 and 5. If the analysis of variance did not fully correct for the factor of disease, then it may be assumed that the difference in the curves

Table 27. Generation means and divergences for 14 to 24 day gains (grams).

Generation	Line	Mean	Divergence[a]
0	-	6.80	0
1	High	8.05	1.02
	Low	7.03	
2	High	6.22	1.40
	Low	4.82	
3	High	7.25	1.87
	Low	5.38	
4	High	8.74	0.95
	Low	7.79	
5	High	7.96	1.99
	Low	5.97	

[a]Calculated as the difference between high and low line means.

Table 28. Generation means and divergences for 24 to 32 day gains (grams).

Generation	Line	Mean	Divergence[a]
0	-	5.84	0
1	High	6.08	0.39
	Low	5.69	
2	High	7.24	0.36
	Low	6.88	
3	High	5.86	0.19
	Low	5.67	
4	High	8.31	3.80
	Low	4.51	
5	High	5.77	0.12
	Low	5.65	

[a]Calculated as the difference between high and low line means.

Table 29. Generation means and divergences for 14 to 32 day gains (grams).

Generation	Line	Mean	Divergence[a]
0	-	12.51	0
1	High	14.14	0.83
	Low	13.31	
2	High	13.47	1.75
	Low	11.72	
3	High	13.11	1.93
	Low	11.18	
4	High	17.15	4.63
	Low	12.52	
5	High	14.05	2.42
	Low	11.63	

[a]Calculated as the difference between high and low line means.

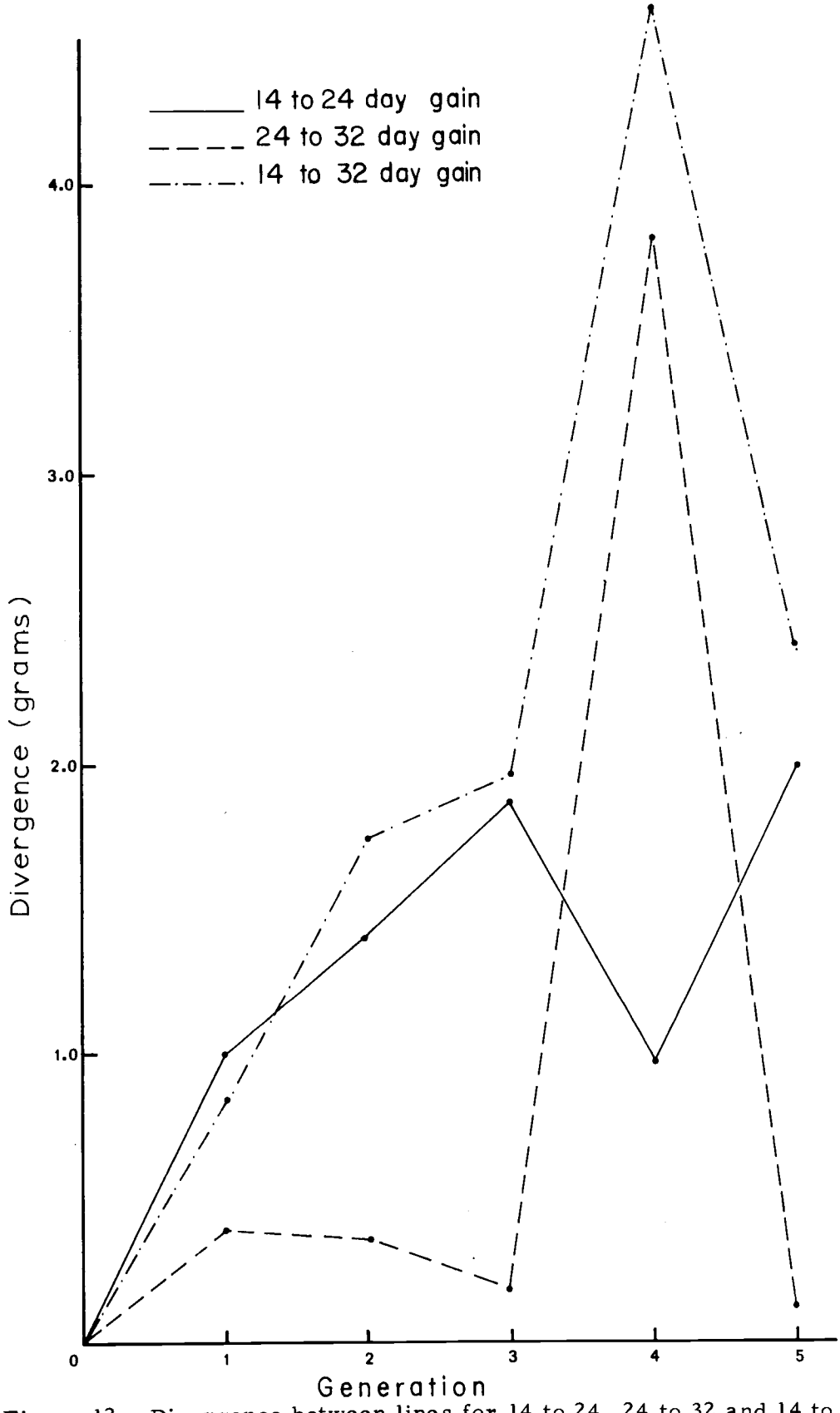

Figure 12. Divergence between lines for 14 to 24, 24 to 32 and 14 to 32 day gain by generation.

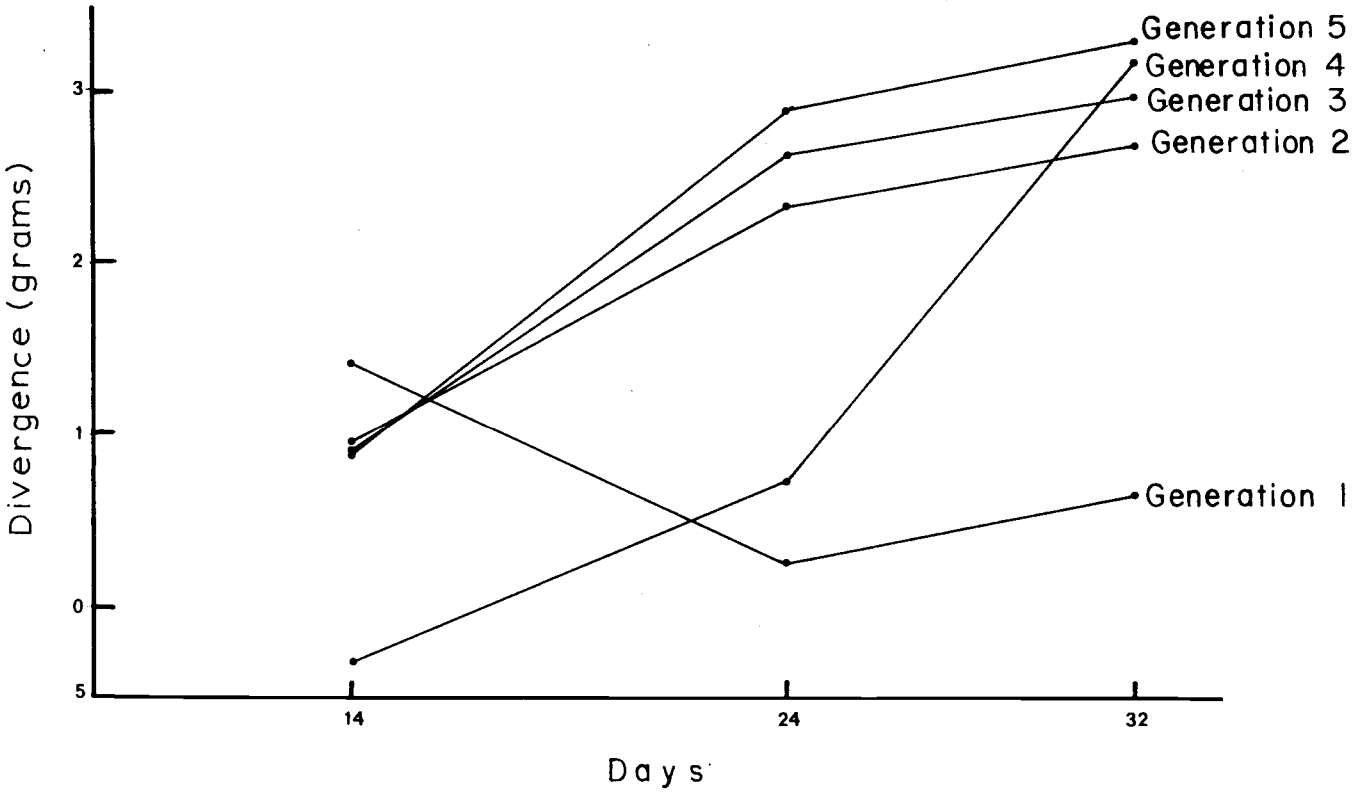

Figure 13. Divergence between lines for each generation at 14, 24 and 32 days.

may be due to an unknown factor, as animals of these generations were less afflicted. However, despite the anomalies, a response to selection was obtained.

Examination of the cumulative selection differentials and responses for each of the variables is useful for the elucidation of line divergence and response. The cumulative selection differential plotted against the cumulative response for the seven variables respectively are shown in Figures 14 through 20. There are relatively consistent negative and positive selection differentials for the low and high lines respectively for index (Figure 14). Both lines show a positive response and both lines culminate by the fifth generation, in a total response of 43 index units.

The selection differentials for 14-day weight (Figure 15) are positive for both lines; however, the cumulative total is higher for the high line. A generally positive response is obtained in 14-day weights for the high line while the low line response though essentially positive shows a large degree of variability.

Both the selection differentials and responses for the low line for 24-day weight (Figure 16) show extreme variability. High line selection differentials and responses for the high line are generally positive. In the second generation a negative selection differential elicited a negative response.

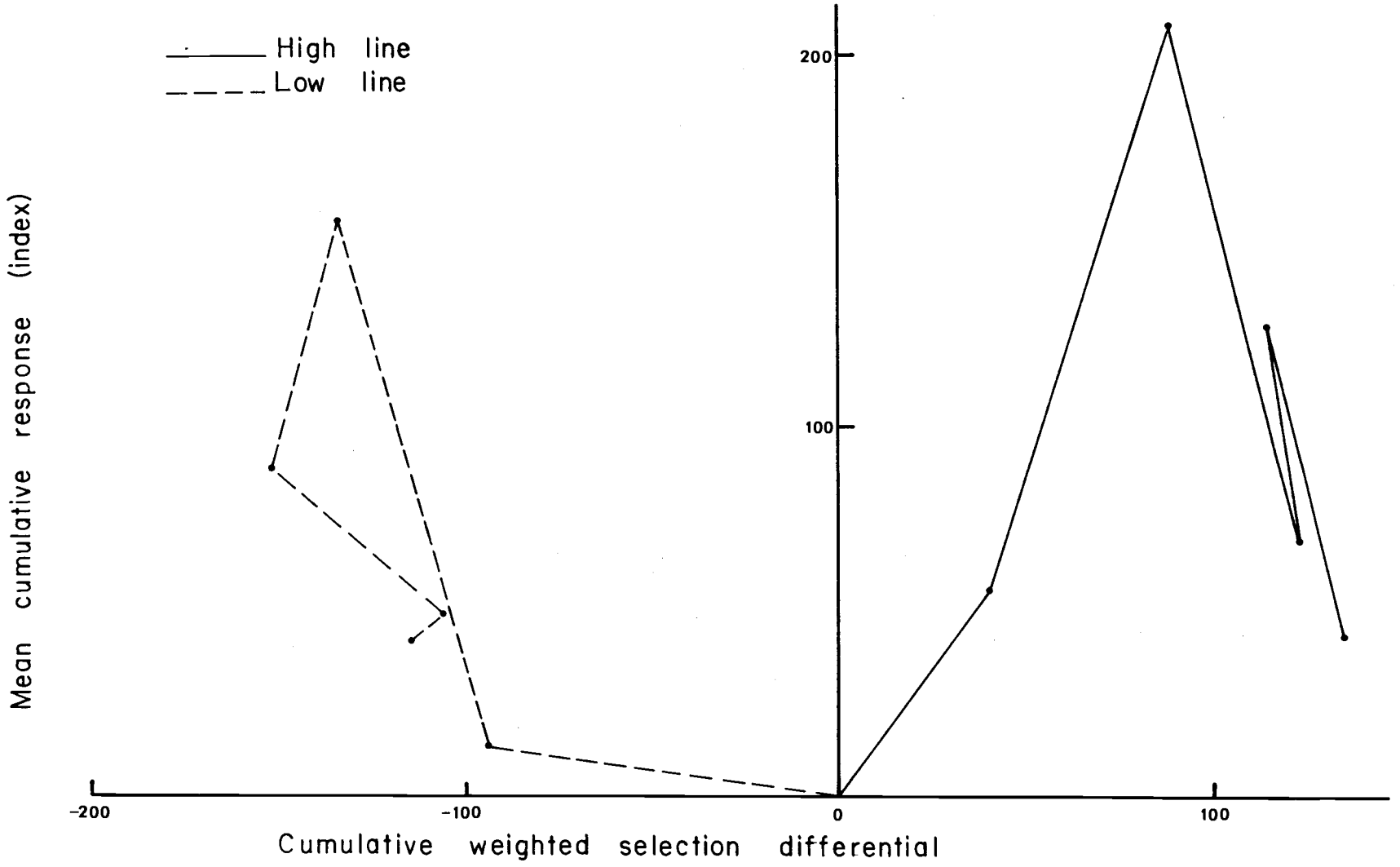

Figure 14. Response to selection for index. Mean response of generations plotted against cumulative selection differentials.

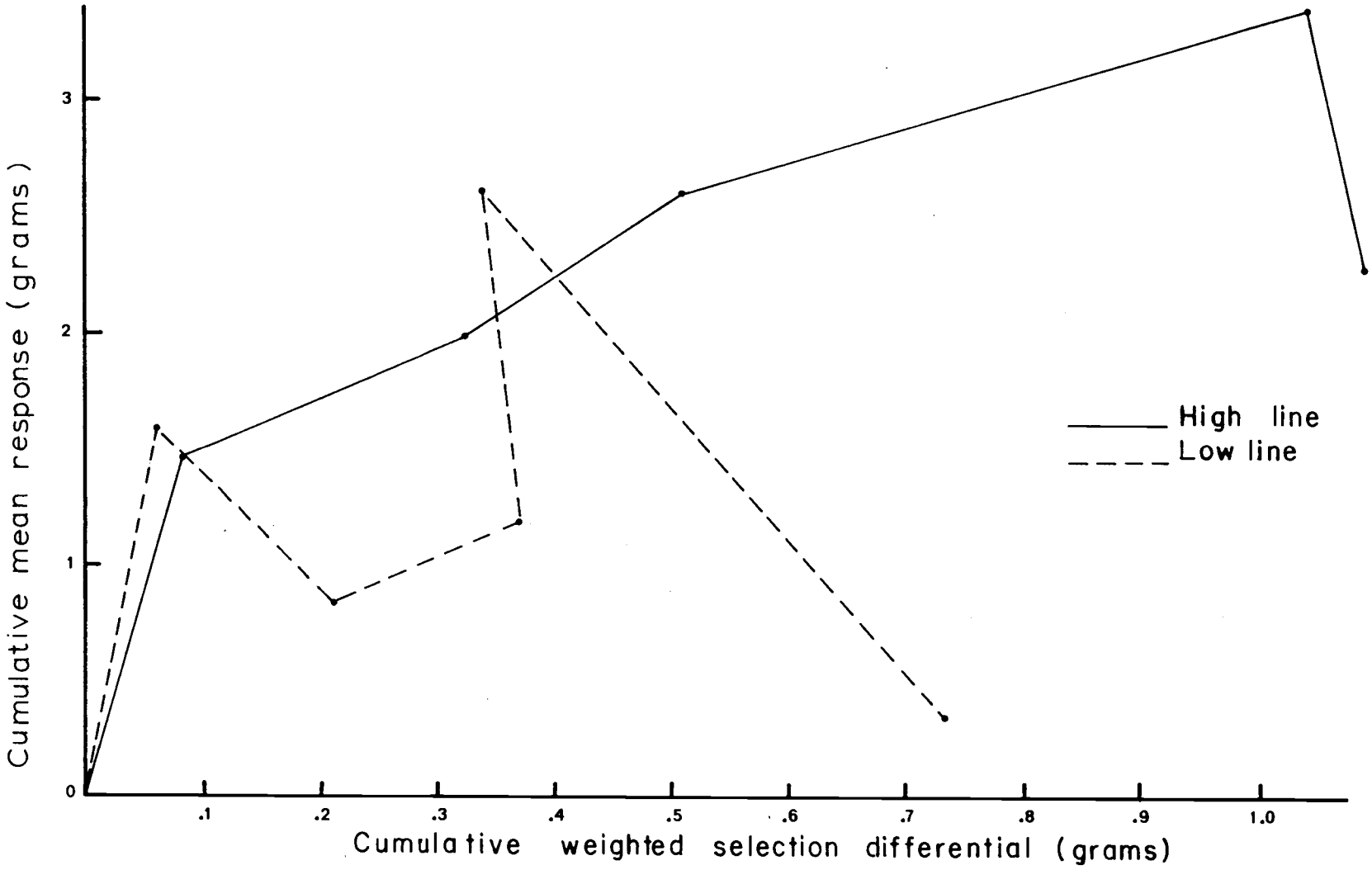

Figure 15. Response of 14-day weight to selection for index. Cumulative mean response plotted against cumulative selection differential.

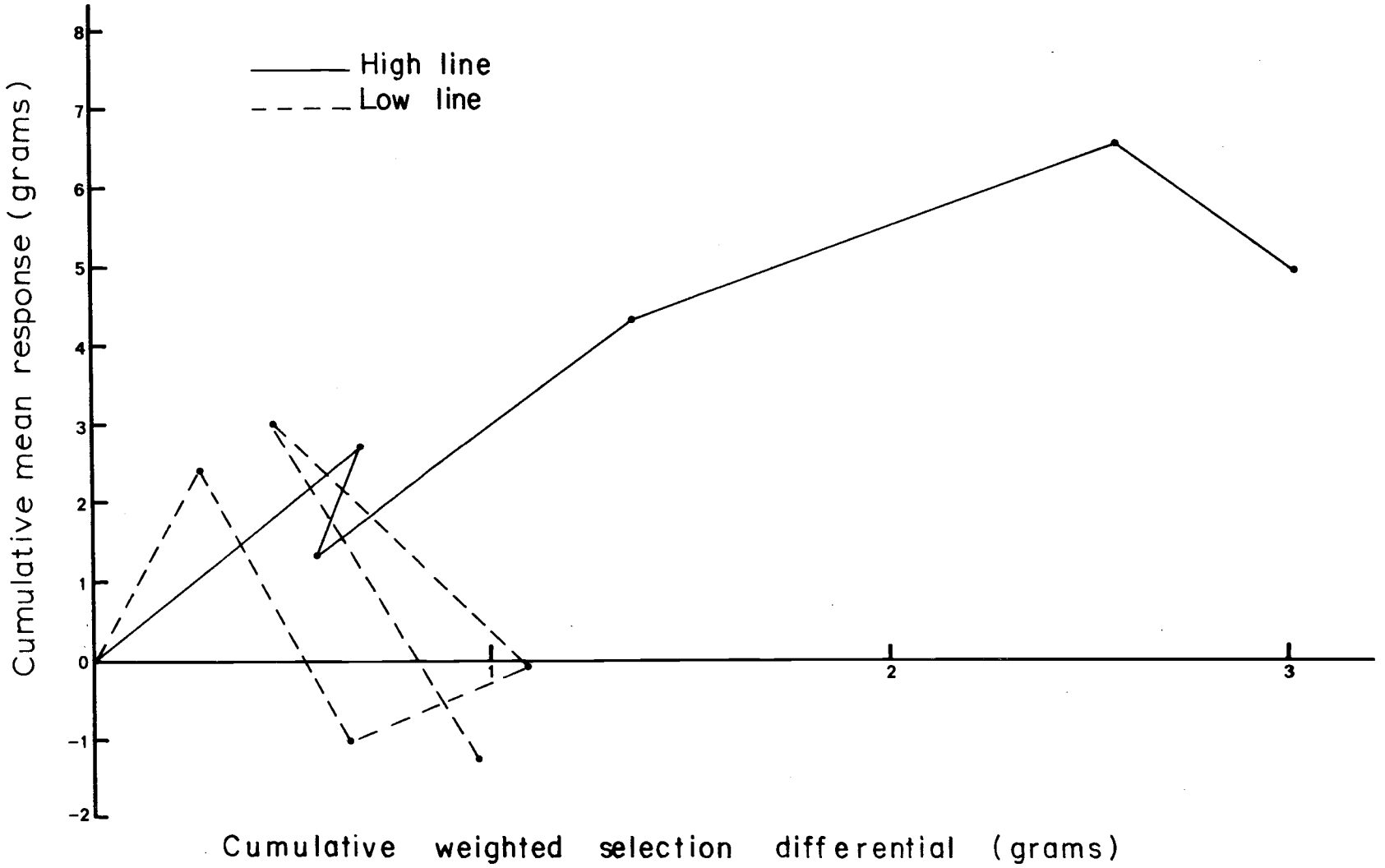

Figure 16. Response of 24-day weight to selection for index. Cumulative mean response plotted against cumulative selection differential.

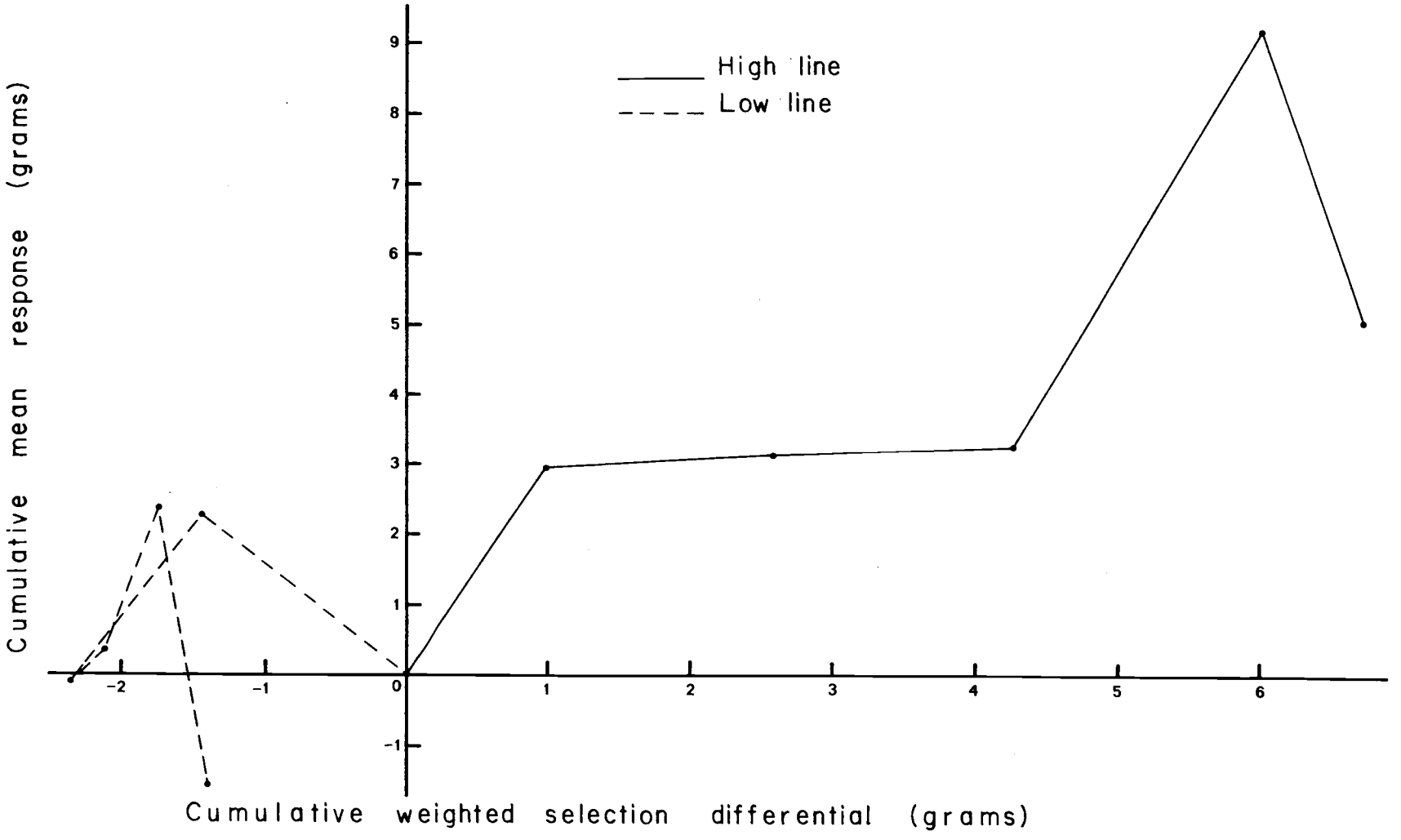

Figure 17. Response of 32-day weight to selection for index. Cumulative mean response plotted against cumulative selection differential.

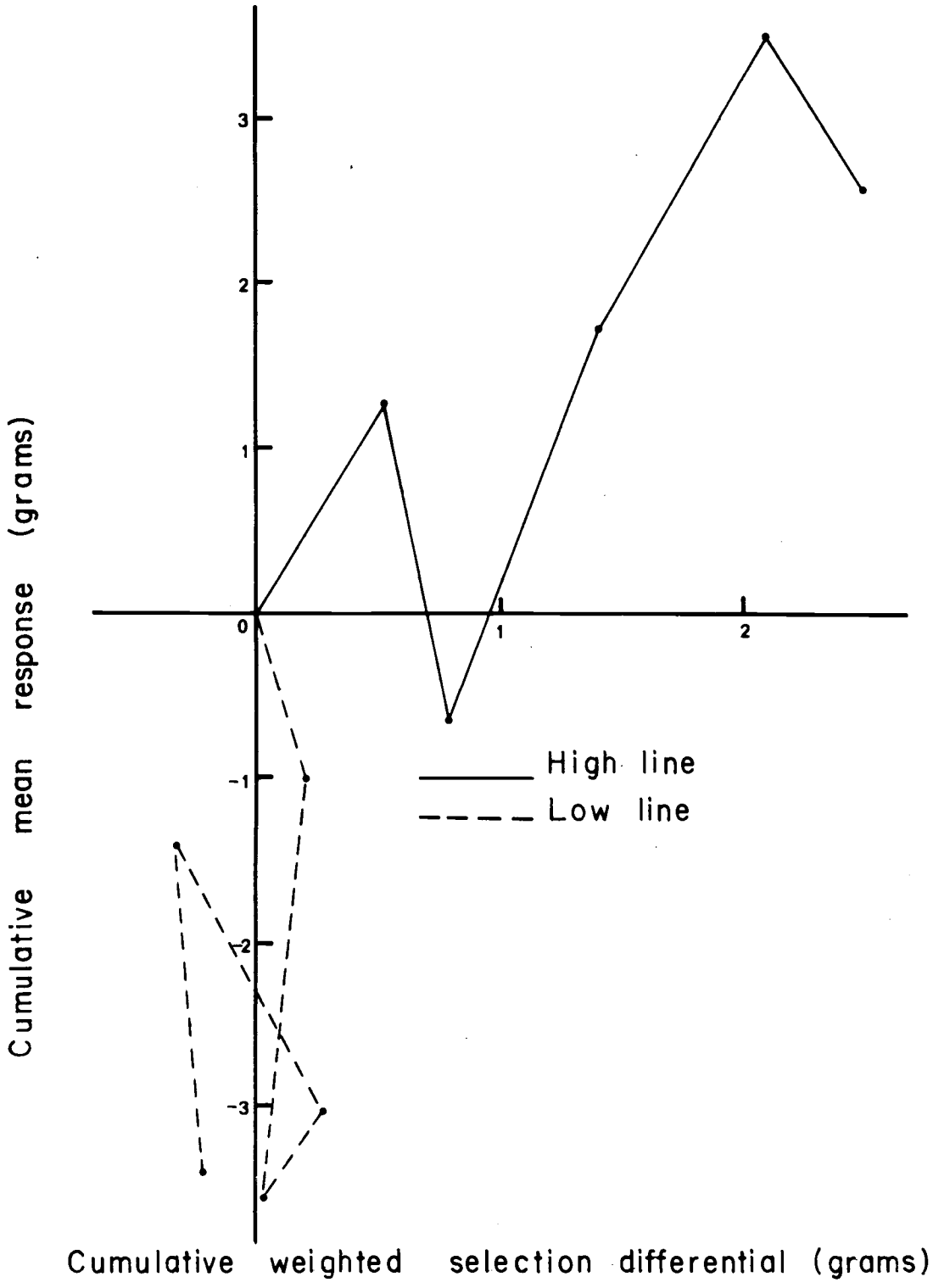

Figure 18. Response of 14 to 24 day gains to selection for index. Cumulative mean response plotted against selection differential.

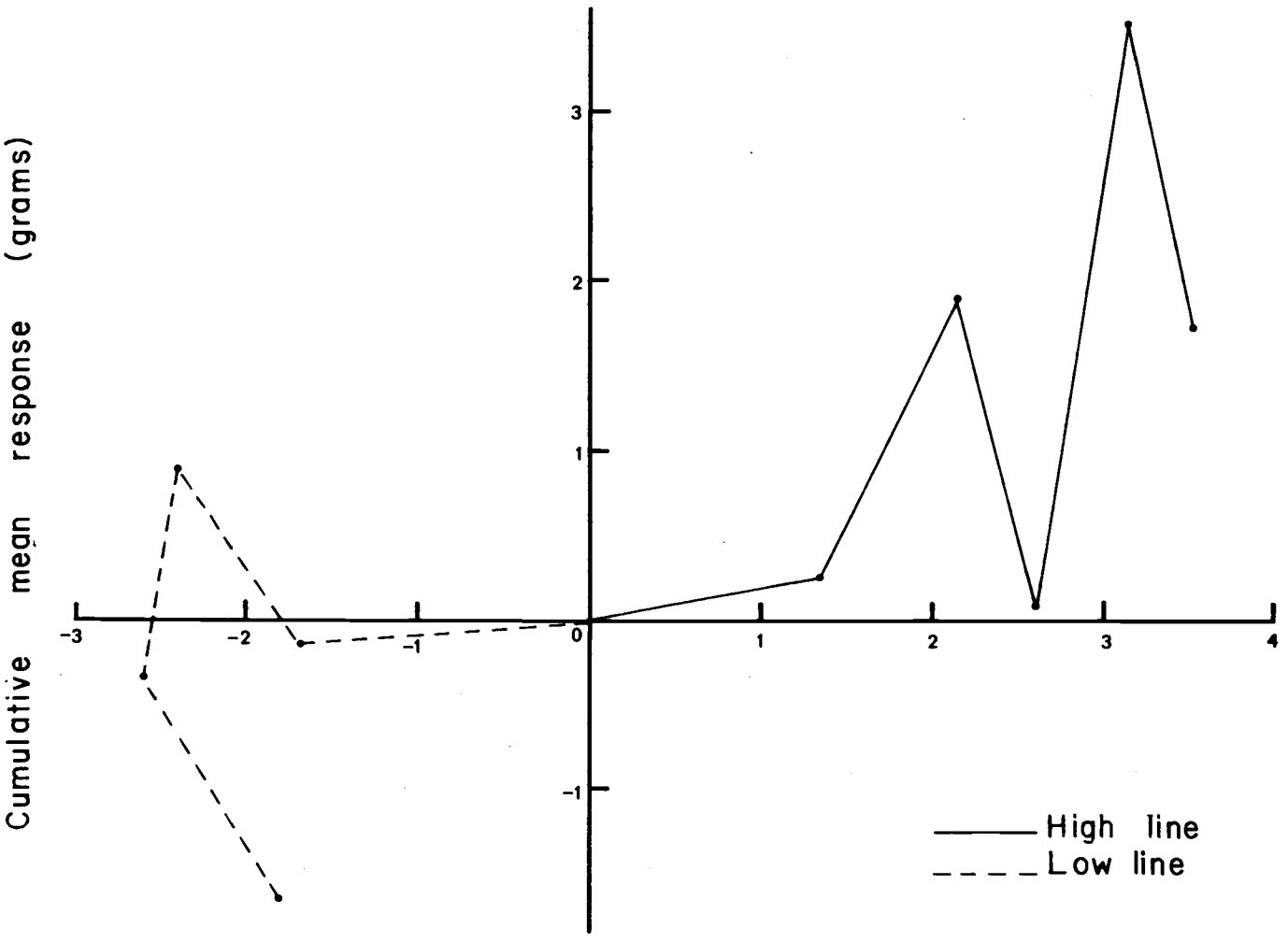

Figure 19. Response of 24 to 32 day gains to selection for index. Cumulative mean response plotted against cumulative selection differential.

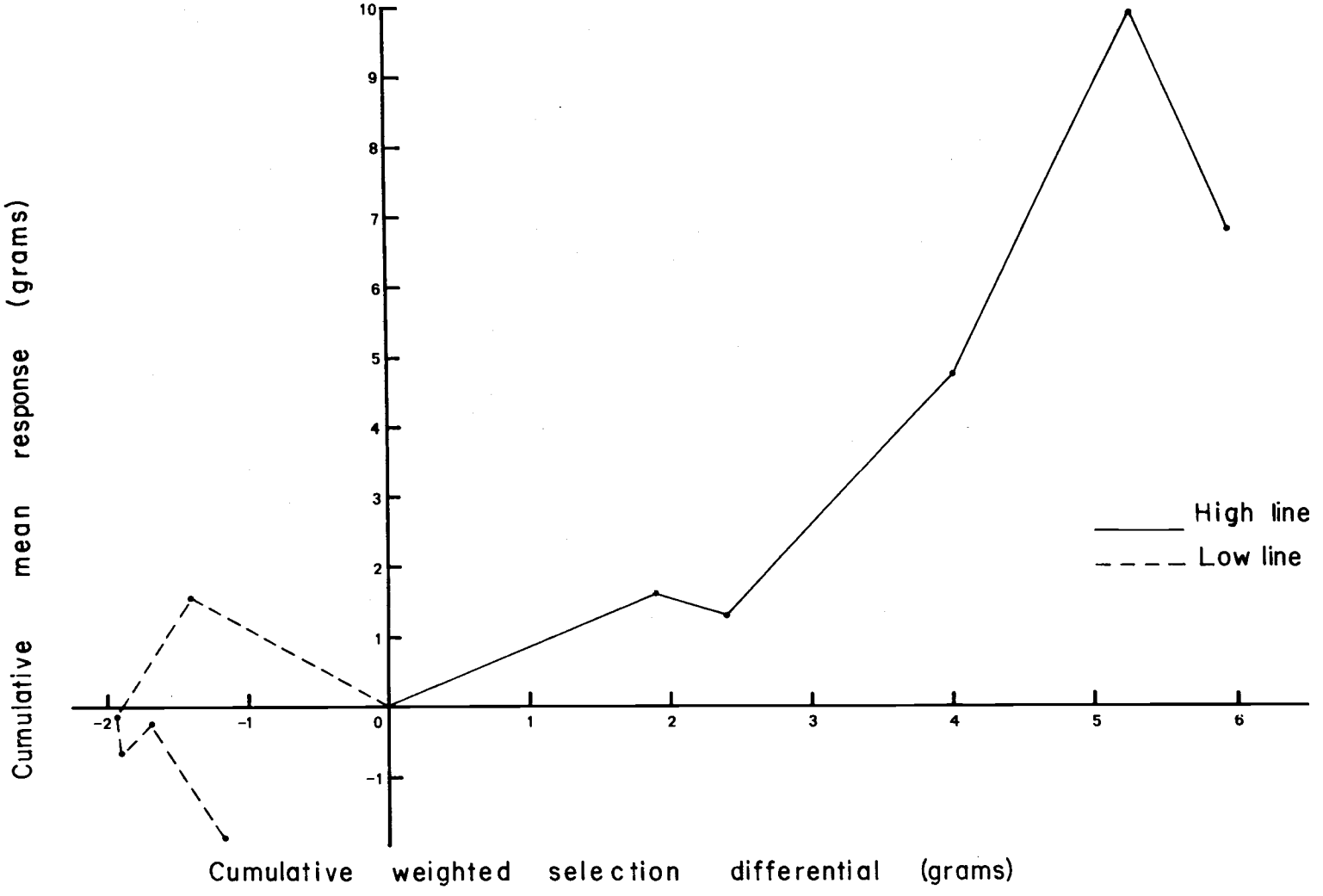

Figure 20. Response of 14 to 32 day gains to selection for index. Cumulative mean response plotted against cumulative weighted selection differential.

Examination of the graph for 32-day weight (Figure 17) shows both positive responses and selection differentials for the high line. In the low line, a large negative selection differential in the first generation elicited a positive response. Thereafter, responses generally follow the respective selection differentials in direction, and an extremely variable response is obtained.

The same patterns are generally found for the gain variables, with the exception of low line response for gains between 14 and 24 days (Figure 18). High line selection differentials are essentially positive and positive responses are found. Low line selection differentials are very erratic and they, in turn, elicit erratic responses. For gains in the 14 to 24-day period, a selection differential that varied around zero elicited a negative response.

Considering high line responses in general, the index was the most variable with the gain variables next and weight variables being the least variable, in relation to the direction and magnitude of the selection pressure applied. A conclusion which may also be made from the preceding figures is that response to selection occurred in the high line while erratic selection pressure of small magnitude with accompanying small, erratic response was obtained in the low line. The divergence is then due to a response to selection in one line with the other line remaining more or less static.

Asymmetry in selection experiments is a common occurrence. Bohren, Hill and Robertson (1966) and Falconer (1955) have stated that only in special instances will symmetry be found. Before true genetic asymmetry can be shown, superficial causes of asymmetry must be shown not to exist. Different generation intervals and different selection differentials between lines and inbreeding during selection resulting in an inbreeding depression are major causes of asymmetry in selection experiments (Falconer, 1955). In this experiment, both lines had equal generation intervals; however, the latter two causes of asymmetry were present. Thus, while an asymmetrical genetic response may have occurred, it is impossible to analyze it separately.

The Response of Litter Size to Two-way Selection for Index

The least squares analysis for litter size is presented in Table 30. The line x generation and disease x line interactions as well as the effect of replicate were all significant at the 2.5 percent level of probability. The replicate x line interaction was significant at the 10 percent level of probability. The standard deviation and coefficient of variation for litter size are presented in Table 31. Litter size was taken at 14 days of age and therefore includes factors which affect litter size at birth, such as ovulation rate and pre- and postimplantation losses along with early postnatal survival. These factors will

Table 30. Least squares analysis of variance of sources of variation affecting litter size.

Source of variation	d. f.	Mean square	F
Total	69	--	--
Regression	35	165.98	51.058***
Mean	1	139.69	42.971***
Random vs. Selected	1	8.57	2.638
Line	1	6.97	2.143
Generation	4	7.01	2.157
Season	1	0.08	0.025
Parity	1	0.63	0.195
Line x Generation	4	12.35	3.799*+
Disease	1	0.02	0.005
Disease x Line	1	20.08	6.389*+
Disease x Generation	4	4.24	1.303
Replicate	8	9.74	2.996*+
Replicate x Line	8	7.11	2.188+
Error	34	3.25	--

+Significant at the 10.0 percent level of probability.

*+Significant at the 2.5 percent level of probability.

***Significant at the 0.5 percent level of probability.

Table 31. Mean and associated variation for litter size.

Trait	Number of records	Mean	Standard deviation	Coefficient of variation
Litter size	70	9.00	1.803	0.20

Table 32. Least squares means for litter size by lines, generations and lines within generations.

Generation	Line	
	High	Low
0[a]	9.61	9.61
1	12.37	8.61
2	9.57	7.53
3	9.31	5.81
4	4.71	7.35
5	15.05	9.75
0-5	10.09	8.11

[a]Generation 0 is random and unselected.

increase the variability of litter size, which is reflected in a larger coefficient of variation than those seen for previous variables measured.

While the effect of line itself is not highly significant, all interactions with line (generation, disease, replicate) are significant. The F-value for line alone is significant at the 25 percent level of probability, which is somewhat low for any distinct statements to be made about differences occurring between the high and low lines. However, coupled with the significant line interactions, it would seem that differences in litter size between the two lines may exist. The trend in litter size over generations in each of the two lines is illustrated in Figure 21. The values for the figure are presented in Table 32. With the exception of Generation 4, the high line had consistently higher litter sizes than the low line. Both lines exhibit a decreasing trend in litter size over the first three generations of inbreeding. This trend extends one generation further for litters in the high line. Litter size sharply increases in both lines in Generation 5. However, for this generation, the generation means consist of data for only three litters per line and the reliability of the values may be questioned.

The general decline of litter size over generations must be attributed to the effect of progressive inbreeding of both the dam and litters. Litter size increased in the first generation in the high line and decreased slightly in the low line. The dams of this generation

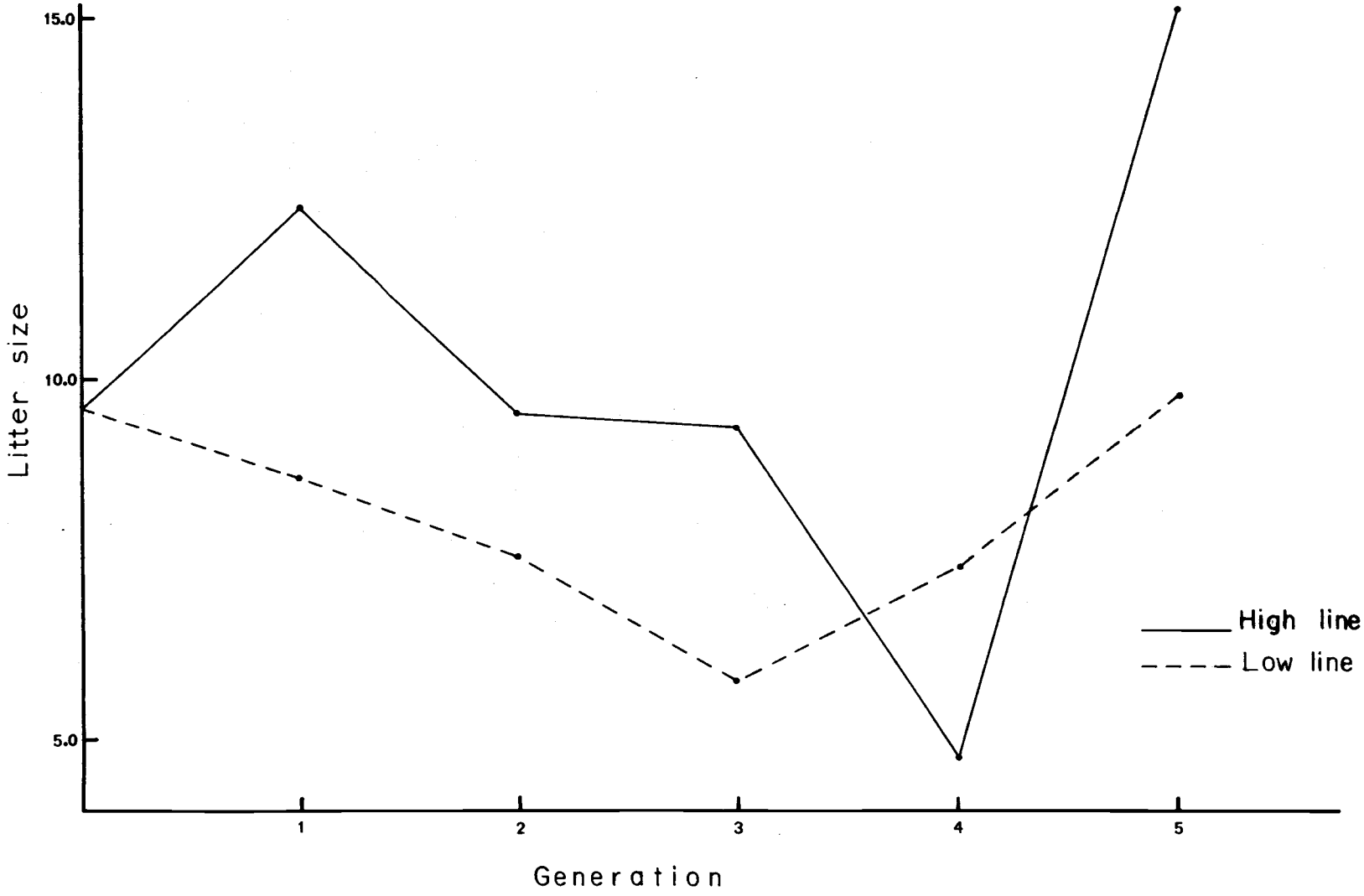

Figure 21. Mean litter size of high and low lines by generation.

were not inbred but litters had a coefficient of inbreeding of 0.25. McCarthy (1967) found a depression of litter size, where dams were not inbred but litters had an inbreeding coefficient of 0.25, which was due to an increased incidence of preimplantation mortality. Subsequent depression of litter size as inbreeding continued (in both dams and litters) was due to reduction of number of eggs ovulated and an additional incidence of preimplantation loss. Both were attributable to increased inbreeding of the dam. Roberts (1960) found no decrease in litter size when the inbreeding of the dam was zero.

Ovulation rate has been found to decrease with increases in inbreeding by some experimenters (King and Young, 1957; McCarthy, 1967). Falconer (1960c), however, found no decrease in ovulation rate with increased inbreeding but rather that ovulation rate is correlated with body weight. As inbreeding progresses, body weight and thus ovulation rate decrease (Falconer and Roberts, 1960). Bradford (1971a, b) also found a correlation of litter size with body weight. However, no increase in litter size was associated with increases in rate of gain.

There was no selection for litter size in the present experiment, so that inbreeding was allowed to have its full depressing effect on litter size over the successive generations.

Neither season, parity nor disease had any significant effects on litter size. Evidently, temperature variations of the housing facility had no adverse effects upon the fecundity of the animals.

Machin and Page (1973) have reported that litter size in mice increases with increasing age of dam. Second parity litters were not significantly larger than first parity litters in the present experiment indicating that either age of dam from first to second parity was not great enough for differences to be detected or that the effects of inbreeding overshadowed effects of age. No dams were diseased at the time of littering and generally animals that had been previously severely diseased were not selected as breeding stock. Therefore, a light case of the disease probably did not interfere with fecundity and the severely infected animals were not tested for litter size.

GENERAL DISCUSSION

The population from which data were taken in the present study consisted of nine replicates each with two lines, high and low. The lines were founded and continued by a strict breeding system of brother-sister matings so that, in effect, each line was represented by only two breeding individuals, replicated nine times. Inbreeding was at a maximum under this system. Attention must be focused on the relative effects such a system has on responses to selection.

It is not precise to state that the effective breeding size of each line for each generation was two as the effective size of a population or the actual number of progenitors responsible for the genetic constitution of the next generation will decrease with increases in inbreeding. Li (1955) has given a formula which describes the changes in the effective population size:

$$N_e = \frac{N}{1 + F}$$

where N_e is the effective size of the breeding population, N is the actual number of breeding individuals in a generation, and F is the coefficient of inbreeding for the breeding individuals. The effective sizes of the breeding populations by generations were calculated using the above formula and are presented in Table 33. It can be seen that by Generation 5, the effective population size was much less (1.2) than

the actual number of 2. Therefore, because parents are both inbred and related each generation, a percentage of the genes which they each contribute to their offspring are identical by descent, causing the reduction in effective population size and a concomitant reduction in genetic variation. The genes, therefore, become progressively fixed in the lines as inbreeding progresses.

Table 33. Effective population size[a] by generation.

Generation	0	1	2	3	4	5
Effective population size	2.00	1.60	1.43	1.33	1.25	1.20

[a]Calculated as in Li, 1955.

Which genes become fixed is determined by several factors. Selection pressure on a trait (either natural or artificial) applied in a certain direction will theoretically cause the genes responsible for the desired expression of the trait to become fixed. Without selection, genes may become fixed due to random drift. In some instances, fixation may occur randomly in the presence of selection. The importance of random drift is accentuated in populations of small size (Bereskin, 1972). Hanrahan, Eisen and Legates (1973) found that random genetic drift was the primary factor causing reduced response to selection for postweaning gain in mice in populations of small size. Variability of realized heritability in replicate populations also

increased at population sizes of 1, 2 and 4 breeding pairs. Falconer (1973) found highly significant heterogeneity between replicates each of which was maintained by 8 pair-matings and selected for high or low body weight.

In the present study, significant ($P < 0.25$ or 0.01) replicate heterogeneity was also found for index, 14, 24, 32-day weights and litter size (Tables 2, 3, 4, 5 and 30). Significant replicate x line interactions were also found, though these were generally of smaller magnitudes. The evidence of highly significant differences between replicates, small effective population size and increasing coefficients of inbreeding suggest the hypothesis that random genetic drift was an important force in this study and that it may have reduced response to selection in both lines. Response to selection was obtained in the high line although it was probably smaller than what would have been obtained had larger populations and a reduced degree of inbreeding been practiced.

The response of the low line to selection, however, was small or non-existent and always highly erratic even after environmental effects were statistically removed.

Examination of the responses to selection of the various components, which are included in the index, give a more detailed picture than looking at the index itself. The index was designed to describe a combined rate of gain for two separate growth periods; preweaning and

early postweaning. However, by algebraic manipulation of the index, weights at different days of age, each having a selection pressure peculiar to itself, were, in fact, the true components of the index. The responses to high line selection followed a pattern which is generally acceptable if one assumes that the heritability for selection of weight at specific days of age increases as age increases. Thus, the greatest response to selection was found for 32-day weight, the least for 14-day weight with the response to selection for 24-day weight at an intermediate level. The selection pressures applied to each of the components by the use of the index complicates the above analysis because, for high line selection, 24-day weight was de-emphasized. This pressure, however, may have been negated by the positive pressure applied to the other two components, 14 and 32-day weights.

Selection for a lowered growth rate or size in both the pre- and postweaning phases of early life may be considered to be selection for reduced vigor. Natural selection favors increased vigor and therefore the two can be thought of as antagonistic. Haldane (1936) has equated at least part of the cause of vigor to heterozygosis. Thus to say that natural selection favors increased vigor is to say natural selection favors heterozygosity. In the present study then, the mating and selection systems were designed to progressively fix genes for lowered vigor (slow growth), in the low line while natural selection was operating to maintain vigor and keep loci for growth heterozygous.

If the two balance, then no progress in either direction will be obtained. It has been previously mentioned that the index used may also have created physiological antagonisms which may have contributed to the reduced response obtained in the low line. Eisen (1972), in a long-term selection study, obtained a plateaued response to selection for 12-day litter weight. However, at the selection limit, no decrease in phenotypic variability was seen. Upon examination of the causes of the variability, Eisen found that genetic variability had not been exhausted. He postulated that the plateau was caused by heterozygote superiority for the trait selected. Hayman and Mather (1953) have suggested that in cases where the heterozygote was at an advantage, inbreeding and selection will come to balance and annul each other's effect. They further state that with full-sib matings, a disadvantage of only 24 percent in the homozygotes will serve to maintain heterozygotes in the population.

Wright (1965) has stated that the true coefficient of inbreeding in biological populations is indeterminable; the coefficient is the theoretical loss of heterozygosity due to inbreeding, expressed as a fraction of the mean heterozygosity in the base population and is only an estimate. While full-sib matings were made in both lines with a concomitant theoretical increase in inbreeding, the true loss of heterozygosity may have been overestimated, especially in the low line.

Supportive evidence of this hypothesis may be found upon close

examination of the litter size data (Table 32 and Figure 21). In the high line, where the theoretical estimate of the inbreeding coefficient may be considered more accurate than that of the low line, a precipitous decline in litter size is seen. This is consistent with the fact that litter size decreases with increases of inbreeding of dams and litters. While a decline in litter size is seen in the low line in the first three generations it is not quite as dramatic as that seen for the high line and it does not continue through the fourth generation. At this generation, litter size increases, while a decline in litter size of nearly five mice occurs in the high line. The increase in litter size in the low line continues into the fifth generation, although the accuracy of this estimate suffers from lack of data. Litter sizes in the low line are then relatively stable when compared with litter sizes in the high line. If the coefficients of inbreeding were identical in fact and the declines in litter size are due primarily to increases in inbreeding, one would expect similar declines in both lines. The fact that there is a difference between lines (the high line litters are generally larger than litters in the low line) does not interfere with the hypothesis as the animals in the high line were generally larger in body size than animals in the low line. Falconer and Roberts (1960) found that litter size is positively correlated with body weight of the dam. The high line animals should produce larger litters in accordance with their weight superiority but the rate of decline in

litter size should be equal if an equal degree of inbreeding exists in both lines.

White (1972) has shown that increasing levels of inbreeding significantly depress body weight in unselected mice at all stages from birth to 56 days of age. As selection for increased weight in the high line was successful in the present study, it would seem that the depressing effects of inbreeding were overcome for body size by selection. However, as noted above, there did exist a general decrease in litter size which must be presumed to be due to the increasing levels of inbreeding over generations. Falconer (1955) has found a positive correlation between the maternal weight and the size of the litter produced. Thus, for the present study, as weight increased while litter size declined, factors other than those connected with maternal size operate on litter size with respect to the depressing effects of inbreeding. It appears evident that inbreeding is directly reducing fertility rather than indirectly through its depressing effect on maternal body size. Whether the reduction in fertility in the high line is due to a reduction in ovulation rate or an increase in prenatal mortality has not been determined.

SUMMARY AND CONCLUSIONS

The responses to selection for high or low rate of gain for five generations of mice as measured by an index, formulated to include both pre- and postweaning gain, was examined. Animals used were randombred Swiss Webster mice. Generation 0 consisted of animals produced by nine random pairs, each of which was the progenitor of a replicate. From within each litter of Generation 0, the male and female having the highest index value and the male and female having the lowest index value were selected as parents of the high and low lines, respectively, for each replicate. Thereafter, the highest male and female within high line litters and the lowest male and female within low line litters were selected as parents of the high and low lines, respectively, for the next generation. In some cases, the second highest or lowest animals were used when the highest animals were diseased or proved to be sterile. Thus, full-sib inbreeding was practiced and the coefficient of inbreeding increased identically in both lines and in all replicates every generation.

Data were collected on litter size at 14 days of age and 14-day, 24-day and 32-day weights. All litters were weaned at 21 days of age. An index value was calculated using the weight data for each animal. The index was designed to stress the more highly heritable

character, postweaning rate of gain. However, when the index was algebraically broken down into component weight values, it was found that for high line selection, 14-day and 32-day weights were positively stressed by factors of 1 and 7, respectively, and 24-day weight was negatively stressed by a factor of 7. The converse was true for low line selection: 14-day and 32-day weights were negatively stressed by factors of 1 and 7, respectively, while 24-day weight was positively stressed by a factor of 7.

A least squares analysis of variance was performed for each of the weight, index and litter size variables. From these analyses, adjusted means for weight, index, litter size and gains from 14 to 24, 24 to 32 and 14 to 32 days were obtained for each generation. Mean responses for generation, cumulative responses across generations, mean weighted selection differentials for each generation and cumulative weighted selection differentials across generations were calculated for each variable. Divergences between the high and low lines were also obtained.

Results from the analyses of the data support the following conclusions:

1. Response to selection for high index was obtained while there was virtually no response to selection for low index.
2. Responses of the component parts of the index (weights and gains) to selection for high index increased with increasing

ages at which data were collected, consistent with the fact that weights and gains at later ages are more highly heritable than those at earlier ages.

3. In the low line, little if any response to selection for index was obtained for the component parts (weights and gains) of the index.

4. The hypothesis was proposed that artificial selection was opposing natural selection maintaining a degree of heterozygosity above that described by calculated inbreeding coefficients. The hypothesis was supported by data on litter size.

5. The hypothesis that the index, as formulated, placed negative or positive emphasis upon 24-day weights for the high and low lines, respectively, could not be positively shown to have occurred. No depression of 24-day weight was noted for animals of the high line, nor was an increase seen for animals of the low line.

6. A disease, which occurred in the colony, was found to have significantly reduced weights, gains and indexes of all animals infected. Differential infection by line did not occur.

7. The disease was contributory in reducing response, in both lines, to selection by effectively masking the phenotypic expression of genes for the characteristics.

8. The depressing effects of inbreeding on litter size in the high line, despite an increase in body size in this line over generations, indicate that inbreeding can directly reduce fertility without a concomitant reduction in maternal body size. Whether the reduction is due to reduced ovulation or increased prenatal mortality has not been determined.
9. Random genetic drift due to small effective population sizes was hypothesized as the cause of the significant differences seen between replicates and may also have reduced response to selection in both lines.

BIBLIOGRAPHY

Barnett, S. A. 1965. Adaptations of mice to cold. Cambridge Philosophical Society Biological Reviews 40:5-51.

Bateman, N. 1954. The measurement of milk production of mice through preweaning growth of suckling young. Physiology and Zoology 27:163-173.

Bateman, N. 1966. Ovulation and post-ovulation losses in strains of mice selected for large and small litter sizes. Genetical Research 8:229-241.

Bereskin, B. 1972. Monte Carlo studies of selection and inbreeding in swine. IV. Selection response. Journal of Animal Science 34:726-736.

Bereskin, B., C. E. Shelby and L. N. Hazel. 1969. Monte Carlo studies of selection and inbreeding in swine. I. Genetic and phenotypic trends. Journal of Animal Science 29:678-686.

Bohren, B. B., W. G. Hill and A. Robertson. 1966. Some observations on asymmetrical correlated responses to selection. Genetical Research 7:44-57.

Bowman, J. C. 1962. Recurrent selection. II. An experimental study with mice and Drosophila. Genetical Research 3:333-351.

Bowman, J. C. and D. S. Falconer. 1960. Inbreeding depression and heterosis of litter size in mice. Genetical Research 1:262-274.

Braden, A. W. H. 1957. Variation between strains in the incidence of various abnormalities of egg maturation and fertilization in the mouse. Journal of Genetics 55:476-486.

Bradford, G. E. 1968. Selection for litter size in mice in the presence and absence of gonadotropin treatment. Genetics 58:283-295.

Bradford, G. E. 1971a. Effects of selecting for litter size and its components in mice. In: Genetics lectures, Vol. 2, ed. by Ralph Bogart. Corvallis, Oregon State University Press. p. 101-117.

Bradford, G. E. 1971b. Growth and reproduction in mice selected for rapid body weight gain. Genetics 69:499-512.

Brumby, R. J. 1960. The influence of the natural environment on growth in mice. Heredity 14:1-18.

Butler, L. 1952. A study of size inheritance in the house mouse. II. Analysis of five preliminary crosses. Canadian Journal of Zoology 30:154-171.

Carmon, J. G. 1963. Heterosis, combining ability and maternal effects in mice. Journal of Genetics 58:225-231.

Castle, W. E. 1926. The explanation of hybrid vigor. Proceedings of the National Academy of Sciences (Washington, D. C.) 12:16-19.

Chai, C. K. 1956a. Analysis of quantitative inheritance of body size in mice. I. Hybridization and maternal influence. Genetics 41:157-164.

Chai, C. K. 1956b. Analysis of quantitative inheritance of body size in mice. II. Gene action and segregation. Genetics 41:165-178.

Chai, C. K. 1957. Analysis of quantitative inheritance of body size in mice. III. Dominance. Genetics 42:601-607.

Chai, C. K. 1961. Analysis of quantitative inheritance of body size in mice. IV. An attempt to isolate polygenes. Genetical Research 2:25-32.

Chai, C. K. 1966. Characteristics in inbred mouse populations plateaued by directional selection. Genetics 54:743-753.

Chai, C. K. 1968. Analysis of quantitative inheritance of body size in mice. V. Effects of small numbers of polygenes on similar genetic backgrounds. Genetical Research 11:239-246.

Cockrem, F. 1959. Selection for relationships opposite to those predicted by the genetic correlation between two traits in the house mouse (Mus musculus). Nature (London) 183:342-343.

Comstock, R. E. 1973. Growth in mice. (Abstract) Proceedings of the 13th International Congress of Genetics, Genetics (Supplement) 74:51-52.

Comstock, R. E., M. Singh and F. D. Enfield. 1963. Selection for growth in mice: crossbred performance. (Abstract) Journal of Animal Science 22:1109.

Cox, D. F., J. R. Legates and C. C. Cockerham. 1959. Maternal influence on body weight. Journal of Animal Science 18:519-527.

Dalton, D. C. and T. L. Bywater. 1963. The effect of selection for litter size and litter weight at weaning in mice maintained on two diets. Animal Production 5:317-326.

Doolittle, D. P., S. P. Wilson and L. L. Hulbert. 1972. A comparison of multiple trait selection methods in the mouse. Journal of Heredity 63:366-372.

Eisen, E. J. 1970. Maternal effects on litter size in mice. Canadian Journal of Genetics and Cytology 12:209-216.

Eisen, E. J. 1972. Long-term selection response for 12-day litter weight in mice. Genetics 72:129-142.

Eisen, E. J., J. E. Legates and O. W. Robison. 1970. Selection for 12-day litter weight in mice. Genetics 64:511-532.

Eisen, E. J. and J. P. Hanrahan. 1973. Genetic drift and inbreeding depression in quantitative traits in mice. (Abstract) Proceedings of the 13th International Congress of Genetics, Genetics (Supplement) 74:70.

El Oksh, H. A., T. M. Sutherland and J. J. Williams. 1967. Prenatal and postnatal maternal influence on growth in mice. Genetics 57:79-94.

Falconer, D. S. 1952. The problem of environment and selection. American Naturalist 86:293-298.

Falconer, D. S. 1953a. Selection for large and small size in mice. Journal of Genetics 51:470-501.

Falconer, D. S. 1953b. Asymmetrical response in selection experiments. In: Symposium on genetics of population structure, ed. by Adriano A. Buzzati-Traverso. Pavia, Italy, p. 16-41.

Falconer, D. S. 1954. Validity of the theory of genetic correlation. An experimental test with mice. Journal of Heredity 45:42-44.

Falconer, D. S. 1955. Patterns of response in selection experiments with mice. Cold Springs Harbor Symposium on Quantitative Biology 20:178-196.

Falconer, D. S. 1960a. Introduction to quantitative genetics. New York, Ronald Press. 365 p.

Falconer, D. S. 1960b. Selection of mice for growth on high and low planes of nutrition. Genetical Research 1:91-113.

Falconer, D. S. 1960c. The genetics of litter size in mice. Journal of Cellular and Comparative Physiology 56 (Supplement i):153-167.

Falconer, D. S. 1963. Quantitatively different responses to selection in opposite directions. In: Statistical genetics and plant breeding, ed. by W. D. Hanson and H. F. Robinson. Published by National Research Council, National Academy of Sciences 982: 487-490.

Falconer, D. S. 1964. Maternal effects and selection response. In: Genetics today. Proceedings of the 11th International Congress of Genetics (The Hague, 1963) 3:763-774.

Falconer, D. S. 1973. Replicated selection for body weight in mice. (Abstract) Proceedings of the 13th International Congress of Genetics, Genetics (Supplement) 74:76.

Falconer, D. S. and M. Latyszewski. 1952. The environment in relation to selection for size in mice. Journal of Genetics 51:67-80.

Falconer, D. S. and J. W. B. King. 1953. A study of the selection limits in the mouse. Journal of Genetics 51:561-581.

Falconer, D. S. and R. C. Roberts. 1960. Effect of inbreeding on ovulation rate and foetal mortality in mice. Genetical Research 1:422-430.

Fowler, R. E. 1958. The growth and carcass composition of strains of mice selected for large and small body size. Journal of Agricultural Science 51:137-148.

Fowler, R. E. 1962. The efficiency of food utilization, digestibility of food-stuffs and energy expenditure of mice selected for large or small body size. Genetical Research 3:51-68.

Fowler, R. E. and R. G. Edwards. 1960. The fertility of mice selected for large or small body size. Genetical Research 1:393-407.

Frahm, R. R. and M. A. Brown. 1973. Direct and correlated selection responses for pre- and postweaning growth in mice. (Abstract) Proceedings of the 13th International Congress of Genetics, Genetics (Supplement) 74:83.

Goodale, H. D. 1938. A study of the inheritance of body weight in the albino mouse by selection. Journal of Heredity 29:101-112.

Goodale, H. D. 1941. Progress report on possibilities in progeny-test breeding. Science 94:442-443.

Gruneberg, H. 1939. Fertility in cross-bred mice. Journal of Heredity 30:83-84.

Haldane, J. B. S. 1936. The amount of heterozygosis to be expected in an approximately pure line. Journal of Genetics 32:375-391.

Hanrahan, J. P., E. J. Eisen and J. E. Legates. 1973. Effects of population size and selection intensity on short-term response to selection for post-weaning gain in mice. Genetics 73:513-530.

Hanrahan, J. P., A. C. Hooper and J. C. McCarthy. 1973. Effects of divergent selection for body weight on fibre number and diameter in two mouse muscles. Animal Production 16:7-16.

Hansson, A. and G. Lindkvist. 1962. Selection for general and specific combining ability with regard to body weight in mice. K. LantbrHogskol. Ann. (Uppsala) 28:215-233. (Animal Breeding Abstracts 31:2351)

Hayman, B. I. and K. Mather. 1953. The progress of inbreeding when homozygotes are at a disadvantage. Heredity 7:165-183.

Hetherington, C. M. 1972. The effect of paternal genotype on parity-dependent changes in the decidual cell reaction, placental weight and fetal weight in the mouse. Journal of Reproduction and Fertility 31:83-89.

Hill, W. G. and A. Robertson. 1966. The effect of linkage on limits to artificial selection. Genetical Research 8:269-294.

Kidwell, J. F. and A. Howard. 1969. The inheritance of growth and form in the mouse. I. Diallel analyses of weight from birth through ten weeks. Growth 33:269-289.

King, J. W. B. and G. B. Young. 1957. Maternal influences on litter size in pigs. Journal of Agricultural Science 48:457-463.

Korkman, N. 1957. Selection with regard to the sex difference of body weight in mice. Hereditas 43:665-678.

Korkman, N. 1961. Selection for size in mice in different nutritional environments. Hereditas 47:342-356.

Land, R. B. 1970. Genetic and phenotypic relationships between ovulation rate and body weight in the mouse. Genetical Research 15:171-182.

Land, R. B. and D. S. Falconer. 1969. Genetic studies of ovulation rate in the mouse. Genetical Research 13:25-46.

Lang, B. J. and J. E. Legates. 1969. Rate, composition and efficiency of growth in mice selected for large and small body weight. Theoretical and Applied Genetics 39:306-314.

Legates, J. E. 1972. The role of maternal effects in animal breeding. IV. Maternal effects in laboratory species. Journal of Animal Science 35:1294-1302.

Lewis, W. L. and E. J. Warwick. 1953. Effectiveness of selection for body weight in mice. Journal of Heredity 44:233-238.

Li, C. C. 1955. Population genetics. Chicago, University of Chicago Press. 365 p.

MacArthur, J. W. 1944a. Genetics of body size and related characters. I. Selecting small and large races of the laboratory mouse. American Naturalist 78:142-157.

MacArthur, J. W. 1944b. Genetics of body size and related characters. II. Satellite characters associated with body size in mice. American Naturalist 78:224-237.

MacArthur, J. W. 1949. Selection for small and large body size in the house mouse. Genetics 34:194-209.

MacDowell, E. C., E. Allen and C. G. MacDowell. 1929. The relation of parity, age and body weight to the number of corpora lutea in mice. Anatomical Research 41:267-272.

Machin, D. and S. Page. 1973. Effects of reduction of litter size on subsequent growth and reproductive performance in mice. Animal Production 16:1-6.

Martin, T. G., F. E. Harrington and D. L. Hill. 1963. Effects of mating system on ovulation, implantation and litter size in mice. (Abstract) In: Genetics today. Proceedings of the 11th International Congress of Genetics (The Hague, 1963) 1:155.

McCarthy, J. C. 1965. The effect on litter size of crossing inbred strains of mice. Genetics 51:217-222.

McCarthy, J. C. 1967. The effects of inbreeding on the components of litter size in mice. Genetical Research 10:73-80.

McCarthy, J. C., I. Byrne and A. C. Hooper. 1973. Effects of selection for body size on the weight and cellular structure of seven different muscles in mice. (Abstract) Proceedings of the 13th International Congress of Genetics, Genetics (Supplement) 74:166.

McLaren, A. 1962. The relation between natural fecundity and response to follicle-stimulating hormone. Journal of Endocrinology 25:137-144.

McLellan, C. R., Jr. and R. R. Frahm. 1973. Direct and correlated responses to two-way selection for hindleg muscle system weight in mice. Journal of Animal Science 36:442-451.

Miller, R. H., J. E. Legates and C. C. Cockerham. 1963. Estimation of nonadditive hereditary variance in traits of mice. Genetics 48:177-188.

Monteiro, L. S. and D. S. Falconer. 1966. Compensatory growth and sexual maturity in mice. Animal Production 8:179-192.

Moore, R. W., E. J. Eisen and L. C. Ulberg. 1970. Prenatal and postnatal maternal influences of growth in mice selected for body weight. Genetics 64:59-68.

Nagi, J. 1971. Heterosis and combining and maternal abilities in mouse litter weight. Canadian Journal of Animal Science 51:687-695.

Nash, D. J. and G. W. Gowan. 1962. Effects of X-irradiation upon postnatal growth in the mouse. Biological Bulletin 122:115-136.

Newman, J. A. 1960. Reciprocal recurrent selection for body weight in the mouse. Ph. D. Thesis, University of Edinburgh. (as cited in Roberts, 1965)

Parker, R. J., L. D. McGilliard and J. L. Gill. 1969. Genetic correlation and response to selection in simulated populations. I. Additive model. Theoretical and Applied Genetics 39:365-370.

Parker, R. J., L. D. McGilliard and J. L. Gill. 1970. Genetic correlation and response to selection in simulated populations. II. Model of complete dominance. Theoretical and Applied Genetics 40:106-110.

Rahnefeld, G. W., W. J. Boylan, R. E. Comstock and M. Singh. 1963. Mass selection for post-weaning growth in mice. Genetics 48:1567-1583.

Rahnefeld, G. W., R. E. Comstock, W. J. Boylan and M. Singh. 1965. Genetic correlation between growth rate and feed per unit gain in mice. Journal of Animal Science 24:1061-1066.

Roberts, R. C. 1960. The effects on litter size of crossing lines of mice inbred without selection. Genetical Research 1:239-252.

Roberts, R. C. 1965. Some contributions of the laboratory mouse to animal breeding research. Part I. Animal Breeding Abstracts 33:339-353.

Roberts, R. C. 1966a. The limits to artificial selection for body weight in the mouse. I. The limits attained in earlier experiments. Genetical Research 8:347-360.

Roberts, R. C. 1966b. The limits to artificial selection for body weight in the mouse. II. The genetic nature of the limits. Genetical Research 8:361-375.

Roberts, R. C. 1967a. The limits to artificial selection for body weight in the mouse. III. Selection from crosses between previously selected lines. Genetical Research 9:73-85.

Roberts, R. C. 1967b. The limits to artificial selection for body weight in the mouse. IV. Sources of new genetic variance--irradiation and outcrossing. Genetical Research 9:87-98.

Roberts, R. C. 1973. Food consumption in mice selected for high and low body weight. (Abstract) Proceedings of the 13th International Congress of Genetics, Genetics (Supplement) 74:232.

Robertson, A. 1961. Inbreeding in artificial selection programs. Genetical Research 2:189-194.

Rutledge, J. J., O. W. Robison, E. J. Eisen and J. E. Legates. 1972. Dynamics of genetic and maternal effects in mice. Journal of Animal Science 35:911-918.

Stanier, M. W. and L. E. Mount. 1972. Growth rate, food intake and body composition before and after weaning in strains of mice selected for mature body weight. British Journal of Nutrition 28:307-325.

Sutherland, T. M., P. E. Biondini, L. H. Haverland, D. Pettus and W. B. Owen. 1970. Selection for rate of gain, appetite and efficiency of feed utilization in mice. Journal of Animal Science 31:1049-1057.

Synenki, R. M., E. J. Eisen, G. Matrone and O. W. Robison. 1972. Thyroid activity in lines of mice selected for large and small body weight. Canadian Journal of Genetics and Cytology 14:483-494.

Timon, V. M. and E. J. Eisen. 1969. Comparison of growth curves of mice selected and unselected for postweaning gain. Theoretical and Applied Genetics 39:345-351.

Warwick, E. J. and W. L. Lewis. 1954. Growth and reproductive rates of mice. Journal of Heredity 45:35-38.

White, J. M. 1972. Inbreeding effects upon growth and maternal ability in laboratory mice. Genetics 70:307-317.

White, J. M., J. E. Legates and E. J. Eisen. 1968. Maternal effects among lines of mice selected for body weight. Genetics 60:395-408.

Wright, S. 1922. Coefficients of inbreeding and relationship. American Naturalist 56:330-338.

Wright, S. 1965. The interpretation of population structure by F-statistics with special regard to systems of mating. Evolution 19:395-420.

Wilson, S. P., H. D. Goodale, W. H. Kyle and E. F. Godfrey. 1971. Long-term selection for body weight in mice. Journal of Heredity 62:228-234.

Young, G. B. 1953. A study of genotype-environmental interactions in mice. Journal of Agricultural Science 43:218-222.

Young, C. W. and J. E. Legates. 1965. Genetic, phenotypic and maternal interrelationships of growth in mice. Genetics 52:563-576.

Young, C. W., J. E. Legates and B. R. Farthing. 1965. Prenatal and postnatal influences on growth, prolificacy and maternal performance in mice. Genetics 52:553-561.