SELECTION FOR SMALL AND LARGE BODY SIZE IN THE HOUSE MOUSE*[1]

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INTRODUCTION

THE animal breeder's main and typical problems concern economic characters, such as meat or wool production, yield and fat content of milk, number and size of eggs. These are complex, quantitative characters, multifactorial and strongly influenced by environmental conditions. The great majority of the fundamental anatomical, physiological and taxonomic characters, and basic processes like growth and reproduction, are of this class. For man to change and guide improvements in such quantitative characters usually requires continuous, gradual selection of large numbers of individuals over a long series of generations. This is practically a return to DARWIN's artificial selection by slow increase of small variations, which must be credited with the principal improvement of domestic animals over past centuries, and appears to be the chief hope of further improvements to come.

The main object of this paper is to describe further the primary and secondary effects of a form of mass selection in an experiment designed to create for laboratory uses from one foundation stock both a small and large race of house mice. Progress reports (MACARTHUR 1944, MACARTHUR and CHIASSON 1945) gave the procedures and results for the first eight generations of the selections. The series is now extended to cover at least 21 generations, averaging three a year over seven years. The environment was kept similar for all the mice at any one time by having them share the same quarters, feed, care, *etc.*, except that sibs were fed and reared by their own mothers. Maternal care itself varied greatly.

SOURCES OF VARIATION

Genetic variations, the necessary raw materials for the changes in size, were presumably supplied by numerous multiple factors in nearly all chromosomes and segments, partly neutralizing each other's effects, some promoting, some retarding general growth. The field of variation was probably widened by intercrossing six inbred strains of mice of average size but of various colors. (GOODALE's (1938) successful size increases in albino mice began without

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much prior hybridization.) It would be expected that fresh new mendelian combinations and interactions of genes would be made rapidly available by segregation and assortment of chromosomes with excess plus or minus balance; and that further cryptic variation would gradually be released by crossovers within chromosomes and such new mutations as may occur. The job was to re-shuffle the size genes, and unpack and reorganize the chromosomes to bring together as many plus genes as possible in the large race, and collect the minus genes in the small race.

TYPE OF SELECTION

It seems misleading to draw sharp contrasts between mass selection and pedigree culture, genotypic selection or discontinuous selection. The traditional usage tends often to confuse the separate problems of accuracy of judging (with or without measurements), thoroughness of pedigreeing (with both, one or neither of the individual parents known), criteria of selection (by performance of the individual, of sibs, parents, progeny, etc.) and systems of mating (random or non-random breeding; as one population, or subdivided into groups). It is easily possible to modernize the cruder old form of mass selection, by adopting more quantitative methods, by keeping pedigrees, and by recognizing that inheritance even of a continuous variable, is particulate and that genotypic selection is superior to phenotypic. Mass selection, proceeding on a wide front, broad-based to avoid ill effects of inbreeding, could even be considered the most generalized form, of which group, line, family, pair and individual selection are special and, often very useful, limiting cases.

In these experiments all mice were earmarked, sexed, and individually weighed. Selections were made by comparing the growth in weight of individuals and sibships with their parents and sometimes with their progeny. Pairings among the large, for instance, were mainly at random within a single closed population, each male with several females, to pool and recombine and concentrate as far as possible the plus size genes within the selected population. Extra litters were bred from pairs proving their transmitting ability by begetting a first litter of promising body size; such reproductive selection multiplied favorable genotypes and effective growth-promoting (or growth-retarding) interactions. It was intended that only the most helpful genotypic combinations were put back into the pool.

CHANGES IN THE PRIMARY CHARACTER, BODY SIZE

From the first the body size increased noticeably in the large and diminished in the small (figure 1). The trends are quite like those made familiar in WINTER'S Illinois maize experiment, PEARL'S selection for egg number in fowls, CASTLE'S for amount of white or dark in hooded rats, several which raised or lowered resistance to specific diseases, and many others with laboratory and domestic animals. Methods used in the several experiments differ chiefly in details of choosing the foundation stock, in the pedigreeing of one or of both parents, in the numbers raised, in the selection differentials or in the heritability of the characters.

The results in our case suggest what can be done by mass selection in general, and particularly if one is interested in the age-old problem of more loaves and larger fishes.

With a little patience one can photograph the living mice. After 14 generations of mass selection, females two months old of the small race averaged less than 12 grams; those of the large race nearly 31 grams (figure 2). This difference, 19 grams, was increased further to 23 grams by seven more generations of the mass selection. Males are about 20 percent larger than females. At 60 days of age the large race males were 2.6 times as heavy as the small in the 14th generation, and 3.3 times as heavy in the 21st generation. Such size differences are maintained to maturity and old age (figure 3). These products of mass selection recall the size range from bantams to Jersey Giants, ponies to Percherons, Chihuahuas to Great Danes or Mastiffs, and even between pigmy Negritos and large races of men. It seems not unreasonable to assume that comparable size changes could be made by selection in other species of domestic birds and mammals where such size differences do not exist. One may note here that the small race mice are excitable, "of nervous temperament," a phrase often used to describe the small Mediterranean breed of fowls, small breeds of cattle, *etc.* A tendency to obesity in the large might be avoided by selecting on the basis of measurements rather than weights.

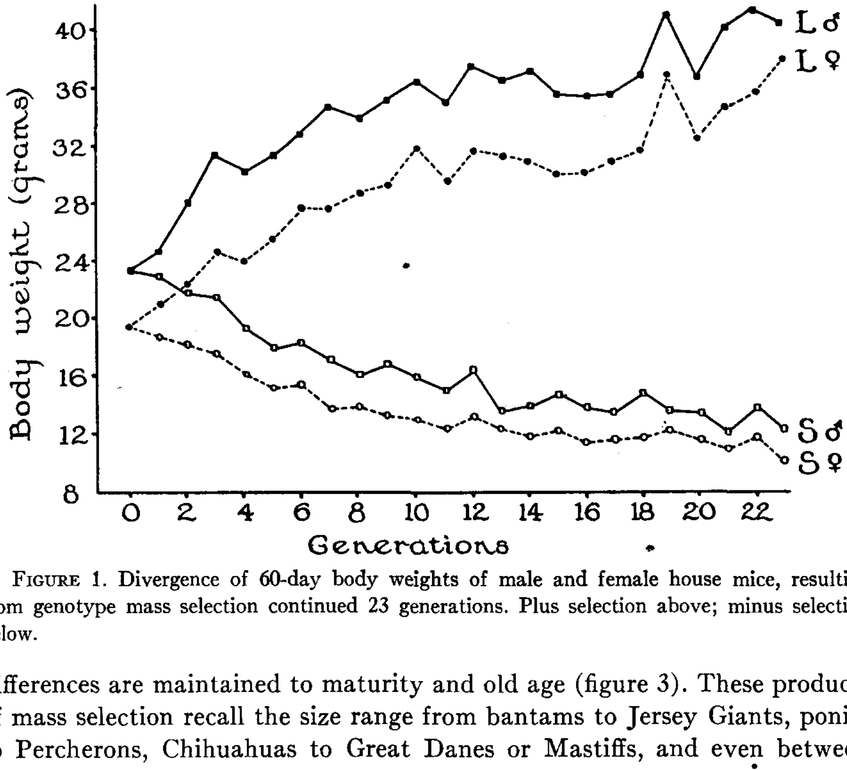

FIGURE 1. Divergence of 60-day body weights of male and female house mice, resulting from genotype mass selection continued 23 generations. Plus selection above; minus selection below.

The weight contrasts developed by the plus and minus selections are shown by a graphic method (figure 4) to help visualize the process. The ranges ceased early to overlap, so that in both sexes the smallest of the large race are distinctly larger than the largest of the small. The weight differences became increasingly evident and significant (table 1) throughout the experiment, but about 60 percent of the total change occurred in the first third of the work. Apparently the early selections picked out the gene and chromosome combinations and interactions with major size effects, and the later selections had to depend more on those with minor size effects and new cross-overs.

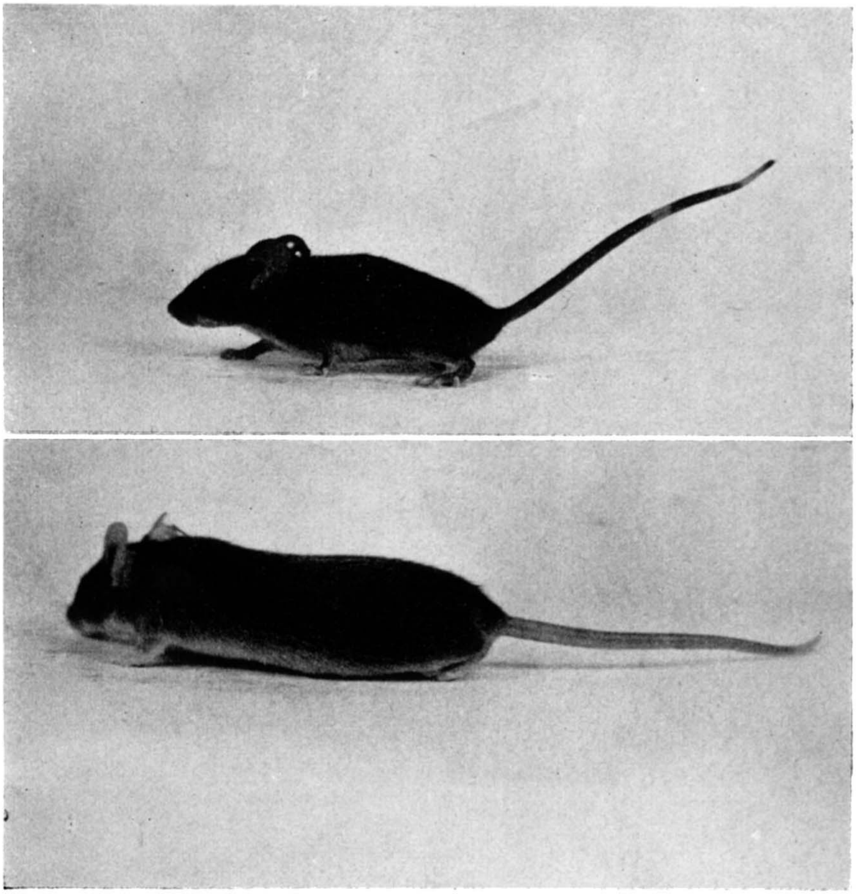

FIGURE 2. 60-day old females of the small and large races in the 14th generation of selection. Note also the differences in coat color, alertness and size of ears and tail.

Other graphs (figure 5) show well the amount of change produced by comparing weight distributions for the initial stock and the selected races. The noticeable asymmetry in most of the distributions suggests that the metric scale needs to be altered to normalize the curves. The range of absolute sizes is, of course, narrow in the small race, wide in the large.

One may quote with approval an apt statement by FISHER (1931), that "natural selection is a mechanism for generating improbability of a high order". Artificial mass selection also generates improbability of a very high order, since it makes sizes beyond the extreme tails of the original frequency distribution the very center and average of the selected populations. In fact extremes such as would and perhaps could never occur in the first generation become common and usual. Under selection pressure minus genes more and more collect in the small, plus genes in the large strain. Two-way selection deliberately culls average specimens and draws non-random samples, the breeding of which makes further and more extreme deviations likely. In terms of generation O the range between S-21 and L-21 means is 10.9 standard deviations. The chance of drawing from the foundation stock an individual male as small as the S-21 mean would be of the order of 1 in 100,000; the chance of picking an average L-21 male would occur only about once in a population of a thousand million; here again the skewness is obvious. The selection process resembles valve action, permitting flow only in a preferred direction. Each step makes possible the next forward step. These steps depending as they do on a particular succession of chance cross-overs, matings,

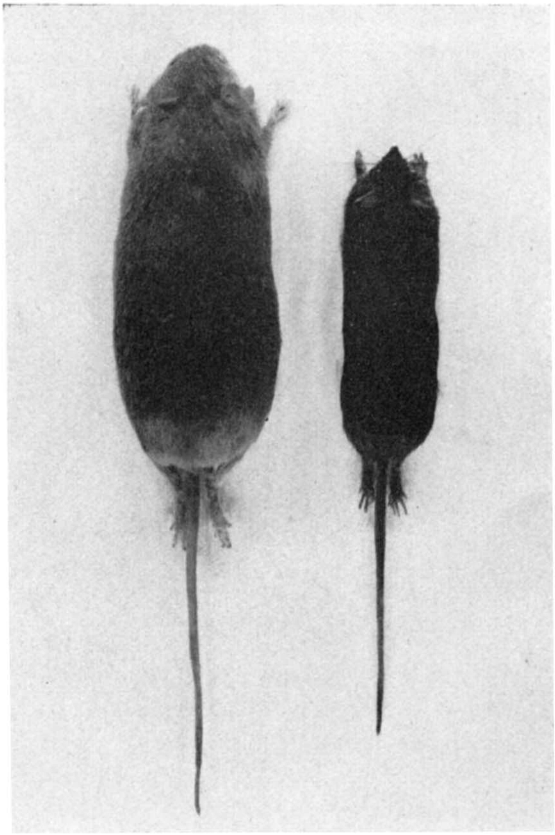

FIGURE 3. Three month old males of the 23rd generation; weight of the small 16.2 gms, of the large 58.0 gms.

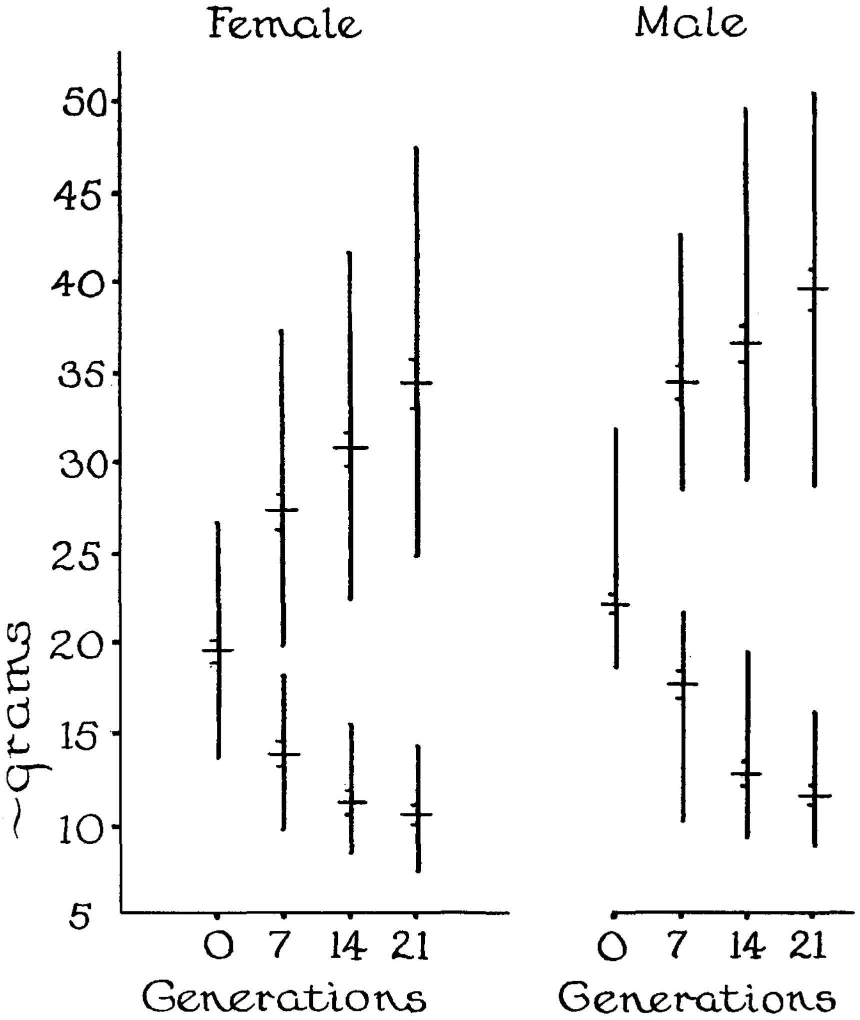

FIGURE 4. Vertical lines show the ranges, cross lines show the mean and three standard errors of the mean for the populations at the beginning and after 7, 14 and 21 generations of the mass selection.

TABLE 1

Divergence of small and large races of mice in grams body weight at 60 days, and significance of the inter-racial differences.

GENERATION	FEMALES		MALES	
	GRAMS	STANDARD ERRORS	GRAMS	STANDARD ERRORS
0	0		0	
7	13.95	29.4	17.44	47.8
14	19.02	51.6	22.86	52.4
21	23.67	55.5	27.88	54.7

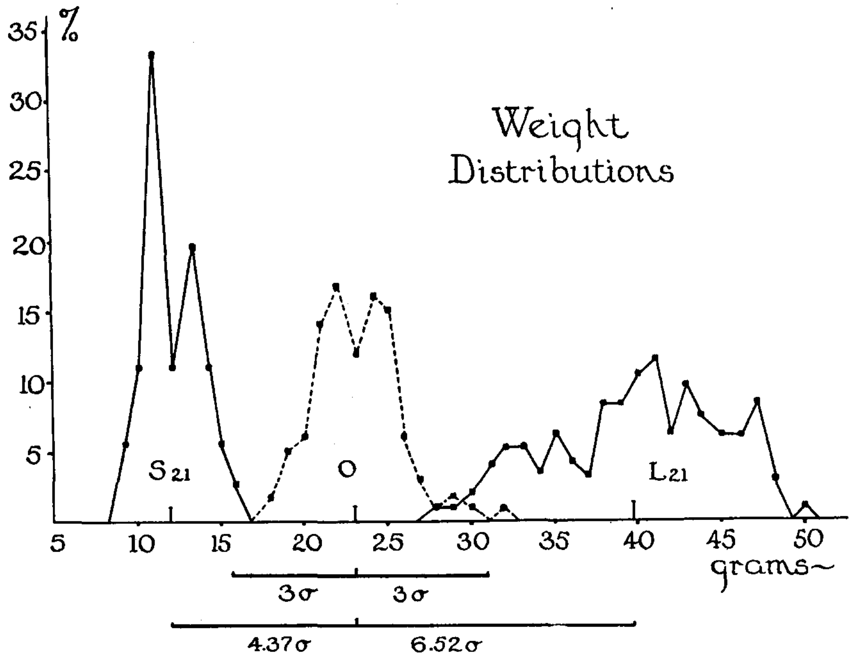

FIGURE 5. The distribution of male 60-days weights for the initial stock (0, at center), and after 21 generations of minus selections (S-21, at left), and of plus selections (L-21, at right). The standard deviations below refer to the foundation stock 0.

combinations, *etc.* must be in any precise sense, largely unrepeatable and irreversible.

As the mean weights increase the standard deviations, of course, also increase (table 2). But it will be noticed that the coefficients of variability con-

TABLE 2

Sizes (body weights in grams at 60 days) of male and female house mice from the unselected foundation stock (generation 0), and from the small and large races after 7, 14 and 21 generations of plus and minus selection.

GENERATION	MALE			FEMALE		
	MEAN WEIGHT	STANDARD DEVIATION	COEFFICIENT OF VARIABILITY	MEAN WEIGHT	STANDARD DEVIATION	COEFFICIENT OF VARIABILITY
L-21	39.85±.47	5.10	12.80	34.46±.49	5.12	14.86
L-14	36.79±.37	3.66	9.95	30.71±.31	3.29	10.71
L- 7	34.69±.37	3.59	10.34	27.51±.39	3.80	13.81
O	23.16±.26	2.56	11.01	19.51±.25	2.65	13.52
S- 7	17.25±.30	2.61	15.13	13.56±.27	2.34	17.36
S-14	13.93±.23	2.13	15.29	11.69±.20	1.74	14.89
S-21	11.97±.28	1.71	14.29	10.79±.26	1.47	13.62

tinue throughout at about the same percentage level undiminished by selection. Apparently the small and large races are not becoming more uniform in weight, though genetic variability is theoretically steadily lessened (compare table 6). This suggests that when genetic variation is reduced, plastic modifications increase to a compensating degree. It is as though the mice develop natural phenocopies of genetic weight differences; and recalls the old principle of organic selection.

TABLE 3

Differences in grams of mean body weights (both sexes) of the small and large races at birth, 30 days and 60 days, and the increase during the first and second months.

	BIRTH-FED	30 DAYS	60 DAYS	MATURE	INCREASE		
					0–30 DAYS	30–60 DAYS	2–6 MONTHS
S-21	1.04	10.81	11.44	17.27	10.4×	1.08×	1.51×
L-21	1.44	22.95	37.16	56.95	15.8×	1.57×	1.54×
L-21/S-21	1.38	2.12	3.24	3.30			

We may ask how these marked size differences came about in ontogeny. Our own data are chiefly for the postnatal period. Taking GREGORY and CASTLE'S (1931) work with rabbits as a cue about the prenatal period, the eggs of small and large mothers are probably still of equal size (perhaps about 0.06 mm in diameter). The suggestion is that, starting without initial differences in capital, the growth of the large race embryo is considerably faster than in the small race embryo (table 3). Birth-fed young are already 38 percent heavier in the large mice. In the first month of postnatal growth, the small race young increase about 10 times, the large race young more than 15 times in weight. The same difference in rate is found also in the second month. The later gains, from two to six months, however, are nearly equal on a percentage basis (151× for small, and 154× for large). At maturity the large are some 3.3 times larger. As we interpret the data, growth during the first 60 days is about half again as rapid in the large mice. That is the gist of the change induced by the selections.

It is as though two racers start from scratch and run as far as they can in the same time. One of them by getting off to a quick start and by showing an early burst of speed, takes a long lead, more than holds it through the race, and at the end has gone three times as far.

Since there is a high correlation between birth weight and later mature weights an early estimate of potential meat production seems practicable. Also since early growth is so important, it might be worthwhile to try selecting directly for birth weight itself, making due allowances for such influences as age of mother and number in litter.

We may also ask whether it is as easy to decrease as to increase body size

TABLE 4

Estimates of the efficiency of the minus and plus selections vary according to scales of measurement used.

DIFFERENCE IN	$O-S_{21}$		$O-L_{21}$	
	MALES	FEMALES	MALES	FEMALES
grams	−11.19	− 8.72	+16.71	+14.95
percent	93.5	80.8	72.2	76.6
logs	.2866	.2572	.2560	.2471

by selection. The answer (table 4) varies with the metric scale adopted. In absolute grams or pounds the gains by plus selection much exceed the losses by minus selection; if mice of the small race had lost as many grams as the large ones gained, their weight would be less than three or four grams, and must soon approach the zero point. The change in the small is, however, greater by a log scale, or in percentage by which a greater value exceeds a lesser.

TABLE 5

Deviations (in σ) from their population means of sires and dams chosen for breeding.

GENERATIONS	SMALL RACE		LARGE RACE	
	SIRES	DAMS	SIRES	DAMS
0– 7	1.71	1.04	2.31	1.41
8–14	.66	.48	1.89	1.41
15–21	1.07	.41	1.60	.63
0–21	1.18	.69	1.80	1.01

We planned to try equally hard to lower and to raise the body size. It turns out in retrospect, however (table 5), that there was actually a higher selection differential in the large than in the small. This may have been due to the more numerous and larger litters from which to choose élite for plus selection.

TABLE 6

Measures of success in selecting for extremes of body size at 60 days.

GENERATIONS	PAIRS PRODUCING YOUNG	DIVERGENCE GRAMS PER PAIR	PROGENY RAISED	DIVERGENCE GRAMS PER 100 YOUNG	DIVERGENCE HELD / DIVERGENCE SOUGHT %
0– 7	201	.077	2205	1.41	23.78
8–14	260	.021	2371	.45	12.28
15–21	326	.015	2474	.40	11.44
0–21	789	.033	7050	.73	16.96

TABLE 7

Relation of number of young per litter to weight of young at birth, and weight of males at 30 days and 60 days in large race mice (L-21).

LITTER SIZE	MEAN WEIGHT (GRAMS) AT		
	BIRTH	30 DAYS	60 DAYS
4– 7	1.58	26.87	43.99
8– 9	1.51	22.22	39.43
10–11	1.52	21.78	39.11
12–14	1.38	23.76	38.90

Through the experiment the average generation consisted of 37 pairs successfully bred and 336 young reared to 60 days (table 6). The response to selection effort was roughly measured in terms of the divergence per pair bred, or per 100 young raised, or by dividing successes by pretensions (last column). This last is an estimate of heritability; it matches the superiority of the young with the superiority (over the parental generation) of the chosen parents. By all three methods it is clear that the selection has achieved diminishing returns as the experiment proceeded. Heritability has declined from about 25 to 10 percent. The size variation is still there, but less of it is genetic. Incidentally, both we and GOODALE are currently troubled with some infertility of matings. Overcoming this, we may expect some further returns until unknown limits are reached. The small race is not yet quite as small as the closely related wild Asiatic species, *Mus bactrianus*.

TABLE 8

The effect of foster mothers on growth of young exchanged between S-18 and L-18 mothers.

STOCK	FOSTERED BY	WEIGHT (GRAMS)		
		BIRTH-FED	30 DAYS	60 DAYS
S-18	Small	1.07	10.21	13.05
S-18	Large	1.17	13.26	15.89
L-18	Small	1.47	21.34	35.40
L-18	Large	1.42	19.61	34.11

If there are size alleles, or an excess plus or minus balance, in each of the twenty pairs of mouse chromosomes, it would require a population exceeding a million million merely to obtain in one generation the full free assortment of the chromosomes. It is, of course, impossible to obtain simultaneously all the various cross-overs which would yield plus or minus imbalance. With a necessarily small population great numbers of promising potential combinations and interactions are continually discarded untested, and irretrievably lost. If such an experiment with mice or any larger domestic animal could be carried out several times or cooperatively in several places, the end products, doubtless differing in genotypes, due to different drift and different selections, could be interbred, both to improve fertility and to make possible new progress by size selection. At this point mass selection would turn into group selection and the intercrossing of temporarily isolated groups could secure for the breeder the equivalent of the rapid evolutionary advances predicted by WRIGHT.

The mother's genetic influence on the birth weight of her young is evident. A relation also exists between the number of young born per litter and their postnatal growth (table 7). Where young are fewer in a litter they have a weight advantage at birth which lasts to 30 and even to 60 days. This could nullify some plus selection and tend to reduce litter size in the large race.

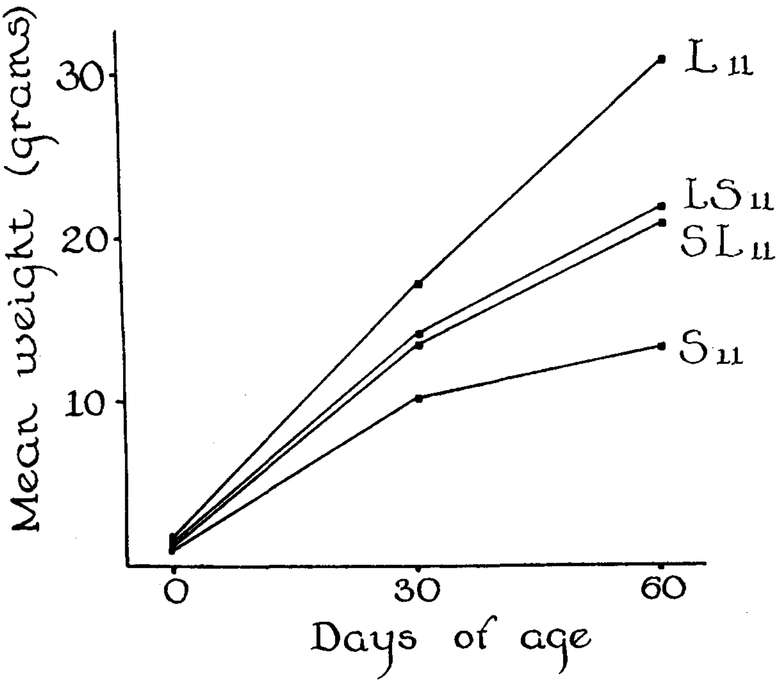

FIGURE 6. Growth of mice of the small race (S-11), the large race (L-11), and of their hybrids (LS from large mother and small father).

The attention recently drawn to milk factors or agents lead to a perhaps unnecessary test of growth when new-born young were exchanged and nursed and reared by foster mothers, a large mother feeding small race young (table 8). The "small" young grew to small size even with a large mother to foster them; the "large" young grew large on the small mother's milk. We can only conclude that if an elephant baby grows by pounds daily, it is not because it was fed on elephant's milk, but because it was an elephant's child. It is the grower's genotype that counts chiefly here, as the limiting factor in growth.

To determine whether any isolation was developing between the small and large races, reciprocal crosses were made in generation 11 (figure 6) and again in generation 17 (figure 7). The races interbred readily, and the few hybrids and F_2 approximated an intermediate size. The young from the cross with the large mother were 11 percent heavier at birth, 2 percent heavier at 30 days, and about equal in size at 60 days and thereafter. There is no clear indication in these small samples of any matroclinal or cytoplasmic inheritance, or of any long persistence of the nutritional advantage of being fed pre- or postnatally by a large mother. This problem can be best approached by the double mating method.

It is planned ultimately to learn more about what selection can do by studying these crosses in adequate numbers. The data from selection and from hybridization should complement; and alternately taking the races apart, and bringing them together a few times, should help us to understand both the action of selection and the nature of size inheritance.

CHANGES IN SECONDARY OR CORRELATED CHARACTERS

There was little surprise at the changes wrought in body size, unless it be in their speed and magnitude. More unexpected were the wholly unsought and unintentional changes in a number of other characters that followed in the wake of the size selections. It early dawned on all who worked with the mice that the small and large races were coming to differ in coat colors, in temperament, in proportion of parts, and in litter size. We should emphasize that at no time was selection directed on any of these secondary characters.

The by-products of mass-selection deserve attention in their own right; the by-products sometimes might have greater value or interest than the main product. It is likely that these, similar, or countless other correlated characters are to be anticipated in any such experiment with other species of animals. Pull one string and you may expect distant parts to move, because of internal hidden connections.

Examples may be given which throw some light on what Darwin called "the mysterious laws of correlation." The correlations we happened to notice affect all kinds of characters, and are caused, as we read the data, by a variety of mechanisms (drift, pleiotropy, relative growth, linkage, etc.). The associations of characters may be spurious (as in drift) or real; ephemeral, as in linkage, or enduring as in pleiotropy.

(1) A few of the large mice, none of the small, are albinos; a few of the small, none of the large, are spotted. These color genes are not known to affect growth rates, but small populations by mere chance losses among neutral genes, will gradually "drift" apart in unpredictable ways not controlled by the selections.

(2) In certain coat colors the mouse races differ sharply, by a true correlating mechanism (pleiotropy). The gene pairs, black-brown, *Bb*, and deep-dilute, *Dd*, are or act as if they are, both color and size genes. The dominants, *B* and *D*, known (CASTLE 1941) to retard general body growth are found in all the small mice; their alleles, *b* and *d*, which accelerate growth are characteristic of the large race.

(3) The small and large races came to differ also in the proportions of their chief appendages to total body dimensions. The small mice have comparatively large ears, feet and tail (figure 2). But as the body grows, the growth of appendages does not keep pace. The relative growth, or allometric constants are such that selection for greater body size will automatically produce mice with relatively smaller appendages, and this without change of genes specifically controlling appendage size (See MacArthur 1944, figs. 1–2 and MacArthur and Chiasson 1945, tables 1 and 4).

(4) When bodies increase in size, their surface areas increase more slowly than their volumes or weights. Small animals therefore present relatively large exposed surfaces, from which comparatively greater heat losses occur. One might possibly expect this to affect general activity and metabolic levels as calorimetric tests have shown. At any rate the small mice are more active, "wild," and nervous; the large ones docile and phlegmatic. The large race mice are also faster growing and more economical in gains from feed taken. A student is looking into various physiological differences, and trying to measure body heat activity, basal metabolism, and to make some endocrine assays for thyroid and pituitary glands.

Table 9

Counts of corpora lutea and fetuses in generations 12 and 13 of small and large race females bred with own and other race males.

MATINGS ♀×♂	DISTRIBUTION OF NUMBERS OF CORPORA LUTEA																			CORPORA LUTEA (MEAN)	FETUSES (MEAN)
	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23		
S S	1	2	1		1	1														7.2	5.3
S L	2		5	3	2	2														8.1	5.5
L S							3	1	3	3	1	4	2	1	1		1			15.2	10.4
L L								3	1	4		1	3	3					1	14.1	10.5

(5) It turns out also that there is an important tie between growth and reproduction. The small race mice develop slowly, breed a little later, and produce fewer young per litter. The large race are earlier and more prolific breeders. Litter size is positively correlated with body size (figures 8,9,10 and table 9). The correlating mechanism may operate through the endocrines (gonadotropin), or through relative growth, a large body having large ovaries, releasing more ova to produce more young in a litter.

(6) Linkage and crossing over of genes is almost certain to cause some correlated changes. Extreme selection for body size involves much sorting and reorganization of chromosomes. Multiple factors affecting two or more different characters are probably interspersed in some segments of various chromosomes. A selection for size could naturally cause a wide-spread sympathetic disturbance in many other quantitative characters, due to genic imbalance. If selection is pushed too far too fast, the organism may well be left without adequate buffer protection. There is indication that fertility is so upset. The fertility imbalance could be temporary and correctable, but mass selec-

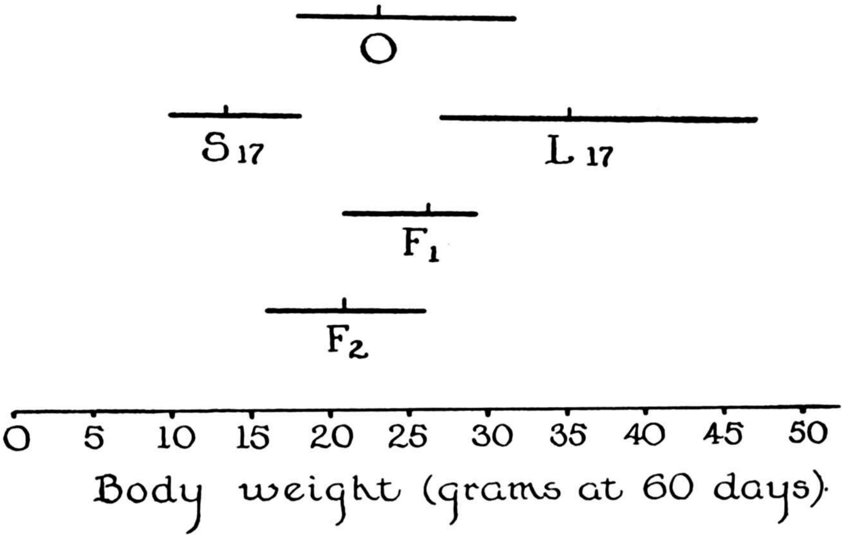

FIGURE 7. Range and mean of 60-day body weights compared in the mice of the foundation stock, the two selected races, and their F_1 and F_2 hybrids (Large ♀ × small ♂).

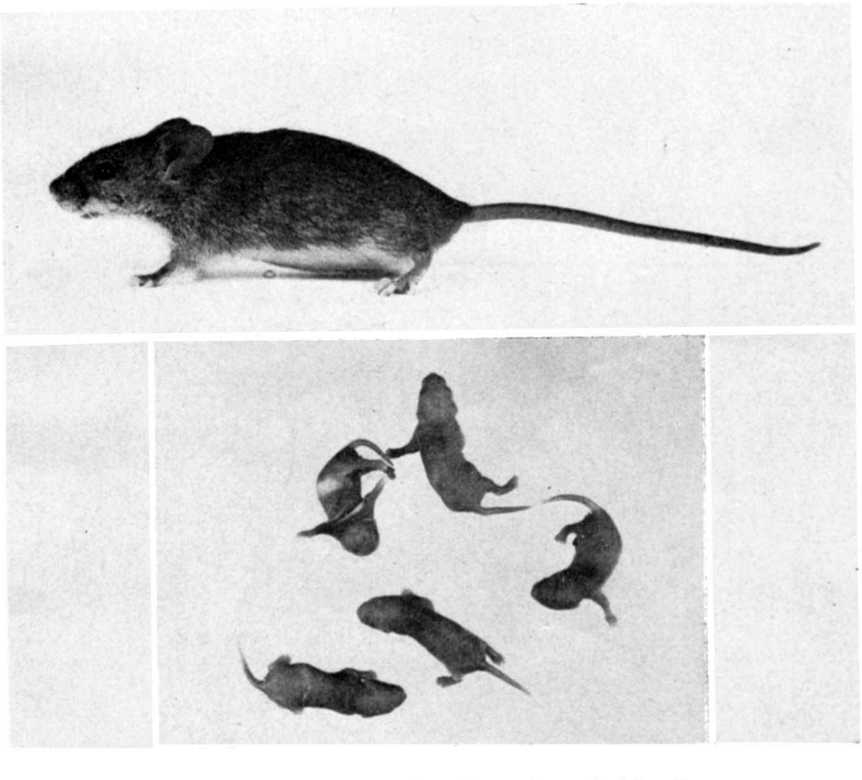

FIGURE 8. A small race (S-14) mother and a typical first litter.

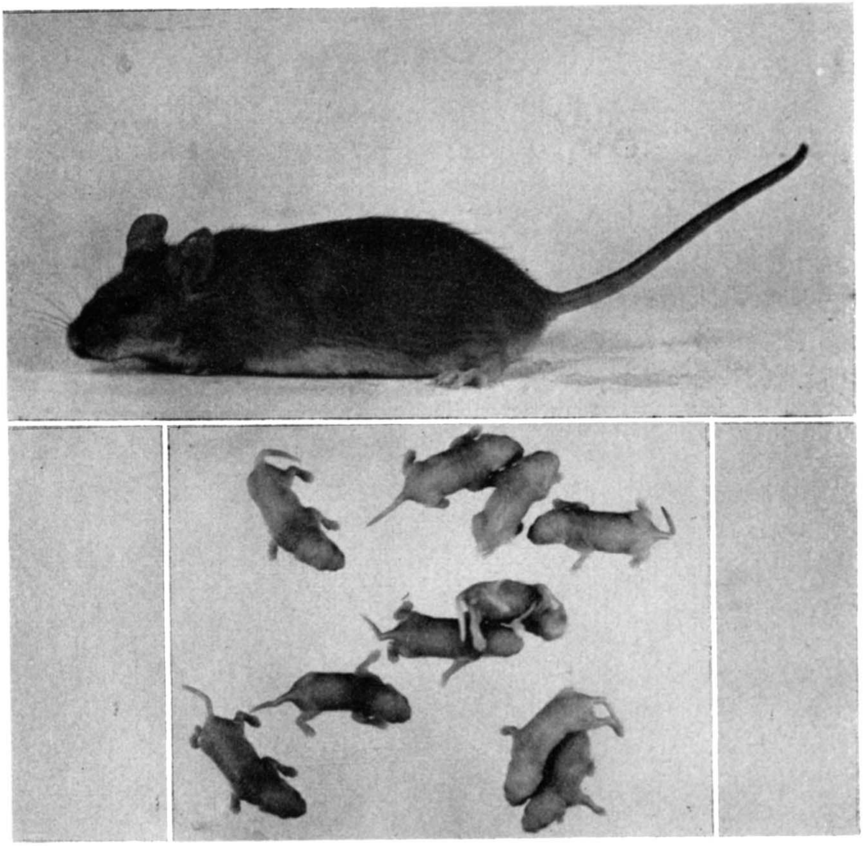

FIGURE 9. A large race mother (L-14) and a typical first litter.

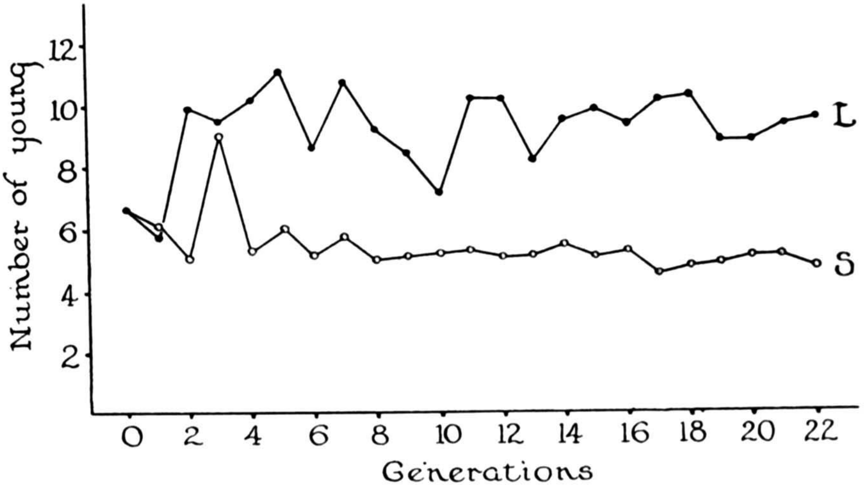

FIGURE 10. Mean number of young in the first litters of races of mice selected only for body size (weight at 60 days).

tion for one character may well necessitate or invite secondary selections for other characters.

It is unnecessary to close with any formal summary. The practical specialist is better able to judge whether the findings reported may find application with other species and other characters. It is conceivable that small races with relatively large surfaces would have some advantage for production of wool, pelts or hides; or in areas where forage is scanty. On the whole, many of the qualities commonly valued in farm animals are closely inter-related in a size complex, including large body size, faster growth, economical gains from feed, tameness in domestication, and early, rapid and efficient reproduction. Greater milk yield is almost necessarily also involved.

It may also be suggested that, since mammalogists and ornithologists have found that races of warm-blooded animals from high latitudes and altitudes are commonly of larger body size with smaller appendages and larger litters, then, possibly, by the principle of "ecological indicators," a type rather like the large race may be naturally "preadapted" to life in colder climates.

Looking back over the experiment, we should be inclined to stress: first, how strikingly an organism may be remodelled by a brief term of mass selection in such fundamental characters as its growth and reproduction; secondly and chiefly, the revealing glimpse it has given of some of the integrating mechanisms which tie together a group of characters usually studied one at a time as if independently inherited.

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