

ON THE RELATION BETWEEN LITTER SIZE, BIRTH WEIGHT, AND RATE OF GROWTH, IN MICE

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I

It was shown previously that the relationship between size of litter and average weight of litter at birth, in several species of multiparous mammals, may be represented by the equation

$$W = N^K + \text{const.}, \quad (1)$$

where W is the average birth weight of a litter, N is the number in the litter, and K is a constant (Enzmann and Crozier, 1934-35). Since $W = w \cdot N$, where w is the mean weight of a single new-born individual, it is obvious that the relation between N and w is of the form

$$w = N^{-k} + \text{const.} \quad (2)$$

The (somewhat unfortunately named) "heterogonic" relationship (Huxley, 1932) in growth rates of structurally associated parts of an organic system, otherwise referred to by the (even more unfortunate) name "dysharmonic" growth (Teissier, 1934), which it certainly does not signify, is of very general occurrence (Huxley, 1932; Teissier, 1934; Needham, 1934). It is of particular interest in its bearing upon the general theory of curves of growth, and this in a manner the consequences of which seem not to have been thoroughly appreciated (*cf.* Crozier, 1926-27). It is from this standpoint, in part, that we have been anxious to test experimentally the possible meaning of constancy of relative growth rates in an organic system. The most convenient situation in which to do this is provided by the intrauterine development of litters of various numbers in diverse species of multiparous mammals. The interpretation given for the adequacy of equation

(1) was (Enzmann and Crozier, 1934-35) that the presence of each additional fetus in a litter called forth, in the average, a proportionate fractional increase in the nutritive level of the mother, the total nutritive material available to the young being shared equally among them. This is the reasonable deduction from the fact that, when equation (1) is adequate,

$$\Delta W/\Delta N = KW/N;$$

or, the increase in weight of litter (at birth) per unit increment of number in the litter is directly proportional to the weight and inversely proportional to the number in the litter. The exponent K is then expected to have the properties of a partition coefficient. It was pointed out (Enzmann and Crozier, 1934-35) that one such important property it does exhibit, since K turns out to be essentially independent of the *kind* of mammal and of the typical mean mass of its newborn; it is thus highly non-specific. It has a magnitude $(\Delta \log W)/(\Delta \log N = 1.0) = 0.80$ to 0.90 in various series of measurements; the range is less when the value of K is obtained from the most homogeneous material, and its "best" value may be given as 0.84 .

The exponent k in equation (2) has a rather different meaning, and its size depends upon the mean birth weight of a single individual, which is comparatively specific; in genetically homogeneous material it may be expected to be even more definitely strain specific.

To extend the observational basis for these considerations we have collected further birth weights of unfed new-born mice of the Bagg albino strain, from a line inbred by brother-sister mating in this Laboratory for over 60 generations. This is the strain involved in our previous observations. Litters containing stillborn young, or in which some of the young had been destroyed by the mother, were rejected; 181 suitable first litters were obtained from mothers less than 30 weeks old. The litters were weighed as a whole, and the mean individual birth weights computed.

To test the two aspects of the interpretation suggested, the weights of the mothers were also recorded and the subsequent growth in weight of the young was measured. It is to be presumed, on the basis of theory, that the supposed increase in nutritional provisioning by the mother, as result of carrying additional young, is shared

between the mother and these young. And the subsequent growth of the young from litters of various sizes may be expected to be suggestive for an understanding of the control of growth.

II

The result of this determination of the relation between W and N is given in Table I. In Fig. 1 the data are compared with those of our earlier series (Enzmann and Crozier, 1934-35) on litters of the same strain. The agreement is satisfactorily close, although W

TABLE I

Litter size and average weight of whole litter, Bagg albino mice; second series; first litters of mothers less than 30 weeks old.

Litter size N	No. of litters	Litter weight W
1	1	(1.63)
2	3	3.07 \pm 0.37
3	6	4.49 \pm 0.07
4	10	5.75 \pm 0.01
5	26	6.28 \pm 0.09
6	31	8.09 \pm 0.09
7	28	9.25 \pm 0.09
8	34	10.09 \pm 0.11
9	15	11.30 \pm 0.09
10	11	12.05 \pm 0.13
11	4	13.10 \pm 0.047
12	6	14.50 \pm 0.089
13	1	(14.91)

tends to be consistently a little higher in the first series. The deviation observable with very small litters, and, less clearly, with very large litters, we have already commented on (Enzmann and Crozier, 1934-35). The present data are more homogeneous, from several standpoints, than those commonly available for testing the adequacy of equation (1). The slope constant in Fig. 1 is a recoverable constant in repetitive experiments with the same strain. The intercept on the $\log N = 0$ axis gives the ideal weight of 1 individual constituting a litter of 1, and thus developed in the absence of the effects of other young in the same litter. This is a little higher for our first series than for the second. It is to be presumed in general

that this weight may exhibit modifications as a function of age of mother, inbreeding, litter rank, and nutritional state. The general care of the animals in the present series was better than in the first series.

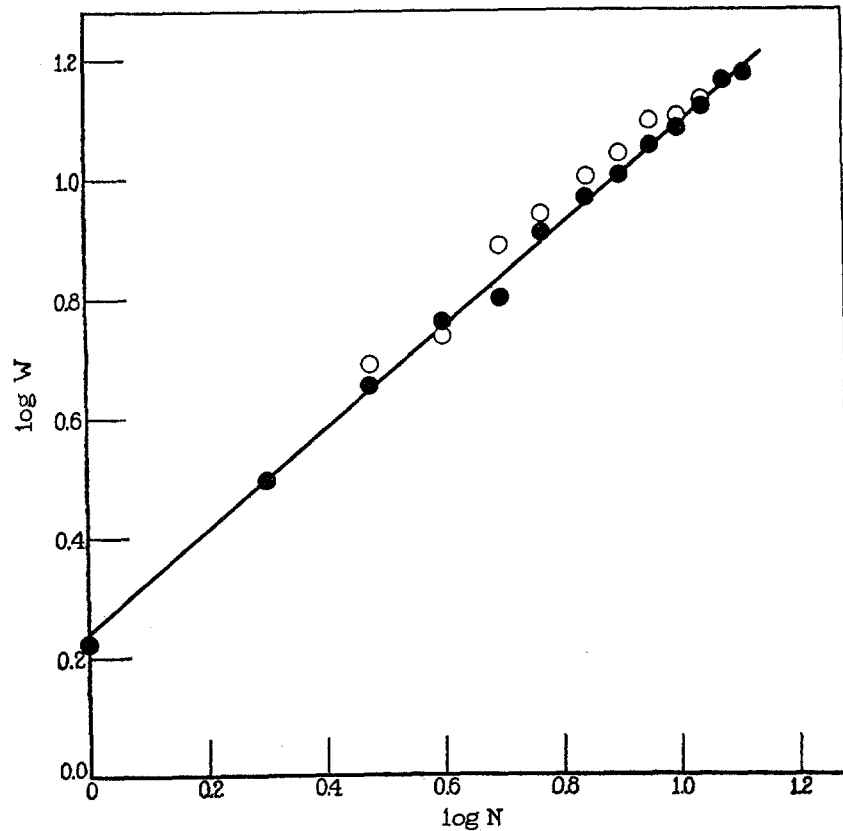


FIG. 1. Weight of a litter of mice as a function of the size of the litter (Table I). (The open circlets refer to data given in a preceding paper: Enzmann and Crozier, 1934-35; see text.)

It is worth while illustrating the really stable character of constant K . The mean birth weight of mice from small litters is about 1.5 gm.; the same value of K (0.87) is obtained from observations on pigs, with a birth weight of about 2,000 gm. (Fig. 2).

Fig. 3 shows the relationship between w , the individual average

weight, and N . This plot is of course more apparently sensitive to variation in w at fixed N than is Fig. 1. Data from diverse series of

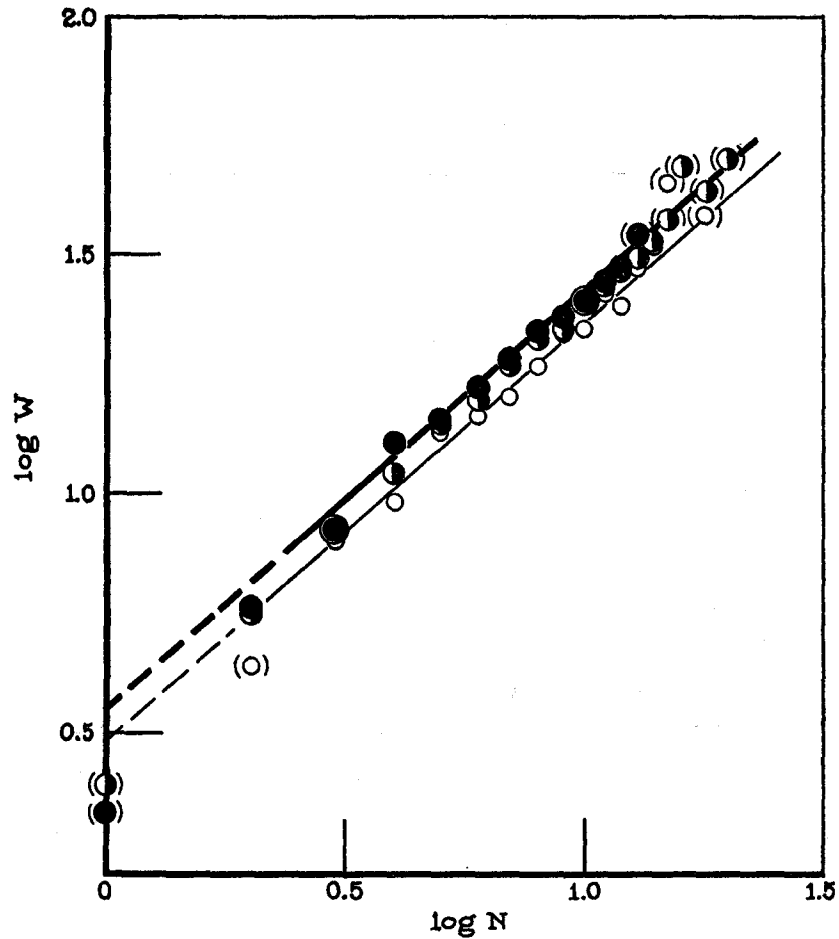


FIG. 2. Data from three series of measurements of the relation between N and W for pigs; *cf.* Lush, Hetzer, and Culbertson (1934). $K = 0.85$ to 0.87 . The points in parenthesis are based upon less than 5 litters; w_1 differs from one stock to another; hence k differs also, in proportion to $\log w_1$.

measurements show that, empirically, the slope constant (exponent) in equation (2) may be more or less type-specific, although the $\log w$ intercept is certainly very clearly strain-specific; for other mammals

this is not observed. From the standpoint of the present analysis there are two quantities which should be kept clearly in view as perhaps subject to independent genetic use. One is the "ideal weight at birth of a litter of 1"— w_1 , the $\log W$ (or $\log w$) intercept. The other is the constant k , which expresses the manner in which $\Delta w/w$ is related to $1/N$. The evidence shows that both w_1 and k may be determined by genetic constitution. The estimated values of w_1

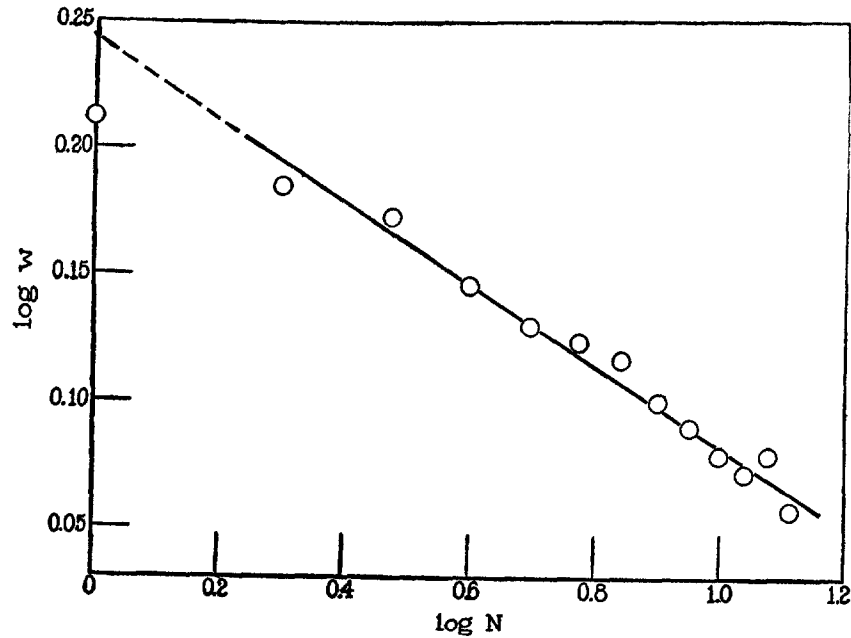


FIG. 3. The relation between average weight of one mouse at birth and the size of the litter (Tables I, II).

should give much more useful data for genetic purposes than the "average weight at birth." It is simpler and more reliable to obtain w_1 from plots such as that given in Fig. 1, but the constant k may also have its uses in comparing strains. k and w_1 are of course interrelated; k is directly proportional to $\log w_1$, since, from (1) and (2),

$$\begin{aligned}
 k (\Delta W/W) &= -K (\Delta w/w) \\
 \log (Nw) &= -(K/k) (\log w) + \text{const.} \\
 \therefore k &= -\frac{(K-1) \log w}{\log N - \text{const.}},
 \end{aligned}$$

and

$$k = \frac{(K - 1) \log w_1}{\text{const.}} \text{ when } N = 1.$$

We have already seen (Enzmann and Crozier, 1934-35) that K is practically non-specific, hence k is determined by its proportionality to $\log w_1$. Studies on the inheritance of birth weights are rarely recorded in such a way that w_1 may be estimated from the data, but it is clear that this procedure should be followed, as the tabulated mean weights are obviously influenced by heterosis phenomena and by factors affecting fertility; it is important to be in position to disentangle these effects.

III

The relationship between litter size and weight of the young expressed by equation (1) or (2) does not undergo any fundamental change during the suckling period.

We have followed the growth of a large number of suckling mice by daily weighings up to the end of the 3rd week after birth. The results are given in Table II and in Fig. 4. Systematic departures from the straight line relationship seem to occur at birth and shortly afterwards with the small litter sizes, the departures noted in connection with Figs. 1 and 2. The birth weights of very small litters seem to be "too low." An explanation for this discrepancy may be that such small litters are artificially brought about by the prenatal death of one or more of the litter. Such prenatal death may easily escape the recorder, who consequently fails to exclude such litters from his statistics. In our new experiments we have taken special care to exclude such cases (*cf.* Fig. 1) and the fit is markedly improved.

Another systematic departure occurs with very large litters from the beginning of the 2nd week; all the weights are "too low." These irregularities, as well as those mentioned before, are theoretically important.

We have expressed the opinion that there is an equipartition of (for each litter size) a limited supply of nutritive material during intrauterine growth. We have also considered that the ability of the mother to provide nourishment (or, the "drawing power" of the

developing litter) does not increase rectilinearly with the number or the mass of young at birth, but in such a way that if F = the total nutritive supply at any value of N , $\Delta F/F$ is constant for $\Delta N = 1$. Then

$$\Delta F/F = K_2(\Delta W/W) N,$$

or

$$= -k_2 N(\Delta w/w).$$

TABLE II

Number in litter (N), average weight of an individual at birth (w) (from data in Table I), average weight of mother after birth, and estimated increase of weight of mother due to bearing the litter (see text); the estimate of increase of weight in mothers is based upon departures from the known mean growth curve for unmated ♀♀ of this strain, and involves an element of uncertainty as regards the precise age of the mothers.

No. in Litter N	Average weight of new born, w	Average weight of mothers, after birth	Estimated increase of weight of mothers
	<i>gm.</i>	<i>gm.</i>	<i>gm.</i>
1	1.63	28.2	6.5
2	1.53	30.5	8.8
3	1.49	28.0	6.3
4	1.41	28.1	6.4
5	1.35	27.4	5.7
6	1.33	27.7	6.0
7	1.31	29.5	7.8
8	1.26	30.0	8.3
9	1.23	30.1	8.4
10	1.20	30.3	8.6
11	1.18	26.7	5.0
12	1.20	31.3	9.6
13	1.14	36.1	14.4

This means that the relative decrease in mean weight of one individual, at birth, will be greater, in inverse proportion to N , for each additional individual in the litter, as result of a proportionate reduction in the nourishment available for each individual. The presence of embryos in the uterus modifies quantitatively the metabolism of the mother. This may be due to the passage of substances from fetus to mother. In any case, the increase in level of nutriment would be expected to be shared between mother and young, on the

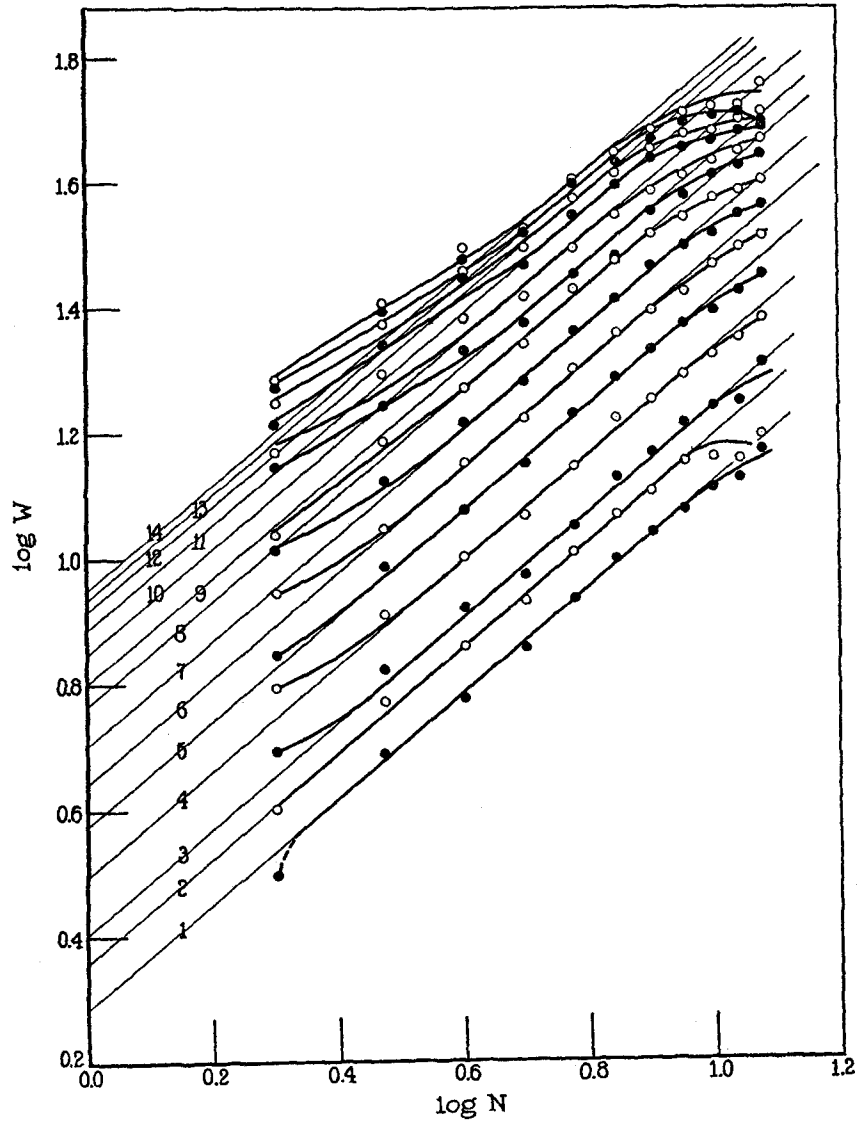


FIG. 4. The growth of suckling mice as a function of the size of the litter (Table III); see text.

general theoretical basis we are considering. We find this effect in the fact that pregnancy in mice results in a permanent increase of weight of the mother (Table II); the increase is a function of the size of the litter carried, but more comprehensive data are required to examine the point before the nature of the function can be determined.

An increase in F with increasing N could not go on indefinitely, but must reach a limiting value. The approach to a limiting value of the nourishing capacity of the mouse mother is shown in two ways.

TABLE III

Average weights of individuals in litters of different sizes, as a function of the number in the litter, at various ages after birth; each litter nursed by one mother (see Fig. 4).

No. in litter	No. of litters	Average weight of 1 individual (= W/N), gm.													
		Age, days after birth.													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
2	2	1.57	2.00	2.48	3.11	3.51	4.41	5.15	5.45	6.95	7.42	8.19	8.83	9.31	9.62
3	2	1.63	1.97	2.22	2.71	3.21	3.72	4.43	5.12	5.82	6.55	7.30	7.85	8.22	8.49
4	6	1.49	1.81	2.09	2.52	3.99	3.56	4.13	4.68	3.55	6.03	7.00	7.16	7.48	7.80
5	8	1.49	1.78	2.01	2.45	2.93	3.56	4.06	4.45	5.15	5.65	6.31	6.70	7.00	7.31
6	7	1.44	1.71	1.88	2.34	2.83	3.34	3.82	4.38	4.73	5.21	5.86	6.25	6.61	6.70
7	10	1.40	1.68	1.92	2.37	2.76	3.26	3.70	4.25	4.33	5.03	5.60	5.86	6.11	6.34
8	3	1.37	1.60	1.84	2.25	2.68	3.10	3.57	4.10	4.47	4.81	5.43	5.63	5.82	6.03
9	4	1.33	1.59	1.82	2.19	2.62	2.96	3.48	3.89	4.32	4.55	5.04	5.30	5.52	5.73
10	3	1.26	1.45	1.74	2.11	2.49	2.94	3.30	3.76	4.08	4.32	4.63	4.81	5.09	5.27
11	3	1.22	1.31	1.70	2.04	2.42	2.85	3.21	3.52	3.85	4.06	4.38	4.57	4.70	5.05
12	2	1.24	1.31	1.71	2.01	2.36	2.72	3.05	3.34	3.67	3.90	4.15	4.31	4.06	4.80

In all the suckling litters there is a decline of growth rate beginning with the 2nd week of life. This decline is due in part at least to the decline in the milk-secreting capacity of the mother (*cf.* Enzmann, 1933). With very large litters the decline is so marked that equation (2) will no longer fit. To keep up the initial growth rate of her offspring a mother suckling 10 or more young would have to produce almost her own body weight in milk every day. Such an increase seems to be beyond the capacity of the mother. Usually the mother kills off part of her litter on reaching the limits of her capacity to

give milk. Our data (Table III) contain only litters which have not been reduced in size by the mother. It is obvious that the large litters are in a state of partial starvation.

MacDowell proved that the growth rate depends on the litter size by artificially reducing litters and by using foster mothers. The litters which were so reduced in size assumed the growth rate characteristic for the new litter size. Still another proof is given by our observation that the *adult* weights are practically the same no matter whether the young were reared in a small or in a large litter. As soon as the suckling period is over and there is an adequate supply of food, the growth rate of mice from large litters increases as compared with the growth rate of small litters, until the two coincide in weight.

If the conditions under which the relationship $\Delta W/W = K (\Delta N/N)$ was deduced should persist unaltered during the suckling period, then the equation should continue to describe the data at equivalent stages of development and K should be fixed and independent of age; K in Fig. 4 = 0.84. The essential conditions are (1) that the animals in each litter should remain healthy and should have equal significance as drawers of milk, and (2) that for each additional one in the litter the mother should provide a constant fractional increment of milk (of constant food quality on successive days, in terms of its efficiency in promoting growth of the young—growth being defined as increase in weight). The second condition is interfered with by the time course of milk production by the mother, which seems to be, basically, a function of a cycle of events in the mother released or initiated by parturition,—although the precise form of this cycle is open to modification according to the number of young suckled (Enzmann, 1933). With a small number suckling, the time curve of milk production rises to a flat maximum in the neighborhood of 10 days; with a large number, the maximum comes earlier and the curve is flatter; thereafter it declines (*cf.* Enzmann, 1933). In case of suckling mice the intervention of a hypothetical substance supposed to be responsible for “supererogation” of the maternal organism with increasing litter size is unnecessary; it is hard to believe that in the act of suckling substances of such a nature should pass from the infant to the mother. In this case the observation that a more complete

emptying of the mammary gland calls forth a more abundant secretion offers a satisfactory explanation. It is possible that in the case of intrauterine growth a similar explanation might hold, and that hormonal control of the litter weight relation to litter size may be excluded.

Data in Table III, plotted in Fig. 4, describe the growth of litters of various numbers, each litter suckled by one mother, as a function of time. For several days after birth larger litters do not receive a

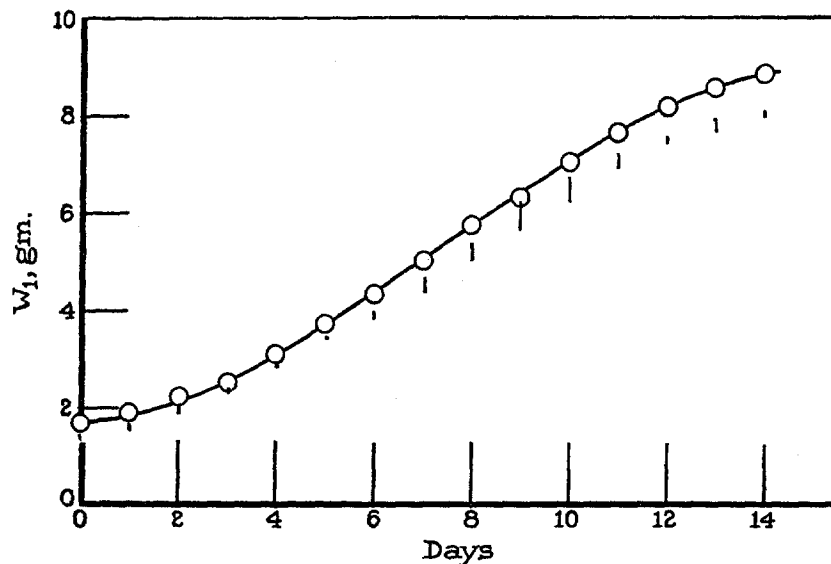


FIG. 5. Growth of young suckling mice; w_1 = the ideal weight of a litter of 1, as deduced from the curves in Fig. 4; see text. The vertical bars extend between direct determinations made of the average weights of litters of 4, the upper limit of each bar being for females, the lower for males.

supply of milk adequate to maintain $\Delta W/W = K (\Delta N/N)$. Later, at 4, 5, 6 days, the departure of the weights of the very large litters from the line defining K is less; as the peak of the time curve for production of milk is passed, the departure becomes more and more extensive and is apparent with progressively smaller and smaller litters (Fig. 4). We have already noted that quite small litters ($N = 1$ or 2) appear at birth "too light," due to death of 1 or more intra-

uterine young; by the 2nd day after birth (Fig. 4) this discrepancy is made up and thereafter, as the milk production of the mother increases to a maximum at 8–9 days the young in small litters gain at a more rapid rate; thereafter (9th to 14th day inclusive) the departure is *relatively* less and less, although affecting progressively larger litters. Only in the case of litters containing 5, 6, or 7 young does the relationship $\Delta W/W = K (\Delta N/N)$ remain intact. It is to be understood that in the absence of series of weights upon successive days (as in Fig. 4), permitting observation of the gradual change of the curve connecting W with N , one would not be permitted to give much importance to the straight portions of the uppermost graphs in Fig. 4. In fact, however, even the slight drop in relative departure of the weights of the smaller litters at the end of the suckling period (12, 13, 14 days) seems quite as expected, since with quite small litters the curve of milk production by the mother falls more rapidly to a low level than is true with larger litters. (The curves drawn for these days, in Fig. 4, give only the drift of the plotted points for the smaller litters.) This interpretation, moreover, leads to a kind of consistency in the treatment of the curve of growth during the suckling period. By the method already used in Fig. 1, the line for constant K at each day after birth (Fig. 4) is projected back to $N = 1$ ($\log N = 0$). One thus obtains a measure of the weight (w_1) of an ideal litter of 1 under the condition that $\Delta F/F = \text{const.}$ over a day; the change in w_1 will therefore reflect changes in the growth-promoting capacity of the mother, free from the specific interrelation between number in litter and curve of milk yield as a function of time. These magnitudes are plotted in Fig. 5. They follow a curve similar to that gotten by direct weighing of suckling young, but higher than the averages so obtained (Fig. 5). After the period of maximum milk yield, the rate of growth estimated in this way declines. The curve in Fig. 5 thus exhibits the ideal growth curve, free from most of the complications due to varying size of litter as these influence the process of milk secretion; the remaining restriction being that the curve is limited by the condition that the mother supplies a constant fractional increase of nourishment for each addition to the litter. The shape of the curve thus reflects the time course of the capacity of the mother to produce milk.

IV

SUMMARY AND CONCLUSIONS

We have been concerned with the connection between size of litter and weight of litter at birth, especially in mice. The weight at birth represents, it is to be presumed (at least in mice, and for certain other cases), the weight at a particular developmental stage. The connection between number in litter (N) and weight of litter (W) has been interpreted as due to the partition of nourishment between mother and young, and on an equal basis among the several embryos of a litter. The "heterogonic" relationship which the data exhibit between N and W shows that the constant K , defined by

$$\log W = K \log N + \text{const.},$$

is independent of the species, and has an essentially constant value ($0.85 \pm$) in all multiparous mammals; it is therefore regarded as a partition coefficient. In the case of power function relationships between masses of components of a single individual, the respective "drawing powers" of the several organs are diverse, and diverse magnitudes of K are encountered. With developing embryos, the intrinsic drawing powers of the tissues concerned in embryos and mothers are in each case of the same general character, at least among mammals; the constancy of K reflects this. A parallel for the case as it appears in the consideration of relative growth rates of organs in a single individual, and in which the varying magnitudes of the heterogonic growth constant K are presumed to reflect diverse drawing powers of the respective tissues, would be given by intrauterine growth of a litter containing individuals with diverse capacities for growth, —that is, individuals differing genetically with respect to the factors determining the magnitudes of w_1 . We have been dealing with the growth of litters in inbred strains. It is to be presumed that in the case of the growth of a litter containing two categories of individuals so far as concerns intrinsic drawing powers with respect to the nourishment provided by the mother, it would be possible to investigate the way in which K is open to modification. Although difficult, from the standpoint of classifying the individual young, it would appear to be distinctly worth while to make such an experiment, and we have planned it for the future.

It is pointed out that for genetic purposes the ideal weight of a litter of 1 is obtainable from a series of measurements of N and W , free from disturbances affecting the apparent value of this quantity as observed in single births. This weight of an ideal litter of 1 should be employed to disentangle the effects of heterosis and fertility factors from those having to do with individual weight at birth.

During the suckling period the relation $\Delta W/W = K (\Delta N/N)$ is maintained for young mice, but with modifications in the case of small and large suckling litters due to (1) the time course of milk yield, and (2) the effect of litter size upon this. It is shown that a growth curve can be obtained for an ideal litter of 1, under the condition of milk supply that on each day the mother is able to provide a constant fractional increase of milk for each additional young mouse in the litter. The rate of growth then adheres to the time curve of capacity for production of milk.

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