

THE INFLUENCE OF THE QUANTITY OF NUTRITION UPON THE GROWTH OF THE SUCKLING MOUSE

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The contrast between the character of the growth curves of the embryo and the suckling mouse demands an explanation. Before birth the curve is a parabola (MacDowell, Allen and MacDowell '27). After birth some of the published averages show a slight concave phase, but this becomes convex by the end of the first week. That this difference might be due to some external condition rather than to internal changes was suggested by the fact that the parabolic curve of the embryo guinea pig continues uninterrupted through the stages of development corresponding to those of the suckling mouse (MacDowell, Allen and MacDowell '27). While a constant environment is maintained (prenatal guinea pig) growth continues to follow the same curve; when a new environment is entered (suckling mouse) the character of the curve is changed. After birth, new uses of energy and a new source of nutrition will account for a general modification in the curve as a whole, but not for the convexity normally found in the second week. The influence of special diets upon growth is well known. The vitamine diets of Osborne and Mendel '26 produce astonishing accelerations in the growth of the rat, which Brody '28 points out change the constants but not the nature of the mathematical formula for the growth curve. In contrast to this, in the suckling period of the mouse, by increasing the quantity of mother's milk available, we now find an equally surprising acceleration in growth, which continues the concave curve of the first week throughout the second week up to the beginning of natural weaning.

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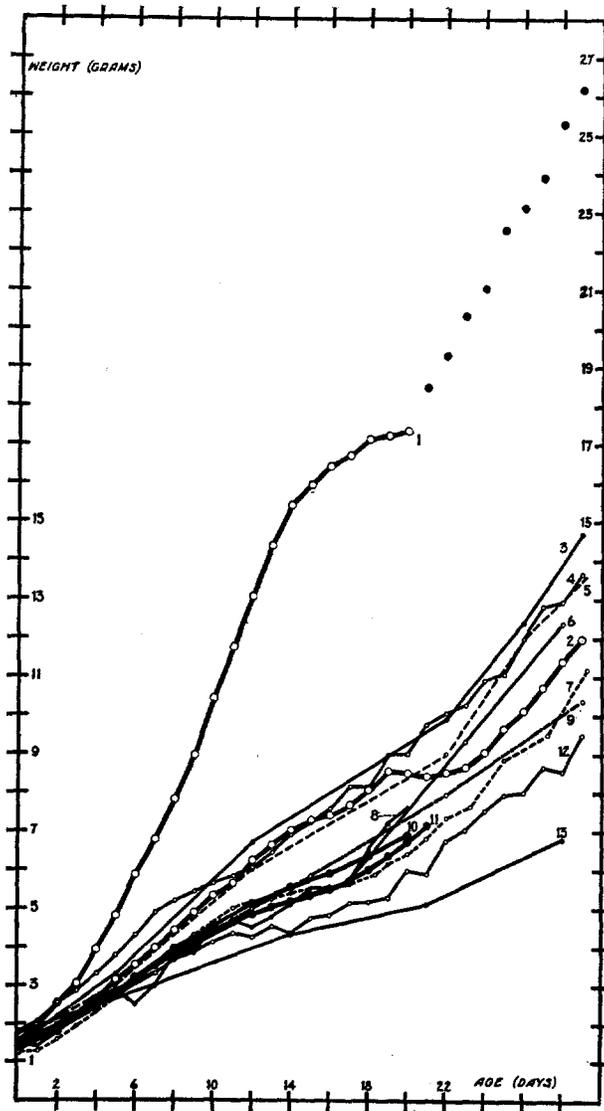


FIG. 1. Published growth curves for the suckling mouse, compared with the curve that can be obtained by increasing the quantity of mother's milk.

Curve 1: Six heaviest females at 14 days in present experiments; number in litter reduced to four at birth and later to one (for details see legend for Fig. 4); beyond 20 days this curve is continued by unconnected points giving the weights of a single one of the six.

Eleven series of published average weights for the suckling mouse are given in Fig. 1, Curves 3 to 13. Considering the great range in material, methods, and laboratories, these curves are fairly consistent. Birth weights are similar; at 14 days the range in weights is 4 to 7 gm. In the first week, as already mentioned, several curves show a tendency toward a concave form; the second week begins with a break which leads to a marked depression in the third week. An acceleration in the fourth week frequently gives a steeper slope than before the depression. This rise, and the preceding depression, form the chief features of the curve that support the theory of growth cycles as formulated by Robertson ('16) ('26), who claims the depression has nothing to do with weaning, since the mother is not removed until a week after the depression begins. Rather, he says, the slowing down represents the end of the dominance of one chemical reaction, while the subsequent acceleration is the beginning of the dominance of a more rapid, independent chemical reaction.

Experiments to Increase the Available Mother's Milk

In the attempt to determine the form of the growth curve of the suckling mouse when the quantity of food is not a limiting factor, several series of experiments have been carried out. Since a maximum

FIG. 1—*continued.*

Curve 2: Six control females from the same strain: mothers fed and cared for as those for Curve 1, but no reduction in number of young.

Curve 3: from Thompson and Mendel '18; 15 males.

Curve 4: from Saller '27; 3 males.

Curve 5: from Judson '16; 20 males.

Curve 6: from Robertson '16; sex not given; numbers range from 24 to 65, no two successive days include same number of mice.

Curve 7: from Ostwald '08: seven mice, sex not given.

Curve 8: from Robertson and Cutler '16; sex not given, numbers range from 18 to 48; great irregularity from day to day.

Curve 9: Davenport and Swingle '27; litters of "7 to 5," males and females; after birth day, numbers range from 102 to 123.

Curve 10: from Gates '25; males and females; numbers decline from 678 to 471.

Curve 11: from Parkes '26; males and females; 407 mice; unweighted averages of averages per size of litter of averages per litter.

Curve 12: from Robertson and Delprat '17; sex not given; numbers irregular, 118 to 60.

Curve 13: Stieve '23; 30 males.

of milk is being sought, a detailed account of the stages by which the technique has developed is not pertinent. The primary item in this technique consists of reducing the number of young nursed by one mother. Studies have been made on the amount and the time of this reduction; on the use of mouse and rat foster mothers under different combinations of age and recency of parturition of the mother; and on the influence of the ovaries on the milk supply. The conclusions reached by these studies may be summarized as follows: reduction to four at birth, to two when 3 days old, and to one when 5 days old has produced our maximum growth; reduction to less than four at birth is a disadvantage. Foster mothers whose young were born 5 days after the young in question may do as well, more often less well, but not better than the own mothers; alternating foster mothers in 12 hour shifts does not increase the available milk; rats make good foster mothers for mice, but not as good as own mothers (neither in this case nor in any other has an unhealthy condition been found as was reported by Parkes '29 as a result of the rapid growth obtained by rat foster mothers); the break in the curve at 15 days is not due to a depression of lactation due to returning oestrus, since spaying mothers at parturition does not modify the break; the independence of the 15 day break and the quantity of milk the mother can produce is shown by the fact that a mother 18 days after parturition can raise four new born young, giving them a larger total amount of milk than was given her own (reduced) litter.

The mothers' food was the regular diet used for the whole colony: fresh milk, Spratt's cod liver oil dog bread soaked in water, oats, hemp and canary seed; this was replenished twice a day in these experiments. The boxes were cleaned daily; the temperature was controlled at approximately 79°F. Daily weighings were made on a Sartorius balance. The mice came from the Bagg albino strain, which has been inbred brother by sister in this laboratory since 1922.

*Immediate Influence of the Mother on the Curve of the Suckling
Young*

The immediate dependence of the growth curve upon the milk supply (mother) rather than upon the young mouse itself is strikingly emphasized by two special series of experiments. In the first of these the growth of suckling mice from another strain (B) was

found to differ from that of mice in the strain (A) used in all other experiments. Fig. 2 gives the averages of 8 mice from Strain A and

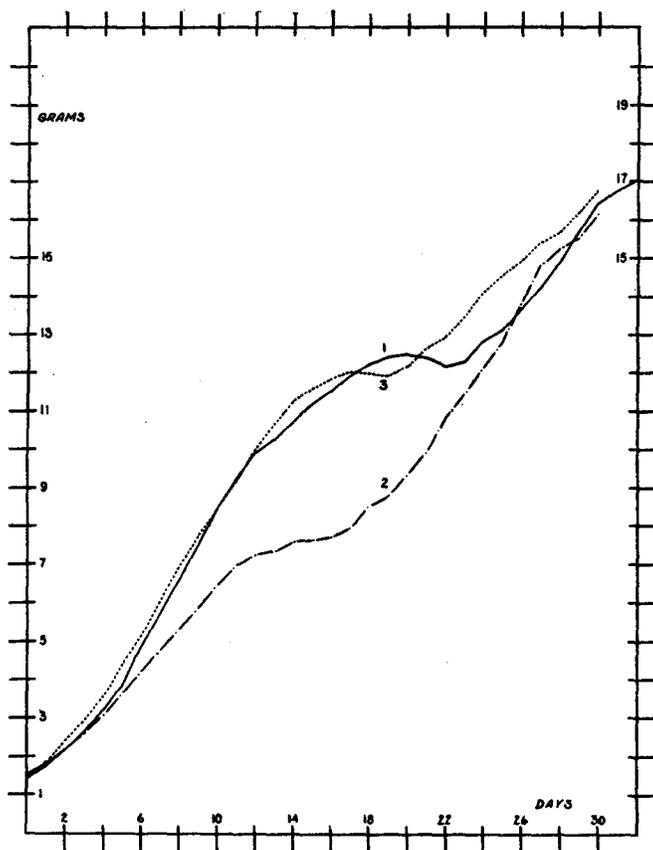


FIG. 2. Difference in growth curves of two strains that depends upon mothers and not upon young themselves.

Curve 1: Solid line; averages of 8 Bagg albino young (2 ♂, 6 ♀) nursed by own mothers with three litter mates for 5 days, then two of these removed; left alone with mother from the 9th day; mothers removed at end of third week.

Curve 2: Broken line; averages of 5 young from Storrs-Little strain (1 ♂, 4 ♀) nursed by own mothers; reductions and removal of mothers as in Curve 1.

Curve 3: Dotted line; averages of 6 young from Storrs-Little strain (1 ♂, 5 ♀), fostered on day of birth by Bagg albino mothers whose own young were born on the same day; each mouse nursed with three litter mates for 4 days, two removed on the fifth day, and the third on the eighth day; mothers removed after 17 days.

5 mice from Strain B. The mice in Strain B did not grow as fast in the first week; they started on the rapid post weaning rate before the mothers were removed at the end of the third week. In Strain A there was frequently a loss for a day or two after the mothers were removed, before the rapid rate was resumed. This difference in the

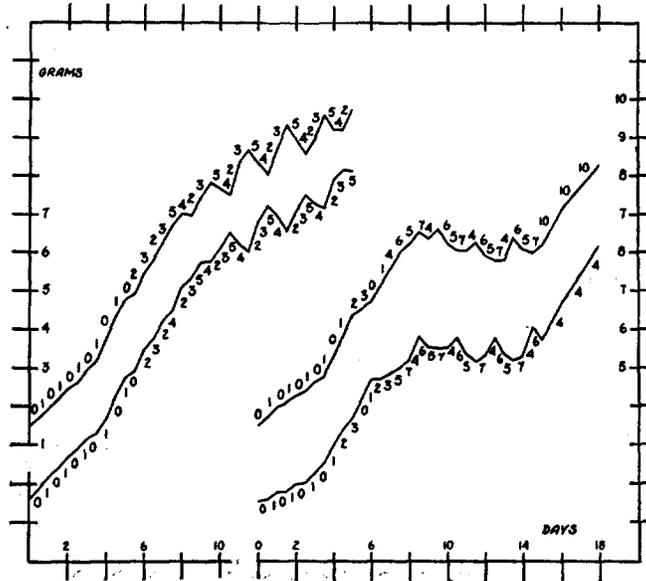


FIG. 3. Two pairs of curves of individual mice fostered by a succession of mothers in 12 hour shifts, showing the dependence of the growth of the young on the mother. Each litter, reduced to four at birth, was separated into pairs after 4 days; and after 7 days each mouse was nursed separately, each foster mother nursing alternately two mice from the same litter. Young weighed at each change of nurses. Numbers along the lines indicate which nurse was on duty; 0 = own mother. Foster mothers first on duty day after parturition, 12 hours after removal of own young. Note that the zero point for weight for the lower curve of each pair is on the base line; the upper curves start 2 units higher.

curves was shown to be due to the mothers and not to any genetic difference in the young themselves, by a set of young from Strain B that were fostered by mothers from Strain A. The difference was entirely eliminated. The mothers in Strain B were not as good as the mothers in Strain A: they did not give as much milk in the first week and natural weaning was completed sooner.

In the second series the complete dependence of the rate of growth on the mother was even more strikingly demonstrated by giving a suckling mouse, in 12 hour shifts, to a series of foster mothers which were not nursed in alternate shifts. The experiments were undertaken in the hope of providing a more bountiful milk supply, but in most cases the foster mothers did poorly. However a few mothers did well under these conditions and a series was obtained showing the results of good and poor nurses in alternate shifts (see Fig. 3). As the weights were taken every 12 hours the curves show the changes in weight for which each mother was responsible. The striking point is that the pairs of curves parallel each other; one mother gives a good gain each time on duty, another gives a loss; the same succession of mothers gives each young practically the same series of gains and losses. The numbers along the curves indicate which foster mother was on duty.

Maximum Curves

The average weights of the six females, in all our experiments, that were the heaviest on the 14th day are plotted in Fig. 1, Curve 1. Beyond the 20th day the curve is continued by the weights of only one of the six. Individual data for these six are given in Table I and Fig. 4. To show that the difference between these and the published curves does not depend upon the particular strain of mice used, nor upon the diet of the mothers, nor upon the methods of feeding and caring for them, the averages are given in Fig. 1, Curve 2, of six females from the same strain, raised on mothers handled and fed in the same way as the others, but without reduction in the number of young. These controls are seen to agree closely with the higher published curves. A further check is given by the averages of mice from the same strain raised under the normal routine of the whole colony; 17 females 22 days old gave an average of 8.59 gm.; 24 other females, 23 days old, averaged 9.30 gm. These points lie between Curves 2 and 6 in Fig. 1.

At 14 days the published averages and the controls show less than half the weight attainable at this time. But more important than the difference in absolute weight is the change in the shape of the curve accompanying the removal of external limitation—a continued upward sweep of the original concave curve lasting until the end of the

second week and terminated by a sudden and continued break. These mice are considered to approach the limit of growth capacity under the general conditions of these experiments. There is no claim that they

TABLE I
Individual Weights (Grams) of the Six Females That Reached the Highest Weight on the 14th Day

Age	G59,2	GS2,3	GS3,4	G108,0	G109,3	G116,0
Birth	1.46	1.39	1.55	1.62	1.61	1.54
1	1.83	1.81	2.01	1.98	2.04	2.08
2	2.37	2.34	2.61	2.52	2.67	2.71
3	3.12	2.92	3.16	3.23	3.20	3.27
4	3.84	3.56	3.93	4.02	4.06	4.19
5	4.66	4.30	4.72	5.02	4.90	5.31
6	5.77	5.38	5.80	6.19	5.89	6.18
7	6.75	6.25	6.84	7.16	6.96	6.79
8	7.82	7.13	7.93	8.17	8.09	7.79
9	8.78	8.44	9.19	9.49	9.16	8.78
10	10.29	10.06	10.54	10.74	10.47	10.47
11	11.58	11.32	12.05	11.90	11.77	11.92
12	13.01	12.71	13.35	13.08	12.70	13.45
13	14.34	14.15	14.80	14.20	14.13	14.60
14	15.53	15.34	15.60	15.28	15.15	15.54
15	16.06	15.64	16.32	16.05	15.79	15.72
16	16.49	16.06	16.57	16.37	16.49	16.52
17	16.58	16.27	17.03	16.83	16.80	16.66
18	17.21	17.09	17.36	17.14	17.28	16.69
19	17.62	17.32	16.59	17.52	17.49	16.78
20	17.72	18.04	16.31	17.68	17.68	16.73
21	17.16	18.48	15.94	17.95	17.59	16.72
22	17.02	19.30	16.18	18.44	17.54	17.40
23	16.32	20.34	16.83	18.96	17.66	17.94
24	15.80	21.04	17.65	19.77	17.96	18.42
25	15.25	22.56	18.56	20.66	18.26	18.89
26	16.00	23.12	18.69	21.46	18.35	19.00
27	15.80	23.92	20.37		18.51	
28	16.23	25.30	20.08		18.90	
29	17.00	26.21	21.55		19.66	
30	17.82	26.47	21.43		19.67	

have actually reached such a point. In many cases the curves of the individual mice show almost mathematical smoothness from day to day, especially in the early part (see Figs. 4 and 5). But at the rate

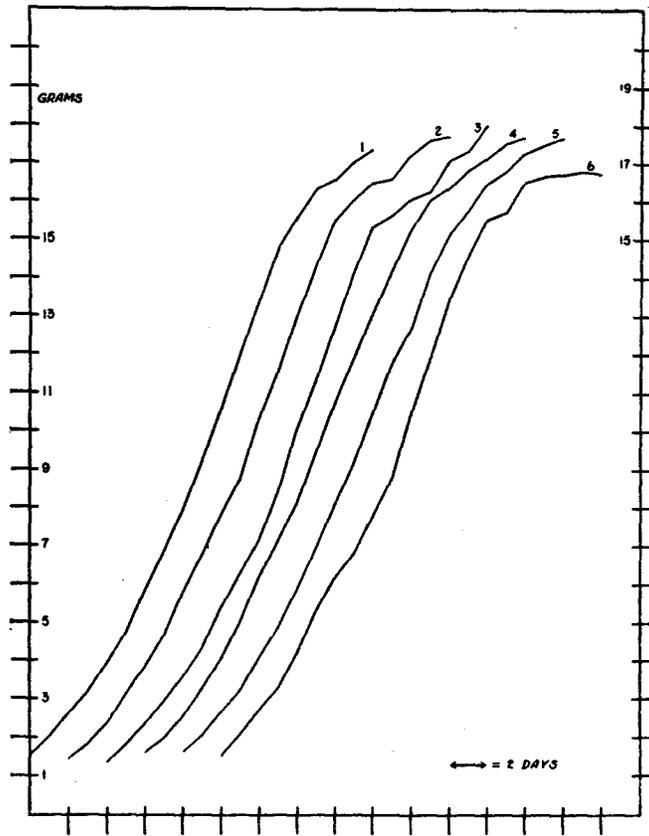


FIG. 4. Individual curves for the six females averaged in Fig. 1, Curve 1.

Curve 1: (GS3, ♀4) born in litter of 11; reduced to four at birth and both ovaries removed from mother; in 5 days three litter mates removed.

Curve 2: (GS9, ♀2) born in litter of 9, reduced to four at birth; in 5 days this mouse was given to a foster mother whose litter had just been born and discarded.

Curve 3: (GS2, ♀3) born in litter of 8, reduced to four at birth and both ovaries removed from the mother; in 5 days other three litter mates removed.

Curve 4: (G108, ♀0) born in litter of 10, reduced to four at birth, in 3 days two more discarded, and in 5 days after birth left alone with mother.

Curve 5: (G109, ♀3) born in litter of 9; reductions as in Curve 4.

Curve 6: (G116, ♀0) born in litter of 7; reductions as in Curve 4.

obtained, growth is influenced by subtle changes in conditions that affect the mother both physiologically and psychologically and are to be controlled only by the greatest caution, a perfection so far clearly not attained.

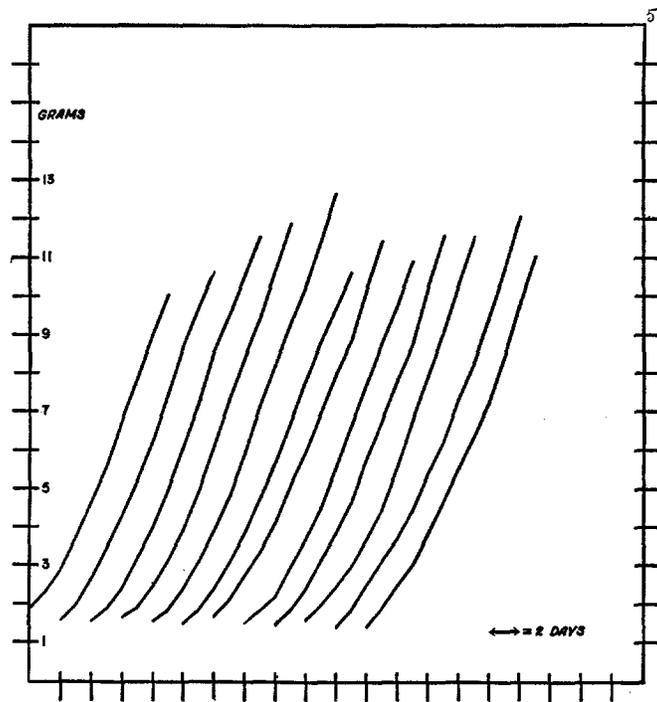


FIG. 5. Individual curves for twelve mice showing the consistency of slope and weight and the smoothness possible for individuals. These curves show that the second week can be entered without either an inflection or a temporary acceleration sometimes found the day after the litter is reduced to a single mouse. These curves are taken from various experiments; they broke at different times before the end of the second week.

The change in shape of the curve as the maximum is approached is illustrated in Fig. 6. Curve 4 (Gates '25) is based on over 600 mice from different strains raised in this laboratory in 1922. Of these 600 the six that were the lightest at 14 days are averaged in Curve 5; the heaviest six at 14 days, in Curve 3. Curve 2 gives the averages of

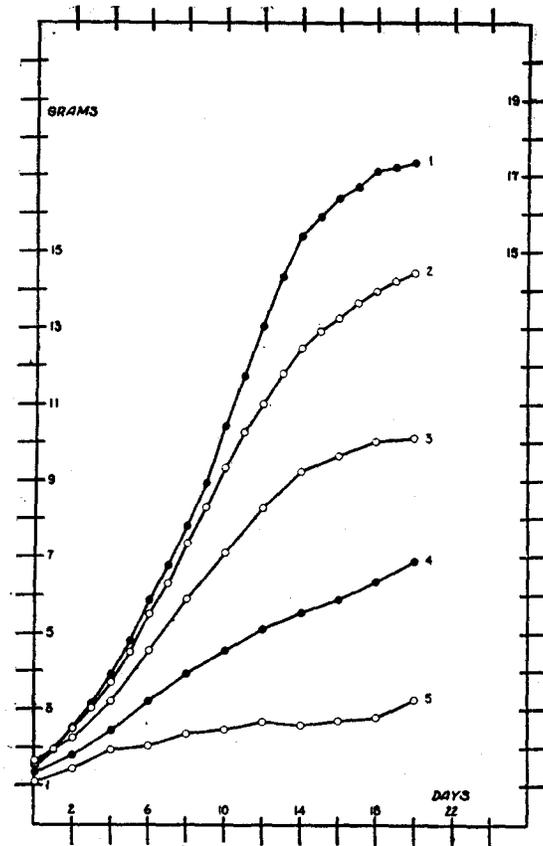


FIG. 6. Changes in the shape of the growth curve of the suckling mouse as the maximum is approached.

Curve 1: Maximum growth obtained; curve repeated from Fig. 1, Curve 1.

Curve 2: Averages for the six females in the present experiments nearest to 12.5 gm. at 14 days.

Curve 3: Averages for the six mice included in Curve 4, that were the heaviest at 14 days.

Curve 4: Averages of over 600 mice reported by Gates '25 (repeated from Fig. 1, Curve 10).

Curve 5: Averages of the six mice included in Curve 4, that were the lightest at 14 days.

six females from the current experiments that weighed between 12.25 and 12.50 gm. at 14 days; Curve 1, repeated from Fig. 1, is for the highest six.

Birth weight is directly responsible for a small part of the differences between Curves 3, 4 and 5; further, it is indirectly responsible through its relation to milk supply. The animals small at birth are born in large litters and hence meet greater competition for milk; and within the same litter large size itself confers an advantage in nursing competition.

It is clear that these five curves form a series in which the point of inflection is more and more delayed as the steepness of the curve increases. During the second week Curve 4 shows a gradual rounding off, while Curves 2 and 3 show a distinct break after the 14th day and in Curve 1 this has become sudden and striking. Attention is called to this break in the individual curves in Fig. 4. There is some variation in the time of its occurrence, and under the technique employed, a slight influence on the day preceding, but its sharpness is characteristic.

The Break at 15 Days

Under normal conditions in the second and third weeks, averages show a gently rounding convex curve, which it has been easy to interpret as due to a single, internal, growth limiting substance; but when the limiting effect of the available milk is largely removed, the smooth curve is changed into a distinct angle. The first part of the convex curve is due to the limitation of the milk supply; the irregularity of this limitation smooths the averages so that they grade imperceptibly into the second part which is due to some other limitation. New factors have suddenly become effective. Our observations indicate that this is a particularly significant and interesting moment in development. At this time comes a sudden change in behavior. Up to this time the large, well fed young are markedly inactive; the eyes have opened the day before; in another 24 hours they begin to run around; they pick up solid food and begin to nibble. (This agrees with the observations of Saller '27, p. 568.) They are indiscriminate in what they eat. If they have a chance they will eat the mother's feces; intestinal looseness develops. They can eat solid food, but are still dependent upon

their mothers, since the removal of the mother at this time will result in a continued and rapid loss of weight for 4 to 6 days. This is the initiation of the natural process of weaning; during this period they take

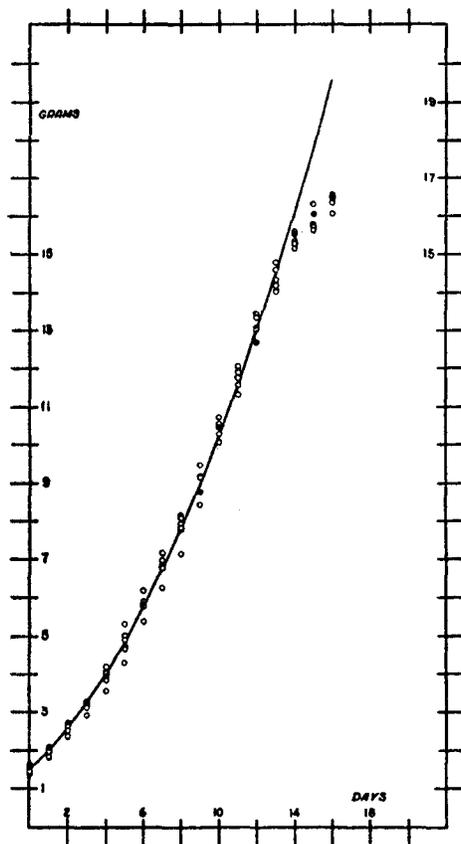


FIG. 7. Distributions of the individual weights of the six mice averaged in Fig. 1, Curve 1. Solid circles indicate two individuals with the same weight at the same age. The continuous line connects by straight lines the points for each day that lie along a parabola with the formula, $W = .0231T^{2.15}$, in which T equals the days from birth plus 7.

less mother's milk but not their full requirement of solid food. The completion of weaning is often indicated by an abrupt upward bend of the curve at a rate that is maintained. This may occur before the

mother is removed, but more often it is not until the mother is actually taken away that, after a slight loss for a day, the rapid phase is begun (see Fig. 2). By keeping all solid food away from the young, this rapid phase can be delayed and nursing prolonged; the depression is continued until the introduction of solid food at once starts the rapid growth. There can be no question but that a new phase of life is inaugurated at the end of the second week by the eating of the first solid food. The transition is not as rapid as that effected by parturition, nor is the change so great as that from uterine to free existence, but none the less it is comparable—a change from one source of nutrition to another. Further experiments will be required before attempting to say what is the primary factor that leads to this break, what initiates this natural process of weaning.

Prenatal and Suckling Periods

The difference in the shape of the curves of the embryo and the suckling mouse is mainly due to the limitation in the quantity of milk in the suckling period. The embryo weights form a parabola. As the quantity of food is increased the post-natal weights also approach a parabola, Fig. 7. From the morning of birth the parabola is taken up, with no post-parturitional depression and no subsequent rebound (Davenport and Swingle '27, p. 418). The slope of the straight line on logarithmic paper is reduced, but this reduction begins at birth. After birth, even when as much milk as possible is made available, new losses of energy—the act of suckling, of digesting, breathing, loss of surface heat—reduce the amount of tissue that can be made from a given amount of food.

CONCLUSIONS

Under usual conditions, the growth of the suckling mouse is limited by the quantity of mother's milk available.

As this limitation is removed the growth curve approaches a parabola, which is abruptly interrupted at the end of the second week, when the natural process of weaning begins.

DISCUSSION

The unreliability of mathematical analyses of growth curves as an approach to the fundamental growth processes, has been discussed by

Gray ('29). The present case would serve as further illustration of the importance of experimental analysis. Chemical methods are needed for the study of the chemistry of growth. The work of Needham ('25), Murray ('25, '26) and Cohn ('25) points the way. In contrast to analytical work of this type is the mathematical theorizing of Robertson ('26, '29) who, finding difficulties in describing mammalian growth in terms of a single autocatalytic chemical reaction, has evolved a theory calling for a series of independent master reactions coming into control at successive periods. The foregoing results do not favor this interpretation.

Robb ('29) has applied a single autocatalytic formula to the post-natal growth curve of the rabbit, interpreting the deviations from the theoretical curve as temporary depressions related to such changes in the conditions of life as birth and puberty, rather than to specific accelerations as called for by Robertson's theory. The present findings fully support the conclusion that the irregularities are in fact depressions related to a change in the conditions of life. In the mouse there appears to be no evidence of a necessary depression following parturition, but the relation of the break at the end of the second week to the beginning of the process of weaning is certain. Ostwald ('08) notes this; Robertson ('16) passes over this relationship, pointing out that the removal of the mother (weaning) at 21 days caused no distortion of the curve and hence no physiological disturbance in the young. We find that this is true if the natural process of weaning has been completed before the mother is removed, but in certain cases, especially good mothers continue to nurse their young and delay the complete shift to solid food. In these cases the depression in the curve of the young is continued until the removal of the mother. Saller, however, recognizes that weaning is a natural process that begins, as we find, on the 15th day. But he still agrees with Robertson that weaning does not cause the break in the curve because the break begins a week before the first eating of solid food. It is now clear that this break, usually found at the end of the first week, is not due to any deep seated feature of growth but to a purely external limitation which usually conceals the sudden nature of the break at 15 days. With the external limitations removed this break appears coincident with the change in food habits. It has been pointed out above that special

experiments are needed to determine the causal relationships between the events of this period. At present it is sufficient to recognize their correlation.

In the embryo trout, a declining food supply near the end of incubation is probably the cause of a break in the growth curve, which resembles the 15 day break in the mouse. Gray ('28) shows that by the time of this break (80 to 100 days) the yolk has become small and is rapidly growing smaller. The dependence of the size of the embryo on the amount of yolk is indicated by the facts that, (1) the growth rapidly rises as soon as extraneous food is eaten; (2) that large yolks produce large embryos; (3) that yolks experimentally reduced in size produce miniature embryos.

Besides showing this relationship between a period of slow growth and a change in the conditions of life, the present findings further support Robb's objection to the theory of growth "cycles" by making it clear that the slope of the curve immediately following weaning shows no acceleration when compared with that of the first 2 weeks when the food limitation is removed. Under normal conditions, the curve is steeper after weaning is completed, than before it begins.

On the application of a single continuous curve to the post-natal growth of the rabbit, certain questions arise. If the same curve fits the quiet nest life of the suckling period as well as the active post-weaning phase, should it not also fit the prenatal period? On the other hand, if growth during the suckling period in the rabbit is limited by the amount of mother's milk as it is in the mouse, it would be necessary to extend the interpretation of depression to cover this whole period. If the quantity of food is normally the limiting factor in the first part, and if the quantity of food after weaning is not limited, it may be necessary to reconsider the significance of a single mathematical curve fitting both periods. The continuity of the fit of a mathematical curve argues for its approach to the underlying processes of growth only so far as secondary influences do not vary. If the periods covered by the curve differ in endocrine development and function as well as in quantity and quality of food, the continuity of the curve may well argue against the theoretical interpretation drawn from the mathematical formula. The desirability of considering differ-

ent phases of life separately, as Schmalhausen has urged, seems manifest.

Taking different life phases separately, Schmalhausen ('29 with full references) has shown a surprising number of growth curves that approach a parabola. The significance of the parabola is fully discussed by Schmalhausen who considers that this inverse relationship between the velocity of growth and the length of time is the result of the regular reduction through differentiation of the relative amount of undifferentiated protoplasm which continues to grow exponentially. Thus the character of the growth curve is rather a phenomenon of differentiation than a measure of the nature of fundamental growth processes.

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