

## TIME RELATIONS OF GROWTH.

### III. GROWTH CONSTANTS DURING THE SELF-ACCELERATING PHASE OF GROWTH.\*

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#### I.

#### INTRODUCTION.

The period of growth of multicellular organisms, and of populations of organisms, may be divided into two fairly distinct phases: (1) a *self-accelerating phase* during which the time rate of growth increases with the increase in size of the organism or the population; and (2) a *self-inhibiting phase* during which the time rate of growth decreases with the increase in size of the organism, or population. The question of mechanisms bringing about the general similarity in the course of growth of animals, plants, and populations, need not be gone into in this place except to note that the course of growth is in all these cases governed, directly or indirectly, by the same two primal forces: (1) the force inherent in all organisms to reproduce at a constant percentage rate; and (2) the growth-inhibiting forces resulting from the finite nature of the universe in which the organisms find themselves.

The purpose of this series of papers is merely to present quantitative analyses of growth curves, with special reference to developing methods for computing *rational* growth constants. The first two papers<sup>1</sup> were concerned with the *self-inhibiting phase* of growth, that is the phase of growth following the major inflection in the time curve

\* The principal portions of this paper have been presented before the Physiological Section of the Botanical Society of America, in Philadelphia, December 30, 1926.

<sup>1</sup> Brody, S., *J. Gen. Physiol.*, 1925-27, viii, 233. Brody, S., Sparrow, C. D., and Kibler, H. H., *J. Gen. Physiol.*, 1925-26, ix, 285.

of growth. This paper is concerned with the *self-accelerating phase* of growth.

## II.

*Proposed Methods for Computing Growth Rates.*

Four methods have been proposed for computing growth rates.

1. *The Method of Minot.*—Minot computed the rate of growth by dividing the gain in weight during a finite unit of time by the weight at the beginning of the unit of time, as represented by the equation

$$R = \frac{W_2 - W_1}{W_1} \quad (1)$$

or

$$W_2 - W_1 = R W_1 \quad (1a)$$

in which  $W_1$  and  $W_2$  are, respectively, the weights at the beginning and the end of the unit of time,  $R$  is the relative (or when multiplied by 100, the percentage) rate of growth.

Employing this method he was led to the conclusion that, in warm blooded animals, the percentage rate of growth declines from 1000 per cent per day shortly after fertilization, to 3 to 7 per cent per day at the time of birth or hatching.

There is this objection against the use of equation (1), for the self-accelerating phase of growth: It is based on the assumption that growth is a discontinuous process; *i.e.*, that the increments are added at arbitrary time intervals,  $t_1, t_2, t_3, \dots$ . As a matter of fact, statistically considered, growth is a continuous process, and the relative rate of growth, must, therefore, be represented by the equation

$$k = \frac{dW/dt}{W} \quad (2)$$

or

$$\frac{dW}{dt} = kW \quad (2a)$$

in which  $k$  is the instantaneous relative rate (or when multiplied by 100, percentage rate) of growth, corresponding to  $R$  in equation (1).

The error introduced by the use of equation (1) is very considerable, as may be seen from the following considerations.

From equation (2), at time  $t_1$ , the weight,  $W_1$ , of the organism is represented by the equation

$$W_1 = Ae^{kt_1} \tag{3}$$

At time  $t_2$ , it is represented by

$$W_2 = Ae^{kt_2} \tag{3a}$$

Subtracting the former from the latter we obtain,

$$W_2 - W_1 = Ae^{k(t_2 - t_1)}$$

Dividing by (3),

$$\frac{W_2 - W_1}{W_1} = e^{k(t_2 - t_1)} - 1$$

Transposing and taking logarithms,

$$\ln \left( \frac{W_2 - W_1}{W_1} + 1 \right) = k(t_2 - t_1)$$

For 1 unit of time,

$$k = \ln \left( \frac{W_2 - W_1}{W_1} + 1 \right) = \ln(R + 1) \tag{4}$$

Numerical relations between  $k$ , the instantaneous rate of growth, and  $R$ , the rate of growth as determined by Minot, may be computed by substituting the values of  $R$  in equation (4). The results for a series of substitutions are presented graphically in Fig. 1. Fig. 1 makes it clear that Minot's method (equation (1)) cannot be used for computing the relative rate of growth when the rate exceeds 10 per cent for the unit of time under consideration.

2. *The Method of Pearl.*—In 1907

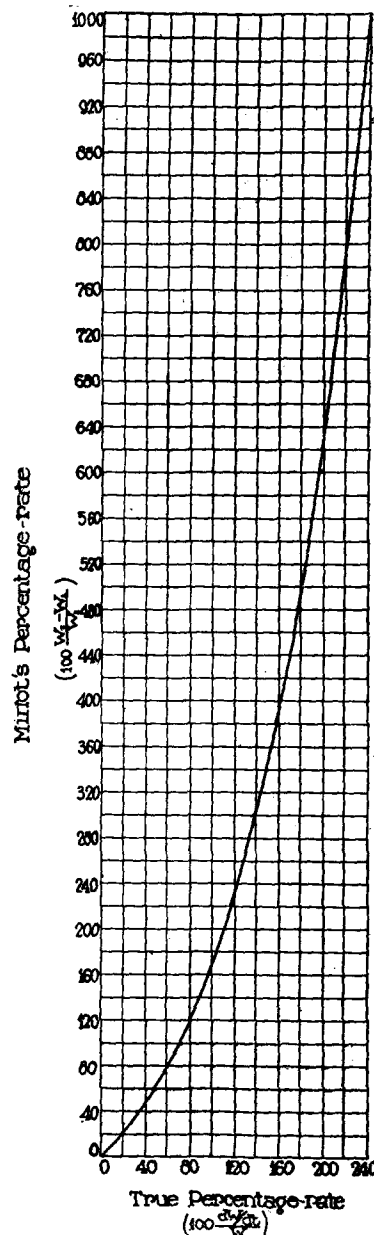


FIG. 1. The relation between the increase in percentage rate as computed by the logarithmic method and by the arithmetical method of Minot.

Pearl proposed the method for computing growth rates represented by the equation

$$\frac{dW}{dt} = \frac{k}{t - a} \quad (5)$$

which in the integrated form is,

$$W = A + k \ln (t - a) \quad (5a)$$

Equation (5) cannot, evidently, be used to represent growth during the self-accelerating phase of growth, inasmuch as the time rate of growth is represented by (5) to decline with time, while during the self-accelerating phase, growth increases with time.

3. *The Method of Robertson.*—In 1908 Robertson suggested that the equation

$$\frac{dW}{dt} = k W (A - W) \quad (6)$$

or

$$\frac{dW/dt}{W(A - W)} = k \quad (6a)$$

may be used to represent certain phases of growth termed by him *growth cycles*. Equation (6) indicates that the velocity of growth is a function not only of the size,  $W$ , of the organism, but also of growth yet to be made,  $(A - W)$ . The objections against this equation are indicated in the following sections.

4. *The Method of Pearl and Reed.*—Pearl and Reed introduced the following modification in the autocatalytic equation (6), employed by Robertson. They replaced  $k$ , by “some as yet undefined function of time,”  $F(t)$ , “since the rate of growth of  $W$  is dependent upon factors that vary with time.” They then assumed that  $F(t)$  may be replaced by the series

$$k_1 t + k_2 t^2 + \dots + k_n t^n$$

thus changing equation (6) into

$$\frac{dW/dt}{W(A - W)} = F(t) = k_1 t + k_2 t^2 + k_3 t^3 + \dots + k_n t^n \quad (7)$$

They found the integrated form of equation (7) to be elastic enough to fit the growth curve of the rat beginning with 10 days after birth.

Since, however, the period preceding 10 days after birth is an exceedingly important one, and since the constants in equation (7) do not have definite physical meaning (thus, when  $(A-W) = 1$ ,  $\frac{dW/dt}{W} = k_1t + k_2t^2 + \dots + k_nt^n$ ; what is the physical meaning of  $k_1t, k_2t^2 \dots$ ?) therefore the method of Pearl and Reed is not suitable for the purpose under consideration (which is to evaluate *rational* growth constants; *i.e.*, constants having well defined physical meaning).

### III.

#### *The Method Employed in This Paper.*

During the self-accelerating phase of growth, when the time rate of growth increases with the increase in the size of the organism, it is reasonable to attempt to relate the time rate of growth,  $\frac{dW}{dt}$ , to the size,  $W$ , of the organism, by the function

$$\frac{dW/dt}{W} = k \quad (2)$$

or

$$\frac{dW}{dt} = k W \quad (2a)$$

The first thought is that the constancy of  $k$  may be tested by integrating (2) and solving for  $k$

$$k = \frac{\ln W_2 - \ln W_1}{t_2 - t_1}$$

As a matter of fact this is an impractical procedure for two reasons. First, it is not known for how long a period equation (2) represents the data; *i.e.*,  $t_2 - t_1$  may represent more than one stage or cycle of growth; second, ratios are very sensitive to slight changes in one or both of the variables. This fact taken with the large experimental errors involved in this work, makes the results apparently erratic.

A better method is to plot the logarithms of the size, or weight, of

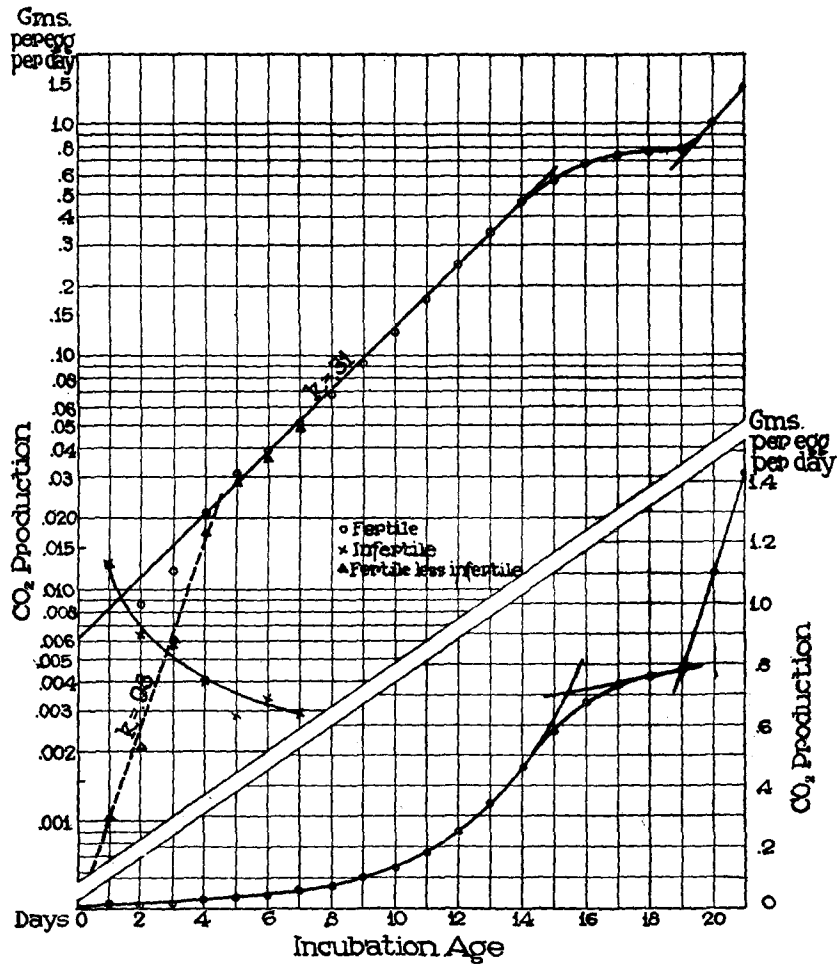


FIG. 2. The course of carbon dioxide excretion in the chick embryo with advancing age plotted from data by Atwood and Weakley. From 0 to 4 days, the instantaneous percentage rate of growth appears to be 98 per cent per day (the amount of carbon dioxide excretion is doubled once in .7 day, or once in 17 hours); between 4 and 14 days, the rate of increase in carbon dioxide excretion is 31 per cent per day (it is doubled once in 2.2 days). The pause in the curve coincides with the maximum in the mortality curve (of Fig. 3), and with the change in the mode of respiration (see text).

the organism, against age, since the integrated form of (2) may be written

$$W = Ae^{kt}$$

Therefore

$$\ln W = \ln A + kt$$

If the data points of the logarithms of weights plotted against age are distributed about a straight line, then the percentage rate of

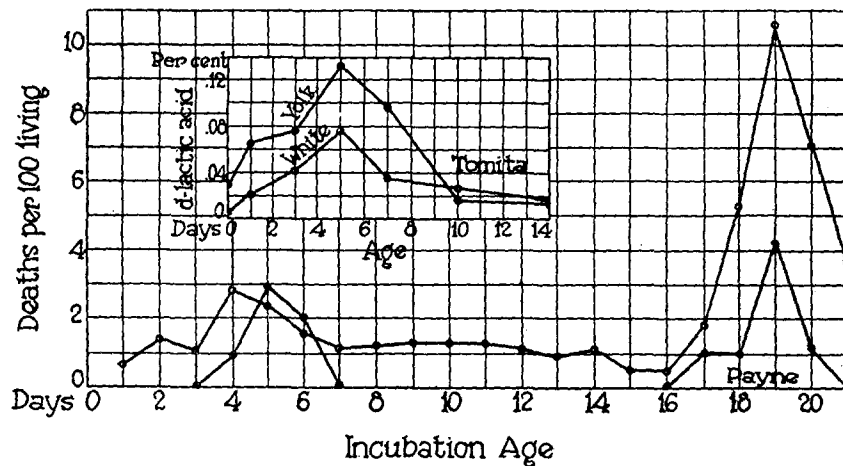


FIG. 3. Age changes in the percentage mortality with increasing age in the chick embryo. Open circles represent mortality data of embryos incubated in an incubator; solid circles represent incubation under hens. The first peak in the mortality curve corresponds with the peak in the concentration of lactic acid as found by Tomita. The second peak in the mortality curve coincides approximately with the pause in the growth curves (Figs. 2 and 5).

growth, represented by  $100k$ , is constant, and  $k$  is the growth constant we are seeking. Instead of plotting logarithms of weights, we may plot the data on paper on which the axis of ordinates is divided logarithmically (*i.e.* on arithlog paper).

IV.

*The Results of Plotting Growth Data on Arithlog Paper.*

Fig. 2 represents the course of increase in carbon dioxide excretion with age in the chick embryo, as plotted on arithlog paper. The rate

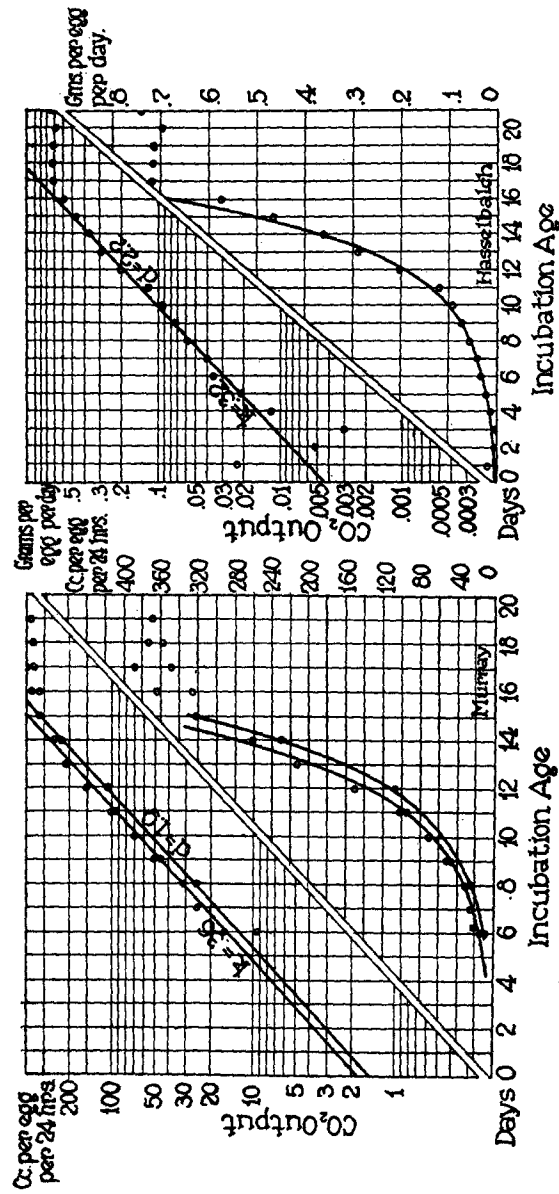


FIG. 4. The course of carbon dioxide excretion in the chick embryo, plotted from data by Hasselbalch and Murray. *d* refers to the time in days in which the magnitude of the carbon dioxide excretion is doubled.



of growth, as measured by the increase in carbon dioxide production, is constant between the 1st and 4th day of incubation. The increase is of the order of 100 per cent per day, and not 1000 per cent as postulated by Minot. From the 4th to the 15th day, the increase is likewise constant; it is 31 per cent per day.

The pause in the curve between 17 and 19 days, is, no doubt, associated with the change in the mode of respiration (from the aquatic

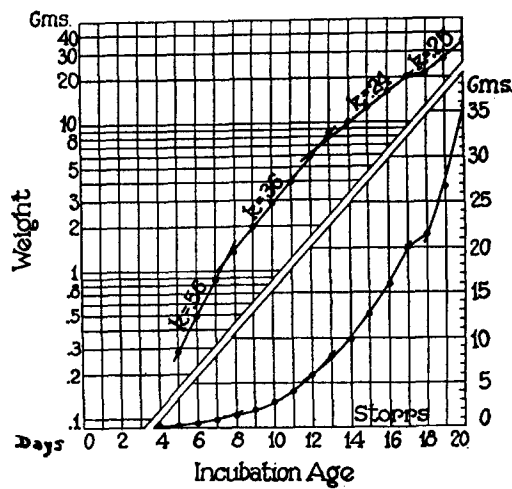


FIG. 5. Growth in wet weight of the chick embryos plotted from data by Lamson and Edmond (Storrs Agricultural Experiment Station). The curve appears to consist of four segments each of which represents growth at a constant percentage rate. The pause in the curve between 17 and 18 days coincides approximately with the second peak in the mortality curve (Fig. 3). Growth at an instantaneous rate of 56 per cent per day indicates that the body weight is doubled once in 12 days; at 36 per cent per day, the body weight is doubled once in 1.9 days; at 24 per cent per day, the body weight is doubled once in 2.9 days.

to the terrestrial mode) which takes place at this time. Fig. 3, representing the course of mortality, likewise presents a disturbance at this time. The peak of mortality at 5 days also represents a critical period as indicated by the presence of a peak in the lactic acid curve.

These results are quite unexpected and no doubt, new. Students of animal growth have accepted the notion of Minot that the per-

centage rate of growth declines in a continuous manner with age. The breaks in the curves substantiate, in a way, the "human metamorphosis" conception recently advanced by Davenport.

Fig. 4 represents the course of carbon dioxide production plotted from data by other investigators. The differences between the curves in Figs. 2 and 4 are due to differences in experimental procedure.

Figs. 5, 6, and 7 represent the curves of growth in weight of the chick embryo. There are differences between the weight and the carbon dioxide curves, which leave room for discussion. There are also differences between the weight curves as plotted from data by different investigators. These differences are probably due to differences in the experimental technique employed, especially differences in incubation temperatures. That differences in temperature bring about changes in the growth rates, especially in the earlier stages of incubation, is illustrated by Fig. 8.

During postnatal life, the fowl grows at 5 per cent per day up to 3 weeks, and at 3 per cent from 3 to 12 weeks. The major inflection in the curve takes place at the age of about 12 weeks.

It may be noted in this connection that the rat, guinea pig, cow, sheep, and probably other domestic animals, grow at approximately the same percentage rate during the juvenile period (the stage preceding the major inflection); namely, 2 to 3 per cent per day. Man, however, grows during this period at quite a different (much lower) percentage rate.

The results obtained with the domestic fowl were practically duplicated, as far as the available data permitted, with the rat, guinea pig, cow, sheep, and domestic pig. The data of the rat are of special interest on account of the break in the curve at birth as shown in Fig. 9. It is probable that there is a break in the curve at birth in all classes of animals.

The curve of man differs in several important respects from the curve of animals. The curve of man requires a more extensive discussion than can be given at this time. For this reason a separate paper will be devoted to the growth curve of man.

The curve of plants is similar to that of animals. However, the inadequacy of the data and the relatively large experimental errors

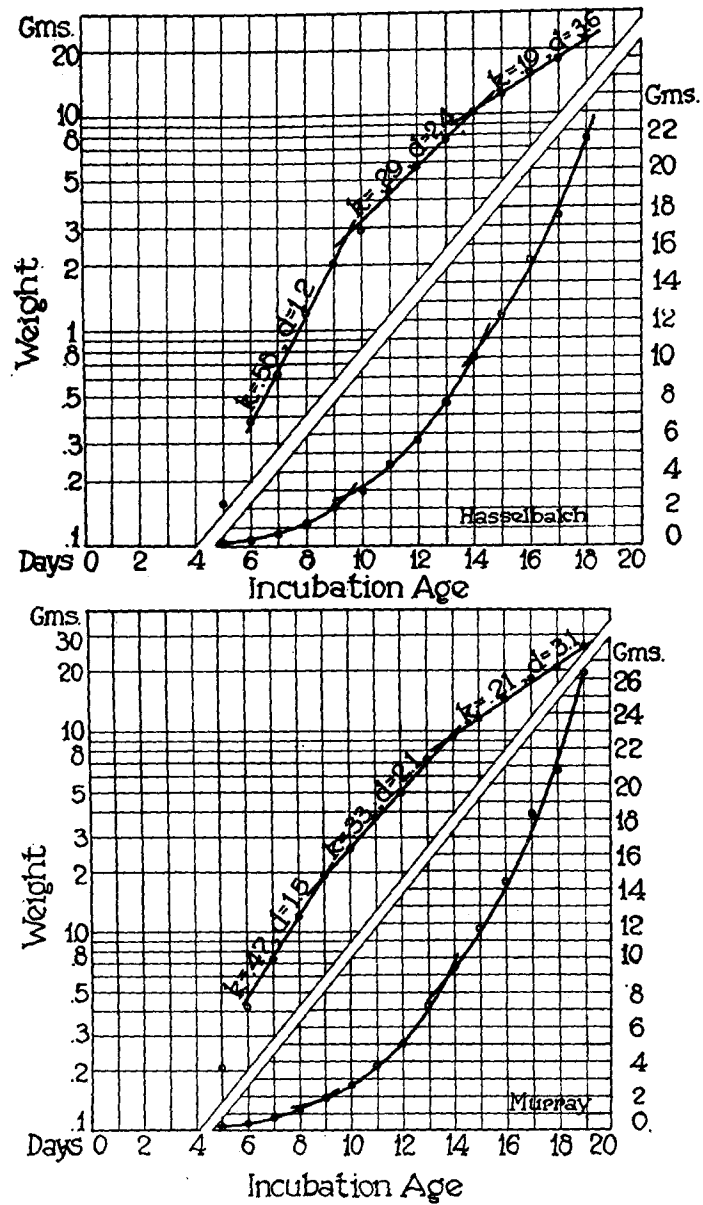


FIG. 6. Growth in wet weight of the chick embryo, plotted from data by Hasselbalch and by Murray. The value of  $100k$  represents the instantaneous percentage rate of growth per day. The values of  $d$  represent the time in days required for the body to double its weight.

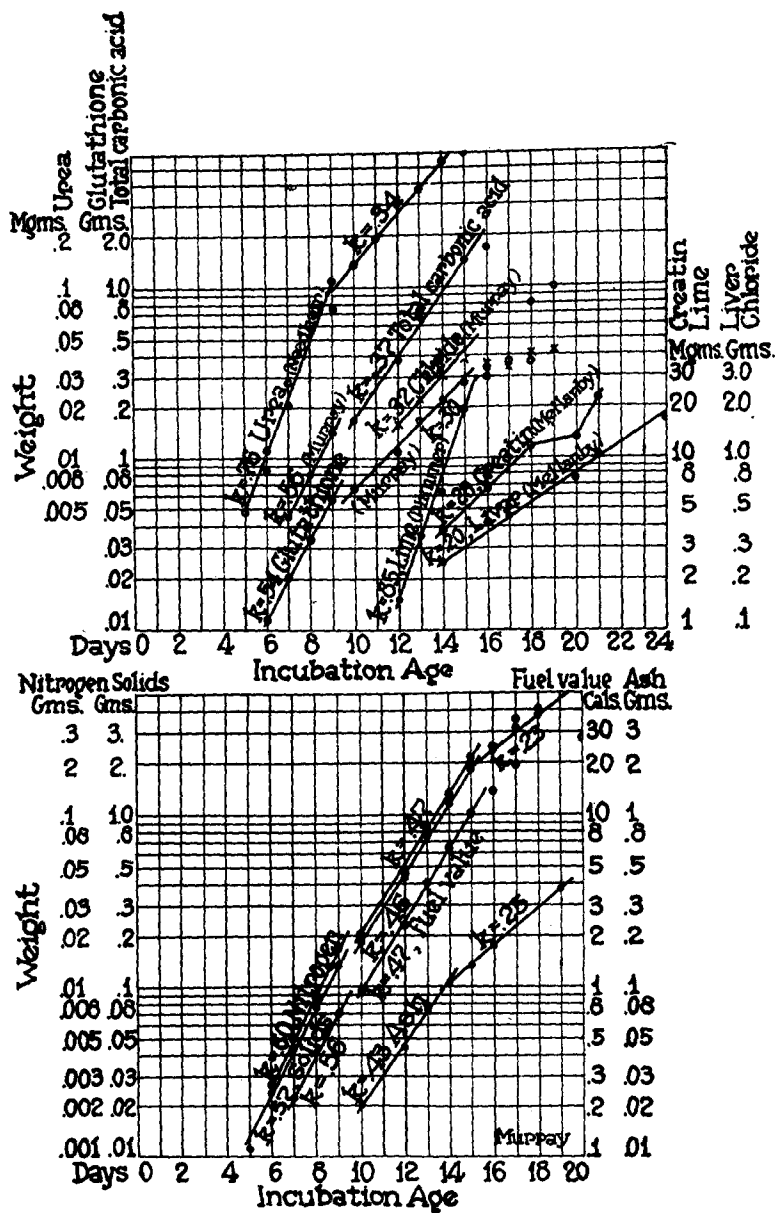


FIG. 7. The course of increase in chemical constituents in the chick embryo with advancing age. The sources of data are indicated on the chart (compare with Figs. 5 and 6).

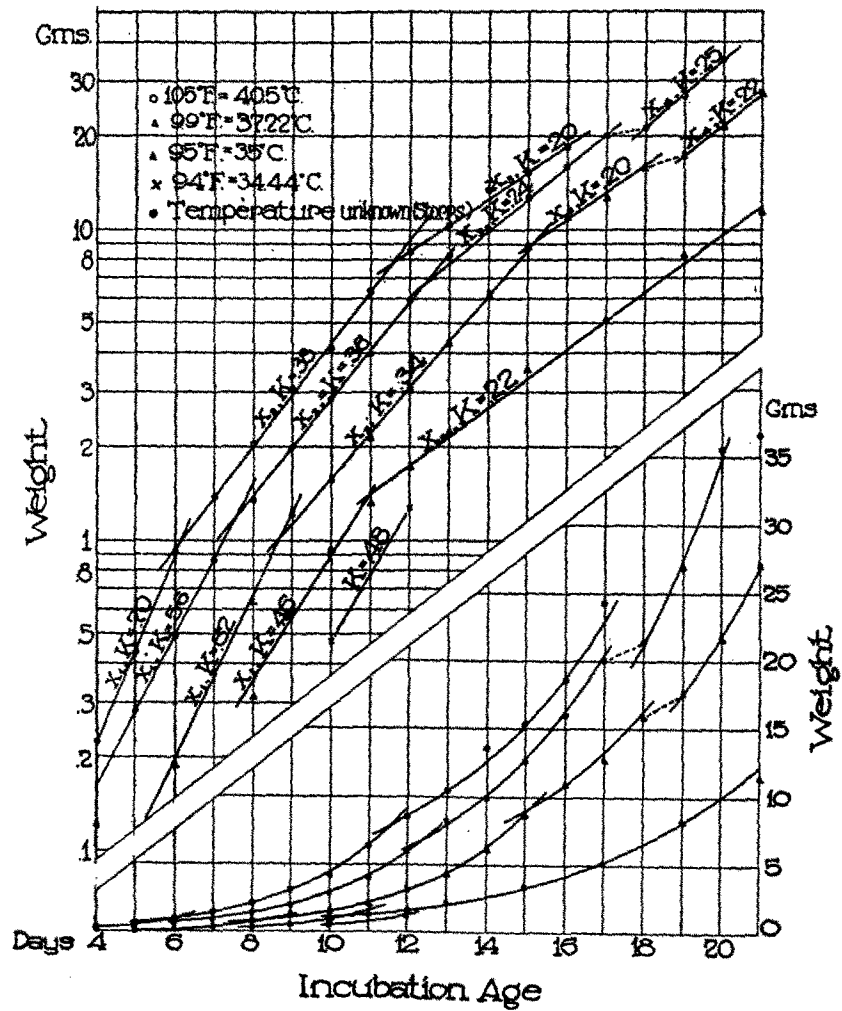


FIG. 8. The effect of temperature on the course of growth of the chick embryo (E. W. Henderson and S. Brody).

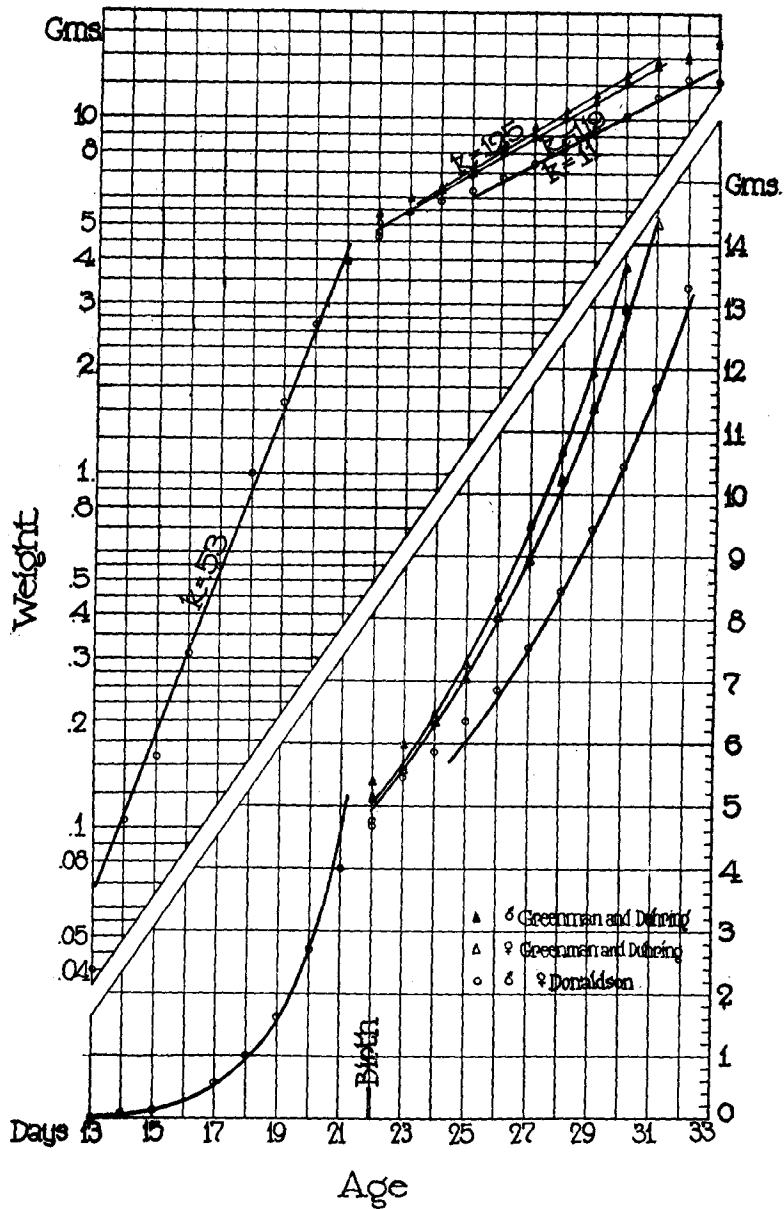


FIG. 9. The course of growth of the white rat plotted on arithlog and on coordinate paper. On the arithlog paper the data points are distributed around a straight line indicating that the percentage rate of growth is constant. There is an abrupt break in the curve at the time of birth and the percentage rate is seen to drop from 53 to about 12 per cent. Data preceding birth by Stotsenburg.

involved in the investigation of plant materials do not permit formulating conclusions as definite as with animals.

Fig. 10 shows the course of growth of the wheat kernel. The development of the seed corresponds, in time, to the prenatal growth in

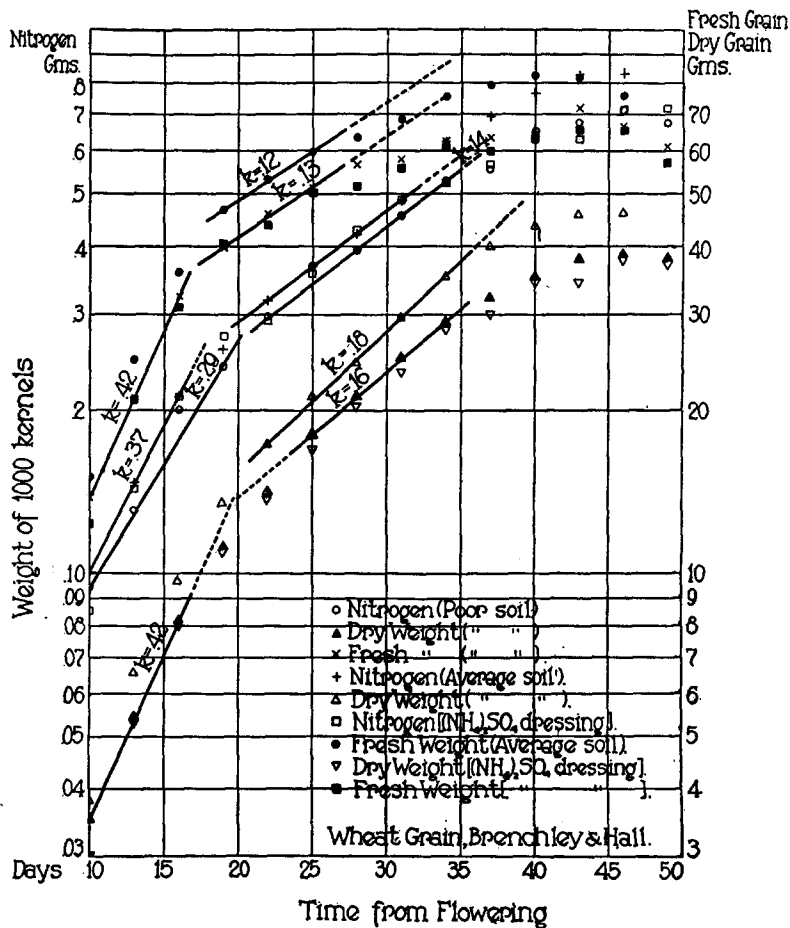


FIG. 10. Growth of the wheat grain.  $k$  and  $d$  have the usual meaning.

animals. However, it so happens that in the wheat kernel the embryo is a small fraction of the whole seed (about one-thirteenth), and so the data represent more than embryonic growth.

Fig. 11 represents the period of independent growth of the maize plant. The segment preceding flowering corresponds to the juvenile period in animals, and as in animals, the percentage rate of growth is constant. The inflection occurs at the time of flowering, which corresponds to puberty in animals. The major inflection in the curve

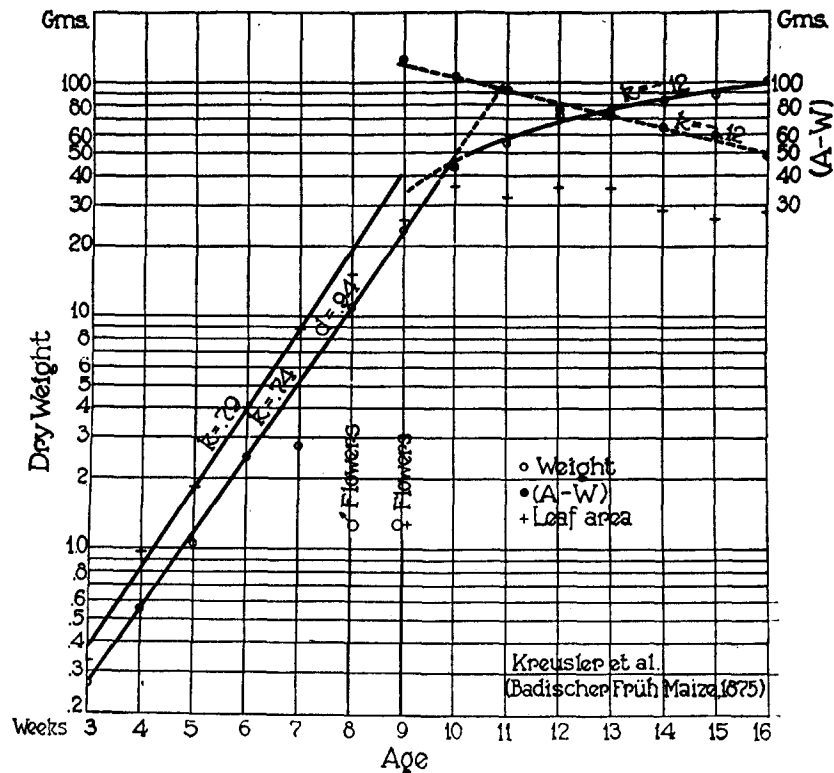


FIG. 11. The course of growth of the maize plant (note that the week is the unit of time in this case).

invariably occurs at the time of flowering in higher plants, and at puberty in higher animals.

Figs. 12 and 13 represent, respectively, the growth of bacterial and human populations. The rate of growth is constant during the period preceding the major inflection.

As to the bearing of this work on the problem of *growth cycles*, the



situation, as it appears to the writer, is as follows: All curves pass through an inflection which joins the strictly self-accelerating phase with the strictly self-inhibiting phase of growth. For this period,

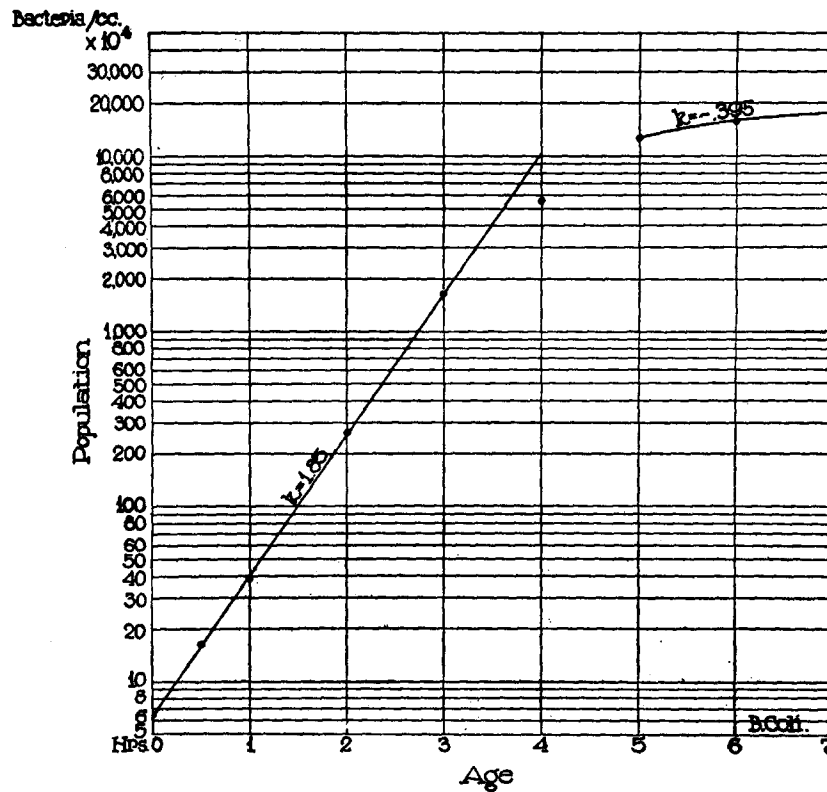


FIG. 12. The course of growth of *B. coli* at 37°C. in a given volume of broth (data from Experiment 7 of McKendrick and Pai). The value of  $k$ , 1.85, indicates the population of bacteria increases at 1.85 per cent per hour. That is, the population doubles itself every  $.69/1.85 = .37$  hours, or 22.2 minutes. Following the 5th hour, the percentage rate of growth is constant with respect to the growth yet to be made.

which is relatively short, equation (6), the "autocatalytic" equation of Robertson, or the "logistic" equation of Pearl, can be fitted satisfactorily, especially, if a constant, or constants, is employed to compensate for the asymmetric nature of the curve. This equation can-

not, however, be satisfactorily fitted to the infantile (except in man), or to the juvenile cycle.

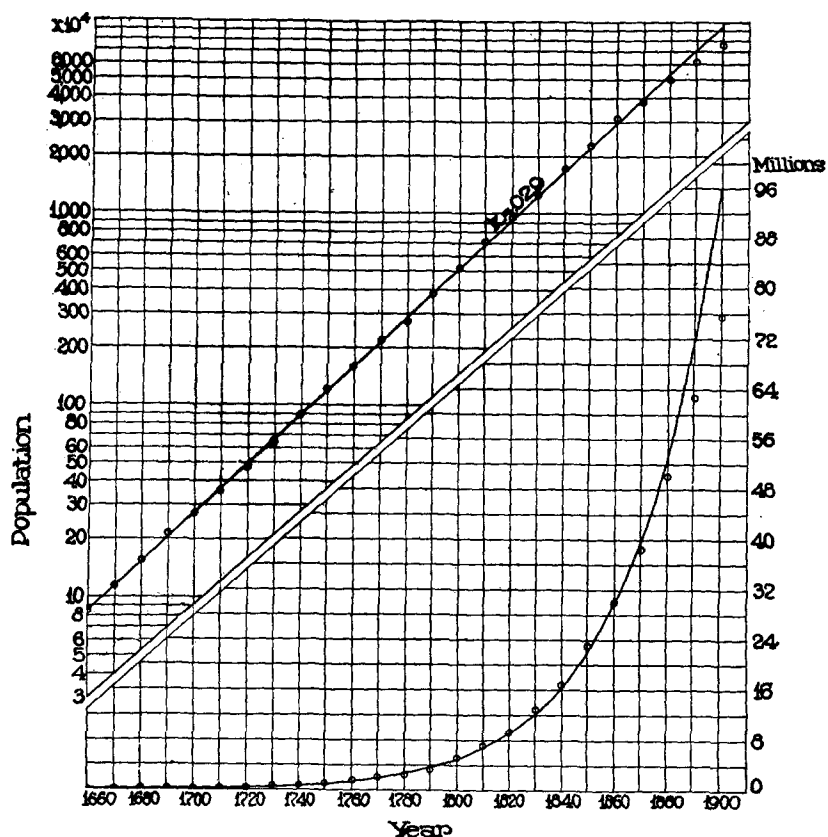


FIG. 13. The course of growth of the human population in the American Colonies and in the United States. The percentage rate is constant from 1660 to 1870. From 1870 on, the percentage rate declines in a manner indicated by the preceding figure on the growth of bacteria.  $k = .029$ ; the population increased 2.9 per cent per year, or 29 per cent per decade; or it doubled itself once in  $.693/.029 = 24$  years. (Plotted from data by Rossiter, W. S., *A century of population growth in the United States* Bureau of the Census, United States Department of Commerce and Labor, Washington, 1909).

What we appear to have during the phase of growth preceding the inflection is a series of segments during each of which growth takes

place at a constant percentage rate. These segments are separated by breaks, analogous to the breaks in the curves of cold blooded animals when undergoing metamorphosis. The present need is for growth data taken at shorter intervals in order to ascertain definitely the presence of breaks, and for an investigation of the threshold mechanisms bringing about these breaks, if there are such.

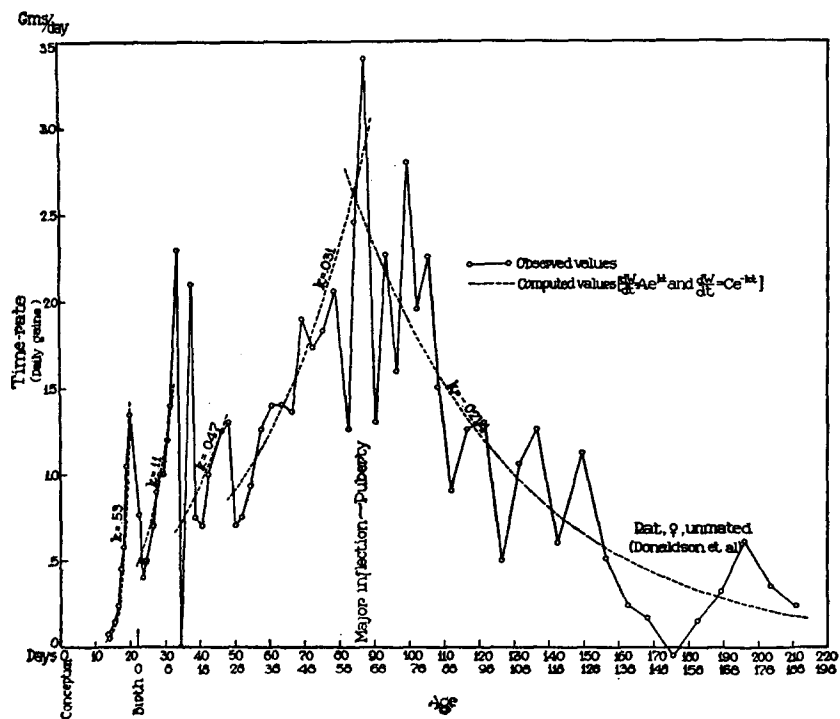


FIG. 14. The daily gains in weight of the rat plotted against age. The curve appears to have three cycles.

When the increments (time rates) are plotted against age, as shown in Fig. 14, there appear to be several cycles preceding the major inflection; as a matter of fact, the drops in the curve are not portions of cycles but breaks between successive stages of constant growth rates, as shown in Fig. 15.

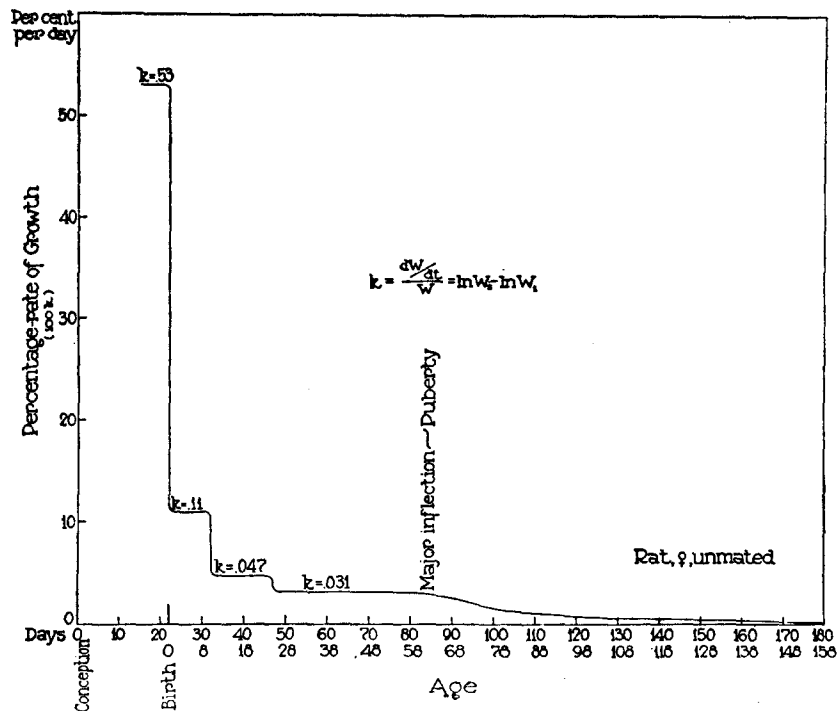


FIG. 15. The values of  $k$  plotted against age to indicate the discontinuous nature of the growth process.

#### V.

#### CONCLUSIONS AND SUMMARY.

Growth curves consist, in all cases, of two major segments. The first major segment is, in the case of higher animals and plants, made up in turn of several (probably five) shorter segments during each of which growth takes place at a constant percentage rate. The transitions between the successive stages are abrupt, the abruptness being of the order of metamorphosis in cold blooded animals.

It has been made clear in the first paper of this series that the time rate of growth following the major inflection *declines* at a constant percentage rate.

The junction between the two major segments occurs at puberty in animals and flowering in plants.

The two major segments are not symmetrical about the major inflection. The slope of the segment following the inflection is always less than the slope of the segment preceding the inflection. The major inflection does not occur in the center of the growth curve.

The instantaneous rate of growth at the beginning of growth is of the order of 100–200 per cent per day (*i.e.* the body weight is doubled in from 7 to 17 hours). It may be mentioned that 2 months after conception the rate of growth in man is only 8 per cent per day. This is contrary to all the published statements. Thus, Minot concluded that growth begins at 1000 per cent per day; Jackson concluded that in man, growth during the 1st month takes place at 57.5 million per cent per month; during the 2nd month 990 per cent per month; during the 3rd month 390 per cent per month (8 per cent per day is only 240 per cent per month). The reason for the discrepancy between the values derived, by the method adopted by the writer, and the values given in the literature is explained by Fig. 1.

This paper is a brief summary of Research Bulletins, 97, 98, and 99, of the University of Missouri Agricultural Experiment Station, at present in press. The reader must be referred to these bulletins for detailed discussions relating to questions that may not have been made clear in this paper.

*Addendum.*—Since this manuscript was submitted for publication, the writer had the privilege of discussing its subject matter with Drs. E. B. Wilson, C. R. Stockard, and H. H. Donaldson, all of whom expressed approval of the two principal ideas. Dr. Wilson called attention to a paper by G. H. Knibbs, on the Laws of population growth which appeared (on January 8) in the *Journal of the American Statistical Association*, 1926, xxi, 381, substantiating in principle one of the two principal ideas of this paper, namely that in the early history of a population the percentage rate of growth is constant. Dr. Stockard called attention to the fact that the peak in the mortality curve of the chick (Fig. 3) at 5 days is a counterpart of the peak in the prenatal mortality curve in man at 3 months. This is the junction between the embryonic period (formation of organs) and fetal period (enlargement of body and organs). The nature of the growth process in the two stages is quite different, and it is not, therefore, surprising to find a high mortality (and break in the growth curve) at this time.

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