

dently had a swelling influence) in a NaCl diffusion field. The assumption is made here that the addition of urea and resorcinol in these experiments did not influence the qualitative behaviour. This appears to be justified by the fact that the presence of these non electrolytes did not qualitatively alter <sup>11)</sup> the general characteristics of the complex coacervation, the latter depending solely on the interaction of the electric charges of both macromolecular colloids.

#### Summary.

1. Drops of complex coacervates, suspended in their equilibrium liquids, show a number of morphological phenomena in the electric field. These phenomena are described in greater detail than hitherto published.

2. In a previous article it was supposed that in the explanation of the motory phenomena local changes of the interfacial tension ( $\sigma$ ) coacervate medium might play an essential part. It was assumed that these changes of  $\sigma$  would be due to pH changes by polarisation of the surface of the drops. Experiments were therefore carried out in order to demonstrate these pH changes in gum arabic (A)-gelatine (G) coacervates.

3. No changes in pH could be proved, which may be due to the use of buffered stock sols. These experiments however indicated that in the electric field gum arabic is accumulated at the anodal and gelatine at the cathodal side of the drop in consequence of electrophoresis of these components within the drop. As most of the indicators we used in these experiments were found to have "protein errors", on account of which systems rich in G had another colour than those rich in A, these shifts of the mixing proportion on both sides of a drop manifested themselves in slight colour differences of the parts of the drops facing the electrodes.

4. It appears from now available data concerning  $\sigma$  that these changes, and not, as far as is now known, changes in pH, can be held responsible for the  $\sigma$ -variations postulated for the explanation of the motory phenomena.

5. Moreover it is demonstrated that the changes in mixing proportion themselves are also important factors in the explanation of a number of the so-called desintegration phenomena.

6. Starting from the results of these experiments and the data on  $\sigma$  explanations have been given for the greater part of the morphological phenomena that have been described.

Laboratory for Medical Chemistry of the University, Leiden.

<sup>11)</sup> H. G. BUNGENBERG DE JONG and E. G. HOSKAM, loc. cit. (1942).

Mathematics. — *The Growth-Curve*. By J. W. N. LE HEUX. (Communicated by Prof. A. PANNEKOEK.)

(Communicated at the meeting of October 25, 1947.)

1. In T. BRAILSFORD ROBERTSON'S "Chemical basis of Growth and Senescence" (No. 1) the growth  $\frac{dN}{dt}$  of an organism  $N$  in a time  $t$  is given by an equation of the form

$$\frac{dN}{dt} = N(b - aN)$$

where  $a$  and  $b$  are constants. Introducing the maximum value of  $N = \frac{b}{a} = A$ , we get

$$\frac{dN}{dt} = aN(A - N) = bN \left(1 - \frac{N}{A}\right)$$

with the solution

$${}^e\log \frac{N}{A - N} = b(t - t_1)$$

or

$$N = A \frac{e^{b(t-t_1)}}{1 + e^{b(t-t_1)}}$$

$t_1$  is the time, corresponding to  $N = 0.5 A$ .

Now, sets of values for  $N$  and  $t$  being given by experiment and admitting, that the given relation holds true, the most probable values of the constants  $A$ ,  $b$  and  $t_1$ , may be calculated by the method of least squares.

In this way and using ordinary logarithms, ROBERTSON finds f.i. the equation

$${}^{10}\log \frac{N}{320 - N} = 0.127(t - 1.57)$$

from the following experimental data:

weight of male British infants in ounces

148 169 194 219 234 252 269 276 283 300 303 314

time in months

1 2 3 4 5 6 7 8 9 10 11 12

If — as often occurs — only an approximate comparison of theory and observation is required, the constants may be found in a much shorter way by using a graphical method, that will be described in the following lines.

This method procures a quick and easy way to test a given graph (if a relation of the foregoing form is suggested) by the construction of the growth-curve or sigmoid

$$N = A \frac{e^{b(t-t_1)}}{1 + e^{b(t-t_1)}}$$

in form well-known from different publications on biological and chemical subjects, but whose application seems largely to have been overlooked.

In a recent work on empirical equations (No. 2) the author says: "Some data take the form of an elongated S when plotted, the curve being characterized by a very small initial slope followed by a period of rapidly increasing slope which gives way to an interval of nearly constant slope succeeded by a period when the rapidly decreasing slope approaches zero. The growth of population and production statistics for iron and steel and for rayon are typical of this class. In the case of the manufacture and sale of some new product, consumer acceptance is slow at first, as shown by the small slope of the sales-time curve. Advertising increases the slope greatly. Later a period of stabilization is encountered and the sales-time curve levels off. The Gompertz equation

$$y = ab^{e^x} \text{ (or } y = a + ab^{e^x}\text{)}$$

has been found to be satisfactory in representing such data".

Especially in questions of growth of living organisms, the sigmoid, that is not at all mentioned here, should be preferred to the Gompertz curve.

2. Construction of the curve  $N = A \frac{e^{b(t-t_1)}}{1 + e^{b(t-t_1)}}$ .

The plotting of the scale  $\frac{e^n}{1+e^n}$  (growth-scale) with modulus  $A$ , against a regular  $t$ -scale ( $n$ -scale with modulus  $\frac{1}{b}$ ) on ordinary coordinate paper results in a S-shaped curve, well-known as "sigmoid" or "logistic" or "growth-curve".

Raising the horizontal  $t$ -axis over  $0.5 A$ , the equation becomes

$$N' = 0.5 A \frac{e^{bt} - 1}{e^{bt} + 1} = 0.5 A \operatorname{th} \frac{bt}{2}$$

proving, that growth, as defined by the equation

$$\frac{dN}{dt} = N(b - aN)$$

may be expressed by a tangens hyperbolicus.

From a nomographical point of view, the scale  $A \frac{e^n}{1+e^n}$  is a projective scale. It may be obtained by projecting the graduations of the scale  $e^n$  ( $n$  from  $-\infty$  to  $+\infty$ ) on a horizontal axis  $O X$  from the centrum  $(-1, A)$

on a vertical axis  $O Y$  (fig. 1). The result is a symmetric scale, for the graduations  $\frac{e^p}{1+e^p}$  and  $\frac{e^{-p}}{1+e^{-p}}$  are equidistant from the centre of the scale, because

$$A \frac{e^p}{1+e^p} = A \frac{1}{e^{-p}+1} = A - A \frac{e^{-p}}{1+e^{-p}}$$

Consequently, to construct this scale only the part  $0-1$  ( $n$  from  $-\infty$  to  $0$ ) needs to be projected.

A plot of this symmetric scale against the regular  $t$ -scale shows a curve, that being turned about its centre through an angle of  $180^\circ$ , is indistinguishable from the original curve.

The sigmoid is of use in the two following problems:

- 1e. The testing of an experimental smooth curve through plotted points and the determining of its equation.
- 2e. The construction of the curve, given by an equation of ROBERTSON

$${}^{10}\log \frac{N}{A-N} = b(t-t_1).$$

3. In the first place, we suppose, that a rather great number of data is known, as in the case already mentioned:

weight of male British infants in ounces

148	169	194	219	234	252	269	276	283	300	303	314
time in months											
1	2	3	4	5	6	7	8	9	10	11	12

These data refer to the first or infantile cycle — the second or juvenile and the third or adolescent cycles of human growth are partially fused with one another and do not permit of such precise formulation as the infantile cycle. The analysis of such a complex curve into its constituent cycles, each defined by three mutually independent parameters  $A_1$ ,  $b$  and  $t_1$  is — as ROBERTSON remarks — a matter of considerable difficulty and tedium.

The conclusion of the first year of post-natal growth in man coincides approximately with the conclusion of a cycle of growth and therefore, the existence of the relation  $\frac{dN}{dt} = N(b - aN)$  may be suggested.

The average weight of British male infants at 12 months of age is 314.3 ounces, hence we may take  $A$  as being 320 ounces.

$0.5 A = 160$  ounces is reached in a time  $t_1$

160 lies between 149 (1 month) and 169 (2 months), so

$$t_1 = 1 + \frac{160-148}{169-148} = 1.57 \text{ months.}$$

On rectangular axes  $O X$  and  $O Y$  (fig. 2) a line  $P Q$  parallel to  $O Y$  is

located at a distance  $t_1 = 1.57$  cm from 0. The length of  $PQ = A = 320$  (16 cm). Now a growth-scale is laid off along  $PQ$ . This growth-scale is taken from a "modulus-chart", which must be prepared beforehand in the same manner as a logarithmic modulus-chart in nomography. The construction is as follows. Because the growth scale is symmetric, mark off half such a scale with a modulus of 40 cm along the line  $AB$  (fig. 3).

The graduations are found by construction or by calculation from  $N = 40 \frac{e^{-n}}{1+e^{-n}}$  and for values of  $n$  from 0—5 (because  $40 \frac{e^{-6}}{1+e^{-6}} \sim 1$  mm) with subdivisions of 0.1.

Project a pencil of lines from the graduations on  $AB$  to the point  $C$ , 20 cm from  $AB$  on a line at right angles to  $AB$  in  $B$ , bearing a half-centimeter scale. The slant lines will cut the vertical modulus lines in scales of moduli between 0 and 40 cm.

For practical use, the chart is cut into two parts, which are rejoined as in fig. 3.

When no modulus-chart is disposable, the points numbered —5, —4 ..... 0 ..... +4, +5 are sufficiently located by the distances 1, 2, 5, 12, 27, 50, 73, 88, 95, 98, 99 from the point ( $-\infty$ ) for a modulus of 100 mm.

Through the dividing-points of the growth scale on the line  $PQ$  lines are drawn parallel to the  $X$  axis.

The regular  $t$  scale on the  $X$  axis has a modulus  $\frac{1}{b}$ .

Suppose that  $B(t - t_1) = 1$  for  $t = t_2$ .

Then  $N = A \frac{e}{1+e} = 0.731 A = 0.731 \cdot 320$  ounces = 234.24 ounces (11.7 cm).

$t_2$  is calculated from the data in the same manner as  $t_1$ .

234.24 lies between 234 (5 months) and 252 (6 months).

So  $t_2 = 5 + \frac{234.24 - 234}{252 - 234} = 5.013$  months and  $t_2 - t_1 = 3.44$  months =  $\frac{1}{b}$ .

Now, the  $X$  axis must be divided in equal parts of 3.44 cm with the zero-point in  $Q$ .

Drawing lines through the dividing points parallel to  $OY$  and joining up the intersecting points of corresponding lines by a smooth curve, the sigmoid, corresponding to the data, appears. Fig. 2 gives a comparison between the observed and the constructed values of  $N$ .

Extrapolation is not permitted: about the epoch of birth, there is a slight arrest in growth and for the pre-natal months, this curve has no significance.

From  $\frac{1}{b} = 3.44$  it follows, that  $b = 0.29$  and as we have found  $A = 320$  and  $t_1 = 1.57$ , the equation becomes

$${}^e \log \frac{N}{320 - N} = 0.29(t - 1.57)$$

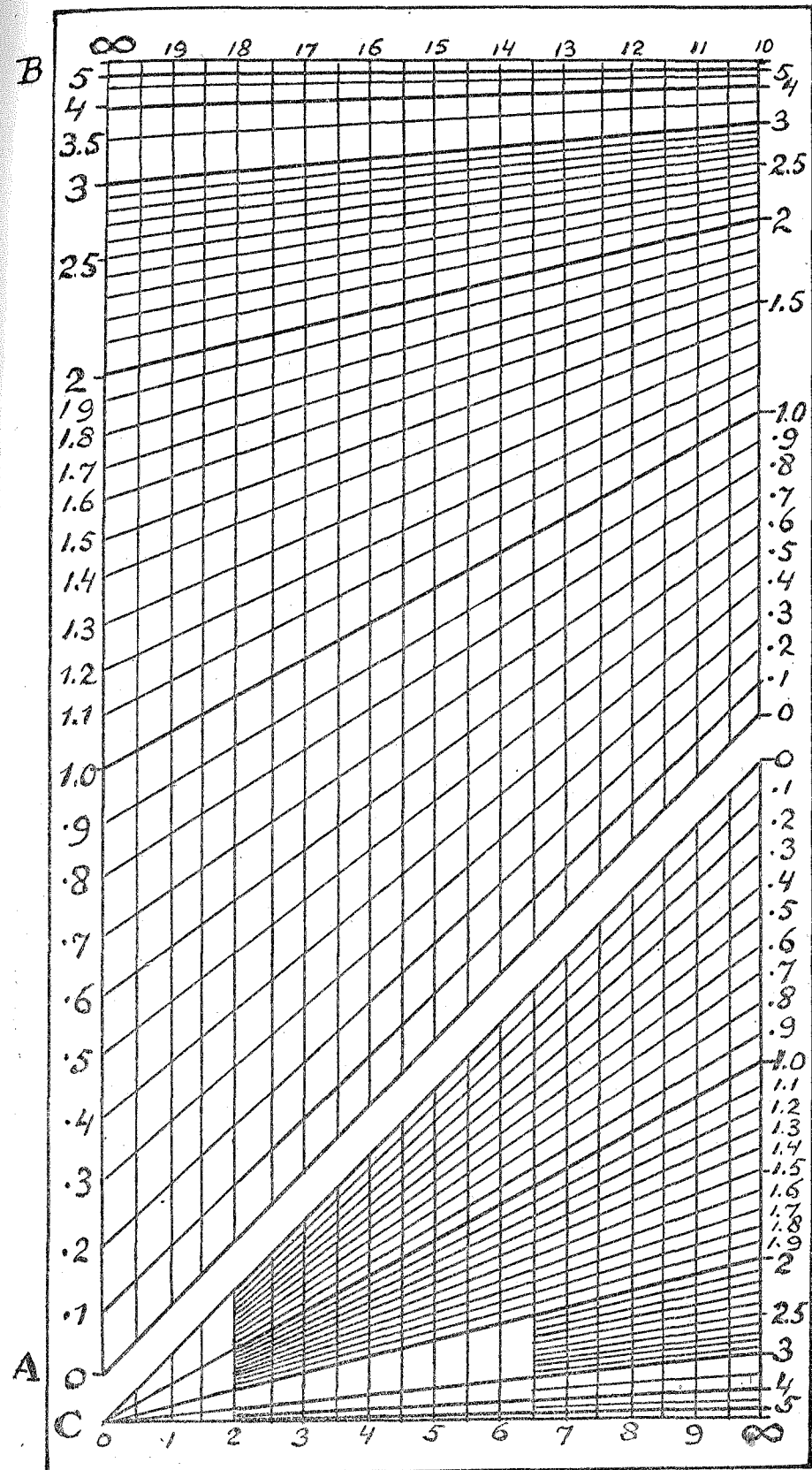


Fig. 3. Modulus-chart for growth-scale.

or

$${}^{10}\log \frac{N}{320-N} = 0.434 \times 0.29 (t-1.57) = 0.128 (t-1.57).$$

ROBERTSON finds with the method of least squares for  $b = 0.127$ . Instead of calculating the values of  $N$  from the equation, the lengths of the ordinates may be measured in the carefully drawn curve, using the growth-scale with graduations of 0.1.

4. In the second place we suppose, that a given graph gives rise to the question, whether this curve may be a sigmoid?

The S shaped curve has two parallel (horizontal) parts with a distance  $A$ . If the (shortened) parts are nearly parallel, we must take in this "trial and error" method a possible value of  $A$ .

The  $X$  axis is laid along the lower part and a vertical axis through the intersecting point of the curve with the line  $Y = 0.5 A$ .

A growth-scale with the modulus  $A$  is laid off along the vertical axis and through the dividing points 1, 2, 3, 4 and 5, horizontal lines are drawn till they meet the curve. If the lengths of these lines are also in ratio 1, 2, 3, 4 and 5, the curve will be a sigmoid. In fig. 4, this method is applied to the curve of pre-natal growth (length) of child in THOMPSON'S "on Growth and Form", according to HIS'S dates (the same curve in Encyclopaedia Britannica, 14th ed. vol. 10) (No. 3 and 4).

THOMPSON writes: "a beautifully regular one, nearly symmetrical on either side of the point of inflexion. A curve, for which we might well hope to find a simple mathematical expression".

This hope can be realized. Fig. 4 shows, that the lower part fits exactly a sigmoid with a time-unity measured in the figure  $\frac{1}{b} = 1.2$ . It is impossible, to find a combination of the same growth-scale with a regular  $t$ -scale for the upper part of the given curve (points 5—10), but we see that, omitting point 5, the points 6 and -4 belong to the same curve as points 1—4, while the points 7, 8 and 9 fit another (dotted) sigmoid with a time unity  $\frac{1}{b} = 1.4$ . So this graphical method suggests the idea of a variable  $b$ : by one reason or another, its value may change into another during a certain interval and return to the initial value.

In fig. 4,  $A = 500$  mm,  $t_1 = 5$  months,  $\frac{1}{b} = 1.2$  months,  $b = 0.83$  (for  $\frac{1}{b} = 1.4$ ,  $b = 0.71$ ). The general equation is

$$N = 500 \frac{e^{0.83(t-5)}}{1 + e^{0.83(t-5)}}$$

with the restriction, that 0.71 must be taken instead of 0.83 in the interval  $t = 6$  to  $t = 10$ . Fit for calculation:

$${}^{10}\log \frac{N}{500-N} = 0.36 (0.31) (t-5).$$

Another instance is the graph for pre-natal growth of child in weight (after Vignes, fig. 5).

The modulus of the growth-scale  $A = 3500$  gram,  $t_1 = 7$  months.

The lower part is exactly a sigmoid with  $\frac{1}{b} = 1$  month,  $b = 1$ .

The upper part is nearly a sigmoid with  $\frac{1}{b} = 0.7$ ,  $b = 1.43$ .

The equation is:

$$N = 3500 \frac{e^{(t-7)}}{1 + e^{(t-7)}}$$

or

$${}^{10}\log \frac{N}{3500-N} = 0.434 (t-7)$$

with 1.43  $t$  instead of  $t$  and 0.621 instead of 0.434 for the last three months.

An inquiry into the growth of *Phycomyces* (fig. 6a after ERRERA, Nr. 6) shows a complex curve with a first cycle of slow growth ending when the production of a sporangium begins and a second cycle of very rapid growth<sup>1)</sup>.

We will try to find a sigmoid, corresponding to each cycle.

According to the given numbers, the first curve may have a maximum value  $A = 8.5$  mm. Now the second sigmoid is plotted by diminishing the ordinates of the original curve with 8.5 beginning with  $t = 24$ . We find  $A_2 = 125 - 8.5 = 116.5$  mm.

On a vertical axis through the intersection-point of the dotted curve with the line  $y = 0.5 A_2 = 57.3$ , a growth-scale is laid off with a modulus 116.5 and horizontal lines are drawn through the dividing points till they meet the dotted curve. Evidently, it is impossible to get a regular  $t$ -scale for the whole curve, but here also the graphical method enables us to see, what is not revealed by calculation. The dividing point 1 of the growth-scale suggests a modulus  $\frac{1}{b} = 7.2$  for the  $t$ -scale (above the point of inflexion) and this modulus fits the inner part of the dotted curve, while the outer part corresponds to a modulus  $\frac{1}{b} = 6$  (below the point of inflexion).

For the first sigmoid  $A_1 = 8.5$ ,  $t_1 = 12$ ,  $\frac{1}{b_1} = 3$  (as read from the graph),  $b_1 = 0.33$ .

For the second sigmoid  $A_2 = 116.5$ ,  $t_1 = 53.4$ ,  $\frac{1}{b_2} = 6 (7.2)$ ,  $b_2 = 0.167$  (0.139).

<sup>1)</sup> I am indebted to Prof. Dr. V. J. KONINGSBERGER for informations about *Phycomyces*.

Fig. 6b shows the two curves

$$N_p = 8.5 \frac{e^{0.33(t-12)}}{1 + e^{0.33(t-12)}} + 116.5 \frac{e^{0.167(t-53.4)}}{1 + e^{0.167(t-53.4)}}$$

and

$$N_q = 8.5 \frac{e^{0.33(t-12)}}{1 + e^{0.33(t-12)}} + 116.5 \frac{e^{0.139(t-53.4)}}{1 + e^{0.139(t-53.4)}}$$

with the experimental data, partly belonging to each curve. For calculation, we have:

$$\left\{ \begin{array}{l} {}^{10}\log \frac{N_1}{8.5 - N_1} = 0.143(t-12) \\ {}^{10}\log \frac{N_2}{116.5 - N_2} = 0.07(t-53.4) \\ N_p = N_1 + N_2 \end{array} \right\} \left\{ \begin{array}{l} {}^{10}\log \frac{N_1}{8.5 - N_1} = 0.143(t-12) \\ {}^{10}\log \frac{N_2}{116.5 - N_2} = 0.06(t-53.4) \\ N_q = N_1 + N_2. \end{array} \right.$$

$$0.434 = {}^{10}\log e.$$

$$0.143 = 0.434 \times 0.33 \quad 0.07 = 0.434 \times 0.167 \quad 0.06 = 0.434 \times 0.139.$$

A comparison between calculated and observed lengths of *Phycomyces* gives:

		first day				second day			
hours		6	12	18	24	6	12	18	24
length in mm.	$b = 0.07$	1.1	4.5	7.8	9.5	11.1	15.2	21.1	42.9
	observed	1.25	4	7	10	10.5	14	28	48
	$b = 0.06$	1.2	4.8	8.3	10.5	12.9	18.1	28.4	46

		third day				
hours		6	12	18	24	6
length in mm.	$b = 0.07$	69.6	95.1	111.5	119.4	122.8
	observed	69	90	107	120	124
	$b = 0.06$	69.2	91.6	107.6	116.7	121.1

5. The construction of the complex curve

$${}^{10}\log \frac{N_1}{185 - N_1} = 0.0252(t-69)$$

$${}^{10}\log \frac{N_2}{90.5 - N_2} = 0.01125(t-170)$$

$$N = N_1 + N_2$$

found by ROBERTSON for the growth in weight of male, unmated white rats, measured by DONALDSON, runs as follows:

$${}^e\log \frac{N_1}{185 - N_1} = 2.3 \times 0.0252(t-69) = 0.058(t-69).$$

$$b_1 = 0.058 \quad \frac{1}{b_1} = 1725.$$

$${}^e\log \frac{N_2}{90.5 - N_2} = 2.3 \times 0.01125(t-170) = 0.026(t-170).$$

$$b_2 = 0.026 \quad \frac{1}{b_2} = 38.6.$$

Axes *O X* and *O Y* at right angles.

Construct the growth-scales with moduli  $A_1 = 185$  and  $A_2 = 90.5$  on lines  $P_1Q_1$  and  $P_2Q_2$  parallel to *O Y* on distances of 69 and 170 from *O*.

Construct regular scales on *O X* with moduli  $\frac{1}{b_1} = 17.25$  and  $\frac{1}{b_2} = 38.6$  with zero-point resp. in  $Q_1$  and  $Q_2$ . Draw the curves by joining up points of intersection of corresponding lines through the graduations on *O X* and *O Y* and add the ordinates with the same abscissae.

Of course, one cm of the *X* axis may represent another number than one cm of the *Y* axis.

### 6. Conclusion.

In many cases, growth may be defined by the equation

$$\frac{dN}{dt} = BN \left( 1 - \frac{N}{A} \right).$$

*A* is the constant maximum value of *N*, dependent upon nutritional and other conditions, constituting the environment of the growing organism.

*B* expresses the specific velocity of the growth-process itself. Commonly, it has the constant value *b* but sometimes a slight alteration is possible during a certain period of the growth-process.

The relation between *N* and *t* (*b* constant) is

$$N = A \frac{e^{b(t-t_1)}}{1 + e^{b(t-t_1)}}$$

$t_1$  is the time for reaching half the maximum.

To construct this "growth-curve", plot a growth-scale with a modulus *A* from a modulus-chart against a regular scale with a modulus  $\frac{1}{b}$ .

The coordinates of the point of inflexion are  $(t_1, 0.5 A)$ .

To calculate the constants from the experimental data for *N* and *t*, the following scheme may be used

$$0.5 A = \dots \quad t_1 = \dots$$

$$0.731 A = \dots \quad t_2 = \dots$$

$$t_2 - t_1 = \frac{1}{b} \quad b = \dots$$

To calculate  $N$  for a given  $t$ :

$${}^{10}\log \frac{N}{A-N} = b(t-t_1).$$

LITERATURE.

1. T. BRAILSFORD ROBERTSON. The chemical Basis of Growth and Senescence (Monographs on Experimental Biology). Philadelphia, 1921.
2. DALE S. DAVIS. Chemical Engineering Nomographs Mc. Graw Hill. New York, 1944.
3. D'ARCY WENTWORTH THOMPSON. On Growth and Form, Camb. Univ. Press, 1917.
4. G. R. DE BEER. Growth. Encyclopaedia Britannica. 14th ed. vol. 10, 1920.
5. J. W. DUYFF and E. M. BRUINS. The significance of the sigmoidal shape of the metazoan growth-curve. Arch., Néerl. de Phys. Tome XXVI, 1942.
6. L. ERRERA. Die grosse Wachstumsperiode bei den Fruchträgern von Phycomyces. Botanische Zeitung, Jahrgang 42. No. 32—36.
7. J. W. N. LE HEUX. De Groeikromme. Æ. E. Kluwer, Deventer, 1946.

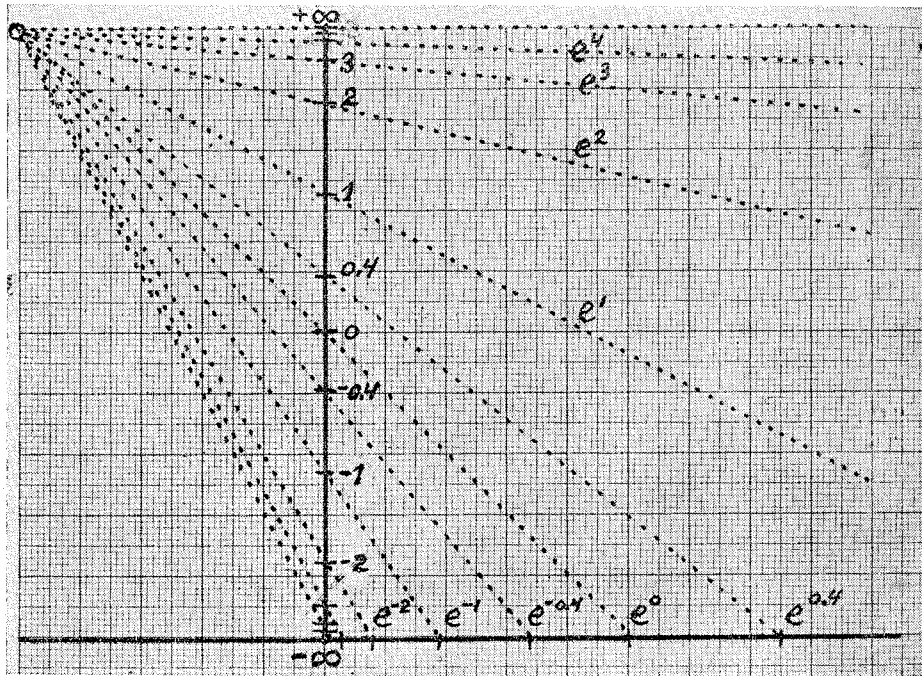


Fig. 1. The symmetric growth-scale.

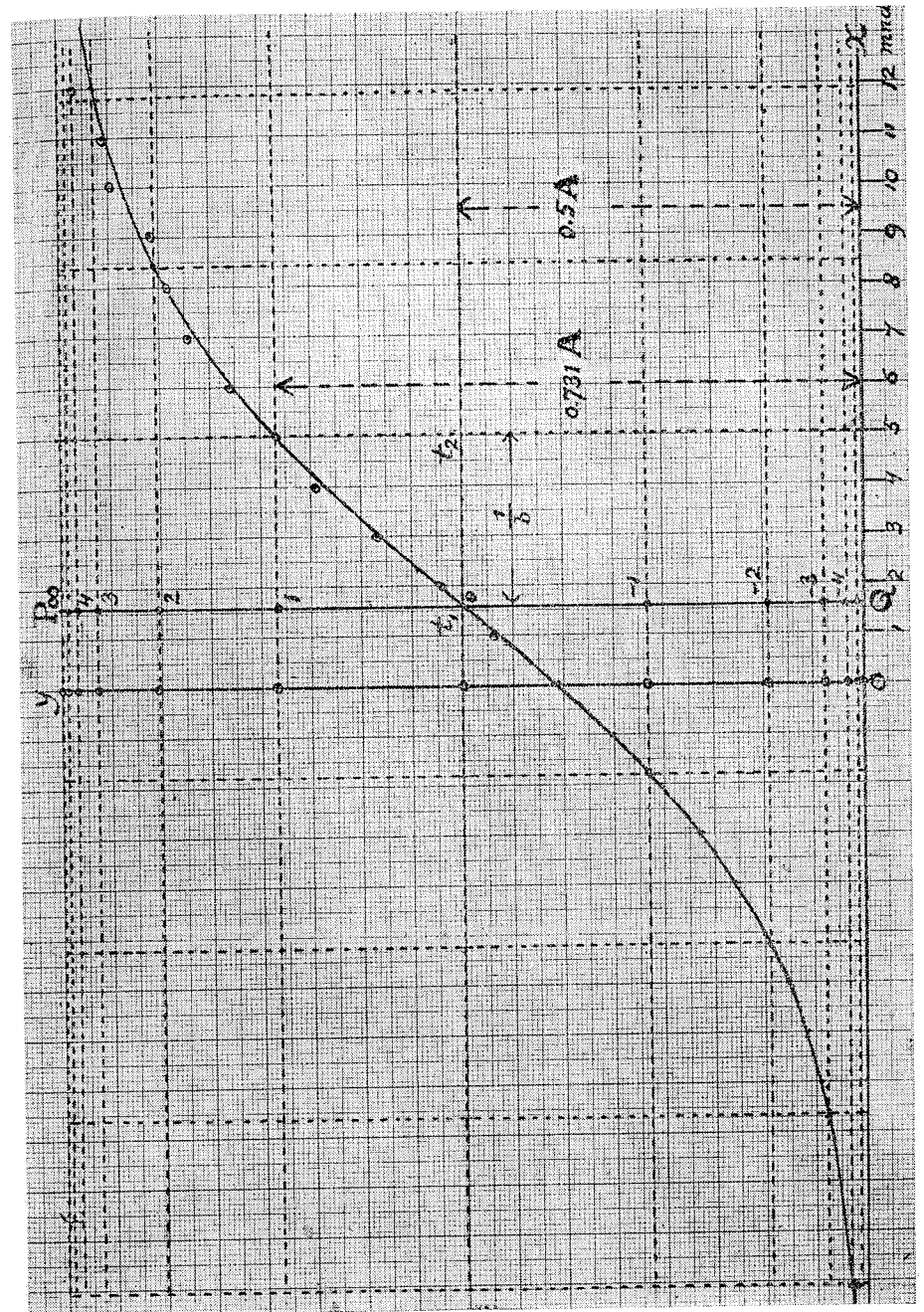


Fig. 2. Post-natal growth in weight.

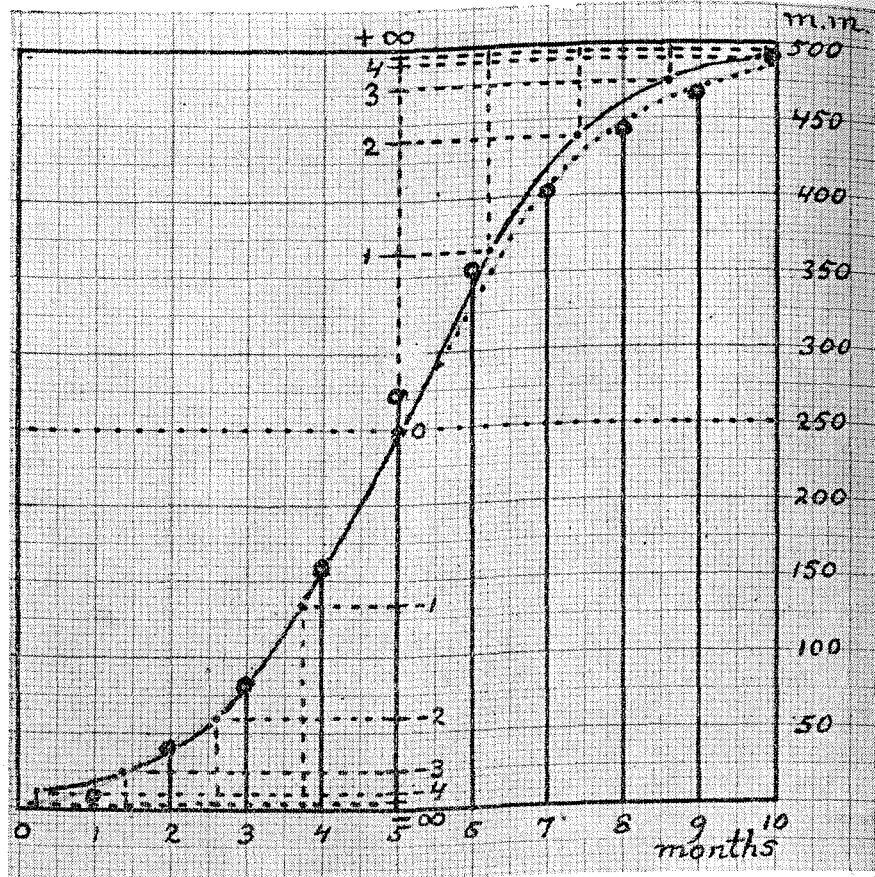


Fig. 4. Pre-natal growth in length.

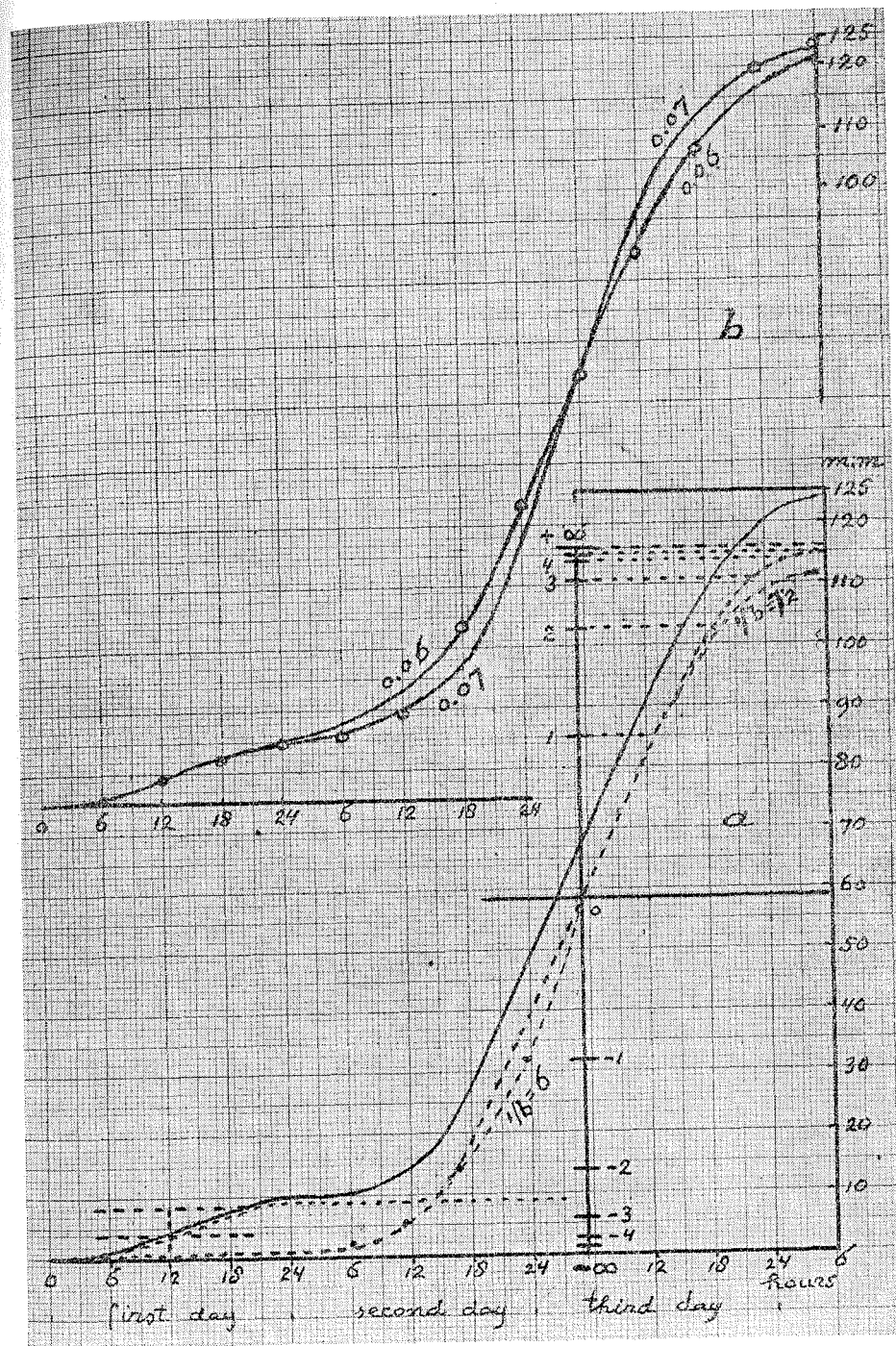
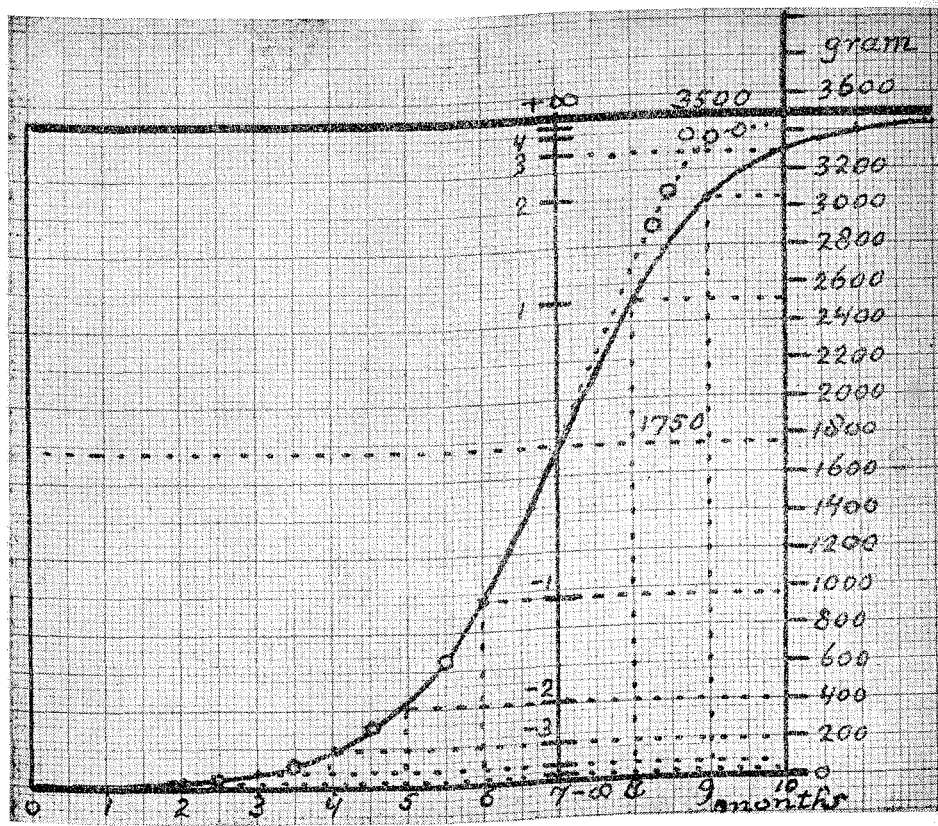


Fig. 6. Growth of Phycomyces.