THE NATURE OF THE FACTORS WHICH DETERMINE THE SEQUENCE OF GROWTH-CYCLES AND ITS RELATIONSHIP TO THE DIFFERENTIATION OF TISSUES.

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The Origin of Asymmetry in Growth-Cycles.

In analysing the growth of the white mouse into its component processes it was found that the first and most prolonged growth-cycle, which extends throughout the growing period in these animals, is of the asymmetrical type which is defined by the equation:

\[
\log \frac{x + b}{A - x} = k(t - t_1)
\]

where \( A \) represents the maximum growth attainable, \( k \) the velocity-constant of the growth-process, \( t_1 \) is the moment of maximum growth-velocity and \( b \) is a constant the essential significance of which is that growth-velocity is already appreciable when \( x \) is zero. It also has the effect of rendering the two halves of the cycle on either side of the moment of maximum growth-velocity, unequal in slope and amplitude.

The remaining growth-cycles (the second and third) which are of comparatively brief duration, are of the symmetrical type which is represented by the equation:

\[
\log \frac{x}{A - x} = K(t - t_1)
\]

in which the constants have the same significance as above, but growth-velocity is zero when \( x \) is zero and the two halves of the growth-cycle, on either side of the moment of maximum growth-velocity, are equal in slope and amplitude.

The applicability of these equations to the growth of mice extends to these animals the rule which has previously been found to obtain in the growth of a variety of other animals and of plants as well, the rule, namely, that the growth of an organism and, frequently, of parts of an organism as well, is an autocatalysed process, by which nothing more is necessarily implied than that growth is a process of such a nature that it facilitates its own occurrence. This follows immediately from an inspection of the differential forms of the above equations which may be written:

\[ \frac{dx}{dt} = kx(A - x) \quad (3) \]

\[ \frac{dx}{dt} = k(x + b)(a - x) \quad (4) \]

each of which may be regarded as an equation of the monomolecular form, in which the velocity-constant increases in the first case in direct proportion to the product, that is, to the amount of growth achieved, in the second case in proportion to the product (growth achieved) plus some quantity (growth not achieved) which remains unaltered throughout the growth of the animal and has the effect of ensuring that at the beginning of the cycle (which, in the mouse, corresponds with the beginning of gestation) the velocity of growth is considerably greater than that which we would otherwise anticipate from the initial weight of the fertilized ovum.

So far as these facts go, and they may now be considered to have been very thoroughly established in a diversity of forms, they may appear to prove nothing beyond the fact, familiar enough when not formulated in mathematical terms, that growth facilitates its own occurrence. They reveal in addition, however, the fact that this facilitation is quantitative and proportionate to the amount of growing material, and also the fact that growth is limited by some factor (\(A\)) which may either represent some fixed amount of material which

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3 For literature see West, C., *Sc. Progr.*, 1921–22, xvi, 382.
is consumed during growth or, on the contrary, some accumulation of material which inhibits growth by its mass-action, as a chemical equilibrium is inhibited by the accumulation and mass-action of the products of the forward reaction. The equations reveal nothing whatever regarding the nature of these facilitating and limiting factors in growth which, so far as this information alone is concerned may be physical conditions just as conceivably as they may be chemical substances, provided only that they fulfill the quantitative relation of proportionality to growth achieved which is involved in the applicability of the equations. We are entitled to state, however, as an empirical law of growth, that the time relations of the growth-process in animals and plants are similar to those which pertain in autocatalysed chemical reactions. Mere mathematical analysis of the growth-curve, taken by itself, will not lead us further in the interpretation of the actual mechanism of the growth-process. To enable this we must seek additional information of a more directly chemical description. Evidence of this type is afforded by Le Breton and Schaeffer's estimations of the changes in the nucleo-cytoplasmic ratio which accompany the growth of animals. 4

It has frequently been observed in the growth of plants that the autocatalysis is of the asymmetrical type which is defined by equations (1) and (4). 5 In animals this asymmetry has been less frequently observed because its effect upon the contour of the growth-curve is greatest at the beginning of growth (when \( b \) is large in comparison with \( x \)), and the beginning of growth, in the higher animals, is generally inaccessible to accurate measurement because it occurs in utero. Nevertheless, one may clearly infer that asymmetry occurs by extrapolating the autocatalytic formulae of the symmetrical type, which are found to fit the post-natal growth of the animals, to the beginning of gestation. It is then found that the calculated weight at the beginning of gestation is of appreciable magnitude instead of being virtually


zero⁸ and this magnitude affords an approximate measure of the constant \(b\) in the asymmetrical formula which truly defines the growth of the animal. We may therefore conclude that asymmetry of the growth-curve is the rule rather than the exception, and we find, in the mouse at all events, that where the growth-curve in any cycle appears to be symmetrical the cycle is one of very brief duration, covering only a fraction, and that a comparatively late one, of the total growing period.

The asymmetrical equation is equivalent to a symmetrical formula in which the velocity-"constant" varies in proportion to the ratio:—

\[
\frac{x + b}{x}
\]

which, of course, approaches unity as \(x\) (= growth achieved) increases. The asymmetry of the curve of growth implies, therefore, that the velocity-"constant" in the autocatalytic formula does not maintain its initial value but falls off as growth proceeds and in the proportion indicated. The relative values of the velocity-"constants" at various stages of the growth of the animal or plant may therefore be computed from the equation:

\[
\frac{k^i}{k} = \frac{x + b}{x}
\]

where \(x\) is the weight-increment from the moment of fertilization which is attributable to the particular (asymmetrical) cycle under consideration.

If we plot the relative values of \(k^i\), thus computed, against the total weights of the animals, we obtain a curve which at first falls steeply and later more slowly, approaching the asymptotic value of \(k^i = k\). If, on the same diagram, we plot the relative magnitudes of the corresponding nucleo-cytoplasmic ratios, as estimated chemically by Le Breton and Schaeffer⁷ we find that the two curves are almost precisely parallel in contour, so that, if laid over one another, they almost coincide.⁸ From this we may conclude, without any assump-

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⁸ Robertson.¹
⁷ Le Breton and Schaeffer.
⁶ Robertson.¹
tion as to causation, that, as an empirical fact, \( k \) is proportional to \( \frac{N_c}{C_y} \) where \( N_c \) is the mass of nucleic acid contained within the nuclei of all the tissues of the mouse, taken collectively, and \( C_y \) is the mass of protein, probably exclusively extra-nuclear.\(^9\)

Although this relationship has as yet been discovered only in the white mouse, because the alteration of nucleo-cytoplasmic ratios with growth has not yet been ascertained in any other organism of which the growth-curve has been accurately defined, yet it is exceedingly improbable that the correspondence of the two curves is accidental, or that any relationship so simple and fundamental is peculiar to one or a few species of animals. It may therefore be justifiable to generalise this result and to state that the velocity-constant in any autocatalytic cycle of growth is proportional to the nucleo-cytoplasmic ratio. In what follows we shall assume this rule to be generally applicable and inquire into the nature of the consequences which must necessarily flow therefrom. The fundamental character of these consequences and their close affiliation to the conclusions which are indicated by modern discoveries in genetics, contribute to justify our assumption that proportionality of growth-velocity to the nucleo-cytoplasmic ratio is of general application and not a specific peculiarity of the mouse.

Before proceeding to the consideration of these consequences, however, it must be pointed out that the absence of quantitatively appreciable asymmetry in the later and briefer growth-cycles of the white mouse does not constitute any exception to the rule which we have assumed, because the alteration of the nucleo-cytoplasmic ratio at the relatively late period of growth at which they occur, and for the duration of the periods which these cycles cover, is too small to affect their velocity-constants to a sufficient extent to distort the symmetry of the autocatalytic curve. Such growth-cycles are presumably asymmetrical, but the degree of asymmetry is so small as to fall within the limits of experimental error.

**The Sequence of Growth-Cycles.**

It has been shown in the communication referred to above\(^10\) that any number of autocatalytic growth-processes, occurring simultaneously

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\(^10\) Robertson.
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within the tissues of an organism, must, provided that they share a common catalyser, fuse into a single autocatalytic curve of weight-accretion. "The several processes, in other words, must lose their identity in the combined result." The experimental fact, now demonstrated in many species of animals, is that there are two or three distinguishable autocatalytic cycles which contribute to the total growth of the animal without losing their identity in so doing. Only one conclusion can be drawn from this fact, namely, that there exist autocatalytic growth-processes or groups of such processes within the animal and probably, of course, in plants also, which do not share a common catalyser. Such processes may occur within the same cells, or, more probably, in different cells and, in this latter case, we must assume that the several growth-cycles which contribute to the total growth represent the growth of different tissues which share a common catalyser with tissue cells of the same kind, but not with cells of other kinds of which the growth is defined by other and separable autocatalytic curves.

This being the case one would expect to find the velocity constant of autocatalysis varying in proportion to changes in the cells which participate in that cycle, but not, as we have found, in proportion to changes occurring in the tissues of the organism as a whole. If the velocity-constant of autocatalysis were truly dependent upon the nucleo-cytoplasmic ratio, we would expect it to vary in proportion to the change of this ratio occurring in the cells participating in the growth expressed by that cycle, but not to the change in other cells which participate in other cycles. But the estimations of Le Breton and Schaeffer were made upon the whole animal, not upon particular tissues, so that we are driven to infer that the several groups of cells, of which the growth constitutes the different cycles which are distinguishable in the total growth of the animal, nevertheless control or modify each other's growth in some other fashion than by the sharing of a common catalyser.

Only two alternative explanations of this phenomenon appear to be

1 Robertson.

12 Thus the growth of a fruit (Robertson, T. B., Arch. Entwicklungsmech. Organ., 1908, xxv, 581), or seed (Prescott) represents an autocatalytic process clearly distinguishable from the growth-curve of the plant as a whole.
open to us. Either we must assume that tissues which do not participate in a given growth-cycle nevertheless control it by some "action at a distance" or unintelligible "entelechy" which is not the sharing of a common catalyser, or we must assume that the nucleo-cytoplasmic ratios in all the tissues not participating in the first cycle remain stationary until, in consequence of the growth of the cells contributing to the first cycle, their nucleo-cytoplasmic ratios fall to the average value which characterises cells of the second cycle, which then, and not until then, begin to grow, so that the nucleo-cytoplasmic ratios of both groups of cells thereafter fall together in the same proportion. Then, when the cells which contribute the first and second cycles have undergone diminution of their nucleo-cytoplasmic ratios sufficient to bring the ratio down to the level characteristic of the third group of cells, they, in their turn, begin to grow, so that the ratios of all of the cells fall thereafter in proportion to one another.\footnote{There may, of course, be sundry subsidiary groups of which the growth is inappreciable when merged in the total growth of the animal, so that their growth does not lead to experimentally perceptible fluctuation of the total growth-curve. Such minute subsidiary cycles would be lost to view in the mathematical analysis of the growth of the entire animal.}

The ratio \( \frac{N_N}{C} \) is, in fact:

\[
\frac{N_{C_1} + N_{C_2} + N_{C_3}}{C_{y_1} + C_{y_2} + C_{y_3}}
\]

where \( N_{C_1}, N_{C_2} \) and \( N_{C_3} \) are the nuclear masses in the cells which participate in the first, second and third growth-cycles respectively, and \( C_{y_1}, C_{y_2} \) and \( C_{y_3} \) are the corresponding cytoplasmic masses. The hypothesis just outlined indicates a means, and, so far as our knowledge extends, the most probable means of ensuring that the fall of nucleo-cytoplasmic ratios with growth shall be uniform in all the cycles, whether one, two or three cycles are participating in the total growth of the animals during the period under consideration, so that, as we have experimentally ascertained, it must follow that the fall of nucleo-cytoplasmic ratios in the animal as a whole correctly represents the fall in any of the groups of cells which are at the moment participating in the growth of the animal.
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There are, however, certain implications involved in this hypothesis which merit most careful consideration. Thus, the true nucleocytoplasmic ratio from the beginning of the first cycle to the beginning of the second, is not \( \frac{N_c_1}{C_y_1} \) but \( \frac{N_c_1 + N}{C_y_1 + C} \) where \( N = N_c_2 + N_c_3 \) and \( C = C_y_2 + C_y_3 \). The velocity "constant" of autocatalysis of growth, during this period, has been found to be proportional to the nucleocytoplasmic ratio in the animal as a whole, that is, to \( \frac{N_c_1 + N}{C_y_1 + C} \) and this cannot be equal to \( \frac{N_c_1}{C_y_1} \) unless \( \frac{N}{C} \) is also equal to this ratio, which it could not be unless it varied proportionately with it, that is, unless growth of the second or third groups of cells were occurring, or unless, alternatively, \( N \) and \( C \) were both so small as to be negligible in comparison with \( N_c_1 \) and \( C_y_1 \). Now nearly all of the cells which will ultimately constitute the adult animal have already been produced at birth, and the great majority of them considerably before this.\(^{14}\) Practically all of the great increase of weight which occurs after birth is due to the increase in the size of cells, only an insignificant fraction of the total growth being attributable, at this stage, to the production of new cells. The data which we are discussing, and the conclusions derived therefrom, apply almost entirely to the growth of pre-existing cells. Clearly, therefore, cells which have not yet undergone growth since their production during embryonic development will constitute, during the earlier stages of growth, a large proportion of the total number of cells in the animal, but a very small proportion of the total weight of the animal. Hence, since the total growth of the animal prior to the initiation of the second cycle is quantitatively attributable to the first cycle\(^{14}\) the contribution to the weight of the animal due to cells of the second and third groups must be a negligible proportion of


\(^{11}\) The "linear increment" which, in mice, is superadded to the growth due to the three autocatalytic cycles, is of inappreciable magnitude at this stage.
the total, so that $N$ and $C$ must, as the second of the above alternatives requires, be negligible in comparison with $N_{c1}$ and $C_{y1}$. It follows, in other words, that during the period that growth remains as yet solely attributable to the first cycle, 

$$N_{c1} + N_{c2} + N_{c3}$$

$$C_{y1} + C_{y2} + C_{y3}$$

remains substantially equal to $\frac{N_{c1}}{C_{y1}}$ because $N_{c2}, N_{c3}, C_{y2}$ and $C_{y3}$ are, as yet, negligibly small quantities, growth having not yet occurred in the corresponding cell groups. Subsequently to the initiation of the second cycle, 

$$N_{c1} + N_{c2} + N_{c3}$$

$$C_{y1} + C_{y2} + C_{y3}$$

remains equal to $\frac{N_{c1}}{C_{y1}}$ because $N_{c2}$ and $C_{y2}$ are, as before, negligibly small quantitatives, and $N_{c3}$ and $C_{y3}$, however large they may become, do not begin to increase until $\frac{N_{c1}}{C_{y1}}$ falls to the initial value of the ratio $\frac{N_{c2}}{C_{y2}}$ and, however large $N_{c3}$ and $C_{y3}$ may become, they increase in the same proportion to one another as $N_{c1}$ and $C_{y1}$, so that $\frac{N_{c2}}{C_{y2}}$, from the beginning of growth due to the second cycle, remains equal to $\frac{N_{c1}}{C_{y1}}$ and therefore to $\frac{N_{c1} + N_{c2}}{C_{y1} + C_{y2}}$.

From this it obviously follows that growth due to the second cycle cannot be initiated until the nucleo-cytoplasmic ratio in the cells which participate in the first cycle has fallen to the initial value characteristic of the cells of the second group, that is, the ratios which they possessed when they arose by division. They must remain in a condition of stasis until cells of a higher ratio have fallen to their level, when all can proceed together. Instances of such stasis in tissues or organs for long periods of development, followed by vigorous growth when the development of other tissues has reached the necessary stage are too numerous to require exemplification here. It will be admitted that the above picture of the course of growth and

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16 In the very earliest stages of embryonic development this, of course, will not be strictly true, but with these we are not here concerned. Our data reveal nothing regarding the time and weight relationships in very early embryonic development.

17 It will, of course, be realized that however small $N_{c3}$ and $C_{y3}$ or $N_{c2}$ and $C_{y2}$ may individually be, their ratios may have any magnitude.
development corresponds in this particular very closely with the facts.

From these considerations, therefore, three conclusions emerge, namely:

1. The cells which participate in the growth composing any autocatalytic growth-cycle have initially lower nucleo-cytoplasmic ratios than the cells which participate in the preceding cycles.

2. Cells of large nucleo-cytoplasmic ratios inhibit growth of cells which possess smaller ratios.\(^{18}\)

3. Subsequently to the production of any cell by division, the increment of cytoplasm always stands in a fixed proportion to the increment of nucleus and this proportion is the same for all of the cells of which the organism is composed.

These conclusions offer a very welcome explanation, hitherto lacking, of the relative positions in time of the several autocatalytic cycles which contribute to the total growth of an animal.

In equations (1) and (2) it is easy to comprehend why \( A \), the maximum growth attainable in any cycle, may differ in different cycles. Its magnitude is determined on the one hand by the abundance of available nutrients (the substrates of growth) and, on the other, by the equivalence of these substrates in terms of the products of the growth-process which constitutes that cycle. For since \( A \) is measured in terms of the products of the growth-process, being their final mass, if the products be such as are expensive to produce, either on account of the high velocity of the reverse reaction (breakdown of tissue elements when produced) or because of the large number of molecules of substrate required to participate in their formation,\(^{19}\) then \( A \) for that

\(^{18}\) Possibly by prior appropriation of nutrients, due to their higher metabolic rate (Robertson\(^3\)).

\(^{19}\) This would be the case, for example, in the synthesis of connective-tissue proteins which are of abnormal amino-acid composition, so that many molecules of protein of average composition might have to be decomposed into their constituent amino-acids to produce those required for the manufacture of a single molecule of the aberrant protein.
cycle will be small in comparison with its value in a cycle in which the products are less expensive to manufacture.\textsuperscript{29}

Similarly, we can understand why $k$ should vary in different cycles, because the reactants in each cycle differ from those in any other. But it is not immediately obvious what physico-chemical mechanisms determine the magnitudes of $t_1$, $t_2$ and $t_3$, the moments, namely, at which the autocatalytic growth-cycles attain their maximum velocities. These are clearly related to the moments at which the growth due to each cycle becomes of appreciable magnitude. Given the values of $k$, $A$ and $t_i$, $2$ or $3$ for any cycle, it is possible to compute the time (that is, age) at which the weight-increments due to that cycle must become of measurable magnitude. The value of $t_i$, however, is simply computed, in practice, from the observations. Its value has not hitherto been predictable from any other consideration, nor has it been possible to refer it to any determinative factors. The hypothesis outlined above establishes such factors and enables us to understand why the onset of later cycles is necessarily delayed until the preceding cycles have attained a certain stage of development.

*The Relationship of Growth-Cycles to Differentiation.*

The conclusions reached above, and derived from a comparison of the time-relations of growth with the corresponding changes of nucleocytoplasmic ratio, fit with remarkable precision into the hypothesis of differentiation which the author has put forward elsewhere, basing it upon data of totally different origin and description.\textsuperscript{21}

It is a well-known fact that the early cleavage-cells produced at the beginning of the development of an embryo, are toti-potent, that is, they are individually capable, even in the absence of the other cleavage-cells, of giving rise to the complete embryo. At a comparatively early stage of development, however, usually within a few cell-divisions, this toti-potency is lost and becomes replaced by a partial capacity for

\textsuperscript{29} The proportion of water incorporated within the living tissue would also constitute an important factor modifying the value of $A$. Attention has been drawn to this fact in communications by Cramer, W., and Pringle, H., *Proc. Roy. Soc. London, Series B.*, 1910, lxiii, 307, 315.

\textsuperscript{21} Robertson.
reproduction capable of replacing large portions of the embryo which may have been lost through mutilation. Progressively the reproductive potency of the cells of the embryo diminishes until, in the adult, it remains only to the extent that tissues possess the power of repairing injury to themselves.

The most natural interpretation of these facts, in the light of the chromosomal theory of inheritance, is that the chromosomal heritage of cells produced in later stages of development is incomplete, so that they retain only a corresponding fraction of the original power, possessed by the fertilised ovum, of reproducing the whole organism. If, however, the chromosomal endowment of the more recent cells is less than that which the parent cells initially possessed, this can only be because division occurred before the nuclear substance of the parent-cell had been completely reduplicated. According to this hypothesis, therefore, differentiation, in the development of an organism, is attributable to the achievement by certain cells of the power of undergoing division at a lower nucleo-cytoplasmic ratio than that at which the parent-cells divided. Such cells must possess a different physiological character from their parents and react, in consequence, in a different manner to their environment. The reaction to the environment determines the type (i.e. structure and composition) of cytoplasm which is produced, so that from the altering nucleo-cytoplasmic ratios of successive generations of cells spring altering physiological responses and consequent differentiations of structure.

Obviously, if this were the case we would expect to find, at the conclusion of cell-production in development, various groups of cells which differ in their nucleo-cytoplasmic ratios, those of latest production being possessed of the lower ratios. The conclusions arrived at in this paper, and based upon quite independent evidence, also point to the existence, within the developing animal, of groups of cells which are distinguishable from one another by the possession of different nucleo-

22 It must be recollected that the element of the nucleus which stains with hematoxylin is nucleic acid (Mathew, A. P., Am. J. Physiol., 1898, i, 445). The chromosomes to which the geneticist traces the inheritable characters of the adult are therefore masses of nucleic acid, whatever else may chance to be associated with them.
cytoplasmic ratios. Our conclusions drawn from the study of growth itself and chemical estimations of the nucleo-cytoplasmic ratio contribute, therefore, very materially, to support the above theory of differentiation.

The Relation of the Nucleus to the Growth of Cytoplasm.

Confining our attention to a single asymmetrical cycle of growth, such as the first growth-cycle in the mouse, since we have found that the velocity constant of growth is given by the proportion:

\[
\frac{k_1}{k} = \frac{x + b}{x}
\]

and we have also found that \( \frac{k_1}{k} \) is proportional to \( \frac{N_c}{Cy'} \) that is, that \( \frac{k_1}{k} = \rho \frac{N_c}{Cy} \) where \( \rho \) is a constant proportionality-factor, it follows that:

\[
\frac{x + b}{x} = \rho \frac{N_c}{Cy}
\]

Now \( x \), the weight of an animal is almost entirely\(^2\) the weight of its cytoplasmic constituents and products. We may, therefore, with very close approximation to the truth, write \( Cy \) for \( x \) in the above equation, from which it follows that:

\[
Cy + b = \rho \ N_c
\]

and hence that:

\[
\rho \frac{dN_c}{dt} = \frac{dCy}{dt}
\]

or, in other phraseology, that the growth of cytoplasm, subsequent to the production of the cell by the cell-division from which it arose, stands always in a fixed proportion to the growth of the nucleus, a conclusion to which we have already been impelled for other reasons.

\(^2\) That is, over 90 per cent. In thymus, which represents a comparatively undifferentiated and richly nucleated type of tissue, the total nuclear constituents, chromosomal and others, constitute 15 per cent of the weight of the gland.
It also follows that, substituting \( C_y + b \) for \( x + b \) in equation (4):
\[
\frac{dx}{dt} = k \rho N_c (A - x)
\]
in which \( k \) and \( \rho \) are constants and \( A \) is the maximum growth attainable in the cycle. From this we derive the very important and suggestive conclusion that the growth of cytoplasm is determined by a monomolecular process which is catalysed by the nucleus in proportion to its mass. The autocatalytic character of the growth-process in animals and plants takes its origin, therefore, in the fundamental dependence of cellular syntheses upon the presence of the nucleus or its products.

The error involved in assuming the identity of \( x \) (total growth achieved) with \( C_y \) (the mass of cytoplasmic material) is very small and diminishes, of course, as the nucleo-cytoplasmic ratio decreases. The simple and fundamental character of the relationship deduced by making this approximation suggests, however, that this represents the true relationship and that the empirical formula:
\[
\frac{dz}{dt} = k(x + b)(A - x)
\]
represents, in fact, a mathematical approximation. We may, in consequence, expect to find, as we approach the beginnings of embryonic development (when \( N_c \) is at its maximum value and the error involved in neglecting \( N_c \) in comparison with \( C_y \) is therefore at its maximum also) that the autocatalytic equations, as hitherto formulated, no longer apply. The necessary measurements of very early embryonic growth...

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\( N_c \) if the chromosomal constituents of the nuclei were to represent as much as 10 per cent of the total weight of the organism, the departure from proportionality of nuclear to cytoplasmic increment would only be 1 per cent, for in equalising \( N_c \) to \( C_y + b \) instead of to \( C_y + N_c + b \) only the square of the nuclear mass need be neglected to ensure proportionality of the nuclear and cytoplasmic increments. The actual error, during the period of development covered by post-natal growth-curves, is probably much less than this and therefore far within the magnitude of the experimental error of weight determinations in animals.
growth have not yet been carried out, however, with sufficient fre-
quency and exactitude to permit the demonstration of these expected
deviations from the autocatalytic formulæ.

The tendency of all of these results, therefore, is to indicate that the
nucleus plays a predominant rôle in determining the growth of cyto-
plasm. This conclusion emerges, be it noted, solely from the quanti-
tative analysis of the growth-process itself, coupled with the empirical
correspondence between growth-velocity and nucleo-cytoplasmic
ratios. This being the case it is a most noteworthy fact that the
conclusions thus derived stand in such remarkable accord with the
indications of modern genetic research. From the study of the time-
relations of growth and the concurrent alterations of nucleic acid
content of the animal, on the one hand, and from the study of cytology
and inheritance upon the other, we attain to the same conception of the
nucleus as the predominating factor in shaping the development of the
cell in which it resides.

CONCLUSIONS.

1. It has previously been shown by the author and many others
that growth, in animals and plants, is an autocatalysed process. In
animals it is usual to find that growth occurs in several superimposed
autocatalytic cycles. In many cases, in plants and animals, especially
if the cycle is one which occupies a large proportion of the growing
period, it is found that the velocity-constant of the autocatalysed
monomolecular formula falls off as growth proceeds, at first rapidly
and later more slowly.

2. It has previously been shown by the author that the fall of the
velocity-constant of growth, in the white mouse, is directly propor-
tional to the fall of the nucleo-cytoplasmic ratio, determined by the
chemical method of Le Breton and Schaeffer. If we assume this
relationship to be generally applicable to the growth of animals and
plants, then the following additional conclusions may be deduced,
without calling in the aid of any other assumption:—

3. The increase of cytoplasm in any given cycle of growth is pro-
portional to the concurrent increase of nuclear material.

4. The growth of cytoplasm takes place in accordance with a
monomolecular formula in which the velocity-constant varies directly
as the mass of the nucleus.
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If we superadd to these facts and deductions the hypothesis that each growth-cycle represents the growth of a separate group of cells within the animal, then the additional conclusions follow:--

5. That the cells which participate in the growth composing any cycle have initially lower nucleo-cytoplasmic ratios than the cells which participated in the preceding cycles.

6. That cells of large nucleo-cytoplasmic ratios in a multicellular animal inhibit the growth of cells which possess smaller ratios.

7. These conclusions collectively imply that the nucleus plays a predominant rôle in determining the development of the cell in which it resides.