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On the Motion of Growth. VII. Fundamental Relations and Quantities of Growth and Metabolism.

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This paper affords, in extension of work already reported,[1] a further description of the fundamental relations and quantities by means of which a dynamical connection between growth and metabolism has been established.

Definition of Growth. Many writers have regarded growth, in the broadest sense, as a matter of increase in size. One of the best expressions of this view has been given by Julian Huxley, who states that growth is "a process of self-multiplication of living substance."[2] For analytical purposes, however, it is better to surrender the position that growth must necessarily or by impiication consist substantially only of an increase in size. It is, in fact, useful to approach the problem in more general terms and thus to conceive of growth as involving a *change* rather than exclusively an increase in size. Yet mere change alone cannot itself characterize growth, for this denotes a difference simply, and above all, a difference without respect to the quantity responsible for generating the resulting surplus or deficit as the case may be. Hence, the essence of growth is held to be change in size per unit size; and, since the process has been shown subject to dynamical constraints we have proposed to consider growth a mode of motion defined in practical terms as change in mass per unit mass. Length and cell number may also serve, where suitable or convenient, as valid measures of size and so of growth as well. The significance of the preceding definition is best brought out by comparing, as in Table I, what may, for the purpose in view, be called true growth and ordinary gain.

Minot[3] was among the first to recognize this "relativity of growth" because he laid great stress upon methods designed to approximate the relative rate of gain and clearly perceived that the latter should be called the "rate of growth". But, even though he

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[1] Wetzel, N. C., PROC. SOC. EXP. BIOL. AND MED., 1932, **30**, 224, 227, 233, 354, 358, 360.

[2] Huxley, J. S., Problems of Relative Growth, New York, 1932, p. 6.

[3] Minot, C. S., *J. Physiol.*, 1891, **12**, 97.

TABLE I.
Comparison between *True Growth* and *Ordinary Gain.*

	Growth	Gain
(1) Definition	Change in Size per Unit Size	Change in Size
(2) Quantity*	$q = \int_0^t \frac{1}{z}\frac{dz}{dt}dt = \text{Log}_e \frac{z}{z_0}$	$\int_0^t \frac{dz}{dt}dt = z - z_0$
(3) Instantaneous Rate	$\frac{dq}{dt} = \frac{1}{z}\frac{dz}{dt}$	$\frac{dz}{dt}$
(4) Unit of Rate	Kg./Kg./T	Kg./T

* Size is represented by z and measured in terms of mass, length or cell number as convenient.

did not define growth, or rather the quantity of growth as here set out, we should ultimately arrive at precisely the statement just given if we proceeded with his method to the limit and integrated the result over some finite interval of time.

The Simplest Law of Growth and Two Amendments. Sufficient experience from various biological fields has accumulated to uphold the following generalization as the simplest law of growth: *Cellular reduplication, once initiated, will continue at a uniform rate in its state of motion until acted upon to change that state.* The closest approach to, and the most familiar example of, this truly ideal mode of augmentation is found during the well-known logarithmic phase of growth so common in bacterial cultures. Various though closely related mathematical expressions describing the course of such unrestricted growth have been widely employed in many investigations, one form representing in plant physiology what is known as Blackman's Law[4] and another constituting the foundation for the extensive analyses of Brody.[5] We prefer, in accordance with the work already reported[1] and with the aid of data from Table I, to write

$$\rho\frac{dq}{dt} = E \tag{1}$$

where, as formerly, ρ is the resistance of growth, and E the external work done per unit of mass, both ρ and E being considered constant for a given case. The ratio $\left(\frac{E}{\rho}\right)$ thus becomes the "velocity constant of growth" employed by previous writers.

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[4] Blackman, V. H., *Ann. bot.*, 1919, **33**, 353.

[5] Brody, S., Univ. Mo. Agr. Exp. Sta. Res. Bul. 97, 1927.

Experience, however, has also shown quite clearly that this geometric law of increase holds true only during periods that are, in actuality, but a fraction of their respective growth "cycles". Reduplication, and hence growth come sooner or later to a close even though food is just as abundant as before. No known example of growth completely escapes the latter effect, and none proceeds strictly in accordance with the simple expression given in (1). Even where successive tissue-cultures appear to continue their multiplication in geometric fashion, they do so only as a result of artificial intervention, failing which, they too, succumb to this additional and equally important law of decline.

Nor does (1) allow for any growth save that which is ushered in with some positive velocity; it cannot, as is evident, provide for a period of lag, another phenomenon that happens to be notable in bacterial cultures, though it, too, is an intrinsic property of all growing systems. For according to (1) the relative velocity of increase must be just as great at the onset as it is at some later stage of reduplication, whence, if this be zero initially, no growth whatsoever will, or can, take place. Yet there are numerous examples in which growth "takes off from a standing start," and even some in which an initial loss is witnessed.

Thus, to meet the conditions of actual experience we need at least two important amendments to the foregoing basic law of growth, and these are: (1) for the "natural" decline of all finite growth, and (2) for the inertial effects exhibited by many familiar examples. Neither of these amendments, it may be noted, in any way destroys the validity, the generality, or the usefulness of the primary statement set forth above.

But, in addition, growth requires sustenance; it is accompanied by heat production; and it is clearly a phenomenon dependent, as Spencer[6] pointed out, upon energy exchange. We are therefore required to unite all of the foregoing characteristics into some single comprehensive expression with which it will then be possible to investigate the various problems of growth.

This entire set of objectives is effectively and most simply achieved if (1) is amended to read, in terms of work per unit mass,

$$\rho\frac{dq}{dt} = E(t) - \lambda\frac{d^2q}{dt^2} - \frac{q}{\kappa}, \tag{2}$$

where the agencies for the initiation, $E(t)$, λ, for the potential geometric progression, ρ, $E(t)$, for the decline, κ, are given in the nota-

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[6] Spencer, H., Principles of Biology, New York, 1898, p. 140.

tion already proposed; ρ, λ, and κ being constant in a given case, whereas $E(t)$ will be understood in general to be either constant or, as in the human example, some function of t. These quantities are further described in Table II. Implied in (2), and easily deduced from it with the aid of appropriate substitutions from the table, is the relation defining the connection with concomitant heat production during growth:

$$\rho\left(\frac{dq}{dt}\right)^2 + E_c(t)\frac{dq}{dt} + A' = U \tag{3}$$

where $E_c(t)$ is the work of cellular synthesis per unit of mass, and A' the power per unit of mass required to maintain tissue, which is at rest with respect to the motion of growth, in a state of nutritional equilibrium.

To facilitate reference and to provide a ready check upon the homogeneity of various relations or procedures, Table II contains a synopsis of the more important symbols, dimensions, equivalents, and units of the quantities entering into the equations of motion.

The dimensions of the various quantities are easily determined by using equation (3) as the key; the dynamical equivalents are chosen from the simplest and most appropriate or suggestive physical analogues; and the practical units are tentatively set up by employing both days or seconds as the unit of time though it is realized that one or the other will need ultimately to be selected as the more appropriate unit.

The various steps which have led to the concepts of growth resistance, inertia, permittance, etc., cannot be properly developed here, though their application has been briefly outlined and illustrated in earlier papers.[1] Emphasis is, however, again placed upon the suggestion that information of particular value can be obtained if extraneous conditions such as temperature, $[H^+]$, and quality of nutriment, on the one hand, or if, on the other, substances known "to promote" growth or to act adversely, are examined in respect of their connection with, as well as their effect upon, the fundamental quantities enumerated in the table. To this end studies of growth require not simply measurements of change in size, which give us the *q's* and *z's* of the equations, but they require also a determination of the remaining quantities, especially ρ, λ, κ, and E, that enter just as importantly, if not more so, into the basic processes of growth. As indicated here, and as illustrated previously, the values of these quantities may be computed from suitable data on growth and simultaneous heat production with the aid of equations (2) and (3) or

TABLE II.

*Synopsis of Fundamental Quantities appearing in the Equations of Growth and Metabolism.**

Name	Symbol	Dimensional Formula	Dynamical Equivalent	Practical Unit
1 Resistance	ρ	L^2T^{-1}	(a) Diffusivity; (b) Action (Quanta) per unit mass	(a) $(Cm.)^2$/Second; (b) Erg Seconds/Gm.
2. Inductance (Inertia Coefficient)	λ	L^2	Moment of Inertia per unit mass	$(Cm.)^2$
3. Permittance	κ	$L^{-2}T^2$	Reciprocal Work per unit mass	Kg./Calorie§
4. Charge or Quantity of Growth	q	Pure Number	Napierian log. of mass	Kg./Kg.
5. Rate of Growth (Flow of Charge)	$\frac{dq}{dt}$	T^{-1}	Time rate of motion per unit of length	Kg./Kg./Day
6. Acceleration of Growth	$\frac{d^2q}{dt^2}$	T^{-2}	Rate of change in velocity per unit length	Kg./Kg./$(Day)^2$
7. Size	z	M	Mass	Kg.
8. Rate of Gain	$\frac{dz}{dt}$	MT^{-1}	Momentum per unit length	Kg./Day
9. Acceleration of Gain	$\frac{d^2z}{dt^2}$	MT^{-2}	(a) Force per unit length (b) (Surface Tension)	(a) Dynes/Cm.; (b) Cal./$(Meter)^2$

Energy Supply:				
10. Energy at Source for Growth and Maintenance $\left\{\frac{dS}{dt} = V_s\frac{dq}{dt} + M'\right\}$	S	L^2T^{-2}	Work per unit mass	Cal./Kg.
11. Potential at Source for Growth	V_s†	L^2T^{-2}	Work per unit mass	Cal./Kg.
12. Power at Source for Maintenance	M'	L^2T^{-3}	Power per unit mass	Cal./Kg./Day
Energy Utilization:				
13. Potential in the Cell	V_c†	L^2T^{-2}	Work per unit mass	Cal./Kg.
14. Energy of Synthesis (Proliferation)	E_c†	L^2T^{-2}	Work per unit mass	Cal./Kg.
15. External Work of Growth $\left\{\begin{matrix} E = E_v - E_c; \\ E_v = V_s - V_c. \end{matrix}\right\}$**	E†	L^2T^{-2}	Work per unit mass	Cal./Kg.
Heat Production:‡				
16. Maintenance Rate of Heat Production per unit mass	A'	L^2T^{-3}	Power per unit mass	Cal./Kg./Day
17. Rate of Heat Production *per unit mass* (Metabolism), by Equation (3)	U	L^2T^{-3}	Power per unit mass	Cal./Kg./Day
18. Rate of Heat Production ($U\times z$)	$\mathfrak{T}'$	ML^2T^{-3}	Power	Cal./Day
19. Total Heat Output in time t	$\mathfrak{T}$	ML^2T^{-2}	Work	Calories

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* Two quantities, $\mathfrak{F}_s$, and $\mathfrak{F}_c$, the field intensity at source and cell respectively, with the dimension LT^{-2}, are basically implied in this scheme, but they have not as yet been described in connection with the present results.

§ Large Calorie.

† When $E(t)$ in (2) is constant and equal simply to E as defined in item (15). Similarly when $E(t)$ involves t, as in the case of human growth, we have:

$$E(t) = E_v(t) - E_c(t) = [E_v - E_1\epsilon^{-\beta t}\sinh(\theta t - \zeta)] - [E_c + E_2\epsilon^{-\beta t}\sinh(\theta t - \zeta)] = E - E_0\epsilon^{-\beta t}\sinh(\theta t - \zeta);\ \text{where, } E_0 = (E_1 + E_2)$$

the dimensions of all the E's remaining the same as in item (15) since the function is and must be transcendental to preserve homogeneity.

‡ Applies solely to basal state.

** The symbol E_v appeared as E_s in previous papers.[1]

their respective integrals. Comparisons made on this fundamental basis will then indicate whether some substance "x", under investigation, has altered growth resistance ρ, inductance λ, permittance κ, or that it has failed to do so.

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Physiology of Shigella paradysenteriae var. Sonne.

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The dissimilation of lactose and sucrose by *Shigella paradysenteriae* var. Sonne has been studied to gain additional knowledge of the phenomenon known as "delayed" or "slow" fermentation. The culture (A.T.C. 31) shows in lactose and sucrose the delayed fermentation characteristic of the Sonne type. In Durham fermentation tubes about 4 days are required for acid formation in lactose broth and about 7 days for sucrose. Colonies on lactose or sucrose agar plates are alkaline or neutral but after a few days develop small secondary colonies as papillae which become acid. If a papilla on sucrose or lactose agar is suspended in sterile broth or saline and plated on agar containing the same sugar, 2 types of colonies appear. One type is acid and does not form papillae even after long incubation, the other type is like the original, alkaline and develops acid papillae. Sugar broth inoculated with the acid type colony is promptly acidified, whereas the alkaline type causes the characteristic delayed fermentation.

Attempts to decrease the time for acid formation in the slow culture by transferring once or twice daily to fresh medium with the same sugar have failed, though this procedure has been carried through 60 transfers. One may easily obtain the rapid variant, however, by plating out a culture which has developed acid, the types of colonies developing on the plates being of 2 types, acid and alkaline, as when the papillae from plate cultures are used.

In order to study the fermentation of lactose and sucrose in more detail than was possible using Durham tubes, flasks have been used, and examination made at least once daily to determine pH, titrable acidity, oxidation-reduction potential, sugar utilized, total population and per cent of population composed of the rapid fermenting variant. In sucrose daily determinations have also been