these 5 methods, gave reactions to the same dilutions as those of the filtrates of the original cultures.

In the case of the 5 colonies selected from one culture, while all of these produced filtrates which gave reactions at the titer of the original cultures, 3 gave reactions smaller in extent than the other 2. Cataphoresis determinations made on 2 occasions showed that the rate of migration of the organisms producing the smaller reactions was about twice that of the other 2 and of that of original culture. It should be stated, however, that we have previously shown[6] that a faster rate of migration is not a specific characteristic of non-toxin producing strains of streptococcus.

Summary. The use of several recognized methods for dissociation of bacteria when applied to scarlet fever strains of streptococci failed to deprive these strains of their ability to produce toxin.

7584 C

On the Motion of Growth. IX. A Scheme for Analysis of Experiments on Growth, Nutrition and Metabolism.

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The quantitative relationships between normal growth and heat production which the author has recently found and applied in the case of bacterial cultures,[1] in *Bufo vulgaris* from fertilization throughout metamorphosis[2] and from birth to adult life in man[3] should likewise be helpful in dealing with the results of many experimental studies on growth, nutrition, or metabolism.

Such studies are carried out, almost without exception, upon the young of some species, and noteworthily, in the present connection, on subjects still immersed in the "flux of growth." It is just at this stage of life, moreover, that characteristic and often conspicuous changes in metabolism are known to occur. Sufficient evidence in the 3 normal cases we have mentioned has already been brought forward to show that these changes in metabolism, as portrayed in

[6] Thompson, R. L., and Megrail, E., *Am. J. Hyg.*, 1934, **19**, 457.

[1] Wetzel, N. C., PROC. SOC. EXP. BIOL. AND MED., 1932, **30**, 360.

[2] Wetzel, N. C., *Proc. Nat. Acad. Sc.*, 1934, **20**, 183.

[3] Wetzel, N. C., PROC. SOC. EXP. BIOL. AND MED., 1932, **30**, 227, 233; *J. Pediat.*, 1933, **3**, 252; 1934, **4**, 465.

the data of other workers, are actually due to, and depend uniquely upon, the underlying and concurrent changes in growth itself.

Thus, taking the relation between *growth, q,* and *size, z,* to be, as before,[2, 4] $q = \mu \log_e \frac{z}{z_0}$, with $\mu = 1 = z_0$, we may express the interdependence of growth and metabolism for the case of laboratory animals as follows:

$$\begin{aligned} &\textit{Growth:} && \lambda\frac{d^2q}{dt^2}+\rho\frac{dq}{dt}+\frac{q}{\kappa}=E && [\mathrm{Cal}/\mathrm{M}/\mu] \\ &\textit{Metabolism:} && \rho\left(\frac{dq}{dt}\right)^2+E_c\frac{dq}{dt}+A'=U && [\mathrm{Cal}/\mathrm{M}/\mathrm{T}] \end{aligned} \quad (1)$$

the significance and dimensions of individual symbols having been outlined and applied elsewhere.[2, 4] For present purposes, however, we have briefly: $\dot{q}$, the rate of *growth* as distinguished from the rate of *gain* (less commonly loss), $\dot{z}$; ρ, the resistance, λ, the inductance, κ, the permittance of growth; E, the net external work of growth, and E_c, the work of synthesis, each of the 2 latter constants being referred to the unit of mass (z) and charge of growth (q); and finally, A', the heat of maintenance, in terms of power per unit mass, liberated even when growth is in the state of rest, that is, when $\ddot{q} = \dot{q} = 0$.

These results lead to several suggestions for further experimental work in the fields of growth, nutrition, and metabolism. For the methods which have succeeded in establishing the dynamic connection (1) between the concomitant events of pure growth on the one hand, and those of heat production or metabolism on the other, would now appear to be of considerable assistance in the analysis of various questions arising in these fields when growth itself is directly or indirectly put to experimental test.

How, for example, does a small quantity of lettuce incorporated into the usual diet of young white rats lead to an increase over the "normal" rate of gain?[5] How, also, does the administration of anterior pituitary extract produce a somewhat similar result, the treated rats ultimately weighing about 16% more than the controls,[6] notwithstanding the fact that the quantity of food remained the same in each group, or, even more unexpectedly, in spite of the fact that the fuel value of sacrificed carcasses proved to be less in the test animals than in the controls? The former, it was found, contained less fat. Their tissues possessed, on the whole, the chemical

[4] Wetzel, N. C., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 1044.

[5] Outhouse, Julia, and Mendel, L. B., *J. Exp. Zoöl.*, 1933, **64**, 257.

[6] Lee, M. O., and Schaffer, N. K., *J. Nutrition*, 1934, **7**, 337.

constituents recognized as characteristic of younger normal animals; and the changes in body composition usually associated with advancing age, increasing size, and with progress toward maturity, did not take place.

The foregoing combination of results is one of the various possible groups of effects to be expected when growth is artificially distorted; but it also turns out that precisely the combination which Lee and Schaffer describe should likewise be accompanied by decreased heat production. This is of especial interest since these authors have been able to show that the administration of anterior pituitary growth hormone is followed by a drop in metabolism.[6] How, then, have the hormone, food, and growth combined, while acting together, to yield such results?

Other questions are likewise suggested: What initiates the process of growth, or which factors are concerned with the natural acceleration of growth that usually takes place after the onset? What, finally, is responsible in chief part for the fact that growth in healthy structures is strictly confined within "normal" limits, and to what, therefore, is "disorganized" growth in unhealthy tissues to be ascribed?

Questions such as these are not necessarily to be considered as beyond the hope of further analysis or investigation. It should, in fact, be possible to attack them on the experimental side with the promise that definite answers might be obtained in terms of the fundamental parameters set out in equation (1). Let us see how the matter could be expected to work out in practice.

To fix ideas, we assume that an investigator proposes to study several substances or procedures, say $x_1, x_2, \ldots . x_n$ by means of their respective effects upon the young of certain species, whose domesticated "normal" rate of growth, $(\dot{q})_0$, may be written, in view of the first of equations (1), in the functional form,

$$(\dot{q})_0 = F[\rho_0, \lambda_0, \kappa_0, (E)_0, \ldots ; (q)_0, (\ddot{q})_0] \tag{2}$$

F, accordingly, being characteristic of the species. Now, $(\dot{q})_0$ will be altered by any one, or suitable combinations of changes in the parameters, $\rho_0, \lambda_0, \ldots .$, induced by some external agent, as here, by $x_1, x_2 \ldots . x_n$, and we shall have,

$$\left.\begin{array}{l} (\dot{q})_1 = F[\rho_1, \lambda_1, \kappa_1, (E)_1, \ldots ; (q)_1, (\ddot{q})_1] \\ \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \\ (\dot{q})_n = F[\rho_n, \lambda_n, \kappa_n, (E)_n, \ldots ; (q)_n, (\ddot{q})_n] \end{array}\right\} \tag{3}$$

F remaining the same since the species is unchanged.

The problems occurring in practice are, however, just the converse of this, for the worker will wish to know which parameters are changed when the normal or control rate of growth, $(\dot{q})_0$, has been experimentally altered. Such a problem is clearly beyond solution, as may be inferred from (1) so long as experimental observations are limited to a study of change in size, z, alone. The best that could be done would be a determination of the ratio ρ/λ, which has the dimension $[T^{-1}]$ simply. But, since $\dot{q}_{(1 \ldots n)}$ can be computed with the help of (1) and (2) from the experimental measurements of size, it is evident that a simultaneous study of heat production will at once permit the numerical evaluation of the individual constants, $\rho_1, \rho_2, \ldots \rho_n; \lambda_1, \lambda_2, \ldots \lambda_n; (E_c)_1, (E_c)_2, \ldots (E_c)_n$, etc., since the data on heat may be adjusted to the accompanying equations,

$$\left.\begin{array}{l} (U)_1 = \phi[\rho_1, (E_c)_1, (A')_1; (\dot{q})_1, (\dot{q})_1^2] \\ \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \\ (U)_n = \phi[\rho_n, (E_c)_n, (A')_n; (\dot{q})_n, (\dot{q})_n^2] \end{array}\right\} \quad (4)$$

for substances $x_1, \ldots . x_n$ respectively, the function ϕ remaining the same as long as the observations are taken on the same species of organism. Equations (4), accordingly, provide a method of determining the ρ's and hence, with the latter known, a method for computing all of the remaining constants along with their probable errors if least square procedure be adopted as in the case of *Bufo vulgaris* previously reported.[2] In experiments $x_1, x_2, \ldots . x_n$ we shall obviously meet the various possibilities suggested by the relations:

$$\left.\begin{array}{l} \left.\begin{array}{c} \rho_1 \\ \rho_2 \\ \cdots \\ \rho_n \end{array}\right\} \gtreqless \rho_0; \quad \left.\begin{array}{c} \lambda_1 \\ \lambda_2 \\ \cdots \\ \lambda_n \end{array}\right\} \gtreqless \lambda_0; \ldots \left.\begin{array}{c} (E_c)_1 \\ (E_c)_2 \\ \cdots \\ (E_c)_n \end{array}\right\} \gtreqless (E_c)_0 \end{array}\right\} \quad (5)$$

The effect, therefore of any foodstuff, or of any procedure that influences growth may always be estimated in terms of the fundamental properties of growth, ρ, λ, κ, and E, which are held to govern the motion of growth in that particular system. Whether such substances "promote" or "inhibit" growth, their action will become manifest by means of the respective changes which they induce in the normal control values of these 4 parameters of state. The point should ultimately be reached where the more important substances or procedures $x_1, x_2, \ldots x_n$ (*e.g.*, vitamins, hormones or other materials) could be classified with respect to their several or individual effects upon the fundamental properties of growth, ρ, λ, κ, E. At that stage it will have become apparent whether a suitable choice of the x's will permit growth to be placed under full control or not.

Summary: (1) Post-embryonic growth of common laboratory animals is governed, in accordance with the first of equations (1), by 4 fundamental properties of growth represented by the constants ρ, λ, κ, and E. (2) Rates of growth ($\dot{q}$) are altered when any one, or suitable combinations of these parameters are changed by experimental means. In practice, however, the problem is more likely to be the converse of this: which parameters are changed when the normal or control rate of growth is known to have been altered? Such a problem is insoluble so long as observations are limited to measurements of change in size, z, alone. (3) Heat production "during growth" ($\ddot{q} \neq 0 \neq \dot{q}$) is quantitatively different from heat production when growth is in the stationary state ($\ddot{q} = \dot{q} = 0$). Heat production per unit time per unit mass is synonymous with metabolism, and the latter is dynamically related to growth *via* the properties represented by ρ and E_c. (4) The values of all constants along with their *P.E.*'s can be computed from simultaneous data on growth and metabolism. (5) The effect of any foodstuff, or of any procedure that influences growth can therefore be estimated in terms of the control values ρ_o, λ_o, κ_o and $(E)_o$, and the substances themselves may be compared by means of the respective changes induced in these four fundamental parameters of state.

7585 C

Effect of Certain Physical Factors on the In Vitro Testing of Anthelmintics.*

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Although certain investigators have done much to destroy confidence in the value of *in vitro* methods of testing anthelmintics by drawing too sweeping conclusions from uncontrolled experiments, these methods are of value and were used successfully by Lamson

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