ral transmission may not be impaired. The more intimate relations between neurons may, however, be affected in such a way that only tests of complex perceptual processes will reveal the visual deficits produced by visual deprivation (*5*).

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Predictions of the Growth Model for Normal Chicken Growth

Abstract. The model of growth control advanced by Weiss and Kavanau has been further evaluated with an I.B.M. 7090 computer. Predictions for the concentration of growth-inhibiting substances and their quantitative distribution in the animal are in good agreement with known developmental changes. Results are being used to predict the course of compensatory organ growth in the immature animal.

The theory of growth control advanced by Weiss (*1*) has been formulated into a set of three simultaneous differential equations by Weiss and Kavanau (*2*). The mathematical model extends beyond a mere representation of normal growth to growth disturbances and regulation and dissects the growth problem into a series of detailed questions which lend themselves to experiment. Some of these questions concern changes in volume of body fluids and concentration of postulated growth-inhibiting substances. Predictions for these changes based upon data for normal chicken growth follow.

The basic assumptions upon which the model was predicated are:

1) The gain in mass of a living system is the net balance of mass "produced" and retained over mass "destroyed" and otherwise lost.

2) The mass M of the system consists of two functionally different components: The generative mass G, comprising the instruments of protoplasmic reproduction, and the differentiated mass D, derived from G and consisting of terminal products and other derivatives that do not reproduce.

3) Each specific cell type reproduces its protoplasm through the self-duplication and catalytic activity of "templates" characteristic of that cell type. Each cell also produces specific, freely diffusible "antitemplates" which can inhibit the activity of the corresponding templates, and which become distributed in the "dilution pool" V (which includes the blood, lymph, intercellular fluids, and other parts of the body to which they gain access).

4) The antitemplates regulate growth by a negative feedback mechanism, in which their increasing populations render an increasing proportion of the homologous templates ineffective, resulting in a corresponding decline in growth rate.

5) Attainment of terminal size represents a stationary equilibrium between incremental and decremental growth components.

6) The generative mass, and the differentiated mass including the antitemplates, undergo continual metabolic degradation and replacement.

Recently, predictions of the model were determined for compensatory organ growth in the adult (*3*). By reason of the model's explicitness, several possible mechanisms considered in the more general scheme of growth control (*2*) were ruled out as unrealistic. For example, of the various alternative sources of production of the antitemplates, all were ruled out except the generative mass.

The model reproduces a number of phenomena observed in the compensatory response to disturbance of equilibrium of organ systems. Thus it reproduces the spurt of compensatory growth of an organ system after artificial reduction and the spontaneous resumption of organ growth after artificial lowering of antitemplate concentration at terminal equilibrium [observed in liver plasmapheresis experiments with adult rats (*4*)]. It predicts that compensatory organ growth will proceed in an undulatory fashion and accounts for the heretofore unexplained secondary spurt of growth (after the first week or so) in partially hepatectomized rats. It accounts for the fact that liver cell-protein synthesis in the regenerating rat liver attains its maximum rate before plasma-protein synthesis does (*5*), and it predicts the decrease in rate of regeneration of organ mass with increasing age. Additionally, the model has directed attention to a number of questions to be decided by future experiments (*3*).

In point of fact, the model represents a class of systems controlled by negative feedback. In a formal sense it is equally valid for alternative biological systems, requiring for conversion merely simplification or reassignment of significance, or both, of variables and parameters. For this reason, and in view of the increasing weight of evidence for negative feedback control of growth processes (*1*, *6*), investigations of its predictions, stability, and general behavior after disturbances of equilibrium are significant for current studies.

Evaluation of the model for compensatory organ growth in the adult was undertaken first because the simultaneous differential equations (*2*) describing the adult system are relatively simple. Although the stability of this process in the adult has been verified for a wide range of mass reductions and other disturbances, it remains to determine predictions for compensatory organ growth in the immature animal. These are of particular interest because almost all experimentation is carried out with immature, rapidly growing animals.

In order to solve the differential equations of the model it is necessary to specify the daily rate of catabolic loss of antitemplates, k_5, and the number x of antitemplates required to inactivate each template. Since these are not known, solutions for the adult system had to be scanned with a range of biologically feasible values (*3*). These solutions, in turn, indicated probable limits for the two parameters. Accordingly, the values 10⅓, 21⅔, and 32 percent for k_5 (half lives of 6½, 3¼, and 2⅙ days), and 4, 8, and 16 for x, were chosen for the present study.

To predict the course of compensatory organ growth in the immature animal, it is necessary to fit the model to the data for normal chicken growth, for each combination of values of k_5 and x. Each value of x generates a curve for the antitemplate concentration C, and each value of k_5 a curve for the number of antitemplates I present in the system during growth (*2*, Eqs. 4, 6a, and 21). From this information, nine curves for the growth in volume of the dilution pool V can be derived ($V = I/C$).

The findings for C, I, and V have interest beyond being prerequisite for computing compensatory organ growth in the immature animal, for they serve as additional criteria of the biological plausibility of the model and its specific solutions. The prediction of unreasonable values for them would have ruled out as inconsistent certain combinations of the parameters k_5 and x.

The new results, determined with the I.B.M. 7090 of the U.C.L.A. computing facility (*7*), are shown in Fig. 1. It is evident that C must build up much more rapidly than either M or G; the higher the order of the reaction of inhibition of templates by antitemplates (that is, the larger x), the more rapid the increase must be. At hatching, values of C for $x = 4$, 8, and 16, are 63, 79, and 89 percent of the adult equilibrium value, respectively. Abrupt changes in the curves at hatching reflect the abrupt slowing of the growth rate of the chick at this time (*2*).

Of the family of nine curves for V, only three are plotted in Fig. 1. The other six lie in the narrow range between the inner and outer curves. All these curves lie close to the curve for G. For the case $x = 4$, $k_5 = 32$ percent, the maximum difference between points on the curves for V and G is only 1.8 percent.

A more readily visualized entity than V is the fraction of the total volume of the animal (V_T) occupied by V, namely, V/V_T (the fraction of the chicken occupied by blood, lymph, and so forth. To derive curves for this quantity (*2*, Eq. 26), several approximations must be made. Of the nine curves obtained, three are plotted, including the limiting curves of the family. These curves indicate that a relatively large fraction of the chick embryo must be permeated by the antitemplates. Upon the basis of an assumed final value of 6 percent in the adult chicken (that is, roughly twice the blood volume), values for V/V_T in the 12-day-old chick embryo range between 7.5 and 18.5 percent; at hatching they range between 6.7 and 12.6 percent. These high early values are in good agreement with the known relative increase in solid bulk during development, as well as with the existence of an accessory fluid system in the extraembryonic area prior to hatching.

These predictions for chicken growth are biologically plausible. The ranges into which the values fall are sufficiently well delimited to permit ready experimental testing. Exploratory tests are feasible at the present time but critical tests must await the identification of the antitemplates. Promising in this connection is Glinos's tentative identification of liver growth-regulating substances with components of the plasma proteins (*4*).

Further explorations of the model are under way. These should more narrowly restrict the range of possible combinations of values of x and k_5, and, consequently, of V and C. Additionally, they will predict the course of compensatory organ growth in the immature animal. These results will provide more useful reference points for past and future experimentation than do the findings for the adult (*8*).

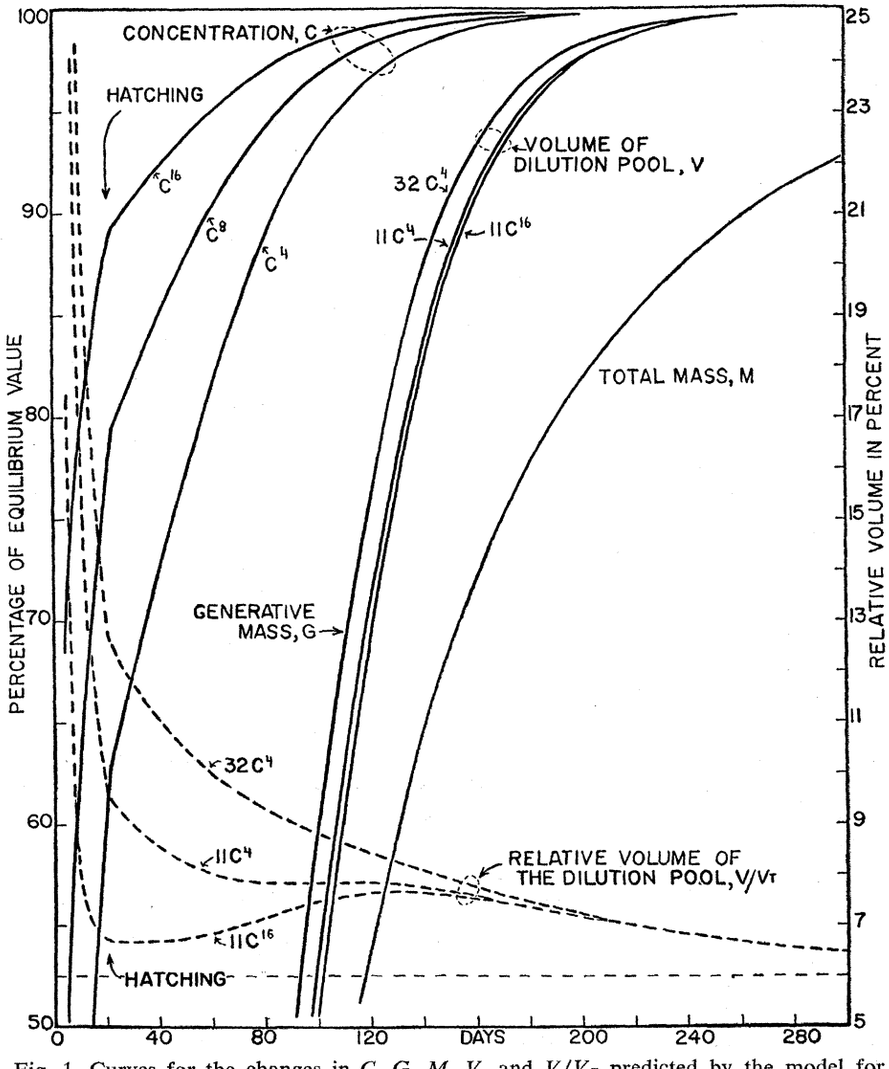

Fig. 1. Curves for the changes in C, G, M, V, and V/V_T predicted by the model for normal chicken growth. Values for k_5 and x are indicated conventionally by the coefficients (rounded off to 11, 21, and 32) and exponents of C, respectively. The right ordinate scale applies only to the curves for the relative volume of the dilution pool, V/V_T. The dashed horizontal line denotes its limiting value of 6 percent.

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