THE KINETICS OF STARVATION.

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During the last few years an increasing number of data bearing on certain gross biological processes have been interpreted in terms of definite physicochemical laws. Robertson,1 for instance, has shown that the growth of human infants may be represented by the curve of an autocatalytic monomolecular reaction. The growth of animals as well as the growth of plants has also been shown to conform to this law.1 Osterhout,2 furthermore, has illustrated the phenomena of injury, recovery, and death of tissues by means of equations which are characteristic of consecutive chemical reactions. More recently, Brody and his coworkers,3,4 have made use of similar equations in studying the course of lactation in the dairy cow and the rate of ovulation in the fowl. To date, such analyses have not been applied to the phenomena of starvation.

In the course of experiments conducted in this laboratory to determine the value of certain vitamin-bearing substances the animals that were used were found to have undergone progressive inanition. When the relative weight loss of the series was plotted against time it was noted that the curve was similar to the growth curve of an infant. Accordingly, it was thought profitable to calculate the neces-

sary constants for the growth equation from the experimental data and then to compare the theoretical with the observed results in order to determine, if possible, the kinetic relationships in the process of starvation.

Method.

The data were obtained from a series of fifty adult pigeons of both sexes which were kept under approximately the same laboratory conditions over a period of 53 days. Rations consisted of a high grade of polished rice with sufficient water. A portion of the animals also received small doses of tomato juice. About one-third of the animals developed beriberi so that the juice was considered practically impotent in the doses administered. The birds were kept in newly built cages, at ordinary room temperature, with plenty of fresh air and daylight entering the quarters. They were weighed twice weekly, and the weights were recorded to the nearest 5 gm.

In the original experiment the weights of the animals were used as one of the measures of the potency of the vitamin substances given the “treated” animals. For this investigation the weights were taken as an index of the progress of starvation, just as they are used as an index of growth. The difference in the weights of the treated animals and the controls who received only rice and water was entirely insignificant. It was not only obvious that the entire group was undergoing starvation, but also that this common process was progressing at identically the same rate. It seemed quite proper, therefore, to consider all the animals as a single group, and to include the weights in a single series.

Although no exact measurement was made of the amount of rice consumed, it was evident that the quantities ingested could have had only a minor effect on the entire course of starvation. Pilcher,\(^6\) working with pigeons under identical conditions in this laboratory, has weighed the amount of food eaten, and has found that it was dependent to a considerable extent on the amount of vitamin administered. From other experiments now being carried on it seems that the small amount of rice and vegetable juice served only to prolong

\(^6\) Pilcher, J. D. (unpublished report).
the starvation period and not to alter the nature of the process. In the strictest sense, starvation was not complete. Yet, on the other hand, it was plain that the animals were receiving far less food than would maintain their weight.

Results.

1. Application of the Simple Autocatalytic Monomolecular Law.—In the third column of Table I is given the observed mean weight loss, expressed in per cent, of all the pigeons in the series over the 53 day period of the experiment. This set of data is graphically illustrated in Fig. 1 by the large dots. The broken line which meets and which is continuous with the smooth curve at the 21st day is the curve plotted from values of the weight loss calculated by means of the simple autocatalytic monomolecular law. The smooth curve is plotted from the values of an equation which has been derived as a modification of the autocatalytic law and which will be considered in detail later.

It will be seen on referring to Fig. 1, that the broken curve, which is understood to be coincident with the smooth curve after the 21st day, meets the observed values very closely from this day to the 53rd day, but that previous to the 21st day there is more and more divergence until the discrepancy becomes maximum at 0 days. The broken line is represented by the equation of an autocatalytic monomolecular chemical reaction

\[
\log_e \frac{x}{a - x} = K(t - t_1) \tag{1}
\]

the differential form of which is given by

\[
\frac{dx}{dt} = kx (a - x), \tag{2}
\]

in which \(x\) is the amount of change at time \(t\), \(a\) is the total amount of change accomplished, \(t_1\) is the time when the reaction is one-half complete, or when \(x = \frac{1}{2}a\), and, in which \(k\) is the velocity constant of the reaction.

Three characteristics of the curve of this equation are evident, and it may be seen that the plotted values representing the observed weight loss also tend to lie along the same curve. They are (1) an initial period during which the slope of the curve gradually increases; (2) a point of inflexion situated approximately at the 21st day; and (3) a gradual diminution in the slope while the curve is approaching asymptotically to an upper limit of 50 per cent.

<table>
<thead>
<tr>
<th>Time</th>
<th>Observed weight loss. k x per cent.</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>days</td>
<td></td>
<td></td>
</tr>
<tr>
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</tr>
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</tbody>
</table>

a, taken approximately as 50 per cent.
T1 = 0.72 month (when x = 0.5a = 25 per cent).
μ, mean value of K in last twelve observations.
P.E. of the series = ± 0.0469.

In order that the theoretical values of the curve could be determined it was first necessary to calculate K, the velocity constant. This could have been done by simply introducing the observed values of a, x, t, t1, and solving for K directly, but by making use of tables prepared by Robertson which gave the values of K(t1 - t) for any value \( \frac{x}{a} \), the...
work was considerably simplified. Table I shows the different values of \( K \) calculated by this method. The factor \( t_1 \) was found to be 0.72 month, since exactly one-half of the total 50 per cent loss had been transformed at this time. Simple division of \( K(t - t_1) \) by the quantity \( (t - t_1) \) estimated from the data gave a value for \( K \) at each recorded observation.

The results of Table I and Fig. 1 may be considered in detail. \( K \) as determined by the above method is seen to be relatively high during the first 18 days of the experiment, but following this date the values of the constant are lower and show greater agreement. The mean of the whole series is 1.18; when, however, only those values after the 18th day are taken into consideration the mean is 1.06. The probable error, \( \varepsilon \), of the series was obtained from the usual formula}\(^7\).\(^8\)

\(^7\) Kelley, T. L., Statistical method, New York, 1923.
\(^8\) Pearl, R., Introduction to medical biometry and statistics, Philadelphia and London, 1923.
It is evident that all the deviations from the mean after the 18th day, with the exception of the last two deviations, are less than twice the probable error of the series. The last deviation is only 2.98 as large as the probable error. On the other hand, all of the values for $K$ calculated from the date preceding the 18th day give deviations from 5.75 to nineteen times larger than the probable error. In biometric studies a deviation which amounts to six times the probable error is considered to be definitely significant. Pearl,⁸ (Table 40), has shown that the probable occurrence of a deviation as small as 0.27 on the 15th day, in 100 observations is 0.0052, or that the odds against the occurrence of a deviation as great as this are 19,300 to 1. It is safe to conclude, then, that the discrepancies between the theoretical curve and the curve of observed values have a definite meaning, and that the latter two-thirds of the theoretical curve represents the course of a process which is significantly modified in its earlier portion.

Since the preceding analysis shows that 1.06 is the better value for the constant, it is easy to substitute this value in equation (1) from which a series of values for $x$, the relative weight loss at any time $t$, may be calculated. The other constants of the equation as obtained from the data are $a = 50$, and $t_1 = 0.72$ month. The mathematics is simplified by writing the equation of autocatalysis in the exponential form

$$x = \frac{ae^{2.3026 K(t - t_1)}}{e^{2.3026 K(t - t_1)} + 1}$$

in which $e$ is the base of natural logarithms. Values for $x$ so calculated are set down in Column 3 of Table III, and when plotted gave the broken curve in Fig. 1 already described.

In this instance again, it is seen that the values for the per cent weight loss are high during the early days of the experiment, but that after the 18th day there is substantial agreement between the observed and theoretical figures. Indeed, if the values at the beginning were to represent the true course of events, the birds weighed 7.72 per cent less than they actually did weigh at this time! Obviously, this is impossible; on the other hand, the agreement after the 21st day is suggestive.
From the above results alone it would be going too far to say, because of the agreement in the latter two-thirds of the starvation period, that the loss of weight followed the autocatalytic monomolecular law of chemical change. So far, only the relative weight loss has been considered because it was this curve that first attracted attention by its similarity to the growth curve. Instead of speaking in terms of relative weight loss it would probably simplify matters if a relation in terms of actual weights of the animals during the experiment could be derived.

2. Derivation of the Weight Equation.—It has been shown that the pigeons were losing weight in such a way that at the end of the experimental period the curve of relative weight loss was approaching an upper limit of 50 per cent. If then,

- \( B_T \) denotes the weight at any time \( T \),
- \( B_0 \) “ initial weight which must be maximum,
- \( T_1 \) “ time when the reaction is one-half complete, i.e. \( B_T = \frac{1}{2} B_0 \), or \( x = \frac{1}{2} a \), according to equation (3),

the differential equation expressing the rate of loss may be immediately written if it is remembered that the lower asymptote of this curve is reached when \( B_T = \frac{1}{2} B_0 \) (50 per cent weight loss), and that the upper asymptote, of course, is limited by the value \( B_0 \). Furthermore, if this reaction is to be of the autocatalytic type, it must conform to the general equation

\[
\frac{dx}{dt} = kx(a - x).
\]

The derived equation would then be given by

\[
- \frac{dB_T}{dT} = k(2B_T - B_0)(B_0 - B_T). \tag{4}
\]

When \( B_T \) is equal to \( B_0 \), the right-hand side of this equation passes to 0; it also passes to 0 when \( 2B_T \) is equal to \( B_0 \), so that at these points the slope of the curve \( \left( \frac{dB_T}{dT} \right) \) is 0, and the conditions of the experimental curve are satisfied. The negative sign before the left-hand member shows that the value of \( B_T \) is diminishing as the value of \( T \) increases. The quantity \( (2B_T - B_0) \) in equation (4) takes the place
of the quantity \( x \) in the general equation; equation (4), therefore, is of the type of equations expressing the rate of change of autocatalytic monomolecular reactions.

The above differential equation may be integrated most easily by the method of substitution:

\[
- \frac{dB_T}{dT} = k(2B_T - B_0)(B_0 - B_T),
\]

\[
\int \frac{dB_T}{(2B_T - B_0)(B_0 - B_T)} = -k \int dT;
\]

letting

\[
2B_T - B_0 = u, B_T = \frac{u + B_0}{2}; dB_T = \frac{1}{2} du;
\]

substituting,

\[
\int \frac{du}{\left(u + B_0 - B_\Theta\right)\left(B_\Theta - \frac{u + B_0}{2}\right)} = -k \int dT.
\]

Performing the indicated operations the equation becomes

\[
\int \frac{du}{u(B_0 - u)} = -k \int dT.
\]

This integral has been evaluated\(^9\) and is

\[
- \frac{1}{B_0} \cdot \log_\star \frac{B_0 - u}{u};
\]

resubstituting,

\[
\log_\star \frac{2B_\Theta - 2B_T}{2B_T - B_\Theta} = k B_\Theta T,
\]

which, on passing to common logarithms, becomes

\[
\log_{10} \frac{2B_\Theta - 2B_T}{2B_T - B_\Theta} = 0.4343k B_\Theta T,
\]

whence

\[
\log_{10} \frac{2B_\Theta - 2B_T}{2B_T - 2B_\Theta} = K(T - T_\ell)
\]

in which \( K \) is equal to 0.4343 \( kB_\Theta \).

\(^9\) Peirce, B. O., Short table of integrals, Boston, 1889.
The exponential form of equation (5) is easily derived and is given by

\[ B_T = \frac{B_0 e^{2.3026 K(T - T_0)} - 1}{2 (e^{2.3026 K(T - T_0)} + 1)}. \]  

(6)

By means of equation (6) the weights at different times were readily calculated with two settings on the slide-rule after the values of the exponential factor had been obtained from an appropriate table.\(^6\)

<table>
<thead>
<tr>
<th>Time (mos.)</th>
<th>Observed weight (gm.)</th>
<th>Calculated weights (gm.)</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>(M)</td>
<td>(B_T)</td>
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<td>0.00</td>
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<tr>
<td>1.76</td>
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</tr>
</tbody>
</table>

\[ A_0 = 30 \quad T_1 = 0.72 \text{ month} \]
\[ B_0 = 400 \quad k_1 = 3.94 \]
\[ t_1 = 0.30 \text{ month} \quad k_2 = 1.06 \]

P. E. of \(M_T\) = ± 1.26

These results are found in Column 3 of Table II. They were based on an initial weight of 400 gm. for an adult pigeon, \(i.e., B_0 = 400\). The plotted values of the weight curve represented by equation (6) lie along the broken curve in Fig. 2. Just as the broken curve of Fig. 1

\(^6\) Hodgman, C. D., and Lange, N. A., Handbook of chemistry and physics, Cleveland, 1922.
was extended into the smooth curve at the 21st day, the broken curve of Fig. 2 also becomes continuous with its smooth curve at this time. The large dots again represent the observed values; the agreement between observed and calculated results after the 18th day is likewise apparent in this graph. In this instance, however, the theoretical curve falls definitely below the curve of observed weights, and by such a margin that a statistical analysis, similar to that employed in estimating the velocity constant, shows that the differences must certainly be significant.

3. Corrections for Equations (3) and (6) with Final Results.—The discrepancies between theoretical and observed weights obtained from the preceding equations led to an hypothesis which will be discussed in the next section. Suffice it to say that a correction has been derived and applied to equations (3) and (6) which accounts for the differences during the early stages.

The corrected weight equation is equation (9); that for the relative weight loss is equation (10). Final theoretical values for the weight
were calculated by means of equation (9) and the results set up in the fifth column of Table II. These results are merely a summation of the values in Columns 3 and 4 of the same table. When the values $M_T$ of the table were plotted they gave the smooth curve of Fig. 2. Table III shows the final results and corrected values of the relative weight loss $m_T$, which gave the smooth curve of Fig. 1. The agree-

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Observed weight loss</th>
<th>Calculated weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$m$ per cent</td>
<td>$b_T$ per cent</td>
</tr>
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</tr>
<tr>
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</tr>
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</tr>
<tr>
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<td>47.50</td>
<td>46.20</td>
</tr>
</tbody>
</table>

$a_0 = 7.72$ per cent  \quad T_1 = 0.72$ month
$b = 50.00$ per cent  \quad k_1 = 3.94$
$t_1 = 0.30$ month  \quad k_2 = 1.06

P. E. of $m_T = \pm 0.331$

ment between the observed and calculated weights is now very close throughout the whole period of starvation.

DISCUSSION.

In the foregoing detailed analysis attention was called to certain discrepancies between observed and calculated results that prevailed
in the early part of the starvation period. Briefly, these were high values for the velocity constant of the reaction, high values for the relative weight loss, and low values for the actual weights. It was statistically shown that these discrepancies were more than a matter of chance, the significance of which was further augmented by the close agreement between theoretical and actual weights during the remainder of the experiment. These facts, accordingly, led to the following interpretation of the results.

After the 18th day of starvation the pigeons were losing weight in accordance with the law of autocatalytic chemical change. Previous to this time, however, certain factors must have been influencing the rate of loss in such a manner that they prevented the reaction from proceeding as rapidly as it did later. Evidently, then, these inhibiting factors had been sufficiently diminished by the 18th day that their influence for practical purposes was negligible. It was plain that the birds had been undergoing a process of inanition relatively complete in the sense that they were receiving insufficient material of various kinds to enable them to maintain their adult weights. Immediate physiological demands as well as the preservation of life necessitated the utilization of all available food supplies exclusive of the small amounts of rice and vitamin that they were ingesting. These supplies could only have been obtained from their own storage depots and from their own body tissues. When the reserve stores had been exhausted their only remaining source of energy consisted of body protoplasm. Accordingly, the rate of loss of body weight after the inhibiting substances had been removed must have been proportional to the rate of destruction of body protein. But, it has been shown that after 18 days of starvation the rate of weight loss could be very closely represented by the equation of an autocatalytic monomolecular reaction. It seemed proper, therefore, to conclude that the destruction of body protein followed the law of autocatalysis.

Such a conclusion appeared justified in the light of Robertson's studies on the kinetics of growth, in consequence of which he has interpreted growth as the final result of many processes primarily governed by the velocity of protein synthesis. Analogously, in the present instance, starvation was construed to be governed by the rate
of protein destruction, a process which was definitely modified in its earlier stages by the presence and by the destruction of storage substances—carbohydrate and fat, which, in turn, are known to prevent excessive protein loss. Many investigations on the metabolism of starvation apparently support this view. The protein-sparing action of carbohydrates and of fat has been substantiated by competent proof; analyses of normal organs and of organs following starvation have shown that carbohydrate and fat are consistently destroyed in favor of protein; the diminution in size of the body cells, the greater part of which is in the cytoplasm, has been frequently described in connection with the pathology of starvation.

At first, it was thought that the preceding conditions might be expressed in terms of a consecutive chemical reaction. Such a reaction is set forth symbolically by

\[ X \rightarrow Y \rightarrow Z \rightarrow O \]

in which the initial substance \( X \) is undergoing change to an intermediate substance \( Y \), which, in turn, is being transformed into a substance \( Z \) and so on. This equation, however, represents a reaction where some measure of the course of the reaction is increasing during the early stages, but where it is decreasing during the later stages. In the general equation above, a measure of this type of reaction would be contained in the factor \( Y \) or \( Z \). The conductivity of tissues, the rate of lactation of the dairy cow, and the rate of ovulation of the fowl are examples of the application of the laws of consecutive chemical reactions to physiological problems. In each of these the index of the process at first increases with time to a maximum value after which it gradually diminishes.

From the above considerations it was at once evident that the phenomena of starvation under the conditions of the present experiment must be represented by a relation that is continually decreasing.

11 MacLeod, J. J. R., Physiology and biochemistry in modern medicine, St. Louis, 3rd edition, 1920.
because in every case the initial weights were maximum. It seems quite possible that, at the very beginning, the process of growth and the process of starvation, measured by increase and by decrease of weight respectively, may have been in equilibrium, and, therefore, that any measure of the starvation process could be evaluated in terms of a consecutive reaction. Nevertheless, this period of equilibrium must have been decidedly short, and, accordingly, not subject to accurate verification. As the simplest explanation, then, these animals were considered to have been in equilibrium at the beginning of the experiment, from which the process of starvation took its origin.

**TABLE IV.**

<table>
<thead>
<tr>
<th>Time</th>
<th>$y$</th>
<th>$k_1$</th>
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</thead>
<tbody>
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<td>0.00</td>
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</tr>
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<td>0.03</td>
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</table>

$A = 30$.
$t_1 = 0.30$ month
Mean of $k_1 = 3.94$
Substance $A$ assumed to be decomposing autocatalytically.
Note fairly constant value of $k_1$.

Consequently, it appeared highly probable that the resultant course of starvation, defined by weight of reacting tissue, could be much better expressed by the laws of simultaneous reactions than by those of consecutive reactions. Symbolically, again,

$$M = A + B,$$

in which $M$ is a heterogeneous system composed of two independent homogeneous systems, $A$ and $B$. Both $A$ and $B$ were assumed to be decomposing autocatalytically; $A$ is taken as the factor of safety with respect to $B$, or, in the present case, the factor proportional to the amount of storage substances, and $B$ is taken proportional to the
amount of primary reacting tissue. As a matter of fact, A was also assumed to be decomposing according to the simple monomolecular law, but when the constants were determined by the same methods as in the previous section, the agreement between the observed and calculated results was much closer in the former case. The monomolecular decomposition of A as calculated from the data is given in Table V and is shown by the broken curve in Fig. 3; the results of Table IV and the smooth curve of Fig. 3 illustrate the autocatalytic decomposition of A; the closer agreement of the latter results to the observed values is apparent.

<table>
<thead>
<tr>
<th>TABLE V.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time.</td>
</tr>
<tr>
<td>ms.</td>
</tr>
<tr>
<td>0.00</td>
</tr>
<tr>
<td>0.16</td>
</tr>
<tr>
<td>0.33</td>
</tr>
<tr>
<td>0.50</td>
</tr>
<tr>
<td>0.60</td>
</tr>
</tbody>
</table>

\( A = 30 \),

Mean of \( k = 3.08 \)

Note increase in the value of \( k \) as reaction proceeds when the monomolecular equation \( \frac{2.3026}{T} \log \frac{A}{A - y} = k \), is used.

On the basis of the above assumptions, which appear reasonably justified, it would follow that

\[
\begin{align*}
\frac{dA}{dt} &= ky(A_0 - y); \\
\int \frac{dA}{y(A_0 - y)} &= -k \int dt; \\
\log \frac{A_0 - A_t}{A_0} &= k_it
\end{align*}
\]

integrating,

or,

\[
A_t = \frac{A_0}{e^{2.3026k(t - t_0)} + 1}
\]
The equation representing the autocatalytic decomposition of $B$ has been derived, and its value is given by equation (6) above. The general symbolical relation, (7), then becomes

$$M_T = \frac{A_o}{e^{2.3026 k_2(T - T_1)}} + \frac{B_o(e^{2.3026 k_2(T - T_1)} + 2)}{2(e^{2.3026 k_2(T - T_1)} + 1)},$$

in which

- $M_T$ is proportional to weight of reacting tissue at time $T$,
- $A_o$ is the initial amount of storage substances,
- $B_o$ is primary body tissue,
- $T_1$ is the time at which one-half of the reaction is complete,
- $t_1$ is time at which one-half of the reaction is complete,
- $e$ is base of natural logarithms,
- 2.3026 is reciprocal of the modulus of common logarithms,
- $k_1$ is velocity constant of the decomposition of $A$,
- $k_2$ is velocity constant of the decomposition of $B$. 

---

**FIG. 3.**
The modified equation for the relative weight loss has been similarly derived. It is given by

\[ m_T = \frac{b_0 e^{2.3026 k(T - T_0)}}{e^{2.3026 k(T - T_0)} + 1} - \frac{\phi_0}{e^{2.3026 k(t - t_0)} + 1}, \]  

(10)

in which the units chosen represent relative weight loss and in which the constants have the same significance as above.

When the modified equations (9) and (10) were used to calculate the theoretical values for the weight and for the relative weight loss respectively during the entire course of the reaction, the results set up in Tables II and III were obtained; in Figs. 1 and 2 these values are represented by the smooth curves, which in both cases meet the observed values throughout the course of starvation with satisfactory precision.

In considering the relative rates of decomposition of substances A and B, it is important to note that while substance A is diminishing from a finite value of \( A_0 \) to a value that approaches 0 during its own time interval \( t \), the substance B, on the other hand, is being transformed from a maximum value of \( B_0 \) to a value of \( B_C \) during the whole interval \( T \). \( B_C \) is taken proportional to the value of the reacting mass of tissue at death. The ratio \( \frac{B_C}{B_0} \), therefore, is proportional to the remaining relative amount of tissue when the reaction is complete, and the ratio \( \frac{B_0 - B_C}{B_0} \), proportional to the maximum relative change that occurs, which, in the present experiment, as shown, is equal to 50 per cent.

From the experimental point of view it is of interest to note that, in those pigeons which develop beriberi on a rice diet, the onset of the disease usually falls within the 18 to 21 day period of starvation\(^{14} \) at precisely the time when, as shown above, one-half of the process of starvation has been completed.

SUMMARY AND CONCLUSIONS.

1. The relative weight loss of pigeons on starving rations may be represented by a simple modification of the law of autocatalysis.

2. An equation giving the actual weight of the animals during the 53 day period of the experiment is derived by means of the hypothesis that the process of inanition is governed by the simultaneous velocity relations between two independent, homogeneous systems, such that

\[ M_T = (A_a \rightarrow 0) + (B_b \rightarrow B_C) \]

in which \( A \) is taken proportional to the amount of carbohydrate-fat reserves, and \( B \) proportional to the amount of reacting body protoplasm.

3. The course of starvation is governed by the rate of destruction of body protein, but it is modified by the amount and by the rate of destruction of reserve materials.

4. The processes of breaking down tissues are analogous to those by which tissues are synthesized.

5. The close agreement between observed and calculated values suggests that the original assumptions set forth in deriving the foregoing equations were valid.

6. Attention is called to the fact that the time of onset of beriberi in pigeons is coincident with the half period of starvation.